J.G. Reves Sheila Ryan Barnett Julie R. McSwain G. Alec Rooke *Editors*

Geriatric Anesthesiology

Third Edition



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J. G. Reves • Sheila Ryan Barnett Julie R. McSwain • G. Alec Rooke Editors

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Printed on acid-free paper

This Springer imprint is published by Springer Nature The registered company is Springer International Publishing AG The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland The editors are privileged to dedicate this edition of Geriatric Anesthesiology to the late Jeffrey H. Silverstein, MD, who at the time of his death (2015) was planning the third edition of the textbook that he personally, tirelessly saw reach its status as the authoritative volume of the knowledge of the anesthetic practice for geriatric patients. The second edition encapsulated his abiding interest in the science and education of anesthesia for the geriatric population. It was his desire that the next edition expand on this important aspect of anesthesiology.

As we reflect on the field of geriatric anesthesiology that has been blessed with many dedicated and visionary leaders, none have been as meaningful as Jeff Silverstein. His untimely death from cancer on July 27, 2015, was a huge loss to the specialty and all of us who knew and worked with him. Jeff was one of the original members of the American Society of Anesthesiologists (ASA) Committee on Geriatric Anesthesia when it was formed in 1992. Since then, he was involved in every significant aspect of the development of geriatric anesthesia. As an example of Jeff's leadership in the early 1990s, the American Geriatrics Society (AGS) began their programs to promote geriatric expertise in nonmedical specialties, including anesthesiology. The AGS began with advisory meetings that included representatives from geriatrics and ten nonmedical specialties. These formal and informal AGS Committees provided advice on outreach programs to be supported by the AGS. Over a 20-year span, Jeff was the most consistent representative from anesthesiology. His participation culminated during his tenure as chair of the AGS Section for Enhancing Geriatric Understanding and Expertise Among Surgical and Medical Specialists (SEGUE), and he was instrumental in the development of the JR and its successor, the NIH-funded Grants for Early Medical/Surgical Specialists' Transition to Aging Research (GEMSSTAR) award.

Jeff was a leading force in the formation of the Society for the Advancement of Geriatric Anesthesia (SAGA) (www.sagahq.org) in 2000 and was its second president. He was an active participant in the educational activities provided by SAGA members to the ASA, the AGS, the New York State Society of Anesthesiologists PostGraduate Assembly, and the Society of Cardiovascular Anesthesiologists. Jeff was active in geriatric research as well, with over 20 PubMed citations in geriatric anesthesiology alone. Most of this research was on the topic of postoperative cognitive decline. Yet as meaningful as the above accomplishments are, they do not do justice to the person that Jeff was to many of us in geriatric anesthesiology. He was a colleague, a mentor, a leader, and a friend. Jeff had that special ability to cut through all the extraneous, distracting information and succinctly define the important issues and how to go about achieving them. His vision and implementation of the vision will perhaps be what is most sorely missed. We miss his insight and his effective, provocative manner that not only entertained us but challenged us to go beyond what we thought possible. Jeff's presence and deep, booming voice commanded attention, but it was his creative mind that really kept us moving forward.

We hope that this book is a fitting tribute to Jeffrey H. Silverstein, MD, who insisted on a thorough approach to the science and practical information required in providing optimal anesthesia care to the elderly.

Preface to the First Edition

Approximately 14% of the current US population is 65 years of age or older. By the year 2020, it is predicted that 20% or 60,000,000 Americans will reach this milestone. Further, if today's statistics continue unchanged, at least half of these individuals will undergo anesthesia and surgery, likely of increasing complexity, prior to their eventual demise. The geriatric patient population represents a huge and growing challenge for anesthesia providers the world over.

My interest in the anesthetic management of geriatric patients was kindled 15 years ago while on the faculty at Bowman Gray. One of our surgeons asked me to anesthetize his healthy 72-year-old father. All went well in the intraoperative and postoperative periods, and he was discharged home in the customary time frame. However, my colleague later reported that he had observed subtle psychomotor changes in his father which persisted postoperatively for 7 weeks. It dawned on me that perhaps the geriatric patient is not simply an older adult, but, rather, a truly different physiologic entity. What could explain the relatively commonly observed delayed postoperative return of normal mentation in the geriatric surgical patient? It is this and other unanswered questions regarding the anesthetic management of the elderly that stimulated the development of this text.

Geriatric Anesthesiology is designed to be a comprehensive text that methodically addresses the aging process while emphasizing important clinical anesthetic considerations. The first two sections of the text define the demographics of our aging population and describe age-related physiologic changes that occur in each major organ system. The third section addresses the multitude of factors that contribute to a safe and successful anesthetic with suggested adjustments in technique that may improve anesthetic management of the elderly. Topics range from preoperative evaluation and risk assessment to the altered effects of various classes of drugs with further discussion regarding positioning, thermoregulation, perioperative monitoring, and postoperative recovery. In addition, issues such as management of pain syndromes, outpatient anesthesia, medicolegal implications, and even special CPR techniques in this age group are considered. The fourth section identifies the ten most commonly performed surgical procedures in the elderly and, for each, offers recommended anesthetic techniques. The text ends with an intriguing exploration into future research opportunities in the field, including molecular mechanisms of aging.

Considerable energy has gone into the creation of this text. I am grateful for the significant efforts made by all the contributing authors and especially appreciate contributions made by the editors from Williams & Wilkins. The text would have been impossible to complete without the encouragement, dogged determination, and professionalism of Ms. Tanya Lazar and Mr. Carroll Cann. Tim Grayson was innovative and supportive during the original design and formulation of this project.

I am optimistic that this text will heighten the awareness of the very real clinical differences presented by the geriatric patient population. Perhaps by referring to appropriate sections in this text, anesthesia providers will be armed with a better understanding of the physiologic changes of aging and the recommended considerations and modifications of anesthetic technique, which we hope will contribute to an ever-improving outcome for the geriatric surgical patient population.

Preface to the Second Edition

Do not go gentle into that good night, Old age should burn and rave at close of day; Rage, rage against the dying of the light.

Dylan Thomas

The goal of getting older is to age successfully. Unfortunately, the majority of our older patients will have acquired one or more chronic medical conditions as they age, and, even if a perfectly healthy older patient presents for surgery, that patient's ability to handle physiologic stress will be diminished, including the stress of surgery. Nearly half of all surgical procedures involve patients older than age 65, and that percentage is likely to increase as the US population ages. Thus, the perioperative care of the older patient represents one of the primary future frontiers of anesthetic practice. Even though perioperative mortality has diminished for the elderly, as well as for the population in general, the growing number of cases spotlights perioperative morbidity and mortality as an important issue for patients and healthcare systems alike. The vision set forward by the first edition (i.e., to apply the growing body of knowledge in this subspecialty area to the everyday practice of anesthesiology) remains the mission and vision of this second edition. The editors believe that the updated contents of this edition represent an important opportunity to consolidate and organize the information that has been acquired since 1997 and to apply that knowledge to the current practice of anesthesiology.

Part I contains several new chapters on topics that may not always seem to be directly involved with anesthetic care, but are important to the future of medical and anesthesia care. An understanding of the aging process may lead to methods of slowing its progression or at least of ameliorating some of its consequences, including the development of chronic disease. Most anesthesiology residency programs provide limited formal teaching of geriatric anesthesia. The editors believe the incorporation of relevant subspecialty material in the anesthesiology curriculum is needed to improve care for this patient population. The realities of reimbursement for services rendered to the older patient, either by Medicare or other payers, warrant the attention of all anesthesiologists who provide care for older patients. Ethics as applied to treatment of the older patient is also addressed. The medical management of this population is often complicated by issues such as patient goals that differ from physician expectations, physician "ageism," patient cognitive impairment, and the physician's failure to recognize the true risk of surgery and attendant recovery time. The last chapter of Part I reviews current knowledge and suggests research areas where the greatest impact on patient outcomes might be realized.

Parts II and III review the physiology of aging and the basic anesthetic management of the geriatric patient, and Part IV examines selected surgical procedures frequently performed in older patients. Not all of these chapters are specific to anesthetic management. Geriatric medicine is a broad field with many relevant topics. Wound healing is a perfect example. The reality is that anesthesiologists can likely have a positive impact on patient care by being better able to recognize conditions that may compromise skin when other medical professionals may fail to and, as a result, can improve protection of the skin, especially during long operating room cases. In contrast, polypharmacy and drug interactions, major topics in geriatric medicine, have direct relevance to anesthetic management. The cardiac surgery chapter is an example of

how age affects outcomes after a specific type of surgical procedure. The unusual aspects of anesthetic management for cardiac surgery revolve mostly around the patient's underlying disease status rather than there being anything specific to cardiac anesthesia in the older patient beyond the principles delineated in Parts II and III.

For chapters similar to those in the first edition, an effort has been made to update content and incorporate studies that examine outcome. Such work helps us challenge conventional wisdom and sometimes test novel ideas that prove beneficial. Even the most casual reader of this textbook will recognize huge gaps in our present knowledge. It is not sufficient, for example, to take an understanding of the physiology of aging and draw conclusions regarding anesthetic management from that information. Oftentimes, however, we are forced to do just that when making anesthetic management decisions. The editors hope the future will provide better research and answers that advance the field of geriatric anesthesiology.

The editors thank the many authors of this text. In addition to their hard work, they responded to entreaties for revisions and updates with admirable patience and promptness. Their contributions expand our knowledge and will improve the care of elderly patients.

Lastly, the editors thank Stacy Hague and Elizabeth Corra from Springer. Without their vision and determination, this book would not exist.

Jeffrey H. Silverstein G. Alec Rooke J.G. Reves Charles H. McLeskey

Preface to the Third Edition

People all over the world are living longer. In fact, by percentage change, the over-65-year-old group is the fastest growing age group worldwide. According to the U.S. Census Bureau, by year 2030, nearly 20% of the population will be 65 years of age and older. Considering the burgeoning population and the fact that patients aged 65 and older are receiving procedures in disproportionate numbers to younger patients, it is imperative that anesthesiologists be prepared to care for an ever-increasing number of elderly patients. Thus, evidence-based perioperative care of the geriatric patient will only continue to grow in importance for the practicing anesthesiologist.

The mission of this edition remains the same as the previous two editions: to assemble the growing body of knowledge in geriatric anesthesia and provide it to the anesthesiologists for use in the everyday practice of anesthesia. However, as our knowledge regarding perioperative care of the elderly surgical patient grows, so do our questions. In this edition, we have asked all authors to include a section within each chapter entitled "Gaps in Our Knowledge." These sections highlight areas in which research is needed, as well as hopefully inspire readers to begin solving some of these questions.

This edition continues to build on the strong foundation of the first two editions. However, as the field of geriatric anesthesiology rapidly evolves, so does our focus on important new developments. Part I contains several new chapters that reflect the evolution of multidisciplinary geriatric care throughout the perioperative continuum. We highlight the evolving development of the Perioperative Surgical Home, as well as expound on the growing body of literature related to prehabilitation. In addition, in the theme of multidisciplinary collaboration, we have also included chapters on the surgeon's perspective and geriatrician's perspective on surgery in the geriatric population. This is important as medical care must continue to be a more collaborative effort as patients get older and sicker.

Parts II and III review the systematic physiologic changes associated with aging and the pharmacologic considerations for the geriatric patient undergoing procedures. These chapters are necessary components to any comprehensive textbook on geriatric anesthesia, and while much of the material is similar to that of the last two editions, an effort has been made to update any information relevant to the changing practice of geriatric anesthesia. For example, in the chapter on chronic medication use in the elderly, particular focus was placed on certain rapidly developing medications that impact practice such as antidepressants and new anticoagulants.

Part IV, special concerns, has also undergone major changes. There are more minimally invasive procedures being performed outside the operating rooms or in hybrid operating suites which pose specific challenges for geriatric patients. We have highlighted these changes in practice within this section, including expanding chapters on cardiovascular procedures related to minimally invasive valvular procedures as well as monitored anesthesia care and NORA procedures. In addition, we included a chapter solely dedicated to implantable pacemakers and ICDs as both perioperative management of these devices and anesthetic management for heart and vascular procedures are growing in volume. The anesthetic management of patients undergoing surgery for cancer entails special considerations, and since the elderly commonly undergo such procedures, a chapter on this topic has been added. The elderly are also subject to trauma, and there is a growing knowledge base on trauma care for the older patient. This

section also includes chapters on management of elderly patients undergoing cardiothoracic/ vascular surgery and orthopedic surgery. There is an especially large body of knowledge on orthopedic surgery in the elderly, much of which has arisen from outside the USA.

Finally, in this edition, we have added a Part V that focuses on postoperative care specific to the geriatric population which includes acute pain management, ICU management, recent evidence and up-to-date practice regarding delirium and postoperative cognitive dysfunction, and palliative care. As the role of the anesthesiologist continues to expand outside of the operating room, it is imperative that we continue to practice evidence-based care for the geriatric patient within these settings.

Charleston, SC, USA Boston, MA, USA Charleston, SC, USA Seattle, WA, USA J.G. Reves Sheila Ryan Barnett Julie R. McSwain G. Alec Rooke

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The editors thank all the authors of this text for their thoroughness in content as well as their prompt responses for revisions and updates. Their contributions will undoubtedly improve the care of geriatric patients. We especially thank our developmental editor Michael D. Sova and Springer Publishing for their encouragement, diligence, and determination to get this book to print.

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Part I Fundamentals

Geriatric Anesthesiology: Where Have We Been and Where Are We Going?

Julie R. McSwain, J.G. Reves, Sheila Ryan Barnett, and G. Alec Rooke

Introduction

The subject of anesthesiology spans the science and art of an entire clinical discipline. This includes material of basic and clinical sciences as well as particular pharmacology that encompass drugs to render man insensitive to pain, induce loss of consciousness, and paralyze muscles [1]. Geriatric anesthesiology is an emerging, important area more narrowly focused on the art, science, pharmacology, and physiology pertaining to the elderly surgical population. Age is an imperfect descriptor of geriatric anesthesia because age alone does not define the important changes that make older patients more challenging and different than normal adults. Nevertheless, age ≥ 65 years old is used arbitrarily to define the geriatric population.

Geriatric medical care has evolved from an empiric discipline in the 1950s and 1960s to a largely evidence-based practice today [2]. An excellent short reference guide called *Geriatrics at Your Fingertips* is available in a small pocket edition as well as on the Internet [3]. Perioperative geriatric anesthesia is very much at the frontlines of developing sufficient primary data on which to base practice guidelines. However, there are still only a few randomized controlled trials that provide class I evidence regarding perioperative care of the elderly, leaving the practitioner to extrapolate findings from literature that has accumulated on geriatric care in other contexts that pertain to the perioperative setting.

S.R. Barnett

This introductory chapter presents some of the foundational concepts of geriatrics and a general approach to caring for geriatric patients presenting for surgery. In approaching elderly patients, the anesthesiologist must recognize that there is tremendous heterogeneity or variability in aging, both in the body as a whole and in individual organ systems. Thus, the alterations described in this book are likely, on average, to be presented in geriatric surgical patients, but each individual patient will manifest these changes differently. The reader is encouraged to develop expertise and judgment to identify those areas in need of improved approaches with the goal of developing an evidence-based practice for perioperative geriatric care. To facilitate this, each chapter identifies gaps in our knowledge that are meant to stimulate investigation to extend our knowledge of geriatric anesthesiology through future research.

History of Geriatric Anesthesia

Interest in geriatric anesthesia can be found as far back as the mid-1940s in the form of a journal article [4] and in the 1950s with a textbook [5], but very little can be found thereafter until the mid-1980s when five textbooks appeared [6–10]. Medical meetings such as the American Society of Anesthesiologists (ASA) annual meeting did not have much specific geriatric content until the mid-1980s, but the Geriatric Anesthesia Symposium held at Washington University was an exception. Believing that geriatric anesthesia was not receiving the attention it deserved, Dr. C. Ronald Stephen, department chair, assigned Dr. William Owens to organize the multiday meeting held annually in St. Louis, MO, from 1974 to 1994 [11].

Awareness of the importance of geriatric anesthesia began to gain momentum in earnest in the early 1990s when the ASA formed the Committee on Geriatric Anesthesia in 1991. The first meeting was held in July 1992. The creation of a formal geriatric section of the ASA proved fortuitous because not long thereafter the American Geriatrics Society (AGS)

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began reaching out to ten surgical-related specialties. The AGS needed each specialty to participate in strategic planning meetings, and anesthesiologists were drawn from the ASA Committee on Geriatric Anesthesia. Simultaneously, the American Federation for Aging Research sponsored two separate 2-year fellowships in geriatric anesthesia that ran from 1992 to 1994, but this was a one-time program.

The ASA Committee on Geriatric Anesthesia has always focused on providing educational opportunities. From 1998 onward, the Committee has organized at least one panel for the ASA meeting every year but one. The Committee has also developed multiple educational products over the years. The first was the Syllabus on Geriatric Anesthesia, published online in 2002 [12]. Later, the Geriatric Anesthesiology Curriculum [13] and a Frequently Asked Questions document were published by the ASA [14]. All of these documents were developed to assist the busy practitioner as well as anesthesia residents and other health-care providers.

In an effort to improve visibility of geriatrics and establish the importance of geriatrics within anesthesiology, the Committee developed and submitted a white paper to the ASA Board of Directors in January of 2013. The major recommendation was to create a geriatric anesthesia educational track for the annual ASA meeting. With acceptance of this recommendation, the Educational Track Subcommittee on Geriatric Anesthesia was created, and the Abstract Subcommittee was moved out of ambulatory anesthesia into its own entity. The track successfully "went live" at the 2016 ASA annual meeting and included an approximately a doubling of the educational material presented on geriatric anesthesia at the meeting. This was a major accomplishment for the Geriatric Committee and the field of geriatric anesthesiology in general.

The Geriatric Committee has served as a liaison to other medical societies and provided many expert reviews both formally and informally. For example, when the American Academy of Orthopaedic Surgeons wanted anesthesiologist input into their management guidelines for hip fractures in elderly patients, the Committee was contacted and provided feedback [15]. Committee members have presented talks and panels on geriatric anesthesia to other societies, including general surgery, thoracic surgery, and geriatric medicine, as well as to multiple anesthesia subspecialty societies.

By the late 1990s, it became apparent that there were many more ASA members interested in geriatric anesthesia than could be accommodated by the Committee. The desire to provide opportunity for involvement by more ASA members and permit greater exchange of ideas led to the formation of the Society for the Advancement of Geriatric Anesthesia (SAGA) in 2000. From the start, the activities of SAGA and the ASA Committee on Geriatric Anesthesia have been intertwined. SAGA members have supported Committee projects, in large part because their leadership has been integral members of both groups. In addition, most of the non-Committee members who have contributed to the Committee's published documents and educational programs have been SAGA members [11]. SAGA maintains an active website [16] (www.sagahq.org) with links to many educational materials, meetings, and grants. SAGA also has an annual meeting that has been held during the ASA national meeting, during which society business is conducted and a scientific presentation is provided. Since 2007 SAGA has made financial contributions annually to the Foundation for Anesthesia Education and Research to support projects with a geriatric basis. SAGA has cosponsored meetings in partnership with the anesthesiology departments at the Hospital for Special Surgery in New York City and the MD Anderson Cancer Center in Houston. SAGA remains small but has a significant impact on geriatric anesthesia because its members are extremely active in ASA leadership; in the anesthesia community at large, educational publications; and in research. The most prominent research topics in geriatric anesthesia have been postoperative delirium and postoperative cognitive dysfunction.

The closest outside relationship for both the ASA Committee on Geriatric Anesthesia and SAGA has been with the American Geriatrics Society [17]. The AGS has taken the position that there will be too few geriatricians to care for our aging population. Consequently, geriatric expertise needs to be present in all medical specialties and that training in geriatrics needs to be a part of residency programs. This concept extends to non-internal medicine specialties as well [18]. The Geriatrics for Specialists Project began in 1994 in partnership with five such specialties and expanded to ten specialties (including anesthesiology) in 1997. With support from the John A. Hartford Foundation, educational grants to these ten specialties began in 1998. The process became more established beginning in 2001, and since then, anesthesia programs have received nine grants to develop educational programs to enhance resident training in geriatrics.

Through 2000, AGS sponsored meetings of AGS geriatricians and representatives from each of the ten non-internal medicine specialties were organized on an ad hoc basis and were primarily planning and strategy meetings. This structure changed with the creation of a section of the AGS, the Section for Enhancing Geriatric Understanding and Expertise among Surgical and Medical Specialists known as SEGUE. The leadership Council for SEGUE comprised leaders as described above, but SEGUE itself now provides an educational program at the annual AGS meeting. The specialty societies became responsible for supporting the meetings of the SEGUE Council, and anesthesiology has been well represented. Dr. Jeffrey Silverstein, one of the founders of SAGA, was also the Council Chair from 2007 to 2009.

The SEGUE Council has also encouraged research in geriatric care in the nonmedical specialties. Toward this goal, the AGS first published a monograph in which each specialty contributed a state of the art knowledge summary and opinions as to where future research needed to be directed [19]. The Council also recognized greater interest in geriatrics could be generated if a core group of researchers and leaders in each field were created. This goal led to the creation of the Jahnigan award that provided not only generous research support but support for education on geriatric medicine and specialty-specific patient care. Beginning in 2002, approximately ten new awards have been given annually among the non-internal medicine specialties [20]. Funding from the Hartford Foundation was for a limited time period, so in 2011 the National Institute of Aging initiated the GEMSSTAR [21] award to cover the research activities of the awardee. Financial support of the educational aspect of the award (what the Jahnigan award now represents) comes from the individual specialties, with the Foundation for Anesthesia, Education and Research often providing partial support for awardees from anesthesiology. From 2002 to 2015, anesthesiology has received a total of 11 awards. Besides supporting research, from 2001 to 2009, the AGS funded projects by academic departments, with the goal of producing educational materials that could be shared with all training programs [22]. Nine grants were awarded in anesthesiology. The resulting teaching materials can be found in the Geriatrics for Specialists section of the American Geriatrics Society website [23].

The future of geriatric anesthesia looks bright. The ASA, as well as the European Anaesthesiology Conference, has formal sections in their meetings that are devoted to geriatrics. SAGA [16] and the Age Anaesthesia Association in the UK [24] represent societies dedicated to geriatric anesthesia. Several recent textbooks address the field [2, 25, 26], and considerable research is ongoing on topics that primarily affect older patients, such as postoperative delirium and cognitive dysfunction. The role of the anesthesiologist with geriatric expertise, however, remains to be fully defined. Certainly such individuals need to serve as resources for others in the specialty, but do elderly patients need to be managed by specially trained anesthesiologists? At present, the answer is "no," but it is also clear that most anesthesiologists could be better informed about the management of the elderly, especially the frail elderly. This text is an attempt to provide much of that knowledge.

Demography

The population of the world overall is increasing, and the USA is expected to see its population grow from 314 million in 2012 to 400 million in 2050, a 27% increase [27]. With

this population increase, there is a particularly large increase in people 65 and over [27, 28] (Fig. 1.1). Less than 5% of the US population was over 65 years old in 1900, and 13% were over 65 years old in 2000. However, by 2030, according to the US Bureau of the Census, approximately 20% of the population may be greater than 65 years of age [28]. In 2050, the over 65-year-old population in the USA is projected to be 83.7 million, almost double the 2012 estimate of 43.1 million. The average life expectancy for men and women in the USA is expected to increase from 82.5 in 2017 to 86.6 in 2050. The life expectancy varies by race and gender, but cumulative life expectancy is increased in each group when reaching the age of 65 and 85. This means that if one attains each of these advanced ages, expectancy increases in the older cohort [29]. Women life's expectancy is greater than men, but this difference becomes less significant as the cohorts increase in age. People over 65 years of age are the fastest-growing age group in the USA [30]. Of note, the fastest-growing segment of the population is that aged 90 years and older, and this will further challenge our physicians and clinical facilities.

Reasons for the marked increase in elderly patients relative to the overall population are many. A simplified explanation is that both mortality and fertility rates are decreasing. This inevitably increases the percentage of elderly. Fundamental contributions to longevity are genetic makeup as well as socioeconomic and geographic factors. Genes determine what diseases develop, as well as whether drugs are effective treatments for disease in specific people. Racial and socioeconomic factors often contribute to longer life with advantages found in white and economically advantaged populations. Another reason for the growth in the over 65 years of age cohort is the baby boom generation. The baby boom generation is defined as people born from 1946 to 1964. As the baby boom generation progresses in age, the percentage of over 65 should stabilize in 2030 (see Fig. 1.1). Other contributing factors to healthy aging include medical advances reflected by the remarkable decrease of early deaths from ischemic heart disease and many cancers. Improved knowledge, diagnosis, medicines, and procedures have led to major improvements in the survival of patients with these chronic diseases. Public health has also played a major role in extending life expectancy. There are better water sources, food, immunizations, sanitation, and approaches to communicable disease that have all led to greater survival. Finally, and importantly, lifestyle changes have conferred longevity, for example, cessation of smoking, regular exercise, improved diet, and drinking habits.

Within the USA, there is a nonuniform distribution of population over 65. In the USA, Fig. 1.2 [31] shows wide variation in each state in the percentage of population over 65. Some states have seen much greater growth in their older populations between 1999 and 2009 than others with Alaska

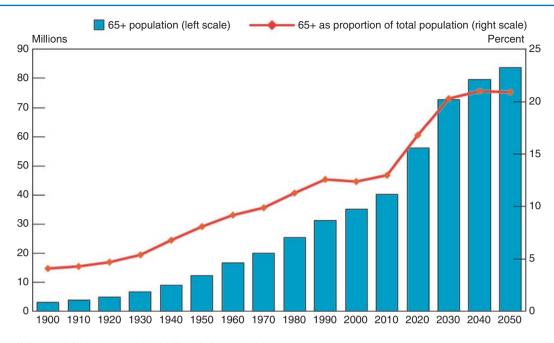


Fig. 1.1 Population aged 65 and over: 1900–2050. This figure depicts (*bars*) the 65 years old population of the USA from 1900 and projected to 2050. Note the marked increase until 2030 when the percentage (*line*) of geriatric people flattens at about 22%. (For information on con-

fidentiality protection, nonsampling error, and definitions, see www. census.gov/prod/cen2010/doc/sf1.pdf) (Reprinted from U.S. Census Bureau, P. et al. [32])

(50.0%), Arizona (32.1%), Colorado (31.8%), Georgia (31.4%), Idaho (32.5), Nevada (47.0%), South Carolina (30.4), and Utah (31.0%) all experiencing 30% or more 10-year increase in their elderly population. However, in absolute numbers of elderly citizens in the 2010 census, over half (56.5%) of persons 65+ lived in 11 states: California (4.3 million), Florida (3.3 million), New York (2.6 million), Texas (2.6 million), Pennsylvania (2.0 million), and Ohio, Illinois, Michigan, North Carolina, New Jersey, and Georgia each having well over 1 million [31].

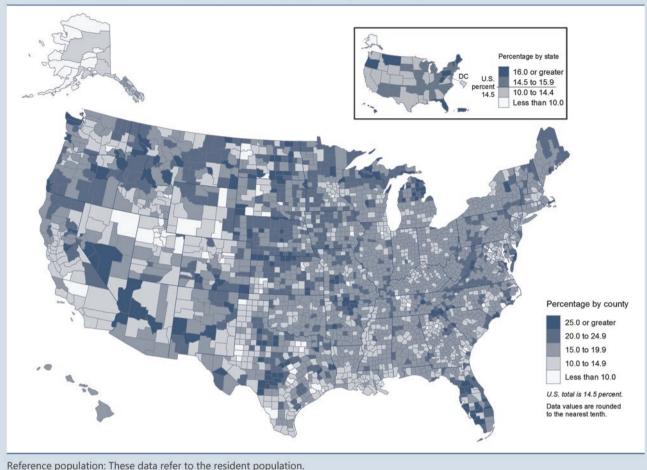
Like the various states in the USA, there is great variation in the world distribution of elderly people. Figure 1.3 [32] shows the forecasted change in global distribution of people over 65. Europe and North America have the largest percentage of over 65 among major world regions. The USA had 13.1% of population over 65 in 2010 and is relatively young compared to some countries like Germany, Italy, Japan, and Monaco with populations of 20% over 65 [32]. The developed countries of the world tend to have the older populations because of increased life expectancy and reduced fertility. However, by 2050 it is predicted that 100 countries will have a population with at least 20 percent of their population over 65. A shift in world population is predicted to occur between 2015 and 2020 when the percentage of people over 65 will for the first time be greater in the world than those under 5. The less developed countries are expected to make gains in their older populations, taxing their ability to provide the necessary medical and social care required by older people. The US Census Bureau has

aptly summarized the impending growth in elderly populations of the USA and world: "Both individuals and society need to prepare for population aging; the cost of waitingfinancial and social- could be overwhelming" [32]. It is clear that there is a need for the medical community to prepare for this major change in our demographic makeup.

Health Implications of an Aging Population

People older than 65 typically have one or more chronic diseases [32]. These diseases may require specific pharmacologic therapy or even surgery and may limit physical activity. The prevalence of chronic diseases that limit activity in geriatric patients is shown in Fig. 1.4. Note that all diseases increase with age, but problems with vision, hearing, and senility become more prevalent by age 85. Arthritis is a very common ailment that can progress even with appropriate therapy. About 50% of people over age 65 have arthritis with women affected more than men.

Geriatric patients can suffer from a number of chronic cardiovascular diseases. For example, coronary artery disease is very prominent and is more common in men. Ischemic heart disease can lead to increased risk of perioperative myocardial infarction which has a high morbidity and mortality. Valvular disease is also prevalent in the elderly and tends to affect the aortic and mitral valves. These valves may either be stenosed or incompetent. Altogether, 96 per 1000 people have cardiovascular disease that significantly impacts their



Percentage of population age 65 and over, by county and state, 2014



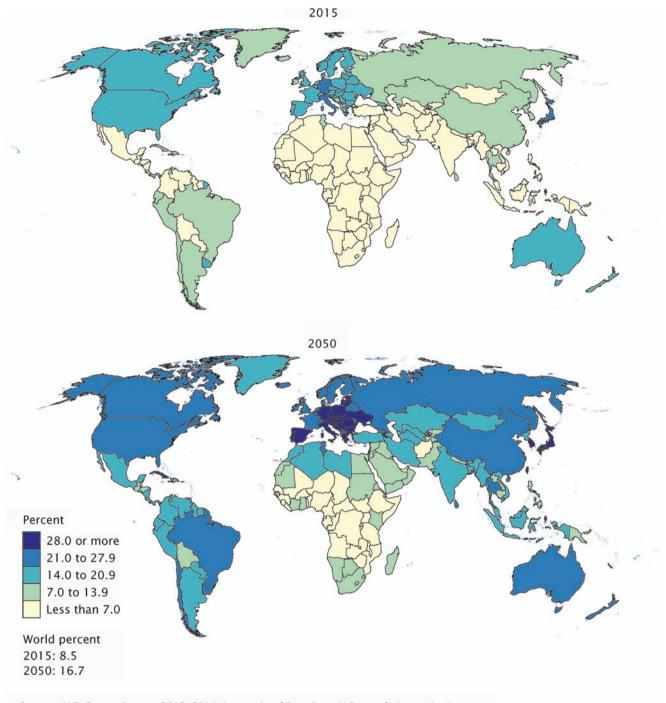
Fig. 1.2 Distribution by state of people over 65 as a percent of population. This figure shows that there is a wide variation in the over 65-year-old population with the greater concentration in the South, Southwest,

Northeast, and lower Midwest. (The *darker* the color the higher the percentage of a state's geriatric population) (Reprinted from Federal Interagency Forum on Aging-Related Statistics [66])

activity [32]. This number increases to approximately 204 per 1000 over the age of 85 years, with women and men being equally affected. The process of atherosclerosis also affects other blood vessels in the body jeopardizing the integrity of the vessels themselves and the organs they supply. For example, stroke is the leading cause of severe long-term disability and affects older Americans more frequently. About 75% of strokes afflict people over 65 years old, and the risk doubles every 10 years after age 55 [33]. A prominent risk factor for stroke is hypertension. Hypertension affects about half of the population over 65, and it is slightly more prevalent in women. It should be treated aggressively to prevent heart disease and stroke as well as contribute to a stable hemodynamic perioperative course.

Common metabolic diseases that affect the geriatric population are diabetes and osteoporosis. Diabetes type 2 afflicts a large majority of older people, but surprisingly its diagnosis does not increase with age. Thus, diabetes is likely a chronic disease that develops before age 65 [32]. Careful management of diabetes is important as it is a precursor to a number of other serious diseases, including ischemic heart disease and stroke. Osteoporosis makes bones more brittle and prone to fracture, and women are more likely to develop this disease than men. The bones most affected by osteoporosis are the spine, hip, and wrist. Osteoporosis can also lead to fractures that require surgery. In fact, hip fractures are common and can lead to serious morbidity and mortality. Older people who have a hip fracture are three to four times more likely to die in 3 months than those who do not suffer a hip fracture [34, 35].

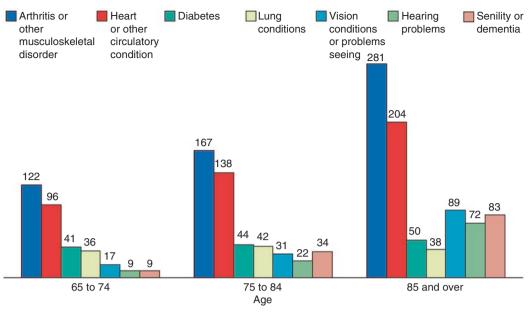
Half of the people diagnosed with cancer are 65 or older [32, 36]. This is a result of the increased longevity



Sources: U.S. Census Bureau, 2013, 2014; International Data Base, U.S. population projections.

Fig. 1.3 Percentage of population aged 65 and over: 2015 and 2050. This figure demonstrates that aging is a global problem. The number of countries worldwide with populations over 65 greatly increases between 1015 and 2050 (Reprinted from He et al. [67])

of people as well as an increase in some cancers in the elderly. The major significance of cancer to the anesthesiologist is that many patients have operations designed to cure or palliate. Prostate and breast cancers now have 5-year survival of \geq 90%. This is in stark contrast to lung cancer with the low survival rate of 16%. The results of surgical treatment of cancer are about the same as younger patients in many types of cancer with slightly higher complication rates seen in the geriatric population [36]. Thus, it is reasonable to expect that as the population ages, there will be more surgical oncologic procedures.



Note: Data are combined from the 2006-2007 National Health Interview Surveys, which cover the noninstitutionalized population.

Fig. 1.4 Limitation of activity caused by chronic health condition by age: 2006–2007. This figure shows the diseases and health limitations per 1000 population, and that with age, there are changes in the distribution of these health burdens (Reprinted from U.S. Census Bureau, P. et al. [32])

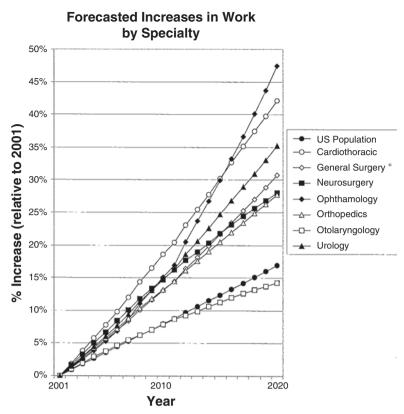
Finally, the aging brain presents several potential challenges. Cognitive impairment is a term that includes the loss of higher mental functions that we associate with being human. Chief among the functions is memory, but there are others like planning, thinking, and performing mathematical skills. All functions tend to deteriorate as we age and each represents a challenge to the geriatric anesthesiologist (see Chaps. 10 and 30). There are two classifications of cognitive impairment, *mild cognitive impairment* and *dementia*. Mild cognitive impairment is common but can progress to more incapacitating dementias like Alzheimer's disease that has an incidence of about 23 per 1000 in people over the age of 70 [32]. All loss of cognitive function is frustrating and when severe is incapacitating to the individual and catastrophic to the family.

Sight and hearing loss are also associated with aging and can lead to loss of activity (Fig. 1.4). Hearing loss is greater in men and advances with age, but as women get older, they tend to equal men in hearing impairment [37]. Visual impairment occurs more frequently in women but advances in both genders. Depression is the major mood disorder of the aging population. It is more common in women than men: the rate of diagnosed depression in women and men over 65 is reported to be 16% and 11%, respectively [32]. This is a relatively high incidence in both genders, and depression needs to be recognized early since it is associated with mortality from many causes in addition to suicide.

Perioperative Implications of the Aging Population and Surgical Risk

The burgeoning elderly population has some very specific implications for anesthesiologists and surgeons. Anesthesia and surgical knowledge and skills have increased over time, and there is a greater willingness to operate on older patients than ever before. Additionally, an older population can have more conditions that are amenable to surgery. The older population has an estimated higher percentage of surgery (58%) than younger, and it is estimated that between 2000 and 2020, there will be an increase in surgery ranging from 14% to 47% depending on the particular surgical specialty [30] (Fig. 1.5). In 2010, approximately 13% of the US population was 65 years or older, yet of all the hospital procedures, 37% were in people greater than 65 years of age. In other words, a disproportionate share of surgical procedures was performed in the elderly. For example, over half of the procedures done involving the cardiovascular system are performed on patients ≥ 65 years old. The only systems that are not more common in the elderly are ENT and those performed on women for genital and reproductive system. The rate of surgery falls once patients reach 85 even though medical hospitalizations increase for this age subset [38, 39]. However, it is probable that surgery will increase in \geq 85 years old as this age group increases in size, and surgeons expand candidacy for surgery.

Generally, morbidity, mortality, and recovery times for elderly patients undergoing surgery are greater than those for younger patients [36, 40–43]. Ambulatory surgery is **Fig. 1.5** Forecasted increases in work by specialty. This figure shows that as time passes (year 2000–2020) there is an increase in the number of elderly patients. The direct result of this is that all surgical specialties except otolaryngology can expect to see marked increase in patients over 65 (Reprinted from Etzioni et al. [68], with permission from Wolters Kluwer Health, Inc.)



* Category includes vascular, breast, hernia, abdominal, gastrointestinal, and pediatric procedures.

increasing in the elderly population in part because older patients are better oriented in familiar surroundings. Two recent reviews summarize many of the issues of ambulatory surgery in the elderly [44, 45]. There is also data showing that unanticipated hospital admission after ambulatory surgery is increased in elderly patients [46]. The mortality for elderly (\geq 65) in 227 surgical high-risk operations is about twice that of younger patients (6% vs 3%) meaning that older patients are less able to withstand the stress of already high-risk surgery [47]. Thus, there is abundant data that shows risk is influenced by age, though thorough risk modeling finds that comorbidities and other factors are stronger predictors than age alone [48]. In addition, the distinction between normal and successful aging highlights one of the principal phenomena in gerontology: that there is tremendous variability in aging between individuals of a given species. Although it is extremely convenient to categorize and even stereotype patients by age, chronological age is a poor predictor of physiologic aging. It therefore should not be used alone to predict risk for surgical procedures.

Since age alone does not necessarily confer added risk because each individual is different and some remain healthy with physiologic reserve in place while others may be weakened during aging by disease or the response to the stresses of life, one theory that explains the individual variability with age is the concept of *homeostasis* and *physiologic* reserve. A homeostatic system is an open biologic system that maintains its structure and functions by means of a multiplicity of dynamic equilibriums rigorously controlled by interdependent regulatory mechanisms [49]. Such a system reacts to change through a series of modifications of equal size and opposite direction to those that created the disturbance. The goal of these modifications is to maintain the internal balances. The term homeostenosis has been used to describe the progressive constriction of homeostatic reserve capacity. Another common means of expressing this idea is that aging results in a progressive decrease in reserve capacity. Diminishing reserve capacity can be identified at a cellular, organ, system, or whole-body level. As an example, glomerular filtration rate (GFR) progressively decreases with aging, limiting the capacity to deal with any stress on this excretory mechanism, be that a fluid load or excretion of medications or other toxic substances. Once again, the variability associated with aging is a key modifier of the decrease in physiologic function. So, although in general GFR decreases 1 mL/year, 30% of participants in a large study that defined this change had no change in GFR, whereas others showed much greater decrements [50]. The concept of reserve has also been used in describing cognitive function [51]. Taffet has expanded the general interpretation of the decrease in physiologic reserve to emphasize that the reserve capacity is not an otherwise invisible organ capacity but the

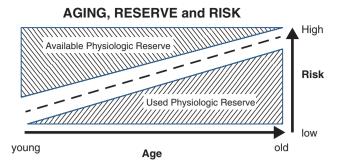


Fig. 1.6 This is a schematic of homeostasis that shows the dynamic process where as age increases more physiologic reserves is required to maintain the status quo. This means that when a major stress occurs like surgery, less physiologic reserve is available, and risk is increased (Adapted from: Silverstein [2], Taffet [69])

available organ function that will be used to maximal capacity by the elderly to maintain homeostasis. When the demands exceed the capacity of the organ or organism to respond, pathology and higher risks ensue (Fig. 1.6). This is ever more likely as aging decreases the capacity of any system to respond. It is likely that the stresses of surgery tip the balance of homeostasis to increased risk in the elderly at least in part because of exhausted physiologic reserves.

Anesthesiologist's Approach to the Patient

Comprehensive evidenced-based perioperative care of the elderly patient is rapidly evolving but far from complete. The preoperative evaluation has become critical in the care of the geriatric patient (see Chap. 4). At minimum, the anesthesiologist should determine the functional status, distinguish age-related organ system changes from disease, attempt to assess reserve capacity, and identify potential gaps in necessary workup prior to surgery. The preoperative visit is also an ideal time to equip the patient and family with realistic expectations and goals for the post-procedural recovery period. Finally, it is also an opportune time to document any advance directive wishes and health-care proxies the patient has designated. The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) and the American Geriatrics Society (AGS) have outlined a formal process for routine preoperative evaluation of elderly patients [52, 53] (see Table 1.1 [52]). Acquiring information may be challenging and may involve discussions with the patient, their immediate caregivers, other family members, and reference to multiple previous medical records. A comprehensive approach to caring for the geriatric surgical patient may also assign preoperative tasks to multiple providers including a geriatrician, anesthesiologist, or surgeon which can present unique challenges for coordination of care.

In 2009, McGory et al. published over 90 validated perioperative quality indicators for patients older than 75 years of age [54]. Five intraoperative indicators have been validated for the geriatric population and are listed in Table 1.2 In addition, many of the measures described were deemed to be specific to the geriatric population, as care for the elderly in the perioperative period may be very different from that of the non-elderly surgical population (Table 1.3). Identifying process measures, especially those specific to the growing geriatric population, can potentially assist in improving quality of care as well as containing costs.

Most recently, the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) in conjunction with the American Geriatrics Society (AGS) has published updated comprehensive perioperative guidelines for the geriatric population. "Optimal Perioperative Management of the Geriatric Patient: A Best Practices Guideline" can currently be found on the American College of Surgeons (ACS) website [55]. This valuable guideline focuses on nine categories of perioperative care that are significant and specific to the care of elderly patients: cognitive and behavioral disorders, cardiac evaluation, pulmonary evaluation, functional/performance status, frailty, nutritional status, medication management, patient counseling, and preoperative testing. All nine areas are covered extensively in successive chapters of this book.

The concept of frailty is an emerging and important topic in the perioperative care of geriatric patients. There are multiple physiological and molecular systems dependent on a coordinated response to stress that allow elderly patients to withstand the stress of anesthesia and surgery. These systems involve the immunological/inflammatory, endocrine, skeletal muscle, and neurologic systems all within the context of genetics, normal aging, and disease [56]. If these multiple factors become dysregulated, then frailty will contribute to the inability to withstand the stress [56–58] (see Fig. 1.7). Frailty thus results in a vulnerable state that can correlate with poor health outcomes during periods of high stress, such as the perioperative period [59, 60]. Frailty has been associated with higher rates of adverse perioperative outcomes including prolonged hospital stay and increased postoperative morbidity and mortality [59, 60]. The frail state may be easily recognizable, but it is often difficult to systematically diagnose, let alone treat. While there is currently considerable research being performed on the concept of frailty [56], little is known in regard to the physician's ability to improve frailty in an effort to ultimately improve perioperative outcome. In fact, one of the growing bodies of literature relates to the concept of "prehabilitation" as a potential means to reverse frailty. Prehabilitation encompasses optimization of nutrition, anxiety reduction, and physical exercise training prior to surgery. A prehabilitation program for patients undergoing colorectal surgery for cancer has shown

 Table 1.1 Checklist for the optimal preoperative assessment of the geriatric surgical patient

In addition to conducting a complete history and physical examination of the patient, the following assessments are strongly recommended:

- Assess the patient's cognitive ability and capacity to understand the anticipated surgery
- Screen the patient for depression
- Identify the patient's risk factors for developing postoperative delirium
- Screen for alcohol and other substance abuse/dependence
- Perform a preoperative cardiac evaluation according to the American College of Cardiology/American Heart Association algorithm for patients undergoing noncardiac surgery
- Identify the patient's risk factors for postoperative pulmonary complications and implement appropriate strategies for prevention
- · Document functional status and history of falls
- · Determine baseline frailty score
- Assess patient's nutritional status and consider preoperative interventions if the patient is at severe nutritional risk
- Take an accurate and detailed medication history and consider appropriate perioperative adjustments. Monitor for polypharmacy
- Determine the patient's treatment goals and expectation in the context of the possible treatment outcomes
- · Determine patient's family and social support system
- Order appropriate preoperative diagnostic tests focused on elderly patients

Reprinted from Chow et al. [52], with permission from Elsevier

 Table 1.2
 Quality indicators rated as valid for intraoperative care of elderly patients

- 1. If an elderly patient is undergoing elective or nonelective inpatient surgery and hair removal is required, then hair removal should not be performed with a razor
- 2. If an elderly patient is undergoing elective or nonelective inpatient surgery, then measures to maintain normothermia of greater than 36 °C during the operation should be instituted
- 3. If an elderly patient is undergoing elective or nonelective inpatient surgery and develops hypothermia less than 36 °C, then additional measures to correct the hypothermia should be instituted
- 4. If an elderly patient is undergoing elective or nonelective inpatient surgery and the procedure is started laparoscopically, then the procedure should be completed in less than 6 h even if converted to an open approach
- 5. If an elderly patient is undergoing elective or nonelective inpatient surgery, then measures to ensure proper positioning on the operating room table should be documented to prevent peripheral nerve damage and maintain skin integrity

Reprinted from McGory et al. [54], with permission from Wolters Kluwer Health

encouraging results [61]. The evolving concepts of frailty and prehabilitation are covered in Chap. 6.

Perioperative medication management can also be a challenge for the anesthesiologist during the perioperative period. Polypharmacy is often seen in elderly patients. In addition, new medications related to cognitive diseases such

Table 1.3 Process measures unique to the elderly undergoing surgery

Domain Process measure				
Comorbidity assessment	 Complete standardized cardiovascular risk evaluation per ACC/AHA guidelines Estimation of creatinine clearance 			
Evaluation of elderly issues	 Screen for nutrition, cognition, delirium risk, pressure ulcer risk Assess functional status including ambulation, vision/hearing impairment, and ADLs/IADLs Referral for further evaluation for impaired cognition or functional status, high risk for delirium, or polypharmacy 			
Medication use	 Indications for inpatient bowel preparation Evaluation of medication regimen and polypharmacy Avoid delirium-triggering medications and other potentially inappropriate medications (e.g., Beers criteria) 			
Patient-provider discussions	 Assess patient's decision-making capacity Specific discussion on expected functional outcome, life-sustaining preferences, and surrogate decision-maker 			
Postoperative management	 Prevent malnutrition, delirium, deconditioning, pressure ulcers Daily screen for postoperative delirium and standardized workup for delirium episode Make staff aware if hearing/vision impairment Patient access to glasses, hearing aid, dentures Consider home health for assistance for ostomy care Infection prevention with daily assessment of central line and indication for use, early Foley catheter removal, and standardized fever workup 			
Discharge planning	 A discussion with the patient or caretaker about purpose of drug, how to take it, and expected side effects/adverse effects for all medications prescribed for outpatient use Assess social support and need for home health prior to surgery Assess nutrition, cognition, ambulation, and ADLs prior to discharge 			

Reprinted from McGory et al. [54], with permission from Wolters Kluwer Health

as Alzheimer's disease, Parkinson's disease, and other neurobehavioral conditions can have untoward interactions with commonly used anesthetic drugs. Finally, the rapid expansion of different oral anticoagulants can present unique challenges in the intraoperative period in relation to surgical bleeding and the use of regional anesthesia. Anesthetic implications of chronic medication use, especially those medications seen more frequently in the geriatric population, are covered in Chap. 21.

There is still considerable variability to the intraoperative management of the geriatric patient as there is in younger patients. There is no recommendation for a single best plan

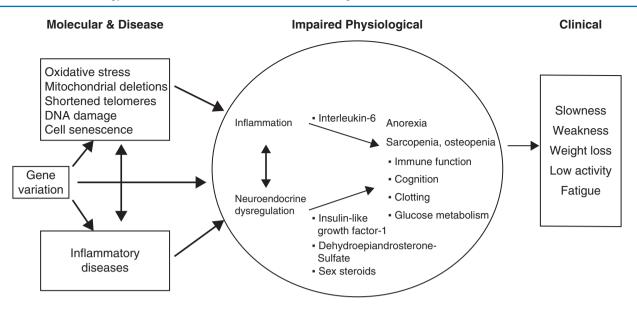


Fig. 1.7 There are a wide array of molecular, disease, physiologic factors that become dysfunctional and lead to the clinical manifestation of frailty. These are depicted here (Reprinted from Walston et al. [56], with permission from John Wiley and Sons)

for older patients undergoing surgery. However, the natural physiological changes that occur in aging organ systems should be considered when designing the intraoperative anesthetic management of these patients. To date, there is no conclusive evidence that suggests one anesthetic technique is superior to others in the elderly in terms of limiting or avoid-ing postoperative dysfunction, including delirium and post-operative cognitive dysfunction [62]. However, current NSQIP/AGS guidelines stress the consideration of regional anesthesia as well as multimodal analgesia to potentially limit parenteral use of opioids and other general anesthetic medications as well as improve postoperative pain control [58]. A more detailed review of regional anesthesia and acute pain management in the geriatric patient are covered in Chaps. 19 and 28.

Patient positioning can also be a challenge for the older patient. The skin and musculoskeletal system can undergo tremendous alterations with aging. In fact, a national study in 2007 reported that up to 8.5% of elderly patients developed intraoperative skin breakdown [63]. Loss of skin integrity also makes patients more susceptible to peripheral nerve injury. It stands to reason that patients with severe arthritis, other limitations of range of motion, or prosthetic joints should be positioned, to the extent possible, on an operating room table in a position they find comfortable before the induction of anesthesia. Age-related changes in the musculoskeletal and integumentary systems are defined in more depth in Chap. 14.

Postoperative complications seen more often in the elderly include delirium, functional decline, physical falls, and poor nutrition. Delirium can be difficult to diagnose; preoperative cognitive impairment, impairments in vision and hearing, and acute infection can all increase the risk of postoperative delirium in the elderly. In addition, delirium has been associated with increased postoperative morbidity and mortality leading to increased hospital costs and longer inpatient hospital stays. Finally, there is limited evidence for the treatment of postoperative delirium, with prevention being the most likely best treatment. Delirium and postoperative cognitive dysfunction are discussed in Chap. 30.

A particularly important issue in perioperative geriatrics is the role of interdisciplinary teams led by geriatric experts. In the 1980s, geriatricians began evaluating a concept generally referred to as comprehensive geriatric assessment (CGA). CGA is a multidimensional, interdisciplinary, diagnostic process used to identify care needs, plan care, and improve outcomes of frail older people [64]. The goals of CGA are to improve diagnostic accuracy, optimize medical treatment, and improve medical outcomes, including functional status and quality of life. In the ward-based model of CGA, patients are typically admitted to a specialized ward with medical staff that have geriatric expertise and retain primary control of the medical decision-making process. This model of CGA is well-established and improves overall care of geriatric patients. In contrast, the team model of CGA typically involves admitting a patient to a non-geriatric primary service (e.g., a specialized surgical service) but having a consultative geriatric team involved in the patient's care [65]. These inpatient geriatric consultation teams (IGCTs) may involve specialty trained geriatricians, anesthesiologists, as well as ancillary support services such as physical therapy, speech therapy, nutritionists, and others. In the perioperative arena, cooperative programs that feature IGCTs have been implemented. Most notably, the concept of the Perioperative Surgical Home (PSH) is starting to take traction and expand in many realms of perioperative care. PSH is described further in Chap. 5. Finally, while there is evidence showing a decrease in mortality rates from the utilization of inpatient geriatric consultation teams (IGCTs) [65], models of consultative services can vastly differ between institutions which make applicability and outcome analysis difficult. In addition, adherence to recommendations made by consultative services can vary and are not often reported in studies. The ultimate goals of these teams are to improve quality of life and return of functional status after surgery. Because of the growing geriatric population will increase demand for surgical services, geriatric anesthesiologists, if they so choose, have a unique opportunity to take the lead in developing and implementing evidence-based perioperative care for the aging population.

Education

Educational opportunities in geriatric anesthesia have grown substantially in recent years; however, there are still challenges to be addressed as the field continues to mature. As mentioned previously, some of the most significant champions of geriatric education in surgical specialties have been the American Geriatrics Society, the John A. Hartford Foundation, and the Reynolds Foundation frequently working in conjunction with the American Society of Anesthesiology. These agencies, through collaboration with academic institutions and specialty societies, have established several excellent educational multidisciplinary programs across surgical specialties, including anesthesia. Many anesthesiologists partnering with surgeons and geriatricians have received education grants supporting the development of innovative educational programs in geriatrics. Similar to many grant supported programs, sustainability beyond the funding period can create a challenge. Fortunately, the role of the American Society of Anesthesiology has become more visible through the development of a track in geriatrics at the national meeting that commenced in 2016. As noted earlier, this has provided a huge opportunity to showcase important geriatric issues for anesthesiologists and reinforce the need for education in our training and continuing education programs.

The changing demographics and medical comorbidities of the older population outlined in this chapter and throughout this text underscore the importance of competence in geriatrics and integration of age-related issues into anesthesia curricula at all levels. Ironically the sheer number of geriatric patients can foster complacency in the anesthesia workforce. When presented with opportunities to receive additional education on geriatrics, anesthesiologists (like other specialists) often comment that "I look after older patients already." However there are many potentially over-

looked topics in geriatric anesthesia that are relevant to anesthesiologists - especially within the emerging role of the perioperative physician. Delirium, postoperative cognitive function, and more recently frailty are excellent examples of important clinical geriatric syndromes that are clinically relevant to anesthesiologists. These areas also represent a major focus of both basic and clinical anesthesia research. Other geriatric issues are also advancing as critical issues, especially within the framework of the Perioperative Surgical Home. For example, shared decision-making and advanced directive discussions are increasingly a focus of a preoperative consultation within anesthesia as well as a more active approach to the risks and dangers of polypharmacy and the potential for preoperative medication management. These are a few examples of the areas that should be included in anesthesia education programs. These topics are covered extensively in this text.

Over last few years, there has been an increased regulation and oversight of postgraduate medical training including anesthesia. In the USA, the ACGME in conjunction with the American Board of Anesthesiology (ABA) has established required competencies and a broad anesthesiology curriculum. All residents must demonstrate proficiency within the competencies, and training programs are regularly reviewed to ensure appropriate educational standards are being upheld. Competency-based residency training uses an outcomebased approach. Assessment and evaluation of trainees is a core component of a well-functioning competency-based curriculum. The relatively new shift toward outcomes has created new challenges for education programs. One advantage for geriatric anesthesia is the volume of elderly patients which can lend itself to these types of clinically intense education programs. A curriculum has been created for educating anesthesiologists with regard to geriatric anesthesia (Table 1.4) [13]. Basic knowledge in aging physiology, pharmacology, and management of elderly patients is required by both the ACGME and the ABA. However, the actual requirements for education in geriatric anesthesia are limited. Essentially the ACGME requires that residents receive appropriate didactic instruction and clinical experience managing geriatric patients. The ABA publishes content outlines for training programs, and this does include geriatrics pharmacology and aging physiology.

Despite the recognition of the importance of geriatric training within disciplines, many barriers are encountered. Fortunately, textbooks such as this one can help to reinforce the depth and breadth of age-related knowledge needed to be a qualified anesthesiologist. Irrespective of the actual framework in place, there is an opportunity to review current guidelines and make recommendations to include geriatrics as a required field of study for anesthesia. The importance of establishing geriatrics as an important entity is the key issue.

Table 1.4 Geriatric anesthesiology curriculum

Background

- 1. Definitions and demographics
- Knowledge of health-care/economical issues related to aged patients
- 3. Knowledge of ethical considerations in aged patients

Organ systems

- 4. Understanding anesthesia and the impact of aging on the central and peripheral nervous systems
- 5. Understanding anesthesia and the impact of aging on the cardiovascular system
- 6. Understanding anesthesia and the impact of aging on the upper airway and pulmonary system
- 7. Understanding anesthesia and the impact of aging on endocrine and metabolic function
- 8. Understanding anesthesia and the impact of aging on thermoregulation

Putting it all together

- 9. Assessment/evaluation of the elderly patient: the perspective of the geriatrician
- 10. Preoperative assessment in the elderly: from the anesthesiologist
- 11. Atypical presentations of physiologic disasters
- 12. Geriatric trauma
- Choosing the anesthetic
- 13. Regional vs general
- 14. Ambulatory surgery
- 15. Fluid and blood administration
- 16. Procedural skills

Drugs

- 17. Understanding pharmacological issues in aging
- 18. Inhalation anesthetics
- 19. Intravenous anesthetics
- 20. Local anesthetics
- Postoperative care
- 21. Postoperative/PACU issues
- 22. Delirium and postoperative cognitive dysfunction
- 23. Acute pain management
- Subspecialty areas
- 24. ICU issues
- 25. Chronic pain syndromes

Modified from: Barnett et al. [70], with permission from Sheila R. Barnett

An obstacle facing geriatrics within anesthesiology can be a lack of a geriatric champion within individual departments. On a national level in the USA, several leadership opportunities exist that can foster the development of rich and multidisciplinary educational programs. For example, as described above, the ASA Geriatric Committee is now a popular committee which regularly provides liaisons to the AGS and SAGA. However there are still not enough geriatric champions within the specialty of anesthesia to guarantee high penetrance across training programs. The lack of leadership impacts the development of geriatrics for both trainees and faculty. Faculty development in geriatric anesthesia is needed and actually provides a tremendous opportunity for junior faculty at the beginning of their careers.

Further Areas of Research

Future areas of research include specific and correctable causes of increased morbidity and mortality of elderly patients compared to younger patients; delirium prediction, prevention, and treatment; the role of anesthesiologist in geriatric models of transitional care; the use of the Perioperative Surgical Home and Enhanced Recovery After Surgery (ERAS) in geriatric population; long-term follow-up measures of patients undergoing elective and emergency surgery (orthopedic surgery, major abdominal surgery); and evaluation of interventional methods to reduce frailty.

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Theories and Mechanisms of Aging

Neal S. Fedarko

The common image of aging is one of thinning of hair and loss of pigmentation in what remains, increased wrinkling and altered pigmentation of the skin, reductions in height and muscle and bone mass, and deficits in hearing, seeing, and memory. While many of these physical changes do occur in older individuals, they do not appear at the same time or occur to the same degree. Even within a single person, there is heterogeneity – organs with two copies (eyes, ears, kidneys) can display asymmetry in the extent of changes with age. This heterogeneity in the phenotype of aging reflects the multicomponent nature of a process that involves internal and external stressors as well as stochasticity impinging on complex homeostatic mechanisms.

Underlying that visual image of aging are changes that occur at the molecular and cellular level. Aging can be defined as the progressive changes in functional properties, beginning with biochemical changes at the molecular level, that eventually expand to encompass the cellular, tissue, and organ system level. Deficits in functional capacity lead to loss of physiologic reserve – a decreased ability to respond appropriately to internal or external stimuli. The gradual and cumulative changes in cells, tissues, and organs of the body lead to decreased homeostatic control and increased morbidity and mortality.

Why do we age? Is aging simply the result of cumulative wear and tear over time? How do age-related changes in different physiologic systems interact? In science, theories are proposed to enable a systematic study of answerable questions. If a theory is proposed that addresses why living things age and whether aging evolved as a process, then that is an *evolutionary theory of aging*. If a theory tries to explain how structural and functional changes arise with increasing age, then it is a *physiologic theory of aging*.

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Why We Age

With evolutionary theory, the focus is on the role of natural selection in maintaining reproductive fitness of a species. Traits and genes are selected for and become more common in a population when they enhance reproductive fitness (adaptive traits). Maladaptive traits are harmful to the organism's fitness, selected against and become less common in a population. Nonadaptive traits which do not impact an organism's survival usually are under less selection pressure. Historically, aging has been viewed at times as an adaptive trait (which promoted survival of the young by freeing up resources that older organisms would otherwise compete for) or as a nonadaptive trait (because older organisms do not reproduce, there is minimal selection pressure on a trait expressed at a later age). Currently, there are two main evolutionary theories of aging, mutation accumulation theory and *antagonistic pleiotropy theory* [1, 2].

In mutation accumulation theory, traits that yield an aging phenotype are neither selected for nor against as the consequences do not impact reproduction. In this theory, older postreproductive age organisms expressing a mutation (which has minimal effects on fitness) are under little selective pressure. These mutations accumulate over time and yield the altered physiology that gives rise to the aging phenotype. In contrast, aging is an adaptive trait in the antagonistic pleiotropy theory of aging. Genes that are favored by natural selection have beneficial effects on early fitness components in the young. These genes may have harmful effects on late in life fitness components, but the force of natural selection lessens with increasing age such that these genes remain expressed in the population. Understanding whether aging is an evolved trait or random accumulations of stuff is relevant to us today as interventions attempting to ameliorate late in life events may have negative effects on early fitness. Laboratory interventions that increase longevity are associated with decreased number of offspring and/or metabolic rate in multiple species. Similarly, restoring proliferative capacity to senescent cells can increase

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the risk for cancer development. While mutation accumulation theory and antagonistic pleiotropy theory were initially proposed halfway through the previous century, the testing of the theories and interpretation of the results continue to be controversial [3–7].

How We Age

Physiologic theories of aging address how aging occurs. To understand how aging manifests itself from molecules to cells to organ systems, one really needs to understand how we live as long as we do. That is, one can view the physiologic theories of aging as addressing sentinel pathways, systems, and mechanisms involved in maintaining homeostasis. The major physiologic theories can be grouped into those that involve specific molecules, macromolecular systems, organelles, or systemic signaling (Table 2.1). For example, DNA and the genes it encodes are central to life, and there are five distinct theories of aging that involve different aspects of DNA metabolism and regulation. The theories are briefly presented below, and the level of supporting evidence is summarized.

DNA/Genetic Theories of Aging

Genes provide the blueprint for RNA, proteins, and the enzymes that synthesize and catabolize nucleic acid, amino acid, carbohydrate, and lipid. The integrity of the genome is

Table 2.1 Physiologic theories of aging

essential for reproductive fitness and survival. DNA sequences can be modified by spontaneous depurination reactions and errors in synthesis (internal stressors), as well as by ionizing radiation, aflatoxin, and alkylating agents (environmental stressors). Organisms have evolved error checking and repair mechanisms that depend on DNA encoded enzymes. The DNA damage theory holds that genes are susceptible to damage and mutations in DNA yield altered sequences that in turn change RNA and protein sequences. These mutations alter the function of structural, signaling, and/or repair molecules, and the accumulation of molecules with changed functional capacity yields the aging phenotype. Supporting evidence for this theory includes findings that whole-body irradiation shortens life span [8, 9], somatic mutations in some cells increase with age [10, 11], chromosomal abnormalities increase with age [12, 13], and mutations in genes involved in DNA metabolism are associated with a number of premature aging syndromes (Werner, Hutchinson-Gilford, ataxia telangiectasia, and Cockayne) [14]. While evidence of an association between DNA damage appears to be strong, whether it is a cause or a consequence of aging is still unclear [15].

The mitochondrial DNA damage theory proposed that damage to this particular organelle's DNA accumulates over time, compromising mitochondrial function (energy production), producing more damaging metabolic by-products (reactive oxygen species, a type of highly energetic free radical containing molecule) that cause further cellular damage. The cell's nucleus has a robust, evolved set of mechanisms for repairing nuclear DNA, while mtDNA does not. Other unique characteristics of mitochondria that contribute to their propensity for DNA damage and aberrant function include that mtDNA is in close proximity to the sites where reactive oxygen species are produced, aberrant mitochondria sometimes replicate faster than undamaged mitochondria, and while each cell translates only 7% of its nuclear DNA, almost all its mtDNA is translated (no spare "junk DNA" to absorb damage). The net results are reduced energy production, diminished control of other cell processes, increased reactive oxygen species, and accumulation of damaged harmful molecules and organelles leading to a progressive aging phenotype. Supporting evidences for this theory include mitochondrial dysfunction is a hallmark of aging [16], aberrant mitochondrial function is associated with an accelerated aging phenotype [17, 18], accumulation of mtDNA mutations is associated with the age-related loss of fast twitch (type II) muscle fibers [19], and damaged mitochondria can initiate cellular apoptosis [20].

The *telomere theory of aging* proposes that aging is a result of telomere shortening and limited cell proliferation. The failure in replication leads to deficits in cell replacement and tissue/organ renewal. Because the DNA replication machinery physically occupies space on the DNA, it can't

make a copy of the "final" sequence of DNA on the chromosome it is replicating. Telomeres are found at the ends of chromosomes and consist of a repetitive sequence. With every DNA replication, that piece of DNA under the polymerase machinery is not copied, and there is progressive shortening of the telomere length. While there is a specialized enzyme, telomerase, which maintains telomere length in stem cells, somatic cells have low levels of the enzyme. Cellular or replicative senescence occurs when telomeres reach a critical size. Supporting evidences include that telomere length is directly proportional to cell age [21], individuals with progerias have shorter telomeres [22], cancer and other immortal cells maintain a constant telomere length [23], and restoring telomerase enzyme in somatic cells in vitro causes an increase in replicative life span of these cells [24]. Additionally, cellular senescence has been linked with an altered expression pattern by cells that promotes a pro-inflammatory state - a chronic state associated with late life changes and morbidity [25]. Evidences that are not supportive include observations that telomere length is not related to life span as mouse telomeres are much longer than those in humans [26] and telomerase protects against replicative senescence but not cellular senescence triggered by other pathways (in response to DNA damage, reactive oxygen species, and activation of oncogenes).

The transposable element activation theory describes a particular mechanism that may contribute to increased somatic mutation with increasing age. Certain sequences of DNA (transposable elements) have the ability to move from one location in the genome to another, and their insertion in a different segment of DNA can lead to mutagenesis. This random insertion can yield mutations that serendipitously improve an organism's fitness and favor evolutionary advance. Conversely, it can lead to DNA damage, replication errors, and genomic instability. As with the repair mechanisms of DNA described above, elaborate mechanisms have evolved to repress transposon activity. Supporting evidences include that transposition increases in frequency with age in mammals [27]; activation of transposable elements (loss of repression) is associated with progressive dysfunction of aging cells, induction of cell senescence, and cell loss [28]; and upregulating transposon activation in Drosophila brain caused progressive memory impairment and shortened lifespan [29].

The *epigenetic theory of aging* posits that epigenetic modifications alter gene expression patterns and cellular function yielding the aging phenotype. Epigenetics refers to changes in gene expression that alter cellular and physiological phenotypic traits but does not involve changes to the genetic code. Epigenetics plays a role in homeostasis through enabling external and/or environmental factors to modulate phenotype. The majority of cells in the human body are somatic cells, and their differentiation into specialized tissue

is a result of epigenetic modifications. The differentiated phenotype is maintained, in part, through nucleic acid and protein interactions, DNA methylation, and histone acetylation. Noncoding RNAs (ncRNAs) that include microRNA, short interfering RNA, piwi-interacting RNA, and long ncRNA also function to regulate gene expression at the transcriptional and posttranscriptional level. These epigenetic changes can be influenced by age, lifestyle, and environment [30]. Supportive evidences for this theory include that DNA methylation increases with age [31], epigenetic silencing of repressive transcription factors can contribute to cells expressing a senescent phenotype [28], and epigenetic changes in mtDNA and mitochondrial ncRNAs not only impact mitochondrial structure, function, and dynamics but also regulate multiple homeostatic pathways including senescence, apoptosis, and energy metabolism [32].

Error catastrophe theory does not directly involve DNA; rather it concerns RNA and proteins involved in the transfer of DNA-encoded information. Normally, a steady state exists where low levels of random errors occur but cause little harm. These errors can be inaccuracies in transcription, proofreading, splicing, and transport of RNA and mistakes in amino acid sequences or in polypeptide folding and conformation for proteins. Error catastrophe theory holds that a critical threshold is crossed when the machinery for biosynthesis is sufficiently destabilized with increasing age such that the rate of errors increases and compromises macromolecular function. The theory predicts that old cells should contain significant levels of abnormal proteins and that mutations that diminish the fidelity of synthesis will accelerate aging. Testing of these two predictions has yielded equivocal results [33]. More recently, error catastrophe theory has been applied to pathological settings of mitochondrial mutations [34], tumor growth dynamics [35], and viral replication [36, 37].

Accumulation Theories

This group of theories focuses on aging as a consequence of the accumulation of cellular components or specific cell types with altered properties that compromise function leading to loss of tissue function and homeostasis. *Clinker theories of aging* involve specific macromolecules, often waste from metabolic processes which amass over time disrupting function. *Lipofuscin* is an oxidized lipid-containing product from catabolic reactions that accumulates in the lysosomes of long-lived postmitotic cells, such as neurons and cardiac myocytes. The failure to degrade lipofuscin further or eject it through exocytosis reduces lysosomal functional capacity (macromolecular catabolism, autophagy, receptor recycling, and cytoplasmic trafficking). *Collagen cross-links* in the skin and bone increase with increasing age and lead to altered properties of this scaffolding protein: loss of dermal elasticity and stiffer less flexible joints and bone. Similarly, the levels of advanced glycation end products increase with normal aging in multiple organ systems altering the biomechanical and functional properties of the molecular components with this nonenzymatic modification. Additionally, advanced glycation end products bind specific receptors that results in a pro-inflammatory immune response. Misfolded protein aggregates such as neurofibrillary tangles in the brain, amyloid deposition in the heart, and crystallin accumulation in the eye are thought to contribute to both normal aging and pathological changes. Whether the accumulation of compromised molecular components is a cause or a consequence of aging has been difficult to disentangle. While it is intuitive that the buildup of insoluble material will eventually compromise function [38], it is also possible that misfolded protein aggregation is a protective response [39, 40].

Clunker theories of aging involve cellular organelles such as mitochondria, lysosomes, peroxisomes, and cell nuclear membranes that have lost functional capacity through agerelated changes in composition, structure, and/or metabolism. The role of aberrant mitochondria in aging initially focused on the accumulation of mtDNA damage that generates more reactive oxygen species which in turn causes further damage (see *mitochondrial DNA damage theory* above). The validity of that original theory has been questioned by observations that antioxidant treatment or genetic manipulation to either under- or over-express key enzymatic regulators of reactive oxygen species had equivocal effects on life span [41] and that reactive oxygen species appear to contribute to metabolic health and longevity [42]. This has led to a reformulation of a *mitochondrial theory of aging* where the emphasis has moved from reactive oxygen species production and mtDNA to other activities of the mitochondria, including biogenesis and turnover [43], calcium mobilization [44], cellular senescence [25], apoptosis [45], and epigenetic changes in mitochondrial DNA and by noncoding mitochondrial RNAs [32]. In this new mitochondrial theory of aging, mitochondrial dysfunction contributes to changes in key homeostatic pathways (apoptosis, senescence, and energy metabolism) that cause cell dropout and altered phenotypic expression and energy metabolism that are associated with an aging phenotype.

The *peroxisome theory of aging* posits that cumulative damage to these organelles compromises the multiple functions of this organelle contributing to cell death and aging. Peroxisomes, like mitochondria, are organelles that can multiply by fission and are involved in the metabolism of reactive oxygen species and in antiviral innate immunity (detecting cytosolic viruses) [46]. Peroxisomes breakdown long-chain fatty acids through beta-oxidation, synthesize ether phospholipids and bile acids, and resupply mitochondria with metabolic (tricarboxylic acid cycle) intermediates.

Evidence in support of peroxisome modulation of organelle and cellular aging includes peroxisome activity in deactivating reactive oxygen species with antioxidant enzymes [47], converting nicotinamide to nicotinic acid (an NAD+ salvage pathway) in response to caloric restriction and various mild stressors (treatments which increase longevity) [48], and operating as a modulator of levels of non-esterified fatty acids which accelerate age-related necrotic and apoptotic cell death [49] and diacylglycerol which sensitizes cells to age-related stresses [50, 51].

Lysosomes were originally described by Christian de Duve as "suicide bags" of hydrolases that played a role in cell death. The lysosome theory of aging proposes that dysfunction of this organelle leads to an aging phenotype. Lysosomes are the major degradative compartment of the endosomal/lysosomal system. They also play roles in other cellular processes, including nutrient sensing, cell development, differentiation and apoptosis, and resistance to stress. Lysosomes are where cellular components are disassembled for recycling (autophagy) and where damaged, defective organelles also undergo cellular component disassembly (e.g., mitophagy, pexophagy). Evidence in support of this theory includes that lysosomes carry out autophagy which catabolizes macromolecules to facilitate survival during temporary starvation [52] and removes damaged proteins and organelles as part of normal cellular maintenance [43]. Additionally, lysosomes are a potential source of lipofuscin [53] which can contribute to their own cumulative dysfunction and lead to an error cascade when lysosomes become dysfunctional and damage proteins and organelles (mitochondria, peroxisomes) accumulate causing cellular dysfunction [54]. This loss of lysosome function provides a potential mechanism for increased cell and tissue loss of function with advancing age.

Systemic Signaling Theories

The *endocrine theory of aging* holds that loss of homeostasis occurs systemically when hormone levels and signaling change with age and that the aging phenotype arises from dysregulated hormone signaling. Hormones provide an organism-wide system of signaling. Hormone activity depends upon synthesis, secretion, and binding to a target receptor. The production of many hormones changes with increasing age. Their secretion patterns (e.g., pulsatile, diurnal) also alter. In addition, the number and functional ability of hormone receptors to transduce signals in target organs are reduced. For example, many organs decrease in size with age; age-related deficits in the levels of growth hormone or sex steroid hormones negatively affect target organs' size and ability to repair and maintain functional capacity. Evidence in support of this theory includes the role of

changes in growth hormone-IGF-I axis and the aging phenotype of diminished mass [55], hypothalamic-pituitaryadrenal axis, dysregulated cortisol, and stress response [56].

The immune theory of aging asserts that diminished systemic defensive and repair responses negatively affect the functional capacity of other organ systems and contribute to the aging phenotype. The immune system has evolved to enable slow-growing organisms to respond to and keep in check rapidly growing pathogens/parasites as well as to deal with wound repair and remodeling of specialized tissue. Innate immune mechanisms consisting of humoral mechanisms (coagulation cascade, complement) and cellular components (natural killer cells, neutrophils, macrophages) and acquired immune mechanisms involving humoral (antibodies) and cellular (T and B lymphocytes) components provide a highly evolved homeostatic system. Increasing age is associated with "immunosenescence" which is a gradual decline in the acquired immunity that has been associated with increased morbidity and mortality in late life. "Inflammaging" is a corollary theory concerning an aging-related increase in innate immunity activity, perhaps as a compensatory mechanism for declining acquired immunity. A ramped up innate system is marked by increased levels of cytokines (such as interleukin-6) and macrophage activation that perpetuates a chronic pro-inflammatory state. The effect of chronic repair and remodeling programs of inflammation results in alterations in protease and growth factor levels, tissue structure, and cellular organization, which negatively alter organ system function. The evidence in support of the immune theory of aging includes associations of immunosenescence with altered function in aging such as decrease in the number of naïve lymphocytes and clonal expansion of memory cells impacting ability to respond to new immune challenges [57], altered functional capacity of multiple immune cell types [58–61], associations of immunosenescence, and inflammaging with age-related diseases and geriatric syndromes [62-64].

The stem cell theory of aging hypothesizes that pluripotent cells exhibit reduced regenerative capacity with age, and this inability to replenish cellular supplies gives rise to the aging phenotype. Hematopoietic stem cells in the bone marrow and adult stem cells in the many tissues and in circulation maintain homeostasis by replenishing depleted reserves. Satellite cells that contribute to muscle mass and repair of muscle tissue, osteoprogenitor cells that replenish osteoblasts and form bone, neural stem cells that give rise to neurons, and astrocytes and oligodendrocytes in the brain are examples of adult stem cells that mediate regeneration and repair. With increasing age, precursor cells become depleted. This deficit in regenerative capacity has multiple potential causes including phenotypic drift, precursor arrest or injury, illness, and environmental challenge consuming progenitors leading to cellular burnout. Evidence in support of this theory includes studies of age-associated cumulative DNA damage driving cell loss for hematopoietic stem cells and hair follicle stem cells [65, 66] and the shift in the pathway commitment of bone mesenchymal stem cells away from osteoblastic or myoblastic cells toward the adipocytic cell lineage being associated with osteopenia, sarcopenia, and an increase in fat content in bone marrow and muscle [67].

Significant Gaps in Our Knowledge

The many theories of aging that have been proposed reflect our current understanding of the individual maintenance pathways and homeostatic mechanisms that allow us to live as long as we do. Is there such a thing as a unified theory of aging? While no single theory accounts for the complete aging phenotype, many of the theories are interrelated, and it is likely that aging reflects a composite of the different theories. As noted earlier there is cross talk between key components of the various theories. Transposable elements, epigenetics, mutation accumulation, and senescence contribute to altered cellular function with increasing age. Stem cell regenerative capacity is influenced by metabolism, telomere length, and mitochondrial function. Apoptosis is modulated by mitochondrial activity and lysosome, and peroxisome functionality impacts cellular senescence. Proteins modified by reactive oxygen species or nonenzymatic glycation induce inflammation. Senescence can be triggered by protein glycation and cross-links, and hormones modulate apoptosis, senescence, and inflammation.

How well do the connected theories account for specific physiologic changes associated with aging? The associations between the aging phenotype (damaged molecules and organelles, cell loss and senescence, altered tissue structure, reductions in mass and functional deficits in specific organ systems) and the homeostatic pathways highlighted by the various theories are still in the process of being defined and may be dependent on cell type (somatic, pluripotent), energy usage, organ environment, and composition. Cross talk between homeostatic pathways has been mostly characterized in simplified aging models. Does the cross talk generate integrated and hierarchical signals that can be predicted? Some of the pathways appear to be contradictory (e.g., senescence versus apoptosis), and the factors that determine which end point (persistence or controlled death) occurs are not clear. Do the theories provide targetable mechanisms/ pathways that could lead to increased longevity and more importantly improved quality of life at old age? Recent work indicates that some mutations that extend longevity in Caenorhabditis elegans also increase the amount of time the worms spend being frail [68]. Understanding the theories of aging enhances our understanding of the complexity and interconnectivity of events that occur with increasing age

and underscores their progressive nature and the challenges in improving the functional capacity of older individuals.

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Ethical and Legal Issues of Geriatrics

Paul J. Hoehner

Medicine is foremost a moral endeavor and every clinical encounter between a physician and patient is an ethical encounter. It is a moral undertaking because medicine is first and foremost an ethical relationship. As obvious as this statement should be, in the eyes of many today medicine is a business, a science, or a body of knowledge. The patient is a "health care consumer" purchasing a commodity, information, advice, or a procedure, from a myriad of "health care providers." Once the exchange has taken place the obligations have been fulfilled and there is no underlying commitment beyond that point. Certainly, this is the conclusion of many philosophers, business administrators, and policy bureaucrats examining and describing the physician–patient relationship. To adopt this mindset, however, is to cease to be a professional in the full sense of the term [1–4].

Much is being discussed about the expanding role of the anesthesiologist in the perioperative period [5–8]. As the nature of modern health care evolves, the anesthesiologist is increasingly taking on the role of a primary care physician in the perioperative period, tasked with evaluating the overall medical condition of the patient with a larger perspective than merely the scheduled procedure. Little, however, has been written about how this expanded medical role will also bring about an expanded ethical role of the anesthesiologist in the perioperative period that will go beyond merely procedural consent issues. Not only will the anesthesiologist need to function as the traditional "internist in the operating room" as the patient's chief medical and safety advocate, but also as the patient's chief ethical advocate.

Along with this comes a host of barriers to effective ethical advocacy of the perioperative patient. Production pressures and shortened operating room turn-around times limit the anesthesiologist's ability to establish an appropriate patient-physician relationship. At the same time, physicians are increasingly becoming employees of large health care delivery systems, which imposes a "dual (or multiple) agency" between physicians, their patients (or health care consumers), populations, and the economic interests of their employers [9, 10]. The use of multiple providers to facilitate the efficient "throughput" of most surgery centers further contributes to the impersonal nature of modern medicine. The universal adoption of comprehensive and shared electronic medical records (EMRs) is also certain to change the nature of the patient-physician encounter in subtle and dramatic ways along with the nature of medical care itself [11-14]. The limited and algorithmic preoperative encounter as "data entry" can reduce the face-to-face and person-toperson establishment of trust and understanding that is central to the ethical practice of medicine [14-16]. Anesthesiologists should not let the pressures of economics, efficiency, and outside agency obstruct their primary duty to put their individual patient's ethical and medical interests foremost.

A Growing Elderly Population

A 2012 National Projections report by the U.S. Department of Commerce, based on the 2010 census, predicts that by 2050 the population in the United States aged 65 and over will be 83.7 million, almost double its estimated population of 43.1 million in 2012 [17]. Baby boomers (those born between mid-1946 and mid-1964) are largely responsible for this increase in the older population as they began turning 65 in 2011.

As the elderly population in this country continues to increase, geriatric care is evolving as a unique medical specialty in its own right. Advancements in medical science and changes in the health care delivery system that impact the care of the elderly are accompanied by myriad ethical dilemmas that confront not only the physician and patient, but social workers, nursing home staff, and relatives. Settings

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involving the extremes of age and illness are the most complex in ethical deliberation. Although anesthesiologists may confront a variety of ethical issues, such as patient confidentiality, care of Jehovah's Witnesses, substance abuse, and so forth, this chapter will focus on those issues unique to and more likely to be encountered in the elderly patient.

Social Views of Aging

Social views of aging are inherently present and basically informative within any application of ethical principles to ethical problems involving the elderly. Therefore, it is important to recognize that one's view of aging can and will influence both clinical decision making as well as the application of ethical principles to individual concrete situations. Although contemporary views of aging are complex and varied, Gadow [18] helpfully outlines a spectrum of views, each of which contribute to the apparent social and moral value of the elderly patient and the resolution of ethical problems. First, aging can be viewed as the antithesis of health and vigor. This negative interpretation of the aging process is expressed in deceptively "objective" descriptions of the clinical changes in aging as "deterioration," "disorganization," and "disintegration," from the level of psyche to the level of cellular physiology. Gadow points out, however, that there is nothing a priori degenerative about changes in aging unless one "uncritically accepts as the only ideal of health the condition that younger individuals manifest." [18, 19]. Furthermore, it is a mistake to think of the elderly as generally sick and impaired. Patricia Jung notes that, "Clearly, to expose as false those myths that portray the old as inescapably and increasingly physically decrepit, mentally incompetent, desexualized persons best kept isolated in nursing homes is an important first step toward discerning what it means to age." [20]. For many, old age is not a time of disability or disease; instead it is a time of remarkably good health. According to one government study, 72.3% of noninstitutionalized elderly persons described their health as "excellent," "very good," or "good," and only 27.6% described their health as "fair" or "poor." [21]. Nevertheless, this same study showed that in 1990 persons over the age of 65 experienced more than two and a half times the number of days of activity restriction because of acute and chronic conditions as persons between the ages of 25 and 44, with 37.5% of people over the age of 65 experiencing some activity limitation caused by chronic conditions. Health care workers, whose contact with the elderly is naturally skewed toward those who are acute or chronically ill, and/or institutionalized, are especially prone to this unambiguously negative account found in the "decline model" that so powerfully dominates our cultural interpretation of aging.

Second, aging can be viewed as an unwelcome reminder of our mortality. Medicine, at least a little like Shelley's modern Prometheus [22], tends to seek for and attain progress within the human condition in ways that defy its own ability to know what to do next. Shaped by the pervasive story of our therapeutic culture [23], health care workers and their patients are driven by an interest in longevity that reaches far beyond the merely academic, emanating as it does from a desire to avoid suffering and certainly from a fear of death. Growing old in our therapeutic culture encourages us to desire perpetual youthfulness and gives us the power to strive for it (to some degree successfully, or, at least, cosmetically), but also forces us to ask just how old we really want to live to be. And as we age, for how long and in what ways do we care for ourselves? Advances in medicine

the elderly as symbols of the unthinkable. Medical and social views of aging can reflect the full diversity of a spectrum ranging from the philosophy that the elderly have less social and moral values than other individuals, to the other extreme of having greater value than others. The most positive of all attitudes is that of the elderly as a cultural treasure, a repository of wisdom, and an embodiment of history. Gadow [18] also observes another emerging perspective that treats the elderly as underprivileged citizens. This view bypasses the question of the intrinsic value of the elderly for society and brings them "out of the closet" to become recipients of our benevolence toward them as an "oppressed" group. The potential danger with this view is that by designating the elderly as "handicapped" individuals, and thereby as a special group needing services, the beneficiaries remain subordinate to the benefactor and may even become victim to the extremes of unwarranted paternalistic care.

bring new psychologic and ethical challenges, both for those

who are older and for those who are living with and caring

for them. For instance, the more natural and acceptable mortality is thought to be for the elderly, the more unthinkable it

is for the nonelderly. This view can lead to the avoidance of

A development inherent to the rise of geriatric medicine as a specialty is the view of aging as a clinical entity in its own right. Positively, aging is viewed as a unique human phenomenon worthy of specialized attention. The elderly are not health deviants but present special problems as well as special strengths not found in other populations. Surely this is a welcome view that will, and has already, greatly contribute to the understanding and care of many issues unique to this growing population (the focus of this textbook being one example). Negatively, the subspecialty approach to geriatric medicine may become a model for a broader social approach to the elderly, whereby aging would be of interest as a "highly specific class of unusual phenomena, bearing little relation to the more general features of experience shared by persons of all ages." [18]. Aging may be viewed not as a normal life process, with little or no purpose, but as a disease in itself. Yet much of what has been assumed mistakenly to be the "plight" of the elderly is in fact the consequence of specific pathologies not properly associated with aging. Chronic illnesses and degenerative diseases often associated with aging are frequently a result of lifestyle choices. Although aging may be associated with some rote memory loss, recent studies repeatedly indicate that the basic cognitive competence of the elderly does not deteriorate with age. There is some evidence of positive growth in certain more complex, integrative mental abilities. Peter Mayer notes in his essay "Biological Theories about Aging" that even physical changes such as osteoporosis among postmenopausal women and immune system decline, which were once presumed to be an inevitable result of growing old are now understood to be the consequence of specific medical conditions or other factors such as malnutrition [24].

Ethical Principles

Modern society's categories of right and wrong or decisions regarding the "good" are frequently characterized by competing rational philosophical theories (such as deontology, utilitarianism, natural law, whether normative or nonnormative, relative, or universal), as cultural and traditiondependent artifacts, or as arising from individualistic or relativistic (e)motives. The classic paradigm of modern medical ethics, often referred to as "principlism," originated as a pragmatic attempt to overcome the impasse of these competing ethical theories in order to derive common and selfevident "principles" that would serve to guide a common language/paradigm of biomedical ethical decision making. This almost universally accepted paradigm of modern medical ethics centers on the principles of respect for personal autonomy, beneficence, nonmaleficence, and justice (along with other values such as veracity or truth-telling, privacy, confidentiality, and fidelity, but these are the "big four") [25]. Medical ethics has always been seen as a branch of applied ethics, a pragmatic program that relies on a multiperspectival and at times multicultural approach to making difficult decisions in health care. For this reason, the "principlism" approach, despite its limitations, has nonetheless provided a good working guideline for clinical medical ethics and is usually assumed in many basic medical ethics texts.

Alternative frameworks based on such concepts as "virtue ethics," the "narrative life," and "personhood" provide alternative or supplemental paradigms to the traditional approach. These concepts may overcome some of the philosophical limitations of the traditional approach and provide a firmer theoretical grounding that can thereby proceed to the level of principles more appropriate for use in the elderly population. One exemplary approach is that of Spielman [26] who appropriates the moral anthropology of Hauerwas to build a more adequate principled approach to geriatric ethics. Hauerwas emphasizes an ethic of virtue that grows out of his conviction that "what one does or does not do is dependent on possessing a 'self' sufficient to take responsibility for one's actions." [27]. Three aspects of the self, which are relevant to applying Hauerwas' work, are its temporal dimension, its social dimension, and its tragic or limited dimension.

Unlike the standard account of post-Kantian ethics in which the moral life is seen in terms of obedience to a set of rational, timeless principles, Hauerwas presents character, developed within the context of a particular story or narrative, as the key to the moral life. According to this temporal dimension, life is not seen as a series of discontinuous decisions but rather as a challenge to be faithful to a true story or history. Contemporary ethical theory tends to view the ideal human as a self-sufficient, independent moral agent, without social ties. Hauerwas' social dimension emphasizes the fact that we are all historical beings and cannot avoid being part of larger communities. Our ability to think and our ability to act are embedded in a social structure in which even the descriptions of our actions depend on language, which is a public possession. Human existence also has a necessarily tragic or limited dimension. Medicine cannot eradicate suffering and death in our lives. By using MacIntyre's characterization of medicine as a tragic profession, Hauerwas suggests that medical ethics cannot be limited to casuistic analyses of particular sets of problems and issues. He notes the continuity between the kind of issues raised by medicine and the rest of our lives and raises important issues involved in the practice of medicine relative to the elderly, such as limited resource allocation. Hauerwas shows that not only are the history and the relationships of the self significant, but that the limitations inherent in medical treatment of the elderly cannot be ignored [28].

Figure 3.1 illustrates how the temporal, social, and tragic or limited dimensions of human existence can be used to develop principles more appropriate to developing a geriatric ethic according to Spielman. The dimensions of temporality and sociality can be recognized in the increasing dependence on others as one ages. A more useful principle than autonomy is one of continuity. This principle may be stated as

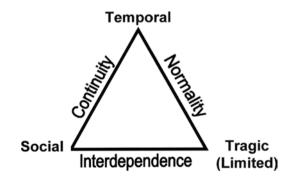


Fig. 3.1 Principles of a geriatric ethic derived from Hauerwas' dimensions of human nature (Based on data from Ref. [26])

"Act so that you avoid disrupting the continuity of past, present, and future values, commitments, and relationships in older people's lives." The purpose of the principle is to prevent the loss, as one ages, of a sense of the unity of one's life. Balancing the aspects of limitation and sociality helps to recognize and not ignore the elderly patient's social needs and desire to maintain some degree of independence. This avoids the temptation of caregivers to rely on institutional care when independence cannot be maintained. Silverstone [29] notes that the tendency for the physician to view chronically impaired patients with a biomedical disease-oriented framework contributes to a hospital-like solution to the patient's problems. This principle can be stated: "seek out the appropriate level of support and care for older patient," a level of care that maximizes independence and maintains the highest level of functioning. Because complete independence is usually neither possible nor desirable, "interdependence" with friends, relatives, and service providers more aptly describes this principle. Finally, the aspects of limitation and temporality suggest the principle of normality. Aging does not have to be seen as a disease or as a form of deviance. This principle would argue against treating every age-related change as a disease or problem to be solved. Rather, the aging process is valued, given the limitations it imposes, as a normal part of the human life narrative.

Informed Consent in the Elderly

Respect for Personal Autonomy

Many ethical conundrums in medical ethics are the result of specific principles coming into conflict in specific cases. Personal autonomy is generally understood to refer to the capacity to be one's own person, to live one's life according to reasons and motives that are taken as one's own and not the product of manipulative or distorting external forces. The principle of respect for personal autonomy, at least in most Western cultures, is sometimes taken to be *the* overriding principle in modern ethical deliberation. However, respect for personal autonomy does not, and should not, exhaust moral deliberation. Other principles are important and not only when autonomy reaches its limits. Childress notes that focusing on the principle of respect for personal autonomy can foster indifference and that the principles of care and beneficence are important even in discussions of informed consent. The role played by the principle of respect for personal autonomy is one of setting limits, such that, "without the limits set by the principle of respect for autonomy, these principles (beneficence, nonmaleficence, and justice) may support arrogant enforcement of "the good" for others." [30]. Yet, the principle of respect for autonomy is not absolutely binding and does not outweigh all other principles at all

times. Two different approaches have been used by ethicists to resolve conflicts or apparent contradictions between competing principles. First is to construct an a priori serial ranking of the principles, such that some take absolute priority over others. Second, principles can be viewed as prima facie binding, competing equally with other prima facie principles in particular circumstances. This view requires one to view more closely the complexities and particularities of individual cases and is more situational in context. The prima facie principle of respect for autonomy can be overridden or justifiably infringed when the following conditions are satisfied: (1) when there are stronger competing principles (proportionality); (2) when infringing on the principle of respect for personal autonomy would probably protect the competing principles (effectiveness); (3) when infringing the principle of respect for personal autonomy is necessary to protect the competing principle(s) (last resort); and (4) when the infringement of the principle of respect for personal autonomy is the least intrusive or restrictive in the circumstances, consistent with protecting the competing principle(s) (least infringement) [30].

Shared Decision Making

Aside from the legal requirements and the specter of malpractice, recent discussions of "informed consent" have focused on the concept of "shared decision making" and the clinical-therapeutic role of the informed consent process in improving patient care. These discussions recognize that there should be a collaborative effort between physicians and patients to arrive at appropriate treatment decisions. The physician brings knowledge and trained judgment to the process, whereas the patient brings individual and unique priorities, needs, concerns, beliefs, and fears. Focusing on the process of informed consent, as opposed to bare legal requirements, increases a patient's participation in his or her own care, which has the practical benefit of increasing patient compliance and self-monitoring. Informed consent as "teaching" (indeed, the origin of the word "doctor" is from "teacher") further diminishes patients' misconceptions or inaccurate fears about their situation and prospects and may improve patient recovery or comfort with a better understanding of the care that is being provided. No good data are available regarding these "therapeutic" effects of informed consent, and further studies seem warranted. Despite these theoretical positive aspects, issues surrounding informed consent remain vexing for physicians in a number of clinical situations from both legal and ethical perspectives. Even the ideal model of "shared decision making" does not address many of the realities of medical practice, including emergency situations, conflicts of interest, and questions of futility.

By emphasizing informed consent as a temporal "process," one can avoid the pitfalls of viewing informed consent as a single event. Informed consent can never be reduced to a signature on a consent form. "Perhaps the most fundamental and pervasive myth about informed consent is that informed consent has been obtained when a patient signs a consent form. Nothing could be further from the truth, as many courts have pointed out to physicians who were only too willing to believe this myth." [31]. Although a matter of routine in many institutions because they are seen as providing protection against liability, informed consent forms actually provide very little. A review of more than 500 separate informed consent forms revealed these documents have limited educational value, go mostly unread, and are frequently misunderstood by patients [32]. The informed consent form does have value in that it provides an opportunity for the patient to read the information on the form and to create a *locus* for the appropriate patient-physician discussion that is the key element. An informed consent form merely documents that the "process" of informed consent has taken place.

Traditionally in the past, consent to anesthesia was subsumed under the consent for the surgical procedure and included within the surgery consent form. The anesthesiologist was one step removed from the formal consent process. Today, separate specific consent for anesthesia is required. It is imperative that the anesthesiologist make a concerted effort to adequately complete this process with the patient and, when appropriate, the patient's family, regarding the anesthetic procedure. This should be adequately documented and may include an additional note with the patient's consent on the chart or anesthetic record.

Beauchamp and Childress [25] have broken down the process of informed consent into seven elements (Table 3.1). These include threshold elements or preconditions, which include (1) decision-making capacity or competency of the patient, (2) freedom or voluntariness in decision making, including absence of overriding legal or state interests; informational elements including (3) adequate disclosure of material information, (4) recommendations, and (5) an

Table 3.1 Elements of the process of informed consent

	Threshold elements (preconditions)		
	1. Decision-making capacity or competency		
2. Freedom or voluntariness and absence of overriding state			
	interests		
	Informational elements		
	1. Adequate disclosure of material information		

- 2. Recommendation
- 3. Understanding
- Consent elements
- 1. Decision
- 2. Authorization

understanding of the above; consent elements, which include (6) decision by the patient in favor of a plan and (7) authorization of that plan. Several of these elements can pose particular challenges in the elderly population.

Threshold Elements

Decision-Making Capacity

Physicians are frequently faced with the problem of making treatment decisions for elderly patients who no longer have decision-making capacity. Many diseases and conditions that can make continued life contingent on life-prolonging therapies can also destroy or substantially impair a person's decision-making capacity and are more likely to do so in older people. In addition, Alzheimer's disease and other forms of dementia are more likely to be present in older persons. One estimate is that 5-7% of persons over 65, and 25% of those over 84, suffer from severe dementia [33]. Assessment of decision-making capacity even in cases of mild dementia can be particularly difficult [34]. Decisionmaking capacity requires (1) a capacity to understand and communicate, (2) a capacity to reason and deliberate, and (3)possession of a set of values and goals [35-37]. Although there is general agreement regarding these three requirements, there is no single, universally accepted standard of decision-making capacity. This is because decision-making capacity is not an all-or-nothing concept. Decision making is also a task-related concept and the requisite skills and abilities vary according to the specific decision or task. The relevant criteria should also vary according to the risk to a patient. Basically, one must ask the following questions: Does the patient understand his or her medical condition? Does the patient understand the options and the consequences of his or her decision? Is the patient capable of reasonable deliberation? Is the patient able to communicate his or her decision? Does the patient possess a coherent set of values and/or goals? Several reviews provide helpful discussions of the clinical assessment of elderly patients' decisionmaking capacity within these contexts [38–40]. Instruments such as the MacArthur Competence Assessment Tool-Treatment (MacCAT-T) may provide a flexible yet structured method with which physicians and other caregivers can assess, rate, and report patients' abilities relevant for evaluating capacity to make treatment decisions [41]. Other standard cognitive assessment tests, such as the Folstein Mini-Mental State Examination (MMSE 1–20) [42], Alzheimer's Disease Assessment Scale-cognition (ADAScog 1–76) [43], and the Global Deterioration Scale [44] have proved useful in providing background semiquantification of cognitive status in relation to competency. For the legal standard for reasoning, word fluency was the best single predictor of competency but the MMSE, memory testing, and verbal reasoning were not good multivariate predictors [45].

Informed consent in the elderly patient presents other unique aspects [46]. Sugarman et al. [47] conducted a structured literature review in the published empiric research on informed consent with older adults (aged 60 years and older). Diminished understanding of informed consent information was associated with older age and with fewer years of education. Although showing some impairment in their quality of reasoning, the elderly are able to reach reasonable risk-taking decisions to the same degree as young adults [48, 49].

To what extent must a patient "understand" his or her condition, treatment options, and risks? [50] If fully "informed" is meant to mean fully "educated" [51] then "informed" consent may be seen as an impossible standard. However, the primary object of information is to facilitate the patients' care rather than providing a litany of possible complications in order to avoid a lawsuit. Factual knowledge is used, not as an end in itself, but as a means to extend the patients' own understanding in such a way as to meet their own unique priorities, needs, concerns, beliefs, and fears so that they may decide about their care in the manner in which they normally make similar choices. This will vary from patient to patient and with the risks of the procedure involved. It is a mistake to assume that a patient must understand information to the same extent and in the same manner as a physician, or even as a well-educated layman. This may indeed be seen as just as paternalistic as not permitting patients to participate in decision making at all [31].

Visual and hearing impairments and diminished memory and comprehension in the elderly patient require the clinician to exercise particular caution when obtaining informed consent [52]. One must also be careful to avoid the mistake of equating recall, a standard endpoint in many studies on the adequacy of informed consent and which may be problematic in the elderly, with understanding and comprehension. Meisel and Kuczewski [31] note that, "While it may be true that someone who cannot retain information for a few seconds might not be said to understand it, people often make reasonable decisions but cannot later recall the premises that supported the reasoning or the process that led to the conclusion." Distant recall of the informed consent process may be an indicator of the adequacy of a patient's understanding, but its absence says little about what the patient understands at the time of consent. Physicians also tend to underestimate patients' desire for information and discussion and, at the same time, overestimate patients' desire to make decisions [53–55]. Elderly patients and their physicians often differ on patient quality-of-life assessments that may be associated with clinical decisions [56]. These studies and others underscore the need for clear communication, individualization, and compassion in obtaining adequate informed consent in the elderly. New strategies to maximize comprehension of informed consent information (e.g., storybooks, videos, and so forth) may be useful [47].

Assessment of patient capacity to enter into the process of informed consent or competency to make rational medical decisions is a complicated issue. Much has been written on the criteria for determining individual capacity and the legally defined characteristic of "competency." [37, 57-60]. Competency, unlike the decision-making capacity, is a legal term and an all-or-nothing concept specific to a given task. Thus, competence is not a unitary concept: there are multiple competencies given specific tasks and the assessment must be fitted to the particular area or task in which competence is required [61, 62]. In the absence of a clear medical diagnosis such as delirium or unconsciousness, decisions regarding competency must be made with assistance from psychiatric services, ethics consult services, and/or legal counsel. In general, decisions must be made in these situations on the patient's behalf, either by "substituted judgment" (a decision based on what the patient would have wanted, assuming some knowledge of what the patient's wishes would have been) with or without the help of proxy consent or by a decision made according to the "best interests" of the patient on the basis of a balancing of a "benefit versus burdens" ratio. An appropriate hierarchy for surrogate decision makers is delineated, for example, in a provision of the Virginia Health Care Decisions Act (Code of Virginia §54.1-2981) as follows: 1. A legally appointed guardian or committee. 2. The patient's spouse if no divorce action has been filed. 3. An adult son or daughter of the patient. 4. The patient's parent. 5. An adult brother or sister of the patient. 6. Any other relative of the patient in descending order of relationship. It must be remembered that the caregiver has an ethical obligation to evaluate the competency of the surrogate's decisions with regard to (1) lack of conflict of interest, (2) reliability of the evidence of the patient's desires on which the surrogate is relying, (3) the surrogate's knowledge of the patient's own value system, and (4) the surrogate's responsible commitment to the decision-making process [63]. All these situations involve complex issues and, again, may require the assistance of hospital ethics committees or consult services.

Voluntariness

A second threshold element is one of freedom or voluntariness. Here one asks the question of whether the patient's decision is free from external constraints. These constraints can consist of myriad social, familial, and even financial factors that can be difficult, if not impossible, to sort out. However, it is not true that the principle of respect for autonomy is at odds with *all* forms of heteronomy, authority, tradition, etc. Competent individuals may autonomously choose to yield first-order decisions (i.e., their decisions about the rightness and wrongness of particular modes of conduct) to a professional, family, spouse, or to a religious institution. In these instances, the person is exercising second-order autonomy in selecting the professional, person, or institution to which they choose to be subordinate. In these cases, second-order autonomy becomes central [64]. The distinguishing feature becomes whether the second-order decision was free and voluntary. Frequently, elderly patients decide on specific treatment options with respect for the opinions of family members, or a concern for their psychologic, physical, and/or financial well-being. As Waymack and Taler observe, "It is often the case that health care professionals find themselves in the care of elderly patients where, because of the nature of chronic care, families often ask or are asked to play a significant role." [65]. It is perfectly appropriate for elderly patients to consider the preferences of loved ones, and they should not automatically be encouraged to make decisions concerning treatment options, particularly life-extending treatments, for exclusively self-regarding or purely selfish reasons. Moreover, although undue pressure and influence are clearly improper, it is a mistake to assume that any advice and counsel from family members constitutes undue pressure or influence. However, when elderly patients possess decision-making capacity, generally they and only they have the moral authority to decide how much weight to give the preferences and interests of family members. While it is true that elderly patients can have ethical obligations toward family members who have a bearing on treatment decisions and the interests of family members can be "ethically relevant whether or not the patient is inclined to consider them," [66], they should generally retain decisionmaking authority even if physicians believe that they are failing to give due consideration to the interests of family members [67].

Informational Elements

Adequate Disclosure

The first of the informational elements of informed consent is adequate disclosure. This is the process of properly informing the patient of his or her diagnosis, prognosis, treatment options, risks, and possible outcomes. The anesthesiologist should reveal the specific risks and benefits of each anesthetic option, the complications of instrumentation of the airway, the risks and benefits of invasive monitoring, the presence and use of a fallback plan, and basis for the anesthesiologist's recommendations [68]. "Transparency" is a useful term describing the openness by which the anesthesiologist discusses the treatment plans with a patient. By "thinking out loud" regarding the options and plans, the anesthesiologist communicates the thought processes that he is making that is going into his or her recommendation, thus allowing the patient to understand and participate in this process. Most patients and parents of patients want assurance and explanation regarding anesthesia, not necessarily detailed and exhaustive information.

The discussion of risks and hazards of the diagnostic or therapeutic options, as well as information about anticipated pain or suffering, is, in theory and practice, the most troublesome aspects of informed consent. According to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, "Adequate informed consent requires effort on the part of the physician to ensure comprehension; it involves far more than just a signature on the bottom of a list of possible complications. Such complications can be so overwhelming that patients are unable to appreciate the truly significant information and to make sound decisions." [37]. The law does not require one to give a list of every possible complication of a planned procedure (which may inflict an undue amount of emotional distress), but only a "reasonable" amount of information. Negligence is neither failure to achieve a good outcome nor failure to disclose all remote risks [69].

But just how does one define "reasonable"? The courts have had difficulty as well assessing what a "reasonable" standard of disclosure may be. The most cited standard is the professional practice standard [70]. This standard defines reasonable disclosure as what a capable and reasonable medical practitioner in the same field would reveal to a patient under the same or similar circumstances. Some courts have ignored this prevailing standard of disclosure and shifted the focus from the professional community as forming the standard to the patients themselves. It focuses on the "new consumerism" in health care, an extension of the patient's right of self-determination, where the patient is viewed as consumer of health care and the physician as provider [71]. The "reasonable patient standard" asks what a reasonable patient would consider reasonable and material to the decision of whether to consent to a procedure offered. The burden, however, is still on the physician to ascertain just what is reasonable and material for a hypothetical "reasonable patient." This recognizes a significant shift in consent law. As legal standards continue to evolve, the reasonable patient standard may become more commonly accepted and eventually displace the professional practice standard as the majority opinion in American informed consent law. A further extension of this line of thinking is the "subjective person standard." This standard recognizes that all patients are different, there is no hypothetical "reasonable person," and hence the standard of disclosure must recognize not only the local standard of care but individual patient needs and idiosyncrasies as well. One important factor in all the above is the notion of "causality," i.e., would additional information have affected this particular patient's decision? What specific, individual

concerns did the patient have that would have most affected his or her decision whether or not they are part of the local standard of care for disclosure? The risk of vocal cord damage from a routine intubation may be so small as to not require mentioning in the normal situation (although this is debatable). It may, however, be very important for a professional singer in opting between regional and general anesthesia.

Recommendation and Understanding

Providing a recommendation and patient understanding are the other two informational elements in the informed consent process. The principle of patient autonomy does not require the physician to present the information in a totally neutral manner, if this were even possible [4]. Indeed, part of the informed consent process is to present information to the patient in a way that buttresses a physician's recommendations. Persuasion is a justifiable way for educating patients. This is different from manipulation, which is defined as inappropriately causing a certain behavior, and coercion, which is actually threatening a patient with a plausible punishment so the patient will act in a certain way.

Assessing patient understanding of the information presented can be a difficult issue, especially if "standard" consent forms are relied upon. In one study, 27% of postoperative surgical patients signing consent forms did not know which organ had been operated upon, and 44% did not know the nature of the procedure [72]. Cassileth et al. [73] showed that 55% of cancer patients could list only one of the major complications for chemotherapy within 1 day of signing consent forms. Other studies have shown that risk-specific consent forms do not aid retention [74] and that decision makers often sign consent forms that they do not understand [75]. Attempts must be made to educate patients according to their individual needs and, as has been stated previously, not to assume that a patient must have complete understanding, but only that which is necessary given their own particular situation to come to a reasonable decision. This will vary from patient to patient and from situation to situation, and consent forms cannot be relied upon to provide this information, no matter how detailed.

Consent Elements: Decision and Autonomous Authorization

Finally, there are the two consent elements: decision and autonomous authorization. The patient must be able to reach a decision and authorize the physician to provide the care decided upon. The physician must document the consented to technique as well as the invasive monitoring to be used. The patient may consent either verbally or in writing, both are ethically and legally just as valid. It may be more difficult to provide evidence of verbal consent after the fact, however, making it all the more important to document adequately the patient's response in the chart. Although the lack of an objection is not equivalent to an authorization, cooperation of patients during performance of a procedure in the absence of overt verbal authorization has usually been deemed equivalent to implied consent and sufficient in cases specifically addressing these issues [76].

Advance Directives

Advance directives are statements that a patient makes, although still retaining decision-making capacity, about how treatment decisions should be made when they no longer have the capacity to make those decisions. California was the first state to legalize the "living will" in 1976; by 1985, 35 states and the District of Columbia had enacted similar laws. In 1991, the Patient Self-Determination Act (PSDA) became federal law involving all Medicare and Medicaid providers. The PSDA provides that all health care providers must give all patients written information at the time of their admission advising them of their rights to refuse any treatments and to have an advance directive. The presence of an advance directive must be documented in the patient's record, and discrimination against a person because they do or do not have an advance directive is prohibited.

There are two general forms of advance directives. Living wills are documents stating the desires of the patient for treatment alternatives, usually to die a "natural" death and not to be kept alive by advanced life-support measures. In many states, the patient may also stipulate wishes regarding fluid and nutrition discontinuation in the event of persistent vegetative state. Living wills become effective on the determination of "terminal illness" or when death is imminent (e.g., within 6 months) or when two physicians make the diagnosis of persistent vegetative state. The strengths and weaknesses of the living will are outlined in Table 3.2. Living wills have several weaknesses, including the frequent lack of specific instructions and the impossibility of any person foreseeing all the contingencies of a future illness [77]. Therefore, many advocate an alternative form of advance directive known as a Power of Attorney for Healthcare (PAHC). A PAHC provides for the appointment of a person to act as a health care agent, proxy, or surrogate to make treatment decisions when the patient is no longer able. The PAHC allows a person to add specific directives, e.g., giving a designated agent authority to have feeding tubes withheld or withdrawn. Most PAHCs become effective when two physicians, or one physician and a psychologist, determine that the patient no longer has decision-making capacity. However,

Table 3.2 Living Will (LW)

Strengths

- Allows the physician to understand the patient's wishes and motivations
- Extends the patient's autonomy, self-control, and self-determination
- · Relieves the patient's anxiety about unwanted treatment
- Relieves physician's anxiety about legal liability
- Reduces family strife and sense of guilt
- Improves communication and trust between patient and physician *Weaknesses*
- Applicable only to those in a persistent vegetative state (PVS) or the terminally ill (patients who have a disease that is incurable and who will die regardless of treatment)
- Death must be imminent (e.g., may be statutorily defined as likely to occur within 6 months)
- · Ambiguous terms may be difficult to later interpret
- There is no proxy decision maker, so:
 - It requires prediction of final illness scenario and available treatment
 - It requires physician to make decisions on the basis of an interpretation of a document

Note: In light of these weaknesses, it is strongly recommended that patients complete a PAHC and forgo a LW

Based on data from Derse and Schiedermayer [204]

this requirement is not universal, and individual state statutes may vary. Table 3.3 lists the advantages of the PAHC that may make it a better option than a living will. Individual state statutes may differ regarding certain components such as witnesses and need for notarization. Whichever form of advance directive a patient chooses to use, both serve a valuable role in preventing ethical dilemmas if designed properly and implemented.

In many instances, elderly patients who lack decisionmaking capacity have neither executed an advance directive nor previously discussed their preferences regarding treatment options. Even when surrogates are available, disagreements among parties (particularly family members with vested interests), legal or regulatory obstacles, or other problems may hinder a clear decision-making process. The American Geriatric Society Ethics Committee has published a position statement that outlines a strategy for dealing with these situations [78]. They recommend that health care providers and institutions have in place policies and procedures to make decisions for incapacitated persons without surrogates and to establish mechanisms for intrainstitutional conflict resolution, such as an ethics committee, to mediate conflicting situations. Surrogate decision-making laws and policies should not hinder the patient's ability to die naturally and comfortably. Evidence from competent patients in similar circumstances should shape the plan of care for an individual patient in the absence of evidence that the patient's wishes would be otherwise [78]. Other strategies include the "prior competent choice" standard, which stresses the values

Table 3.3 Power of Attorney for Healthcare (PAHC)

Activation of PAHC

Lack of decision-making capacity must be certified by two physicians or one physician and a psychologist who have examined the patient. Until then, the patient makes all the decisions *Advantages*

- Physician has someone to talk with—a proxy, a knowledgeable surrogate—who can provide a substituted judgment of how the patient would have chosen. If the agent is unable to provide a substituted judgment, the agent and physician together can use the best-interest standard (how a reasonable person might choose in consideration of the benefit–burden concept of proportionality)
- Provides flexibility; this decreases ambiguity and uncertainty because there is no way to predict all possible scenarios
- Authority of agent can be limited as person desires
- Avoids family conflict about rightful agent
- · Provides legal immunity for physicians who follow dictates
- Allows appointment of a nonrelative (especially valuable for persons who may be alienated from their families)
- Most forms can be completed without an attorney
- Principal may add specific instructions to the agent, such as the following: "I value a full life more than a long life. If my suffering is intense and irreversible, or if I have lost the ability to interact with others and have no reasonable hope of regaining this ability even though I have no terminal illness, I do not want to have my life prolonged. I would then ask not to be subjected to surgery or to resuscitation procedures, or to intensive care services or to other life-prolonging measures, including the administration of antibiotics or blood products or artificial nutrition and hydration."

Based on data from: Derse and Schiedermayer [204] and Bok [205]

the patient held while competent. The "best interest standard" moves the focus to the patient's subjective experience at the time the treatment is considered [39].

There remains an urgent role for physicians to educate their patients, their institutions, and their legislatures regarding the important role of advance directives in clinical decision making and the need to remove legislative and institutional hindrances to providing excellent care to dying patients and their families. Although playing an important role in unique circumstances, advance directives are not a substitute for adequate communication among physicians, patients, and family about end-of-life decision making and do not substantially enhance physician–patient communication or decision making [79].

EMRs and Patient Autonomy

The comprehensive EMR is becoming a ubiquitous feature of modern medical practice. EMRs have the potential to reduce the risks of error, improve care coordination, monitor care quality, enable patients to participate more fully in care management, and provide the data needed for research, compliance, and surveillance. Considerable funding has been made available for the development of "health information technology architecture that will support the nationwide electronic exchange and use of health information in a secure, private, and accurate manner" (American Recovery and Reinvestment Act § 9202(a)(1) 2009). Yet even beneficial technologies almost always bring about unintended or unforeseen consequences and, especially in medicine, have the potential to change in fundamental ways the nature of the patient-physician relationship. Technology is always a two-edged sword. In terms of ethics, EMRs can greatly benefit patient care by providing legible, timely, accurate, and comprehensive data, prompts, reminders, alerts to preventable errors, and links to scholarly ethics resources and practice guidelines and policies. EMRs can also act to introduce new harms and interferences into the physician-patient relationship. Excessive attention to data entry and gazing at the computer screen can effectively remove the physician's attention from a patient, resulting in limited socioemotional and psychosocial engagement [15]. This may be most critical for anesthesiologists and other perioperative health care providers where there is already a limited context for establishing adequate patientphysician/health care provider relationships.

The patient-physician relationship has traditionally been a fiduciary relationship based on trust and confidentiality. The American Medical Association Code of Medical Ethics states that, "The information disclosed to a physician during the course of the patient-physician relationship is confidential to the utmost degree" (American Medical Association Code of Medical Ethics) and this assurance of confidentiality has been seen as necessary for patient's to be able to safely disclose sensitive personal information essential to the medical evaluation [16]. EMRs potentially multiply the immediate access to a patient's record and confidences. Aside from unwarranted breaches of medical confidentiality, electronic access to individual patients' medical records raises a host of ethical questions, including issues of informed consent and a patient's ability to make autonomous decisions about whether to grant or refuse authorization for the use of their personal health information [80].

Aside from their direct application to patient care, EMRs and the more expansive vision of a National Health Information Network (NHIN) are being utilized to provide patient health data for quality improvement, research, public safety, and public health, as well as payment, advertising and other commercial uses [81]. These secondary uses of health data present numerous issues regarding individual informed consent. For instance, a recent report of the Institute of Medicine (IOM) supports exempting the use of patient data (whether for quality assurance or research) that does not involve actual patient intervention from patient authorization guarantees of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. On the other hand, a Kaiser Family Foundation poll found two-thirds of patients would not want the government to have access to

their medical data in efforts to reduce medical errors (OI) if their individual names and addresses were needed [82], although the IOM recognizes poll data indicating a significant percentage of patients would like control of the use of their data in research by means of individual consent [83-85]. These discussions represent an ethical conflict between utilitarian arguments that participation in quality improvement and some forms of noninterventional research is a moral responsibility of patients receiving care and the argument from patient autonomy that restricts the use of data for purposes extrinsic to the trust relationship of patient care. These discussions highlight how new technologies raise new and unanticipated ethical questions while exposing the limitations and conflicts of underlying and often unstated and assumed moral principles that are guiding public policy and individual health care decisions.

A more troubling use of health care data is commercial, including the selling of data for financing regional health IT networks [81]. Such use violates patient trust as it is clearly outside the purpose of the physician–patient relationship. HIPAA requires specific authorization for the disclosure of data for marketing purposes [12].

Do-Not-Attempt-Resuscitation Orders in Perioperative Care

The anesthesiologist is most likely to come into contact with ethical issues involving advance directives when a patient is scheduled for surgery with a "do-not-resuscitate" (DNR, or the preferred and more realistic terminology "do-notattempt-resuscitation," DNAR [86]) order on the chart. As many as 15% of patients with DNAR orders will undergo a surgical procedure [87]. Wenger et al. [88] studied a subgroup of the SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment) database and found that of 745 patients presenting to the operating room, 57 had a DNAR order. Operative procedures ranged in complexity and risk from tracheostomy and vascular access to liver transplantation and coronary artery bypass grafting. Twenty of the 57 patients had their DNAR order reversed preoperatively. Two of these patients suffered an intraoperative cardiac arrest and were resuscitated. Both patients subsequently died postoperatively. Only one patient without DNAR order reversal arrested during surgery and died without attempted resuscitation.

Anesthesiologists and surgeons are generally reluctant to proceed with surgical intervention if they are not allowed to intervene in the dying process. They feel that consent for anesthesia and surgery implies consent for resuscitation and is inconsistent with a DNAR order [89, 90]. Anesthesiologists tend to claim that the induction and maintenance of anesthesia can often involve creating conditions in which

resuscitation is required [89]. Indeed, anesthesia itself has at times been referred to as a "controlled resuscitation." Because anesthetic agents or procedures may create conditions requiring resuscitation, the anesthesiologist ought to have the right to correct those conditions when possible. Surgeons and physicians doing other procedures use similar arguments to claim that if cardiac or pulmonary arrest is a consequence of their actions they should be allowed to prevent or reverse those conditions. In a 1993 survey of anesthesiologists by Clemency and Thompson [90], almost two-thirds of the respondents assumed DNAR suspension in the perioperative period and only half discussed this assumption with the patient/guardian. A more recent survey of 500 consecutive patients in a preoperative evaluation clinic found that over half (57%) of patients agreed that preexisting DNAR requests should be suspended while undergoing a surgical procedure, but 92% believed a discussion with the physician regarding perioperative resuscitation plans should still occur. About 30% of physicians in the survey believed that DNAR orders should automatically be suspended intraoperatively. Anesthesiologists were significantly less likely to suspend DNAR orders (18%) than surgeons (38%) or internists (34%) [91].

This dilemma represents a classic problem in the principled approach to medical ethics: the conflict of two or more prima facie ethical principles. If the physician chooses to act paternalistically to provide what is believed to be the best treatment at the time, he or she is giving precedence to the concept of beneficence over the patient's autonomy. If, however, the physician acts to preserve patient autonomy, he or she may feel that the duty to do good, as directed by the principle of beneficence, has been compromised. Further complicating the issue is that "DNAR" has multiple definitions and interpretations and involves a spectrum of procedures that the general public is not aware of [92].

Although automatic suspension of DNAR orders during a surgical procedure and for an arbitrary period postoperatively is the most unambiguous and straightforward policy, it is now argued that this is inappropriate [93, 94]. Statements from both the American Society of Anesthesiologists [94], the American College of Surgeons [95], the American Association of Nurse Anesthetists [96], and the Association of perioperative Registered Nurses [97] recognize that this policy effectively removes patients from the decision-making process, even if they are willing to accept the risk of operative mortality, and is inconsistent with the Patient Self-Determination Act of 1992. They recommend instead a policy of "required reconsideration" of the DNAR order, as the patient who undergoes a surgical procedure faces a different risk/benefit ratio. Both statements are, however, ambiguous about just how resuscitation is to be handled in the perioperative period. Two alternatives are presented: (1) to suspend the DNAR order in the perioperative period and

(2) to limit resuscitation to certain procedures and techniques. Because of the complexities surrounding the nature of resuscitation, public misconceptions, and lack of awareness of these complexities, and the desire to honor the goals reflected in a patient's decision to forgo CPR, a third alternative has been proposed involving a values-centered [92] or goal-directed [98] approach. By ascertaining the patient's goals, values, and preferences rather than individual procedures, the anesthesiologist is given greater flexibility in honoring the objectives of the DNAR order within the clinical context of the arrest. Although seeking to honor both the autonomy of the patient and the physician's duty to beneficence within the spirit of the original DNAR order, this alternative is not without its problems [99]. The establishment of a physician-patient relationship that will facilitate a full understanding of a patient's values and goals is a daunting, if not impossible, task for the anesthesiologist confronted with the demands of a limited preoperative encounter. These concerns may be even more profound in the elderly population [100]. Physicians have not been good at predicting the wishes of their patients regarding resuscitation in other situations, even after discussion has taken place [101–103]. It does, however, provide a third alternative and recognizes that, despite its practical limitations and high regard for patient autonomy in our society, there must always exist a degree of physician-patient trust in any clinical encounter.

Anesthesiologists need to be actively involved in their own institutions to develop policies for DNAR orders in the perioperative period. Open communication among the anesthesiologist, surgeon, and patient or family must exist to reach an agreement about DNAR status. Appropriate exceptions to perioperative suspension of a DNAR order should be honored. Timing of reinstitution of DNAR status should also be addressed and agreed upon before the procedure. Actual experience shows that very few times will a patient insist on a DNAR status during the procedure.

Treatment Futility

With respect to informed consent, what if the patient's decision is counter to the recommendations of the anesthesiologist or amounts to something the anesthesiologist regards as dangerous? Must the physician necessarily do whatever a patient wants? In short, no. In nonemergent circumstances, physicians are not obligated to provide care that they feel is not in their patients' best interest. "First, do no harm" is the operative principle in these situations. It is important again to distinguish in these cases the negative and positive rights based on or related to the principle of respect for personal autonomy and to recognize that the limits on positive rights may be greater than the limits on negative rights. For example, the positive right to request a particular treatment may be severely limited by appropriate clinical standards of care, physician judgment, or just allocation schemes. Clinicians should, however, be very cautious when making this claim and should only do so if absolutely convinced that no other options are available.

Occasionally, physicians have found it necessary to justify unilaterally deciding that certain medical interventions (such as CPR) are "futile" and withhold these interventions even when a patient or a patient's family wants them. The notion of medical futility is particularly confusing and open to different interpretations and abuses. "Futility" can be defined in several senses. "Strict sense futility" or "medical" futility is defined when a medical intervention has no demonstrable physiologic benefit, e.g., when there have been no survivors after CPR under the given circumstances in welldesigned studies, or in cases of progressive septic or cardiogenic shock despite maximal treatment. There are no obligations for physicians to provide medically futile treatment, even when families want "everything done." Unilateral decisions to withhold treatment (such as DNAR orders) are appropriate under these circumstances. Usually, a DNAR order may be written on the basis of "futility" when two or more staff physicians concur in writing and give justification for their decision. The patient or surrogate need not agree with the decision but must be notified. If there is disagreement, an ethics consultation may be appropriate and helpful.

It is rare that a given medical intervention is unlikely to have any physiologic effect whatsoever and hence futility may also be defined in a "less strict sense." In this instance, there may be a low survival rate but the rate is not zero. In this case, although the physician may have the particular expertise to determine whether a particular intervention is reasonable according to a particular standard of reasonableness, setting a particular standard involves a value judgment that goes beyond that expertise. For example, a 79-year-old cancer patient wants CPR in the event that he suffers cardiopulmonary arrest because he believes that any chance that CPR will restore cardiopulmonary function is worthwhile and that any prolongation of his life is also valuable and worthwhile (for instance, by allowing for a family member to return from overseas). Whereas the physician may assess that the chance of CPR restoring function is x%, x is greater than zero and whether the chance of restoring function is reasonable, valuable, or worthwhile only if it is greater than x% depends primarily on the patient's own values. Unilateral decisions may not be appropriate in this instance, and discussions with the patient and family should be initiated to provide information and advice.

Whereas a physician may have the expertise to assess whether a particular intervention is likely to achieve a specified outcome, determining whether an outcome is an appropriate or valuable objective for a patient is dependent on the

patient's own value judgments. A medical intervention can be futile in a third sense when it will have no reasonable chance to achieve the patient's goals and objectives. For example, CPR is futile in this sense if there is no reasonable chance that it will achieve the patient's goal of leaving the hospital and living an independent life. Because medical interventions are futile in relation to the patient's goals, this sense of futility provides a very limited basis for unilateral decisions to withhold medication interventions that patients want. The American Medical Association Council of Judicial and Ethical Affairs have commented that resuscitative efforts "would be considered futile if they could not be expected to achieve the goals expressed by the informed patient. This definition of futility not only respects the autonomy and value judgments of individual patients but also allows for the professional judgment and guidance of physicians who render care to patients." [104].

Because the term "futility" tends to communicate a false sense of scientific objectivity and finality and to obscure the inherent evaluative nature of the judgments, physicians should avoid using the term to justify unilateral decisions to withhold life-sustaining treatment. Rather, physicians should explain the specific grounds for concluding that interventions generally, or particular life-sustaining measures, are inappropriate in the given circumstances. Whereas the statement that a given intervention is futile tends to discourage discussion, explaining the grounds for a given judgment in light of the circumstances and with an understanding of the patient's own values and goals tends to invite discussion and point it in the right direction.

Treatment Redirection and Palliative Care

Jean Paul Sartre said that "the meaning of life is found in death," and how we deal with the aging process determines how we deal with death and our philosophy of life. This is most important for the physician and patient when faced with end-of-life decision making involving treatment redirection and palliative care options.

Treatment redirection refers to that point in the patient's care plan when the patient or surrogate, along with the health care team, recognizes the need to move from aggressive curative treatment to supportive palliative care. The 1995 SUPPORT study found that as many as 50% of patients were subjected to burdensome, curative treatment because the patient, family, and physician had not recognized or discussed the realities of the patient's condition [105]. Potter suggests three barriers to meeting the need for treatment redirection [106]. First, clinicians and patients often are narrowly focused on curative or ameliorative intervention. Lack of communication between the physician, who assumes that "they want everything done," and the patients and families,

who have different expectations, contributes to this problem. Furthermore, patients and their families often assume that physicians have reliable knowledge about what therapies are effective and which are not because of their intense focus on curative treatment. A study by Feinstein and Horwitz [107], however, shows that evidence-based medical decisions can only be claimed for less than 20% of clinical situations.

Second, physicians and patients are often reluctant or unable to discuss palliation as a treatment option [108]. Although evidence suggests that physicians are more willing to withhold or withdraw treatment from seriously ill patients [87], patients and families continue to report that there is a lack of physician communication in the area of shifting treatment to palliative care [109]. Disparity of beliefs and preferences causes much of this communication problem.

Finally, there is a lack of knowledge of and confidence in palliative care by both physicians [110] and society [111]. Part of the problem is that patients are referred to palliative care and hospice programs far too late in their hospital course to do any good. Furthermore, Potter notes that, "although there is a growing trend toward patients wanting to be in control of their own death, cultural diversity factors, belief in the power of medical technology, and a strong tendency to deny death prevent a working consensus about how to approach the experience of dying." [106]. Patients and their families may also be suspicious that palliative care is a way to save money, a form of rationing, although there is no empirical evidence that palliative care is more cost effective [112].

Effective treatment redirection involves three sequential steps [106]. First, there must be a system to recognize clues, both patient signals and physiologic signs, to indicate that the current form of treatment may not be wanted or may not be warranted [113]. Second, there must be deliberation as part of the informed consent process that focuses on the appropriateness of the current treatment options. Potter reminds one that "because the patient is embedded in a social context of family and friends, there must be an inclusive attitude that searches out the wider origin of beliefs and preferences in the patient's moral community." [106]. Furthermore, the health care providers themselves must analyze their own personal beliefs and preferences that can create biases and distort clinical judgment. An open dialog is a necessary part of the deliberation process. Third and finally, there must be an implementation plan that activates excellent palliative care [114]. The aim is for both the patient and the health care team to make a smooth transition from the ultimate goal of curing to that of caring.

The elderly trauma patient presents unique ethical issues. The number of patients older than 65 years presenting with serious acute injury is increasing as life expectancy and quality is increasing with increased opportunities for travel and recreation [115]. Compared with younger trauma patients, the elderly patient frequently presents with multiple preexisting comorbidities and a decreased capacity to recover from acute injuries, and have a higher in-hospital death rate when adjusted for severity of injury, and require greater commitment of resources [116–119]. Treatment decisions regarding withdrawal of therapy are frequently made without the patient being capable of actively participating and documentation regarding end-of-life decisions is usually absent or fragmentary. The acute, unexpected, and urgent nature of trauma medicine can add to the complexities and confusion of already ambiguous situations. Decisions regarding initiation or withdrawal of therapy are usually based on developing consensus among several individuals over a period of time, usually several days [119]. Trauma centers should develop standardized and explicit practice guidelines for withdrawal of therapy in elderly injured patients, including appropriate documentation of decision making including who is making the decision in the absence of the patient's ability, what evidence, including severity of injuries, preexisting medical condition, and projected outcome to hospital discharge is available to support the decisions.

End-of-Life Care

End-of-life palliative care options and decision making have become increasingly complicated as new forms of therapy and pain control become available. Pain control in the terminal stages of many illnesses is one of the primary goals of effective palliative care and is an area in which anesthesiologists have a great deal to offer. One of the most pervasive causes of anxiety among patients, their families, and the public is the perception that physicians' efforts toward the relief of pain are sadly deficient. Studies indicate that their fears may be justified. In a study of 1227 elderly patients, approximately 20% experienced moderate or severe pain during the last month of life and the final 6 hours before death [120]. In another study of a random sample of 200 elderly community residents in the last month before death, 66% had pain all or most of the time [121]. Pain influenced behavioral competence, perceived quality of life, psychologic well-being, depression, and diminished happiness. A recent editorial raises concern that medical, radiation, and surgical oncologists are not effectively treating the pain of patients with cancer [122].

Fear of inadequate pain relief during the terminal stages of illness may be responsible for the increasing interest in euthanasia and physician-assisted suicide (PAS). It is now commonly accepted that the administration of large quantities of narcotic analgesics is not euthanasia when the purpose is to alleviate pain and suffering, not to shorten the life of the patient. Wanzer et al. [123] note that:

In the patient whose dying process is irreversible, the balance between minimizing pain and suffering and potentially hastening death should be struck clearly in favor of pain relief. Narcotics and other pain medications should be given in whatever dose and by whatever route is necessary for relief. It is morally correct to increase the dose of narcotics to whatever dose is needed, even though the medication may contribute to the depression of respiration or blood pressure, the dulling of consciousness or even death, providing the primary goal of the physician is to relieve suffering. The proper dose of pain medication is the dose that is sufficient to relieve pain and suffering, even to the point of unconsciousness.

In this regard, there is clearly a strong need for increased physician and patient education as well as careful ethical analysis.

The terminal stages of the dying process can be accompanied by a number of other disturbing symptoms, both for the family and the patient. Symptoms recorded in the last 48 hours of life include noisy and moist breathing (death rattle), restlessness and agitation, incontinence of urine, dyspnea, retention of urine, nausea and vomiting, sweating, jerking, twitching, plucking, confusion, and delirium [124– 126]. Appropriate palliative care must take into account the comfort and care of the patient with regard to these symptoms as well [127, 128].

Despite even the highest quality of palliative care, many patients still report significant pain 1 week before death [129], some of whom request help in hastening death. Furthermore, patients request a hastened death not simply because of unrelieved pain but because of the wide variety of other unrelieved physical symptoms in combination with loss of meaning, dignity, and independence [130].

Confusion may exist about the physician's moral responsibility for contributing to the patient's death. The principle of double effect has an important role in ethical decision making in these instances. Double effect acknowledges that the intent and desired effect of treatment is mitigation of symptoms rather than cessation of life, even though life may be shortened. As frequently formulated, the principle stipulates that one may rightfully cause evil (shortening of life) through an act of choice (treatment of pain) if four conditions are verified: (1) the act itself, apart from the evil caused, is good or at least indifferent; (2) the good effect of the act is what the agent intends directly, only permitting the evil effect; (3) the good effect must not come about by means of the evil effect; and (4) there must be some proportionately grave reason for permitting the evil effect to occur [131].

Public and professional debate over PAS is escalating in many states. Anesthesiologists should be particularly concerned with the debate for two reasons: (1) because of their unique skills, anesthesiologists may have a very active role as practitioners of euthanasia [132], and (2) the fear of uncontrolled pain relief, an area that anesthesiologists can provide particular expertise, is a primary motivation for euthanasia and PAS [133].

PAS differs from euthanasia in that the physician is not the direct agent in PAS whereby in euthanasia the physician is the direct agent. However, not all ethicists agree that PAS and euthanasia differ significantly because of agency. The 1994 edition of the American Medical Association Code of Medical Ethics states that PAS and euthanasia are, "fundamentally incompatible with the physician's role as healer, would be difficult or impossible to control, and would pose serious societal risks." [134]. The Second Edition (1989) of the American College of Physicians Ethics Manual reads, "Although a patient may refuse a medical intervention and the physician may comply with this refusal, the physician must never intentionally and directly cause death or assist a patient to commit suicide." [135]. The position statement of the American Geriatrics Society Ethics Committee recommends that, "For patients whose quality of life has become so poor as to make continued existence less preferable than death, the professional standard of care should be that of aggressive palliation, not that of intentional termination of life.... Laws prohibiting VAE [voluntary active euthanasia] and PAS should not be changed." [136]. A study by Koenig et al. [137] showed that the majority of elderly patients attending a geriatrics clinic did not favor legalization of PAS. Furthermore, relatives of these patients could not consistently predict the patients' attitudes or agree among themselves. Recently, public and professional attitudes toward PAS and euthanasia have shifted. The Third Edition (1993) of the American College of Physicians Ethics Manual, although maintaining that physicians should make relief of suffering in the terminally ill patient their highest priority, does not include the strict prohibition included in the previous edition and is much more ambiguous regarding PAS and euthanasia [138].

The politics of euthanasia and PAS remain controversial. Physicians should be concerned that renewed interest in euthanasia and PAS will not divert attention from the pressing concerns of adequate pain control, treatment of depression, and symptom management in the terminally ill and should actively seek alternate ways to address patient worries regarding loss of control, indignity, and dependence during the final stages of an illness. The elderly, particularly the severely demented, are at the cutting edge of the debate over PAS and VAE. "Senicide" is a very real entity in cultural anthropology. It is not unthinkable that in our aging society, pressure will mount to take moral guidance from anthropologic data, with economic concerns replacing the nomadic [139]. Physicians need to resolve not to let public policy matters interfere with their duty to the health and welfare of their individual patients, regardless of age, and to maintain a commitment to both healing and caring. Anesthesiologists can provide a unique service to their physician colleagues,

patients, and general population through education and consultation regarding chronic pain and symptom control in the terminally ill. Measures must go beyond education and become an established part of quality assurance [140]. Anesthesiologists can contribute by assisting their hospitals with means to monitor the treatment of patients in pain. Despite the growing acceptance among the general population and the medical community regarding physician involvement in euthanasia, it is not compatible with the healer's mission and art. At its core, killing patients should never be the means by which symptoms or sufferings, psychologic or physical, are relieved.

Resource Allocation and the Elderly

Concerned over the increasing cost of health care in the United States, many health care policy makers claim that health care rationing is unavoidable. Rationing by age seems to offer a means of reducing spending on health care [141]. Many patient-selection decisions in the United States, such as for heart transplantation, intensive care, and kidney dialysis and transplantation, have long been based on age criteria [142–145]. A recent study by Hamel et al. [146] concludes that older age was associated with higher rates of decisions to withhold ventilator support, surgery, and dialysis even after adjustments for differences in patients' prognoses and preferences. Older patients with coronary artery disease were less likely to undergo invasive and noninvasive testing [147–149], although studies in octogenarians show that coronary artery bypass surgery is highly cost effective and improves their quality of life in a manner equal to that of a younger population [150–152]. "Age-rationing" implies that elderly patients are denied access to potentially beneficial health care services to which younger patients are not denied access. This is to be distinguished from cost-containment measures that merely result in withholding medical services that are not expected to benefit these patients [153].

There are several arguments advanced to defend the denial of access to scarce and/or costly medical care to the elderly. One argument is to suggest that elderly patients are not medically suitable candidates for certain life-sustaining measures. Even if these measures were to succeed, the quality of elderly patients' lives, because of continued ill health and chronically poor functioning, will remain poor. Extending life under such circumstances is not deemed to provide a substantial benefit. This argument is "ageist" at its core because it is based on false universal generalizations regarding all elderly patients. Although the chances of experiencing ill health and impaired functioning increase with age, many elderly people are medically suitable candidates for a wide range of treatment options, and many enjoy good health and unimpaired functioning. A patient's overall health status is generally a more reliable indicator of medical suitability than age alone.

Another defense of age-rationing holds that greater benefits are obtained when life-extending treatments are received by younger patients. These benefits include overall social welfare (because younger persons are more productive than the elderly) and cost effectiveness (because younger patients can be expected to benefit more and at a lower cost) [154]. There are three major difficulties with this line of argument. First, it again is ageist in its underlying generalizations. It assumes that elderly persons are unproductive and fails to take into account other standards of productivity (general health status, employment history, and current employment status, etc.). Second, elderly persons who would fail to receive treatments and who would die because of age rationing would bear the burdens, but they would not enjoy any of the benefits derived from the increased productivity that is said to result from this argument. The shift in the benefitburden ratio to a particular class on the basis of age reveals its injustice and inherent age bias. Finally, even if it can be claimed that it is more cost effective to deny certain classes of people access to beneficial health care, this fails to provide a reason for it being fair or just. Justice can require greater expenditures.

The economic, social, and public policy issues are enormously complicated and beyond the scope of this chapter. Rationing scarce medical resources purely on the basis of a certain age cut-off, however, does not seem to be ethically justifiable [153, 155–157]. The growing support in the United States for age criteria in health care does not have a sound medical basis. Support more likely reflects certain social, economic, or even philosophical attitudes and values not universally shared by society or by other cultures. This is different from saying that age cannot be taken into account as a predictor of medical benefit or prognosis. Kilner [158] endorses the use of age as a "symptom" or "rule of thumb" in relation to medical assessments of patients. He states that age "may serve as a tool the physician uses in applying a medical criterion, not as a criterion in its own right." Both the acute physiology and chronic health evaluation (APACHE) III and the SUPPORT model include age as one prognostic element, along with other physiologic variables. In neither study does age seem to have a major role, compared with other variables [159, 160]. Physicians must utilize the best available data on treatment outcomes and costs and assume responsibility for developing criteria for appropriateness and medical necessity across the spectrum of patient age and economic status. Physicians should practice appropriatenessbased, not cost-based medicine [161]. The rapid changes occurring in the health care system and the recurring emphases on "bottom-line" management require physicians to be involved in allocation decisions at both the professional and public policy level. Rationing policies and managed care

plans must be accompanied by full disclosure to patients regarding the limits to their care resulting from these policies and plans, along with a process of patient advocacy and appeal. Gag rules that restrict such disclosures are inherently unethical [162].

Clinical Research and the Elderly Patient

The elderly patient with severe dementia or depression, or incapacitated in the critical care or emergency setting, represents an extremely vulnerable population, not unlike that of young children or infants, and presents unique dilemmas in the area of clinical research ethics. The ethical issues raised can be summarized as one of balancing: (1) protecting potentially vulnerable research participants (respect for autonomy), and (2) advancing knowledge and providing potentially beneficial new therapies for a special group of patients (distributive justice). These issues become most manifest when dealing with psychiatric patients, children, and the adult or elderly incapacitated patient, usually in a critical care or emergency setting [163–169].

Until the 1980s, people over the age 65 were generally excluded from clinical trials without meaningful scientific justification [170]. Although the situation has improved considerably, by 2005 one study noted that 15% of clinical still excluded older subjects without due justification [171]. Comorbidity, reduced life expectancy, polypharmacy and specific drug use, cognitive and physical impairment examined as main exclusion criteria in two recent studies and results supported the poor justification claims [172, 173]. Hence, older people receive a disproportionately lesser share of the burdens and benefits of clinical research compared to young and middle aged adult subjects [174, 175].

In terms of the elderly population in particular, there is no doubt or argument against the proposition that including the elderly, even those incapacitated or suffering from severe dementia or depression, in clinical research designed to benefit this particular population is both important and necessary. Simply to exclude such patients from clinical research trials because they lack the capability for providing informed consent subjects the entire population of such patients to a trial-and-error, anecdotally driven practice of medicine that may, ultimately, end up doing more harm to these patients and result in increased and unnecessary morbidity and mortality in the long term. Balanced against this noble task of advancing our knowledge base for the benefit of future patients is the necessity of maintaining high ethical standards in the process and protecting those participants in current research trials who may or may not directly benefit from being subject to the nontherapeutic particularities and randomization of a research program design. The focus on the prior concern is on the many, i.e., the entire population of patients who will potentially benefit from such studies. The focus on the latter is the one, i.e., the individual patient who, by voluntary informed consent, has forfeited the right to individualized and purely therapeutic concern for participation in the artificial environment of the research protocol, whereby the focus of concern will be primarily on the efficient and statistically valid accumulation of specific information for the sake of future benefits. For this reason, patients who elect to participate in clinical research studies are protected from study designs that impose more than minimal risk that are not designed with expectations to maintain or improve the condition of the patient, or that are flawed in their design such that a valid answer to an appropriate question cannot be obtained. The bar for protection needs to be raised to a higher level for those patients who are incapacitated and cannot understand the nature of the research proposal and/or cannot provide appropriate consent to participate. These patients represent a particularly vulnerable population that can easily be exploited.

Clinical research on demented or cognitively impaired patients presents two opposing dilemmas: on the one hand a patient may be legally incompetent to judge whether they should consent or not; on the other hand, trials that could provide valuable practical scientific information, such as the use of medications in the treatment of dementia, or providing safer anesthetic techniques that will prevent further dementia, will not be done. One must remember that there are degrees of cognitive impairment and elderly patients with mild dementia generally have the capacity to consent [176]. Competency capacity is based on understanding the risks and benefits of the research, its purpose, and being able to make the choice to agree or disagree to participate. Even patients with Mini-Mental State exam scores as low as the 10-20 range may be able to give valid consent for certain projects. Assessing competency for consent in elderly who may have varying degrees of cognitive impairment or dementia for clinical research is a difficult area and guidelines for carrying out such assessments have been laid down by multidisciplinary professional committees [177]. One such methodology is the MacArthur Competency Assessment Tool for Clinical Research (MacCat-CR). A hypothetical research protocol in standard language is read to the subject, followed by a structured interview about the protocol, in which area assessed the subject's ability of choosing, understanding, appreciation, and reasoning; the degree of cognitive impairment is reflected in the MMSE score [178–180]. Another suggestion is following oral consent, a trial for the treatment/research for a week and then returning to assess how well the patients had understood it. After 1 week's experience, it was discovered that a significantly greater number than previously now understood the purpose and content of the research, its risks, and possible inconvenience. The study authors that 68% of the group studied subsequently signed a

consent form for the proposed study [181]. The limitation of this method is that it cannot be used with research involving invasive procedures or drugs with unknown side effects [182]. As the need and opportunity for clinical geriatrics research continues to increase, the methodology of capacity assessment for inclusion in clinical research trials is an ongoing subject that must be continually addressed and researched in its own right.

Proxy or surrogate consent has a longstanding history in the realm of the purely therapeutic clinical situation. But to what extent does the ethical reasoning inherent in proxy or surrogate consent still apply in the clinical research situation and can the ethical conclusions drawn from the purely therapeutic physician/patient situation be univocally transferred to the physician–researcher/patient–subject research situation? In general, the legal status of research advance directives is not clear [174]. It is common for clinical researchers to presuppose that there is no problem with transferring the standards of proxy consent that exist in the therapeutic relationship into the domain of clinical research.

There are two major difficulties with this view. These difficulties stem from a close examination of the two theoretical foundations upon which proxy or surrogate consent to treatment rests. The first relies on the ability of close family members, friends, or appointed surrogates to provide evidence of the patient's own wishes as to what they would want in a particular foreseeable circumstance (substituted judgment). This can either be through personal knowledge or through available written documents executed by the patient beforehand. Few patients, however, actually end up discussing relative issues in any direct way with friends, family, or their physicians regarding their future medical care [25, 183]. Even fewer are likely to discuss involvement in clinical research trials in the event they are incapacitated by an injury or illness. Even when these discussions have been conducted, studies show that surrogates and physicians do not accurately predict patient wishes, in both therapeutic and research situations [167, 184–186]. Many ethicists have raised the question as to whether anyone can speak with authority for "what the patient would have wanted" and question whether this "mythological foundation" for proxy consent should, in fact, be abandoned. Yet even if a case could be made that sickness, illness, and death are universal concerns that can provide at least a point of "sympathy" for a close friend or relative and thereby provide a modest grounding for substituted judgment, this is categorically different from choices that involve participating in medical research. Choosing to forgo the "therapeutic" for the "experimental" is, with few extenuating circumstances, a uniquely personal decision, a decision that is grounded on the individual particularities of any given research protocol. If this foundation for substituted judgment (speaking for what the patient would have wanted) in the therapeutic situation is in any sense called into

question, it certainly must be even more so in the experimental situation. Richard McCormick [187] states, "Whether a person *ought* to do such things [enroll in a research study] is a highly individual affair and cannot be generalized in the way the good of self-preservation can be. And if we cannot say of an individual that he *ought* to do these things, proxy consent has no reasonable presumptive basis."

The second foundation for proxy or surrogate consent is that of speaking for the "best interest" of the patient. Therapeutic decisions are often made, in the absence of any compelling evidence of what the patient specifically would have wanted, on the basis of what would be in the best interest of the patient (in emergency situations, treatment is often assumed to be in the "best interest" of any patient until proven otherwise). Yet it is difficult to apply this to the research situation, for in this situation the "best interest" of the patient is always relegated to the needs of the study design (e.g., randomization to a particular treatment group). To think otherwise is to fall victim to the so-called "therapeutic misconception." [188-190]. Even physician investigators are prone to blur clinical trial and patient care such that their attention is diverted from the inherent conflicts between the pursuit of science and the protection of research participants [191]. The ethical challenge is to define the limits on the kinds of research risks that the proxy can accept on behalf of a noncompetent patient/subject. Most ethicists and institutional review boards (IRBs) would agree that if the research is potentially beneficial or presents minimal risks and that the knowledge that may be gained would be important to the class of subjects under study, it would be appropriate for a surrogate or proxy to grant consent on behalf of the patient/ subject. But how does one define what "minimal risk" and reasonable benefit is within the context of any given research proposal? Similarly, how does one balance the risks against the potential benefits for the subjects or against the knowledge the research may produce?

In a recent commentary, Karlawish [169] proposes that a distinction should be made between risks that are justified by potential benefits for the subjects and risks that are not justified by those benefits. Proxy consent is permissible if the risks posed by the components of the research that do not offer potential benefits for the subjects are no more than minimal and are justified by the importance of the knowledge to be gained. The risks posed by components with potential benefits are justified by the state of equipoise: the expert consensus is that the interventions being compared are within the standard of care so that equilibrium exists in the balance between risks and benefits in the intervention and control groups.

Federal regulations for the protection of research participants, known as the "common rule," require that research involving "vulnerable" subjects include "additional safeguards" and that the investigator obtains informed consent

from a "legally authorized representative." [192]. Although the rule does not describe safeguards in detail, and most states have not addressed the question of who is legally authorized to provide consent, it does underscore the necessity of protecting vulnerable patients and their families from exploitation. One possible consideration (variously proposed by others) is to provide for two patient surrogates, one of which would be the normal surrogate that would be provided for in the strict therapeutic context, and the other a courtdesignated or IRB-approved representative that would be able to look after the particular interests of the patient and family within the research context. Consent would be required from both, and either would be able to withdraw the patient from the clinical trial at any time. Truog et al. [193] have noted, "The most effective protection against exploitation comes not from the process of informed consent, but, rather, from the careful oversight and scrutiny of conscientious institutional review boards." If this is the case, then review and control boards, particularly those of organizations responsible for the publication and dissemination of the results of research studies, need to take their role very seriously. The identification and discussion of ethical flaws in current research studies need to be more openly discussed in the mainstream medical literature in the hope that these discussions would elevate the level of ethical practices in human research conducted by physician-scientists [194].

Medical Malpractice

Approximately 35–40% of perioperative physicians will encounter a lawsuit at some point in their practice. Lawsuits are nearly inevitable in certain specialties if a physician practices long enough. Surgeons and anesthesiologists, involved in high-risk interventional practices, are sued about once every 4 to 5 years [195, 196]. It is also estimated that only one in eight preventable medical errors committed in hospitals results in a malpractice claim [196]. Malpractice suits can be expensive and disruptive to a physician's practice, and can result in considerable emotional distress, loss of selfesteem, and damage to one's reputation and career.

Medical malpractice involves tort law, civil wrongs causing injury to a person or property in which the plaintiff seeks redress, usually financial compensation, through the court system. Malpractice claims do not involve criminal charges, unless a district attorney decides that the harm committed was intentional. The most common claims involved in perioperative medicine are those involving informed consent and medical negligence (wrongful death being the worst form).

In order to establish negligence, including wrongful death, a plaintiff must demonstrate (1) that the provider had a duty to the patient, (2) that the duty was breached, (3) an injury occurred, and (4) the breach of duty was a "proximate

cause" of the injury. Duty arises from the patient-physician relationship and even a documented peripheral involvement in a case can subject one to a "duty." A breach of duty involves determining whether the physician met the standard of care (what a reasonable practitioner would do under the same or similar circumstances with similar training and background) based on testimony from experts. Many times a breach of duty is obvious (res ipsa loquitur meaning "the thing speaks for itself") as when a surgical instrument is accidentally left in a patient. Injury can have a multitude of connotations and is dependent on distinguishing bad practice from a bad or unfortunate outcome. Patient expectations are usually a prominent factor in questions of injury. Finally, in a civil tort, the burden of proof for establishing "proximate cause," especially in wrongful death situations, is much lower than in criminal proceedings and is established by a "preponderance of the evidence" or "more likely than not," rather than the more stringent "beyond a reasonable doubt." That is, a plaintiff has to show only that the chance that malpractice occurred was greater than 50%. Hence, it is not unusual for a plaintiff's attorney to speculate why a patient died and because the plaintiff's burden of proof is so low it may not help the defense to argue that particular events were related is pure speculation.

Malpractice damages and financial compensation fall into three categories: (1) economic, the monetary costs of an injury (loss of income, medical bills, rehabilitation), (2) noneconomic (pain and suffering), and (3) punitive (damages to punish a defendant for willful and wanton conduct). Punitive damages are generally not covered by malpractice insurance policies, but rarely involve cases against individual physicians and are usually reserved for the "deep pockets" of large entities (hospital systems or insurance companies) when a jury wants to punish the entity for doing something believed to be willful.

Most malpractice claims are settled out of court. Settling a case is often less expensive and easier than going to court, but a physician's reputation may be permanently damaged due to required reporting to the National Practitioner Data Bank. When a claim is litigated fewer than half (42%) of verdicts are won by plaintiffs [197]. However, malpractice awards can be costly when plaintiffs win. According to the National Practitioner Data Bank the mean malpractice payment in the United States in 2006 was \$311,965 and cases involving wrongful death resulted in payments averaging \$1.4 million [198].

While many malpractice suits cannot be avoided, Michota and Donnelly [199] have outlined a number of steps physicians can take to minimize the risk of being sued, which they have simplified to the "four C's" of competence (practicing within the standards of care for their specialty), communication (communicating adequately and fully expectations, risks, and treatment alternatives, and include the patient's family when possible), compassion (establishing a compassionate and caring rapport with patients and their families), and charting (documentation). Communication is probably the most important factor in determining whether a physician will be sued, irrespective of the competency of treatment. Closely related to communication is careful charting and documentation, including reasons for management decisions.

Summary

- A clinician's own view of aging can and will influence both clinical decision making as well as the application of ethical principles to individual concrete situations. Aging does not have to be seen as a disease or as a form of deviance but rather, the aging process can be valued given the limitations it imposes as a normal part of the human life narrative. Furthermore, the geriatric patient can present with a number of unique perioperative ethical dilemmas that can challenge accepted medical ethics paradigms.
- 2. Informed consent is a temporal "process" and can never be reduced to a signature on a consent form. Proper informed consent is centered on the notions of open communication and shared decision making. Compassion, understanding, and creativity are necessary to overcome many of the challenges geriatric patients present to the formal elements of the informed consent process.
- 3. Advance directives are statements that a patient makes, while still retaining decision-making capacity, about how treatment decisions should be made when they no longer have the capacity to make those decisions. There are two general forms of advance directives: living wills and PAHC. PAHCs have several advantages over living wills. Although playing an important role in unique circumstances, advance directives are not a substitute for adequate communication among physicians, patients, and family about end-of-life decision making.
- 4. Anesthesiologists need to be actively involved in their own institutions to develop policies for DNAR orders in the OR. Open communication among the anesthesiologist, surgeon, and patient or family must exist to reach an agreement about DNAR status. Clinicians should not automatically assume DNAR status to be suspended in the OR and appropriate exceptions to suspension of a DNAR order in the OR should be honored. Timing of reinstitution of DNAR status should also be addressed and agreed upon before the procedure and carefully documented.
- 5. "Futility" is a value-laden term and tends to communicate a false sense of scientific objectivity and finality. It is recommended that clinicians avoid the use of the term and

focus on explaining the specific grounds for concluding that particular interventions are inappropriate in the given circumstances. Whereas the statement that a given intervention is futile tends to discourage discussion, explaining the grounds for a given judgment in light of the circumstances and with an understanding of the patient's own values and goals tends to invite discussion and point it in the right direction.

- 6. There are times when clinicians, patients, and their families need to redirect care from aggressive curative treatment to supportive palliative care without a sense of "abandoning" the patient. Anesthesiologists have an active role in end-of-life palliative care, both in terms of pain and symptom management. Inadequate pain relief in the terminal stages of most diseases is a continuing problem. Anesthesiologists can contribute by assisting their hospitals with means to monitor the treatment of patients in pain. Despite the growing acceptance among the general population and the medical community regarding physician involvement in euthanasia, it is not compatible with the healer's mission and art. Whereas there are times the dying process should not be prolonged, it should not be intentionally hastened either. At its core, killing patients should never be the means by which symptoms or sufferings, psychologic or physical, are "relieved."
- 7. "Age rationing" implies that elderly patients are denied access to potentially beneficial health care services to which younger patients are not denied access. This is to be distinguished from cost-containment measures that merely result in withholding medical services that are not expected to benefit these patients.
- 8. Some elderly patients in particular settings (such as with severe dementia or depression, or incapacitated in a critical care or emergency setting) are extremely vulnerable, similar to young children or infants, and may present unique dilemmas in the area of clinical research ethics. Whereas including the elderly in clinical research designed to benefit this particular population is both important and necessary, there is the equal and sometimes competing necessity of maintaining high ethical standards in the process and protecting those patients in research trials who may or may not directly benefit from being subject to the nontherapeutic particularities and randomization of a research program design.
- 9. Medical malpractice suits can be costly, damaging, and inevitable. Practicing competent, compassionate, and ethical medicine can go a long way to minimizing malpractice risk. The importance of adequately and honestly communicating expectations, risks, and treatment alternatives and fully documenting communications and reasons for management decisions cannot be overemphasized.

Future Directions in Medical Ethics

Future areas of study in medical ethics will include priorities and conflicts in medical principles, both for patients, health care providers, and clinical researchers. For example, the ubiquity and standardization of EMRs will raise new issues regarding patient privacy and drive changes in the patient– physician encounter that have yet to be revealed.

As physicians and other health care professionals become integral parts of larger health care delivery organizations, the concept of "dual agency" has already elicited numerous ethical dilemmas [9, 10]. Dual agency occurs when professionals face conflicts between obligations to the patient and obligation to another individual or organization [200]. In the past, these "divided-loyalty" dilemmas were most dramatic when health care professionals were employed by prisons, the armed forces, or government agencies in public health scenarios that pit population health over individual liberties and concerns. More and more large private institutions are indirectly dictating certain aspects of medical care, whether in the name of quality assurance, cost-cutting, efficiency, or perceived standards of care [201]. In terms of taking care of an individual patient health care professionals can face the critical question of "Who do I serve? The institution or agency that employs them or the individual patient?" What are the moral claims on the physician in such situations? Whose claims should take precedence when these claims are in conflict? Moreover, moral and religious values that impact aspects of health care delivery may not be shared by physicians, their patients, and health care institutions. The conflict of "liberty of conscience" and perceived public or institutional contracts and rights has already generated both ethical and political unrest [202, 203].

In terms of clinical research, increasingly complex clinical trials are juxtaposing the needs of population studies versus individual informed consent, especially in geriatric populations where informed consent is not always possible or practical. Here again is a conflict between the group and the individual and the divided loyalties of health care professionals to both society and individual patients. Methodology of capacity assessment for inclusion in clinical research trials in the cognitively impaired or demented elderly patient must be continually studied and addressed.

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Basic Preoperative Evaluation and Preoperative Management of the Older Patient

Linda Liu and Jacqueline M. Leung

Abbreviations

ACC/AHA	American College of Cardiology/			
	American Heart Association			
AKI	Acute kidney injury			
ASA	American Society of Anesthesiologists			
AT	Anaerobic threshold			
BMI	Body mass index			
CKD	Chronic kidney disease			
COPD Chronic obstructive pulmonary dis				
CPET	Cardiopulmonary exercise testing			
CXR	Chest X-ray			
ECG	Electrocardiogram			
GFR	Glomerular filtration rate			
IMT	Inspiratory muscle training			
MACE	Major adverse cardiac event			
MET	Metabolic equivalent			
NICE	National Institute for Health and Care			
	Excellence			
NRS	Nutritional Risk Screening			
NSQIP	National Surgical Quality Improvement			
	Program			
POCD	Postoperative cognitive decline			
RCRI	Revised cardiac risk index			
VAS	Visual analog scale			
VE/CO ₂	Ventilatory equivalents for carbon			
	dioxide			
VE/VO ₂	Ventilatory equivalents for oxygen			
VO ₂	Oxygen consumption			

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The US population of individuals aged 65 years or older is expected to more than double to 80 million by the year 2080 [1]. The population aged >60 years will double to 21.8% in 2050, while the portion aged \geq 80 years will increase to 4.3% [2]. Older individuals undergo surgery four times more often than the rest of the adult population; thus, a substantial proportion of patients presenting for surgery in the near future will be 65 years of age or older with an even greater increase in proportion for those older than 85 years of age. Older adult surgical patients require special considerations to minimize postoperative complications, functional decline, and loss of independence. The preoperative period may offer an opportunity to optimize health status by modifying risk factors and decreasing perioperative morbidity and mortality. This chapter will review the preoperative testing recommendations for the older patient and summarize the current literature in terms of preoperative optimization.

Cardiac Evaluation

In healthy older humans, aging leads to vascular stiffness of the aorta and large arteries, which increases systolic and mean arterial blood pressure and widens pulse pressure [3]. There is increased left ventricular wall thickness secondary to enlargement of cardiac myocytes, which leads to decreased myocardial compliance and reduced diastolic filling rate. Because of these changes, there is increased reliance on the contribution of the atrial contraction to late left ventricular filling. It is a common misconception that systolic function decreases with age, but in fact, in the absence of coexistent cardiovascular disease, resting systolic cardiac function is well preserved even at very advanced age. Other cardiovascular-related changes in aging include decreased baroreceptor responsiveness, decreased circulating blood volume, and sclerosis and calcification of the cardiac conduction system.

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Preoperative Assessment

Compared to their younger counterparts, while older patients may have a higher rate of perioperative cardiac complications, age *alone* is not as important as the patient's overall health status including the number and severity of coexisting diseases when determining risk. Recent data suggest the following factors are important in predicting adverse postoperative cardiac outcomes, particularly in the older surgical patients: American Society of Anesthesiologists (ASA) classification (\geq III) [4], emergency surgery [4], poor functional status [such as <1–4 metabolic equivalent (MET)] [5], poor nutritional status (low albumin level) [6, 7], and nursing home patients [8].

A cardiac risk index developed by Goldman in the 1970s has been revised, and a "new" cardiac index has been developed [9]. In this revised cardiac risk index (RCRI), the following six independent predictors of postoperative cardiac complications after major noncardiac surgery were identified: high-risk type of surgery, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative treatment with insulin, and preoperative serum creatinine >2.0 mg/dL. Rates of major cardiac complication with 0, 1, 2, or >3 of these factors were 0.5%, 1.3%, 4%, and 9%, respectively. A recent systematic review showed that the RCRI discriminated moderately well between patients at low versus high risk for cardiac events after mixed noncardiac surgery [10]. However, it did not perform well at predicting cardiac events after vascular surgery or predicting death.

Poor preoperative functional status is associated with increased surgical risk and poor surgical outcome [11], but formal assessment of preoperative functional status is not routine. Cardiopulmonary exercise testing (CPET) measures some components of anaerobic threshold (AT), peak oxygen consumption (VO_2) , and ventilatory equivalents for oxygen (VE/VO₂) and carbon dioxide (VE/VCO₂), but CPET results require careful interpretation by an experienced physiologist or clinician, and all measures need to be considered in the context of the surgical procedure that is being performed. There is not enough evidence to recommend CPET testing before surgery. Other cost-effective use of resources, like the 6-min walk test, may be more suitable, but functional status can often be estimated from activities of daily living and a good history and physical exam [12]. A summary of how to evaluate METs is provided in Table 4.1. However, accurate assessment of functional capacity may be difficult in the older population because many older individuals may have comorbid conditions or chronic pain, which limits their functional capacity. As a result, the functional limitation may be secondary to noncardiac causes, rather than attributable to a primary cardiac cause. Therefore, direct adoption of the American College of Cardiology/American Heart

Table 4.1 Estimate of metabolic equivalent for different activities

Metabolic equivalent	Activity
1	Watching television
2	Walking very slow (<2 mph)
3	Office work
4	Golfing with a cart
5	Normal walking
6	Shoveling snow
7	Fast jogging
8	Jumping jacks
9	Running 4–5 mph
10	Running 6 mph

Association (ACC/AHA) algorithm without knowing the reason for the functional limitation may result in a great majority of older patients needing additional preoperative cardiac stress testing.

The general approach in assessing patients for adverse cardiac events involves risk stratification [5]. The goal is to estimate the perioperative risk of a major adverse cardiac event (MACE) on the basis of a combined risk of the surgical procedure along with clinical risk factors. This estimate can be obtained from the American College of Surgeons NSQIP surgical risk calculator [13] or with the use of the RCRI with an estimation of risk from the surgical procedure. The proposed ACC/AHA algorithm starts with step 1 in Fig. 4.1. Patients undergoing emergency procedures or who are at low risk of MACE (<1%) should proceed without additional work-up, because routine screening with noninvasive stress testing is not useful for low-risk patients. For patients with elevated risk, further evaluation such as functional status should be assessed. If the patient can tolerate >4 METS activity, then it may be reasonable to proceed without further testing. Exercise testing or noninvasive pharmacological stress testing to assess for myocardial ischemia should be considered for high-risk patients with unknown or <4 METS function capacity if the results will change management. For patients who have undergone further testing, they may proceed with surgery if the stress test is negative for ischemia.

Whether myocardial revascularization should be performed before noncardiac surgery depends on whether the combined risk of coronary angiography plus myocardial revascularization exceeds the risk of the proposed noncardiac surgery without revascularization [14, 15]. Coronary revascularization is not recommended before noncardiac surgery exclusively to reduce perioperative cardiac events [5].

Preoperative Management

Beta-Blockers

Beta-blockers are anti-ischemic because inhibition of beta receptor stimulation by catecholamines results in slowing of

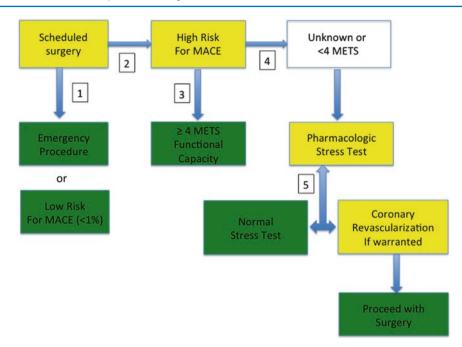


Fig. 4.1 Suggested approach for cardiac work-up of patient presenting for noncardiac surgery. *Step 1*: Proceed with surgery if procedure is emergency or patient is at low risk for MACE. *Steps 2 and 3*: Patients at high risk for MACE with good functional status (\geq 4 METS) can reasonably proceed. *Step 4*: Cardiac stress testing should be considered in patients with unknown or low functional status (\leq 4 METS) if manage-

ment will change depending on the results. *Step* 5: If stress testing is negative for ischemia, patients may reasonably proceed with surgery. If stress testing is positive for ischemia, risks and benefits of coronary revascularization will need to be assessed against the risk of the surgery (Based on data from Ref. Fleisher et al. [5])

heart rate and contractility, and the resulting action is a decrease in myocardial oxygen consumption. However, a multinational trial of metoprolol versus placebo in 8,351 patients found that although fewer patients in the metoprolol group had a myocardial infarction, more patients in the metoprolol group died and had an increased incidence of stroke [16]. Results from this study substantially dampen the enthusiasm in implementing new preoperative beta blockade in at-risk patients. Beta-blockers should be continued in patients who are on them chronically, but beta-blocker therapy should not be started on the day of surgery [5]. Currently, there is insufficient data on the efficacy and safety of starting beta-blockers days to weeks in advance of the noncardiac surgery to make a firm recommendation [17].

Statins

Lipid-lowering drugs have been shown to help prevent adverse cardiac events [18], but the data are limited in terms of the number of enrolled patients and the type of surgical procedure. Durazzo et al. studied the effect of short-term treatment with atorvastatin in patients undergoing vascular surgery. The placebo group had a threefold higher incidence of adverse cardiac events than the intervention group (26% vs. 8%, p = 0.031) [19]. Although, the time of initiation of therapy and the duration of therapy are not clear, current recommendations are that statins should be continued in patients currently taking them, and perioperative initiation is reasonable in patients undergoing high-risk procedures [5].

Hypertension

Hypertension is a risk factor for ischemic heart disease, congestive heart failure, and stroke. The risk of nonfatal myocardial infarction in patients with diastolic hypertension (>90 mm Hg) is increased markedly in the presence of hypercholesterolemia, cigarette smoking, and ECG abnormalities [20]. Although the presence of preoperative hypertension has not been conclusively shown to increase the incidence of postoperative cardiac complications, preoperative withdrawal of antihypertensive medications, such as beta-blockers, calcium channel blockers, or clonidine, is associated with greater perioperative blood pressure lability.

Congestive Heart Failure

Depressed preoperative ejection fraction (<35%), determined by radionuclide angiography, has been found to correlate significantly with early perioperative infarction [21]. Of importance is that clinical diagnosis of heart failure in older patients is particularly difficult because of the lack of typical symptoms and physical findings [22]. In patients with a history of congestive heart failure, one-third may present with normal systolic function [23], making assessment of diastolic filling in these patients particularly important. The prognostic importance of preoperative diastolic dysfunction on perioperative cardiac morbidity remains to be determined. However, the presence of clinical signs of congestive heart failure is a major risk predictor of postoperative cardiac complications, and surgery should be delayed if possible until the heart failure is stabilized [24].

Other Risk Factors

The relative importance of other preoperative risk factors such as hypercholesterolemia, cigarette smoking, valvular heart disease, and site of surgery has not been conclusively determined to increase perioperative cardiac risk.

Pulmonary Evaluation

With aging, there is loss of elastin and increased lung compliance with decreased lung elastic recoil, air trapping, and hyperinflation. Residual volume increases 5–10% per decade, and functional residual capacity (FRC) increases 1–3% per decade [25]. The loss of elastic recoil also increases closing volume and leads to early collapse of small airways, which leads to more ventilation-perfusion mismatch and a larger A-a gradient [26]. There is also an age-related increase of pulmonary vascular resistance that averages to 1 mm Hg increase of pulmonary artery systolic pressure per decade [27].

With increasing age, there is narrowing of the thoracic intervertebral disk space and the intercostal space, which can change the vertebral angle and decrease the forced exhaled volume in 1 s (FEV1) and vital capacity by up to 30 cc/year. Chronic smokers have a more accelerated decline in lung function [28]. Older patients also develop sarcopenia which leads to decreased skeletal muscle mass and strength. Weaker diaphragmatic inspiratory effort may decrease the patient's ability to increase minute ventilation on demand. There is also dysfunction of the mucociliary clearance ability.

Preoperative Assessment

Five preoperative predictors of increased risk for postoperative respiratory failure have been identified which include type of surgery, emergency case, poor functional status, preoperative sepsis, and higher ASA class [29]. In contrast, no laboratory value or preoperative testing performed in unselected patients has been associated with predictive value for postoperative respiratory failure. Pulmonary function tests can assess the presence and severity of disease, but they do not have great ability to predict postoperative need for mechanical ventilation or complications. In a study involving critically ill patients, the CO_2 levels on arterial blood gas and not spirometric testing better predicted the need for postoperative intubation [30]. The evidence to date suggests that pulmonary function tests should be selectively performed in patients undergoing nonthoracic surgery, because they can assess the presence and severity of the disease, but they do not have great predictive value for postoperative pulmonary complications.

Preoperative Management

Asthma

The incidence of asthma in older patients has been reported to be around 7%, which is comparable to other adult age groups [31]. Asthma can be underdiagnosed in the older individual because the symptoms may be misinterpreted as normal aging or other conditions such as heart failure, gastroesophageal reflux, pneumonia, or side effects of medications such as beta-blockers or angiotensin-converting enzyme inhibitors. The treatment of asthma is basically similar to the general adult population because there is lack of data targeting the older patient. Specifically, many of the trials excluded patients > age 60. Once the diagnosis is established, disease optimization should focus on smoking cessation, optimization of medications, exercise training, and patient education [32].

Chronic Obstructive Pulmonary Disease

The preoperative management should be focused on medically optimizing patients with pulmonary disease. Acute exacerbations of chronic obstructive pulmonary disease (COPD) should be aggressively treated, and surgery may need to be delayed until symptoms improve. COPD is more an independent predictor for postoperative pulmonary complications than asthma [33].

Smoking Cessation

Smoking cessation counseling is probably the most essential risk modifier for pulmonary complications. Moller et al. showed that smoking intervention successfully reduced the incidence of postoperative complications in patients undergoing elective hip or knee arthroplasty [34]. While maximal reductions in postoperative respiratory complications are seen with at least a 2-month abstinence, smoking cessation should be encouraged even immediately before surgery, because smoking cessation immediately preoperatively has been associated with decreased carbon monoxide levels, increased oxygen carrying capacity, and reduced operative risk measured at 6 weeks after surgery [35].

Obstructive Sleep Apnea

Moderate to severe obstructive sleep apnea (OSA) occurs in about 10–20% of the general population [36]; importantly, the prevalence of OSA increases with aging due to weakening

of pharyngeal muscle tone, which may lead to upper airway dysfunction. Obesity may increase with age and also contributes to OSA. More than one-third of older adults aged >65 years met definition for obesity in 2007–2010 [37]. In nonsurgical patients, patients who have severe sleep apnea and are not treated have a greater rate of death than heavy smokers over a 10-year period [38]. OSA is also associated with higher risk of postoperative desaturation, respiratory failure, postoperative cardiac events, and transfers to the intensive care units in adults [39]. The optimal time to administer continuous positive airway pressure (CPAP) treatment before surgery is not clear, but Mehta et al. showed that patients who were newly diagnosed with sleep apnea in the preoperative clinics and were referred to receive their CPAP therapy were able to have improved sleep quality, less daytime sleepiness, and greater reduction in medication for other comorbidities such as hypertension and diabetes [40].

Exercise

Exercise training interventions preoperatively have shown mixed results in terms of preventing pulmonary complications. Part of the inconsistency is due to the heterogeneity in study design in terms of type of exercise used, duration, frequency, and timing. Preoperative exercise programs can be effective in promoting quality of life among patients diagnosed and treated for locally advanced rectal cancer [41], but not all studies have shown efficacy due to issues with patient compliance. Hopefully in the near future, studies that objectively measure functional capacity and perioperative morbidity will be able to expand our understanding of the effects of exercise training preoperatively.

Inspiratory Muscle Training

After surgery, reductions in inspiratory and expiratory muscle strength can persist for up to 12 weeks. Preoperative inspiratory muscle training (IMT) is intended to increase strength and endurance by adding a resistive load during inspiration. Although not specifically studied in the older patient, a recent Cochrane review found reduced postoperative atelectasis, pneumonia, and hospital length of stay with IMT preoperatively for adult patients undergoing cardiac or major abdominal surgery [42]. More studies are needed before IMT can be recommended for all older patients undergoing surgery.

Neurologic Evaluation

The human brain begins to atrophy by the third decade. Normal age-related changes include decrease ability to multitask, reduced speed of information processing, and decreased language comprehension for complex text. The pulsatility and velocity induced by aortic stiffness penetrates further into the brain's microcirculation and can cause damage to the small vessels because of its low vascular resistance. This small vessel disease then can lead to lacunar infarcts and microbleeds and may lead to loss of cognitive function in some patients.

After noncardiac surgery, the two most common complications in the older individual are delirium (10-60%) [43] and postoperative cognitive decline (POCD) (7-26%)[44]. Delirium is an acute confusional state with alterations in attention and consciousness [45] (see Chap. 30), while POCD refers to declines in cognitive functioning that can occur in the absence of delirium and are detected through neuropsychological testing. Delirium occurs in 14-50% of hospitalized medical patients, and it is associated with higher mortality rate [46, 47], increased medical complications, longer hospital stay, and poorer short-term functional outcome. Delirium can be superimposed on dementia or other neurologic disorders associated with global cognitive impairment. As a result, the course of delirium can vary considerably and depends on the resolution of the causative factors.

Preoperative Assessment

The development of delirium is thought to be a multifactorial process involving baseline patient vulnerability and precipitating factors or insults [48]. The diagnosis of chronic cognitive decline in the preoperative period has been found to be the strongest predictor of postoperative delirium [43]. Other preoperative risk factors for postoperative delirium include sensory impairment, age >70, polypharmacy, poor functional status, dehydration, medical comorbidities (especially cerebrovascular or other brain diseases), electrolyte abnormalities, low albumin, depression, and pain [12]. The estimated prevalence of cognitive impairment not categorized as dementia is over 20% in the older population [49]. Identifying individuals with cognitive impairment before surgery is important for risk stratification and helps providers anticipate perioperative cognitive problems and postoperative management needs [50].

Preoperative testing for preexisting cognitive impairment is not yet a part of routine clinical practice because many tests can be time-consuming, but several quick and simple cognitive screening tools suitable for the preoperative setting with sensitivity ranging from 79% to 99% and specificity ranging from 70% to 98% have been proposed (Table 4.2) [51]. One final quick test is the animal fluency test. This test requires patients to name as many animals as possible within 60 seconds. Patients with lower scores on the animal fluency test are at higher risk of developing postoperative delirium [52]. Recently, the American Geriatrics Society published a best practice statement about

 Table 4.2
 Cognitive screening tests that can be administered in less than 3 min

Test name	Abbreviation	Components
6-item screener	6-IS	Three-item recall (i.e., apple, table, penny) Three-item temporal orientation (i.e., day of week, month, year)
8-item screener	8-IS	Three-item recall Attention/calculation exercise for five iterations (i.e., subtract 7 from 100 for 5 iterations)
6-item cognitive impairment test	6-CIT	Three-item temporal orientation Five-item address (i.e., first name, last name, house number, street, city)
Sweet 16	S-16	Eight temporal/spatial orientation (i.e., time, place) Three-item immediate recall Two sustained attention questions (i.e., digit spans backwards) Three-item recall
5-item recall and fluency	5-IRF	Five-item address recall 1-min animal fluency (i.e., name as many different animals as possible in 1 min)
Mini-cog		Three-item recall Clock drawing (i.e., draw numbered clock face with hands showing 11 o'clock)

Based on data from Ref. Long et al. [51]

postoperative delirium and strongly recommended assessment and documentation of preoperative cognitive function in older adults at risk of postoperative delirium [53]. The hope is that utilization of cognitive screening tools can contribute to early recognition of cognitive decline and serve as a record of baseline cognitive status.

Preoperative Management

Comprehensive Assessment

Management of postoperative delirium centers on prevention and early recognition. Medical prophylaxis has been demonstrated to have limited utility since most of the therapeutic options are for symptom management and not for prevention and do not improve outcomes [54]. Other successful interventions of postoperative delirium are limited as well. The most successful study was by Marcantonio et al. [55]. In this study, older patients admitted for emergency surgical repair of hip fracture were randomly assigned to an intervention (a comprehensive geriatrics assessment) or the usual care. Delirium occurred in 32% of the intervention patients and in 50% of the usual care patients. Despite this reduction in delirium, the length of hospital stay did not differ significantly between the two groups.

Multimodal Pain Management

The use of multimodal pain management regimens involves several different anesthetic and analgesic techniques that have been shown to decrease postoperative opioid use. For a detailed discussion of intraoperative anesthetic management (regional versus general anesthesia), the reader is encouraged to refer to Chaps. 19 and 28 in this book, but the use of multimodal pain management regimens often start in the preoperative period. While not selecting specifically for older patients, studies that look at treatment for hip fractures often end up predominantly with older patients, because hip fractures are a leading cause of morbidity and mortality in this age group [56]. Multimodal regimens include non-opioid medications such as acetaminophen, regional blocks, and gabapentin or pregabalin. Kang and colleagues showed that among cognitively intact older patients undergoing bipolar hemiarthroplasty, multimodal analgesia including preoperative oral oxycodone and celecoxib and intraoperative periarticular injections led to lower visual analog scale (VAS) scores and less fentanyl use. The incidence of postoperative delirium and hospital stay did not differ between the two groups, but the study was small and did not have enough power [57]. With preoperative planning and use of multimodal pain management regimens, older patients may be mobilized earlier, use less narcotics, and have lower pain scores without unwanted narcotic side effects.

Exercise

There is reduced risk for mild cognitive impairment and dementia in older adults who participate in physical exercise. Multiple physiologic mechanisms such as elevated neurotrophin levels, improved vascularization, facilitation of synaptogenesis, mediation of inflammation, and reduced disordered protein deposition along with reduction of cardiovascular risk factors likely account for the neuroprotective effects of exercise on brain structures. Regular aerobic exercise may well provide a protective effect on brain health and cognitive performance through the prevention and management of hypertension and subsequent enhanced cerebral blood flow. Women in the Nurses' Health Study, age 70-80, who walked 90 min per week, had global cognitive scores higher than those who walked less than 40 min per week [58]. For men in the Honolulu-Asia Aging Study, those who walked less than 1 mile per day were at significantly higher risk (1.7-1.8 times) for developing dementia compared to men who walked more than 2 miles per day [59]. Although the optimal exercise amount and type remain unknown, positive relationships between a higher dosage of exercise and cognitive health have been reported in aging adults [60]. There is some evidence that resistance-only training can also have a positive effect [61]. Moderate intensity physical exercise can lead to significant changes in brain health and cognitive performance, including memory, attention, and executive

function. While the benefits of exercise are considered preventative, this is probably more of a long-term effect, and it is not realistic to expect benefit in the few days before surgery. Also, exercise training has not been tested extensively in presurgical populations for postoperative outcomes, nor have specific types of beneficial exercise been well delineated [62].

Hydration

Radtke et al. enrolled over 1000 surgical patients at a single center and found that patients who had preoperative fluid fasting of 2–6 h had a significantly reduced incidence of delirium in the recovery room (odds ratio 2.69, 95% confidence interval 1.4–5.2) and on the ward (odds ratio 10.57, 95% confidence interval 1.4–78.6) compared with those who fasted for more than 6 h. While preoperative dehydration does hold biological plausibility, it seems unlikely that the fluid management intraoperatively did not reduce this association. Further work including randomized controlled trials will be needed to determine if treatment of preoperative dehydration alone can lead to a reduction in the occurrence of postoperative delirium [63].

Depression/Anxiety

The incidence of depression increases in the older individual. In female patients age > 65 years, the number of patients who screened positive for depression across age groups was 5.9% (age 65–74 years), 6.3% (75–84 years), and 10% (85 years and older) [64]. Depression is associated with poorer prognosis, longer recovery times, increased health-care utilization, and postoperative delirium [65]. Preoperative anxiety along with depression symptoms have been associated with increased mortality [hazard ratio = 1.88 (95% CI = 1.12–3.17), P = 0.02] [66] and worse functional status [67]. Studies looking at psychological interventions have been difficult due to preexisting personality type and traits, confounding medical factors, and heterogeneity among trials. Further research is needed to determine what preoperative interventions would be effective in the short preoperative time period.

Multicomponent Packages

The literature about preoperative optimization of cognitive status is growing rapidly. The positive evidence so far points to reduction in the incidence of delirium with the use of multi-component/multidisciplinary prevention packages. The individual components of the interventions varied between studies but commonly included reorientation strategies, ensuring hydration/nutrition, and early mobilization [68]. There remains a lot to study about target-specific interventions.

Frailty

Frailty, a syndrome that is thought to be separate from delirium, is also common among the older population. Frailty is currently conceptualized as a syndrome that results in a myriad of signs and symptoms and is characterized by susceptibility to impending decline in physical function and negative health outcomes including increased risk of mortality [69] (see Chap. 1). In other population studies, such as the Rush Memory and Aging Project, a longitudinal study of aging [70] found that increasing frailty was associated with Alzheimer's disease and increased rate of cognitive decline. Other studies reported that signs of frailty, such as grip strength, gait disturbance, and body composition, have been related to mild cognitive impairment [71–74]. In surgical patients, preoperative frailty has been shown to increase the risk of postoperative complications [75–77] and postoperative delirium [78] in patients undergoing elective surgery.

Preoperative Assessment

Currently, there is no consensus as to how frailty should be measured. Although there are different views on the specific criteria, operational definitions of frailty have been proposed including excessive reduction in lean body mass, poor endurance associated with a perception of exhaustion and fatigue, and a reduction in walking speed and mobility [69]. Other features have been described such as loss of appetite, reduced nutritional intake, and deteriorations including but not confined to the cardiovascular, metabolic, and immunologic systems [79-81]. Although there is no consensus as to how frailty should be defined, two proposed definitions, including physical frailty [69] and cognitive frailty [82], have been shown to be associated with outcomes such as functional decline, cognitive decline, mortality, readmission, and nursing home placement [83].

In one study of older patients admitted to a Veterans Hospital, 27% were found to be frail. Our study showing that one-third of the patients had a frailty score of 3 or greater is similar to that reported by a previous study showing that 27% of older patients admitted to a Veterans Hospital were considered frail [84]. Another important consideration is whether frailty is dynamic and potentially reversible. Considering that half of the patients in one study were pre-frail [78], whether interventions would reduce the development of frailty is clinically relevant.

Preoperative Management

Prehabilitation

Prehabilitation, which is defined as the enhancement of the preoperative condition of a patient, is a possible strategy to improve the postoperative outcome of patients who are identified to be frail preoperatively. This emerging concept proposes the preoperative optimization of physical, nutritional, and mental status for those who are identified to be frail preoperatively. A more detailed review of this topic is discussed in Chap. 6.

Renal Function

The prevalence of renal insufficiency is quite common in the older individual because of a decrease in glomerular function with age. Chronic kidney disease (CKD) is not an inevitable consequence of aging, but age-associated changes probably enhance susceptibility to the development of CKD. In populations \geq age 70, an abnormal glomerular filtration rate was observed in 75% of community-dwelling older individuals, 78% of the patients from the geriatric ward, and 91% of nursing home patients. In populations > age 85, 99% had evidence of renal impairment necessitating dosing adjustments for drugs [85]. Kheterpal et al. identified aged \geq 59 years along with emergent surgery, liver disease, body mass index (BMI) ≥ 32 kg/m², high-risk surgery, peripheral vascular occlusive disease, and COPD necessitating chronic bronchodilator therapy as independent preoperative predictors of postoperative acute kidney injury (AKI) [86]. Emerging evidence suggests that even minor changes in serum creatinine are associated with increased patient mortality after major surgery [87]. In fact, it is estimated that acute renal failure contributes to at least one of every five perioperative deaths in older surgical patients [88].

Preoperative Assessment

There are no clinical trials demonstrating that preoperative assessment for renal dysfunction will lead to better outcomes, but preoperative testing may identify patients with unrecognized renal impairment. While serum creatinine is used to determine AKI, it is not sensitive, and a rise may not occur until glomerular filtration rate (GFR) drops below 50%. The creatinine is also influenced by nonrenal factors such as muscle mass, gender, race, and diet. AKI may go unnoticed in older adults because the reduction in creatinine clearance is usually not associated with a notable rise in serum creatinine due to the decreased muscle mass that occurs with aging.

Preoperative Management

It is probably more important just to be cognizant that all older patients are at risk of developing renal complications due to decreased renal function. The goals are to try to avoid hypovolemia, hypotension, electrolyte imbalances, and the effect of nephrotoxic drugs (aminoglycosides, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and contrast dye) in the preoperative period.

Diabetes Mellitus

The incidence of diabetes mellitus increases with age. According to the Centers for Disease Control and Prevention, the rate of diabetes for those aged 75 years or older increased from 8.0 to 19.2 per 100 from 1990 to 2014 [89]. Hyperglycemia has been shown to be associated with higher rates of postoperative complications. The National Veterans Administration Surgical Quality Improvement Program identified diabetes in a multiple logistic regression analysis as a significant preoperative risk factor for surgical site infection [90], and high preoperative mean glucose levels were the main risk factor for development of postoperative deep sternal wound infection in diabetics undergoing coronary artery bypass grafting [91].

Preoperative Assessment

The duration of diabetes has significance. The recent clinical guidelines from the National Institute for Health and Care Excellence (NICE) removed recommendations for random blood glucose and replaced it with recommendations for a HbA1c within 3 months in patients with diabetes. In a retrospective study of 6088 patients from the Veterans Health Administration undergoing total joint arthroplasty, researchers found that patients with higher HbA1c had an elevated risk of having at least one surgical complication [92]. The preoperative HbA1c measurement should not be used as a screening tool for the presence of diabetes. Instead, it should be used to identify patients that are at high risk for complications from long-term diabetes.

Preoperative Management

The main goal for the management of diabetes is to avoid hyperand hypoglycemia. Unfortunately, the optimal perioperative glycemic target is unknown. A reasonable approach would be to maintain blood glucose at less than 200 mg/dL intraoperatively and less than 180 mg/dL postoperatively but avoid hypoglycemic episodes with levels less than 80 mg/dL [93].

Nutrition

The prevalence of malnutrition in the older population varies from 9% to 15% in the outpatient clinics, 12–50% in the acute inpatient hospital, and 25–60% or more in the chronic institutional setting [94]. Poor nutrition is a key factor related to perioperative complications such as increased risk for pneumonia, extended intubation, prolonged wound healing, infection, sepsis, and 30-day mortality [95]. Turrentine and colleagues studied data from their NSQIP database and found that preoperative transfusion, emergency operation, and weight loss best predicted morbidity for those 80 years of age and older [96].

Preoperative Assessment

Basic evaluation of the preoperative older patient should include documentation of height, weight, and body mass index along with inquiry about unintentional weight loss in the past year. A study from the Veterans Administration identified preoperative albumin level as a good predictor of postoperative mortality in the older population [7]. The researchers examined 43 preoperative risk factors, 14 preoperative laboratory values, and 12 operative variables for predicting postoperative complications. The mean age in this study was 61 ± 13 years, and 97% of the subjects were men, but the results should apply to the general older surgical patient. The most important variable in predicting postoperative mortality was preoperative albumin level with ASA PS classification as the second best predictor. Albumin levels <2.1 g/dL were associated with 29% mortality and 65% morbidity. Despite the evidence linking albumin to postoperative outcome, albumin is difficult to rely on due to its long halflife (18–21 days) and its fluctuations based on intravascular and extravascular fluid status.

Preoperative Management

Recently, studies have focused on identifying malnutrition with tools other than albumin or weight loss. Jie and colleagues use the Nutritional Risk Screening (NRS) Tool 2002 and found that patients with a high score (\geq 5) had lower complication rates and shorter hospital stays if they received preoperative nutritional support. For those with mild malnutrition (an NRS score from 3 to 4), the complication rate and the postoperative hospital stay were similar between patients with and without preoperative nutritional support [97]. The American College of Surgeons NSQIP and the American Geriatrics Society recommend for patients at severe nutritional risk to obtain a dietician consult to develop a perioperative nutritional plan with possible preoperative nutritional support [12].

Medications

Older patients are more likely to regularly take multiple medications, both prescription and over-the-counter medications. Polypharmacy (see Chap. 21) has been associated with increased risk of cognitive impairment, morbidity, and mortality, as well as compromised medication compliance. Specific medications such as antihistamines or benzodiazepines contribute to the risk of falls or confusion. Agostini et al. showed that there is a linear relationship between the number of medications used and the risk of two frequently reported adverse drug effects—weight loss and impaired balance [98]. This effect persisted despite adjustment for comorbidities.

Preoperative Assessment

The perioperative period has been proposed as an ideal time to critically review the medication list for polypharmacy, drug interactions, and adverse drug events [12]. The medication list should be thoroughly reviewed with the patient.

Preoperative Management

Nonessential medications should be discontinued preoperatively. Medications with potential for withdrawal symptomatology or disease progression if discontinued should be continued throughout the perioperative period. Prescribing additional new medications should be minimized. Although these proposals make intuitive sense, no randomized trials have specifically addressed this issue.

Preoperative Laboratory Tests

Complete Blood Count and Chemistry

Preoperative tests are ordered to gain additional information that cannot be obtained from history and physical examination alone. The test should detect unsuspected abnormalities that impact perioperative morbidity. Optimally, an abnormal test would point out possible risk modification areas in order to reduce postoperative complications. Dzankic et al. [99] used a prospective cohort of patients \geq 70 years of age undergoing elective noncardiac surgery to evaluate the prevalence and predictive value of abnormal preoperative laboratory tests. The prevalence of abnormal laboratory tests was quite high—electrolyte abnormalities (0.7%–5%), abnormal platelet counts (1.9%), glucose (7%), hemoglobin (10%), and abnormal creatinine (12%)—but for patients classified as ASA 1–2, the incidence of laboratory abnormalities was as low as those in the general population (3.6%). None of the abnormal laboratory values were significant independent predictors of adverse outcomes with multivariate regression. Although the actual rate of laboratory abnormalities is small in the healthy older individual, laboratory abnormalities are still higher in the older individual as a group compared with the younger population. These results suggest that routine preoperative testing in older surgical patients, particularly in those patients classified as ASA 1–2, generally would produce few abnormal results.

Routine preoperative medical testing before elective surgery is estimated to cost \$30 billion annually. Data show that laboratory abnormalities on routine screen often are from spurious results that do not lead to changes in management and are of unknown clinical significance. Schein et al. [100] studied nearly 20,000 patients undergoing cataract surgery who were randomized to either routine laboratory testing or no routine testing. They reported no difference in perioperative morbidity and mortality between those who did versus those who did not receive routine testing. Despite the data, 15 years later, recent review of the Medicare database showed that 53% of over 440,000 patients still have at least one preoperative test performed in the month before cataract surgery [101].

Total abandonment of routine testing based on age must be balanced against the probability that unexpected disease may be detected by the testing and that the extent of surgery may be modified. Recommendations from the UK National Institute for Health and Care Excellence (NICE) clinical guidelines for routine preoperative tests for elective surgery are listed in Table 4.3.

Electrocardiogram

Abnormalities on preoperative electrocardiogram (ECG) are common but are of limited value in predicting postoperative cardiac complications in older patients undergoing noncardiac surgery. We found that 75.2% of the patients had at least one abnormality on their preoperative ECG [103]. On multivariate analysis, only the ASA physical status classification \geq 3 and a history of congestive heart failure were associated with postoperative cardiac complications. The presence of abnormalities on preoperative ECG was not associated with an increased risk of postoperative cardiac complications. Results from our study and others [104, 105] suggest that the prevalence of ECG abnormalities in this age group is high but has low sensitivity and specificity in predicting postoperative cardiac complications.

While there are no controlled clinical trials to show that routine laboratory tests, ECG, or chest X-ray (CXR) are associated with a decreased adverse event rate, information from some preoperative tests (i.e., ECG) may establish a baseline measurement for later reference in the hospitalization. The European Society of Anaesthesiology (ESA) guideline currently recommends resting ECG for patients undergoing intermediate or high-risk surgery with risk factors for ischemic heart disease, heart failure, stroke, diabetes, or renal dysfunction [106]. The NICE clinical guideline panel also felt that patients >65 years of age are at greater risk of asymptomatic changes that would be highlighted by a resting ECG. Recommendations from the NICE clinical

	Surgery type		
ASA status	Minor	Intermediate	Major
1	CBC/chemistry/ECG: not routine	CBC/chemistry/ECG: not routine	CBC: obtain Chemistry: consider in patients at risk for AKI ECG: consider if age >65, and no baseline within 12 months
2	CBC/chemistry/ECG: not routine	CBC: not routine Chemistry: consider in patients at risk for AKI ECG: consider for patients with CV, renal, or DM comorbidities	CBC/chemistry/ECG: obtain
3 or 4	CBC: not routine Chemistry: consider in patients at risk for AKI ECG: consider if no baseline within 12 months	CBC: consider for patients with CV, renal, or DM comorbidities Chemistry/ECG: obtain	CBC/chemistry/ECG: obtain

Table 4.3 Recommendations for routine preoperative tests (complete blood count, chemistry, and electrocardiogram)

Based on data from Ref. National Guideline Centre [102]

CBC complete blood count, AKI acute kidney injury, CV cardiovascular, DM diabetes mellitus, ECG electrocardiogram

guidelines for routine preoperative ECG for elective surgery are listed in Table 4.3. Expert panels mostly agree that routine preoperative ECG is not useful in asymptomatic patients undergoing low-risk surgical procedures [5].

Chest X-Ray

Chest X-rays are used to detect diseases such as chronic obstructive pulmonary disease, heart failure, tuberculosis, or lung cancers, but they are of questionable benefit in asymptomatic individuals, in whom the rate of lung disease is low. In patients younger than age 50, the likelihood of an abnormal chest film ranges from 0% to 20%, whereas the likelihood increases to 20–60% in patients older than 50 [107]. But the data are unclear as to whether CXR findings impact perioperative management and whether rates of perioperative pulmonary complications are affected by the performance of a preoperative CXR. The NICE clinical guideline panel recommended that the chest X-ray should not be used as a routine preoperative test in any population.

Conclusion

With aging, most older patients will require surgical treatment, but age alone should not be the sole contraindication to surgery. The presence of comorbidities is a more important predictor of morbidity and mortality than age alone. The preoperative period is an opportune time to proactively assess this group of patients who have reduced physiological reserve. Prior investigations have provided many results to target the areas of preoperative evaluation for this population. Preoperative risk identification is a critical portal of entry to begin the perioperative care of older surgical patients. Information gained from preoperative evaluation is essential for the development of subsequent intra- and postoperative strategies to enable successful perioperative outcomes.

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The Perioperative Surgical Home for the Geriatric Population

Gary E. Loyd and Anahat Dhillon

History

The modern Perioperative Surgical Home (PSH) is a reinvention of an old idea. The original PSH concept was started in the 1960s by a group of pediatric hospitals in an effort to improve patient outcomes and the patient experience, all while lowering costs. They were too successful in achieving their goals to the point of costing their institutions revenue because at that time, insurance paid for services provided and not the outcomes. Therefore, the project failed as it succeeded. There was increasing awareness of cost and quality through the 1990s as healthcare was becoming more expensive around the world. "Fast-tracking" studies started to appear in the literature as a way to reduce costs while improving quality. Studies identifying the optimal preoperative testing and the reduction in duplicative testing also appeared. At the same time, Enhanced Recovery After Surgery (ERAS) protocols appeared in Europe as cost containment and improved outcomes were a primary focus in their healthcare market [1].

The adoption of the Patient Protection and Affordable Care Act of 2010 in the United States provided the financial stimulus for a comprehensive approach to perioperative care. The PSH became more organized as the American Society of Anesthesiologists (ASA) took the lead in exploring the work being done at the University of Alabama Birmingham and at the University of California Irvine. In 2013, the term "Perioperative Surgical Home" started to appear in the medical literature [2]. With the adoption of the Medicare Access

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A. Dhillon Department of Anesthesiology, University of California Los Angeles, Los Angeles, CA, USA and CHIP Reauthorization Act (MACRA) legislation of 2015 and other changes in healthcare reimbursement, a further shift occurred in the United States from fee-for-service to value-based purchasing. Under value-based purchasing, the PSH has a financial environment in which it should thrive [3]. In 2014 the ASA initiated the Perioperative Surgical Home Learning Collaborative. This is a multi-organizational initiative to promote the development of the PSH concept into more tangible processes that healthcare organizations everywhere can adopt.

Introduction

The PSH can generally be defined as a patient-centered, physician-led care delivery model that uses multi-specialty care teams to promote cost-efficient use of resources at all levels through a patient-centered, continuity of care delivery model using a shared decision-making process. The ASA, the American Academy of Orthopedic Surgeons, and the American College of Surgeons have similar definitions and descriptions [4, 5].

The PSH emphasizes "prehabilitation" of the patient before surgery, preoperative optimization of comorbidities, optimal use of intraoperative resources, improved return to function through timely and effective follow-up, and effective transitions to home or post-acute care to reduce complications and readmissions. The time period of the PSH usually begins at the contemplation of surgery until the time of optimal return of patient function after surgery. This time period (which varies according to the surgery) may be as short as a month or as long as a couple of years, such as with neurological surgery. The PSH shares the same three interdependent goals as the Institute for Healthcare Improvement (IHI) called the triple aim: (1) improving the individual experience and quality of care, (2) improving the overall health of the population, and (3) reducing the per capita costs of care [6].

The ASA suggests the following benefits of the Perioperative Surgical Home:

- 1. Reduction in preoperative testing and unnecessary consults
- 2. Reduction in day of surgery cancelations
- 3. Improvement in clinical outcomes
- Development of post-procedural care initiatives: coordination to improve postoperative nausea and vomiting (PONV), postoperative pain
- 5. Reduction in postoperative complications
- 6. Cost reduction (through reduced testing, reduced complications, and decreased length of stay)
- 7. Improved coordination of care and discharge planning [7]

Multiple studies have shown the benefit of using the PSH in reduced length of hospital stay, reduced admissions to skilled nursing facilities, and reduced complications [8].

Operationally, the PSH is usually broken down into several interdependent, working teams which concentrate their efforts on their respective areas of the process (see Fig. 5.1). The decision/preoperative team works to (1) streamline the decision to operative period with the education of the patient (and their families or support structures) about the PSH process, (2) perform baseline assessments, (3) provide appropriate prehabilitation, (4) optimize the patient's comorbidities, (5) begin perioperative care coordination with the patient's primary care provider, and (6) initiate Enhanced Recovery After Surgery (ERAS) protocols. Streamlining the preoperative process is important for several reasons. Some of the geriatric population still work and must take time from that work to attend office visits. Reducing the number of office

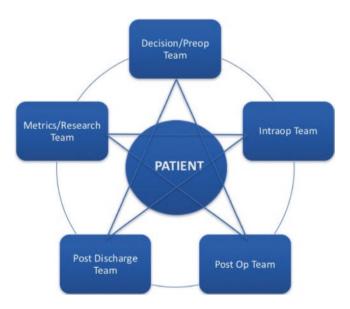


Fig. 5.1 Typical diagrams of modern PSH interactions with patient involvement the central focus

visits reduces the cost to the patient which is usually not reflected in published healthcare costs. Conversations with and education of the patient about the PSH process help to enhance patient cooperation and adherence with prehabilitation and ERAS protocols. Baseline assessments of activities of daily living (ADLs) and other PSH-generated metrics allow for gathering of data which will drive the aggregate of marginal gains, addressed later in this chapter. The concept of prehabilitation is primarily focused on improving nutritional, cardiopulmonary, and cognitive function. Studies have shown that the geriatric population has poorer nutritional status, less cardiopulmonary reserve, and less cognitive function than their younger counterparts. Just several weeks of prehabilitation have been shown to improve outcomes [3]. Comorbid disease states have been identified as independent risk factors for postoperative complications, and optimizing these comorbidities has also been shown to improve outcomes. The combination of prehabilitation, comorbidity optimization, and ERAS protocols is considered the "low hanging fruit" of the PSH accomplishments.

The intraoperative team concentrates on (1) continuing and enhancing ERAS protocols, (2) assessing and reducing costs of providing intraoperative care, (3) improving intraoperative efficiency, (4) optimizing individualized anesthetic care, and (5) providing information to the postoperative care team, the primary care providers, and the preoperative team (as feedback). Depending on the service line, the intraoperative stage is usually either the first or second most expensive step in the perioperative process. Cost reduction in this resource-intensive period is a primary focus for this team. During the intraoperative phase, very complex and intensely interdependent subprocesses take place not only for the staff but also for the patients. Therefore, coordination of care is a key for success.

The postoperative phase is the period when acute complications are most likely to occur. The postoperative team not only concentrates on early detection and treatment of these complications but also fast-tracking the rehabilitation process and continuing the PSH conversation with the patient (and their families or support structures) to improve adherence to rehabilitation protocols and to learn from the patient about their experience and new concerns and expectations. Beginning the transition to environments where healthcare provider intervention is not as immediately available is a very important step as geriatric patients may not fully comprehend what is required of them as they participate in their recovery. Adhering to ERAS protocols and assessing early outcomes are important functions of the postoperative team.

The post-discharge team addresses areas which have previously been poorly investigated. In some cases, up to 50% of the healthcare perioperative dollar is spent during this period [9]. This team focuses on (1) ERAS protocols; (2) periodic assessment of ADLs and other PSH metrics; (3) acute, intermediate, and long-term sequelae of surgery; (4) transitioning of care to the primary care provider; and (5) continued PSH conversations with the patient and their support systems for education and to gather information for process improvement. ERAS protocols have now been extended to the post-discharge period to address issues such as physical rehabilitation. Social, mental health, and nutritional health aspects are areas for assessment and intervention. There is a dearth of information in these areas as it relates to the perioperative process. The combination of ADL assessments, other PSH metrics as discovered through analysis, and feedback from the patient through conversation and surveys are key components of driving the aggregate of marginal gains to achieve further improvements in the PSH process.

The metrics/research team is responsible for (1) creating lead and lag metrics; (2) providing data analysis; (3) transforming the data into meaningful, actionable information; (4) communicating this information back to the appropriate parties; and (5) performing associated research activities. Lag metrics tend to be those items which are reported to payors and administration as quality indicators as commonly seen on websites rating the quality of healthcare providers, hospitals, and systems. They can also be financial in nature. Cost accounting is also an important function of the metrics/ research team. Lead metrics are the meaningful, actionable data which impact the lag metrics. Discerning what is important from the millions of points of data and appropriate lead metrics is where data analysis becomes valuable. The lead metric data is not useful to the healthcare provider unless it is placed in context to baselines, expected outcomes, benchmarks, and actionable options to assist the PSH teams in making decisions. Providing appropriate communication is also important as the balance of benefit versus detriment has to be constantly addressed. The metrics/research team functions like an internal research operation. As such, IRBapproved studies and grant acquisitions are natural extensions of this team, as is grant writing and funding.

Geriatric Focus

It is predicted that by 2030 in the United States, almost 20% of the population will be over the age of 65, and this age group will consume approximately 50% of the US health-care budget. Surgical complications are one of the most expensive, preventable aspects of this cost. The most common complications in the surgical geriatric patient are pulmonary (7%), cardiac (12%), and neurologic (15%) [10]. Given this data, it is apparent why the geriatric population has been the most appropriate target for most of the PSH initiatives to date. Orthopedic surgery in particular has lent

itself to surgical home techniques given the vulnerable patient population and long-term impact on quality of life.

While increasing physiologic age confers added risk [11], it remains apparent that comorbidities and type of surgery confer a greater risk [12]. As we transition philosophically from concentrating on mortality to considering morbidityassociated quality of life, risk stratification becomes increasingly important in preoperative decision-making in regard to choosing the right surgery or surgery at all. Frailty is increasingly becoming recognized as an independent risk factor and a target for many surgical home initiatives. According to the National Surgical Quality Improvement Project (NSQIP) database, 7.4% of patients from home undergoing elective vascular procedures did not return home, with frailty conferring a twofold increase in nonhome discharge [13]. The majority of patients undergoing joint replacements are elderly, and in this population, frailty confers increased risk of 1-year mortality, admission to an intensive care unit, length of stay, readmissions, and discharge to institutional care, thereby increasing costs and decreasing quality of life [14]. Preoperative assessment in a PSH could initiate components of prehabilitation to mitigate risk as well as coordinate planning for discharge with the patient and potential caregivers.

A large number of older patients who suffer a hip fracture have a significant loss of mobility and decrease in ADLs as well as change in where they live and other social impacts [15–17]. In the current environment, there are economic and quality pressures to decrease length of stay. Given the risk of loss of mobility and functionality, rehabilitation is a crucial part of long-term recovery. However, inpatient geriatric rehabilitation, while effective, can be costly and require a longer LOS. Utilization of aggressive home, multidisciplinary, rehabilitation services has had variable results with some studies showing a decrease in length of stay and improved ability to perform ADLs and decreased burden on caregivers, while others have shown no difference [18-21]. Additionally, models of early transfer to an intermediate care facility after acute hospitalization of geriatric patients have not been shown to decrease the number of days living at home during a year, but in orthopedic patients it may increase mortality [22, 23]. The variability in outcomes may be related to differences in baseline patient characteristics such as presence of dementia and differences in resources for a particular healthcare system in terms of inpatient versus home rehabilitation. This variability is the perfect opportunity and example of how a Perioperative Surgical Home could tailor the care for an individual patient in a particular system by assessing underlying risk and advising appropriate rehabilitation and discharge planning.

In developing a model of best teams, there is variability in the perioperative team members. Geriatric patients have a history of being particularly vulnerable and may be the "orphan" on a ward or in a preoperative clinic. The PSH allows for an opportunity to gather expertise in the care of specialized patients. The VA (Veterans Administration) has instituted a robust medical home that uses patient-aligned care teams in which the registered nurse (RN) care managers provide continuity and coordination of care. The aging veteran population, much like the general population, faces increasing disability from chronic illness, cognitive decline, and increasing functional dependence in the last few years of their lives. Healthcare in these scenarios is often accessed during a crisis, at an emergency room or at fragmented multiple specialists' visits. Implanting an onsite geriatrician and geriatric RN manager increased detection of dementia, decreased subspecialty clinic visits while maintaining primary care clinic visits, increased phone call contacts, and increased facilitated planned transitions [24]. Integration of a specialist in geriatrics may similarly augment thoughtful care coordination for a vulnerable patient population. This concept has been implemented in a number of different models including inpatient comanagement by a geriatrician with positive results including a decrease in LOS and delirium rates [25-27].

Patient-centered care and shared decision-making are other venues that are considered "low hanging fruit" for a geriatric surgical home. Elderly patients are at increased risk for postoperative complications not related to surgical sites, and when they do have complications, there is elevated risk of long-term and short-term mortality. For example, patients older than 66 years old who are on mechanical ventilation for greater than 96-h post-surgery have a fourfold increase in 30-day mortality. If they survive the traditional 30-day mark, they still have a fourfold increase in 1-year mortality with almost half dying at 1 year and significantly more living in a skilled nursing facility [28]. This in conjunction with the general feel that older patients, particularly those with chronic illnesses, have a tendency to emphasize quality of life over quantity provides an opportunity for informed discussion [29, 30]. Perioperative care coordination should include a detailed discussion prior to surgery with the patient and surrogate decision-makers in terms of likelihood of quality of life return. Discussion around specific scenarios such as prolonged ventilatory support needs to be conducted preoperatively which could mitigate some of the conflict and stress around decision-making after the operation.

PSH Techniques

To quote H. James Harrington: "Measurement is the first step that leads to control and eventually to improvement. If you can't measure something, you can't understand it. If you can't understand it, you can't control it. If you can't control it, you can't improve it." The PSH uses a multitude of techniques to achieve its quality improvement goals. Most institutions do not have the resources to try to acquire data and perform full overhauls of their perioperative systems. Their cost-effective pragmatic approach has been to choose a few service lines from which to learn how to capture the right data, analyze it, and make improvements. Based on the successes of these pilot projects, extrapolations can be made to the general perioperative processes when appropriate.

Data analysis is the key to providing the measurements, understanding, and decision-able options in order to improve the perioperative care. Acquiring data either from electronic health records or paper documentation and compiling it into usable information are a challenge for every institution. Data marts housed on separate computer servers have been advocated as the number crunching analysis of millions of points of data tend to slow down electronic medical record systems.

Six Sigma and Lean Management are two quality improvement concepts which share similar methodologies and tools. Six Sigma's focus is on reducing variability and eliminating defects, while Lean Management's focus is on eliminating waste and improving efficiency. Both use dozens of statistical tools as well as defined methodology to achieve their goals. Having access to talent and experience in both methods can facilitate change and improve value.

Aggregate of marginal gains is a term made popular by the British Olympic cycling team as they cruised to multiple medals in the 2012 Olympic Games. The concept is to combine small gains in multiple areas (which by themselves would be individually insignificant) to achieve a significant improvement, especially over time. One of the challenges to this method is doing valid statistical analysis on moving variables. The ERAS protocols implemented in Europe can be considered medical examples of both "low hanging" fruit and aggregate of marginal gains.

Actuarial science is seldom thought of outside of insurance companies. Many of the statistical and mathematical models used in actuarial science can assist in determining which parts of a process will provide the greatest benefit or return on investment. These benefits are not only in terms of financial concerns but also patient return to health and satisfaction with the care they have received. Since there are finite resources available to apply in improving any process, choosing the most appropriate places to apply these resources is important.

Morphomics

A relatively new area of research has been in the area of morphomics in which the morphological human features are examined as they relate to surgical outcomes. It has been shown that muscle mass is a more important feature of outcomes than is age after surgical stress for predicting mortality and length of stay [31]. This has been intuitive to most

Table 5.1	Significant components of morphometric age

Total psoas area
Average psoas density
Paraspinous muscle area
Paraspinous muscle density
Bone mineral density
Abdominal aortic calcification
Gender
Height
Weight

practitioners who perform an "eyeball" test. When giving report from one anesthesiologist to another during a care handoff, it is not uncommon to report that the patient is 50 years old going on 80 or 70 years old going on 40 with reference to physiologic age by practitioner assessment. This rough assessment in now being analyzed into a morphometric age. Englesbe has identified several significant components of morphometric age (Table 5.1) [32].

Though still in its infancy and needing more studies for corroboration, this concept holds much promise in redefining how we approach risk stratification and assessment of physical status and prehabilitation regimens.

ERAS

Enhanced Recovery After Surgery (ERAS) began as an idea about multimodal surgical care from Henrik Kehlet, from the University of Copenhagen in Denmark in the 1990s. It achieved application in the early 2000s from an international European study group which instituted multimodal, comprehensive care for surgical patients using evidencebased medicine to standardize practices. Success was achieved in reducing complications and improving outcomes in colorectal surgery [33]. Since then, an ERAS society has been formed, and multiple publications have appeared in several surgical service lines such as colorectal, gynecologic oncology, bariatric, pancreas, cystectomy, breast reconstruction, hip/knee replacement, kidney transplant, and esophagogastrectomy.

As ERAS evolves, the distinction between it and PSH blurs. ERAS began as an intense examination of the narrow perioperative period with a heavy emphasis on the intraoperative details. Since then, the scope has broadened more intensely into the preoperative preparation of the patient and postoperative follow-up. Analysis is moving from published evidence-based medicine to analysis of collaborative databases for improvement of protocols, much like the PSH models do. Evidence-based protocols have been the cornerstone of ERAS systems, and decreasing deviation from the ERAS protocols has been shown instrumental to increasing the value of the perioperative experience.

Precision Medicine

Even though deviation from ERAS protocols is discouraged, it must be understood that not all patients fall in the middle of the Gaussian curve and will not respond to the protocols as predicted. Understanding what makes these patients unique, being able to identify them when they appear in the process, and then choosing what alternative pathway to take are the cornerstones of precision medicine. Geriatric populations not only bring their genetic variation to perioperative process, but their individualized goals, disease states, and socioeconomic variables also contribute to skewing them from the middle of the curve. An effective PSH is intended to improve value to all patients, no matter where they fall on a curve.

Conclusion

The Perioperative Surgical Home while in its infancy in many ways is a concept trialed under different names for decades with the goals being to improve patient outcomes and satisfaction while decreasing costs. This can be achieved by decreasing variability, utilizing multidisciplinary teams, coordinating care across the continuum, and engaging the patient in the process. Geriatric patients serve as the prime population to benefit from these concepts given their increased risk and cost due to their comorbidities, increased concentration on quality of life, and the magnitude of impact of a "simple procedure." With increasing operative and nonoperative procedures being performed in these patients, development of rigorous programs utilizing concepts of the PSH will improve care into the future.

Areas of Future Research

While various components of the PSH have been utilized and studied for a long time, the field as a whole is in its infancy so there is a vast space for future research. Further definition is needed around patient risk stratification and assessment whether it be in traditional areas, morphometrics, or precision medicine. In the area of ERAS or other bundles of best practice research around best implementation techniques, further definition of which individual elements of a bundled pathway have the biggest impact will allow for more thoughtful decision-making around implementation. Refining communication strategies with geriatric patients on goals and engagement in the surgical home may mitigate overutilization. Finally, a large area of research would thoughtfully evaluate the financial and patient outcome impacts of implementation of these pathways.

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Improving Perioperative Functional Capacity: A Case for Prehabilitation

Francesco Carli and Guillaume Bousquet-Dion

The Metabolic Cost of Surgery

Surgery represents a major stressor for elderly patients, and the outcome includes loss of muscle mass, autonomic deconditioning, poor oxygen delivery, cognitive disturbances, and sleep disorders. As people are living well into their late 1970s and early 1990s, the prevalence of many conditions requiring surgery is increasing, and, as a result of improved perioperative care and advances in surgical techniques and anesthesia, a higher number of older patients undergo major surgery [1]. The annual rate of surgical interventions during the last three decades has almost doubled for men and women 75-84 years of age compared to the middle-aged population. However, elderly patients generally unfit, frail, and with significant comorbidities tend to have more postoperative complications and a longer convalescence than younger patients. In fact, surgical morbidity and mortality increase with advancing age and rise sharply after the age of 75 [2].

It has been reported by the National Cancer Intelligence Network of England that, contrary to our expectations, the rate of surgical procedures for cancer declines sharply after the age of 70, indicating a decline in access to cancer surgery [3]. One of the reasons proposed for this reduction in surgical access might be the decrease in physical function with advancing age; therefore there is an expectation that it might not be worthwhile to intervene in view of the possible burden during the recovery period which can lead to poor quality of remaining life. Denial of surgical care might be preventable if the physical status of older, more frail patients could be improved.

Surgery and Loss of Functional Capacity

Hospitalization and surgery cause deconditioning which can be defined as the multiple changes in organ system physiology that are induced by inactivity and reversed by activity. Processes which contribute to deconditioning as individuals age include changes in body composition and function, loss of muscle mass and strength, demineralization, loss of aerobic capacity, loss of vasomotor stability, and changes in respiratory function [4]. During hospitalization, elderly patients tend to spend more time in bed, which is associated with negative impacts on muscles, bones, and cartilages and to the cardiovascular system. As a result of surgery, breakdown of proteins is accelerated, thus releasing amino acid nitrogen, primarily used to build proteins in visceral tissues and other organs [5]. The loss of lean body mass is directly related to the intensity of the surgery, and in elderly this leads to deconditioning which can prolong the convalescence period. The combination of preoperative medical comorbidities and other risk factors such as poor physical and nutritional status, together with surgery, promote a cascade of events which represent the metabolic response to stress, having ultimately an impact on short- and long-term aspects of recovery and quality of life.

Minimizing the Impact of the Stress Response

It is likely that the stress response to injury developed in order to allow animals to catabolize stored substrate, retain fluids, and survive without food until healing occurred [6]. While some inflammatory response is needed for tissue healing, attenuating the degree of the stress response is a key strategy for improving surgical outcomes. Perioperative care is a complex intervention made up of multiple smaller interventions provided by multiple clinicians in the preoperative, intraoperative, and postoperative phases, each of which may accelerate or delay recovery and contribute to morbidity.

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Enhanced recovery after surgery (ERAS®) programs are multidisciplinary care pathways that integrate multiple evidence-based perioperative interventions into a cohesive plan [7]. Minimally invasive surgery is a major component of the ERAS as it mitigates the inflammatory response and reduces the pain of the incision. However, when implemented as a sole intervention, it does not significantly modify outcome [8]. Similarly, preoperative carbohydrate drink and early feeding appear to have a beneficial impact on perioperative insulin resistance, thus decreasing the metabolic cost of surgery and accelerate recovery, but their impact on general outcome is for now limited [9]. Furthermore, revising clinical practice such as the insertion of drains, the use of nasogastric tube, and the mechanical preparation of the bowel has highlighted how important it is to challenge some of the surgical dogmas and the need to reorganize perioperative care [10]. Although more than 20 elements of the ERAS program have been proposed to impact postoperative outcome, it appears that some of them such as early feeding, multimodal analgesia, minimally invasive surgery, and early mobilization remain the most important ones [11]. A metaanalysis of 38 randomized trials concluded that ERAS programs reduce the risk of complications by about 30% and are associated with reduced hospital stav by about 1 day overall and no increase in readmissions [12]. However, there is limited information about preoperative optimization and postdischarge functional recovery, an outcome of importance for patients and clinicians. Specifically, little is known on the postoperative effects of improving physical capacity preoperatively.

Strategies to minimize the effect of the surgical stress response and metabolic deconditioning and accelerate the return to baseline levels of functional capacity have also focused on the postoperative period as part of various rehabilitation programs such as specific exercises after breast cancer surgery, aerobic exercises after cardiac surgery, swallowing exercises after oral cancer surgery, and strengthening exercises after hip and knee arthroplasty. However, this period might not be the most appropriate time to intervene as many elderly patients are tired, unwilling to be engaged in activities which make them fatigued, and depressed while waiting for the results of pathology and the adjuvant treatment they might need. Patients appear to receive little advice when they go home on how to be active, thereby potentially prolonging the recovery period.

Preventing the decline in older frail patients in anticipation of surgery should focus on restoration of function and increase of physiological reserve. Although many older patients going for surgery are not apparently frail or functionally impaired, those who are more vulnerable to the surgical stress need appropriate screening as they are at higher risk of experiencing postoperative complications, leading to prolonged hospitalization, disability, and risk of mortality. Therefore, preoperative intervention aimed at decreasing the risk of postoperative deconditioning can be a valuable method, thus leading to better outcome and less social burden [13].

It is reasonable to assume that increasing patients' functional capacity through increased physical activity prior to surgical admission (as opposed to after the operation) would allow them to retain a higher level of functional capacity over their entire surgical admission, with an increase in quality of life.

The process of enabling patients to withstand the stress of surgery by augmenting functional capacity is termed *prehabilitation* (as opposed to rehabilitation, which is enhancing functional capacity after an injury or post-surgery) [14, 15]. Such an approach would facilitate the postoperative recovery process and achieving a minimal level of functional ability earlier than patients who remain inactive through the entire surgical admission (Fig. 6.1).

Surgical Prehabilitation

Prehabilitation is an attractive care strategy for the older population as it aims to increase functional capacity during the preoperative period in anticipation of the upcoming stress of surgery and the metabolic cost of recovery. It begins in the preoperative period and is part of an integrated enhanced recovery after surgery (ERAS) program which include best intra- and postoperative practices to attenuate surgical stress, encourage patient autonomy, and preserve function. The importance of education and empowerment cannot be understated. Treatment of coexisting medical conditions includes glycemic control, anemia and malnutrition correction, and smoking and alcohol cessation [7].

Assessment of Functional Reserve

Evaluation of physiological status and identification of agerelated diseases, rather than chronological aging itself, should be the focus for preoperative assessment of the elderly population and for planning perioperative care. To optimize organ function in preparation for surgery, the functional reserve has to be assessed and the specific disease process within each organ system identified. Functional reserve is not only limited to the physical status but also includes nutritional, metabolic, and mental components. Therefore, the functional reserve represents a safety margin that may be needed to meet increased demands for cardiac output, carbon dioxide excretion, protein synthesis, immune responsiveness, etc. Since the functional reserve decreases with age, any organ system dysfunction places the elderly population at risk [13]. When analyzing components of mortality in the

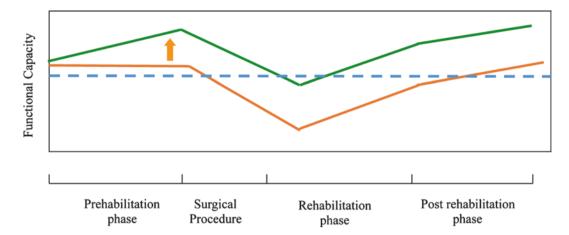


Fig. 6.1 The red line represents the trajectory of functional capacity for patients receiving usual care which doesn't include a preoperative exercise and nutrition program. The green line represents the trajectory of patients who participate in such an intervention. The dotted blue line is the threshold of independent mobility. It is notable that both groups

deteriorate as a result of surgery and hospitalization, but the prehabilitation group reaches baseline functionality faster and spends less time below the independency threshold than the usual care group (Based on data from Ref. [13])

elderly population, the probability of death from cardiac, vascular, and pulmonary causes increases dramatically in the oldest fractions of the geriatric group, while malignancy and metabolic disorders play a lesser role [16]. There is strong evidence that older adults who are physically active, in good nutritional state, and with adequate mental function have higher levels of functional health and lower postoperative complications [17].

Limitations in aerobic capacity have repeatedly been shown to affect outcomes. Diminished peak oxygen uptake (VO2 $_{Peak}$) and oxygen uptake at anaerobic threshold (AT), as assessed by cardiopulmonary exercise testing (CPET), have been identified to increase risks of postoperative mortality and morbidity after major surgery [18–20]. These factors may well influence access to surgery in this age group, a view that the elderly are unable to withstand the rigors of major surgery and contribute to the steep decline in survival rates after the age of 70 years seen in most cancers. Bowel cancer 5-year survival is 65% in 60–69-year-olds, while in the over 80-year-old age group, 5-year survival drops to 43% [21].

Enhancing Physical Status Through Exercise

A structured exercise program is the central component of prehabilitation. The premise is that repeatedly exposing patients to the physiological stress of physical activity will improve reserve and allow them to tolerate surgery better. Participating in regular physical activity has been shown to decrease mortality and risks of developing chronic conditions such as diabetes mellitus, cardiovascular disease, chronic lung disease, Alzheimer's disease, and most types of cancers. Studies in colorectal cancer survivors found that physical activity may decrease cancer recurrence and mortality [22]. The US Department of Health and Human Services guidelines recommend that older adults should perform at least 150 min per week of moderate-intensity or 75 min of vigorous-intensity physical activity to have substantial health benefits (Table 6.1). It is also recommended that aerobic activity should be spread throughout the week with sessions of at least 10 min and be accompanied with muscle strengthening exercises [23].

Exercise decreases inflammation, increases aerobic capacity, improves insulin sensitivity, increases the ratio of lean body mass to body fat, decreases sympathetic reactivity, improves mood, and decreases anxiety [13]. For optimal results, a presurgical exercise program should consist of both resistance and aerobic training and be supplemented by flexibility exercises. It has been shown that aerobic and resistance training in elderly patients increases muscle strength and endurance, favors weight loss, reduces incidence of falls, and increases range of motion in a number of joints. Of course, one type of exercise does not fit all, and personalization of the exercise intervention is necessary to achieve success without harm. In terms of defining the specific exercise requirements of an effective prehabilitation program, it must be pointed out that there is a difference between physical activity and exercise: physical activity can be defined as any body movement produced by skeletal muscle that results in a measurable energy expenditure. Exercise encompasses regular physical activity that is incorporated into a planned and structured program for the specific goal of improving fitness, that is, enhancing aerobic and anaerobic capacities, strength, and balance. In the case of prehabilitation, a structured program that specifies exercise intensity, frequency, and

Table 6.1 Physical activity guidelines for older adults

Key guidelines for older adults (2008 physical activity guidelines for Americans)

The following guidelines are the same for adults and older adults:

- All older adults should avoid inactivity. Some physical activity is better than none, and older adults who participate in any amount of physical activity gain some health benefits
- For substantial health benefits, older adults should do at least 150 min (2 h and 30 min) a week of moderate-intensity or 75 min (1 h and 15 min) a week of vigorous-intensity aerobic physical activity or an equivalent combination of moderate- and vigorous-intensity aerobic activity. Aerobic activity should be performed in episodes of at least 10 min, and preferably, it should be spread throughout the week
- For additional and more extensive health benefits, older adults should increase their aerobic physical activity to 300 min (5 h) a week of moderate-intensity or 150 min a week of vigorous-intensity aerobic physical activity or an equivalent combination of moderate- and vigorous-intensity activity. Additional health benefits are gained by engaging in physical activity beyond this amount
- Older adults should also do muscle-strengthening activities that are moderate or high intensity and involve all major muscle groups on 2 or more days a week, as these activities provide additional health benefits

The following guidelines are just for older adults:

- When older adults cannot do 150 min of moderate-intensity aerobic activity a week because of chronic conditions, they should be as physically active as their abilities and conditions allow
- Older adults should do exercises that maintain or improve balance if they are at risk of falling
- Older adults should determine their level of effort for physical activity relative to their level of fitness
- Older adults with chronic conditions should understand whether and how their conditions affect their ability to do regular physical activity safely

Adapted from Services DoHaH. [23], published by the US Department of Health and Social Services

modality is the goal [24]. The aerobic exercise prescription is based on the American College of Sports Medicine (ACSM) Guidelines for Exercise Testing and Prescription [25]. Training intensities are based on percentage of heart rate reserve (HRR) calculated with the Karvonen formula (target heart rate = [(heart rate_{max} - heart rate_{rest}) \times %intensity] + HR_{rest}). Individuals who are classified as having low initial fitness will show improvements in functional capacity with training intensities that produces heart rates above their resting rate. It is recommended for them to start exercising at an intensity of 55% of heart rate reserve (HRR), which, in a 75-year-old adult with a resting heart rate of 55, would correspond to a target heart rate of 105 beats per minute. Another tool to assess exercise intensity is the Borg scale, or rating of perceived exertion (RPE) scale. It is a visual scale on which patients are asked to rate how intense they felt their effort from 6 (being no perceived effort) to 20 (being maximal exertion) [26]. Moderate intensity would be quantified as 12–14 on the RPE or 50–70% of HRR and vigorous intensity 15–17 or 70–85% of HRR.

Age-related declines in muscle strength are directly related to sarcopenia (loss of skeletal muscle mass). Since total muscle cross-sectional area decreases by 40% between the ages of 20 and 60 years, strength training should be implemented to prevent this decline. Thus, strength training should be implemented in elderly people because of its positive effects on their functionality, health, and quality of life [24]. If elderly people are properly supervised, shown how to use the equipment, and taught the appropriate techniques, then there is no reason why weight training should not be implemented given the huge potential benefit that certainly outweighs any minimal risk. In general, individuals who have been the least fit and the most sedentary show the most improvements when they initiate an exercise program. Since their physiologic reserve is limited, even small amounts of physical training can yield significant improvements.

Prescribing Exercise According to the F.I.T.T. Principle

Great care must be taken in designing an exercise program for seniors, as only 30% of individuals over the age of 65 years old regularly participate in physical activities [27]. The F.I.T.T. principle is the basis of a structured exercise program, and its acronym stands for the four important parameters to define when prescribing such a program [25]:

- Frequency How often is the patient going to exercise Recommendations are that aerobic activities should be performed at least three times per week to generate health benefits. Strength training should be done 2–3 times per week and have a resting day in-between to allow for muscle recuperation and prevent injuries.
- 2. Intensity How hard is the patient going to exercise

To benefit the most from an exercise program, its intensity should be higher than what the patient already does. For sedentary older adults, aerobic training can be initiated at moderate intensity (12–14 on the RPE, 50–70% of HRR), while more active individuals can start at a more vigorous level. Strength training should be done at an intensity at which it is possible to do 2 or 3 sets of 8–12 repetitions of an exercise, but at the end of which, it would be difficult to perform an additional repetition.

3. *Time – For how long is the patient going to exercise*

The goal is for patients to do 75 min of vigorous intensity, 150 min of moderate intensity, or an equivalent mix of both exercises per week. The duration will change according to the aerobic exercise modality chosen (brisk walk, jogging, biking) and the intensity of the strength training, with patients doing less intense exercises having

	Frequency	Duration, intensity, and RPE for weeks 1-2	Progression
Warm-up	Before every session	30% HRRPostureDeep breathingJoint range-of-motion exercises	NA
Aerobic training	Mon, Wed, Thu (steady-state aerobic training)	20 min, 50% HRR, 12 RPE	Progressive up to 65% HRR, 15 RPE
	Sat (aerobic intervals)	24.5 min total or seven sets of 30 s at 85% HRR, 15 RPE + 3 min rest between sets at 35% HRR, 10 RPE	Progressive up to 12 sets of 1 min at 85% HRR, 16 RPE + rest
Resistance training	Tue	 45 min, 60% of 1RM (15 reps per set), 1 min rest between sets, 3 sets per exercise, 14 RPE Lower body multi-joint: machine leg press, machine hamstring curl, lunges Upper body multi-joint: machine bench press, upright-seated row, push-ups or modified push-ups, machine or dumbbell military press Upper body single-joint: front deltoid raise with books, dumbbell biceps curls, sit-ups (abdominal crunches) 	Progressive up to 50 min, 85% of 1RM (six reps per set), 1 min rest between sets, four sets per exercise, 17 RPE
	Fri	 45 min, 60% of 1RM (15 reps per set), three sets per exercise, 14 RPE Lower body multi-joint: step-ups, machine hamstring curl, lunges Upper body multi-joint: machine incline bench press, push-ups or modified push-ups, latissimus pull-down, seated row Upper body single-joint: triceps extension, barbell biceps curl, sit-ups (abdominal crunches) 	Progressive up to weeks 9–12: 50 min, 85% of 1RM (six reps per set), 1 min rest between sets, four sets per exercise, 17 RPE
Flexibility		Stretches of about 20–30 s for each muscle group	

 Table 6.2
 An example of an exercise program

Adapted from Gan et al. [28], with permission from Professional Communications Inc

HRR heart rate reserve, RPE rating of perceived exertion (Borg scale), 1RM one-repetition maximum

to do them for longer than patients performing more intense ones to achieve the same health benefits.

4. Type – The sort of exercises the patient is going to do

Any type of activity that increases a patient's heart rate counts as aerobic activity and has cardiovascular benefits. Choices include walking, jogging, biking, and dancing. Strength training can be done with any device that generates resistance to movement, such as elastic bands, dumbbells, free weights, machines, or own body weight (calisthenics). Resistance training should be composed of eight to ten exercises targeting major muscle groups of the arms, shoulders, chest, back, abdomen, hips, and legs. Additionally, it is recommended that older adults perform balance exercises such as sit to stand and backward, side, heel, and toe walking. The choice of exercise modality should be tailored to patient preference and comorbidities.

Another important element in the implementation of a personalized exercise program is to identify when and how exercise progression should occur to maximize functional status improvement over a short period of time. Exercise intensity should be increased to match the increase in fitness, for instance, when a patient doesn't reach their target heart rate or RPE target when performing the prescribed exercises. For example, for aerobic training, walking speed or incline can be increased, and for resistance exercise, weight or number of sets and repetitions could be increased. As for balance exercises, they could initially be done with the help of a stable support with progression to no support [23]. See below (Table 6.2) an example of an exercise program.

Step counting devices (accelerometers and pedometers) offers an opportunity to monitor and encourage daily ambulatory activity, particularly in the elderly, although it is not clear what amount is required according to the public health guidelines. It is recommended that with a daily background of 5,000 steps/day (which can be too high for some older adults and special populations), 7,000 steps will include a target of achieving 30 min of moderate-to-vigorous physical activity.

The Role of Nutrition in Enhancing Functional Reserve

The nutritional aspect of aging has lately received more attention in view of the strong relationship between malnutrition and poor postoperative outcome. In addition, there seems to be a better understanding of the synergy between physical activity and protein intake. Early studies into the role of protein turnover in age-related sarcopenia reported that muscle wasting in the elderly was due to a decline in basal rates of muscle protein synthesis, elevated rates of muscle protein breakdown, or a combination of the two processes resulting in a negative protein balance [29, 30]. The elderly are less able to utilize amino acids for muscle protein synthesis, and this can be explained by some sort of anabolic resistance of elderly muscle to a physiological dose of amino acids. Thus older muscles appear to be blunted in their capacity to mount a robust response to resistance exercise similar to the one achieved by a young person [31]. The superimposed stress of surgery and the elevated state of insulin resistance make the blunted anabolic sensitivity to low doses of amino acids even greater. A dietary plan that includes sufficient high-quality protein per meal will provide sufficient essential amino acids, particularly leucine, which is needed to elicit muscle protein synthetic response and accretion of muscle protein. The addition of resistance exercise to an intake of high dose of proteins favors muscle mass buildup and will improve strength and physical function [32].

Nutrition Counseling and Supplementation as a Complementary Intervention

Many elderly arrive to surgery poorly nourished. Malnutrition can be defined simply as "bad nutrition." More specifically, it arises from inadequate intake and/or metabolic and inflammatory changes that alter nutrient requirements or absorption, which, ultimately, leads to wasting and diminished physical function [33]. Malnourished patients have been found to suffer increased morbidity, longer hospital stay and readmissions, prolonged surgical recovery, and poorer quality of life. Moreover, recent North American surgical consensus recommendations suggest moving beyond treating malnutrition to preventative preoperative nutrition therapy in all at-risk patients to potentially mitigate any malnutritioninduced complications throughout the perioperative period [34]. As a result, early identification of malnutrition risk, for the purpose of eliciting a comprehensive dietary consult, throughout the continuum of care surgical patients is increasingly recognized as a significant component of quality care [35]. A systematic approach to identify and treat patients at risk of malnutrition must be established.

Nutritional Care Plans

Observational evidence suggests that patients with higher preoperative lean body mass (i.e., reserve) are better able to cope with surgical stress as determined by reduced complications and earlier discharge [36, 37]. The primary goal of perioperative nutritional care is thus to promote GI tolerance, enhance immunity, support normoglycemia, and provide sufficient protein to achieve anabolism and sufficient energy to maintain body weight. A combination of both individualized nutrition counseling and oral nutrient supplementation (ONS) has proven to be effective in building functional

capacity in prehabilitation trials [38]. Prehabilitation nutritional care plans are therefore focused on meeting the aforementioned nutritional goals as well as supporting the exercise component of prehabilitation to build and maintain physiologic reserve prior to surgery. After a single bout of resistance exercise, both muscle protein synthesis (MPS) and muscle protein breakdown are simultaneously stimulated in healthy individuals [39]. In order to generate a positive net protein balance in favor of lean body mass accretion, exogenous amino acids must be administered to produce a state in which protein synthesis exceeds that of protein breakdown [40]. Indeed, exercise alone, in the absence of adequate nutrition, will not lead to muscle protein accretion [41] or maximal improvements in functional capacity [42]. Twenty to thirty grams of protein taken immediately after resistance exercise in liquid form is regarded as sufficient to maximally stimulate MPS in healthy individuals [32]. The optimal postexercise diet to support lean body mass accretion in elderly patients is still not known. Finally, supplemental omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are found naturally in fish oils, have been identified in several randomized controlled trials to reduce oxidative stress and inflammation [43]. Prehabilitation nutritional care should also focus on meeting established *dietary* requirements of these essential fatty acids. Attention to nutrition is an important component to prehabilitation primarily because it supports other aspects essential to the improvement of functional reserve (Fig. 6.2).

Assessing Outcome of Prehabilitation

Recently a consensus was reached among a group of surgeons that preoperative exercise is beneficial in the management of cancer patients, and more work in this field should be supported [44]. As prehabilitation encompasses the whole perioperative period and impacts on short- and long-term recovery, constructs must be appropriate. The first assessment should include whether the prehabilitation intervention is feasible. Can a program of prehabilitation be implemented in the present hospital structure? Is there a support for this type of initiative? What are the barriers and the costs? Where should the program be administered? Compliance by participants to the program needs to be assessed together with their level of satisfaction. The second assessment would include performance measures testing the value of the physiological outcome and those measures based on self-reports by the patient. These tests would address whether the intervention (e.g., exercise, nutrition) impacts on aspects of functional capacity, a proxy measure of physical activity and strength.

A. Performance measures test the individual actual performance of an activity in a given environment at a specific

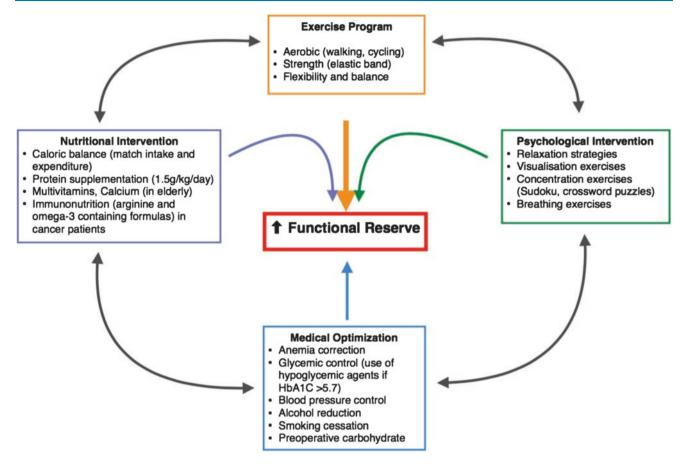


Fig. 6.2 Individual program components are made more efficient with the help of the other components. Moreover, interventions in the different elements of the program can help achieve a goal. For example, the

exercise program, the nutritional intervention, and the use hypoglycemic agents can help to achieve glycemic control (Adapted from Gan et al. [28], with permission from Professional Communications Inc)

time and provide more accurate data than self-reported measures. However, these measures can be inaccurate due to equipment, operator, test situation, individual fatigue, effort, and time of the day. The gold standard assessment of physiological performance is the cardiopulmonary exercise test (CPET) which provides information on the integrated cardiopulmonary and musculoskeletal functions during an exercise gradually increasing in intensity [45]. Other measures of functional capacity that can be used are the 6-min walk test (6MWT), the sit-to-stand test, or the timed up and go test. The 6MWT is a well-validated test which has been shown to correlate to maximum body oxygen consumption and is a measure of force, endurance, and balance [46, 47]. This test can be measured at baseline and repeated after the intervention to determine the change in functional capacity. An increase of 20 meters or more has been shown to be clinically meaningful to patient and clinician [48].

B. Self-reported measures are used mainly in health care facilities and obtained in person or by telephone by

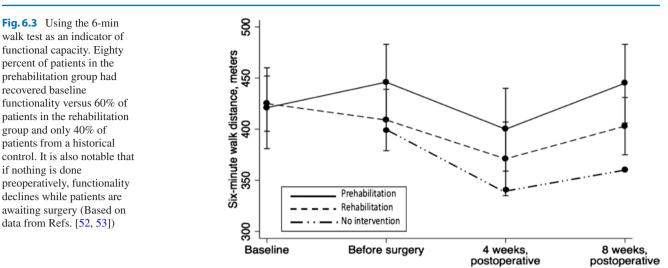
research and clinical personnel. Self-reporting is most useful when assessing subjective items such as pain or energy level which cannot be directly measured. Although self-reporting requires few resources, there is a great likelihood of a low response rate and missed items. However, information on quality of life, physical activity, and social and emotional burden can be obtained in this manner.

The impact of prehabilitation on postoperative outcome can be then examined at 4 weeks after surgery and will include changes in specific performance measures as well as clinical outcomes such as length of hospital stay, complications, and rate of readmission.

Scientific Work on Surgical Prehabilitation

The terms preconditioning, preoperative rehabilitation, and more recently prehabilitation are used to indicate the same concept, preparing patients in the best physiological manner to deal with the incoming stressor. Most of the literature on prehabilitation in humans focuses on cancer whereby both prehabilitation and rehabilitation have been applied as interventions throughout the continuum of cancer care, starting with the initiation of therapy and finishing with palliative care. Several programs have attempted to prepare patients for the postoperative recovery with education tools and positive reinforcement; however little has been published on how to systematically enhance functional capacity before surgery and decrease postoperative morbidity. Interventions before and after surgery focus on either physical activity (aerobic and resistance exercise for lung cancer) or organ-specific exercise (limb exercises for arthroplasty). In addition, surgical prehabilitation tends to be limited to a variable period leading to surgery and in some occasions continuing for a few weeks after surgery. Although most of the published literature on surgical prehabilitation deals with patients of over 60 years of age, none of the studies have addressed the elderly and frail.

Particular attention has been paid to orthopedic surgery (hip and knee arthroplasty); however other surgeries studied include cardiac, vascular, abdominal, and pelvic. The focus on using exercise as a major intervention in the surgical prehabilitation programs has been based on the well-known primary role of exercise in disease prevention, and the benefits of physical activity have been shown in many medical conditions, such as hypertension, stroke, coronary artery disease, diabetes, and COPD. Regular exercise improves aerobic capacity, decreases sympathetic over-reactivity, improves insulin sensitivity, and increases ratio of lean body mass to body fat. Exercise training, particularly in sports medicine, has been used as a method of preventing a specific injury or facilitating recuperation. The application of preoperative exercise training to the surgical specialties has been slow to gain acceptance; however, there is emerging interest in studying how exercise can influence postoperative recovery and disease progression. By increasing the patient's aerobic capacity and muscle strength through increased physical activity before surgery, physiologic reserve would be enhanced, the body would be in better condition to attenuate the negative aspects of surgery, and postoperative recuperation would be facilitated. Three systematic reviews [49–51] of fair to good methodological quality involving less than 500 patients showed some effectiveness of 4-8 weeks of preoperative exercise therapy in reducing postoperative complication rates and accelerate discharging from hospital in patients undergoing cardiac and abdominal surgery. Conversely, the outcome after joint arthroplasty and in particularly knee arthroplasty was not significantly different whether exercise was used or not [49]. The second systematic review examined 15 studies and concluded that totalbody prehabilitation improved postoperative pain, length of stay, and physical function, but it was not consistently effective in improving health-related quality of life or aerobic fitness in the studies that examined these outcomes [50]. Another systematic review of eight studies reported some physiologic improvement with preoperative exercise but with limited clinical benefit. Overall there were several limitations with some of the studies, and the exercise regimens were not always structured and were also of different intensity. Finally, the adherence to the exercise programs was not systematically reported. Although some physiologic improvement during the preoperative period was shown in most of the studies, this change did not consistently translate into improved clinical outcomes [51]. In view of the paucity of studies in abdominal surgery, the impact of 4-week, homebased, high-intensity structured exercise was compared with a sham intervention based on walking and breathing in a 2010 study [42]. Unexpectedly, the control group performed better than those who engaged in intense exercise. A large proportion of these patients' functional walking capacity decreased during the presurgical period. Compliance to intense exercise was recorded at a mere 16%, thus indicating that the prescribed exercise regimen could not be maintained. Predictors of poor surgical outcome included deterioration while waiting for surgery, age greater than 75 years, and high anxiety. These results suggested that an intervention based on intense exercise alone may not enhance functional capacity in elderly patients unless factors such as nutrition, anxiety, and optimized perioperative care are taken into account. This is particularly true when attempting to utilize physical activity as a single modality in patients who lack physiological reserve, such as frail, elderly patients known to have decreased muscle mass and low protein reserve and therefore not able to tolerate an increase in exercise prior to surgery without sufficient protein and energy supplementation. In view of these findings, further studies were conducted, and a multidisciplinary approach was used whereby nutritional counseling and nutritional supplements, relaxation sessions, and deep-breathing exercises were provided together with a moderate exercise program which included aerobic and resistance exercise [52]. In addition, their surgical care was standardized following the ERAS perioperative care guidelines which included smoking and alcohol cessation, glycemic control, anemia correction, pharmacological optimization of medical conditions (hypertension, arthritis, coronary heart disease, metabolic disorders), and intraoperative control of intravenous fluid administration, body temperature, and pain. Such a multidisciplinary protocol was more accepted by patients, with over 70% overall compliance and leading to significant preoperative increased functional capacity and maintained postoperative physical activity. Over 80% of patients receiving prehabilitation had their functional capacity return to baseline values by 8 weeks after surgery, compared to 40% of patients who did not receive the prehabilitation (Fig. 6.3).



Similar to the ERAS program, prehabilitation requires a multimodal approach whereby different stakeholders need to be engaged in preparing patient for surgery. Therefore, internists, surgeons, geriatricians, anesthesiologists, nutritionists, kinesiologists, and hospital managers should all be involved.

Considerations for Effective Prehabilitation

Who Could Benefit and For How Long?

Silver [54] defined cancer prehabilitation as a process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment, includes physical and psychological assessments that establish a baseline functional level, identifies impairments, and provides targeted interventions that improve a patient's health to reduce the incidence and severity of current and future impairments. This implies that any prehabilitation program needs to be structured and customized to the patient by taking into consideration the type of surgery, patient's current health status, and state of the disease. In the cancer rehabilitation conceptual model, surveillance and anticipation of future impairments are essential steps in improving health outcomes and decreasing costs. This is particularly true in older patients who are more prone to comorbidities, have limited functional capacity, and are in need to often undergo elective and emergency surgery.

In view of the potential costs that might be incurred in setting up a multimodal prehabilitation, it would make sense to target population who could most benefit from either unimodal or multimodal programs and have an impact on postoperative recovery. Intuitively, elderly, frail, and those with several comorbidities could be identified and offered multimodal interventions. A recent study showed that elderly patients whose 6 min functional walking distance was below 400 m (a value that would indicate independence and mobility) responded to structured multimodal prehabilitation by increasing their functional capacity between 10 and 15% above the baseline value during the preoperative period and maintained this value after surgery [55].

Although there is a strong evidence of the beneficial effect in initiating the multimodal program before surgery, there is also a benefit in initiating it after surgery if prehabilitation cannot be implemented. It has also been shown that patients who started the same multimodal program after they were discharged from the hospital saw their walking capacity return to baseline values in 60% of patients at 8 weeks after surgery [53]. Sprod et al. [56] examined the prevalence of exercise participation in elderly patients throughout the cancer treatment, and over 60% of them reported exercising 6 months after therapy. Those patients who exercised were less fatigued and reported less shortness of breath. Two recent case reports exist where deconditioned elderly patients underwent multimodal prehabilitation that continued after surgery. One such case is illustrated in Table 6.3. Both recovered well after surgery and had no postoperative complications [57, 58], illustrating that any intervention aimed at increasing functional reserve that begins preoperatively and is maintained throughout the perioperative period can have positive impact on clinical outcomes.

How Long Should Prehabilitation Be?

Some concern has been expressed that enrolling a patient in such a program might put a patient at risk of disease progression, particularly for patients with cancer. There is limited published work on preoperative exercise in elderly cancer patients, especially in a time frame dictated by national can
 Table 6.3
 Case report of a frail octogenarian who received a prehabilitation intervention

88-year-old women scheduled for robotic-assisted total abdominal hysterectomy for endometrial cancer

Past medical history: CAD (post CABG×3 and PCI ×2 post MI), severe MR, moderate AS, CHF, HTN, MCI, 15 kg weight loss in the past year, significant POCD ×2 in the past

Prehabilitation program: 3 weeks of thrice weekly training at home by a kinesiologist focusing on upper and lower extremities training, abdominal breathing exercises, and cardiovascular function improvement. Protein intake was supplemented by 30 g daily of soy kefir

Perioperative course: The surgical procedure was uneventful. Blood loss was minimal, MAP was kept above 75, and the patient received less than 1 L of intravenous fluids over the 3 h robotic-assisted procedure. She stayed in the PACU 4 h and left the hospital on POD 2. Of note, she experienced no postoperative complications including cognitive dysfunction

Postoperative course: The exercise and nutrition program was resumed by the patient at home 1 week after the surgery. Outcome measures included the RBANS for cognitive function, the 6MWT for functional capacity, and the SF-36 for health-related quality of life, all of which were assessed at start of program and at 4 weeks and 8 weeks after surgery. Her postoperative results were superior to her initial assessment in all fields, especially in the mental health and concentration aspects. Changes in both components of the SF-36 and to the 6MWT are well above previously published threshold of clinically significant difference. She was able to restart reading short newspaper articles, which she hadn't been able to do before. She attributed these improvements to her increased physical activity

	SF-36			RBANS
Time of assessment	Physical component (SD)	Mental component (SD)	6 Min walk test	Total score (percentile)
Initial assessment	33.7 (-0.7)	47.2 (-0.8)	91.2 m	58 (<1)
4 Weeks after surgery	39.6 (-0.1)	45.4 (-1.0)	136.8 m	75 (5)
8 Weeks after surgery	65.3 (1.2)	65.3 (1.2)	144.8 m	81 (10)

Based on data from Ref. [57]

Abbreviations: *PMH* past medical history, *CAD* coronary artery disease, *CABG* coronary artery bypass graft, *PCI* percutaneous coronary intervention, *MI* myocardial infarction, *MR* mitral regurgitation, *AS* aortic stenosis, *CHF* congestive heart failure, *HTN* hypertension, *MCI* mild cognitive impairment, *POCD* postoperative cognitive dysfunction, *RBANS* Repeatable Battery or the Assessment Neuropsychological Status, *SD* standard deviation.

cer waiting time limits [44]. The duration of prehabilitation can vary according to the type of surgery, for example, chronic conditions such as arthroplasty might require 6-10 weeks of exercise to increase muscle strength and balance. The limitation to exercise and training as a result of pain can prolong the duration of time necessary to increase the physical reserve. Provision of adequate analgesia in these patients can expedite the physical preconditioning and increase muscle strength as illustrated by a recent case report of prehabilitation of an elderly patient scheduled for total knee arthroplasty who underwent a radiofrequency block 6 weeks before surgery to relieve pain and who was able to complete the prehabilitation program with earlier recuperation of her functional capacity in the first 2 months after surgery. For patients with cancer, the time frame is more limited, but 4-6 weeks of prehabilitation may be a more acceptable time period to increase physiological reserve [59, 60]. The question remains whether those patients with poor physical condition and functional status who need surgery should wait to be optimized before surgery. There is strong evidence that surgery in these patients represents a serious risk leading to postoperative complications and prolonged recovery [61]. The high rate of postoperative complications and the prolonged length of hospital stay make these high-risk patients more vulnerable and prone to readmission and higher mortality [62].

Prehabilitation as Part of the ERAS Pathway

The development of fast-track surgery has addressed at least some of the pathophysiological elements that have an impact on outcome. The ERAS program attempts to attenuate the stress response with such interventions as the preoperative carbohydrate drink as a metabolic modulator of the insulin resistance and postoperative early feeding and mobilization. Also, the ERAS guidelines at its inception emphasized the role of patient education. Nevertheless, the ERAS guidelines, while emphasizing the notion of risk assessment and risk stratification, have paid little attention to risk attenuation or prehabilitation. For example, considerations of preoperative nutritional, functional, and mental status deserve to be addressed as there is strong evidence these represent independent risk factors of postoperative outcome. Given the aging population, surgeons are going to treat large numbers of elderly patients, and every effort must be done to attenuate the progression toward deconditioning, which, if ignored, results in reduced mobility, functional status, and quality of life. A comprehensive program requires teamwork. Multidisciplinary collaboration can define the most appropriate approach for surgical preparation and reduce unnecessary variability in health care. Such changes require a major transformation in the culture of surgical decision-making and would demand a novel concept of trust, not only between clinicians and patients but also between clinicians of different disciplines. Certainly there are many barriers raised to implementing prehabilitation by those who argue that such teams are resource intensive, interfere with professional independence, and are costly.

Significant Gaps in Our Knowledge on Surgical Prehabilitation

Although the prehabilitation approach has the potential for identifying reversible limitations in the preoperative period and targeting intervention strategies to ameliorate postoperative outcomes, there are still gaps in our understanding on how to identify those patients who would benefit from the prehabilitation program, select the appropriate interventions, determine program effectiveness in the context of a specific type of surgery, and examine the impact on patientcentered and clinical outcomes. Further research is needed on the following aspects: role of different types of exercise in the aged population, importance of nutrition optimization, and psychological stress reduction in order to increase physiological reserve, cost-effectiveness of single and multiple modalities, and short- and long-term impact on clinical outcomes such as length of stay, hospital readmissions, emergency department visits, perioperative complications, and time to rehabilitate. It is encouraging that over 20 clinical trials on such programs are currently underway, implying that health practitioners are interested in supporting this concept.

In summary, we have reached a tremendous amount of knowledge in perioperative pathophysiology and surgical care to be able to modulate effectively the perioperative stress. However, there is a need to develop strategies not only to recognize and assess the surgical risk in the older population but primarily to attenuate the impact on postoperative outcome. The preoperative period is an opportune time to intervene and to reach intensive collaboration between anesthesiologists, surgeons, internists, physiotherapists, and nutritionists and develop a sustained prehabilitation program in the surgical home.

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Care of the Geriatric Surgery Patient: The Surgeon's Perspective

Melissa A. Hornor, James D. McDonald, Daniel A. Anaya, and Ronnie Ann Rosenthal

Introduction

Providing high-quality surgical care for older adults is much more challenging than it is for younger adults, even when the magnitude of the surgical illness is similar. In addition to the increased number and complexity of comorbidities that accompany aging [1], geriatric patients present with a variety of specific age-related conditions, "geriatric syndromes," that create added challenges during the perioperative period and increase the overall risk of postoperative adverse events [2]. Any adverse event can be devastating to the vulnerable older adult. Even treatable complications can cause serious loss of physical and/or cognitive capacity and loss of independence; this may be a worse outcome than loss of life to some older patients [3]. Recent studies have emphasized the relevance of outcomes focused on recovery and maintenance/regaining of independence, among other patientcentered measures, and the increased weight these carry for the geriatric population [2, 4, 5].

While in the past surgeons assumed full responsibility for all aspects of care during the surgical episode, there is now a growing understanding that caring for this complex and challenging population must be a shared effort of a team composed of many disciplines. Starting in the preoperative period, each team member has a unique yet interconnected role

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focused on screening, prevention, and management of geriatric conditions, creating an interdisciplinary environment designed to improve overall outcomes [6]. The surgeon plays a leading role, incorporating valuable input from other disciplines in the decision-making process and during overall care in the pre-, intra-, and postoperative periods. The overall goal of the team is to facilitate functional recovery following surgery by optimizing physical and cognitive function before surgery and during the perioperative continuum. Every team member should strive to minimize the impact of identified risks for surgical complications and promptly identify and treat age-related complications such as delirium, decreased mobility, falls, pressure ulcers, and bowel and bladder problems. Ideally, members of the team should include representatives from internal medicine/primary care/geriatrics, anesthesiology, nursing, social work, and additional services such as pharmacy, physical therapy, and occupational therapy as indicated. The use of these interdisciplinary teams has been shown to decrease mortality, improve function, and reduce hospital length of stay [7, 8]. We present from the surgeon's perspective the important considerations in caring for the geriatric patients in the preoperative, intraoperative, and postoperative periods and the role that various members of the interdisciplinary team play in that setting.

Preoperative Phase

Goals of Care

The Role of the Surgeon

The decision to perform surgery on an older adult is first and foremost based on the patient's healthcare goals, both for the specific episode of care and overall. The need for the surgeon and the whole surgical team to understand these goals cannot be overemphasized. Age-related physiologic decline, combined with multiple medical illnesses, diminish the reserves that the older adult can call on to handle the stress of surgery. Morbidity and mortality rates are markedly higher in geriatric

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patients when compared to younger patients even when adjusting for comorbidities [9]. Functional and/or cognitive decline following surgery can alter the patient's whole way of life. The surgical decision-making process should be addressed in detail by the surgeon in the outpatient setting prior to any elective operation. Input from the patient's primary care provider also can be invaluable in helping to understand the patient's overall health and life goals. In these discussions, it is essential to:

- Ascertain the patient's overall healthcare goals.
- Assess decision-making capacity.
- Describe the potential risks of the operation in terms of the possibility of functional or cognitive decline in addition to standard mortality and morbidity risks.
- Ensure and document that a surrogate decision-maker is identified in the event that the patient becomes incapacitated.

A vital aspect of surgical decision-making process is assuring that the patient's overall health goals align well with the goals of the procedure. Every patient's overall health goal is unique - it could be to live as long as possible, to be made comfortable, or to be able to attend his or her granddaughter's wedding in a month's time. It is essential that the consent process addresses the concordance of the patient's healthcare goals and the goals of the surgical procedure at hand, which is not always the case [10], particularly in emergency situations [11]. In order to ensure the delivery of highquality patient-centered care in critically ill patients in the acute setting, Cooper et al. proposes a structured, standardized approach to shared decision-making that centers around assuring that the patient's goals and values are heard and that palliative treatment options are offered alongside lifeprolonging treatments [11].

Once the patient's goals have been discussed, it is important to determine if the patient has the capacity to make the decision for or against surgery. It is estimated that as many as 26% of medical inpatients may not have capacity for decision-making, making a capacity assessment a vital step in the process [12]. The assessment for capacity is defined in terms of four criteria: understanding, appreciation, reasoning, and expression of a choice [13]. In short, the healthcare provider must assess whether the patient understands the medical procedure and the alternatives, appreciates the consequences of the procedure, and can express their reasoning behind making a particular choice. If the patient cannot fulfill all four criteria of capacity assessment, then it is necessary to identify a healthcare proxy or surrogate decision-maker. Regardless of the patient's capacity, it is prudent to encourage all older adult patients to establish advanced directives and identify a surrogate decision-maker prior to surgery.

Discussions of the risk of surgery usually focus on the chances of complications and death. However, older adult surgical patients are at high risk for postoperative functional and cognitive decline as well. For example, after major abdominal surgery, the estimated average recovery period for previous functional status is 3 months and, for previous strength and conditioning levels, 6 months [14]. Geriatric patients have been found to value functional recovery more than traditional morbidity when compared to younger patients [3]. Therefore, it is pertinent to disccuss the possibility of cognitive and functional decline and the need for discharge to a facility other than home. Nonoperative treatment alternatives should also be discussed in the context of functional/cognitive decline and loss of independence.

It is also essentiacl for all older adults to be offered resources for advanced care planning including formal advanced directives and a healthcare power of attorney or proxy. For high-risk older adults, a physician order for lifesustaining treatment (POLST) form is recommended. A POLST form is a set of medical orders reserved for seriously ill patients, which specifies their expressed treatment preferences, ensuring that the patient's values are upheld in an actionable manner in emergency situations. The POLST form has been shown to be more effective in preventing unwanted life-sustaining treatment than DNR orders [15]. A living will that specifies preferences for cardiopulmonary resuscitation, mechanical ventilation, feeding tubes, intravenous nutrition, hemodialysis, and blood transfusion is imperative in order to deliver care that is aligned with the patient's wants and needs. In contrast to the POLST form, a living will does not directly affect what emergency medical treatments a patient receives, as it is a legal document and not a physician order.

Preoperative Evaluation

The Role of Internist/Primary Care Provider/ Geriatrician or Geriatric Nurse Specialist

The value of including a provider with geriatric expertise during the perioperative period stems from his or her knowledge of geriatric syndromes and experience working with teams in multiple disciplines when caring for the overall health needs of the older adult [16]. Although supporting data for incorporating geriatric specialists is derived from a variety of models of care (see below), this approach has been associated with improved delivery of care as well as decreased costs and better overall outcomes including shorter length of stay, decreased complications, decreased incidence of geriatric syndromes, and overall faster recovery.

A key role for the geriatric specialist is in the preoperative evaluation and preparation phase. The preoperative evaluation should focus on identifying modifiable risk factors that predict adverse outcomes and on engaging the other members of preoperative team in making a surgical plan. The comprehensive geriatric assessment (CGA) is a multidisciplinary diagnostic and treatment process, originally developed by geriatricians, that examines the general health status of the older individual through a series of validated scales and tests. A CGA is a useful method for quantifying risk and identifying opportunities for risk mitigation prior to surgery and has been found to identify those patients who are at high risk for major postoperative complications [17, 18]. Depending on how the acute care model is established, it may be the nurse specialist's role to deliver each of the CGA tools/questionnaires and alert the team regarding abnormalities so that corresponding plans may be activated.

Careful screening for deficits preoperatively will identify those older patients at high risk of adverse outcomes and aid in decision-making. Optimization strategies can then be employed to mitigate the negative impact in the postoperative period. The recommended screening tests are divided broadly into two categories – those related to the "brain," or mental health, and those related to the "body," or physical health.

The brain screens are essential to assess the older adults' overall mental status. Positive screens in this category identify patients at high risk for delirium in the postoperative period. Delirium, an acute and fluctuating change in mental status characterized by inattention and either disorganized thinking or a change in level of consciousness, has been shown to result in poorer functional outcomes and increased morbidity and mortality [19, 20]. The "brain" screens include:

- Cognition
- Depression
- Sensory impairment
- · Alcohol or illicit drug use
- · Chronic pain or opioid use

Cognitive impairment often goes unrecognized in the older adult and is a risk factor for adverse events after surgery, institutionalization following hospitalization, and increased mortality [21, 22]. An estimated 13.9% of individuals in the United States aged over 71 have dementia [23]. A simple example of a screening test for cognition is the Mini-Cog [24] which includes a brief test of memory and a clock drawing exercise to determine executive function. For a more in-depth evaluation, the Mini Mental State Exam (MMSE) [25] or a Montreal Cognitive Assessment (MoCA) [26], among others, may be used.

Depression is not often considered as part of the routine preoperative assessment. However, older adults with depression have been found to have higher rates of functional decline and mortality [27]. The Patient-Health Questionnaire-2 [28] is often utilized for depression screening. The following two questions are asked of the patient, and if either of the questions is answered affirmatively, then further evaluation by a primary care physician or mental health specialist is warranted:

- 1. In the past 12 months, have you felt sad, blue, depressed, or down for most of the time for at least 2 weeks?
- 2. In the past 12 months, have you ever had a time, lasting at least 2 weeks, when you didn't care about the things that you usually care about or when you didn't enjoy the things that you usually enjoy?

Sensory and hearing impairments are common in older adults and have been found to have a negative effect on functional status, social functioning, and mental health [29]. Hearing and vision impairments are also risk factors for postoperative delirium. Ensuring that older adults are provided with the assistive devices for adequate hearing and vision is an essential element of multicomponent interventions for delirium prevention [30].

While not always appreciated, alcohol use is common in the older population and can lead to increased postoperative complications and mortality [31, 32]. Alcohol or other substance use should be identified prior to surgery; the CAGE questionnaire is a quick, evidence-based assessment for alcohol abuse, which asks four questions:

- 1. Have you ever felt you should cut down on your drinking?
- 2. Have people annoyed you by criticizing your drinking?
- 3. Have you ever felt bad or guilty about your drinking?
- 4. Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (eye opener)?

If the answer is yes to any of the four questions, the patient should be referred for preoperative abstinence or medical detoxification if medically feasible [28]. Lastly, it is important to perform a detailed history regarding the patient's past or current opioid use in order to properly formulate a perioperative analgesia plan.

The body screens identify patients at risk for functional decline and loss of independence. They serve to recognize common geriatric syndromes that, if identified, can be optimized (if not corrected) preoperatively. These screens include:

- Frailty
- Function
- Falls
- Mobility
- Multiple chronic illness

- Polypharmacy
- Nutrition

Frailty is "a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, causing vulnerability to adverse outcomes" [33]. The frail older adult is more vulnerable to declines in mobility and disability, multiple hospitalizations, and death [33, 34]. There are numerous screening tools for frailty based on the physical phenotype model [33] or the accumulated deficit model [35]. Positive screens will identify those patients at high risk for adverse events postoperatively and will provide valuable information for patient-centered decision-making and postoperative care.

A physical functional assessment is key to understanding the patient's overall risk for an untoward postoperative event, as functional status has been found to be a strong predictor of nearly all postoperative complications and death [21, 36]. In addition, a functional assessment provides valuable information about the patient's baseline status and their likelihood of further functional decline and a nonhome discharge destination [21]. Physical function can be measured in a number of different ways ranging from self-reported activities [e.g., activities of daily living (ADLs) and instrumental activities of daily living (IADLs)] to real-time tests that measure physical function (e.g., grip strength, timed-up-and-go, etc.) [28]. The frailty assessment described above, while a broader concept focused on identifying overall vulnerability, can also serve to highlight specific deficits in physical function [37]. Regardless of the tool used, decreased physical function has been associated with longer hospital stays, increased risk of complications, and more postoperative pain when compared to patients with better preoperative functional status [38]. Furthermore, in patients undergoing complex general and vascular surgeries, functional dependence is associated with a statistically significant increased risk of mortality, morbidity, and reoperation when compared to functional independence [39].

The Role of the Physical and Occupational Therapist

Involvement of physical therapists and occupational therapists becomes important when deficits in function are encountered. During the preoperative period, a number of studies have examined the role of different interventions focused on optimizing physical function. These range from focused training to more comprehensive exercise and multidimensional programs, often referred to as *prehabilitation*. Although the studies published report on different population of patients and different types of interventions, there is a clear positive impact on physical function, which generally translates to improved outcomes [40]. Falls are common in the geriatric population and are a leading cause of mortality [41]. In geriatric patients who underwent colorectal and cardiac operations, those who had a preoperative fall history were more likely to have postoperative complications, require discharge to an institution, and require readmission to the hospital [42]. Undergoing surgery puts an older adult at a higher risk of falling owing to the side effects of anesthetic agents, increased postoperative pain (with need for opioid pain medications), decreased mobility (with muscular weakness and joint stiffness), and use of multiple other medications that can precipitate orthostatic changes and gait instability. A positive history of a fall in the 12 months prior to surgery indicates a high risk for postoperative fall and warrants further work-up with consideration for preoperative gait and balance training [43] if time allows.

The Role of the Nutritionist

The risk of malnutrition is increased in the elderly patient owing to decreased lean muscle mass, changes in the regulation of appetite and satiety, poor dentition, a decline in smell and taste, and financial constraints, among other factors [44, 45]. Malnutrition should be assessed for by inquiring about unintentional weight loss in the last 6 months; measuring BMI, serum albumin, and prealbumin [28]; and getting a dietary history. If malnutrition, or a risk for malnutrition, is identified, the patient may benefit from referral to a nutritionist for a preoperative nutritional support plan [46] focused on improving the overall preoperative nutritional status [47]. Nutritional therapists can participate by administering and/or interpreting screening tests. If there is not adequate time for nutritional optimization prior to the operation, then a plan must be made to initiate nutrition support early in the postoperative period. In patients who are found to be malnourished or at risk of undernutrition, the use of oral nutrition supplementation is recommended to improve survival [44]. During the postoperative period, one must ensure that the patient has the necessary support in order to eat properly such as dentures, adapted utensils, and correct positioning with assistance at mealtime if necessary.

The Role of the Pharmacist

Older adults often take a significant number of prescription and nonprescription medications, some of which are vital to the daily management of specific conditions and some that are not required and/or may complicate management during the postoperative period. Polypharmacy is defined as the usage of five or more prescription medications [48] and has been found to lead to increased rates of delirium and adverse drug events [49]. A thorough preoperative review of current essential and nonessential medications should always be conducted.

It is also essential to have a plan, established preoperatively, for medication management in the perioperative period, especially when the patient is taking anticoagulants, cardiac medications, psychoactive drugs, or other medications where disruption in dosing may present a serious risk. In circumstances where the complexity of medications received is high or when the patient has (or develops) decreased organ function that requires more detailed dosing (e.g., renal failure), a pharmacist can help guide medication and dose management. The correction and appropriate management of polypharmacy is associated with fewer adverse events including decreased risk of delirium and other cognitive-based deficits during the perioperative period. The American Geriatric Society's (AGS) Beers criteria is a valuable resource for the practitioner to help identify potentially inappropriate medications that should be stopped or changed in the perioperative period if possible [21].

The Role of the Social Worker

A number of studies have established the increased need for post-acute care services among geriatric surgical patients [21, 50]. These vary from continuing health service provided in the home, to institutional discharges (i.e., to nursing homes or, rehabilitation centers) and readmission [2, 4, 5]. In addition to age and postoperative complications, functional decline (both physical and cognitive) and lack of appropriate social support are important drivers of post-acute care needs [2]. Other risk-stratification tools focused on determining the risk of readmission can identify patients likely to require post-acute care needs upon discharge [51]. By carefully assessing the needs and risk, social workers can start working with patients and families during the preoperative period, anticipating these needs and adjusting discharge plans based on the social support. This provides the whole team with critical and actionable information for advanced planning to setup transfers to other institutions for post-acute care and to establish detailed plans for the care transitions.

The Role of the Anesthesia Specialist

The anesthesia specialist has the opportunity to critically assess the overall health of the patient and, working in concert with the surgeon and geriatrician, can help guide optimization of medical and geriatric-specific conditions. This process requires integrating the information obtained from initial screening into a risk profile and a plan to address identified deficits. There are a number of tools for *operative risk stratification* (e.g., ASA, POSSUM, ACS-NSQIP risk calculator, etc.) that although not geriatric-specific can help provide an overall estimate of the risk of adverse outcomes [28].

An ongoing initiative sponsored by the American College of Surgeons (ACS) Geriatric Surgery Task Force is working to develop a risk-stratification model for geriatric surgery patients that includes geriatric-specific preoperative variables (e.g., history of dementia, history of falls) and relevant outcomes (e.g., occurrence of delirium, decline in function). It is hoped that the addition of these variables will provide better information about specific risk and will provide a platform to guide quality improvement efforts (see below) [52].

The Intraoperative Phase

The Role of the Surgeon

In the OR, the surgeon should be sure that all team members are focused on the special considerations required in older adult patients and that each understands his or her role. He or she should personally aim to minimize the physiologic impact of the surgical stress. Keeping surgical times as short as possible is key, as longer operative times have been associated with more complications [53]. Minimally invasive techniques should be used when feasible to minimize fluid shifts and tissue injury [54]. Careful tissue handling is also a necessity as age-related changes, such as loss of subcutaneous matrix, make tissues such as skin and fascia more susceptible to injury.

The Role of Anesthesia Specialist

Close collaboration between the anesthesiologist and the surgeon is of utmost importance when optimizing the outcomes of geriatric patients. As always, the anesthetic strategy should be individualized based on the surgery being performed, the duration of the surgery, and patient factors. From a surgeon's perspective, the overarching goal is to create an anesthetic plan that minimizes the impact of geriatric syndromes.

Anesthesia protocols, either stand-alone or as part of enhance recovery after surgery (ERAS) programs [55], incorporate measures associated with decreased complications and faster recovery. Such measures are for the most part applicable to the geriatric patient and include shorter fasting period, use of regional anesthesia, multimodal preventive and pain management regimens, minimizing narcotic use, risk stratification and prevention of postoperative nausea, goal-directed fluid management, hypothermia prevention, and safety practices to prevent postoperative complications and functional deficits (i.e., pressure ulcers, neurapraxias, etc.). Although ERAS programs are procedure specific and are not developed for the geriatric population specifically, they provide recommendations applicable to geriatric care and a framework through which additional geriatric-specific recommendations can be incorporated.

The physiologic changes of aging, compounded by the effects of multiple chronic diseases, make it necessary to individualize the type and dose of anesthetic drug administered. For example, older adult patients have decreased renal cell mass, reduced glomerular filtration rate, decreased lean muscle mass, increased adipose tissue, and decreased total body water [28] compared to younger patients. Together these changes lead to alterations in the pharmacokinetics and pharmacodynamics of anesthetic agents. Regional anesthetic techniques offer the benefit of limiting the systemic effects of inhaled and intravenous agents that can have a detrimental effect on organ physiology and cognitive function. Epidural anesthetics, for example, have been shown to reduce the time to return of gastrointestinal function and the risk of perioperative cardiovascular complications in select patients [56, 57].

Adequate pain management begins in the operating room and is critical for enhancing recovery and preventing surgical and geriatric-related complications. The indiscriminate use of opioids is associated with prolonged ileus, delayed return of bowel function, and an increased risk of delirium. This can, in turn, cause a cascade of events leading to increased length of stay, altered cognitive function, and increased need for post-acute care [58]. Analgesia must be titrated to provide adequate pain control for good mobility and deep breathing. Oversedation can cause hypoxemia, increase aspiration risk, and precipitate delirium. Multimodal approaches to pain control create the best outcomes in all patients and especially older adults. Multimodal pain programs combine medications that target different pain receptors (local, epidural, and intrathecal anesthetics, opioids, NSAIDs, COX-2 inhibitors, acetaminophen, gabapentin), providing the patient with pain control from multiple areas of perception. Multimodal analgesia plans have been found to offer significantly better analgesia and decreased nausea and vomiting [59]. Patient-controlled analgesia allows the patient to selftitrate their analgesia, which is an optimal strategy in an awake and alert patient. Caution must be exercised in prescribing patient-controlled analgesia to older adults with cognitive deficits or those at high risk for delirium as the ability to understand and cooperate with dosing instructions is key. Nerve blocks may be used to reduce pain without negatively affecting mentation or respiratory drive. Appropriate medication regimens for controlling pain, in addition to preferential use of regional blockades over narcotic-based regimens, are associated with improved outcomes and rely on the daily involvement of the anesthesia/ pain management team [60]. It is important when formulating any analgesic plan to avoid potentially inappropriate medications as defined by the Beers criteria [21].

Nausea and vomiting is one of the most common anesthetic complications and, while not as common as in older adults as in younger adults, is especially devastating in the geriatric patient owing to the increased risk for aspiration and postoperative pulmonary complications [61, 62]. Aging is associated with a decrease in the number and function of respiratory tract cilia, a decrease in cough reflex, and an

 Table 7.1 Medications to avoid in older patients according to the Beers criteria

Postoperative nausea and vomiting	Analgesics	
Corticosteroids (for prophylaxis)	Barbiturates	
Transdermal scopolamine	Benzodiazepines	
Metoclopramide	Hypnotics (i.e., zolpidem)	
Promethazine	Pentazocine	
Prochlorperazine	Meperidine	
	Skeletal muscle relaxants	
	Non-COX NSAIDs	

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increase in swallowing dysfunction [63]. These changes, combined with the effects of common diseases, such as gastroesophageal reflux disease, diabetes, and stroke, predispose to older adult to aspiration and subsequent pneumonia [63]. Unfortunately, the best medications in the arsenal for fighting perioperative nausea and vomiting also can precipitate delirium in older patients. The healthcare team should be aware of the antiemetic medications that appear on the Beers list (see Table 7.1), such as promethazine and scopolamine, and use them sparingly in this population.

Optimum fluid management in the operating room is essential in older adults because of the physiologic and disease-related changes in the cardiovascular function that accompany aging. Maintaining adequate cardiac output and end-organ perfusion becomes challenging when the effects of vasoactive anesthetic agents are combined with these changes. The autonomic nervous system, myocardium, and arterial and venous vasculature are all impacted by age in a manner that challenges hemodynamic stability during surgery [64]. The sympathetic portion of the autonomic nervous system becomes desensitized to beta-receptor stimulation, limiting the myocardial contractility and heart rate in response to hypovolemia [65, 66]. Arteries become stiff and calcified, increasing outflow resistance and leading to ventricular hypertrophy. This, combined with other changes in myocyte cellular function, leads to impaired cardiac relaxation and diastolic dysfunction. The aging heart is therefore increasingly reliant on preload and atrial contraction to maintain cardiac output [65, 66]. Hemodynamic stability is easily compromised with atrial fibrillation, where the atrial component of filling is absent [64, 66].

Older adults are also at an increased risk for intraoperative hypothermia owing to age-related changes in hypothalamic temperature regulation and peripheral vascular reactivity, and to decreased lean muscle mass (sarcopenia) and basal metabolic rate [63]. Hypothermia in the operating room increases the likelihood of developing pressure ulcers, surgical site infections, cardiac events, and coagulopathy requiring blood transfusion [63, 67–69]. Intraoperative hypothermia (temperature <36 °C) should be avoided by keeping the operating room at an appropriate temperature, using fluid warmers and forced warm air blankets.

Role of the Operating Room Nursing Team

Safe and proper patient handling and positioning on the operating table to avoid undue pressure is of paramount importance in the older adult. A pressure ulcer is a devastating but preventable complication, which has been shown to significantly increase morbidity and mortality and decrease quality of life [70]. Proper alignment, positioning, padding, and pressure-relieving devices all contribute to maintaining adequate arterial blood flow to pressure points [71]. Patients aged over 65 experience the highest incidence of pressure ulcer development owing to age-related changes in skin and inadequate nutrition. Transfers should always be performed using a lateral transfer device to reduce friction and shear force and protect against accidental skin damage [71].

Postoperative Phase

The key to successful management of the geriatric surgical patient is the prevention of postoperative complications. In addition to the usual surgical complications, such as surgical site infections, older adults are at increased risk of "geriatric complications" such as delirium, aspiration, malnutrition, falls, urinary tract infections (UTI), pressure ulcers, deconditioning, and functional decline. The prevention of these complications requires input from all members of the interdisciplinary team. A postoperative rounding checklist created for the ACS National Surgical Quality Improvement Program (NSQIP)/AGS Best Practices Guideline: Optimal Perioperative Management of the Geriatric Patient provides a template for the evaluations and management strategies that should be performed daily in the geriatric patient to reduce complications postoperatively (Table 7.2). This checklist provides guidance for all of the members of the team.

Prevention and Management of Delirium

Of all the postoperative complications in the older adults, delirium is the one that is the most challenging and requires the most input for all of the team members to prevent and manage. The prevalence of postoperative delirium ranges from 9% to 44% depending on the patient population [72]. Thirty to forty percent of postoperative delirium episodes are thought to be preventable [73]. Patients who develop delirium after undergoing elective surgery have been found to have a significantly increased

risk of an institutional discharge, prolonged hospitalization, readmission, and death [72].

Factors associated with delirium can be thought of as predisposing (i.e., patient risk factors) and precipitating. The predisposing factors should be determined in the preoperative assessment (see above), and a plan should be in place to mitigate the impact of these risk factors. Precipitating factors include those related to the physiologic insult of surgery, metabolic derangement, infection, inappropriate medications, use of tethers, unfamiliar environment, disturbance of bowel or bladder function, under or over treated pain, or a combination of these factors. When delirium occurs in the postoperative period, it is essential to make a careful search for the precipitating factors and promptly address them.

The initial treatment of delirium is based on removing precipitating factors where possible (i.e., stopping inappropriate medications) and instituting a multicomponent, multidisciplinary nonpharmacological strategy [58], which includes interventions such as:

- · Early mobility
- · Beside presence of a family member whenever possible
- Cognitive reorientation the presence of a window and clock in each room
- Adaptations for visual and hearing impairment available
- Appropriate pain management
- Adequate bowel regimen
- Removal of tethers such as catheters and lines
- Nutrition and fluid repletion

Pharmacologic treatment with antipsychotic medication (i.e., Haldol) and the use of physical restraints should be reserved only for situations where other interventions have failed and the patient is in danger of harming themselves or others. When physical restraints are required, a plan must be in place to provide frequent reassessment of the need and to assist with nutrition, hydration, personal hygiene, and toileting [74].

Delivery of Care Models

As mentioned above, older adults are at increased risk of other serious complications including functional decline and deconditioning, poor nutrition and aspiration, falls, UTI, and pressure ulcers [37, 75]. In this context, input from all of the members of the team is required to provide safe high-quality care. Several models of interdisciplinary care have been developed, tested, and shown to improve care for older adults hospitalized for a variety of conditions, including surgery. For the most part, each model uses the same principles which include multidisciplinary participation, appropriate preoperative evaluation/screening, and standardized geriatric care

Table 7.2 Checklist for adverse event prevention/managem
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Adverse event	Prevention/management strategies
Delirium/cognitive impairment	 Pain control Optimize physical environment (ie sleep hygiene, minimize noise, encourage family to be present) Provide vision and hearing aids if applicable Minimize catheters and monitors Monitor for substance withdrawal syndromes Avoid inappropriate medications
Perioperative acute pain	 Perform pain history pre-operatively Multimodal, individualized pain control Vigilant dose titration
Pulmonary complications	 Nursing directed prevention strategies-incentive spirometry and cough/deep breathe Early mobilization/ambulation Aspiration precautions
□ Fall risk	 Universal fall precautions Scheduled toileting Early physical/occupational therapy if indicated Assisted walking devices
□ Malnutrition	 Resume diet as early as possible Dentures made available Supplementation of indicated
Urinary tract infection	Remove Foley catheter if medically indicatedSterile and clean catheter care
☐ Functional decline	 Structural: uncluttered hallways, large clocks and calendars Multidisciplinary rounds Family participation Nutritional support Minimize patient tethers
□ Pressure ulcers	 Reduce/minimize pressure, friction, humidity, shear force Maintain adequate nutrition Wound care Early mobilization

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with interventions based on baseline deficits or those developed during the perioperative period. Clear communication strategies among members of the multidisciplinary team have been identified as an essential component of these models of care [76]. As with any other intervention in healthcare, appropriate implementation of proven practices is critical to obtaining improved results. As such, multidimensional elder care "programs" have been shown to be more effective than any given isolated intervention [37, 76, 77].

The vast majority of data evaluating different acute care models for the geriatric surgical patient originate from studies of older adults undergoing orthopedic procedures, in particular hip fractures. As such the data is limited by both the specific population included (typically frail and vulnerable to other geriatric conditions) and the specific surgical procedure. Nevertheless, the different models provide frameworks through which geriatric surgical care can be improved and optimized in a given clinical surgical practice.

Geriatric Consultation Model

One type of model is based on selective or mandatory geriatric consultation for older adult surgical patients (general surgery, orthopedics, and trauma). Models of this type have been associated with an overall improvement in the process of care including increased geriatric-based assessment and recognition of geriatric syndromes and better advanced care planning [78]. However, a prior non-randomized controlled trial, evaluating the impact of geriatric consults on specific outcomes (length of stay, functional status, mortality, new nursing home admission, and hospital readmission), found no added benefit with the intervention. The authors hypothesized that an independent geriatric consult lacking a more comprehensive program may improve the process of care but not overall patient outcomes [79].

Comanagement Model

A more sophisticated model is one with comanaged perioperative care by surgeons and geriatricians that integrates the multidisciplinary care of the core group and the additional support services (as described above) through a true unified team approach. Although it is difficult to methodologically prove the added benefit of these kinds of models, a systematic review, and other recent studies in the orthopedic literature, has demonstrated improved outcomes (length of stay, mortality, and readmissions) and cost-effectiveness [80-82]. A recent study evaluated the implementation of this model when applied to a number of different surgical specialties and found it to be feasible and associated with overall improved process of care and a trend toward higher rates of regaining independence with increased return to the community upon discharge [83]. The advantages of such a model include the true interdisciplinary care throughout the perioperative continuum and the ability for the different team members to provide added expertise to the day-to-day care.

There are a number of in-patient programs that essentially rely on a comanagement strategy and have proven benefits in different geriatric domains and outcomes after surgery. These programs rely heavily on existing hospital resources, including unit nurses and ancillary staff to implement routine assessment and deliver specific interventions to patients. Such programs include Nurses Improving Care for Health-System Elderly (NICHE- www.nicheprogram.org) and the Hospital Elder Life Program (HELP) [84].

Specialized Units

Lastly, a model that cohorts geriatric patients on a specialized ward or unit has also been advocated by some investigators. There are good data supporting the added benefits of admission to geriatric units in regard to decreased functional decline, 30-day readmissions, and costs, for a general geriatric population [85, 86]. One well-studied example is the Acute Care for Elders (ACE) model [86, 87]. This model provides care for older adults through daily interdisciplinary rounds focusing on geriatric syndromes and through the hardwiring of geriatric care processes into nursing care [86]. It is important to note that "passing on" all the surgical care to the geriatric specialist should not be the goal of care on this kind of unit. The surgical team must continue to provide daily direction and input. Bringing the principles of ACE unit care to all the wards where older adult patients may receive postoperative care is the ideal and is possible if best practices for both medical providers and staff become engrained in the institutional culture [88].

Transition of Care Following the Perioperative Period

As previously discussed, geriatric patients more often require post-acute care prior to returning to their home environment. The transition of care from one phase to another can be a challenging and fragmented process for patients and families [89]. The incidence of readmission following surgery can be up to 20%; many of these represent failures in regaining independence and the ability to return to their baseline state [90]. Additionally, the burden of post-acute care in costs to the patients and the healthcare system is significant. It is among the fastest growing cost in Medicare expenses, representing close to \$62 billion annually [4]. There are two welldescribed models to improve the transition of care, the patient-centered medical home and the transitional care models, both of which have been shown to improve outcomes for older adult patients with multiple comorbidities [91–95]. The patient-centered medical home model works to improve access and coordination of services through a

team-based approach achieved through community engagement [93]. The transitional care model centers around an acute hospitalization, where an advanced practice nurse leads a multidisciplinary effort to coordinate the patient's care from the hospital to the home and has been shown to decrease resource use in cognitively impaired older adults [93]. Patient navigation is a care model with many similarities to the transitional care model, which utilizes trained external coaches or support personnel in a similar fashion, assisting high-risk individuals through the healthcare process and improving their communication with providers and understanding of treatment decisions [96].

As opposed to the young healthy patient who recovers from an uneventful operation, the older adult patient often requires ongoing care even in the absence of complications or geriatric syndromes. The coordination of care during these transitions is essential to prevent readmissions and hasten recovery. The geriatric surgical team must facilitate this process by providing care for any new complications, providing a strategy to prevent functional and cognitive decline, reinitiating presurgical care processes, and communicating effectively with primary care providers. Key components of any given transitional care model include appropriate communication/coordination with the patient's providers. engagement of family/caregivers, sharing of necessary medical information (medical record), post-discharge follow-up, medication management, education of warning signs specific to each individual patient/procedure, and clarification of ongoing care [6].

Programmatic Efforts to Improve Geriatric Surgical Care

Guidelines for the preoperative assessment and perioperative care of the older adult surgical patient have been developed and disseminated [6, 28], but guidelines alone are not sufficient to bring about a sustained change in practice and improve quality. Over the past several decades, to address a similar problem in other surgical areas, the American College of Surgeons has developed formal quality improvement and verification programs in trauma, cancer, and bariatric surgery, among others. Successful implementation of these programs has been shown to improve quality and outcomes [97, 98]. These successful quality programs are all built on four pillars:

- 1. Set the standards for what constitutes quality care.
- 2. Define the infrastructure necessary to provide that care.
- 3. Collect data on outcomes that can be used to benchmark and continually improve the quality of the care.
- 4. Verify that the standards, infrastructure, and data collection are in place.

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Coalition for Quality in Geriatric Surgery

Using this framework, the ACS and the John A. Hartford Foundation have partnered to develop a formal geriatric surgery quality improvement program, similar to the other ACS quality verification programs. This project, the Coalition for Quality in Geriatric Surgery (CQGS), brings together 59 national stakeholder organizations, representing surgical, medical and nursing specialists, allied health professionals, social workers, insurers, regulators, and most importantly patients and families to develop a formal program to improve the quality of care for geriatric surgical patients. The coalition will define the standards, processes, resources, and infrastructure necessary to provide high-quality, patientfocused care. Quality geriatric surgical care is built on an interdisciplinary perioperative team that can meet these standards, measure outcomes that matter to the patient, and use the data to continue the cycle of quality improvement. The standards will be based on peer-reviewed evidence and expert consensus opinion. They will include the patient goalcentered consent process, pertinent screening exams, perioperative management strategies, and the team leadership structure that will allow the system to flourish. Meeting the standards consistently requires a multidisciplinary team approach. The infrastructure in place must assure that the standards are met for every patient and are protected from system and human error.

ACS-NSQIP: Geriatric Surgery Pilot

As mentioned above, surgical outcomes usually focus on mortality and morbidity, but older adults are also at risk for functional decline and loss of independence. Factors contributing to these later outcomes, or identifying patients are risk for them, are not routinely measured. To address this gap, the Geriatric Surgery Task Force of the ACS began a Geriatric Surgery Pilot in 2014 to collect geriatric relevant variables in

Table 7.3 Geriatric-specific variables

Preoperative variables	Postoperative variables	30-day outcomes
Origin from home with support	Pressure ulcer	Functional status
Use of mobility aid	Delirium	Living location
Fall history	DNR order	
Dementia history	Palliative care consult	
Competency on admission	Functional status	
Palliative care on	Fall risk	
admission	Use of mobility aid	
	Discharge needs	

Modified from Robinson and Rosenthal [52]

a subset of 23 ACS-NSQIP hospitals across the USA and Canada. Preoperative risk factors and outcomes data were and still are being collected on surgical patients over the age of 65, specifically addressing issues that are important to the geriatric patient (see Table 7.3) [52]. Analysis of this unique data set will allow for the implementation and subsequent measurement of interventions designed to reduce risk and improve outcomes for the geriatric patient population. To learn more about the CQGS program and the Geriatric Surgery Pilot, visit https://www.facs.org/quality-programs/geriatric-coalition.

Summary

Providing high-quality care for the older adult surgical patients is challenging and requires input from more than just the surgeon and his or her immediate team. It requires a well-coordinated effort by an interdisciplinary team of specialists each of whom always maintains the focus on meeting the patient's goals of care and preserving the patient's quality of life. It requires detailed evaluation and planning at every phase, from the decision to do surgery, through the intraoperative and postoperative hospital management, and back to the community. It requires a system-wide awareness of the special issues that older adults face when subjected to the stress of surgery and hospitalization and a programmatic, effective response when predictable issues arise. It requires measurement of outcomes that matter to patients to guide quality improvement efforts. Most of all it requires strong engagement of the whole team with the patient and his or her family to provide a framework where the individual's vulnerabilities can be anticipated and addressed, in order to provide maximum benefit from the surgery with minimal negative impact on overall function.

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The Geriatrician's Perspective on Surgery in the Geriatric Population

Thuan Ong, Joe C. Huang, Carol A. Crawford, and Katherine A. Bennett

The Geriatrician's Role

Geriatricians play a unique role in the care of older patients who are preparing for surgery. They may supply insight as a primary care provider and/or provide specialized recommendations in the pre- and postoperative care of a patient. Geriatricians have clinical skills in caring for a heterogeneous older adult population in different care settings. Geriatricians entering into practice, in and across all care settings (hospital, home office, and long-term care and subacute rehabilitation facilities), are able to provide patient-centered care that optimizes function and/or well-being; prioritize and manage the care of older patients by integrating the patients' goals and values, comorbidities, and prognosis into the practice of evidence-based medicine; assist patients and families in clarifying goals of care and making care decisions; coordinate health care and health-care transitions for older adults with multiple chronic conditions and multiple providers; provide comprehensive medication review to maximize the number of medications and adverse events; provide geriatrics consultations and comanagement; and collaborate and work as a leader or member of an interprofessional healthcare team. All these skills potentially add value to the anesthesiologist [1]. Many of the problems and issues that arise in caring for older adults are common and complex enough that expertise would be a benefit to the patient (Table 8.1).

There is great heterogeneity and variability in aging. Age is a demographic variable used as a surrogate to reflect medical complexity, disease burden, frailty, and physiologic decline in many organ functions. Some members of the oldest old (defined as people age 85 and above) maintain high physical function and should not necessarily be regulated to

C.A. Crawford

non-operative management. Caution should be given in ensuring chronological age itself is not used as a tool to determine treatment choices. Geriatricians balance a deep respect for the potential harms of interventions with the potential benefits given a patient's individualized life trajectory. In this chapter, we identify aspects of the geriatrician's role and assessments that may improve perioperative care.

Geriatric Medicine

What makes geriatric medicine different from, say, internal medicine and family medicine? There is not an absolute singular answer even among geriatricians themselves. However, most geriatricians will identify some commonalities: a focus on our patient's functional capacity, identifying the presence of geriatric syndromes and its impact on function, and comfortably and effectively working in multidisciplinary teams to maximize our patient's function [3]. All three of these aspects are important to the management of older adults in perioperative care.

Functional Assessment

Geriatricians are originally trained in family medicine or internal medicine and are able to evaluate chronic medical conditions that are prevalent in older adults such as heart failure, diabetes, or chronic kidney disease. Geriatricians will also routinely assess patients in terms of functional status and identify geriatric syndromes (see below) that may impede maximal functional abilities. Studies have shown an association between functional dependence and mortality after surgery [4–6]. Functional status is one of the most important predictors of outcomes after anesthesia. In general, low levels of function and functional dependence were associated with postoperative complications and operative mortality.

The geriatric assessment extends beyond the traditional medical evaluation and management of medial illnesses. It involves an evaluation of issues including physical, cognitive, affective, social, environmental, and spiritual aspects that may have a great impact on older adult's life. The goal of such an

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Table 8.1 G	Beriatrician's	specialized	clinical	skills	and know	wledge
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Physiology of aging
Geriatric syndromes
End-of-life care
Preventive gerontology
Ability to provide patient-centered care to older adults with complex health issues such as multimorbidity, frailty, and disability
Ability to care for older adults across multiple settings from outpatient to the hospital to the nursing home to the home
Desire and skill to work in interdisciplinary care teams
Commitment to advocate for the best care for older adults
Ability and desire to provide clinical care to the full heterogeneous range of older adults: from the robust to the frail to the dependent
Based on data from Ref. [2]

Tab				assessment		

Functional capacity assessment of activities of daily living and	
instrumental activities of daily living	
Fall risk and mobility assessment	
Cognitive assessment	
Affective and mood assessment	
Polypharmacy	
Social support and environmental assessment	
Nutrition and weight change	
Urinary continence	
Vision impairment	
Hearing impairment	
Goals of care and advanced care preferences	

The CGA is an evaluation and diagnostic framework that seeks to maximize functional status by identifying and treating the presence of common geriatric syndromes and conditions common to frail older adults

assessment is to delay the onset of functional impairment while maintaining the highest level of independence, autonomy, and quality of life possible over a patient's life course.

The comprehensive geriatric assessment (CGA) is a tool that is familiar to all geriatricians. It is an evaluation and diagnostic framework that aims to maximize function by identifying common conditions such as geriatric syndromes and issues that reduce quality of life. Table 8.2 captures the core aspects of almost all CGAs. CGAs may vary by having additional components in the assessment.

The use of CGAs in community-dwelling older adults guides management that in turn results in a decrease in mortality and a reduction in functional decline [7, 8]. However, there is significant variability in the implementation of CGAs in the outpatient environment. Positive results come from programs where a greater number of recommendations are implemented compared to those where there is limited or no implementation of recommendations [9]. In hospitalized older adults, care that is based on CGAs provided more consistent benefits in comparison to standard medical care. A Cochrane Review shows subjects who received CGA were more likely to be alive and in their own homes throughout the surveillance period (median 12 months). Hospitalized subjects who received CGAs were also less likely to be institutionalized, were less likely to suffer death or deterioration, and were more likely to experience improved cognition compared to the usual care group. These effects are consistently demonstrated from trials of geriatric wards (patients admitted directly to the specialist geriatric team) but not replicated in trials of geriatric consultation teams where the geriatric team passes on their recommendations to the primary team and may or may not be involved in delivering direct care [10]. Again, trials showing the most clinically and statistically significant improvement in mortality and functional decline are where recommendations are implemented.

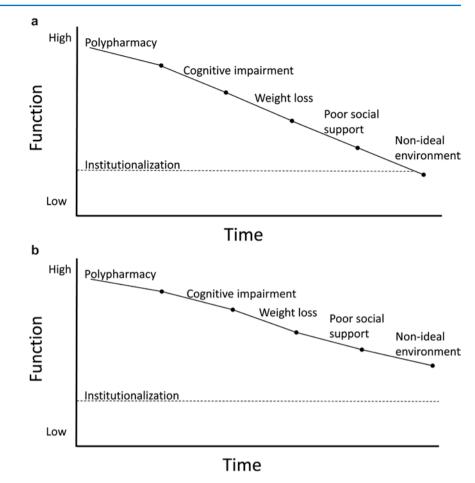
Figure 8.1 illustrates the concept of maximizing function and using aspects of the CGA to achieve that goal. Over time older adults will experience a decline in function due to physiologic changes and conditions that are prevalent among older adults. Many of these changes and conditions are chronic, and cure is not possible. However, mitigating the impact of each condition may be enough to maintain one's level of function above the threshold of losing independence.

Geriatric Syndromes

Geriatric syndromes are multifactorial health conditions that occur when the accumulated effect of impairments in multiple different systems renders an older adult vulnerable to situational challenges [11]. These situational challenges can be a change in an environment such as a hospitalization or an acute exacerbation of a chronic medical condition.

A key aspect of geriatric syndromes is that underlying risk factors often overlap with other fields of medicine (e.g., physical therapy or occupational therapy) because the syndrome is impacted by different physiologic systems. An example of a geriatric syndrome is falls. It is easy to imagine how the decline illustrated in Fig. 8.1 could contribute to falls. Assessment of physical deconditioning, cognition, the physical home environment, medications, and social support all involves different systems and assessment from different specialties. Intrinsic and extrinsic risk factors are identified with the goal of mitigating each risk factor's impact on the geriatric syndrome. Risk factors are often not reduced to zero, but its impact on overall function can be lessened where the cumulative effects have a significant positive impact similar to what is illustrated in Fig. 8.1, Panel b.

Delirium can be used to exemplify this above concept. Delirium occurs not uncommonly in hospitalized older adults and often has multifactorial causality. The Hospital Elder Life Program (HELP) is a multifaceted nonpharmacologic intervention that addresses some of the risk factors that contribute to developing delirium. Table 8.3 outlines HELP's interventions. The HELP interventions have been shown to reduce delirium [12]. More importantly, HELP has been shown to be Fig. 8.1 Preservation of maximal function. Preserving high levels of function for as long as possible is one of the goals for geriatric medical care. The dotted line represents a low level of function where some form of institutionalization may be required. The comprehensive geriatric assessment is an evaluation and diagnostic framework that aims to maximize function by identifying common conditions such as geriatric syndromes and issues that reduce quality of life. Panel (a) shows how common issues can have an impact upon function over time. Panel (b) shows those same conditions being mitigated as represented by a change in the slope of the line. The impact of these conditions on function has been lessened, and loss of independence is delayed



dose dependent [13]. The more the risk factors mitigated, the better the results.

In 2012, the American College of Surgeons (ACS) NSQIP and the American Geriatrics Society (AGS) published "Optimal Preoperative Assessment of the Geriatric Surgical Patient: A Best Practice Guidelines." The preoperative domains addressed were those most likely to affect the elderly, including cognition, frailty, polypharmacy, nutrition, and social support [14]. In the following sections, we will be addressing these areas from a geriatrician's perspective.

Interprofessional Care

Many aspects of the geriatric functional assessment require multidisciplinary input. The CGA as outlined above is an inherently multidisciplinary diagnostic and treatment process. The geriatrician identifies the need for mitigating the risk factor's impact on functional decline but then recruits the necessary discipline to evaluate and recommend a treatment course that is integrated into a patient-centered care plan.

Another central task of geriatricians is to coordinate care among several subspecialists and to define, sustain, and communicate clear goals of treatment to all providers involved. In addition to coordinating subspecialist providers, geriatricians must generally work in multidisciplinary teams. Their training and clinical practice often includes long-term care, rehabilitation, and hospice facilities where there is daily side-by-side collaborative care in furthering the patients' goals. Geriatricians' collaborative care coordination among family members, nurses, nurse practitioners, therapists, aides, social workers, and others is a particular skill that is not usually taught in physician training. When a patient depends on others, the patient's physician should have a working knowledge of who is providing that help. In fact, most older adults depend on many individuals to maintain function and independence. The decisions as to whether an older adult should live at home alone, drive independently, or proceed with surgery with anticipated postoperative rehabilitation all can be improved by multidisciplinary input.

Table 8.3 Hospital Elder Life Program (HELP)	Та	ble 8	8.3	Hospital	Elder	Life	Program	(HELP
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Targeted delirium risk factor	Standardized intervention
Cognitive impairment	Orientation protocol: board with names of care-team members and day's schedule; communication to reorient to surroundings Therapeutic-activities protocol: cognitively stimulating activities three times daily (e.g., discussion of current events, structured reminiscence, or word games)
Sleep deprivation	Nonpharmacologic sleep protocol: at bedtime, warm drink (milk or herbal tea), relaxation tapes or music, and back massage Sleep-enhancement protocol: unit-wide noise-reduction strategies (e.g., silent pill crushers, vibrating beepers, and quiet hallways) and schedule adjustments to allow sleep (e.g., rescheduling of medications and procedures)
Immobility	Early-mobilization protocol: ambulation or active range-of-motion exercises three times daily; minimal use of immobilizing equipment (e.g., bladder catheters or physical restraints)
Visual impairment	Vision protocol: visual aids (e.g., glasses or magnifying lenses) and adaptive equipment (e.g., large illuminated telephone keypads, large-print books, and fluorescent tape on call bell), with daily reinforcement of their use
Hearing impairment	Hearing protocol: portable amplifying devices, earwax disimpaction, and special communication techniques, with daily reinforcement of these adaptations
Dehydration	Dehydration protocol: early recognition of dehydration and volume repletion (i.e., encouragement of oral intake of fluids)

Based on data from Ref. [12]

Multicomponent nonpharmacologic interventions for the management of six risk factors for delirium: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration. HELP has been shown to reduce delirium incidence

Goal Setting and Hospitalization-Associated Disability

Goal Setting

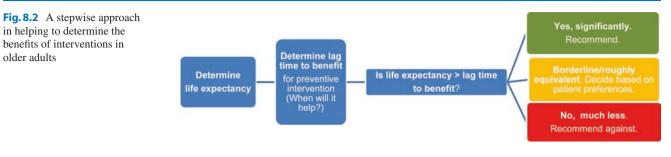
It is important to ensure that the patient's goals for care and expectations are in line with anticipated outcomes prior to both elective and nonelective surgical procedures in older adults. The surgical intervention is only the beginning of a longer course to recovery for many older adults. Approximately 65% of Medicare patients who had a lowerextremity joint replacement surgery required stays in either a skilled nursing facility or inpatient rehab after surgery [15]. Incorporating discussions about the typical clinical course after surgery should be an important part of informed consent for surgery. A priority should be placed on understanding the patient's goals and expectations for surgery.

The concept of *lag time to benefit* is helpful when thinking about goals of care for older adults [16]. Lag time to benefit refers to the time between the intervention (in this case surgery) and when positive health outcomes are received (e.g., improvement in mobility, cure from cancer, prevention of repeated bouts of cholecystitis). In other words, lag time to benefit addresses the question "when will it help my patient?" The model was originally intended for decisions of outpatient preventive interventions, such as cancer screening, but can be adopted for decisions regarding surgical interventions. One would expect that most surgical interventions have an immediate benefit. However, when extensive rehabilitation is required before the primary goal is achieved (e.g., improved function), surgery may not be the ideal solution.

Figure 8.2 illustrates a stepwise approach in helping to determine the benefits of offering interventions in older adults. This model incorporates life expectancy, the lag time to benefit, and patient preferences. It is important to elicit your patient's preferences whenever you are delivering care and is most essential when the risks and benefits for a particular intervention are not straightforward.

It can be difficult to estimate life expectancy. Although age is an important factor in life expectancy, it is not the only predictor. At any given age, an older adult's life expectancy may be shortened by comorbidities or decreased functional status (i.e., dependence for activities of daily living) [17]. Life expectancy is also shortened by the presence of frailty. Although most clinicians will have a general clinical gestalt about any given individual's life expectancy, incorporating different mortality models based on demographic variables can provide for a more standardized discussion based on evidence. Many models exist that attempt to prognosticate mortality and life expectancy. These models differ in the cohorts that generate the data for their modeling and range from community-dwelling to hospice cohorts and have variable time frames (months to a decade). ePrognosis (Fig. 8.3) is an application that incorporates many of these models into a simplified step-by-step process in estimating mortality [18, 19]. By inputting patient demographic variables, one can get an estimate of mortality risk for patients in the realm of days to years based on location of care and other patient-specific factors.

Avoiding chronic debility, morbidity, and poor quality of life is often more important to older adults than staying alive. Understanding the patients' hierarchy of what is important in their lives and their goals is a key component of shared decision-making in medicine and not solely regarding surgery. If a patient is not willing to live in a skilled nursing facility, even for a short period of time, it may not be helpful to have them undergo an elective procedure such as posterior spinal fusion that might require such a stay. Alternately, delineating that the patient highly values independence may lead one to recommend such a procedure that could improve their mobility and ability to participate in self-care for the



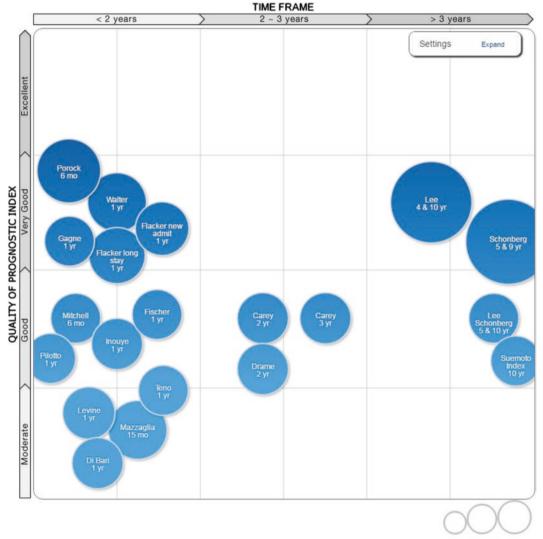




Fig. 8.3 A bubble view of the different models incorporated into ePrognosis. ePrognosis is a repository of published geriatric prognostic indices [18]. Each bubble represents a different prognostic model. The size of each bubble represents the cohort size of the model. The x-axis represents the duration of years of the studied cohort, and the y-axis represents the quality of the data. For example, the Lee SJ et al. model is derived from a cohort of 11,701 community-dwelling older adults

and validated in 8009 Health Retirement Survey interviewees and provides all cause 4- and 10-year mortality estimates [20]. The information on patients' prognosis is intended as a rough guide to inform clinicians about possible mortality outcomes and is not intended to be the only basis for making care decisions, nor is it intended to be a definitive means of prognostication (Created using ePrognosis: http://eprognosis. ucsf.edu/index.php) long term. If a patients' main goal is quality of life or comfort, then their acceptance of risk of discomfort or complications from a procedure with a lower potential to add quality years would be lower.

To find out a patient's preferences, one can simply start by asking the patient the following question: Is one of the following goals more important to you than anything else: (1) Living as long as possible? (2) Keeping your ability to care for yourself and live independently? (3) Keeping comfortable, with minimal symptoms? If the discussion is not straightforward, consultation with a palliative medicine specialist, a geriatrician, or a provider who either has a strong rapport with the patient or with experience in goals of care discussions can be helpful [21].

Hospitalization-Associated Disability

An important part of the discussion of potential treatments is letting patients know what the potential next steps are and expected outcomes after a procedure, including recovery time in the hospital, estimated time in a rehabilitation facility, and frequency and timing of follow-up. Hospitalizations itself is commonly associated with functional loss in older adults. Hospitalization-associated disability is the loss of the ability to perform one of the basic activities of daily living (ADLs) and occurs between the onset of the acute hospitalization and discharge from the hospital [22]. Declines in ability to perform ADLs and mobility after hospitalization are common [23–27]. Age is the most important risk factor [28]. Thirty-five percent of patients declined in ADL function between baseline and hospital discharge in a prospective observational study of nearly 3000 patients aged 70 and older (mean age of 80) hospitalized to medical services. This rate of functional decline had a striking relationship with age, with rates exceeding 50% in patients aged 85 and older [28]. Similarly, in another prospective observational study in medical patients involving over 2000 patients, 40% of older adults continued to have a new or additional disability in ADL at 3 months post discharge compared to prior to admission. At 1 year, nearly a third of patients still had not recovered their prior function [23].

Striking reductions in mobility after hospitalizations for older adults are also seen. Nearly 500 hospitalized medical patients aged 70 and older followed prospectively showed that low mobility and bed rest were common [24]. Using average mobility level, scored from 0 to 12, the low mobility group was defined as having a score of 4 or less, high as higher than 8, and bed rest was assigned a score of 0. Complete bed rest episodes occurred 33% of patients. The development of new functional decline, becoming newly institutionalized, and having in-hospital death were all shown to have an inverse relationship with the initial level of mobility. In other words, the lower one's mobility, the worse the outcomes.

Similar results were shown in a separate observational prospective study involving nearly 700 community-dwelling 65 years or older surgical and nonsurgical patients. On average, patients hospitalized for any reason experience decline in mobility [25]. Patients with a nonsurgical admission had little to no recovery of mobility to their baseline even after 2 years. Interestingly, surgical patients had better mobility before admission and recovered to at least their preadmission mobility within a year of hospitalization. The authors speculated that preoperative screening helped to determine the best candidates for surgical procedures.

Sager et al. developed a simple instrument to help identify patients at risk of functional decline following hospitalization. The Hospital Admission Risk Profile (HARP) was developed and validated in two separate cohorts from four university and two private nonfederal acute care hospitals [29]. Using logistic regression analysis, the authors identified increasing age, lower admission Mini-Mental Status Exam scores, and lower preadmission IADL were independent predictors of functional decline. A scoring system was developed for each predictor variable, and patients were assigned to low-, intermediate-, and high-risk categories (Table 8.4). The HARP reinforces the value of identifying prior cognitive function and physical function as markers of

 Table 8.4
 The Hospital Admission Risk Profile (HARP)

Variable	Risk score
Age	
<75	0
75–84	1
≥85	2
Cognitive function (abbreviated MMSE)	<u>a</u>
15–21	0
0–14	1
IADL function prior to admission ^b	
6–7	0
0–5	2
Total score	
Risk categories	Total score
High risk	4–5
Intermediate risk	2–3
Low risk	0-1

Based on data from Ref. [29]]

An instrument that can be used to identify patients at risk of functional decline following hospitalization

^aAbbreviated Mini-Mental State Exam includes only the orientation (10 items), registration (3 items), attention (5 items), and recall (3 items) portions of the original 30-item test

^bA person is judged independent in an activity if he/she is able to perform the activity without assistance. A person is scored dependent if he/ she either does not perform an activity, requires the assistance of another person, or is unable to perform an activity. IADL activities include telephoning, shopping, cooking, doing housework, taking medications, using transportation, and managing finances posthospitalization outcomes. Other authors have also demonstrated that including information from short multidimensional prognostic assessments identifies older adults most likely to develop hospitalization-associated disability [30, 31].

There are multiple other tools available to assess for functional status. As recommended by the American College of Surgery/American Geriatric Society Guidelines, one can quickly screen for functional status at baseline [14]. One can ask patients these four screening questions:

- 1. Can you get out of bed or chair yourself?
- 2. Can you dress and bathe yourself?
- 3. Can you make your own meals?
- 4. Can you do your own shopping?

Deficits in any of these areas should prompt a more indepth look at functional status and involvement of physical and occupation therapy as well as a geriatrician to further assess for reversible factors and help assess expected trajectory after surgery. A number of interventions have been implemented to reduce the incidence of hospitalizationassociated disability. Many of these interventions are multidimensional addressing cognitive function, sensory impairment, mobility, nutrition and hydration, and limiting iatrogenesis [32].

Geriatric Syndromes

There is a growing recognition that geriatric syndromes such as cognitive impairment, sensory impairment, falls, malnutrition polypharmacy, and frailty have an impact on surgery and postoperative outcomes. Screening for many of these syndromes in the preoperative assessment is considered the best practice.

Cognitive Impairment

Cognitive impairment is common among older adults and includes both dementia and mild cognitive impairment. The prevalence of dementia increases with age. In persons 71–79 years old, the prevalence is 5% and increases to nearly 25% in those 80–89 years old and 37% in those 90 years old and older [33]. Mild cognitive impairment (MCI) is a state of cognitive function where the impact is not severe enough to interfere with essential daily tasks referred to as instrumental activities of daily living (IADLs) (e.g., medication management and finances). Dementia, however, is severe enough cognitive impairment that it impairs one's abilities to manage their own IADLs and eventual basic ADLS (e.g., dressing, bathing, etc.). MCI is classified into two subtypes, amnestic and non-amnestic. Amnestic MCI is clinically significant memory impairment that does not meet the criteria for dementia. Non-amnestic MCI is characterized by a decline in function in other non-memory cognitive domains such language or visuospatial skills. The rate of progression of MCI to dementia is uncertain [34]. MCI prevalence widely varies because of differences in the definition of MCI and methods used to determine cognitive impairment and ranges from 3% to 42% in adults 65 years and older [33].

Older adults with cognitive impairment have higher postoperative mortality and are at higher risk of postoperative delirium with potential for chronic impact on cognition and postoperative cognitive dysfunction (Chap. 30, Postoperative Delirium and Cognitive Dysfunction) and institutionalization. A systematic review found that cognitive impairment (defined as a chart diagnosis of dementia) was an independent predictor of postoperative mortality with risk of death ranging from 1.8 to 5.8 times higher compared to those without cognitive impairment [21]. Delirium risk in those who are cognitively impaired increases by two- to seventeen-fold, and the risk of nursing home placement on discharge doubles in comparison to those who are cognitively intact [21]. A discussion of the increased risk of delirium, discharge to a skilled nursing facility, and mortality should be included as part informed decision-making for patients with cognitive impairment and their families.

Screening for baseline cognitive impairment can help identify individuals whom collateral informants are needed to ensure accurate history of medical history and medication list. A validated quick screening tool for cognitive impairment is the Mini-Cog [35]. This tool involves a three item recall and a clock draw (Fig. 8.4). Another useful validated clinical tool is the Ascertain Dementia 8-item Informant Ouestionnaire (AD8). The AD8 can be used in a questionnaire form and is filled out by informants rather than the patient [36]. The AD8 can be particularly helpful in seeking corroborative history for dementia and can be used clinically over the phone when informants may not be present. Those who have a history of cognitive impairment or a suspicion after screening should have collateral informants involved and strong consideration for referral to a geriatrician or other providers who can further assess their cognitive impairment.

Identification of preexisting cognitive impairment is not only important because it increases the awareness of postoperative delirium risk but also because the multicomponent nonpharmacologic interventions such as the Hospital Elder Life Program (HELP) have the strongest evidence for *preventing* delirium. The strength of the evidence of multicomponent nonpharmacologic interventions for *management* of delirium is lower [37]. Nevertheless, multicomponent nonpharmacologic interventions are an integral part of caring for a patient at risk for delirium. HELP (Table 8.3) reduced the incidence of delirium in hospitalized medical older adult patients (mean age 80 year old) by 5% compared to those who received usual care. The number needed to treat is 20. The multicomponent

Step 1: Three Word Registration

Look directly at person and say, "Please listen carefully. I am going to say three words that I want you to repeat back to me now and try to remember. The words are [select a list of words from the versions below]. Please say them for me now. If the person is unable to repeat the words after three attempts, move on to Stee 2 (clock drawino).

The following and other word lists have been used in one or more clinical studies.¹³ For repeated administrations, use of an alternative word list is recommended.

Version 1	Version 2	Version 3	Version 4	Version 5	Version 6
Banana	Leader	Village	River	Captain	Daughter
Sunrise	Season	Kitchen	Nation	Garden	Heaven
Chair	Table	Baby	Finger	Picture	Mountain

Step 2: Clock Drawing

Say: "Next, I want you to draw a clock for me. First, put in all of the numbers where they go." When that is completed, say: "Now, set the hands to 10 past 11."

Use preprinted circle (see next page) for this exercise. Repeat instructions as needed as this is not a memory test. Move to Step 3 if the clock is not complete within three minutes.

Step 3: Three Word Recall

Ask the person to recall the three words you stated in Step 1. Say: "What were the three words I asked you to remember?" Record the word list version number and the person's answers below.

Word List Version: ____ Person's Answers: _____

Scoring

Word Recall:	(0-3 points)	1 point for each word spontaneously recalled without cueing.
Clock Draw:	(0 or 2 points)	Normal clock = 2 points. A normal clock has all numbers placed in the correct sequence and approximately correct position (e.g., 12, 3, 6 and 9 are in anchor positions) with no missing or duplicate numbers. Hands are pointing to the 11 and 2 (11:0). Hand length is not scored. Inability or refusal to draw a clock (abnormal) = 0 points.
		Total score = Word Recall score + Clock Draw score. A cut point of <3 on the Mini-Cog™ has been validated for dementia screening.
Total Score:	(0-5 points)	A cut point of <3 on the Mini-Log ⁻ has been validated for dementia screening, but many individuals with clinically meaningful cognitive impairment will score higher. When greater sensitivity is desired, a cut point of <4 is recommended as it may indicate a need for further evaluation of cognitive status.

Fig. 8.4 Mini-CogTM (© S. Borson. All rights reserved. Reprinted with permission of the author solely for clinical and educational purposes. May not be modified or used for commercial, marketing, or research purposes without permission of the author (soob@uw.edu))

nonpharmacologic interventions reduced the total number of days with delirium and the total number of episodes of delirium [12]. However, once an initial episode of delirium had occurred, the intervention had no significant effect on the severity of delirium or on the likelihood of recurrence placing emphasis on the importance of identifying those at risk for delirium then implementing preventative nonpharmacologic measures. Perhaps more importantly is that the HELP interventions have been shown to have a dose-response curve. Higher levels of adherence to the interventions resulted in reduced rates of delirium in a directly graded fashion [13].

Falls

Falls are common in older adults with one in three older adults falling each year [38]. In the inpatient setting, the rate of falls in older patients is between 3.4 and 5.2 per person year with over half of these falls resulting in serious injury including fracture and head injuries. Risk factors for falls in the inpatient setting include gait instability, agitated confu-

sion (e.g., delirium), urinary incontinence, a history of prior falls, and use of psychotropic medications [39]. Screening for a history of falls and/or performing a mobility assessment such as the Timed Up and Go Test in the outpatient setting may identify older adults at risk for falls in the postoperative period and those who are more likely to be institutionalized after surgery. Screening for falls can be as simple as asking "have you fallen in the past year?" If a yes response is given, the individual is considered at increased risk of falling.

The Timed Up and Go Test (TUGT) is performed by having an older adult stand up from a chair, walk 10 feet, turn around, and return to the seat [40]. If it takes greater than 12 s, the patient is considered at increased risk of falls, and a more comprehensive geriatric assessment prior to elective surgery may be needed. Several small studies have found having an abnormal preoperative TUGT to be associated with an increase in postoperative institutionalization, length of stay, postsurgical complications, and one-year mortality [41, 42]. Inpatient care providers should be made aware in advance of those who are at increased risk of falls, so preventive strategies can be implemented. Successful strategies for preventing inpatient falls have included patient education and multifactorial interventions (with variation of interventions between studies) that target fall risk factors (e.g., therapy or exercise for decreased mobility, medication review). Further research is needed to elucidate which interventions are most effective.

Polypharmacy

The elderly are four times as likely as those under 65 years of age to be hospitalized due to a medication mishap [43]. This is in part due to the higher risk of polypharmacy in this population secondary to an increased number of medical conditions and greater number of physicians involved in their care [44]. Polypharmacy has been associated with adverse outcomes including risk of hospitalizations, falls and fall-related injury, weight loss, decline in functional and cognitive status, and mortality [45, 46]. The frequency of these geriatric syndromes as well as risk of adverse drug reaction (ADR) increases in proportion to the number of used medications [47]. In fact, polypharmacy has been recognized as the most important risk factor for an ADR. The risk increases from 13% for a person taking two medicines to 58% and 82% when taking five and seven or more medications, respectively [47-49].

While no consensus definition exists for the term "polypharmacy," a threshold of five or greater concurrent medications is generally accepted [50–52]. Some studies and authors have tried to be more specific by using the term "inappropriate" polypharmacy when multiple medications are used to treat a single ailment or condition. The lack of consensus in defining polypharmacy has proven problematic when attempting to compare different strategies aimed at reducing medications and their associated clinical endpoints [52].

Believing that a patient is taking too many medicines does not help the clinician know which ones to stop [46]. Medical training often fails to supply providers with adequate knowledge and skills needed to prescribe appropriately to individuals who use multiple medications. As a result, physicians may inadvertently cause drug-drug-related problems. This is especially seen in older adults because of the multiple prescription medications and an inadequate understanding of pharmacology [53].

The term "deprescribing" has been used to describe the complex process of planned and supervised tapering or ceasing of inappropriate medicines with the goal of managing polypharmacy and improving outcomes (Table 8.5) [54, 55]. This is especially important in the inpatient setting as polypharmacy is a preoperative risk factor for delirium and falls [56]. In addition, patients taking medications unrelated to their surgery are 2.5 more likely to develop postoperative complications [57, 58].

Table 8.5 A guided assessment of a "deprescribing process"

- 1. Obtain a complete medication list
- 2. Determine the indication for each medication
- 3. Evaluate each medication's potential for drug-induced harm
- 4. Determine if a medication should be discontinued by evaluating the:
 - Appropriateness of the indication
 - Efficacy
 - Whether it is being used to treat adverse effects of other medications
 - Benefit-to-harm ratio
 - Treatment burden
 - The patient's life expectancy exceeds the time to therapeutic benefit (i.e., lag time to benefit, e.g., the use preventative medications such as statin use for primary prevention)
- 5. Develop a plan for discontinuing medications one at time, starting with medications with the highest treatment burden and lowest benefit (e.g., benzodiazepines)
- 6. Discontinue medications and monitor for withdrawal or return of symptoms
- Based on data from Refs. [46, 50, 59]

Medication reconciliation is a framework used to help reduce medical errors by ensuring accuracy of a patient's medication list. This process is the first step in deprescribing and is particularly important at times of transitions in care when prescribing errors are high [47]. A "brown bag" review in which patients bring in all of their medicines (including all prescriptions and over-the-counter medicines, vitamins, supplements, and herbal preparations) for documentation can be invaluable preoperatively. This type of review provides useful information about what a patient is actually taking versus what they have been prescribed. Utilizing a list from medical records or from the patient may not accurately reflect how and which medications are being taken in the home.

There are numerous decision aid tools to assist providers in reducing polypharmacy with little direct evidence to support one specific method of review over another. These tools have been developed in various settings and have varying levels of support for their use [44]. Although few have been used or validated in the perioperative setting, they all have face validity and could be of benefit. The selected tools below have been chosen for their usefulness and practicality of application when assessing polypharmacy in the elderly (Table 8.6). One shortcoming is while these tools do make recommendations regarding specific medications and medication classes, they do not offer guidance on dosing or alert providers to potentially harmful doses of appropriate medications for the geriatric patient.

Although each type of surgical procedure requires different precautions, there are some general principles for management of medications in the perioperative period. An accurate and comprehensive medication list is essential to appropriately manage patients' medications perioperatively. Review of this list and a straightforward, clear plan regarding discontinuation or continuation for each of the patient's

Table 8.6 Clinical tools to reduce polypharmacy

Tool to reduce polypharmacy	Description	Applications	Limitations
Beers Criteria ^a	Widely adopted consensus-based list identifying potentially inappropriate medications in the elderly	Easy to use. Requires little individualization or time-consuming decision-making. Can be incorporated into computerized decision support systems	Many of the drugs are not in current clinical use. There is insufficient evidence to include some drugs on the list. Harm resulting from the use of some of the inappropriate medications on the list may be minor compared with other inappropriate prescribing
DBI ^b	Evidence-based tool used to assess a patient's total sedative and anticholinergic drug load	Shown to be superior to the Beers Criteria in predicting functional decline. Shown to be correlated with poorer physical and cognitive performance, falls, frailty, and reduced functional capacity [48]. Can be incorporated into computerized decision support systems	Not widely available limiting usability for most clinicians
STOPP/START ^e	STOPP is a multidisciplinary validated consensus derived tool with check lists based on guidelines validated for geriatric prescribing. START consists of evidence-based indicators of medications commonly omitted by physicians	Logically organized and structured with easy-to-use explicit lists of medication criteria. Requires a short time to complete (3 min). Can be incorporated in computerized decision support systems	Does not take into account the particularities of the health system (funding, co-payment) or the comorbidity of the patient. Clinical judgment is essential for each patient
GRAM ^d	Clinical informatics tool prospectively monitoring for potential risk of falls or for delirium within 24 h of nursing home or hospital admission	Shown to significantly reduce the rate of delirium	Not widely utilized

DBI Drug Burden Index, STOPP/START Screening Tool to Alert Doctors to Right Treatments and Screening Tool of Older Persons' Potentially Inappropriate Prescriptions, GRAM Geriatric Risk Assessment Medguide

^aAmerican Geriatrics Society 2015 Beers Criteria Update Expert Panel [60]

^dLapane et al. [63]

chronic medications should be made at a preoperative appointment. In the immediate preoperative period, providers should repeat their review of the patient's medications and confirm that recommendations regarding management have been implemented. Ensuring nonessential medications have been stopped can reduce perioperative complications. In particular, herbal use can pose important cardiovascular, coagulation, and sedative risks in the perioperative period (see Chap. 13, Preoperative Risk Stratification and Methods to Reduce Risk, Table 13.8) [58]. A general practice of stopping self-prescribed OTC medications, herbals, or supplements 2 weeks before surgery is a strategy supported by the American Society of Anesthesiology and will ensure that longer-acting medications (e.g., St. John's wort or garlic) will be fully eliminated [58]. Instructions should be kept simple for geriatric patients and caregivers such as stopping all nonessential medications at one time rather than a staged fashion will increase the likelihood that patients will be compliant with instructions. Clearly communicating continuing mediations with that are medically necessary or have the potential for withdrawal is equally important.

Most medications are tolerated well through surgery, and most drugs should be continued through the morning of surgery unless completely unnecessary (e.g., vitamins) or contraindicated. In particular, antihypertensives, anticonvulsants, and psychiatric medications should be given unless specifically contraindicated [64]. Notable exceptions to this continuation rule include:

- Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) may be held 24 h prior to anesthesia induction and surgery because of the potential for adverse circulatory effects such as hypotension [58].
- Anticoagulants/antiplatelets including nonsteroidal antiinflammatory agents (NSAIDs) could be held but are vari-

^bGallagher et al. [62]

^cHilmer et al. [61]

able depending on the particular medication, indication for use, and type of surgery.

- Selective estrogen receptor modulators (SERMs) and estrogens should be held at least 1 week preoperatively (4 weeks for estrogen if possible) for surgeries associated with a moderate to high risk of deep vein thrombosis [64].
- Diabetic oral agents should be held the morning of surgery. The exception is metformin which should be held for at least 1 day before surgery and restarted after 2–3 days when it is certain that no acute renal dysfunction has developed postoperatively [64].
- Postprandial insulin should be held the day of surgery. Sliding-scale insulin can be used instead as needed to control serum glucose periprocedurally. Long-acting insulin can be administered but should be reduced by 50% of the usual dose day of surgery.

The long elimination half-life of some medications (e.g., the half-life of amiodarone is 58 days) may make it unreasonable to stop them to achieve low-serum drug concentrations before surgery.

Preoperative medication management in the elderly is commonly nuanced. Special attention to standardized surgerv order sets with preset medications is imperative because medications in order sets are commonly inappropriate for older patients. Uniformity and ease of clinical care are some advantages of using a standardized order set. However, the preset doses may put older adults at high risk for hemodynamic, cognitive, or respiratory impairment. Discontinuation or dose adjustment of as needed (or routine) antihistamines, antiemetics, acetaminophen, narcotics, muscle relaxants, and anticonvulsants may be warranted. In some instances, the prescribing provider should be contacted for an in-person evaluation. For example, acute coronary syndromes (ACS) may present as nausea rather than typical chest pain. Atypical presentations of ACS are more common in older patients. In comparison to typical chest pain, patients with atypical pain or dyspnea were older and had more cardiovascular risk factors yet were significantly less likely to receive evidencebased therapy and suffered worse in-hospital outcomes. The mortality rates were 3%, 2.5%, and 6% in patients presenting with typical chest pain, atypical chest pain, and dyspnea, respectively [65].

Given the high likelihood that medications with central nervous system effects will likely be added postoperatively, an effort to reduce a patient's anticholinergic or sedative medication burden when possible is ideal. The authors of this chapter consider each clinical encounter as an opportunity to reconcile medications and identify the appropriateness of each medication. Discontinuation or dose reduction starting with the least destabilizing agents is ideal. For example, urinary anticholinergics like oxybutynin and non-benzodiazepine sleeping agents like zolpidem can potentially be stopped, and centrally active muscle relaxants like methocarbamol often can be titrated down (if on high/prolonged doses) or stopped as well. Thought should also be given to employing opioid-sparing techniques to reduce the potential untoward effects of opiate use. These may include scheduled preoperative acetaminophen or the addition of regional techniques such as neuraxial blockade or peripheral nerve blocks when appropriate (see Chap. 19) [56]. Initiating narcotics at half the dosage of typical younger patients and avoiding initiation of long-acting opiates (e.g., topical fentanyl, methadone) or opiates with active metabolites (morphine, meperidine) will also reduce central nervous system burden and potentially lessen delirium and fall risk [56].

Ensuring medications are scheduled in a way to avoid dosing in early morning or very late at night can reduce risk of sleep deprivation and fragmentation and consequently incidence delirium [12]. The National Institute for Health and Clinical Excellence (NICE) recommends efforts to improve sleep quality (i.e., avoiding unnecessary night time interruptions and to reducing environmental noise) to reduce delirium in hospitalized patients [66]. Clinical evidence linking sleep fragmentation with delirium comes from preventative nonpharmacologic strategies in the Hospital Elder Life Program. The nonpharmacologic sleep intervention not only reduced the use of sedative and hypnotics but also reduced delirium incidence [12, 67].

Sensory Impairment

Sensory impairment including vision and hearing loss is extremely common and places inpatient older adults at risk for delirium, falls, and miscommunication with providers. Nearly one in three adults over the age of 65 has hearing loss, and 12% of adults 65-74 years of age have visual impairment with prevalence of both conditions increasing with age [68, 69]. Inquiring about these deficits and use of assistive devices (i.e., hearing aids and glasses) can aid in planning for the patient's hospital stay. Older adults with sensory impairment should be encouraged to bring these assistive devices with them to the hospital to aid in communication and reduce their risk of delirium. For those with visual or hearing impairment without access to assistive device, interactions can be enhanced by the use of devices such as hearing amplifiers, magnifying glasses or reading glasses, and using reading materials with larger font. Most hospitals will have access to resources such as large-print versions of reading materials for those with low vision. Speaking slowly, in a lower tone (i.e., deepening voice), at moderate volume at eye level can be very helpful in enhancing understanding for those who are hearing impaired. Counterintuitively, yelling does not usually help those with sensorineural hearing impairment. Yelling increases the pitch of the voice and making it harder for most with sensorineural hearing impairment to understand.

Malnutrition and Weight Loss

Malnutrition is common in community-dwelling older adults impacting over 20% of older adults. It is more even more prevalent in institutional settings. Malnutrition places older adults at increased risk for postoperative complications including infections, poor wound healing, delirium, and prolonged length of stay [14, 70]. There are multiple tools available to screen for malnutrition. One brief validated tool is the Mini Nutrition Assessment (Fig. 8.5) [71]. Another approach recommended by the American College of Surgery/American Geriatric Society preoperative guidelines for older adults is to screen for risk of malnutrition by identifying those with one of the following three factors: (1) BMI < 18.5 kg/m², (2)

Fig. 8.5 Mini Nutrition Assessment (MNA©). (The MNA a simple validated tool that can be used for adults 65 years of age in identifying malnutrition. The MNA form is protected by copyright laws © Nestlé, 1994, Revision 2009. N67200 12/99 10 M and is also a registered trademark of ®Société des Produits Nestlé S.A., Vevey, Switzerland, Trademark Owners. www.mnaelderly. com)

Social Support and Environmental Assessment

For older frail patients, the presence of a good social support is often the determining factor of whether a functionally dependent older adult remains at home or is institutionalized. The lack of available family and friends as caregivers may lead to poor posthospitalization outcomes [72]. Those who are cognitively impaired and without reliable family mem-

Mini Nutritional Assessment

Nestlé Nutrition Institute

La	st name:				First na	me:			
Se	ex:		Age:	Weight, kg:		Height, cm:		Date:	
Con	nplete the s	screen by	filling in	the boxes with the appro	priate numb	ers. Total the	numbers fo	or the final so	reening score.
S	creening								
A		intake de		over the past 3 months	due to loss	of appetite,	digestive p	problems, cl	hewing or
	0 = severe decrease in food intake 1 = moderate decrease in food intake 2 = no decrease in food intake								
в	0 = weigh 1 = does	not know	ater than	t 3 months 3 kg (6.6 lbs)					
	2 = weigh 3 = no we		ween 1 a	nd 3 kg (2.2 and 6.6 lbs)					
С	Mobility 0 = bed o	r chair boi	und						
	0 = bed or chair bound 1 = able to get out of bed / chair but does not go out 2 = goes out								
D	D Has suffered psychological stress or acute disease in the past 3 months?								
E	E Neuropsychological problems 0 = severe dementia or depression 1 = mild dementia 2 = no psychological problems								
F1	Body Mas	ss Index (BMI) (w	eight in kg) / (height in	m) ²				
	0 = BMI less than 19 1 = BMI 19 to less than 21								
		1 to less to 3 or great							
	IF BMI IS NOT AVAILABLE, REPLACE QUESTION F1 WITH QUESTION F2. DO NOT ANSWER QUESTION F2 IF QUESTION F1 IS ALREADY COMPLETED.								
F2	F2 Calf circumference (CC) in cm 0 = CC less than 31								
3 = CC 31 or greater									
	Screening score								
(n	(max. 14 points)								
	2-14 point			ormal nutritional st trisk of malnutritio	Care Care -				Print
	7 points			Alnourished					Reset

bers or caregivers may have difficulty remembering preoperative instructions and following through on postoperative plans including wound care and medication changes. It is often prudent to question who would be available to help if the patient becomes ill even in robust and healthier older adults.

The older adult's social support structure can be assessed by asking questions during the social history and also be triggered if dependency is noted during the functional assessment. For example, the clinician should inquire as to who provides help for the specific ADL and/or IADL functions and what time and days these individuals are available. Social work can assist in inquiring about social support prior to surgery allowing for more careful investigation and planning. For some, the lack of adequate social support may mean bringing in other paid or unpaid/family caregivers postoperatively, and for others, this may mean at least a temporary need for nursing homestay after surgery. Careful planning for those with inadequate social support can reduce unnecessary prolongation of hospitalization after surgery to make necessary arrangements and can help ensure that the patient has the needed support to follow through on postoperative recommendations.

Frailty

Frailty is a clinical syndrome that affects 10%-20% of community-dwelling older adults and is one of the leading causes of morbidity and mortality in older adults [73]. A recent consensus statement defined frailty as "a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death" [74]. Due to rapid population aging, the prevalence of frailty is expected to exponentially increase over the next few decades. The care of older adults with frailty will continue to pose significant and unique challenges to providers and the health-care system. Moreover, as the number of older adults undergoing major surgery increases, the impact of frailty on the perioperative management of older adults will require further research to optimize care and outcomes for these vulnerable patients.

Factors that influence frailty include age, body mass index (including obesity), comorbidity, cognitive impairment, dementia, and environmental or lifestyle factors. Frailty exists on a spectrum to a state of failure to thrive, inanition, and ultimately death. Frailty in older individuals is characterized by diminished physiologic reserve with a heightened vulnerability to decompensation and serious adverse health outcomes following acute stressors. Acute stressors can be minor in nature and result in significant morbidity in frail older patients.

Frailty is an adverse prognostic risk factor for many chronic diseases prevalent in older adults, such as cancer, dementia, coronary artery disease, congestive heart failure, and chronic kidney disease. Thus, there is a relationship between frailty and comorbidity. Frailty is associated with functional decline and disability but can occur independent of these outcomes. Interventions that impact upon frailty are a rapidly developing area of basic and clinical research, and more data are needed to provide optimal medical and surgical care for frail older individuals. Interventions that influence the progression of frailty are currently limited and thus a high research priority.

Pathophysiology

Frailty is a dynamic, accelerated aging process where genegene and gene-environment interactions play a significant role in its development and progression. On a systems level, age-related declines in multiple physiological systems, such as the neurologic, musculoskeletal, endocrine, and immune systems, contribute to frailty. Dysregulation of these physiologic systems along with chronic inflammation and changes in levels of steroid hormones and 25-hydroxyvitamin D influences the development of sarcopenia, which is a key feature in those with moderate to severe frailty. Elevations in pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF- α), and C-reactive protein (CRP) promote chronic low-grade inflammation and contribute to the high prevalence of subclinical and clinical cardiovascular disease among frail individuals.

On a cellular level, cell senescence is a driver of aging phenotypes. Senescence is a state of irreversible growth arrest that occurs in cells upon genotoxic damage, which is a protective mechanism against cancer development. Senescent cells accumulate with aging in tissues. However, this protective mechanism early in life paradoxically promotes aging phenotypes such as cancer in late life. This observation occurs due to elaboration of the senescenceassociated secretory phenotype (SASP) by senescent cells, which is pro-inflammatory and pro-tumorigenic in nature [75]. Clearance of senescent cells with small molecule inhibitors has shown promise in reversing signs of agerelated pathologies, such as sarcopenia in preclinical models [76]. Thus targeting of senescent cells holds promise to improve our ability to potentially treat and reverse frailty and other age-associated diseases, such as cancer and cardiovascular disease.

Diagnosis

Screening

There is currently no gold standard for the diagnosis of frailty. Many frailty tools exist in the literature; however, most are difficult to operationalize into routine clinical practice due to their length or need for technology to measure handgrip strength and gait speed. The gestalt approach to diagnose frailty is unreliable and bias prone. Frailty among obese individuals, termed "sarcopenic obesity," can be overlooked due to excess adipose tissue masking low muscle mass.

Fried and colleagues characterized the frailty phenotype in a longitudinal study of community-dwelling older adults, which was predictive of adverse health outcomes [77]. The frailty phenotype was defined as a clinical syndrome with three or more of the following features: unintentional weight loss (10 lbs. in the past year), self-reported exhaustion and weakness (measured through grip strength), and slow gait speed and low physical activity. Individuals meeting two features were considered pre-frail and were at intermediate risk for adverse outcomes compared to non-frail individuals. The frailty phenotype was independently predictive of falls, disability in activities of daily living, hospitalization, and mortality. The study also showed that frailty was not synonymous with either comorbidity or disability. Rather, comorbidities were a risk factor for frailty, and disability was an outcome of frailty. Frailty was associated with lower socioeconomic status and education as well, demonstrating that extrinsic factors contribute to the syndrome of frailty.

Another conceptual model of frailty is based upon the accumulation of deficits with advancing age. The Frailty Index was devised by Rockwood and colleagues which evaluates impairments in medical, social, psychological, nutritional, and functional domains along with laboratory abnormalities. The more deficits that accumulate in an individual, the more likely for the development and progression of frailty [78]. In addition, there is a positive correlation in the severity of cognitive impairment with frailty.

Prior to the diagnosis of frailty, it is important to exclude potential conditions that can also present with signs and symptoms of weakness, weight loss, and functional decline. Depression, cognitive impairment, thyroid dysfunction, cardiovascular disease, and hematologic and malignant conditions should be considered in the differential diagnosis. A careful medication review should be performed and evaluation for potential drug-drug interactions and adverse drug effects. Other considerations in evaluation of frail patients are psychosocial factors such as food insecurity or dependency for feeding and activities of daily living. A general laboratory work-up for frail patients should include a complete blood count with differential, chemistry panel, liver function panel, prealbumin, vitamin B12, 25-hydroxyvitamin D, thyroid function tests, and hemoglobin A1c. Ageappropriate cancer screening should be considered.

The ability to detect frailty is important because it can help guide clinical decision-making and identify patients at high risk for adverse outcomes. A positive frailty screen should be followed by a comprehensive geriatric assessment (CGA). The 2013 Frailty Consensus recommended screening for frailty for all persons 70 years or older and those with significant (>5 lbs.) unintentional weight loss in the past year [74]. The current evidence to date supports screening for frailty as a variable in the perioperative risk assessment in older adults. Baseline preoperative frailty has been consistently correlated with poor surgical outcomes, serious adverse events, prolonged length of stay, discharge to an institutional care facility, hospital readmissions, and short- and long-term mortality.

However, no consensus exists on which frailty screening and measurement tool to use. The most well-developed and well-validated are the Fried criteria, Frailty Index, Edmonton Frail Scale, FRAIL Scale, and Clinical Frail Scale-9 (CFS-9). The CFS-9 developed by Rockwood and colleagues was found to be the best predictor of 1-year mortality in hospitalized geriatric patients, when compared to other frailty screening methods [79]. A study by Revenig and colleagues demonstrated that frailty assessment is feasible and provides critical information not captured by traditional surgical risk assessments. These authors used a modified version of the Fried frailty phenotype with shrinking and grip strength and inclusion of hemoglobin and American Society of Anesthesiology Class as additional variables [80].

Following the identification of frailty on a screening tool, comprehensive geriatric assessment can identify other geriatric syndromes that can be optimized in frail individuals and improve perioperative outcomes [81]. Among the criteria in the frailty phenotype, as a single measure for screening, gait speed (m/s) appears to be the best predictor of many adverse health and postoperative complications.

Consequences of Frailty

Frailty increases risk of mortality by twofold, independent of age and comorbidities. For frail older adults who are hospitalized or undergo surgery, these individuals are at increased risk of complications, delirium, cognitive decline, infection, sepsis, prolonged length of stay, institutionalization, disability, and death. In a recent analysis of the National Surgery Quality Improvement Program database, frailty was shown to have a significant impact on postoperative outcomes that varied with type of surgery but did not necessarily correlate with complexity of surgery. Colectomy, esophagectomy, lung resection, pancreatic resection, cardiac procedures, gastrectomy, nephrectomy, endovascular abdominal aortic aneurysm repair, and lower-extremity bypass surgery had the highest to lowest mortality rates in severely frail individuals [82]. Frailty has an important role in trauma care as well. Trauma centers are experiencing a disproportionate rise in the number of elderly trauma patients. Knowledge of the magnitude of frailty on trauma outcomes is needed. However, measures that are easy, reliable, and validated in the trauma population are limited [83]. Surgical intervention in patients who are frail requires knowledge of the patient's priorities and goals of care in order to set realistic expectations on outcomes, impact on quality of life, and prognosis.

Frailty in Cardiovascular Disease

The majority of cardiovascular deaths occur in older adults. Frailty is common in older adults with cardiovascular disease (CVD) and confers a twofold increase in mortality even after adjusting for age and comorbidities [84]. Congestive heart failure, chronic angina, and symptomatic atrial fibrillation may limit exertional capacity and contribute to frailty by reducing exercise tolerance and muscle function. Cardiac rehabilitation, which is underutilized, improves outcomes in patients with CVD and may be of particular benefit for frail patients.

The Cardiovascular Health Study screened for subclinical CVD in 4735 older adults. Frail individuals had increased prevalence of wall motion abnormalities and LVH on echocardiography, prehypertension, abnormal ankle brachial indexes, carotid artery stenosis, and brain infarcts on magnetic resonance imaging, which were clinically silent [85]. Current guidelines by the American College of Cardiology/ American Heart Association (ACC/AHA) do not discuss frailty. A better understanding of the impact of frailty on CVD outcomes may improve the care of patients with CVD.

Interventions for Frailty

Frailty is potentially reversible if diagnosed early. Teambased and multimodal care which emphasizes physical exercise and treatment of protein-calorie malnutrition improves outcomes for frail older adults [86]. Physical exercise provides benefit to frail persons. However, the type of exercise, such as strength training, resistance, and/or aerobic exercises, and the optimal duration remains unclear [87]. Inclusion of palliative care services is also important for patients who are moderately to severely frail to establish patient-centered goals of care and provide support and symptom management.

Many questions regarding frailty remain to be answered by the field, from the best screening and measurement tools to the most effective interventions. Tools to screen and measure frailty need to be easy to administer, reliable, objective, and validated in the population specific to the patient. Identification of frailty or pre-frailty biomarkers is a rapidly developing area of investigation with the goal to standardize diagnoses, improve prognostication, and monitor the response to interventions. Pharmaceutical drugs are being developed and investigated in preclinical models that can potentially reverse frailty or halt its progression. Clinical trials are needed to evaluate the impact of "prehabilitation" on surgical outcomes in older adults with frailty. The optimal strategy for anesthesia on patients who are frail remains to be defined with the goal to reduce postoperative delirium and cognitive impairment.

Conclusion

A geriatrician's assessment integrates goals setting, prior functional assessment, and identification of complicating geriatric syndromes into the usual perioperative assessment. Many geriatric conditions and syndromes have multiple causes and contributors that lead to weakness, unintentional weight loss, poor endurance with reduced physiologic reserve, and heightened vulnerability to disability and/or death. Improving the standard of care for these vulnerable patients requires multimodal and interdisciplinary care. Reducing disability and frailty will substantially impact patient quality of life, improve patient-centered outcomes, and reduce health-care utilization and costs.

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Medicare, Administrative, and Financial Matters in Caring for Geriatric Patients

9

Laura Tarlow

Glossary of Technical Terms

АА	Anesthesiologist Assistants
ACA	Affordable Care Act
ACO	Accountable Care Organizations
AMA	American Medical Association
AMCs	Academic Medical Centers
APM	Advanced Alternate Payment Method
ASA	American Society of Anesthesiologist
CJR	Comprehensive Care for Joint Replacements
CMS	Centers for Medicare and Medicaid Services
CPIA	Clinical Practice Improvement Activities
CRNA	Certified Registered Nurse Anesthetists
DME	Direct Graduate Medical Education
DSH	Disproportionate Share Hospitals
EHR	Electronic Health Record
ERSD	End Stage Renal Disease
FPL	Federal Poverty Level
GDP	Gross Domestic Product
GME	Graduate Medical Education
GRNA	Graduate Registered Nurse Anesthetists
HCFA	Health Care Financing Administration
HI	Hospital Insurance also known as Part A
HIPAA	Health Insurance Portability and Accountability
	Act of 1996
IME	Indirect Graduate Medical Education
MACRA	Medicare Access and CHIP Reauthorization Act
	of 2015
MACs	Part A/B Medicare Administrative Contractors
MAV	Measure Applicability Validation
MedPac	Medicare Payment Advisory Committee
MFS	Medicare Fee Schedule
MIP	Merit Incentive Program

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MMA	Medicare Prescription Drug Improvement
	and Modernization Act
OCR	Office for Civil Rights
OIG	Office of the Inspector General
ONC	National Coordinator for Health Information
	Technology
Part A	Medicare Hospital Expenses Insurance
Part B	Medicare Voluntary Physician and Related
	Services Insurance
Part C	Medicare Advantage Plans
Part D	Prescription Drug Plans
PCMH+	Patient Centered Medical Homes Plus
PHI	Patient Health Information
PQRI/PQRS	Physician Quality Reporting Initiative
PRA	Per-Resident Amount
PSH	Perioperative Surgical Home
QCDR	Qualified Clinical Data Registries
RBRVU	Resource Based Relative Value Unit
RUC	Relative Value Update Committee
RVUs	Resource Value Units
SGR	Sustainable Growth Rate
SMI	Supplementary Medical Insurance; Also
	Known as Part B
SRNA	Student Nurse Anesthetist
THCGME	Teaching Health Centers GME
TRHCA	Tax Relief and Health Care Act of 2006

Many anesthesiologists' practices include geriatric care primarily for patients who are insured via Medicare, the federal health insurance program for citizens over the age of 65. The Medicare program has grown steadily in complexity and cost since its inception in 1965. It is expected to come under significant financial pressure as the population of the United States ages and the costs of providing healthcare continues to grow at ever-increasing rates.

This chapter provides those anesthesiologists who care for the geriatric patient population with an introduction to key health policy issues related to the Medicare program and facilitates understanding of the demographics and economics of geriatric care with special emphasis on Medicare. The first part of the chapter is a general introduction and overview of the demographic and financial issues facing Medicare in the near future. The second part of the chapter raises some of the major policy issues that are specific to the practice of anesthesiology under the Medicare program. The third part poses thought-provoking questions for consideration on the societal impact of a growing geriatric population.

Medicare : Organizational and Financial Overview

The Enactment of the Medicare Program

Medicare is the federal program that provides healthcare insurance to all citizens who are at least 65 years old, those with end stage renal disease (ERSD), and to qualifying disabled Americans. The program was enacted in 1965 with passage of one of the most important pieces of domestic legislation of the post-World War II period until 2010 when the Patient Protection and Affordable Care Act (ACA) was signed into law [1]. The legislative process that preceded the passage of the Medicare legislation was marked by years of debate and controversy setting the stage for a continued history of legislative compromises on public policy for the Medicare program.

From the Eisenhower administration onward, the US government struggled with how best to meet the high cost of healthcare for the elderly. Results of the 1950 census revealed that since 1900 the aged population had grown from 4% to 8% of the total population. Two-thirds of the elderly had annual incomes of less than \$1000, and only 1 in 8 had health insurance [2]. In response to the crisis, bills proposing hospital insurance for the aged were introduced in every Congress from 1952 through 1965 [3].

Legislators recognized and feared the power of organized medicine to thwart passage of legislation that involved government-sponsored health insurance. Therefore, when the Johnson administration made its proposal, it included a mandatory plan only covering hospital expenses for the elderly. This plan is what eventually became known as "Medicare Part A."

It was the Chairman of the House Ways and Means Committee in 1965, Congressman Wilbur Mills, who fashioned a compromise that led to the creation of "Medicare Part B," a voluntary plan for coverage of physician expenses for the elderly that was acceptable to the American Medical Association (AMA). In the compromise proposal for Medicare Part B, physician expenses were to be reimbursed on "usual and customary" charges as long as they were "reasonable" [4]. Physicians also retained the right to bill patients directly and in excess of the amount reimbursed by the government. On July 30, 1965, President Lyndon Johnson enacted the Medicare and Medicaid programs by signing the Social Security Act of 1965 with these words:

There are men and women in pain who will find ease. There are those alone and suffering who will now hear the sound of approaching help. There are those fearing the terrible darkness of despair and poverty—despite long years of labor and expectation—who will now see the light of hope and realization. [3]

The Organization and Funding of Medicare

The Social Security Administration administered the Medicare program from 1965 until 1977, when Medicare was reorganized under the Health Care Financing Administration (HCFA) within the Department of Health, Education, and Welfare. In July 2001, HCFA was renamed the Centers for Medicare and Medicaid Services (CMS) [5]. In 1966, the Medicare program covered more than 19 million citizens over the age of 65. Coverage for the disabled began in 1973 and in 2015 the program served more than 55 million Americans composed of 46 million elderly and 9 million disabled individuals [6].

The Medicare program provides coverage to the aged, the permanently disabled, and people with end stage renal disease under two parts: Hospital Insurance (HI) or Medicare Part A and Supplementary Medical Insurance (SMI) or Medicare Part B. The Medicare + Choice-managed care plan, also known as the "Medicare Advantage" program or Medicare Part C, was added by the Balanced Budget Act of 1997 and allows beneficiaries to opt for enrollment in private sector-managed Medicare insurance plans. The Medicare Prescription Drug Improvement and Modernization Act (MMA) of 2003 became effective in 2006, and extended a new prescription drug benefit to Medicare beneficiaries known as Medicare Part D.

The CMS contracts with private sector agents to administer Medicare program services comprised of provider enrollment, claims administration processes, local coverage determination/policies, provider education, and provider compliance with claims processing and policies. Prior to the Prescription Drug Improvement and Modernization Act (MMA) of 2003, Hospital Part A administrative function was handled separately from Part B. The MMA directed CMS to establish regions or jurisdictions upon which CMS awards contracts to Part A/B Medicare Administrative Contractors (MACs). In 2016 there are 12 A/B MACs serving different regions of the country. Many of the MACs have been providing services to Medicare since 1966, while others already in the health insurance business added a governmental service line specifically for Medicare. These MAC contractors are barred by law from making a profit on services provided to the Medicare program.

Enrollment in Medicare Part A is automatic for eligible beneficiaries and covers inpatient hospital care, after-hospital care in skilled nursing facilities, hospice care, and some home health services. Beneficiary enrollment in Medicare Part B is voluntary and covers physician services, outpatient hospital services, diagnostic tests, some home health services, medical equipment and supplies. By law, 25% of Part B program costs must come from beneficiary premiums [7].

Employers and employees, through payroll taxes, make mandatory contributions to the Part A Hospital Insurance (HI) Trust Fund, financing 87% of the Medicare HI program costs in 2016. Other funding sources include general tax revenues, patient funded deductibles and copayments, and premium payments from a small subset of beneficiaries. Part B is primarily funded 73% from general revenues and by law 25% from beneficiary premiums, while Part D is funded 74% from general revenues, 15% from premiums, and 11% from state payments for the dual eligible beneficiaries [8, 9].

Of the Medicare program's annual expenses of approximately \$648 billion in 2015, covering 55 million people of which 46 million were elderly, the total program income was slightly under \$645 billion. Expenditures were composed of 30% payment to hospitals, 26% for Part C premiums and administrative expenses, 13% for pharmaceuticals under Part D, and 11% for physicians with the remainder allocated to other expenses such as skilled nursing homes, home health, other general expenses, and administration costs [9]. This pattern of expenditures exceeding income has occurred since 2008 adding pressure for Congress to take further action to ensure the sustainability of the Medicare programs.

The Social Security and Medicare Boards of Trustees in their 2016 report noted that the Hospital Insurance Trust Funds are projected to be depleted by 2028. The report also predicts that the Supplemental Medical Insurance (SMI) Trust Fund, which pays for physician services and the new prescription drug benefits, will have to be funded by larger increases in premiums and increased transfers from general revenues. The trajectory of cost increase is estimated to go from 2.1% of GDP in 2015 to 3.5% in 2037 with general revenues funding three quarters of these costs and the balance funded by the beneficiaries through higher premium costs [6]. The combined HI and SMI expenditures are projected to increase from 3.6% of GDP in 2015 to 5.6% in 2040 [6]. Increases in the allocation of GDP to the Medicare program adds urgency for policy makers to bend the cost curve and to extract the best value for the dollars expended.

Twenty-First Century Realities and the Future of the Medicare Program

Baby Boomer Demographics

The so-called "baby boomer generation," the post-World War II Americans born between 1946 and 1964, will have a significant impact on the demographics of our society and on the Medicare program. (See Chap. 1). It is predicted that as the boomers age, the number of people in the United States aged 65 years and older is expected to nearly double with

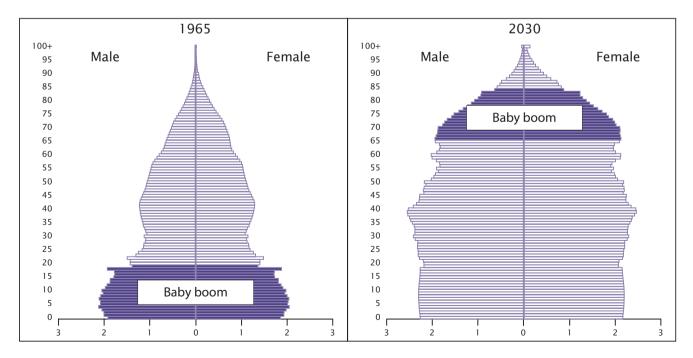


Fig. 9.1 Comparison of US population shifts from 1965 to 2030 highlighting the impact of the baby boomer generation Scale represent millions. United States Census Bureau.https://www.census.gov/prod/2014pubs/p25-1141.pdf

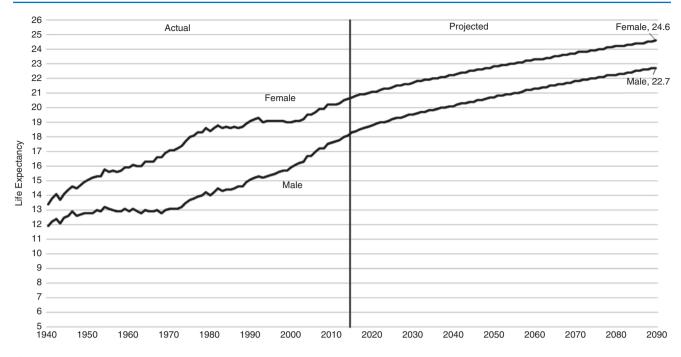


Fig.9.2 Life expectancy of 65-year-olds. Period life expectancy – 2015 OASDI trustees report (Based on data from Social Security Administration [16]).

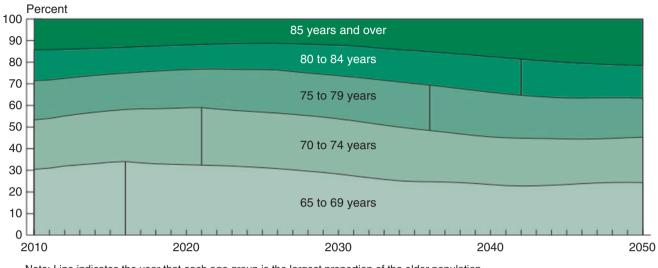
Medicare beneficiary levels increasing from 54 million beneficiaries in 2015 to over 80 million by 2030 [10]. Figure 9.1 highlights the continual demographic impact of the boomer generation as it ages [11, 12].

Given the existing methods of funding Medicare, it is clear that the aging of the American population will bring fiscal pressures to bear on the Medicare program in two ways: There will be more retired beneficiaries, as boomers age and live longer than their parents, and there will be relatively fewer workers to pay for the retiree expenses [13, 14].

It is predicted that the age group of those 65 and older will grow from approximately 13% of the total population in 2011 to 20% in 2030 and will remain above 20% for at least several decades, thereafter [15]. Life expectancies are continuing to increase with typical boomers projected to live approximately 2 years longer than their parents did and spending more years in retirement (Fig. 9.2). Life expectancy in the 15-year period before the enactment of Medicare (1950–1965) grew by 1% for males and 8% for females compared to a growth rate of 9% for males and 13% for females in life expectancy in the 15-year period immediately following the enactment of Medicare (1965-1980) [16]. From Medicare inception to 2014, overall life expectancy of the elderly increased by 5 years [17]. Prior to the start of the Medicare program in 1965, 48% of the elderly population had no insurance coverage compared to 2% of uninsured elderly in 2015 [17]. Access to care is one key variable influencing the gains in life expectancy. Life expectancies in 2011 were age 82.7 for 65-year-old males and age 85.2 for 65-yearold females [16]. See Fig. 9.2 for life expectancy trends.

With improvements in life expectancy, the older of the elderly cohort grows to represent a larger portion of the total elderly population. By 2050, close to 31% of the Medicare elderly population will be age 85 or older [18, 19]. See Fig. 9.3. This older population has the highest rates of disability and institutionalization and their medical care shifts from acute care to treatment of chronic conditions [20]. The prevalence of chronic disease drives healthcare expenditure where those with one chronic condition incur twice as much expense as those with no chronic conditions, and those with multiple chronic conditions have health expenditures seven times more than those with one chronic condition [21]. Those ages 80+ in 2011 represented 24% of the Medicare population but consumed 33% of the spending [18]. End of life care is a major contributing cost factor, but is not the sole reason for the increase in expenditures in the 80+ age group. In 2010 the elderly account for 75% of all inpatient hospital deaths [21, 22] with those age 85+ representing 27% of hospital deaths [21]. Within the population of the elderly, in 2009 32% of the elderly died in a hospital [20], and deaths of the other two-thirds occurred in their homes, post-acute care settings, nursing homes, or in hospices. For the latter two categories, the cost of care moves from Medicare to Medicaid as the care shifts from hospitalizations to facilities funded by Medicaid [23]. Where the elderly die may be one of the reasons why Medicare per capita spending for Part B services peaks at age 83 [18]. Whether it is Medicare or Medicaid expenditures, growth in medical care expenditures of the elderly population adds to the financial stress on governmental funding.

Distribution of the Projected Older Population by Age for the United States: 2010 to 2050



Note: Line indicates the year that each age group is the largest proportion of the older population. Source: U.S. Census Bureau, 2008.

Fig. 9.3 Distribution of the projected older population by age for the United States 2010 to 2050 (Based on data from Vincent and Velkoff [24])

As the elderly boomer population grows, the US working age population (ages 18–64) that contribute revenues to Social Security and the Medicare Part A fund will grow at a much lower rate. This dynamic will produce a decreasing ratio of working population to elderly with the rate of 4.6 workers to the elderly population in the late 1960s dropping to a projected rate of 2.4 workers to the elderly population by 2030 [10, 25]. With fewer workers supporting a larger elderly population for a longer period of time, the financial instability of the Medicare program will drive policy makers toward new solutions (Fig. 9.4).

Boomers and the Great Recession: Impact on Disposable Income

The Great Recession (2007–2009) contracted the economy to such an extent that the older boomers may not have sufficient time to recoup their lost income nor the value of their key assets, including their homes. Just prior to the Great Recession, those ages 65–69 saw their unemployment rate jump from 3.3% in 2007 to 7.6% in 2010. Due to the contracted economy, 42% of boomers and the Silent Generation (born between 1940 and 1960) stated in a Pew Research survey that they have already had to delay their retirement and 66% of those boomers who are closer to retirement age (50– 61) believe they too will need to delay their retirement date [26]. Currently 34% of boomers remain in the workforce with 29% expecting to retire at age 70 or later [27]. The level of seniors in the workforce is the highest in over half a century [28]. The Great Recession has also impacted financial support among generations with 44% of those 65 and older giving financial support to their adult children and 39% of adult children giving support to parents age 65 and older [26]. Over time there have been shifts in employer retirement plans, shifting from defined benefit plans to defined contributions plans. This shift is one more factor contributing to boomers having fewer retirement dollars, a greater reliance on social security income, and consequently less disposable income to fund healthcare expenses. It is estimated that 48% of the elderly population is economically vulnerable, defined as having income levels two times the supplemental poverty threshold, a rate that jumps to 58.1% for those 80 and older [29]. Due to Social Security coverage, the elderly are less likely to fall below the federal poverty level [29]. The Great Recession's impact on disposable income may have farreaching repercussions on healthcare decisions which require out-of-pocket expenses.

Baby Boomer Expectations

The baby boomer generation will bring millions of people into the Medicare program and these new beneficiaries will also bring with them a new set of expectations and a tremendous voting faction. They are the most educated generation with close to 90% having obtained a high school degree or GED and 24% in 2012 having earned a bachelor's degree or higher [15, 30, 31]. With their higher levels of education, the boomer population is expected to be more involved in their healthcare, exhibit more control on how they spend their health dollars, and have higher expectations of returning to

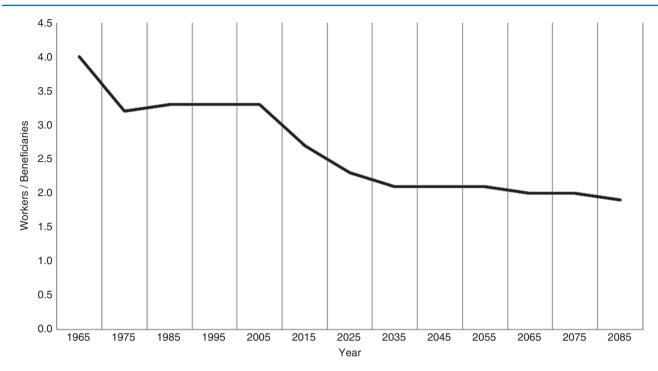


Fig. 9.4 Ratio of population ages 20–64 to population ages 65 and older (Based on data from Ref. [6])

an active lifestyle after a health event [30]. Baby boomers constitute the first generation born to the Medicare program and the first with significant experience with managed medical insurance plans. Over 70% of the older boomers (those ages 24-42 in 1988) started their work careers with traditional employer-sponsored plans that had few limitations on choice of providers, insurance paying large percentages of provider costs, and consequently almost no out-of-pocket costs. In contrast, the younger boomers have experience with managed care plans with defined narrow provider networks and high deductibles. For those boomers without employer insurance plans, they may have experience purchasing their health insurance through the federal and state exchanges under the Affordable Care Act [10]. A small statistic but interesting new trend is that close to half a million grandparents ages 65+ have primary responsibility for their grandchildren who live with them [15]. Baby boomers also include a significant number of women with work experience and, in general, are more affluent than their forebears. They expect to enter retirement with more assets yet remain concerned about their ability to fund their retirement experience. According to the Federal Reserve Bank of New York, 65-year-old borrowers have incurred more mortgage and auto debt (an increase of 47% and 29% respectively) in 2016 than in 2003 [32].

A survey conducted by Woelfel Research for the American Association of Retired Persons (AARP) and entitled, "As First Baby Boomer Turn 65, They're Feeling Good and not Ready to Quit" [27] and the more extensive paper "Approaching 65: A Survey of Baby Boomers Turning 65 Years Old" [33] examined the expectations, attitudes, and concerns of the baby boomers as they approach retirement. There were several key attitudinal findings from the survey which have important implications for the Medicare program.

In the survey 84% of boomers expressed a desire to take better care of their health, 31% are concerned about their health, and 28% believe their health will prevent them from achieving their retirement goals over the next 5 years. Unlike previous AARP surveys, where one in five expected to move to a new geographical area, in the current survey, only 2% stated their desire to relocate. Finances remain a large concern with 32% believing their financial situation is worse than they previously expected and 28% considering their finances to be an obstacle to achieving their dreams. Overall the boomers feel good about their accomplishments and where they are in life at this point in time. They are optimistic about the next 5 years and look forward to spending time with family, traveling, volunteering, and making time for interests and hobbies.

A Pew Research study in 2011 found that boomers overwhelmingly (85%) viewed Medicare and social security as good for the country and nearly two-thirds supported using Medicare benefits for purchasing private health insurance [34]. Only 37% of boomers (who, at the time of the study, were just entering the Medicare program) rated service as excellent. This contrasts with the 66% of those already fully in the program who rated Medicare as excellent [34]. The Pew Research study also found that additional solutions to extending the solvency of Medicare, such as gradually rising the eligibility age, was supported by 38% of boomers and 57% supported reducing Medicare benefits of those with higher incomes [34]. The generations ranging from the Millennials (Generation Y, those born in the early 1980s to early 2000s) to the Silent Generation were in agreement (52–64%) that the government does not do enough for our senior citizens with 43% of boomers believing it is the job of the government to ensure that the elderly have at least a minimum standard of living [34]. These expectations impact how the elderly interact with all aspects of their healthcare experiences.

Medicare Coverage Gaps

Medicare has not traditionally covered some services, requiring beneficiaries to fund those through out-of-pocket payments. Uncovered services included long-term nursing care, outpatient prescription drugs, routine vision, dental, hearing, and foot care. The Balanced Budget Act of 1997 extended coverage to include annual mammograms, Pap smears, prostate and colorectal screenings, diabetes management, and osteoporosis diagnosis. The Medicare Modernization Act of 2003 added pharmaceutical benefits. Further reductions in beneficiary out-of-pocket expenses are expected to be achieved through newly mandated coverage for wellness or preventative care services added under the Patient Protection and Affordable Accountable Care Act (ACA) of 2010. Even with all of these extensions of covered benefits, Medicare beneficiaries face significant out-of-pocket costs from age 65 until their death. Increases in life expectancy, prevalence of chronic conditions, the growth of premium costs, and the rising cost of medical care contribute to a rise in the Medicare lifetime out-of-pocket costs for the elderly. It is estimated that the lifetime out-of-pocket costs for a 65-year-old in 2010 will increase 72% by 2030 to an estimated \$223,000 of lifetime Medicare costs [35]. The composition of these projected costs is \$119,000 for out-of-pocket Part A costs, \$85,000 for Medicare Part B premiums and coinsurance, and \$19,000 for Medicare Part D [35]. Unaccounted costs from this list include extended home care, assisted living services, and uncovered nursing home costs. Relative to total personal expenditures, the elderly spend approximately 12% of their income on healthcare expenditures which is double that spent by all other consumers [15]. Figure 9.5 depicts the trajectory for increases in out-of-pocket and premium costs compared to average social security benefits [9].

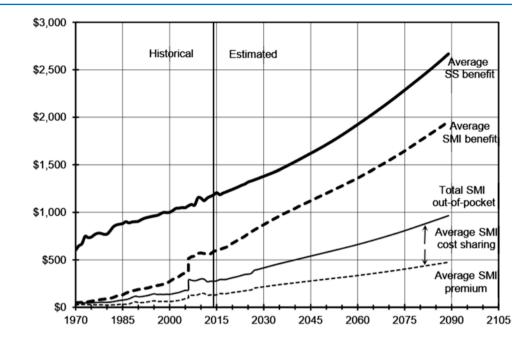
Medicare beneficiaries rely on privately purchased or government-sponsored supplemental insurance plans to "tie in" and complement the array of services covered by the Medicare program. Supplemental insurance coverage for these services has been historically provided by Medicaid plans (for the poor) and by so-called "Medigap" policies for those able to afford additional coverage. Approximately 90% of Medicare beneficiaries have supplemental insurance plans. Of those with supplemental insurance, in 2013 15% purchased Medigap insurance, 31% received supplemental insurance through employer retirement programs, and 28% purchased Medicare Advantage plans [10]. An additional 21% qualified for coverage through Medicaid. Medigap coverage is paired with traditional Medicare Part A, whereas Medicare Advantage plans combine Part A with Part B and may provide additional services typically not covered under the traditional Medicare plan. Enrollment in Medicare Advantage plan is growing at a pace of 10% per year [10].

Within the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) is a provision that Medigap insurance coverage will be prohibited from funding Medicare Part B deductibles for those who enter the Medicare program starting January 2020. Within the family of available Medigap policies, the Medigap Plan F currently provides coverage of a subscriber's Part B deductibles and Part B costs in excess of Medicare approved amounts. While Plan F may continue to exist for those currently in the plan, it will not be allowed to be offered to new entrants starting 2020 [36]. This MACRA policy goal is to shift the burden of additional healthcare expenditures to beneficiaries with hopes they will be better consumers and lower their utilization of services.

The Medicare Advantage plans (Part C) combine the coverage of Part A with Part B and may provide additional benefits found in the various Medigap plans. For example, some Part C plans include the Part D pharmaceutical coverage. Currently, the federal government pays Part C private insurers a percentage above the combined cost for traditional Medicare Part A and Part B plans largely due to their higher administrative costs. Federal policy efforts are underway to reduce this additional government funding to bring it closer to the actual premium costs of the traditional (original) Medicare. In 2016, the Medicare Advantage private insurers succeeded in obtaining a delay in proposed rate reduction. Unknown is how the benefits offered under Part C plans will be adjusted upon the occurrence of anticipated government funding reductions.

Some employers, mostly large companies, also sponsor health insurance plans that cover retired workers and their spouses. In 1988, before implementation of the Part D drug benefit, 66% of large firms offered retiree coverage [37, 38]. In 2010, 31% of Medicare beneficiaries had this type of employer-based coverage. In 2013, 28% of firms with more than 200 employees offered retiree health benefits [38]. This downward pattern of fewer employers covering retiree health benefits is well established.

As a result of these various coverage options and variability of out-of-pocket beneficiary costs, there is a level of Fig. 9.5 2015 annual report of the Boards of Trustees of the Federal Hospital Insurance and Federal Supplementary Medical Insurance Trust Funds. Comparison of average monthly SMI benefits, premiums, and cost sharing to the average social security benefits. Amounts are in constant 2015 dollars (Reprinted from 2015 annual report of the boards of trustees of the federal hospital insurance and federal supplementary medical insurance trust funds. https:// www.cms.gov/researchstatistics-data-and-systems/ statistics-trends-and-reports/ reportstrustfunds/downloads/ tr2015.pdf)



financial unpredictability. This variability challenges practicing geriatric medicine providers to become knowledgeable about the specific financial situation in which each of their Medicare-eligible patients can find themselves, especially as it may relate to the patient's ability to comply with treatment plans.

Prescription Drug Benefit

Medicare was late in providing prescription drug coverage relative to most private insurance plans and the universal public health plans in other developed nations that have traditionally provided this benefit as an important part of comprehensive health coverage. Drug therapies can reduce the need for hospitalization by effectively managing chronic health problems of the elderly such as heart disease, diabetes, and depression. Chronically ill patients have been found to underuse essential medications because of cost considerations and to suffer serious health consequences, including an increased number of emergency room visits and inpatient admissions, as a result [39].

All 55 million people on Medicare, including those ages 65 and older and those under age 65 with permanent disabilities, have access to purchase the Medicare drug benefit through private plans approved by the federal government. These Medicare plans are known as Part D or Prescription Drug Plan (PDP). In 2015, 68% or 37.8 million of the Medicare beneficiaries purchased Part D directly or had coverage through a Medicare Advantage plan [40].

In a nationwide survey of chronically ill older adults, it was reported that 33% underuse prescription drugs because

of concerns about out-of-pocket drug costs. Furthermore, 66% of these patients failed to discuss their intention to underuse medications with a clinician citing that no one asked about their ability to pay and that they did not believe that providers could offer any assistance [41].

The Part D plan requires beneficiaries to fund the first dollars known as the deductible. Once the deductible is funded (\$360 dollars in 2016), the Part D plan will pay 75% with the beneficiary paying 25% of the remaining pharmaceutical costs. In 2016, when the out-of-pocket costs reach \$3,310.00, the beneficiary enters the coverage gap known as the "donut hole" period where they encounter the greatest personal funding exposure. Not until their out-of-pocket drug expenditure reaches \$7,063.00 will the beneficiary exit the donut hole and then enter the catastrophic coverage phase where their Medicare Part D cost sharing is reduced to a more manageable 5% level. While in the coverage gap, Medicare beneficiaries pay between 45% and 58% of drug costs depending upon whether they purchase generic or brand name pharmaceuticals. Recognizing the financial burden of the donut hole, the 2010 Affordable Care Act gradually lowers the level of cost sharing to 25% for generic drugs by 2020. See Fig. 9.6 for the 2016 schema on prescription drug coverage cost share [42].

Part D financing comes from general revenues, beneficiary premiums, and state contributions. In 2016 enrollees' monthly premium is expected to cover 25.5% of the standard drug coverage. Medicare subsidizes the remaining 74.5%, from plans for their expected benefit payments. Enrollees who have incomes over \$85,000/individual and \$170,000/ couple pay a higher portion of Part D costs, ranging from 35% to 80%, depending on their income levels. In 2016,

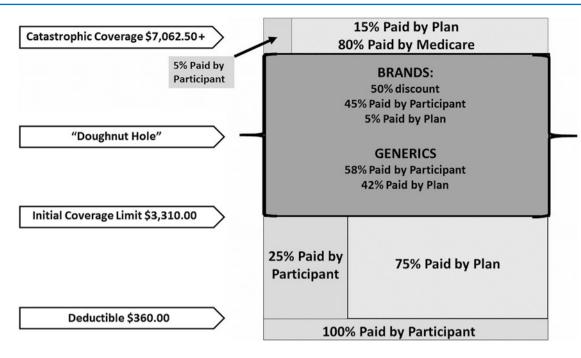


Fig. 9.6 Prescription drug coverage under Medicare effective 2016 (Based on data from Ref. [42])

almost half (49%) of the drug plans will offer basic Part D benefits (although no plans will offer the defined standard benefit), while 51% will offer enhanced benefits. Deductibles will be charged to most beneficiaries with 53% of PDPs charging the full amount (\$360). Copayments will be tiered, for covered drugs [42]. Additional gap coverage in 2016 will not be provided beyond what is required under the standard benefit. Additional gap coverage is often limited to generic drugs only [42].

Impact on the Near-Poor

In 2013, the Federal Poverty Level (FPL) was defined as between \$11,490 for an individual and \$23,550 for a family of four. At that time, 9.5% of the 65 and older population were considered in poverty and 14.6% or 6.5 million elderly were at the supplemental poverty rate [43]. Low-income seniors enrolled in Medicare are eligible for Medicaid coverage and are known as "dual eligible" beneficiaries. While Medicare funds Part A portion for dual eligible beneficiary, the Medicaid portion of funding is applied to assist with Medicare Part B and Part D premium costs, out-of-pocket costs, and services not covered by Medicare such as longterm care. The poorest of the dual eligible will have Medicaid fully fund both Part A and Part B premiums, and per the beneficiary's state-specific Medicaid regulations, a prescribed level of their Medicare deductibles and coinsurance. Medicaid coverage includes benefits such as prescription drugs, hearing aids, and payment for nursing home services.

In 2010, approximately 10 million elderly persons were dually eligible [44]. The rate of dual eligible beneficiaries increases with age, is more prevalent for females and is higher for non-whites. This population also tends to have more chronic conditions which is evident as the 14.6% of dual eligible consumed 34% of Medicaid expenditures in 2010 [43].

The Affordable Care Act (ACA) expanded the definition of the poverty from 100% to 138% of the Federal Poverty Level, thereby expanding Medicaid eligibility. States had the option of accepting the new definition along with additional federal funding or electing to maintain their current Medicaid program. In 2014, 29 states elected to expand their Medicaid programs resulting in a 9% expansion of newly coverage Medicaid eligible adults [45]. Further growth of Medicaid eligible adults is stymied by a number of factors: lack of awareness of eligibility, perception on whether or not they qualify, the difficulty of the application process, and the required reassessments to retain coverage. These factors result in an estimated 8 million eligible individuals not enrolling in Medicaid [46]. The ACA regulations are addressing enrollment issues through mandated improvements in outreach, enrollment assistance programs to reduce the number of eligible not enrolled in Medicaid and better coordination through the newly established Federal Coordinated Health Care office also known as the Medicare-Medicaid Coordination office.

It is the near-poor, those with annual incomes between the poverty level and 200% of Federal Poverty, who are most often caught in the prescription drug cost quandary. In 1999,

only 55% of the near-poor had coverage for the entire year and more than 20% of those with prescription drug coverage received it via a Medicare Advantage plan. Access to prescription drugs and levels of reimbursement for prescription drugs has decreased significantly under these managed-Medicare plans since the Balanced Budget Act of 1997. As a result, the near-poor had higher out-of-pocket costs for prescription drugs in 1999 than other Medicare beneficiaries who were poorer (and therefore, Medicaid-eligible), and those with higher incomes [47]. While the ACA program expands assistance for Part D, the near-poor who fall into the coverage gap of this voluntary program will continue to be plagued by out-of-pocket prescription drug costs

The Medicare Trustees 2016 report stated that over twelve million beneficiaries are currently receiving the Low-Income Subsidy. For dual eligible beneficiaries, who do not enroll, Medicare will automatically enroll them into a prescription drug plan.

Medicare and the Academic Medical Center

The Medicare program has many shortcomings and, over the next two decades, significant reform will be required to maintain even the current level of protection that it offers to America's elderly. This looming crisis in healthcare insurance, for the elderly, is of great concern to lawmakers and the public but should also be of similar concern to healthcare providers, hospitals, and physicians, who rely on Medicare as a significant source of their revenues. The healthcare share of the GDP for the entire population (not just the Medicare population) including out-of-pocket costs is expected to rise from 17.5% in 2014 to 20.1% by 2025 [48]. The combined efforts of all levels of government (federal, state, and local) are projected to finance 47% of national health spending by 2025 representing an increase from 45% in 2014 [48].

Academic medical centers (AMCs) represent about 5% of the total hospitals in the nation and treat approximately 37% of all charity care and 26% of Medicaid care [49]. AMCs account for 80% of the designated level 1 trauma centers and offer specialized services such as burn centers and transplant service not readily found in other hospitals within their geographic catchment areas. With higher rates of caring for the disadvantaged population, higher costs associated with the specialized care, and reduced opportunities to shift the costs to private insurers, the federal government provides additional financial assistance through what is known as disproportionate share payments. Most hospitals receive some level of these payments and are referred to as disproportionate share hospitals (DSH). Hospitals with the highest DSH payment are also known as safety net hospitals. The ACA also addressed DSH payments by dividing it into two pools: (1) 25% of the pool allocated for the traditional/current formula of determining hospital payments and (2) 75% to be allocated for uncompensated care [50]. Because the ACA program provides for expansion of Medicaid coverage and coverage for the uninsured, the second pool under the ACA is set to decline over time. The reductions were set to occur in the periods of 2014–2020 and were then expected to return to pre-ACA funding levels in 2021. The MACRA legislation delayed the start of the reduction date to 2018 thereby extending the reduction period through 2025 [51]. With reductions in DSH payments, academic medical centers will bear additional financial pressures.

Physicians in academic practice have even greater reason to be interested in the plight of the Medicare program. In addition to the significant flow of funds received by academic medical centers (AMCs) in the form of clinical revenues, AMCs are dependent on the Medicare program for support of graduate medical education (GME) and care provided to indigent patients. All undergraduate medical students and almost 50% of all residents are trained in AMCs. AMCs differ from many community hospitals due to the patient population of higher levels of charity care and offering highly specialized services such as neonatal, burn, trauma intensive care, and organ transplant services [52].

Graduate Medical Education Payments

Since the initiation of the Medicare Prospective Hospital Payment System in the mid-1980s, graduate medical education (GME) payments have been made to AMCs to reimburse them for Medicare's share of the costs of resident physician education. AMCs are eligible for two types of reimbursements: direct graduate medical education (DME) covering direct costs such as resident and faculty salaries and benefits and indirect graduate medical education (IME), recognizing the relatively larger inpatient costs at hospitals with teaching programs.

GME is funded by the federal government to the tune of approximately \$9.5 billion in Medicare funds, \$2 billion in Medicaid dollars [53], and \$300 million via a new program called teaching health centers GME (THCGME) funded through the ACA. THCGME trains residents in communitybased ambulatory settings and through contributions from other agencies, including the Department of Defense, the Department of Veterans Affairs, the Health Resources and Services Administration, and the National Institutes of Health [54].

GME relies heaviest on Medicare for its funding of over 90,000 residents in 1100 hospitals. In 2012 \$9.7 billion dollars were provided to teaching hospitals for the training of physicians. Medicaid added another \$3.9 billion dollars [55]. GME costs are comprised of direct graduate medical education payments (DME) to hospitals for residents' stipends,

faculty salaries, administrative costs, and institutional overhead and an indirect medical education (IME). IME provides funds to teaching hospitals due to the higher patient care costs of teaching hospitals relative to non-teaching hospitals. DME payments are predicated on each teaching hospital's base reporting period of 1984 or 1985. Utilizing the base year DME costs and the number of residents, a per resident amount is established and updated annually for inflation. Medicare limits the growth in DME costs in two other ways: (1) CMS caps the number of residents it will support and (2) they reduce the DME count of a resident from 1.0 FTE (full time equivalent) to 0.5 FTE for any resident that exceeds their initial residency training period or exceeds a 5-year training period.

The ACA legislation touched upon DME and IME funding when it expanded coverage in 2010 to include nonprovider settings such as physician offices. As long as the hospital incurs the cost of the resident stipend and fringe benefits for this patient care setting, Medicare will allow the resident's time to be counted toward DME and IME payments. As care migrates from the inpatient setting to the outpatient setting and to physician offices, resident training may be expanded to cover office-based care including anesthesia services [56].

In 2012 Medicare GME payment was allocated to \$2.6 billion dollars for DME and \$6.8 billion dollars for IME. The Medicare Payment Advisory Committee (MedPac) testified before congress in July 2015 that the formula for these payments is outdated and out of alignment with the marketplace. MedPac recommended that 60% of IME dollars be aligned with educational and teaching program criteria that touch upon a range of clinical settings and where the resident curriculums encompass team-based care and a focus on improvements in the value of care [50]. These recommendations align with Medicare's payment reforms transitioning from volume to value for provider payments.

Hospital and physician providers at the AMCs serve important roles in meeting the healthcare needs of underserved populations and in advancing the science of healthcare through education and research. These providers are paid by Medicare to perform these vital functions in shaping the future of the healthcare system. However, the same federal system continually challenges these providers to maintain a commitment to education, research, and charity care despite declining reimbursement for these activities.

"Pay for Performance" Initiatives

Payments to physicians from the Medicare Part B program originally employed a payment formula based on regional "usual and customary" charges by physician specialty. In 1989 the Omnibus Budget Reconciliation Act was signed into law ushering in a new physician fee schedule construct that was predicated on a resource-based relative value scale (RBRVU). The new fee schedule began in 1992. However, ASA successfully argued that anesthesiologists should not be part of the RBRVU system, but compensated for time and a relative value system long used. Thus, Medicare reimburses anesthesia services via a separate methodology under RBRVS that uses the sum of procedure-specific relative value units and the variable time units. The sum of these units is then multiplied by an anesthesia-specific conversion factor that is adjusted for geographic cost differences. It was the retention of the time unit factor in the anesthesia payment methodology that drove HCFA (CMS) to create a separate anesthesia conversion factor under RBRVS.

The AMA and specialty societies have input on establishing the resource unit values for each procedure code (CPT code), and CMS establishes the national conversion factor which is then adjusted geographically to reflect regional differences in practice costs. The regionally adjusted conversion factor is multiplied by the resource value units (RVUs) to determine the payment for professional services. Included in the Omnibus act was a safety valve known as the sustainable growth rate (SGR) which served to restrict fee schedule increases if total volume of services increased at a rate greater than the gross domestic product (GDP), thereby maintaining budget neutrality. The first SGR-related rate reduction occurred in 2002, setting in motion Congressional fixes every year from 2003 until 2014. The SGR's annual and sometimes biannual "kicked the can" down the road fix was permanently replaced with the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) providing a new framework of adding rewards and risk to physician payments.

Since the inception of the Medicare program in 1965, hospitals have had utilization review programs and quality reporting requirements. Over time Medicare has imposed financial constraints tied to hospital outcomes such as length of stay or more recently penalties for hospital readmission rates. For physicians, quality reporting started as a voluntary program in 2007 known as the Physician Quality Reporting Initiative (PORI), now called the PORS, which emulated from the 2006 Tax Relief and Health Care Act (TRHCA). The voluntary program was made permanent in 2008 under the Medicare Improvement for Patient and Providers Act. This act also requires CMS to publicly post group names and eligible provider names who satisfactorily reported the PQRS measures, giving the public an opportunity to check on their physicians and compare physician results. The Affordable Care Act of 2010 further embraced quality reporting and created a budget neutral penalty and reward program. The first set of incentives and penalties were awarded to physicians in 2015 based on PQRS measures providers reported in 2013.

Anesthesia Pay for Performance

Starting in 2016, anesthesia practices report their PQRS measures through Medicare Qualified Clinical Data Registries (OCDR). Each registry can elect to utilize the ASA's Anesthesia Quality Institute's (AQI) Medicare approved list of quality measures or elect other certified registries which have their own Medicare approval measures. Measures are broken into six domains which include (1) patient safety, (2) person and caregiver-centered experience and outcomes, (3) communication and care coordination, (4) effective clinical care, (5) community/population health, and (6) efficiency and cost reduction. To successfully report PORS through a registry in 2016, anesthesiologists must select a minimum of nine measures which come from a minimum of three domains and include two measures related to outcomes [57]. Not all anesthesiologists will be able to successfully report on nine measures due to the sub-specialization of their practices-such as a high percentage in OB or pediatrics or non-cardiac care cases where some of the measures are not applicable. For those providers reporting fewer than nine measures, Medicare employs a measure applicability validation (MAV) tool to verify that all applicable measures were applied to a provider's Medicare cases [57]. Those reporting fewer than the nine measures and having passed the MAV process will not incur a penalty. The PQRS reporting process can be challenging for anesthesiologists.

New Value Based Programs: Merit Incentive and Alternate Payment Models

The passage of MACRA solidified the direction CMS is taking the provider community relative to cost efficiency and clinical outcomes. For the 2017 reporting year, there are two pathways for engaging in quality programs: merit incentive program (MIPS) and a more robust advanced alternate payment method (APM). Each program has rules of engagement and reporting that will produce incentive payments, neutrality, or financial penalties [58].

In general, under the MIPS program, reporting providers have the opportunity in the initial year to acquire or lose a maximum of 4% of their Medicare payments. As this is budget neutral, all providers are competing against one another with the top performers obtaining a maximum 4% Medicare Part B incentive payment acquired from all the providers' assessed penalties ranging from 1% to 4%. In the initial year CMS has an additional budget of \$500 million to be awarded to the best of the best potentially bringing their total incentive payments to a 10% level. By 2022 the base incentive and penalties will grow to 9% of Providers' Part B payments [58, 59]. The MACRA regulations require the publication of providers' annual results on the Medicare Compare website accessible by all consumers.

The MIPS program, under which CMS expects the largest percent of physician participation versus the APM program, has four weighted categories of reporting requirements. These categories are: (1) quality measures, (2) clinical practice improvement activities (CPIA), (3) advancing care communication, and (4) resource use. The weights of the first two categories shift from 50% to 30% for the quality measures and from 10% to 30% for CPIA [58, 60]. Changes in the weights demonstrate CMS's continuing emphasis on bending the cost curve and improving clinical outcomes. The CPIA measures highlight CMS's desire to move providers from simply reporting quality measures to finding opportunities within those measures to modify clinical behavior toward improving clinical outcomes. The advancing care category replaces the electronic health record (EHR) meaningful use measures with more of a focus on using the benefits of electronic communication to improve care coordination. The last category, resource use, is not under a provider's control as CMS will assign beneficiary costs of care to providers. CMS recognizes that "non-patient facing" specialties such as anesthesiologists will not be able to report in all weighted categories (i.e., advancing care), and CMS will reallocate the weight(s) of any category where zero measures are expected to be reported. As with any new legislation, the details are complicated, and it behooves each practitioner to learn how best to adapt the rules to their practice to achieve maximum financial and reporting benefit.

The second pathway under MACRA is known as the advanced alternative payment method or APM. This is a "team sport" requiring participation in Medicare shared savings programs such as Next Generation Accountable Care Organizations (ACOs), Patient-Centered Medical Homes Plus (PCMH+), and new care models for which the participants accept financial risks. These models will require more than "nominal" financial risk where CMS has yet to define "nominal". In addition to assuming financial risk, CMS will determine key criteria such as outcomes improvements, EHR interoperability and other metrics for a program to be classified as an advanced APM.

One example of a surgically oriented APM is the multiyear CMS bundled payment program for comprehensive care for joint replacements (CJR). However, to add complexity, the CJR is not considered an "advanced" APM program, and participation in this will not be counted toward the APM pathway. A unique aspect of this program is in November 2015 CMS mandated approximately 800 hospitals to participate in the program starting in April 2016 [61]. A similar step is being taken for 2017 by mandating the hospitals required to participate in a cardiology and cardiac surgery bundled program. Most of the other APM models solicit voluntary applications from which CMS selects the participating groups/hospitals.

Under the APM program, providers who have at least 25% of the Medicare payments flowing through an approved APM model place their Medicare payments at risk [58, 59]. Participating providers in the APM program will obtain an automatic 5% lump sum bonus payment per year for each year from 2019 to 2024. After 2024 providers in APMs will receive a higher increase in their Medicare fee schedule than those providers that remain in the MIPS program [58, 59]. Upside financial rewards for providers in APMs will include shared savings.

The American Society of Anesthesiologists (ASA) is proposing to CMS that the perioperative surgical home (PSH), similar to the patient-centered medical home (PCMH), be included as a model payable under the APM. The perioperative surgical home is defined by the ASA as "a patient centric, team-based model of care created by leaders within the American Society of Anesthesiologists to help meet the demands of a rapidly approaching health care paradigm that will emphasize value, patient satisfaction and reduced costs" [62]. The ASA is actively engaged in identifying ways in which to monetize the PSH for the provider participants. With APMs, a single entity assumes responsibility for both Part A and Part B costs and sets the rules through collaborative agreements with all participating providers on how the net income (loss) is distributed. An APM's success will be gauged not only on controlling costs, but utilization of electronic records and improvements in health outcomes. Collaborative agreement serves as the legal mechanism for "splitting the pie" and, as such, anesthesiologists must become adept at defining their contributions and knowing their costs.

In any calendar year, providers will report to CMS either under the MIPS or the APM. The entry level to report under APM in 2016 is for a provider to have a minimum 25% of their Medicare Part B payments associated with an APM; otherwise, the default reporting program is the MIPS. Providers not participating in either program would be assessed a penalty on their Medicare payments. Figure 9.7 depicts the CMS timeline highlighting the incentives and penalties associated with each of the two MACRA programs [63].

In 2015, CMS established targets for 2016 and 2018 as to the percentage of fee for service payments that will be linked to either MIPS quality programs or APMs. For 2016 the goal was to have 30% of Medicare payments tied to APMs and

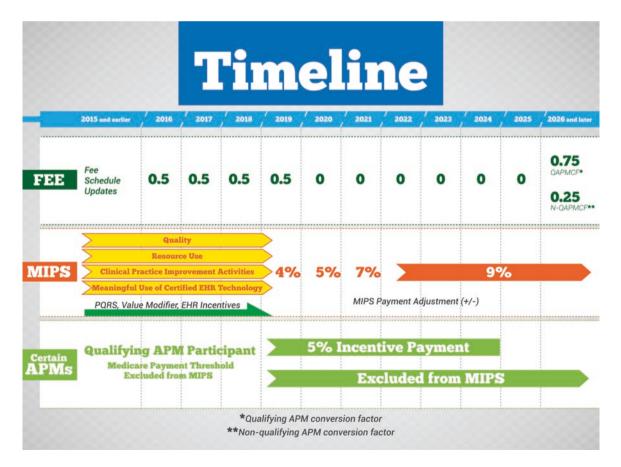


Fig. 9.7 CMS timeline for MACRA incentives/penalties (Reprinted from the Centers for Medicare and Medicaid services [63])

85% associated with any type of CMS quality and value programs including the PQRS and APM programs. By 2018, CMS's goal is for 50% of Medicare provider fees to be paid through APMs with another 40% paid under the other value programs [64]. In March 2016, CMS announced they achieved their APM target 11 months ahead of schedule. The APM programs are influencing private payers to collaborate with hospitals and physician practices in episodes of care and bundled payment initiatives. Medicaid through the Medicare-Medicaid Coordination office is also establishing APM programs and in 2016 announced an OB episode of care program. CMS ambitious targets for payments tied to quality programs along with private payer initiatives highlight the need for anesthesiologists to be actively involved with their hospitals in collaborative models to become familiar with the clinical and economic challenges of establishing, implementing, and monitoring all aspects of each APM program. Unlike specialized surgeons who may participate in a single APM (e.g., CABG, joint replacement, or GI), anesthesiologists will face the additional challenge of simultaneously participating in multiple APMs. Some of these challenges will require further investment in infrastructure to maintain the multitude of clinical pathways as well as the accounting of provider resources associated with each APM.

Medicare Policy Issues for the Geriatric Anesthesiologist

The regulations and processes governing a physician's interaction with the Medicare program are quite complex and a full description is well beyond the scope of this chapter. However, it is the author's intention to provide the practicing geriatric anesthesiologist with an introduction to policy issues specific to the practice of anesthesiology under the Medicare program. These key issues include:

- 1. Participation status in the Medicare program
- 2. Medicare's resource-based relative value system (RBRVS) for physician reimbursement
- 3. Medicare's rules for the anesthesia care team
- 4. Compliance-related issues for anesthesiologists

CMS provides a specialty-specific page on its website that is dedicated to Medicare regulations and information specific to the practice of anesthesiology. Physicians interested in further study of Medicare claims processing, fees, and policies for the reimbursement of anesthesia services should consult CMS's anesthesiologist web page at https:// www.cms.gov/Center/Provider-Type/Anesthesiologists-Center.html.

Anesthesiologist Participation in the Medicare Program

The decision to enroll as a participating provider in the Medicare program is one of the first decisions that an anesthesiologist faces when starting a clinical practice. Anesthesiologists engaged in geriatric practice can expect that the Medicare program will be the primary insurer for most of their patients. Anesthesiologists, who typically encounter their patients in an operating room setting where they are not the patient's primary provider, need to be aware of the political, patient satisfaction, and reimbursement issues related to their participation status in the Medicare program.

In 1990, only 30.8% of anesthesiologists participated in the Medicare program; this was the lowest rate of participation as a percentage of physicians by medical specialty. In 2000, participation by anesthesiologists was 93.7% and by 2011 the rate increased to 98.8%. This rate of participation closely matches that of physicians in related practices such as surgery, cardiovascular disease, ophthalmology, orthopedic surgery, pathology, radiology, urology, and nephrology [65].

It is likely that the anesthesiologist's obligation to care for all surgical patients and new Medicare rules limiting charges from nonparticipating providers, influenced anesthesiologist enrollment decisions in the 1990s. Unfortunately, as anesthesiologist Medicare participation rates increased dramatically in the period from 1990 to 2003, the Medicare anesthesia conversion factor in the same period was decreased by almost 20% [66]. One might speculate that, during a decade of significant growth in managed care and public outcry concerning increasing healthcare costs, the pressures from patients, colleagues, local government, affiliated institutions, and the Medicare charge limitations combined to favor participation by anesthesiology providers.

In general, participation in the Medicare program by anesthesiologists is a voluntary decision. Medicare participation by certified registered nurse anesthetists (CRNAs) and anesthesiologist assistants (AAs) is mandatory [67]. However, some states encourage physician participation through legislative actions and regulatory requirements, such as in the Commonwealth of Massachusetts, where Medicare participation is a condition of medical licensure. Physicians can consult with their local Medicare participation requirements [68].

Physicians who enroll as participating providers enter into a 1-year, automatically renewable agreement to accept assignment for all covered services provided to Medicare beneficiaries. When a physician accepts assignment, he or she agrees to accept the Medicare allowable charge as payment in full for the covered services rendered. After patients satisfy an annual deductible, Medicare pays 80% of the approved allowable charge. The remaining 20% is termed the "coinsurance," and it is the responsibility of the patient to pay this and any remaining portion of the annual deductible. Participating providers must bill the patient, or the patient's Medigap insurance plan, for coinsurance, deductible, and charges not covered by the Medicare Part B program.

In addition to the likely political and patient satisfaction advantages to Medicare participation, there are also financial and administrative opportunities. The most significant are that Medicare fee schedule allowances are 5% higher for participating physicians, and assigned Medicare claims filed with Medigap insurance information are automatically forwarded by Medicare to supplemental insurance carriers for processing of coinsurance and deductible charges [69]. A copy of the Medicare Participating Physician or Supplier Agreement (Form CMS-460) is available at https://www. cms.gov/Medicare/CMS-Forms/CMS-Forms/Items/CMS007566.html.

Medicare Payment Methodologies for Anesthesia Services

Medicare's Resource Based Relative Value System

In 1992, Medicare implemented the resource-based relative value system (RBRVS) that established a Medicare fee schedule (MFS) of national values for each clinical procedural code. The RBRVU value comprises three components representing the physician's work effort in rendering the service—the practice's overhead expenses for items such as rent, office staff salaries and supplies, and malpractice insurance premiums. A conversion factor is applied to convert the RVU into payment for services. Geographic adjustment factors are also applied to recognize variance in regional practice costs. Under RBRVS, Medicare also implemented a new definition of allowed charges that paid physicians based on the lesser of the submitted charge or the new relative value scale fee schedule-based amount [70].

At the time of the introduction of the MFS in 1992, anesthesiology already had a relative value scale for anesthesia payment in place for 30 years [71]. The American Society of Anesthesiologists (ASA) Relative Value Guide, adopted almost in its entirety by the HCFA in 1989, uses values that represent components of anesthesia services: the base unit value (related to the complexity of the service performed) and the time units (based on the actual time the anesthesiologist spends with a patient). The CMS definition of anesthesia time is as follows:

Anesthesia time means the time during which an anesthesia practitioner is present with the patient. It starts when the anesthesia practitioner begins to prepare the patient for anesthesia services in the operating room or an equivalent area and ends when the anesthesia practitioner is no longer furnishing anesthesia services to the patient, that is, when the patient may be placed safely under postoperative care. [72]

Medicare does not reimburse for modifier units, such as those designated by the ASA recognizing physical status, extremes of age, or unusual risk [73].

The Medicare Fee Schedule for Anesthesia Services

The distinction in the MFS for anesthesiologists has disadvantaged the specialty. A good illustration of the problem is the differential between Medicare and private insurance fees for anesthesiologists versus the differential for other medical and surgical specialists. The July 2007 GAO (US Government Accountability Office) report to congress noted that Medicare anesthesia fees were 61% lower than private payers while all other medical specialty average Medicare fees were 17% lower [74]. This differential continues as evidenced by the 2015 ASA survey for commercial fees with the national median commercial rate of \$68.00 per anesthesia RVU compared to the July 2015 national anesthesia conversion factor of \$22.6093 [75].

The ASA has raised this issue of disparity in Medicare fees many times with the AMA/Specialty Society Relative Value Update Committee (RUC). The RUC is the body charged with reviewing and advising CMS, by law, at least every 5 years on updates to work-related relative value units. In the first 5-year review, HCFA acknowledged the undervaluation and approved a nearly 23% increase in work values for anesthesia procedures, effective January 1, 1997 [76]. In the fee schedule effective after the second 5-year review, CMS again received endorsements for reconsideration of the anesthesia work relative value units but responded with an insignificant adjustment [66]. The President of the ASA in a letter dated May 30, 2013, wrote to US Senate Chairman of the Committee on Finance noting the "33% problem" and stated that the "ASA believes that acknowledgement and remedy of this inequity must be a precursor to moving forward in any future alternative payment model that is based upon the Medicare anesthesia conversion factor. Reductions to incorrect and inadequate payment are not sustainable for anesthesiologists and the patients they serve." [77]

The MFS is often referenced by private insurers as a standard in setting physician reimbursement rates. It is also common for physicians from other specialties, who enjoy a more favorable Medicare-to-private insurer fee ratio, to suggest the MFS as a proxy for valuing physician services. This often occurs during joint negotiations such as those used in dividing fees for contracts paid on a global or episode of care basis to physician groups. Anesthesiologists are disadvantaged when the MFS is used in this manner. It is, therefore, important for anesthesiologists to remain active in the discussion of these physician payment disparities and to work to educate others and thereby mitigate the effect of these disparities in the Medicare system and beyond.

The Anesthesia Care Team

There are a variety of ways for anesthesiologists to provide services for reimbursement under Part B of the Medicare program. Medicare reimburses the services of an anesthesiologist when the physician personally provides them or if an anesthesia care team provides them under medical direction or supervision. Anesthesia submitted claims modifiers are used to denote whether services were provided personally, "medically directed," or "medically supervised." Medicare reduces reimbursement based on the series of claims modifiers that denote how the services were delivered (Table 9.1).

The anesthesia care team is defined as an anesthesiologist working with any of the following professionals:

CRNAs AAs Residents or interns Student nurse anesthetists (SNAs) [78]

In most cases, when an anesthesiologist and a CRNA are providing a single anesthesia service, Medicare recognizes the service as if personally performed by the anesthesiologist. Graduate registered nurse anesthetists (GRNA) are not recognized by CMS as a qualified provider until they become certified. As such when an attending anesthesiologist is covering two or more rooms with a GRNA, the reimbursement is reduced 50%.

Medical Direction Versus Supervision of Concurrent Procedures

When an anesthesiologist is involved in directing up to four concurrent procedures, Medicare recognizes the services as concurrent medical direction and sets out specific guidelines for documentation and reimbursement of these services. (See Compliance section for documentation requirements.)

Anesthesiologists are allowed to furnish additional services to other patients under an exception to the four concurrent case limits. This exception, which varies by state,

Table 9.1 CMS anesthesia care team claims modifiers matrix

Modifier	CMS definition	Payment % of allowable to provider
AA	Anesthesia services performed personally by anesthesiologist	100% to anesthesiologist
AA/GC	Anesthesia services performed personally by anesthesiologist with resident involvement	100% to anesthesiologist
QK	Medical direction of up to 4 concurrent anesthesia procedures involving qualified individuals	50% to anesthesiologist 50% to qualified provider ^a
QK/GC	Medical direction of up to 4 concurrent anesthesia procedures involving 2–4 residents	50% to anesthesiologist
QX	CRNA service with anesthesiologist medical direction (reported by CRNA)	50% to CRNA
QY	Medical direction of CRNA by anesthesiologist for 1 case (reported by anesthesiologist)	50% to anesthesiologist
AD	Medical supervision by a physician; more than 4 concurrent anesthesia procedures	3 base units per procedure, no time units. 1 unit if anesthesiologist documented presence at induction
QZ	CRNA without medical direction by a physician	100% to CRNA

^aResidents are not qualified for reimbursement

Based on data from Medicare carriers manual, part 3: claims process. Transmittal 1690, section 4830, claims for anesthesia services performed on and after January 1, 1992. Department of Health and Human Services, the Health Care Financing Administration. Published January 5, 2001 and ASA Payment and Practice Memo July 2013

generally applies to the following services, if they do not "substantially diminish the scope of control exercised by the physician" providing the medical direction:

- Addressing an emergency of short duration in the immediate area;
- Administering an epidural or caudal anesthetic to ease labor pain;
- Providing periodic, rather than continuous monitoring, of an obstetric patient;
- Receiving patients entering the operating suite for the next surgery;
- Discharging patients in the recovery room; or
- Handling scheduling matters [78].

When services are provided in excess of four concurrent cases and the allowed exceptions, the services will fail to meet the medical direction requirements. These services are considered as being provided under what Medicare terms medical "supervision" and are reimbursed to the physician at a fraction of the MFS allowable through limits in billing for base and time units. Under the supervision requirements, the physician must still ensure that a qualified individual performs any procedure in which they do not personally participate [79].

Requirements of the Attending Physician Relationship

Physicians in academic practice fall under additional Medicare requirements that govern the "attending physician" relationship. This relationship exists when an attending anesthesiologist provides care to a patient in a teaching hospital involving anesthesia residents.

In 1992, when RBRVS was introduced, a new rule was announced that was to eliminate the practice of full reimbursement for an anesthesiologist medically directing two concurrent cases with anesthesia residents. The ASA was able to persuade Medicare to postpone implementation of the new rules until 1994; however, the impact of this change has been significant. The ASA estimates that the cost to academic anesthesiology programs of this change alone exceeds \$50 million annually [80]. In January 2004, CMS took an interim step toward changes in the reimbursement guidelines for medical direction of residents, and in 2010 the ASA succeeded in having CMS restore full payment for two concurrent teaching cases.

The new rules specify that a teaching anesthesiologist may receive payment under the MFS, at the regular fee schedule level, if he or she is involved in the training of residents in:

- A single anesthesia case;
- Two concurrent cases; or
- In a single case that is concurrent to another case paid under the medical direction rules.

The last of these provisions applies specifically when the concurrent case involves a CRNA, an anesthesia assistant (AA), or a student nurse anesthetist. Starting in January 2010, Medicare restored full reimbursement for the teaching anesthesiologist when concurrently supervising two cases whether those cases involved residents in both operating rooms or one resident in a room in concert with a medically directed CRNA in another room. Two conditions are required to be supported by the teaching physician's documentation in the medical record: (1) the teaching physsician or other anesthesiologist from the teaching physician's group was present for all critical or key portions of the anesthesia services, and (2) the teaching physician or other anesthesiologist from the teaching physician's group practice was immediately available during the duration of each anesthetic service. Attesting to having met these two conditions via the teaching physician's documentation, the Medicare claim submission includes both the AA modifier signifying performed personally services by the anesthesiologist and the GC modifier recognizing the case as a resident supervised case.

New Rules also Refine CRNA Payment

Prior to January 2010, a teaching CRNA who is not under the medical direction of a physician was traditionally paid under Medicare Part B, at the regular fee schedule rate, when he or she was present continuously and supervising a single case involving a student nurse anesthetist. Since January 2010, a teaching CRNA concurrently supervising two student nurse anesthetists is paid their full fee. Under this rubric the teaching CRNA cannot perform any other activities unrelated to the two concurrent cases [81].

Independent CRNAs

In 2001, federal legislation was approved that allowed individual States to be exempt from the Medicare requirement of CRNAs practicing under the direct supervision of physicians. States that elected this exemption are known as opt out States, of which there are 17 such States in 2016. Hospitals in opt out States determine through their medical staff by-laws if they want to proceed with the no physician supervision requirement or continue to require direct physician supervision. The Department of Veteran's Affairs has proposed through its Nursing Handbook that APNs (which includes CRNAs) be allowed to provide professional services in their facilities without requiring physician led team based anesthesia care. If the policy is approved by Congress, VA hospitals in non-opt out States could have independent CRNA anesthesia care practicing within their State. The ASA and the Chiefs of Anesthesiology at the VA hospitals support physician led team based care as providing the best quality of care.

Compliance Issues

Anesthesia Billing

All physicians who interact with the Medicare program are obligated to assure that their business practices conform to the requirements of the CMS program. This can be a daunting task because, although a busy participating physician can delegate Medicare transaction authority to others, he/she retains all of the responsibility and risks related to the actions of his/her agents. Furthermore, the stakes for providers are high. Physicians who are found to be in violation of Medicare regulations can suffer both civil and criminal penalties as well as exclusion from the program which can set in motion loss of hospital privileges and participation in other insurance programs. Physician practices can minimize the risks by adopting comprehensive compliance plans and assuring compliance of the plan and regulations through internal controls and training for all physicians and staff.

The Office of the Inspector General (OIG) does not mandate the adoption of compliance programs, but they have formulated seven fundamental elements of an effective compliance program. These elements are:

- Implement written policies, procedures, and standards of conduct
- Designate a compliance officer and compliance committee (e.g., a billing clerk and physician in a small practice)
- Conduct effective training and education
- Develop effective lines of communication
- Enforce standards through well-publicized disciplinary guidelines
- Conduct internal monitoring and auditing
- Respond promptly to detected offenses and develop corrective action plans [82].

Anesthesiologists should consult with their Compliance Officer to gain, what should be, an in-depth understanding of their obligations as providers in the Medicare program. An introduction to some of the key compliance issues affecting anesthesia practice, including reassignment of benefits, Medicare fraud and abuse initiatives, and medical record documentation follows.

For further information on compliance programs, one should consult the OIG postings in the Federal Register and on the OIG Web site at http://oig.hhs.gov/compliance/101/.

Reassignment of Medicare Benefits

Anesthesiologists who provide care to Medicare beneficiaries undertake responsibility for compliance with myriad, complex, and sometimes conflicting regulations. Anesthesiologists who practice in a group or academic setting, where administrative duties for billing and collections are delegated and Medicare payments are frequently reassigned to another entity, should be best informed of these responsibilities.

When a physician reassigns benefits under the Medicare program, they legally authorize another person or entity to bill Medicare on their behalf and to receive payments that would otherwise be sent directly to them. However, despite this written delegation of authority, the physician retains all responsibility for ensuring that the claims made on their behalf are in full compliance with Medicare regulations. In addition, the physician retains responsibility for assuring that their agent meets all confidentiality obligations and other state and federal regulations.

Even the best-intentioned physician may encounter difficulties in determining how to meet his/her obligations for compliance with Medicare regulations. The GAO tested the accuracy of carriers' responses to inquiries in a telephone audit. The GAO asked staff at the Medicare carriers to respond to "frequently asked questions" concerning physician billing procedures that were taken from the carriers' own Web sites. The GAO survey report concluded that physicians who do call their carriers with questions would "more often than not receive wrong or inaccurate answers." These problems in 2001 were attributed to limits on resources for information system modernization and oversight activities, and limits on CMS's authority imposed by the Congress and Executive branches [83].

Medicare Fraud and Abuse

CMS has significantly increased funding to address fraud and abuse. The ACA has strengthened compliance enforcement by adding \$350 million over a 10-year period from 2010 to 2020 to fight fraud. Penalties of \$50,000 can be assessed for each false statement or misrepresentation of a material fact. Penalties triple the claim amount that can be assessed for known overpayments not returned. Furthermore, federal sentencing guidelines have been increased for crimes involving over \$1 million dollars [84]. In fiscal year 2013, CMS estimated that improper payments amounted to nearly \$50 billion [85]. This amount represents a significant Medicare program cost off-set and the reason why federal dollars are allocated toward Medicare compliance.

Many federal agencies are involved in protecting the Medicare program and ensuring provider compliance with all regulations. The OIG in the Department of Health and Human Services investigates suspected Medicare fraud or abuse and develops cases against providers. It has the authority to audit and inspect CMS programs and to act against individual providers with civil money penalties and/or exclusion from participation in all federal healthcare programs. The OIG also has authority to refer cases to the United States Department of Justice for criminal or civil action [86]. In its 2015 annual report, the OIG evidenced an active role in combating waste, fraud, and abuse, citing recapture of more than \$29 billion since inception of the program, over 4000 exclusions, more than 600 defendants convicted of healthcare fraud, and over 1000 pending and 272 civil actions. The OIG reported that for every \$1.00 spent on enforcement, they returned \$6.10 to the Medicare program [87].

Every year the Office of Inspector General releases its work plan which outlines its planned focused reviews where it suspects fraudulent activity. From 2013 through the current 2016 OIG work plan, the OIG continues to note its intent to focus on personally performed anesthesia services (modifier AA) to verify these services were correctly documented and not in fact medically directed cases which would be paid 50% of the allowed professional Medicare fee schedule [88]. New to the 2016 midyear report is the addition by the OIG to review non-covered services to confirm those services performed were medically necessary.

Medicare defines fraud as "the intentional deception or misrepresentation that an individual knows to be false or does not believe to be true and makes, knowing that the deception could result in some unauthorized benefit to himself/herself or some other person." Abuse relates to practices that directly or indirectly result in unnecessary costs to the Medicare program. It is similar to fraud but is found when there is no evidence that the acts were committed knowingly, willfully, and intentionally [89].

Some examples of fraud that should be immediately apparent to providers include activities such as the falsification of records, billing for services that were not furnished, or misrepresenting the type of service provided by using inappropriate codes or modifiers. However, other actions that also constitute fraud and abuse may not be as apparent to providers. These include providing incentives to Medicare patients not provided to other patients such as the routine waiving or discounting of patient coinsurance and deductible payments. Other actions include billing Medicare on a higher fee schedule than other patients, breaching the agreements to accept assignment or participate in the Medicare program, or failing to provide timely refund of overpayments made by Medicare and beneficiaries [89].

Over the years there have been high profile fraud cases involving anesthesiologists. An AMC Department of Anesthesiology in April 2011 was fined \$2.2 million dollars for claims submitted over a six and half year period. CMS assessed liability associated with the failure of the attending physicians to document the supervision of residents in both the pain clinic and bedside procedures as well as for improper recordation of time for services in the critical care unit [90]. A Dallas anesthesiologist was indicted and found guilty of having defrauded Medicare of \$10 million dollars for the following: falsely representing he was "present for" services when evidence showed otherwise; inflating anesthesia time; pre-signing patients' medical records showing that his services were provided before the procedures actually took place; and directing others under his supervision to fraudulently document the records. He is at risk for being sentenced to a maximum of 70 years in prison plus millions of dollars in fines [91].

Physicians at Teaching Hospitals: Office of the Inspector General Initiative

Physicians in academic practice have been made most keenly aware of government efforts to enforce compliance with Medicare rules. Over the past decade, the government recovered \$149 million from 15 universities that failed to document compliance with Medicare payment policies related to attending physician supervision of services provided with resident involvement [83].

The Physicians at Teaching Hospitals (P.A.T.H.) initiative of the OIG has had long-lasting and costly effects on academic practices.Physician groups that paid settlements or were subject to civil or criminal prosecution were required to enter into multi-year Institutional Compliance Agreements with the federal government. These agreements impose requirements that closely follow the structure of a compliance program but can be more stringent [92]. They obligate practices to develop and adhere to a rigorous set of compliance standards involving audits of physician billing practices and annual physician and staff education, under threat of additional penalties. AMCs have reported that annual compliance program costs, after P.A.T.H. settlement, are absorbing millions of dollars [93].

Documentation Requirements

Medical record documentation is the primary source used for judging compliance with Medicare regulations. Documentation should be timely and must support the medical necessity of the service as well as the level and scope of service provided. As with all medical record documentation, it must be legible and signed by the provider. Medicare claims should not be submitted unless adequate documentation exists for the services.

Documentation of Anesthesia Time

The prominence of time in the Medicare reimbursement methodology for anesthesiologist services drives documentation requirements. Since January 1, 1994, Medicare has reimbursed anesthesia time based on the actual number of minutes of anesthesia provided calculated in fractions of 15-min units, rounded to one decimal place [72]. This standard for the precise documentation and reporting of anesthesia time presents challenges, especially in practices without automated anesthesia record-keeping systems.

Unsynchronized timepieces within the operating room suite can create disparities in timekeeping documentation as recorded by the anesthesiologist and other members of the surgical team such as nurses, perfusionists, and surgeons. Unsynchronized timepieces between anesthetizing locations and a lack of diligence can also cause an anesthesiologist to create the appearance of overlap of anesthesia services (i.e., concurrency) when indeed the services were provided consecutively. These discrepancies frequently become apparent upon subsequent audit of the documentation when it is more difficult to initiate corrections.

Documentation of Medical Direction

When an anesthesiologist is involved in directing up to four concurrent procedures, Medicare recognizes the services as concurrent medical direction.

Documentation of concurrent medical direction must support the physician's completion of "7 steps." This documentation evidences that the physician:

- 1. Performs a pre-anesthesia examination and evaluation;
- 2. Prescribes the anesthesia plan;
- 3. Personally participates in the most demanding procedures in the anesthesia plan, including, if applicable, induction and emergence;
- 4. Ensures that a qualified individual performs any procedures in the anesthesia plan that he or she does not perform;
- Monitors the course of anesthesia administration at frequent intervals;
- 6. Remains physically present and available for immediate diagnosis and treatment of emergencies; and
- 7. Provides indicated post anesthesia care [78].

In May 2004, CMS issued new interpretive guidelines for surveyors regarding the documentation of the inpatient post anesthesia assessment as required in the Hospital Conditions of Participation for the Medicare Program. The revision allows the post anesthesia follow-up to be performed and documented by the individual who administered the anesthesia, or by a delegated practitioner who is qualified to administer anesthesia [94]. In 2014 the ASA released guidelines for post anesthesia assessment stipulating that it must be completed and documented no later than 48 h after surgery or a procedure requiring anesthesia services. The release also reaffirmed the 2004 ruling that any practitioner qualified to administer anesthesia can render the post anesthesia assessment [95].

With documentation requirements becoming more stringent, some physicians practicing medical direction have elected to report the QZ modifier as a means to alert CMS that one or more of the seven steps was not completely followed or properly documented. The original purpose of the QZ modifier is to signal that the case was performed by a CRNA without medical direction. This misuse of the QZ modifier was noted by the ASA in the June 2011 Newsletter in which they purported the misuse will produce inaccuracies on the level of anesthesia cases performed without medical direction and thus potentially have major implications on policy decisions concerning CRNA supervision [96].

Documentation by Teaching Physicians

In January 1997, Medicare imposed a requirement for use of the "GC" claim modifier to denote the involvement of residents in the delivery of anesthesia services and to certify that the teaching anesthesiologist was present during key portions of the service and immediately available during other parts of the service. In 1999, CMS extended the requirement to include a written attestation from the attending physician that these requirements were met [97].

In November 2002, CMS implemented revised guidelines governing the documentation requirements for teaching physicians who care for patients with the involvement of resident physicians. These requirements restrict payment for teaching physician services to those that support the presence of the teaching physician during key portions of an anesthesia procedure and during the entire time for separately reimbursable procedures such as line and catheter insertions. In January 2010 Medicare allowed attending physicians to be paid when supervising up to two concurrent resident cases. The concept of being "immediately available" during the entire procedure was thereby introduced. The ASA House of Delegates amended their policy in 2014 on defining "immediately available" when medically directing. They encourage anesthesia departments to establish written policies to specify the physical proximity required for the medically directing physician to re-connect with the patient in an urgent or emergency situation [98].

The most complex of these guidelines govern the documentation of teaching physician involvement with residents in the provision of evaluation and management services such as critical care or postoperative pain follow up care. Interested physicians should consult the *Medicare Carriers Manual*, Section 15016 for specifics of these guidelines. There are important general principles that the anesthesiologist should follow in all cases whether or not the resident and teaching physician services are provided contemporaneously:

- Teaching physicians cannot evidence their presence and participation via documentation of these activities by the resident or by "countersigning" a resident's note. They may reference the resident's note in their own note, but must independently document presence and participation in the critical portions of the service.
- The composite of the teaching physician's note and the resident's note may be used to support the medical necessity and level of service billed [99].

Physician providers must be proactive in assuring compliance with the complex and dynamic requirements of participation in the Medicare program. Development of a compliance program, review of physician billing and documentation, and ongoing education and training of providers and staff will help physicians minimize compliance risk.

HIPAA Compliance: Privacy and Security of Patient Health Information

In addition to billing compliance programs, physicians are responsible for the protection of patient health information (PHI) in every format including paper, oral communication, and every type of electronic device that stores, captures, and modifies PHI (e.g., cell phones and the EHR and practice management systems). All of the rules and regulations on privacy of security of patient health information emulates from the Health Insurance Portability and Accountability Act (HIPAA) which was signed into law in 1996. Similar to fulfilling Medicare's billing compliance program requirements, physicians are expected to have a HIPAA privacy and security compliance plan along with an active program of education, assessment, monitoring, reporting and, where necessary, corrective action. CMS has a model HIPAA compliance plan as well as specific elements that constitute a security risk assessment. Facilities in which you practice, AMCs, and those in private practice are required to train all practitioners and staff on protection of PHI information. In addition, the facilities, AMC, and private practices that employ electronic devices that store, capture, or modify PHI are responsible for completing a Medicare/Office for Civil Rights (OCR) risk security audit, implementing any necessary corrective actions and maintaining all aspects of security. The Office of the National Coordinator for Health Information Technology (ONC) and Office for Civil Rights (OCR) released a Security Risk Assessment tool in 2014 that can be found on the website: https://www.healthit.gov/providers-professionals/securityrisk-assessment. Insurance companies that provide Medicare products have also established their governmental compliance departments and as such are deploying their security audits of contracted providers.

Relationships between parties that involve PHI must be spelled out in privacy notices for patients and in business associate agreements with other entities such as a billing company or practice consultants with access to patient information. Akin to the assignment of benefits where the practitioner retains liability for claims submitted under their names, PHI associated liability can remain when practitioners who outsource any aspect of their revenue cycle management. Data breaches, inappropriate access of information, improper handling, and securing of PHI by a vendor may create liability for the practitioner. Similar to CMS's view of billing compliance, failure to adhere to CMS privacy and security requirements places providers at risk for legal penalties and fines. Some examples of HIPAA violations are as follows: a radiology oncology group was recently fined \$750,000 for failing to have a risk security plan, an orthopedic practice was fined \$750,000 for handing over PHI (x-ray films) to a potential business partner without having a business associate agreement in place, a provider of respiratory care and infusion services was fined over \$230,000 for removing PHI documents from the office and leaving it in areas where unauthorized individuals had access, and an AMC hospital agreed to a settlement of \$750,000 for not performing a risk security assessment. As of May 2016, the Office of Civil Rights (OCR), (which has oversight of HIPAA violation complaints), has settled cases for payments totaling over \$36 million dollars. OCR noted in their May 2016 report that the most frequent types of entities required to take corrective action to achieve voluntary compliance are private practice followed by general hospitals and then outpatient facilities [100]. Providers can expect the continuation of investigations, fines, and penalties surrounding failure to uphold compliance plans, misuse of PHI, and inadequate security measures and are encouraged to adopt a culture of compliance.

Summary

Medicare is the primary health plan serving our nation's elderly, an important source of revenue for physician and hospital providers, and a major underwriter of medical education and charity care in the United States. The program will continue to experience growing annual deficits, as the baby boomers begin to retire. As health expenditures grow as a percentage of GDP, pricing transparency improves, relationships between resources expended and quality outcomes become more evident, and new payment models test the delivery of healthcare, additional pressure will be placed on policy makers for new solutions on how and to whom healthcare dollars are allocated.

Many solutions to the looming Medicare crisis have been proposed. Common reform measures include changes to the age of eligibility, linking premiums to beneficiary incomes, increasing revenues via higher payroll taxes or counting Medicare benefits as taxable income, altering the concept of Medicare as a defined benefit program, and injecting quality outcome components in payments to providers in order to encourage bending the cost and utilization curves without negatively impacting quality of care.

Pundits will continue to debate the strategy of choice for addressing the Medicare funding crisis. Meanwhile, physicians and hospitals, especially those with academic missions, can have an important role in the public policy debate. Healthcare providers, working with their professional organizations, can serve as patient advocates in the ongoing debate to facilitate the improvement of insurance coverage and to help define what constitutes quality of healthcare services provided to the growing elderly population.

The baby boomer generation represents a significant voting block with high expectations on what they want from their healthcare and how they want to interact with their providers. Medicare policy programs are aiming to serve this need by providing the healthcare consumer with more information about treatment, providers (hospitals and physicians), and the cost of care. These programs include physician performance information via websites, giving patients access to their medical information via mandated patient portals, and measures focusing on patient experience.

Medicare's mandate through the ACA legislation to change the manner in which it reimburses providers by emphasizing value over volume is transformative for all specialties. Defining value is evolving as CMS refines the measures for MIPS program and constructs the details behind the APM programs. With CMS's target of 90% of providers by 2018 having payments linked to value, every specialty will be impacted. The perioperative surgical home is being promoted by the ASA to CMS as a viable APM model. Geriatric anesthesiologists will be at the forefront as CMS mandates hospitals to participate in APMs such as bundled payment programs, episode of care and coordinated care programs that will yield the greatest cost savings to the Medicare program. Challenges remain for the specialty to define its value contributions on cost savings and efficacy of clinical outcomes.

Nearly all anesthesiologists in the United States are enrolled as participating providers in the Medicare program. Many of the rules and regulations governing their interactions with the program are unique to the practice of anesthesiology and have significant implications for how clinical and business operations are conducted. Geriatric anesthesiologists, by virtue of their subspecialty focus, should be best informed of Medicare policy issues and should participate in ongoing discussions to reshape Medicare as it enters an uncertain future.

Questions for Consideration

- What changes to the specialty will occur given the explosion of the elderly population while the number of anesthesiologists and CRNAs are not keeping pace? Will we see an increase in the use of physician extenders? Will less complex procedures and anesthetic techniques currently provided by anesthesiologists be performed by non-anesthesiologists?
- 2. Will Medicare become the single payer program for all patients regardless of age, economic need, or employment status? Can sufficient cost savings be made within the medical system to allow hospitals, academic medical centers, and medical providers to survive on Medicare payment rates under a single payer model? How will technological advances, research, and medical teaching be funded with fewer dollars available for investment?
- 3. Will the Medicare "33% problem" payment for anesthesia services continue to plague the specialty with alternate payment model programs when payment for services is split between the hospitals and physicians and among the participating physicians?
- 4. If the Medicare program is extended to a younger population (e.g., 50–64-year-olds), what impact will the "33% problem" have on hospital financials and the practice of anesthesiology. If the Medicare program becomes a public option for all ages, what challenges will it create for anesthesiologists?
- 5. Will Medicare continue to pay a premium for the training of medical specialties or will new sources of funding have to be found? Will CMS adopt Medpac recommendations to create new program requirements and metrics for GME payments which align with their goals on cost efficacy, medical necessity, and population outcomes?
- 6. As hospitals face further reductions by Medicare including reductions in IME and DSH payments, how will that impact stipend payments to anesthesiology practices? What concessions will be made by both with fewer available dollars?
- 7. Will financial pressures on already tight profit margins at AHCs result in mergers with non-academic hospital systems? What concessions will be required of teaching programs resulting from these mergers?
- 8. Will the continual downward pressure on provider fees for professional services conflict with the economic realities of the cost of medical school, residency, and fel-

lowship training? Given these economic realities, will the most capable individuals continue to be attracted to practice medicine?

- 9. How large will private practices have to become to support the resources required for the administrative burdens associated with compliance programs and quality programs? Will these administrative and infrastructure requirements push practices toward employment models, greater consolidations through mergers and acquisitions, and away from independent practice?
- 10. As more surgical practices participate in APM programs, how will anesthesiology practices be able to manage their contributions to multiple APM models given different clinical pathways, a variety of outcome measures, and potentially different incentive and penalty structures? What technology will be required to support multiple APMs? What changes will be required from a practices revenue cycle team to manage income, expenses, and compensation arrangements?

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Part II

System Changes

Geriatric Anesthesia: Age-Dependent Changes in the Central and Peripheral Nervous Systems

10

Anushree Doshi, Roberto Cabeza, and Miles Berger

Introduction

Aging is an inevitable process that involves multiple mechanisms including telomere shortening, free radical accumulation, oxidative stress, and mitochondrial DNA damage. Collectively, these changes have a significant impact on the biochemistry, morphology, physiology, and function of the nervous system. Although initial studies were limited to human autopsies and animal models, advances in neuroimaging, genetics, and other techniques have contributed greatly to our understanding of both normal and pathological aging of the human nervous system.

In this chapter, we will discuss these normal and pathological age-dependent changes in the human nervous system, and studies that have examined these changes in groups of individuals and patients, and at the population level. Given that the current population of Americans age 65 and over (~43 million) is expected to double by 2050 [1], it is important to appreciate the significant age-dependent changes to the central and peripheral nervous system and associated implications on their anesthetic management. Nonetheless, it is important to remember that there is considerable individual variability in the aging process of the human nervous system, due to each individual's distinct genetics and environmental milieu [2]. Indeed, the population variance or standard deviation of most measurements of the human nervous system increases with age, an example of the general principle in

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geriatrics that biological processes of aging occur at different rates across different individuals, and an important point to keep in mind when anesthetizing older adults.

Central Nervous System

Natural Changes of the Central Nervous System

Morphologic Changes

The brain is known to lose mass during middle age, with an accelerated decline in older adults. This reduction is not uniformly distributed; regions with increased atrophy after middle age include the hippocampus, caudate, cerebellum, and prefrontal cortex [3, 4]. White matter also appears to degenerate with age, with up to 45% age-related loss of myelinated fiber tracts [5]. While early data suggested that there is no appreciable change in gray matter mass, newer studies indicate that gray matter volume is also impacted by aging [6, 7]. Furthermore, with age there is an increase in cerebrospinal (CSF) volume, cerebral ventricular space, and cortical thinning [6]. These findings have been corroborated by stereology and magnetic resonance imaging [5, 8].

Neuronal dendrites themselves undergo regression through a decrease in number, length, branching, and spines with the greatest changes seen in the cortex [9–11]. Additionally, axon degeneration has been observed in the elderly and manifests as accumulation of filaments or glycogen deposits [12]. Axonal degeneration is also accompanied by myelin sheath pathology, such as the accumulation of debris and microvacuoles. These pathologic changes disrupt myelin sheath function, impairing axonal impulse conduction [13]. A 2010 study led by Bartzokis analyzed myelin integrity in men between the ages of 23 and 80 years old using an indirect in vivo and MRI-dependent marker of myelin integrity, R_2 . This marker is based on the principle that myelin formation is a dehydrating process whereas myelin breakdown increases water content. R_2 increases

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with myelin formation and decreases with myelin breakdown. Bartzokis found that in frontal lobe white matter R_2 peaked at 39 years of age and declined thereafter [14]. This group later confirmed that tracts that myelinate later in brain development, such as the temporal and prefrontal cortex, are more vulnerable to age-dependent pathology [15]. Rhesus macaques serve as an ideal model of human brain aging because they undergo age-related cognitive decline similar to humans, and thus have been used in several studies. The rhesus macaque brain displays the age-related myelin changes detailed above, as well as decreases in synapse density, and alpha 1 and 2 adrenergic receptor binding densities [16].

Collectively, it is thought that these morphological changes impair nerve fiber conduction, which may contribute to age-dependent cognitive changes such as impairments in executive function, visuospatial skills, attentional focus, and memory encoding and retrieval [17, 18].

Physiologic Changes

The changes in myelin and white matter tracts detailed above have profound implications for the electrophysiology of the aging brain. The age-related disruption in myelin integrity prolongs refractory periods, decreasing synaptic transmission speed and neural network synchrony. These processes then disrupt connections between the cerebral cortex and peripheral nerves. Aging also changes the expression of neurotransmitter receptors, decreases soma size, and causes loss of synapses; these changes further impair neural communication as shown in Fig. 10.1 [19]. These neural communication changes were highlighted in a prospective clinical trial to understand age-related changes in memory conducted in 1993 that studied 200 people (20 male and 20 female per decade from 30 to 85) who had no primary comorbidities. The study was able to identify a relative deficiency in longterm memory, defined as remembering large amounts of data over delays longer than a few minutes, for patients above 50 years old that was correlated with EEG evidence of desynchronization, increased CSF volume, and white matter changes [20]. Moreover, this study helped dispel the notion that the aging nervous system could be simplified solely as a loss of neuronal mass with the use of MRI and CT. While there was a decrease in white matter, it appears that neuronal dysfunction, as evidenced by desynchronization, played a crucial role in healthy aging. However, this study did not employ biochemical or neurohistological methods to help appreciate these changes on a microscopic level.

Years later, neuroimaging studies demonstrated that after middle age, there is increased neural recruitment compared to adolescence and young adulthood [21]. This increased neural recruitment has been interpreted as a compensatory response to decreased neural network integrity in older adults [22–26]. This hypothesis has been supported by prospective trials that found greater engagement in prefrontal and hippocampal regions in older adults performing memory tasks [27, 28]. This concept (i.e., "less wiring more firing") has also been extended to motor pathways [29].

The regulation of cerebral vasculature is similarly impacted by the passage of time; after middle age, patients are susceptible to a decline in cerebral blood flow and cerebral blood velocity [30]. There is limited data to determine the extent to which there are age-dependent changes in cerebral metabolism or autoregulation. Nonetheless, a prospective study from 2003 determined that dynamic cerebral autoregulation remains preserved in healthy people above age 60 after undergoing a 30-min tilt test [31, 32].

Additional changes in cerebral physiology are seen in the regulation of CSF production and turnover, and in the function of the choroid plexus and blood brain barrier (BBB). The choroid plexus plays a pivotal role in neuronal development early in life by supplying trophic factors needed for growth and differentiation. In adulthood, it helps maintain homeostasis within a mature nervous system by helping regulate transport across the BBB, repairing injury with the presence of neuro-progenitor cells and clearing toxins. CSF turnover diminishes in older adults and thus hinders clearance of metabolic waste and transport of bioactive nutrients. Indeed increased CSF volume has been associated with neurocognitive impairment [20, 33]. With senescence, there is also increased leakage in the BBB as confirmed by brain imaging [34]. Rodent models suggest that this may be a function of oxidative stress, increased permeability to TNF-alpha, decreased presence of GLUT-1 glucose transporter expression, altered iron accumulation, and hormonal imbalances [35-39].

Biochemical Changes (Neurotransmitter Associated)

Whereas early studies stated that neurotransmission was largely preserved with aging [40], technological advances in neuro-imaging and neuroreceptor ligand binding unearthed alterations in neurochemistry and signaling through several key neurotransmitter receptors. Key age-dependent changes in specific neurotransmitters and their cognate receptors are detailed below. It is important to note that our knowledge remains incomplete in this area; future studies will be necessary to more fully understand age-related changes in neurotransmission.

Serotonin

Serotonin is well known to play a pivotal role in memory formation, emotion and mood regulation, sleep homeostasis, and pain modulation. Additionally, serotonin plays a key role in platelet biology, gastric motility regulation by the enteric nervous system, and numerous other physiologic processes outside of the nervous system [41]. There appears to be a

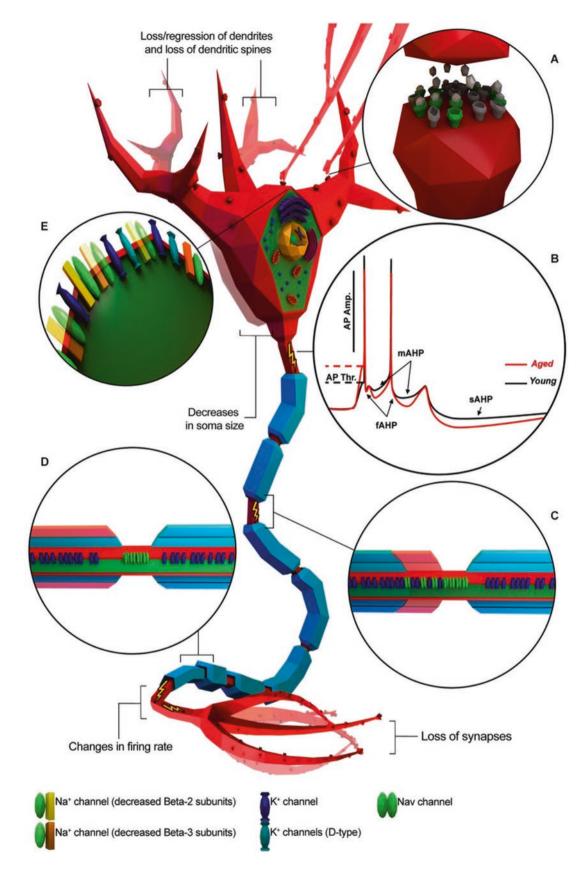


Fig. 10.1 Several age-related changes are shown in this image. (a) The impact of aging on neurotransmitter receptors is illustrated. (b) AP traces of both young and aged neurons are illustrated. (c) Age-related changes as seen by the right side of this section show translocation of

potassium receptors. (d) Age-associated myelin depletion is seen compared to the healthy neuron shown on the *left side* of this image. (e) Receptor types and properties also are shown to change with age (Reprinted from Rizzo et al. [19])

preservation of serotonin content and innervation with time, but neurochemical and PET imaging reveals an agedependent decrease in cortical serotonin receptor numbers. Therefore, while neurochemical deficits are not present, there is the potential for impaired neurotransmission [42, 43]. Though direct clinical implications have yet to be identified, it is reasonable to suspect this may play a role in mood modulation and sleep dysfunction seen in the elderly, as similar symptoms are often seen in depressed adults. Given the success of selective serotonin reuptake inhibitors (SSRIs) in treating depression, it would be worthwhile to study the implications of SSRIs on aging individuals both with and without depression. Would supplemental serotonin by any means alter progression of memory impairments? Would this help prevent depression in the elderly? There is evidence that use of SSRIs poststroke improves physical recovery, presumably by enhancing neuronal plasticity and neurogenesis [44]. Data also suggests that SSRIs mediate hippocampal neurogenesis, potentially enabling plasticity to help build a more productive pattern of thought and behavior [45]. Additionally, further studies will be needed to help appreciate the pharmacological adjustments required when prescribing SSRIs for older adults. While one could argue that aging individuals may need higher doses due to their inherent impairments in serotonergic neurotransmission, their aging renal and hepatic systems may suggest lower dose requirements for a similar clinical impact.

Dopamine

Dopamine receptors are found in the central nervous system in addition to the cardiovascular, pulmonary, gastrointestinal, and renal systems. In the central nervous system, dopamine is primarily localized to the striatum and implicated in motor and cognitive functions such as reward processing, memory encoding/retrieval, and verbal fluency. Dopamine is also instrumental in communication between the ventral tegmental area and nucleus accumbens, a central reward processing unit responsible for positive reinforcement and reward behavior [46]. Key neural receptors are D1 and D2; whereas both are postsynaptic receptors, there are also presynaptic D2 receptors that are instrumental for autoregulation of dopamine release. There is a significant age-related decline in dopamine concentration and dopamine receptor numbers [47–49]. This downregulation is thought to be secondary to age-related loss of dopaminergic synapses and neurons; however, the mechanism behind these changes is unresolved and likely multifactorial [50]. Regardless, the changes likely contribute to diminished cognition and motor performance in older adults [51–53]. Presumably, these changes can also lead to increased susceptibility to anhedonia and altered affective responses to normally rewarding stimuli in older adults.

Acetylcholine

Acetylcholine is ubiquitous in the peripheral and central nervous system. Nicotinic and muscarinic acetylcholine receptors are found in both the brain and periphery, and play a key role in higher cognitive functions, the autonomic nervous system and the neuromuscular junction. M1 receptors are typically found in the cortex, hippocampus, nucleus accumbens, globus pallidus, and caudate nucleus. M2 receptors are largely present in the thalamus, brain stem, pons, and cerebellum. An evaluation of 58 postmortem human brains revealed that muscarinic receptor expression decreased in the frontal regions (largely M1) and increased in the thalamus (mainly M2) with healthy aging. To evaluate nicotinic receptors, the group used two different ligands: nicotine and acetylcholine. Nicotine binding-associated data showed regional changes similar to those seen with muscarinic receptors; however, no significant age-related changes were seen with acetylcholine as a ligand. The investigators attributed this disparity to nicotine having increased binding sites and changes in receptor subtypes with aging [54]. In addition to changing receptor densities, there is likely a decrease in cerebral choline uptake with age even in the presence of increased plasma choline [55]. These changes depict diminished cholinergic function with aging, highlighting the need to avoid anticholinergic medication in already cholinergicdeficient older patients. Anticholinergic medications worsen cognitive function and can precipitate postoperative delirium in the elderly [56, 57].

NMDA Receptors

N-methyl D-aspartate (NMDA) receptors regulate learning, memory, and synaptic plasticity and are largely localized to the hippocampus and cortex. The NMDA receptor has multiple ligands including glycine, glutamate, zinc, and magnesium. Although there are multiple NMDA receptor subunits for the NUMDA receptor, the GluN1 and GluN2 subunits have been most extensively studied and show strong homology between rodents and humans. Early studies indicated an age-related decrease in receptor density for these subunits and NMDA binding with associated impairments in hippocampal-dependent memory function [58]. These effects can be attenuated by environmental changes such as dietary supplementation (omega-3 fatty acids, ginseng, etc.) and caloric restriction [59]. Despite these neuroprotective factors, there appears evidence that even the receptors that remain function less effectively in memory consolidation than those found in younger individuals [60]. These findings suggest that in addition to age-related decreases in NMDA receptor expression, there are also age-related decreases in downstream intracellular signaling and functional neuronal responses to the remaining NMDA receptors.

GABA

Gamma-aminobutyric acid (GABA) is a key inhibitory neurotransmitter in the mature nervous system, but interestingly is predominantly an excitatory neurotransmitter in the developing nervous system [61]. There are three well-established receptors: GABA_A, GABA_B, GABA_C. However, we will focus on the GABA_A receptor, since it is a molecular target of many anesthetics such as inhaled anesthetics, barbituates, etomidate, propofol, and benzodiazepines. The GABA_A receptor is composed of five subunits and each distinct fivesubunit formation has unique pharmacological and electrophysiological properties. While several configurations are known and have been identified, we will speak of GABA_A receptors globally in this chapter. GABA_A receptors are distributed throughout the cortex, hippocampus, cerebellum, and inferior colliculus, and play a role in memory formation, sedation, and anxiolysis. Much of our knowledge about the aging nervous system and changes in the GABA_A receptor comes from rodent models; it is prudent to recognize that the rodent nervous system may not translate perfectly to our own and, therefore, these studies must be interpreted with caution. Though total GABA_A receptor binding does not change with healthy aging, there appears an increase in binding density in the hippocampus [62]. Additionally, there is evidence that benzodiazepines produce a greater GABA-mediated current in cells found in the matured nervous system, signifying that increased sensitivity to benzodiazepines occurs in the elderly due to biochemical changes and not just decreased drug elimination or other pharmacokinetic changes [63, 64]. This information could explain why older patients have an increased sensitivity to other anesthetic ligands of the GABA_A receptor.

Histamine

Histaminergic neurons are involved in the sleep wake cycle, temperature regulation, endocrine pathways, cognitive processing, appetite, attention, and memory. Peripherally, they are also involved in chemotaxis, uriticaria, gastric acid secretion, bronchoconstriction, and vasodilation. Within the CNS, histaminergic pathways originate in the tuberomammillary nucleus and project to the hippocampus, cerebral cortex, hypothalamas, amygdala, and nucleus accumbens. While four histamine receptors have been isolated, only three receptors (H1, H2, and H3) appear in the CNS. H1 and H2 pathways affect physiologic functions, memory formation, and emotion regulation. H3 receptors regulate histamine pathways by acting presynaptically and also moderate release of other neurotransmitters such as norepinephrine, acetylcholine, and dopamine [65].

Aging is associated with a decline in H1 binding in the frontal, temporal, and parietal regions by 13% per decade (as measured by positron emission tomography) without any appreciable change in receptor density seen in vitro

binding [66]. Though this study did not study the direct clinical impact of their findings, later research revealed that diminished histamine plays a role in the increased cognitive deficits seen in senescence. Additionally, H3 antagonists reverse cognitive deficits in a mouse model of accelerated aging (i.e., the senescence-accelerated mouse), likely by blocking presynaptic H3 receptor-mediated inhibition of histamine release [67]. While the H3 receptor regulates the release of several different neurotransmitters, the simplest interpretation of this study is that increasing histamine release in the aging brain ameliorates age-related cognitive deficits.

Orexin

Orexinergic neurons have their cell bodies in the lateral hypothalamus and play a role in wakefulness, energy balance, and appetite. Orexin is most commonly linked to narcolepsy, where there is a profound loss of orexin production in the brain. Animal models demonstrate a significant loss of orexin production with age with concurrent increases in lethargy, diet-induced obesity, insulin signaling dysregulation, and altered brown adipose tissue thermogenesis [68]. Yet, aged rodents that were given supplemental orexin had a smaller increase in arousal, appetite, and a smaller alteration in their circadian rhythms than younger rodents who received identical supplementation [69]. Taken together, these findings suggest that older animals not only have lower levels of orexin, but are also less sensitive to exogenous orexin. Whether similar changes in orexin biology and physiology occur with age in humans remains to be seen; the recent FDA approval of orexinergic antagonists will likely help us understand this question in humans [70].

Plasticity

Aging is not simply a function of cellular death as previously believed; it is a culmination of structural, biochemical, and physiological changes over time. These changes cannot be simplified as a process of inevitable decline, as there is clear evidence of plasticity even in the final decades of life. In fact, the scaffolding theory of aging and cognition (STAC) integrates the ability of the maturing brain to adapt to agedependent morphological changes to preserve cognitive function. STAC acknowledges that even if angiogenesis and neurogenesis are hindered, they remain present and compensate for white matter changes, decreased dendritic branching, altered synapses, and neurotransmitter changes. This new circuitry may not be as efficient, but does allow for continued neural functioning and resilience as illustrated in Fig. 10.2 [71]. This has been reinforced with rodent models and their demonstrated improvements in learning and memory, neurogenesis in the hippocampus, dendritic branching and synaptogenesis in the cerebral cortex, and basal ganglia with environmental enrichment [72]. In addition to these cel-



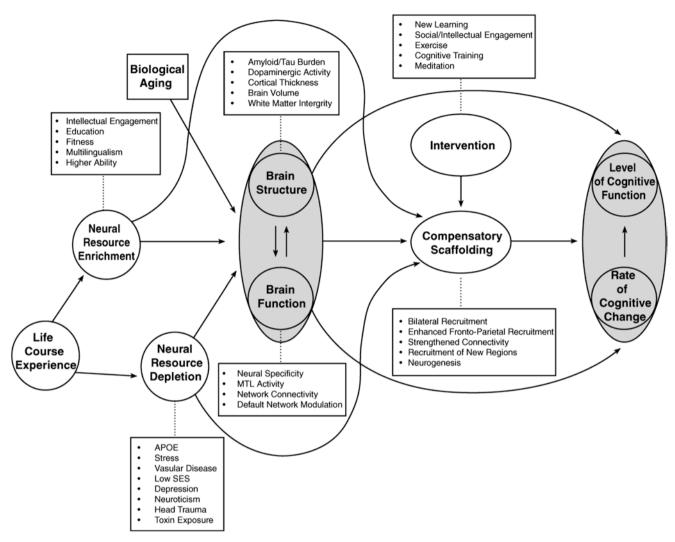


Fig. 10.2 A revised model of scaffolding theory of aging and cognition (STAC-R) is shown here. It encompasses both progressive dysfunction of the nervous system along with behavioral and biological compensa-

tory mechanisms seen with aging (Reprinted from Reuter-Lorenz and Park [148])

lular examples of adaption/resilience in the aging nervous system, it is also clear that there are large-scale shifts in the neural networks and brain regions that give rise to cognitive task performance in older adults [26].

However, not all neuroscientists are as optimistic about the preserved function of the aging brain. Mahncke identifies four core factors that precipitate the "downward spiral of degraded brain function in older adults": reduced schedules of brain activity, noisy processing, weakened neuromodulatory control, and negative learning. Collectively, he states these processes cause brain plasticity to negatively impact functional pathways in an inevitable fashion. Therefore, this group poses that preventing or minimizing these changes is the best hope to preserve neurological function [73]. Though neural plasticity is still present with age, an examination of recovery from stress-induced neuronal atrophy in the prefrontal cortex of rodents established that aging impairs neural resilience and synaptic plasticity. Therefore, the advances that can be made with behavioral and biochemical interventions cannot completely counterbalance the impact of healthy aging [10, 74]. This area remains ripe for further research and continued efforts to promote regeneration and rejuvenation in the maturing brain have included physical and cognitive exercise, careful caloric restriction, young plasma administration, and stem cell use [75, 76]. Furthermore, it is unclear to what extent rodent models faithfully reflect the aging human brain, and therefore, it will be critical to evaluate where

these therapeutic strategies are also effective in the aging human brain.

Pathologic Changes in the Central Nervous System

While there are numerous pathologies associated with the central nervous system, here we will focus on disease states that commonly occur in older adults.

Alzheimer's Disease

The diagnosis of Alzheimer's Disease (AD) is largely clinical; patients commonly follow an insidious course with progressive deficiencies in short-term memory (i.e., anterograde amnesia), word finding, spatial cognition, and executive function. A small fraction of AD cases display Mendelian inheritance patterns due to specific genetic mutations (and are thus termed familial AD), but the vast majority of AD cases are not caused by simple dominant or recessive acting genetic mutations, and thus occur sporadically. In either case, the diagnosis of AD requires the absence of another likely causes such as significant cerebrovascular disease or evidence of other dementias. This diagnosis can be further corroborated by MRI findings of hippocampal atrophy, CSF changes in amyloid-ß and tau levels, neuroimaging evidence of brain amyloid- β and tau deposition, autopsy findings of neurofibrillay tangles and senile plaque deposition, and temporoparietal dysfunction. Patients with genetic mutations such as APO-E ɛ4 are also at increased risk of developing sporadic AD, and additional genetic variants that may contribute to the risk of developing "sporadic AD" are still being discovered [77, 78]. Acetylcholine is the neurotransmitter most influenced by the disease - with postmortem studies showing preferential nicotinic receptor loss [48], though changes in dopamine and serotonin have also been observed [79].

Due to the concern that the first pathological changes in AD occur decades earlier than behavioral or cognitive manifestations, there is a tremendous focus to identify features of preclinical AD to further direct therapeutic options. Additionally, due to concern that perioperative stress and anesthetic drugs may cause an accumulation of amyloid- β and worsening of tau pathology, understanding the pathophysiology of AD is immensely important [80].

Research has demonstrated that in addition to the heterogeneous myelin breakdown seen with aging there is a global myelin breakdown in AD due to extrinsic insults such as amyloid- β peptide [81]. An attempt to model the progression of the disease by the emergence and evolution of biomarkers was published in 2013. Jack et al. warned that amyloid- β reliably leads to plaque formation but will not always lead to clinical symptoms. This group proposed that even with biomarker evidence of AD there was individual variability in associated cognitive impairments. This variable manifestation of the disease was likely due to differing levels of cognitive reserve and concurrent medical conditions such as vascular disease [82].

Parkinson's Disease

Parkinson's Disease (PD) is a progressive neurodegenerative disorder caused by the death of dopamine neurons in the substantia nigra. This cell loss is accompanied by the formation of Lewy bodies, intracellular inclusions that contain the protein α -synuclein; mutations in α -synuclein have been implicated in Parkinson's disease [83]. Similar to AD, the diagnosis of PD is made on clinical grounds, due to the presence of the cardinal motor symptoms including resting tremor, en bloc turning, bradykinesia, rigidity, and instability [84]. These motor manifestations trail other overt symptoms, such as olfactory dysfunction and sleep disorders [85, 86], so there has been a focused attempt to identify these early PD symptoms and genetic risk factors to help identify patients who might benefit from early symptomatic or even prophylactic treatment.

Currently, PD is often treated with the dopamine precursor levodopa, or L-DOPA. Unfortunately, patients often still develop nonmotor side effects including autonomic dysfunction, neuropsychiatric problems ranging from dementia to psychosis, and sleep disorders [87]. Levodopa offers symptomatic relief and delayed clinical progression, but it is not curative, and its benefits wane over time as the underlying disease process advances. Patients who have failed medical therapy are candidates for deep brain stimulation (DBS). An impulse generator is connected to either the subthalamic nucleus or the internal segment of the globus pallidus which results in local release of adenosine and glutamate, increase in cerebral blood flow, and potentially proliferation of neural precursor cells. DBS also has chemical and electrical effects on dopaminergic pathways, and multiple clinical trials have shown clinical improvement in persistent motor symptoms [88]. Adverse effects include infection, hemorrhage, and unanticipated brain damage.

There are a host of genetic risk factors responsible for the development of PD, though environmental toxins and poisons can produce selective dopamine loss with a similar clinical profile [49, 73]. Regardless of etiology, patients with Parkinson's disease are vulnerable to neurocognitive decline after exposure to general anesthesia in the setting of noncardiac surgery [89].

Lewy Body Dementia

Lewy Body Dementia (LBD) shares several neuropathological and neurochemical characteristics with PD and AD. LBD is characterized by the presence of cholinergic and dopaminergic dysfunction, lewy body pathology, cognitive impairment, and neuro-psychiatric symptoms. However key features that are relatively unique to LBD include vivid visual hallucinations, larger visuospatial deficits, and autonomic dysfunction [90].

AD and LBD may both demonstrate fluctuating cognitive deficits in additional to the clinical symptoms detailed above. However, morphological comparisons often help differentiate these two disease states. LBD is associated with cortical and subcortical atrophy but the temporal lobe and hippocampus remain preserved [91] (unlike AD, in which hippocampal and medial temporal lobe atrophy is often seen).

In comparison to PD, LBD patients typically develop cognitive symptoms before motor symptoms. LBD patients also cannot tolerate dopaminergic drugs as they often precipitate or exacerbate psychotic symptoms. As LBD patients cannot tolerate antipsychotics due to their autonomic dysfunction, it is imperative to avoid inappropriately treating LBD patients with antipsychotics [92].

Frontotemporal Dementia

Frontotemporal dementia (FTD) is a neurodegenerative disorder that is characterized by Pick bodies, intraneuronal inclusions, and generalized atrophy in the frontotemporal regions with associated emotional lability, poor social tact, and repetitive or compulsive behaviors. FTD onset typically occurs in middle age, though the age at diagnosis ranges from 35 to 75 years of age. Since many psychiatric disorders such as bipolar disorder and schizophrenia also commonly manifest in that age range and with similar symptoms as those seen in FTD, FTD is often misdiagnosed as a primary psychiatric disorder [93].

Additionally, it is also frequently misdiagnosed as early onset Alzheimer's disease. One way to distinguish these disorders is to note that AD does not typically present with such social impropriety or impulsiveness. Furthermore, FTD is accompanied with progressive language dysfunction, and motor abnormalities such as muscle wasting and wasting. Objective testing, such as neuropsychiatric inventory scores, also demonstrate increased apathy, euphoria, and aberrant motor behavior in FTD and can help differentiate between these disease states [94].

This remains important when considering treatment options for patients with FTD. Unlike patients with Alzheimer's, patients with FTD show no improvements and some undergo worsening of symptoms with acetylcholines-terase inhibitors such as donepezil [95]. SSRIs have been identified as a possible therapeutic avenue for the behavioral symptoms that accompany FTD [96].

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune neurological condition defined by the presence of CNS plaques in at least two separate areas of the CNS associated with at least two differ-

ent episodes of clinical symptoms that are at least 1 month apart [97]. These symptoms are a function of demyelination and associated inflammation. The clinical course of the disease often follows one of three pathways: relapsing and remitting, progressive, or a combination of the two. Though typically diagnosed in young adulthood or middle age, it is a disease that is still present in older adults. The cumulative effect of recurrent attacks can cause chronic inflammation with associated sustained sensory disturbances, ataxia, muscle weakness and spasms, visual disturbances, bladder dysfunction, fatigue, and neuropathic pain. Depression and anxiety are commonly found as well. A characteristic feature of multiple sclerosis is Uthoff's phenomenon, a transient exacerbation of symptoms with an increase in temperature. Thus, vigilant monitoring of temperature during anesthesia is vital [98, 99].

Additional Pathologic Changes

It is difficult to isolate the specific disease process-associated changes in the central nervous system noted above from the age-dependent effects of common systemic diseases often seen in older adults. For example, hypertension has been shown to accelerate hippocampal shrinkage in a cumulative and progressive fashion [100]. Higher systemic pressures are also known to shift the autoregulatory curve for cerebral perfusion to the right, requiring relatively higher pressures for adequate cerebral blood flow. A prolonged history of hyperlipidemia, altered glucose homeostasis, and pro-inflammatory states may lead to accelerated aging or create alternative dysfunctional mechanisms in the central nervous system. It is therefore fundamental to understand the profound influence a patient's overall health has on potentially exacerbating the specific disease-associated changes detailed above.

Peripheral Nervous System

Natural Changes

The peripheral nervous system (PNS) is also susceptible to progressive age-related changes. PNS neurons show a nonlinear atrophy pattern similar to that seen in the CNS: a selective decline in neuronal density and organization with loss of myelin integrity. Moreover, there is a reduced rate of axonal transport (neurotrophic factors, neurotransmitters, and receptors) and an increase in inflammatory markers (mast cells and macrophages) within the endoneurium. Collectively, these morphological changes are associated with a decrease in nerve conduction velocity that was initially observed in rodent models, and which is also seen in humans [101]. These findings likely also contribute to the decreased muscle strength, coordination, and proprioception commonly observed in older adults. Loss of muscle mass and function with age are perpetuated by changes in the neuromuscular junction.

Histological and in vivo imaging demonstrate fewer synaptic vesicles and altered mitochondrial content in the aging neuromuscular junction [102]. Despite the decrease in synaptic vesicles, each vesicle appears to release a greater number of neurotransmitters. However, this increase in quantal size may be offset by increased neurotransmitter turnover and decreased postsynaptic end plate number and density [103, 104]. It is currently believed that oxidative stress and mitochondrial dysfunction may mediate some of these changes. The changes seen at the neuromuscular junction are summarized in Fig. 10.3 [105].

Protective mechanisms help offset these effects; studies demonstrate that older peripheral nerves have lower energy requirements than younger peripheral nerves, which may protect these nerves against potential ischemia due to decreased vascular blood flow [106]. Neurogenesis also counteracts the deficits detailed above, but the degree and rate of regeneration diminishes with age. This is attributed to the impairments in both Wallerian degeneration (less mitogenic factor release from macrophages) and axonal regeneration (less robust response from Schwann cells) [107–109].

Natural Changes in the Autonomic Nervous System

The Autonomic Nervous System (ANS) is likewise affected by aging. The sympathetic nervous system has a more robust neurotransmitter presence in the elderly, particularly in the heart and skeletal muscle. This is partly due to an augmented release of norepinephrine and decreased clearance of norepinephrine and epinephrine [110, 111]. Additionally, older individuals demonstrate a concurrent decrease in alpha and beta receptor sensitivity, and decreased alpha-dependent intracellular responses. Together, these changes in adrenergic receptor expression result in a lower maximal heart rate and vasoconstriction [112, 113]. Therefore, despite increased catecholamine concentrations, physiologic responses to stress are considerably diminished [114].

While there are likely changes in the parasympathetic nervous system with age, there is limited research to appreciate such changes and their clinical outcomes. Given the increase in orthostatic hypotension with age, and the delete-

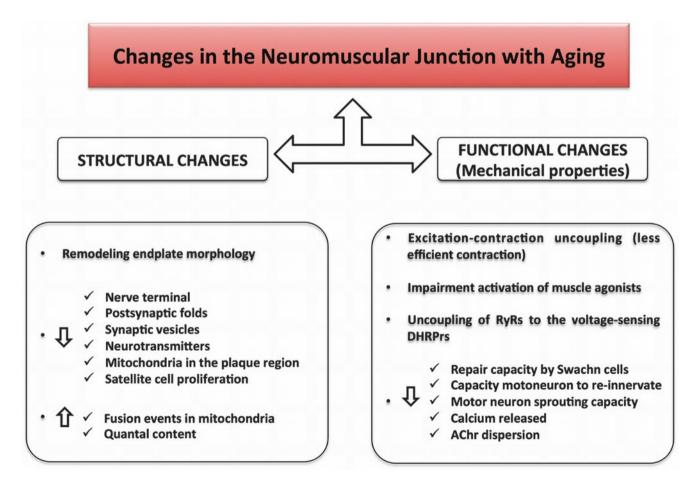


Fig. 10.3 Summarized are the functional and structural changes seen with aging in the neuromuscular junction (Reprinted from Gonzalez-Freire et al. [105])

rious consequences of poor perfusion or syncope in advanced age, age-related changes in the carotid baroreflex have been studied by many groups. It appears that despite the reflex being present with age older individuals have a blunted and delayed response to hypotension compared to their younger cohorts [115, 116]. Though the mechanism behind these changes remains unresolved, it is likely a confluence of neural and mechanical impairments in the reflex arc as well as potential gender-mediated differences [117].

Natural Changes in the Enteric Nervous System

An often overlooked part of the nervous system is the enteric nervous system (ENS), which is composed of epithelial cells, muscles, and neurons and regulates gastrointestinal function. The ENS is also known to undergo dynamic changes with aging through poorly elucidated mechanisms. Substantial age-associated neuronal loss (quoted as high as 40-60%) has been demonstrated in animal models, with a particular emphasis on cholinergic neuron loss. However, consistency regarding the degree of loss is lacking across animal species. It is believed that oxidative stress, free radical damage, decrease stores of neurotrophic factors, replicative senescence, and degenerative changes in the intestinal epithelial barrier are potential mechanisms for enteric neuron loss. While caloric restriction may help mollify such changes, neurogenesis in the ENS during adulthood has not been identified [118]. The clinical implications of ENS impairments seen in older patients should prompt anesthesiologists to consider adjusting aspiration prevention guidelines for older adults due to delayed motility and transit of intestinal contents, increased incidence of gastroesophageal reflux, and diminished oropharyngeal responses including the gag reflex [119].

Age-Dependent Pathological Changes in the Peripheral Nervous System

ALS

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder defined by progressive motor dysfunction secondary to loss of upper and lower motor neurons. The etiology remains unknown though possible mechanisms include oxidative stress, mitochondrial dysfunction, glutamate-mediated neuronal excitotoxicity (perhaps leading to increased intracellular calcium homeostasis), and inflammatory stress. Familial ALS has been associated with mutations in the SOD1 gene; however like AD, the vast majority of ALS cases are not inherited in a Mendelian fashion, and thus can be considered "sporadic" [120]. Histological hallmarks seen in familial and sporadic ALS include astrocytic gliosis and intraneural inclusions in the affected neurons [121].

Sensation remains intact in ALS, as the disease affects only motor pathways, though it typically spares muscles involved in eye movement and the urinary sphincter. The progressive loss of motor neurons causes patients to experience fasciculations, cramps, spasticity, weakness, and muscle atrophy. Patient psyche is also affected, and patients show an increased incidence of dementia and depression. Curative therapy remains elusive, and patients inevitably face a steady decline in function and independence requiring discussions about ventilatory support and ultimately end-of-life care. Anesthesiologists often care for ALS patients undergoing tracheostomies and gastric tube placements.

Peripheral Neuropathies

Peripheral neuropathy in older adults most frequently occurs secondary to systemic events such as peripheral vascular disease and diabetes, though it can also be caused by malignancy, autoimmune disease, toxins (alcohol and drugs), nutritional deficiencies (particularly vitamin B12), medications (chemotherapeutic agents), and idiopathic causes [122]. Therefore, one must appreciate the complete medical history of a patient and the cumulative impact of these conditions when contextualizing neurological findings. Ascertaining the etiology of peripheral neuropathy in older adults is essential, for treatment modalities vary drastically and depend greatly on the mechanism of denervation.

Anesthetic Implications

Currently, more than one third of inpatient surgeries in the USA are performed in patients over age 65, and with the aging baby boomer generation this number will only increase. Thus, it is pivotal for anesthesiologists to learn the acute nuances in treating the geriatric population [123] (see Chap. 1). Anesthesia in elderly patients must be tailored to appreciate these age-dependent changes in the physiology of the human nervous system, and the increased incidence of nervous system pathology in older patients. As patients often cannot communicate during intraoperative management, our clinical judgment relies heavily on monitors that must be interpreted appropriately for older patients.

Even management of vital signs differ in the geriatric population, since older adults frequently do not adequately respond to stressors such as hypovolemia, hypothermia, hypoxia, and infection. Studies demonstrate that older adults have a lower maximal heart rate, require higher systolic pressures for adequate perfusion of vital organs, have impaired cardiovascular responses to hypotension, and exhibit impaired vasoconstriction during cold exposure [124, 125]. Given these attenuated physiologic responses and heightened activation of the sympathetic nervous system detailed earlier, one can conclude older individuals will have an unpredictable response to direct sympathomimetics with possible lower ceiling effects, highlighting the need for careful titration of vasopressors and inotropes.

Nonetheless not all reflexes are attenuated in older adults; dynamic cerebral autoregulation remains preserved with age despite impediments in cerebral blood flow and the baroreceptor reflex when exposed to orthostatic stress [31]. When studied in the context of volatile anesthetics, elderly patients require maintenance of mean arterial pressure and cerebral blood flow for preservation of dynamic autoregulation and tissue oxygenation [126]. This further emphasizes the importance of cardiovascular and respiratory intraoperative management to preserve neurological function in the geriatric population.

It is well accepted that the minimal alveolar concentration (MAC) for inhaled anesthetics declines by ~6% per decade after age 30 [127] (see Chap. 16). This is unsurprising as older patients are also more susceptible to other CNSassociated medications such as benzodiazepines, antidepressants, and antipsychotics [128] (see Chap. 17). Likely, this is due at least partly to altered pharmacokinetics, pharmacodynamics, and receptor sensitivity. Equally important is the notion that with "less wiring more firing" there are fewer functional myelinated tracts for anesthetics to act on. This would imply that anesthetic dosing is dependent upon white matter mass and functional neural fibers and not upon electrical activity which is largely preserved with age. However, as the correlation between anesthetic dosing and white matter mass and whole brain responses has not been studied, this remains a ripe area for research.

Emergence from anesthesia was initially felt to be predominantly dependent on metabolism and elimination of anesthetic agents. Therefore, delayed emergence often seen in the elderly was attributed to impaired renal and hepatic pharmacokinetics, and prevention was aimed at judicious dosing and timing of anesthetics. Recent research illustrates that emergence also relies heavily on the activation of arousal pathways, elucidating another means to combat delayed emergence in the elderly. Rodent models have demonstrated that dopamine agonists and direct stimulation of the VTA tract can catalyze reanimation (conscious behaviors such as kicking and clawing) from isoflurane-induced general anesthesia [129]. Additional behavioral studies in rodents show that inhibition of orexinergic signaling delays emergence from sevoflurane and isoflurane [130]. Given our previous discussion about age-related dysfunction in these pathways, their role in delayed emergence in older adults cannot be underappreciated and remains a rich avenue for future research.

Postoperative outcomes remain a grave concern in the elderly, particularly postoperative cognitive dysfunction (POCD) and delirium (see Chap. 30). Both complications are associated with increased morbidity and mortality, decreased quality of life, and higher healthcare costs to

patients and taxpayers [131, 132]. Known risk factors for both include poor preoperative cognitive reserve, repeat surgeries, higher ASA status, duration of surgery, and older age. These factors are fairly immutable in the immediate preoperative period. Therefore, much research has been directed at the role of intraoperative management in preventing POCD and delirium.

Many anesthesiologists use proprietary-processed EEGbased monitors as a surrogate for raw continuous EEG recordings and analysis. Many of these devices apply a proprietary algorithm to raw frontal EEG data to create a numeric value reflecting "anesthetic depth." A prospective, randomized, double-blinded study of patients over the age of 60 undergoing major surgery found that BIS-guided anesthesia (between 40 and 60) decreased both delirium and POCD incidence, suggesting that avoiding lower BIS values and delivering less anesthetic agent may help older adults avoid these outcomes [133]. Another study found that EEG burst suppression was associated with postoperative delirium [134]. A Cochrane review similarly found that BIS-guided anesthesia could help prevent delirium [135]. Collectively, these studies indicate that while further research needs to be done, current EEG-based monitors may help prevent neurocognitive dysfunction after surgery. These results are further muddled by the fact that commercial EEG monitors do not take into account inherent EEG changes seen with aging such as increased burst suppression and reduced alpha band power coherence [136]. Therefore, it is unclear if BIS recordings even have equal value in younger and older patients. Clearly, there remains much to be discovered about the relationship between intraoperative monitoring, dementia, delirium, and neurocognitive outcomes [137–139].

These studies could be interpreted to mean that excessive anesthetic dosage causes EEG burst suppression, and thereby contributes to POCD and delirium in older adults. Still, it is equally plausible that EEG changes occur due to inherent subclinical neural pathophysiology, and this underlying neural pathophysiology predisposes patients to these adverse postoperative neurocognitive outcomes. However, studies do show that awake BIS scores are significantly lower in patients with dementia, suggesting that they are at higher risk of delirium and may need more careful anesthetic titration [140]. Clearly, we need further research and technology to faithfully reflect the impact of anesthetics on the aging brain, and especially on the brains of patients with preclinical neurodegenerative disease pathology.

A 2010 meta-analysis revealed that general anesthesia poses no greater risk than regional anesthesia of developing postoperative delirium, and may pose a nonsignificant risk of developing POCD [141]. However, many of the regional anesthesia studies cited in that meta-analysis were confounded by the administration of sedative drugs to patients who received regional anesthesia. Very few prospective

studies have compared cognitive outcomes in surgical patients randomized to receive regional anesthesia (without any sedation) versus general anesthesia.

Like general anesthesia, regional anesthetic administration should also be tailored to the aging population. Older adults require decreased doses of local anesthetics due to decreased clearance, altered distribution, and increased sensitivity secondary to changes in neural density and conduction [142]. Furthermore, older patients have an increased incidence of peripheral nerve pathology due to hypertension, diabetes, vascular disease, exposure to medications and toxins, and predisposition to poor nutrition and vitamin deficiencies in this population. The American Society of Regional Anesthesia notes that such preexisting neuropathies increase the risk of peripheral nerve injury at least 10-fold in the setting of regional anesthesia, demonstrating the unique risk regional anesthesia poses in older adults [143].

Neurobiological and neuroanatomical changes with healthy aging may also impact the ability to process and manage pain. There is evidence of age-related changes in nociceptive fiber function with possible dysregulation of neuronal tracts involved in descending inhibition, and a decline in central opiate receptors within the limbic system [144]. Dementia further complicates our understanding of pain in older adults, because it is difficult to obtain accurate pain ratings in demented patients. The pathophysiology of FTD causes a decrease in pain processing, secondary to decreased regional blood flow and mass reduction in the anterior temporal cortex, and consequently a decrease in the affective expression of pain [145]. Additionally, age-related decrements in renal and hepatic physiology that will alter the metabolism, distribution, and elimination of many pain medications, which makes it difficult to assess steady-state concentrations in each individual. Therefore, it is imperative to titrate pain medication in response to desired clinical effects in individual patients, avoid polypharmacy when possible, and reassess pain scores frequently [146].

As our population ages and our medical technology and knowledge advances, it is inevitable that both the pathophysiology of our patients and their surgical needs will become more complex. As discussed earlier, this places them at increased risk of neurocognitive and physical decline. Evidence indicates that physical activity can help promote neuroplasticity throughout the brain even in the final decades of life [147], and thus may promote cognitive recovery after perioperative care. Thus, although it is important to ensure that older patients are well managed during the intraoperative and postoperative periods, it is also worth considering the benefits of optimizing our older patients *preoperatively* with cognitive and physical therapy (i.e., prehabilitation) to help promote postoperative cognitive and physical resilience.

Future Areas of Research

- 1. What forms of cognitive and/or physical prehabilitation can best promote postoperative cognitive and physical recovery in older patients, and after which types of anesthesia and surgery?
- 2. How should intraoperative brain function be monitored in the elderly? Do current processed EEG monitors properly account for age-related changes in brain function, and are they appropriate to use on older patients?
- 3. What intraoperative anesthetic techniques or drugs can be used to optimize postoperative cognitive recovery in older patients, and to avoid POCD and delirium?
- 4. Do anesthesia and surgery, or specific anesthetic drugs or surgical techniques, cause long-term increases in the pathogenesis of Alzheimer's disease and/or other types of neurodegenerative disease? If so, how can we mitigate such effects?
- 5. How should preoperative cognitive function be assessed on a systematic basis in older adults undergoing perioperative care?
- 6. What is the pathophysiology of postoperative delirium and cognitive dysfunction, from the molecular and cellular level to the whole brain level?
- 7. How should older patients be told about the risks of delirium and/or POCD, and by whom?
- 8. Should older patients be told about the increased risk of intra and postoperative complications in older adults?

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Cardiovascular System

Shamsuddin Akhtar and Thomas J. Ebert

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Introduction

Cardiovascular disease (CVD) is an expected consequence of aging due to multiple processes such as coronary artery disease (CAD), morphological changes in the myocardium, valve disease, or neural circuitry aberrancy. These changes lead to disability and death. In the most recent 2016 update published by the American Heart Association, 30.8% of all deaths in the United States in 2013 were attributable to CVD [1]. The majority of the deaths related to CVD occur in people aged 65 and older. The prevalence of CVD in American men and women aged 60–79 is 69.1% and 67.9%, respectively. For those aged 80+, prevalence is 84.7% and 85.9%, respectively [1].

The prevalence of CV disease with aging increases in an exponential manner. This makes it highly likely that anesthesia delivery to elderly patients requires "fine-tuning" to compensate for the underlying disease processes. Some of the more important diseases demonstrating high prevalence with age include hypertension that rises from 36.8% of men and 32.7% of women between ages 45 and 54 to 76.4% of men and 79.9% of women over the age of 75 years [1] and CAD increases from 6.3% of men and 5.6% of women between ages 40 and 59 years to 32.2% of men and 18.8% of women over the age of 80 [1]. The prevalence of congestive heart failure increases from 1.5% of men and 1.2% of women between ages 40 and 59 years to 10.6% of men and 13.5% of women over the age of 80 [1]. At 80 years of age, remaining lifetime risk for development of new heart failure remains at 20% for men and women, even in the face of a much shorter life expectancy. The prevalence of stroke also increases with age from 1.9% of men and 2.2% of women between ages 40

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and 59 years to 15.8% of men and 14% of women over the age of 80 (Fig. 11.1) [1]. Elderly patients >85 years of age make up 17% of all stroke patients [2].

Not only does the aging process contribute to the development of CV disease, aging appears to worsen the outcome of disease. For example, elderly patients are not only more likely to experience myocardial infarction, but they are also more likely to develop heart failure as a consequence of a myocardial infarction than their younger counterparts [3–5]. Furthermore, elderly patients are also more likely to die from their myocardial infarction, develop cardiac arrest and papillary muscle rupture, and acquire ventricular septal defect and free wall rupture [3].

Assigning a high ASA physical status number to an elderly patient is often a result of the presence of coexisting cardiovascular diseases, but it is often the underlying physiological adaptations to CV disease that impact decisions with anesthesia delivery. This impact of CV disease devalues the importance of the chronological age of an individual and emphasizes the functional aging process in determining the physical status. The functional aging process has known variability because the CV system is constantly adapting to short-term and long-term influences. Assessment of functional age requires a focused history to better understand a patient's activity level and abilities to manage CV demand such as walking, climbing stairs, or more advanced endurance activities. In the process, a composite picture of adaptation to age-related effects on interdependent variables of heart rate, coronary blood flow, afterload or impedance, preload or diastolic filling, and inotropic state is obtained. All show relative degrees of age-dependent changes. Modulation of these factors is in part via the autonomic nervous system (ANS) acting through both sympathetic and parasympathetic control mechanisms. Age-related changes of the ANS further contribute to modifying cardiovascular function and adaptation to stress in the elderly. The sum of all changes typically results in a reduction in the overall cardiovascular reserve with age. In order to produce the best possible patient outcome, the anesthesiologist must demonstrate both knowledge

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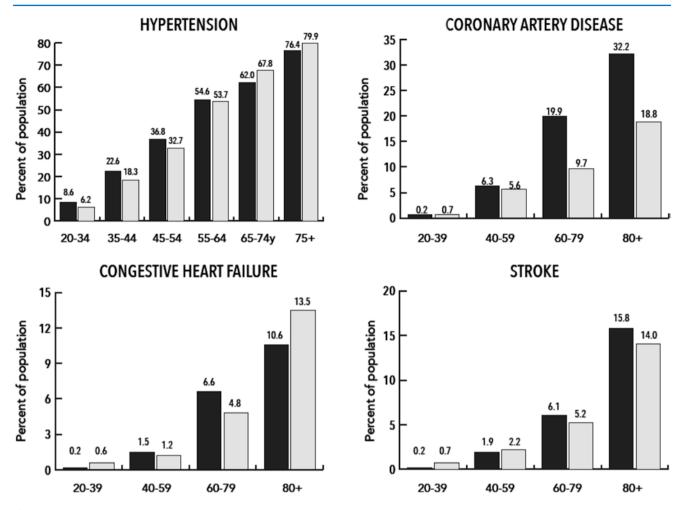


Fig. 11.1 Prevalence of hypertension, coronary artery disease, congestive heart failure, and stroke with aging (Based on data from Mozaffarian et al. [1])

and skill when managing the autonomic responses to surgical pain and intravascular volume changes, the functional status of individual components of the CV system, and their interdependence.

This chapter addresses predominantly the physiological and pathophysiological effects of aging on the cardiovascular system. It is difficult to clearly differentiate the aging process from age-related diseases. In a particular patient, both processes interact to yield the specific physiological state of the system. In this chapter, the age-related changes in the cardiovascular system will be discussed first. The general morphologic changes induced in both the vasculature and the heart are similar with stiffening, thickening, dilatation or enlargement, and endothelial or myocardial dysfunction as common themes. The vascular system is closely coupled to the ventricles, and the progressive changes in the vasculature lead to compensatory changes in the cardiac function. The cardiac conduction system and the cardiac valves also degenerate over time. Changes in the autonomic regulation and the neuroendocrine system, which

occur with aging, and their impact on the cardiovascular system, will be then reviewed. Finally, fluid management and general principles of cardiovascular management in the elderly will be discussed.

Cardiac and Vascular Morphologic Changes with Aging

As the human body ages, it undergoes a variety of changes, some are relatively benign although some can have major influences to impair the overall health of the aging person. An example of such a detrimental digression accompanying increasing age is the increased stiffness of the heart and vascular tree.

Vascular stiffness is the result of increased collagen, decreased elastin, glycosylation of proteins, free radical damage, calcification, and chronic mechanical stress (also described as "fatigue failure"). The concept of "fatigue failure" is extrapolated from the effect of that observed in rubber tubing subjected to repetitive stretch/relaxation cycling [6]. Aging can radically transform the endothelial layers via changes in extracellular matrix compositions. Elasticity in connective tissues depends primarily on the properties of its constituent collagen and elastin. Both connective tissue proteins are long-lived but slow in their production. By the age of 25, production of elastin has essentially ceased, and the rate of turnover of collagen decreases with increasing age. With aging, the elastic lamellae undergo thinning and fragmentation [7] with gradual transfer of mechanical forces to collagen. The consequent increase in the collagen-to-elastin ratio, plus an accumulating damage to collagen by glycation and free radicals, results in progressive connective tissue stiffness. Thus, the arteries, veins, and myocardium become less compliant over time.

Nonenzymatic glycation is a reaction between reducing sugars and proteins on the vascular endothelium. Over time, these glycation sites cause tight cross-linking of proteins called advanced glycation end products (AGE). This AGE formation leads to changes in the physiochemical properties of endothelial tissues. AGE cross-linking structurally results in vessels with less elasticity and compliance [8]. Furthermore, the interaction of AGE with receptors for AGE (RAGE) on endothelial cells has been implicated as an initiating event in atherogenesis. In smooth muscle cells, binding of AGE-modified proteins to RAGE is associated with increased cellular proliferation of smooth muscle cells. This interaction also causes an increase in vascular cell adhesion molecule-1, which enhances binding of macrophages to the endothelial surface. This induces oxidative stress on the vascular endothelium and contributes to vascular stiffness [9].

Another factor that contributes to vascular stiffening with aging is progressive vascular calcification. This is a complicated process whereby in certain disease states, vascular smooth muscles cells, pericytes, and endothelial cells change their phenotypes to mesenchymal cells, osteoblasts, and chondrocytes [10]. All these processes can then lead to increased calcium deposition in the vasculature and cause vascular stiffness [10].

Vessels thicken with age, primarily from intimal thickening that is attributed to increases in collagen, fibronectin, proteoglycans, and migrating smooth muscle cells [11]. These changes are stimulated by TGF- β 1, angiotensin-II, and decreased levels of inhibitory cytokines and degrading enzymes [12]. ACE inhibitors produce beneficial effects by reducing connective tissue remodeling, smooth muscle hypertrophy, and arterial stiffness.

Several studies have shown that the nitric oxide pathway becomes less functional with age. This has implications on vascular compliance. Nitric oxide suppresses key events in atherosclerotic development such as vascular smooth muscle proliferation and migration. It also inhibits the adhesion of monocytes and leukocytes in the endothelium, as well as platelet-vessel interaction. Furthermore, nitric oxide is known to regulate endothelial permeability, reducing the flux of lipoproteins into the vessel wall [13]. The reduced effects of nitric oxide on all of these pathways may contribute to vascular stiffness in aging.

Another mediator that may contribute to endothelial dysfunction is endothelin-1. Endothelin-1 is 50 times more potent at vasoconstriction than norepinephrine [14]. Though the endothelin-I expression is variable in different vascular beds, increased levels of endothelin-1 have been noted with aging and may be responsible for the glomerulosclerosis that is observed in aging kidneys [15, 16]. Endothelin-1 levels are positively associated with aging and account for increased endothelin-1-mediated vasoconstriction in older people [17, 18].

Increased expression of prostanoid vasoconstrictor proteins, altered cyclooxygenase, and prostaglandin H synthase activities [19] develop with aging. In contrast, vascular endothelial growth factor (VEGF) and hypoxia-induced factor (HIF) are reduced with aging. Endothelial dysfunction leads to an attenuated vasodilator responses in skin microvasculture [20, 21] and contributes to microvascular dysfunction of the skin. The latter may predispose the elderly to impaired wound healing [22].

Atherosclerosis and arteriosclerosis are inflammatory processes. Increased levels of C-reactive protein and increases in erythrocyte sedimentation rate suggest an increased inflammatory propensity in the elderly [10]. Some have coined the condition as "inflammaging," and the process is thought to be due to upregulation of a range of proinflammatory cytokines [23, 24]. However, concurrent immunodeficiency has also been noted in the elderly that makes them prone to infection and immune-mediated diseases. It is not unreasonable to assume that the inflammatory milieu affects vascular aging.

The above mechanisms serve to explain the pathogenesis of vascular stiffness associated with aging. As the heart is closely coupled to the vascular system, it is important to note that many of the changes to the aging heart are closely linked to progressive changes in the vascular system [25]. The vascular system serves both as a reservoir and a conductive system. It serves a critical role in buffering the effects of intermittent ejection (stroke volume). In a young person, the aorta and proximal arteries expand 10% with each contraction, whereas the distal muscular arteries expand only 3% [26]. Generalized stiffening of the arterial tree leads to increased arterial wave reflectance, increased systolic blood pressure, decreased diastolic blood pressure, and a widened pulse pressure.

As arterial walls stiffen, blood vessel compliance is reduced, leading to an increase in systolic blood pressure and pulse wave velocity (Fig. 11.2). A number of studies demonstrate a significant association between increased pulse wave velocity and all-cause mortality and adverse cardiovascular events [27]. The reflected waves return earlier to the thoracic aorta, arriving by late ejection instead of early diastole. Thus, the left ventricle must pump against a higher pressure in late ejection than under normal circumstances. This additional afterload places an increased burden on the heart, particularly because it occurs late in systole when the myocardial muscle is normally losing its strength, and therefore provides a significant stimulus for cardiac hypertrophy (Fig. 11.3).

Diastolic Dysfunction The cardiac muscle hypertrophy that develops secondary to the increased late systolic afterload also leads to myocardial stiffening and diastolic dysfunction. Diastolic dysfunction is defined as impairment in the relaxation phase of the ventricles. The aging heart contains AGE cross-linked collagen, which has the same effect

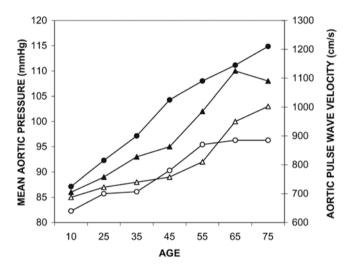


Fig. 11.2 Mean aortic pressure (*triangles*) and pulse wave velocity (*circles*) in two Chinese populations: rural Guanzhou (*unfilled symbols*) and urban Beijing (*filled symbols*) (Adapted from Avolio et al. [123]. With permission from Wolters Kluwer Health)

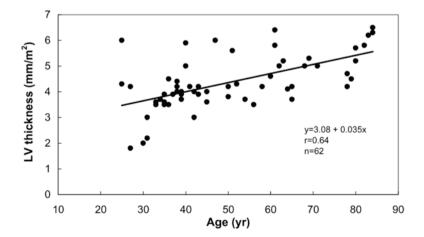
Fig. 11.3 Left ventricular (LV) posterior wall thickness (mm/m²) in normotensive men as a function of age (years) (Adapted from Gerstenblith et al. [124]. With permission from Wolters Kluwer Health)

on stiffness as it does in the peripheral vascular system. It is implicated in the signaling of macrophage recruitment in hypertensive myocardial fibrosis that contributes to deteriorating diastolic function [8]. Another consequence of altered extracellular matrix formation is that scar formation and healing are impaired in the elderly making them more prone to severe complications after myocardial infarction [12].

In diastolic dysfunction, there also is a functional component to the impairment of relaxation. It has been proposed that alterations in the myocyte calcium-handling proteins disturb the calcium transient in failing hearts. The rate of calcium uptake in the sarcoplasmic reticulum declines with heart failure because of reduced expression of certain calcium channel enzymes [28]. This contributes to increased duration of contraction and slowed relaxation of the myocardial muscle fibers, and the stiff ventricles have less ability to "spring open" in early diastole [29].

As a consequence, there is a progressive decrease in ventricular filling during early diastole between the ages of 20 and 80. At its worst, the early diastolic filling period is reduced by 50% compared with younger controls. With increased stiffness, there also is a decline in the diastolic filling rate (Fig. 11.4). However, resting end-diastolic volume does not change with increasing age. Because the early ventricular filling is impaired with age, the heart is increasingly dependent on an adequate atrial filling pressure and the atrial contraction (Fig. 11.5). The atrial pressures must rise to maintain the end-diastolic volume in the presence of stiffened ventricles. The increased atrial pressure can result in increased pulmonary blood pressures and ultimately lead to congestion in the systemic venous circulation. The cumulative effect of these alterations results in diastolic dysfunction (Fig. 11.6).

About half of heart failure in the elderly population (older than 75 years) is associated with impaired left ventricular diastolic function, with a relatively preserved left ventricular systolic function [30]. Unfortunately, patients with isolated left ventricular diastolic dysfunction are not as likely to pres-



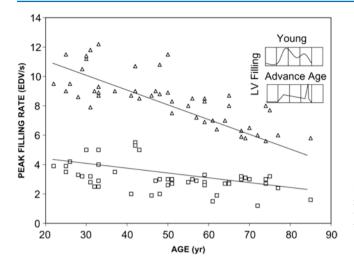


Fig. 11.4 Changes in early diastolic left ventricular filling and the atrial contribution to filling associated with increased age. Age and peak filling rate relationship was obtained at rest (*squares*) and maximum workload (*triangles*). *Inset: top image* = left ventricular filling, young; *bottom image* = left ventricular filling, advanced age (Adapted from Lakatta [125]. With permission from Elsevier)

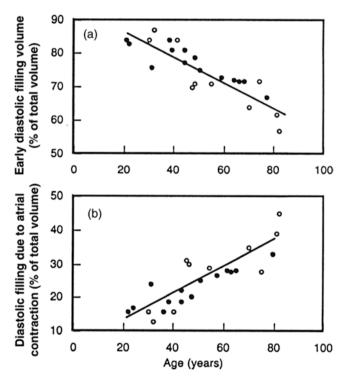


Fig. 11.5 Echo-Doppler evaluation of diastolic filling in healthy men and women as a function of age. (**a**) Early diastolic filling volume (% of total volume). (**b**) Diastolic filling caused by atrial contraction (% of total volume) (Adapted from Lakatta [126]. With permission from Oxford University Press)

ent with the traditional physical manifestations of heart failure. Instead, they are frequently asymptomatic or subtly present with only mild pulmonary congestion, exertional

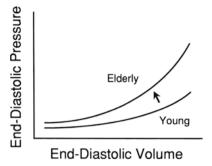


Fig. 11.6 The increased ventricular stiffness associated with age requires an increased atrial pressure to achieve the same end-diastolic volume (Adapted from Dauchot et al. [127]. With permission from Wolters Kluwer Health)

dyspnea, and orthopnea. These symptoms may be aggravated by systemic stressors such as fever, exercise, tachycardia, or anemia. As a result, detection of diastolic heart failure during a history and physical exam may be difficult since it is often recognized only by echocardiography.

Systolic function of the heart also is affected by the aging process. From a functional standpoint, the prolonged myocardial contraction maintains the flow delivered to the stiffened arterial tree, thereby maintaining cardiac output (Fig. 11.7). The functional adaptation to vascular stiffening and afterload is able to maintain cardiac output at rest; however, an agerelated decline in systolic function may be unmasked in the presence of exercise or sympathetic stimulation. For example, administration of an α -adrenergic agonist such as phenylephrine will acutely increase afterload to the heart, increasing left ventricular wall stress during systole, and unmasking an agerelated decrease in contractile reserve [31].

Further studies have shown that there is abnormal systolic function in many patients who have hypertension-induced concentric hypertrophy with a normal ejection fraction. Reduced midwall shortening in relation to stress is clearly evident in patients with greater relative wall thickness. This translates to abnormal pump function and reduced cardiac output. Subtle systolic dysfunction may be present even if patients have seemingly normal ejection fractions and are without clinical heart failure, and it would be incorrect to equate a normal ejection fraction with normal systolic function [32].

Reduced vascular compliance, diastolic dysfunction, and systolic dysfunction in the elderly are all interconnected. It is reasonable to assume that these are not separate pathologies and in fact develop in parallel. Reduced vascular compliance resulting in hypertension, increased afterload, and eventual cardiac remodeling, is an extremely common finding in the aging population. In a large portion of this group, this inevitably results in some evidence of diastolic dysfunction. Furthermore, the above concepts demonstrate that some systolic dysfunction exists in many of these same hypertensive elderly patients.

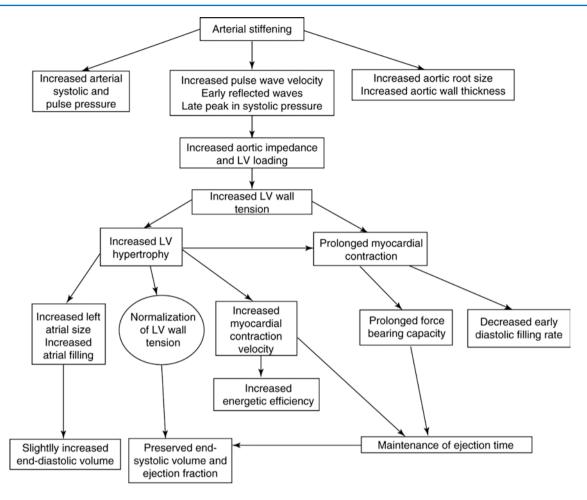


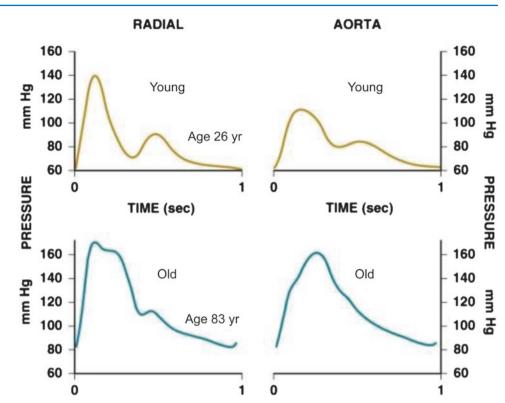
Fig. 11.7 A cascade of functional adaptations to vascular stiffening in the elderly. LV Left ventricle (Adapted from Lakatta [125]. With permission from Elsevier)

Other physiological consequences of increased arterial wave reflectance are increased systolic blood pressure, decreased diastolic blood pressure, and a widened pulse pressure (Fig. 11.8) [33, 34]. Data from the Framingham Heart Study shows that systolic blood pressure increases by 5 mmHg per decade until the age 60 and then increases by 10 mmHg per decade, while the diastolic pressure remains the same. This leads to a large difference between systolic and diastolic blood pressure, for example, 80 mm Hg, and is sometimes alluded to as "pulse-pressure hypertension" [32]. Widened pulse pressure is a hallmark of aging and has been associated with poor clinical outcomes.

A relatively high systolic pressure in comparison to diastolic pressure is harmful for several reasons. First, a high pulse pressure indicates that the patient's arterial conduit system is stiff. Low compliance means that a high systolic pressure is required in order to distend the aorta and other large arteries as the stroke volume is received. Even though this increase in pressure occurs relatively early in ejection, it still forces the ventricle to pump against a high pressure and stimulates hypertrophy that, in turn, increases myocardial stiffness and further impairs diastolic relaxation. Indeed, there is a strong correlation between the severity of reduced arterial compliance and the severity of diastolic dysfunction [35]. Second, when the diastolic pressure is low compared with systolic pressure, there is an immediate predisposition to an imbalance of myocardial oxygen supply and demand. Demand correlates most closely to systolic pressure [36], whereas coronary blood flow occurs mostly during diastole, making supply highly dependent on diastolic pressure. With rapid transit of reflected arterial waves, there is loss of the accentuated pressure in early diastole. This lowering of aortic pressure during diastole potentially diminishes coronary perfusion. In patients with coronary disease, this imbalance could result in subendocardial ischemia, thereby worsening diastolic relaxation and increasing atrial pressure.

Because of the consequences of arterial stiffening, arterial compliance has been suggested as a better measure of biologic age, as opposed to chronologic age [37]. And it is not surprising that there is great interest in strategies to reduce or even reverse arterial stiffening in the hope of preventing CVD. Current human therapy primarily involves drugs that

Fig. 11.8 Directly measured arterial waveforms from a peripheral (*radial*) artery and calculated aortic pressure waves for a 26-year-old man (*upper panels*) and his 83-year-old grandfather (*lower panels*) (Courtesy Michael O'Rourke, MD, University of Sydney, Australia)



relax smooth muscle tone. Statins not only inhibit myocardial remodeling but may lessen vascular stiffness. Angiotensin blockers and aldosterone seem to lessen fibrosis, and exercise slows vascular stiffening and remains a useful therapy for all ages.

Neuroendocrine Changes with Aging that Affect the Cardiovascular System

Aging of the neuroendocrine system can have a significant effect on the cardiovascular system. Changes include the number of adrenergic receptors in the cardiac and vascular tissues, attenuation of signal transduction pathways, and changes in the balance between sympathetic and parasympathetic activity. The renin-angiotensin-aldosterone system, vasopressin, and natriuretic peptides are also affected by aging.

Adrenergic Receptor Activity and Aging

Aging has been associated with a decrease in the response to stimulation of β -receptors. This is noted in the peripheral circulation by a reduced arterial and venous dilation response to the β -agonist, isoproterenol, and the mixed agonist, epinephrine, in the elderly. In cardiac muscle, there is a reduction in the inotropic response to exercise and to exogenous catechol-

amine administration in the aging patient [38]. In isolated cardiac myocytes, it has been shown that the EC_{50} for isoproterenol (a β_1 - and β_2 -agonist) is nearly twice as high in the elderly [39]. As a result of the decreased contractile response to β -adrenergic stimulation in the elderly, there is a greater dependency on the Frank-Starling (length-tension) mechanism of contraction to maintain cardiac output.

Although multiple studies indicate that the heart rate increase to β -stimulation of the heart is attenuated with age (Fig. 11.9), at least one study has questioned the age-related attenuated chronotropic response [38]. Studies also provide conflicting results regarding age-related changes in myocardial β-adrenoceptor density. The mechanism for decreased cardiac inotropic response to sympathetic stimulation is more likely attributable to changes in the second messenger system. Impaired coupling of the β -adrenoceptor to the Gs protein and to the catalytic unit of adenylyl cyclase is consistently observed in the elderly myocardium. Furthermore, an increase in Gi protein levels observed in aged myocardial tissue indicates a reduction in the catalytic subunit of adenyl cyclase [40]. Both of these mechanisms will attenuate 3',5'-cyclic adenosine monophosphate (cAMP) formation and subsequent β -adrenoceptor response. This desensitization of the intracellular processing of receptor signaling is likely a compensatory adaptation to an increase in endogenous norepinephrine resulting from age-related increases in sympathetic activity and reduced neuronal uptake of norepinephrine. Furthermore, the decrease in proportion of β -1 vs

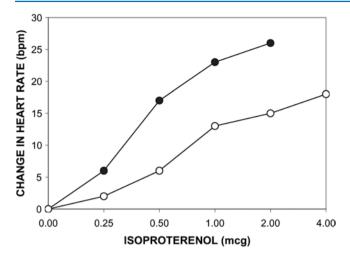


Fig. 11.9 The effect of intravenous isoproterenol infusions on increasing heart rate in healthy young (*filled circles*) and older (*unfilled circles*) men at rest (Adapted from Lakatta [125]. With permission from Elsevier)

 β -2 with aging and in heart failure is implicated as a potential mechanism of decreased responsiveness to β -adrenergic stimulation in the elderly [41]. In addition to β -1 and β -2 adrenergic receptors, cardiac myocytes have β -3 receptors. Cardiac β -3 adrenergic receptors are coupled to cGMP/NO pathway and cause negative inotropic effects, serving thereby as a brake in sympathetic overstimulation which is seen in heart failure [42].

This attenuated β -adrenoceptor response as a result of changes in second messenger function has implications in the peripheral vascular system. Vasorelaxation is accomplished in vascular smooth muscle cells via cAMP. cAMP activates protein kinase A (PKA) that then lowers cytosolic calcium levels, causing vasorelaxation. Decreased generation of cAMP in the vasculature leads to impairment of this pathway. This may be a contributing factor for hypertension in the elderly. Because cAMP is an antiproliferative agent, this deficiency may be associated with the progression of atherosclerosis [40].

Genetic variation in β -adrenoceptors is documented and has a significant role in CVD heterogeneity among individuals. There are many known polymorphisms of both β_1 - and β_2 -adrenoceptor subtypes. These variants may have differing effects on the cardiovascular system with age. The most common polymorphism, whose allele frequency is 60%, causes enhanced down regulation of β_2 -adrenoceptors. Because peripheral β_2 -receptors cause vasodilation and a reduction in blood pressure, individuals with this polymorphism are more prone to hypertension with increasing age. This fact has been confirmed in familial studies, which show increased prevalence of this allele in families with a history of essential hypertension. Another β -adrenoceptor polymorphism with important implications in cardiac disease is one that causes blunted agonist responsiveness. Studies have shown that in heart failure patients, this variant carries a relative risk of death or transplant of 4.8 compared with the normal allele. There also exists a particular polymorphism that tends to improve survival in those with heart failure. The existence of β -receptor polymorphisms may have additional implications for the efficacy of β -blockade. However, at this time, little is known about their particular impact on patient therapy [43].

Alpha-adrenergic receptors (AR) are also affected by aging [44–46]. Decreased expression of α -1A and α -1D receptors (involved in contractile function) has been noted with aging, which may be an adaption to cardiac hypertrophy [47]. A reduced responsiveness with age has been also reported for alpha-adrenergic receptors in healthier elderly patients [20] with potential implications for reduced muscle blood flow and augmented blood pressure during exercise. Interestingly, in normotensive older subjects, an increased rate of infusion of an α -agonist is required to achieve the same degree of vasoconstriction compared with young subjects [30]. Animal studies have shown that maximal binding of vascular α_1 -receptors is significantly reduced with age.

The α_2 -receptors appear to show some age-related decline. Normally, α_2 -receptors predominate in the venous side of the circulation, suggesting that a compromised venoconstrictor response to the upright posture, secondary to α_2 -receptor loss, might contribute to orthostatic intolerance in the elderly [48]. The evidence of adrenergic receptor desensitization with age has further implications as hypertension develops in the elderly. In normotensive elderly subjects, the decrease in responsiveness of α -adrenergic receptors seems to be a regulated compensatory effect of the heightened level of sympathetic nervous system activity in the elderly. Despite some evidence of diminished α -adrenergic responsiveness, it seems that the overall baroreflex control of vasoconstriction is well preserved with age and might be heightened compared with young adults [28, 49].

As with β -adrenoceptors, polymorphisms in α -adrenergic receptors may have implications on hypertension and cardiac disease in the elderly. It has been proposed that individuals with a particular α_{2B} -adrenergic receptor polymorphism may be at greater risk for acute coronary events and sudden cardiac death [50]. In addition to the changes in α - and β -adrenergic receptors, dopaminergic receptor content and dopaminergic transporters decrease, and cardiac contractile responsiveness to dopaminergic stimulation is blunted with aging [51].

Sympathetic Nervous System Activity

The sympathetic nervous system exerts various effects on the cardiac physiology, including increase in atrioventricular conduction (positive dromotropy), heart rate (positive chronotropy), cardiac contractility (positive inotropy), and cardiac relaxation (positive lusitropy). Likewise, it plays a crucial role in the regulation of vascular tone due to its abil-

ity to control at the same time both peripheral resistances and cardiac output.

The sympathetic nervous system plays an important role in both aging and cardiovascular disease. Sympathetic nervous system activity increases with age, and by some estimates the sympathetic nerve activity is almost two times higher in a 65-year-old than a 25-year-old person [52]. This is probably due to increased catecholamine release, decreased neuronal uptake, and increased sympathetic nerve activity [53]. These alterations seem to be region specific and are seen in the skeletal muscle, splanchnic areas, and the heart [21]. Circulating norepinephrine concentrations increase by 10–15% per decade after adulthood [21, 54]. In addition, there is an age-dependent reduction in activity of the cardiac neuronal noradrenaline reuptake mechanism, resulting in higher concentrations of noradrenaline at β 1-receptor sites in the heart [55]. Similarly, the increase in norepinephrine levels during exercise is greater in elderly subjects. The decrease in catecholamine sensitivity of adrenergic receptors in the heart and blood vessels reduces the response to the increased catecholamine release [56]. In the vasculature, however, the vasoconstrictor response is at least equivalent, if not exaggerated, in comparison to younger adults [52].

At the vascular level, systemically circulating or locally released catecholamines trigger two main classes of adrenergic receptors, α -1 AR and β -2 AR, causing vasoconstriction and vasodilatation, respectively. With aging, such a fine equilibrium is progressively shifted toward increased vasoconstriction, most likely due to a defective vasodilatation in response to β -2 AR stimulation. Supporting this hypothesis, β -AR agonist administration in the human brachial artery induces vasodilatation, and this response appears to be attenuated in hypertensive patients. The mechanistic role of β -2 AR in the vasculature is also corroborated by the fact that genetic variants of β -2 AR causing excessive desensitization have been shown to lead to reduced vasodilatation, promoting the development of atherosclerosis [57]. Long-term sympathetic stimulation is detrimental to the heart, and increased noradrenaline levels lead to changes in the collagen turnover and increased fibrosis [58].

Parasympathetic Nervous System Activity

Aging is associated with decreased responses to parasympathetic stimulation in cardiac and vascular tissues. Sympathetic tone predominates and vagal tone diminishes with the aging process. Females maintain greater vagal tone than males [59]. Vagal terminals and axons in cardiac ganglia will degenerate with the aging process [60]. One way to assess autonomic outflow of the cardiovascular system is to assess the heart rate variability. Heart rate variability has two components, a high-frequency component, which is under parasympathetic control, and a low-frequency component, which is under sympathetic control. Both components of heart rate variability decrease with age. Poor responsiveness to β -adrenergic receptor stimulation may explain depression in the sympathetic component, whereas low vagal output at rest is the likely mechanism behind the diminished parasympathetic, high-frequency variability [52].

The decreased vagal tone can be either due to reduced vagal outflow or reduced intracellular responses to muscarinic receptor activation with age [61]. Both changes seem to be present in the elderly. Lower resting vagal tone in the elderly has been implicated in the diminished heart rate increase in response to a large dose of atropine compared with younger controls. Studies have shown that right atrial muscarinic receptor density is significantly and negatively correlated with age [30]. Furthermore, it has also been shown that muscarinic receptor function declines in the elderly population. This is evident by a reduction in carbachol-induced inhibition of forskolin-activated adenylyl cyclase in muscarinic receptors of aged myocardium [62]. Finally, autoantibodies to M2-muscarinic receptors exist in the sera of normal individuals and are found in high levels in those with idiopathic dilated cardiomyopathy. The prevalence of these autoantibodies is significantly increased in the elderly [63]. All of these mechanisms, taken together, contribute to reduced vagal activity in the elderly. The implications of these findings on muscarinic receptor function and cardiac performance have yet to be determined.

Reflex Control Mechanisms and Aging

Reflex autonomic cardiovascular control mechanisms are altered in the elderly. The aging process affects autonomic cardiovascular control mechanisms in a nonuniform manner. Attenuated respiratory sinus arrhythmia in older individuals suggests that parasympathetic control of sinus node function declines with age. Because the reflex regulation of heart rate in humans is primarily dependent on cardiac vagal activity, it is correct to assume that the impaired baroreflex regulation of heart rate is related to deficient parasympathetic mechanisms (Fig. 11.10). Although the parasympathetic component of the arterial baroreflex becomes diminished in the aging population, the baroreflex control of sympathetic outflow and the vascular response to sympathetic stimulation are well maintained in moderately old, active individuals [48]. It is well established that basal levels of plasma catecholamines and sympathetic nerve activity increase with age.

Endocrine Changes with Aging

The renin-angiotensin system (RAS) is central to physiologic control of sodium and water homeostasis. The RAS exists not only as an endocrine system but also as a local network in

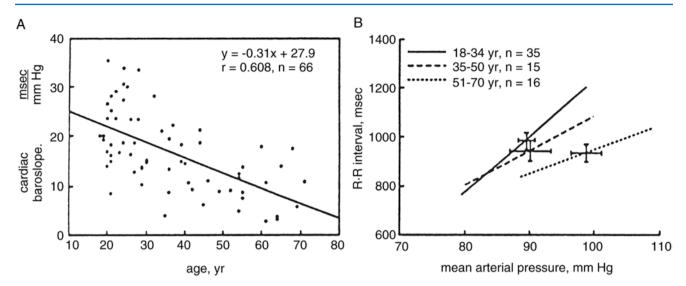


Fig. 11.10 (a) Individual cardiac baroreflex sensitivities versus age. Regression revealed a significant (p < 0.05) inverse relationship between reflex sensitivity and age. (b) Mean regression lines describing relationship between mean arterial pressure and corresponding R-R interval for

each of the three age groups. Regression line slopes were smaller in older and middle-aged subjects than in younger subjects. Baseline values (mean \pm SE) are superimposed on regression lines (Adapted from Ebert et al. [48]. With permission from the American Physiological Society)

different organs, especially in the heart and brain. There, local conversion of angiotensinogen to angiotensin by regional angiotensin converting enzyme occurs. Angiotensin (AT) II principally mediates its effect through AT-I and AT-II receptors. AT-I receptors mediate fibrosis, oxidative stress, and myocardial hypertrophy among other effects. Although aging decreases overall RAS activity via decreased levels of systemic renin-angiotensin, increased local RAS activity has been observed in the heart. In addition, both AT-I receptors and AT-II receptors are upregulated. These changes in the RAS system contribute to age-related changes with cardiac remodeling [64]. Aging also affects sodium balance in the kidney. This results in decreased ability to conserve sodium in the face of sodium restriction as well as a decreased sodium excretion in the presence of increased sodium load. Despite the increased sympathetic activity accompanying old age, the elderly experiences a decrease in plasma and renal levels of renin. Plasma renin activity is diminished in the supine position, and physiologic stimuli such as hemorrhage, sodium restriction, and orthostasis are followed by attenuated increases in renin release and consequently lower concentrations of angiotensin in the circulation [65]. Although reninangiotensin levels are decreased in the elderly, the aging population shows an enhanced vasoconstriction in response to angiotensin I and angiotensin II. The above finding helps to explain the key role that angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have in improving renal structure and function in the elderly [66].

In the elderly, there seems to be an elevation in plasma vasopressin levels under basal conditions and a heightened response to an osmotic challenge such as water deprivation. Surprisingly, after a water restriction period, older subjects demonstrate a relatively low spontaneous fluid consumption as well as diminished thirst [65]. In addition, by age 80, the total body water content has declined to 50% of body mass from the average content of 60% in younger persons [67]. Such decreases in thirst mechanism, total body water, and fluid consumption in combination with an age-related decrease in glomerular function cause older persons to be increasingly vulnerable to water imbalance.

Another group of hormones that are important in volume regulation are the natriuretic peptides. Atrial natriuretic peptide (ANP) is secreted primarily by the cardiac atria in response to atrial stretch, while brain natriuretic peptide (BNP) is secreted by both atrial and ventricular myocardial cells. Natriuretic peptides are primarily counter-regulatory hormones. They antagonize the effects of a number of sympathetic hormones and the renin-angiotensin-aldosterone system [68]. Seventy percent of all cardiac BNP is derived from the ventricles under normal conditions. In pathological conditions, the proportion of BNP derived from ventricles increases significantly [68]. Activation of these systems is seen most frequently in congestive heart failure, although many other conditions can also stimulate the release of NPs [68]. For example, increased levels of BNPs have been associated with aging, renal insufficiency, and anemia [69]. The changes in peptide levels are impressive enough to warrant higher cutoff levels of BNPs for diagnostic and prognostic purposes in the elderly [70].

Global Consequence of Cardiovascular Changes with Aging

The overall changes in the cardiovascular system are summarized in Table 11.1. Normal age-related changes in cardiovascular physiology present as decreases in peak heart rate, peak cardiac output, and peak ejection fraction [71]. Due to the overall dampening of autonomic and baroreceptor activity with aging, a decreased resting heart rate and a decreased ability to increase cardiac output with changes in heart rate are observed [72]. Compared to younger patients, increases in cardiac output in the elderly are achieved more by increasing enddiastolic volume, as opposed to increasing heart rate and contractility. This results in an increased reliance on atrial filling for maintenance of cardiac output. Overall, the ability of the cardiovascular system to withstand stress is significantly decreased [73]. Aerobic capacity, as evaluated by maximum body oxygen consumption, decreases with aging by 10-12% per decade in healthy men and women beginning at age 50 years. [74] This is due to the reductions in both maximal cardiac output and the maximal arteriovenous oxygen difference. The reduction in cardiac output is primarily due to the reduction in maximum heart rate, which is approximately 1 beat/min per year [30].

 Table 11.1
 Age-associated changes in the cardiovascular system in older people

Vasculature	Increased intimal thickness Arterial stiffening Increased pulse pressure Increased pulse wave velocity Early central wave reflections Decreased endothelium-mediated vasodilation
Ventricles	Increased LV wall tension Prolonged myocardial contraction Prolonged early diastolic filling rate Heart failure (with or without preserved systolic function) Decreased maximal cardiac output
Atria	Increased left atrial size
Valves	Sclerosis, calcification
Conduction system	Atrial premature complexes Atrial fibrillation Increased conduction time Right bundle branch block Ventricular premature complexes
Reflex and autonomic nervous system	Decreased maximal heart rate

Small Vessel Pathology and Aging

Small vessel vasculature, particularly in the cerebral circulation, is also affected by aging [75]. Transcranial Doppler studies have shown evidence of increased arterial stiffness in cerebral circulation with aging. Endothelial cells become elongated, mitochondrial content decreases, capillary number is reduced in the cerebral cortex and hippocampus, and the basement membrane thickens and becomes fibrotic [76, 77]. Perivascular fibrosis, replacement of vascular smooth muscle cells by fibrohyaline material, and generalized small vessel atrophy are noted with aging. Collectively these changes lead to derangement in microcirculatory controls and predispose the elderly to ischemic and neurological events. These small vessel changes are also closely related to the development of Alzheimer's disease, Parkinson's disease, and other neurodegenerative diseases such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy [78, 79].

Vein Remodeling

Like the large arteries [6, 80], veins also stiffen with increasing age [81]. Aged veins display subintimal fibrous thickening, fibrosis of the three media layers, a decrease in elastic tissue, increased collagen cross-linking, and hyperplasia of the smooth muscle cells [82]. About 70% of the total body blood volume is contained in the low-pressure venous system [83]. Fluctuations in the compliance of the venous system play a very important role in the development of hypertension and compensation to hypovolemia [83]. An age-related decrease in venous compliance has been demonstrated, similar to that seen in the arterial system [84]. This decrease in venous compliance does not seem to be due to increased sympathetic or adrenergic influences in the elderly [81]. Other factors such as increased endothelin or myogenic factors may be responsible. However, it is clear that this decrease in venous capacitance contributes to the development of hypertension in a group of patients [85]. It also impairs cardiovascular control and reduces the ability of elderly vasculature to buffer hemodynamic stresses, such as hypovolemia [84].

Coronary Vasomotor Tone

Coronary vasomotor tone is regulated by neural control, endothelium-dependent modulation, and myogenic regulation. Though resting coronary blood flow is not significantly affected, there is some animal data to suggest that the coronary blood flow reserve is significantly reduced with aging [86]. The adaptive reserve capacity of the endocardium is reduced compared to the epicardium, and that may be responsible for the greater vulnerability of the endocardium to ischemic episodes in the elderly [87, 88]. Though vascular smooth muscle function and its neural control change with aging [89], myocardial oxygen demand is the principal controller of coronary blood flow even in the elderly. Aging alters metabolic activity in cardiac myocytes, which can alter coronary vascular tone in arterioles [86, 90]. However, the overall effect of aging on coronary blood flow regulation and myocardial oxygen extraction is unknown.

Arrhythmias

Cardiac conduction system degenerates progressively with aging and predisposes the older patient to arrhythmias. Sinus node dysfunction develops with the progressive loss of pacemaker cells and contributes to the risk of sick sinus syndrome and/or bradycardia [91]. Sinus node dysfunction occurs in 1 of every 600 cardiac patients >65 years of age and accounts for approximately 50% of implantations of pacemakers in the United States [1]. Bradycardia promotes atrial fibrillation as does age-related atrial fibrosis and atrial enlargement. Atrial fibrillation is diagnosed in approximately 4% of subjects without clinical coronary artery disease over the age of 60 years. The overall prevalence of atrial fibrillation reaches about 17.8% in people aged 85 years and above [92]. This predisposition to atrial fibrillation undoubtedly contributes to the relatively high incidence of new-onset atrial fibrillation (and supraventricular tachycardia) not only after thoracic and cardiac surgery but after most major surgical procedures. Patients presenting for surgery who are found to have previously undiagnosed atrial fibrillation should be evaluated before surgery, including an echocardiogram to rule out structural abnormality. Perioperatively, the management of new-onset atrial fibrillation is initially rate control [93, 94]. For patients with chronic atrial fibrillation, early anticoagulation after surgery may be important, especially if the patient is at high risk for thromboembolism [94]. Heart block and ventricular ectopy are examples of other arrhythmias prevalent in older patients [95]. Heart block below the atrioventricular node most often occurs secondary to idiopathic degeneration of the conduction system but is not likely to carry adverse consequences unless there is concomitant cardiac disease.

Valvular Changes with Aging

As in the vasculature and the heart, the composition of the cardiac valves changes progressively with aging. The valves become fibrotic, less mobile, and myxomatous. The thickness of the aortic and mitral valve leaflets increases with aging. Annular dilatation is very common, and 90% of healthy 80-year-olds demonstrate some form of mild multivalvular regurgitation, which is typically mild and central and present with normal-appearing leaflets [96]. Specifically, the incidence of aortic regurgitation increases with age, and 16% of the elderly have been noted to have some form of moderate to severe aortic regurgitation [97]. The incidence of mitral annular calcification and regurgitation also increases with age. Up to 50% of females and 36% of males were noted to have significant mitral annular calcification [96]. These valvular changes are associated with coronary events, heart failure, atrial fibrillation, endocarditis, thromboembolic strokes, and transient ischemic attacks [96]. Similarly, the incidence of aortic stenosis increases with aging, and 80% of the elderly have some degree of aortic sclerosis. This is due to increasing stiffening, scarring, and calcification of valves. The presence of significant aortic stenosis is associated with a higher incidence of new coronary events and 2-3 times increased risk of adverse perioperative cardiac events [98].

Ischemic Preconditioning

An episode of myocardial ischemia reduces the severity of myocardial damage associated with a subsequent, more prolonged ischemic event. This phenomenon, known as ischemic preconditioning (IP), exists in both an immediate (minutes to a few hours) and delayed (many hours to days) form [99]. Clinically, IP is likely involved with warm-up angina in which patients who exert to the onset of angina, rest, and exert again can then achieve higher levels of exertion before developing the second bout of angina. Patients who suffer a myocardial infarction are much less likely to die or develop heart failure if they experience angina within 48 h of their myocardial infarction. Exposure to volatile anesthetics yields a preconditioning effect as well [99].

Unfortunately, aging is associated with the loss of IP [100]. Warm-up angina is nonexistent beyond age 75, and in patients older than 65, myocardial infarction with or without antecedent angina is associated with the same high rates of death and heart failure as younger subjects who did not have prior angina [101]. Age-related IP reduction may be due to alterations of mediator release and intracellular pathways. Several pharmacological stimuli failed to mimic IP in the aging heart, although IP may be exogenously activated by nicorandil, a mitochondrial potassium channel opener. Interestingly, lifestyle interventions such as exercise training and caloric restriction separately and, more powerfully, taken together are able to completely preserve and/or restore the age-related reduction of IP in both animal and human studies [100]. At least in aged rats, anesthetic cardioprotection from preconditioning is essentially abolished [102].

Implications in Anesthesia and Fluid Therapy

Normal aging affects virtually all components of the cardiovascular system, many of which have important influences on anesthetic management in the elderly. Compounding these age-related changes are the well-described depressant effects of the intravenous and volatile anesthetics on the myocardium, vascular tone, and the ANS.

Elderly patients coming to the operating room are in a relatively volume-depleted state because of NPO guidelines, reduced thirst mechanisms, and diminished renal capacity to conserve water and salt. Additionally, increases in heart rate and contractility during volume loss are limited by diminished reflex control systems and by reduced β-receptor responses. Consequently, additional volume loss, e.g., intraoperative blood loss, can result in substantial hypotension. This volume sensitivity of the elderly has been demonstrated in the laboratory during head-up tilt testing after subjects had been made hypovolemic with diuretics and low-salt intake. The older subjects had greater decreases in blood pressure during upright tilting than both the younger hypovolemic control subjects and the older normovolemic control subjects [103]. Impaired responses to hypovolemia are further confounded by volatile anesthetics and the sedative-hypnotics that impair baroreflex control mechanisms [104, 105]. Healthy or preserved baroreflex control mechanisms can lessen the cardiovascular changes that result from anesthetics. For example, diabetic patients with preserved autonomic reflexes had a lower incidence of hypotension during induction and maintenance of anesthesia than diabetics with impaired reflexes [106]. Thus, the net effect of physiologic changes with aging, compounded by anesthetic effects, leads to more frequent and significant blood pressure changes in the elderly patients. Such blood pressure lability has been observed in older patients [107].

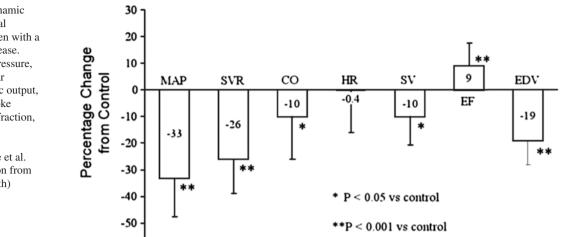
Fluid management is never routine in the elderly. It requires as much forethought as any other medication. Due to advanced atherosclerosis, stiff ventricles, diastolic dysfunction and occult coronary artery disease, elderly patients do not tolerate hypovolemia or hypervolemia. Hypovolemia leads to hypotension and organ hypoperfusion, while overhydration can lead to congestive heart failure. In 1999, the UK National Confidential Inquiry into Perioperative Deaths at the extremes of age concluded that "errors in fluid management (usually excess fluid) were one of the most common cause of avoidable perioperative morbidity and mortality" [108]. Their report states that "fluid management in the elderly is often poor; they should be accorded the same status as drug prescription. Multidisciplinary reviews to develop good local working practices are required." The most recent report from 2010 reemphasizes the same issue [108].

In the aged patient, the relative hypovolemic state has many important clinical implications. The elderly heart is heavily dependent on an adequate end-diastolic volume to maintain stroke volume, and cardiac filling is in turn dependent on higher atrial filling pressures because of a stiffened ventricle and possible diastolic dysfunction. As a result, the elderly are very sensitive to hypovolemia. In this setting, decreased systemic blood pressure should generally be treated with intravenous fluids rather than vasopressors to maintain proper ventricular filling. One study has shown that volatile anesthetics do not impair diastolic function, whereas propofol has some negative effects [109].

As important as maintenance of an adequate cardiac preload is to an older patient, it is equally important to avoid excess fluid administration. There are two ways in which one can be misled into administration of excess volume. First, with volatile anesthetic relaxation of vascular smooth muscle and/or with propofol-mediated sympathetic inhibition comes venodilation and increased venous pooling of blood. Restoration of preload would therefore seem to require significant volume administration just to compensate for the effects of the anesthetic. However, at the end of surgery, when the anesthetic drugs are exhaled or metabolized, vascular smooth muscle relaxation lessens, and sympathetic tone is restored or possibly heightened because of pain and surgical trauma. Restoration of normal to increased venous tone will then shift that excess volume back to the heart and potentially lead to pulmonary and cardiac dysfunction as the elderly heart copes with what now is volume overload. The risk of hypervolemia, at least so far as the heart is concerned, can also be seen when significant amounts of third-space fluid become mobilized. Judicious use of furosemide may prevent overt pulmonary congestion or edema.

The second mechanism that can mislead practitioners into giving excess volume occurs when cardiac filling and cardiac output are maintained near normal but the patient is still hypotensive from arterial vasodilation. The natural reaction to hypotension is to assume the patient is hypovolemic and therefore give more volume. That treatment may not be appropriate with older patients. Young, healthy patients have minimal sympathetic tone when supine and at rest. Thus, anesthesia is likely to decrease blood pressure in young patients more by the direct effects of the anesthetic on blood vessels than by removal of sympathetic tone. Elderly patients, however, often have high levels of sympathetic tone, and removal of that tone can produce more than just an apparent hypovolemia. In a study of older men with varying degrees of cardiac disease, high spinal anesthesia produced an average decrease in blood pressure of 33% (Fig. 11.11) [110]. Even though pooling of blood in the abdomen and legs caused a 19% decrease in left ventricular end-diastolic volume, cardiac output only decreased by 10%, largely because

Fig. 11.11 Hemodynamic response to high spinal anesthesia in older men with a history of cardiac disease. *MAP* Mean arterial pressure, *SVR* systemic vascular resistance, *CO* cardiac output, *HR* heart rate, *SV* stroke volume, *EF* ejection fraction, *EDV* left ventricular end-diastolic volume (Adapted from Rooke et al. [110]. With permission from Wolters Kluwer Health)



the decrease in blood pressure (afterload reduction) allowed the ejection fraction to increase. The primary mechanism for hypotension, however, was the 26% decrease in systemic vascular resistance. It is physically impossible to increase end-diastolic volume indefinitely and fully compensate for such a significant decrease in vascular resistance. In fact, it could be argued that the attempt would merely predispose the patient to volume overload, especially on emergence as discussed above. Increased left ventricular end-diastolic pressures from excessive volume could also precipitate or aggravate myocardial ischemia by creating high left ventricular subendocardial wall stress [111].

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Though not specifically addressed in elderly patients, goal-directed fluid therapy seems to improve outcomes. One of the primary goals of fluid therapy is to achieve adequate cardiac index/stroke volume, for a particular clinical situation, by maintaining optimal preload. In the perioperative setting, one of the biggest challenges has been to determine accurately (and easily) the fluid status of the patient. Static markers of preload (central venous pressure, pulmonary artery wedge pressure, etc.) have been used for decades and are still used to guide fluid therapy. However, these markers are not very accurate [112]. Noninvasive, dynamic indices like pulse pressure variation (PPV), systolic pressure variation (SPV), and stroke volume variation (SVV) may be better predictors of volume status [113]. Though the British guidelines recommend using flow-directed monitors to determine fluid status, one should keep in mind that most of these studies are small and results may not be applicable to elderly patients. Thus, even though the "best" method to manage fluids in the elderly is unclear, it is clear that a keen sense of pathophysiology, effects of anesthetic drugs on CV function, and attention to volume losses will promote a good outcome.

When are vasopressors a good option? In all but the sickest of older patients, the most likely mechanism of intraoperative hypotension is either decreased vascular resistance or hypovolemia. Bradycardia could be involved but is easily detected and treated. Vasopressors are to be considered in managing the hypotensive patient even after adequate volume deficits are replaced and both ephedrine and phenylephrine are the most frequently used drugs. Phenylephrine has the advantage over ephedrine in that it does not exhibit tachyphylaxis and will not promote tachycardia that is unwanted in diastolic dysfunction. Furthermore, α-receptor activation promotes venoconstriction in addition to vasoconstriction, thereby shifting blood from the periphery back to the heart and alleviating the anesthetic-induced peripheral pooling [114]. As with all drugs, adverse consequences can occur. Coronary vasoconstriction, decreased cardiac output, imbalance in the distribution of the cardiac output, and wall motion abnormalities are all potential undesired effects. The key to the rational use of pressors such as phenylephrine is to ameliorate the effect of hypovolemia or maldistribution of volume, not necessarily striving to increase vascular tone back to preanesthetic levels, in other words, tolerating a mild decrease in blood pressure. The cardiac side effects that have been observed with phenylephrine are typically associated with elevated blood pressure above the patient's normal state [9] or under unusual cardiac loading conditions such as deep anesthesia [115].

Anesthetic choice and dose in the elderly are driven by a theme of maintaining cardiac stability. Volatile agents are direct vasodilators and are known to depress baroreflex responses. Furthermore, volatile anesthetics can produce myocardial depression and nodal rhythms that are poorly tolerated in patients with cardiac abnormalities such as aortic stenosis, mitral stenosis, or hypertrophic obstructive cardiomyopathy [116]. A preference might be given to less soluble, volatile anesthetics because they can be titrated up or down quickly and emergence times as well as time to orientation are remarkably better than with the older volatile anesthetics

[55]. Maintenance can include nitrous oxide when appropriate, despite its controversial side effects, because it helps to maintain sympathetic outflow and lessens the need for higher concentrations of the potent volatile anesthetics. Importantly the MAC of volatile anesthetics decrease by 6-8% per decade after 40 years [117], and end-tidal concentrations should be adjusted downward. Unfortunately, this is rarely achieved in contemporary practice [118]. Intravenous anesthetics have a more pronounced hemodynamic effect, with smaller doses being required to achieve the same anesthetic level. This is due to pharmacokinetic and pharmacodynamic changes in the elderly. The dose of induction agents should be decreased by 25-50% [119, 120]. Adjusting the anesthetic dose for patient age may help reduce unnecessarily deep anesthesia and associated hypotension and potentially reduce adverse outcomes [121, 122].

Hypertension and tachycardia should be recognized as undesirable events in the elderly because of the increased myocardial oxygen demand and the reduced time for atrial filling and coronary flow. Esmolol is useful (0.5–1.0 mg/kg) to attenuate the intubation response and avoid excessive increases in heart rate. α_2 -agonists such as dexmedetomidine also are effective in reducing the sympathetic response to laryngoscopy and intubation but add to intraoperative hypotension. Additionally, adequate analgesia is an important aspect of heart rate and blood pressure control, but dosage of opioids should be adjusted for age. Benzodiazepines should be minimized or avoided because they interact with opioids to produce sympatho-inhibition and hypotension and can be associated with postoperative delirium.

In the postoperative period, the older patient will be at risk for developing pulmonary congestion when significant extravascular fluid becomes mobilized. Patients with no history of heart failure, but who have borderline diastolic dysfunction, nondistensible vessels, and/or poor renal function, may experience significant increases in atrial pressure with even modest increases in intravascular volume. Careful and frequent bedside examination of the patient during the first several hours and postoperative days allows for timely use of diuretics; avoiding fluid overload may prevent progression to more serious complications such as hypoxia, respiratory failure, cardiac dysfunction, or myocardial infarction.

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The Aging Respiratory System: Strategies to Minimize Postoperative Pulmonary Complications

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The Physiology of the Aging Lung

Cellular Mechanisms

Lung function gradually deteriorates with age [1] even in healthy individuals who maintain aerobic capacity [2, 3]. Aging is a complex process that begins at the cellular level. Normal cells undergo senescence as a result of multiple mechanisms such as telomere shortening during continuous proliferation, oxidative stress, DNA damage, and aberrant oncogene activation [4]. Normal mitochondrial respiration is associated with oxidative stress for the cell because of a continuous production of superoxide and hydrogen peroxide, inevitably resulting in minor macromolecular damage. Damaged cellular components are not completely recycled by autophagy and other cellular repair systems, leading to a progressive age-related accumulation of biologic "waste" material, including defective mitochondria, cytoplasmic protein aggregates, and an intralysosomal nondegradable material called lipofuscin [5]. At the physiologic level, aging is associated with multiple changes in the respiratory system, including structural changes of the lungs and chest wall, leading to alteration in mechanical properties of the respiratory system and interference with gas exchange. Aging also decreases the function of central chemoreceptors and peripheral mechanoreceptors resulting in an impaired response to hypoxia and hypercapnia.

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R. Cartin-Ceba Department of Anesthesiology, Mayo Clinic College of Medicine, Scottsdale, AZ, USA The respiratory system is a network of organs and tissues that exchanges gases between the individual and the environment, delivering oxygen to venous blood in exchange for carbon dioxide [6]. The lungs continue to develop throughout life with the maximal number of alveoli attained before 12 years of age. The maximal function of the respiratory system, defined as a maximal ability to exchange gas, is achieved at approximately the mid-third decade of life [7].

The three most important physiologic changes associated with aging are a decrease in strength of respiratory muscles, a decrease in the elastic recoil [8] (Fig. 12.1) of the lung, and a decrease in the compliance of the chest wall [7].

Age-Related Changes in Mechanics of Breathing

Chest Wall and Respiratory Muscles

The chest wall progressively stiffens with aging because of structural changes of the intercostal muscles, intercostal joints, and rib-vertebral articulations, leading to a decrease in static chest wall compliance [7, 9]. The increase in the rigidity of the rib cage is secondary to multiple factors, including changes in rib-vertebral articulations, changes in the shape of the chest (mainly because of osteoporosis that increases both dorsal kyphosis and anteroposterior chest diameter), costal cartilage calcification, and narrowing in the intervertebral disk spaces [7, 9].

The changes in the chest wall geometry with aging result in flattening of the diaphragm curvature (Fig. 12.2) [1], which has a negative effect on the maximal transdiaphragmatic pressure [1, 7]. A reduction in muscle mass contributes to a decrease in the force produced by respiratory muscles. In a healthy 70-year-old individual, maximal skeletal muscle electromyographic activity is reduced by approximately 50% [10]. In frail or malnourished elderly patients, respiratory muscle strength may be further affected [11, 12]. The main consequence of the reduction in the

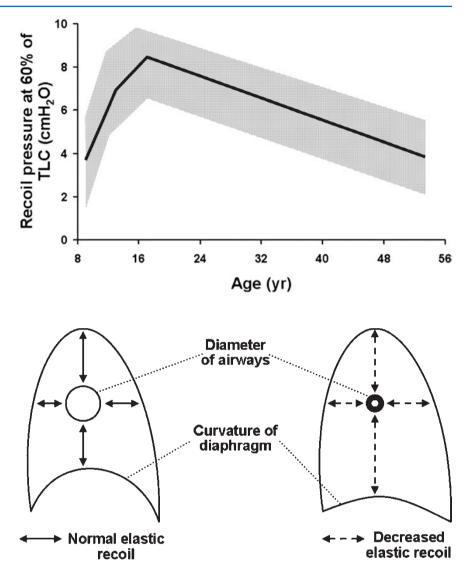
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Fig. 12.1 Static elastic recoil decreases throughout life starting around the age of 20. TLC total lung capacity. Shaded area represents mean ± 1 SD(This material has not been reviewed by the European Respiratory Society prior to release; therefore, the European Respiratory Society may not be responsible for any errors, omissions, or inaccuracies or for any consequences arising therefrom, in the content. Reproduced with permission of the European Respiratory Society ©: Janssens et al. [7])

Fig. 12.2 Aging-induced reduction of elastic recoil results in an enlargement (barrel shaped) of the thorax and flattening of the diaphragm. The flatter diaphragm is less efficient in generating muscle power which increases the work of breathing. The loss of elastic recoil results in narrowing of small airways. Left panel, juvenile lung; right panel, aged lung (Reprinted from Zaugg and Lucchinetti [1]. With permission from Elsevier)



maximal transdiaphragmatic pressure is predisposition of the diaphragm to fatigue in the presence of increased ventilatory load; [13] this could manifest clinically by difficulty weaning an elderly patient from the ventilator.

Lung Parenchyma

Lung compliance increases with aging primarily because of the loss in parenchymal elasticity (Table 12.1) [7, 8]. As a result, elastic recoil pressure of the lungs decreases with age (Fig. 12.1) [7, 8, 14]. The presumed mechanism for this decrease in elasticity is changes in the spatial arrangement and/or cross-linking of the elastic fiber network [9]. Changes in lung parenchyma become pronounced after 50 years of age, resulting in a homogeneous enlargement of air spaces and a reduction of alveolar surface area from 75 m² at age 30 to 60 m² at age 70 [9]. Because these changes functionally resemble emphysema, they are sometimes referred to as "senile emphysema" [6, 15].

Spirometry: Static and Dynamic Tests and Underlying Physiology

All lung volumes increase from birth until somatic growth stops. Age has interesting effects on total lung capacity (TLC), the net effect being only slight changes with increasing age. TLC is correlated with height. With advancing age, height diminishes because of vertebral changes (e.g., flattening of the intervertebral disks, compression fractures), and TLC reduces but, if normalized for height, remains unchanged (Fig. 12.3) [7, 16, 17]. The age-associated effects of the loss of inward elastic recoil and decline in the chest wall outward force are typically balanced so that TLC remains unchanged [9]. Because TLC remains relatively stable with age, changes in other measured lung volumes and capacities offset each other and are balanced. An understanding of these changes helps to explain the decline in pulmonary function.

The reduction of the alveolar surface area results in a gradual increase in the residual volume (RV) with an increase

Function alteration	Change	Pathophysiology	Potential complications
Upper airway patency	Ţ	Hypotonia of hypopharyngeal and genioglossal muscles, obesity (redundant tissues)	Upper airway obstruction and OSA
Swallowing reflexes and cough	ţ	↓ Clearance of secretions	Aspiration risk, inefficient expectoration, pneumonia, atelectasis, hypoxemia
Chest wall compliance	ţ	Structural changes of the intercostal muscles and joints and rib-vertebral articulations	↑ Work of breathing, delayed weaning from mechanical ventilation
Airway resistance	ſ	↓ Diameter of small airways	Air trapping, propensity for developing intraoperative atelectasis; ↓ maximal expiratory flow (airflow limitation) during exercise
Lung compliance	↑	↓ Lung static elastic recoil pressure	Air trapping, potential for dynamic hyperinflation during mechanical ventilation
Closing volume	Î	Closing of small airways, sometimes within normal tidal volume breathing	Intraoperative hypoxemia, especially with ↓ FRC airflow limitation
Gas exchange	↓ Oxygenation	 ↑ Ventilation/perfusion heterogeneity and ↓ diffusing capacity 	Hypoxemia
Gas exchange	$\leftrightarrow \text{In CO}_2$	↑ In dead space ventilation counteracted by \downarrow in CO ₂ production because of \downarrow in basal metabolic rate	
Exercise capacity	↓ From deconditioning	\downarrow VO ₂ max because of \downarrow in cardiac output	Associated with higher incidence of postoperative pulmonary complications
Regulation of breathing	ţ	Dysfunction of central chemoreceptors and peripheral mechanoreceptors	↓ Ventilatory response to hypoxemia. Risk of hypercarbia and hypoxemia during use of opioids

Table 12.1 Changes in respiratory function associated with aging and pathophysiologic mechanisms that explain perioperative complications

of 5–10% per decade [18]. The RV/TLC ratio increases from 25% at 20 years to 40% in a 70-year-old subject. The increase in RV results in a compensatory decrease of vital capacity (VC); after age 20, VC decreases 20–30 mL per year [18]. Functional residual capacity (FRC) is determined by the balance between the inward recoil of the lungs and the outward recoil of the chest wall. FRC increases by 1–3% per decade (Fig. 12.3) because at relaxed end-expiration, the rate of decrease in lung recoil with aging exceeds that of the rate of increase in chest wall stiffness [18, 19].

Forced expiratory volume in 1 s (FEV₁) and forced VC (FVC) increase up to 20 years of age in females and up to 27 years of age in males, followed by gradual decrease (up to 30 mL per year) (Fig. 12.4) [9, 20, 21]. After 65 years of age, this decline may accelerate (38 mL per year) [22]. Smoking dramatically accelerates these age-related changes in FEV₁ and FVC [23]. In healthy, elderly subjects from 65 to 85 years of age, the normal FEV₁/FVC ratio may be as low as 55%, compared with expected \geq 70% in younger individuals [24]. Lung volume is a major determinant of airway resistance,

but, when adjusted for age-related change in mean lung volume, aging has no significant effect on airway resistance [25]. A decrease in small airway diameter with aging, associated with reduced mean lung volume (Fig. 12.2, Table 12.1), contributes to a decrement in maximal expiratory flow with aging [26], present even in lifetime nonsmokers [26].

Airway Closure Concept (Closing Volume)

The loss of elastic recoil [7, 16] also affects the caliber of intrathoracic airways (Fig. 12.2) [27]. These airways are kept open by the transpulmonary pressure gradient (P_{tp}), i.e., the pressure gradient from inside the airway (0 cmH₂O) to the pleural space (-10 cmH₂O) (Fig. 12.5A) [28]. When the patient exhales, active contraction of the expiratory muscles generates a pleural pressure that is above atmospheric (+10 cmH₂O, Fig. 12.5B) [28]. The pressure inside the airway decreases downstream due to flow resistance, and at some point the intraluminal pressure equals the pleural

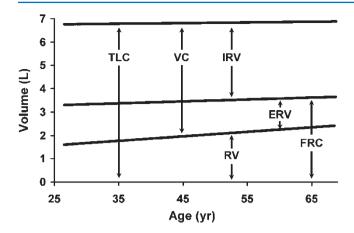


Fig. 12.3 Evolution of lung volumes with aging. *TLC* total lung capacity, *VC* vital capacity, *IRV* inspiratory reserve volume, *ERV* expiratory reserve volume, *FRC* functional residual capacity, *RV* residual volume. Aging produces an increase in RV with consequent reduction in ERV and VC, without changing TLC (This material has not been reviewed by the European Respiratory Society prior to release; therefore, the European Respiratory Society may not be responsible for any errors, omissions, or inaccuracies or for any consequences arising thereform, in the content. Reproduced with permission of the European Respiratory Society ©: Janssens et al. [7])

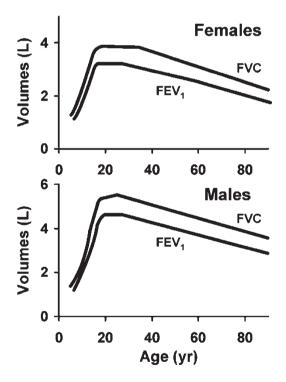


Fig. 12.4 Effect of aging on FEV_1 (forced expiratory volume in 1 s) and FVC (forced vital capacity) in males and females. Both progressively decline after 20 years of age (Reprinted from Burrows et al. [20]. With permission from Elsevier)

pressure ("equal pressure point," * in Fig. 12.5B). Downstream compression of airways limits the effectiveness of the expiratory muscles and sets a maximal flow rate for each lung volume ("airflow limitation") [29–31].

With aging-induced loss of lung elastic recoil pressure, flow limitation occurs at higher lung volumes compared with younger subjects. This expiratory airflow limitation in elderly subjects causes a significant alteration of the ventilatory response to exercise compared with younger adults (Fig. 12.6) [32, 33]. Older subjects have less reserve to accommodate the increased ventilatory demand of exercise because of increased airflow limitation [33]. During similar levels of maximal exercise (minute ventilation of 114 L/ min), 45% of the tidal volume of the 70-year-old subject is flow limited because of airway compression, in comparison to less than 20% in the 30-year-old untrained adult (Fig. 12.6) [32]. Despite these limitations, arterial Pco₂ and Po₂ are well maintained, even during maximal exercise.

Because of the existence of vertical gradient in transpulmonary pressure, airway closure occurs earlier in dependent lung regions. The volume of lung when small airways in the dependent parts of the lung begin to collapse during expiration is termed "closing volume." Subsequent research has shown that this closing volume concept is an oversimplification of a more complex process. Nonetheless, this concept is a useful means of conceptualizing lung behavior at low volumes. Because lung static recoil decreases with age, closing volume increases with age. In younger subjects, closing volume is less than FRC, and the airways remain open during resting tidal volume breathing. The increases in FRC with aging are less than the increases in closing volume, such that in erect subjects without lung disease, the closing volume starts to exceed FRC around the age of 65 [26]. Because FRC decreases when a subject assumes the supine position, airway closure may be present during resting tidal volume breathing, and this typically occurs around the age of 45. Airway closure during tidal breathing can lead to gas-exchange abnormalities (discussed below); indeed, changes in closing volume with age are correlated with hypoxemia [1].

The Effects of Aging on Gas Exchange

The efficiency of alveolar gas exchange decreases with age. One explanation is an imbalance in the ventilation/perfusion ratio mainly caused by increases in physiologic dead space and shunting [34, 35]. This imbalance leads to a gradual decrease in arterial Po₂ with aging (Fig. 12.7) [19, 36, 37]. At the same time, once arterial Pco₂ reaches 40 mmHg in the newborn, it remains virtually constant for the remainder of life, and CO₂ elimination remains unaffected despite an increase in dead space ventilation [38] and reduction in CO₂ sensitivity with aging. The latter is attributable at least in part to a decline in CO₂ production associated with a decrease in basal metabolic rate. Multiple factors contribute to the decline in arterial Po₂ related to age. In young, seated subjects breathing air at rest, the alveolar-arterial pressure dif-

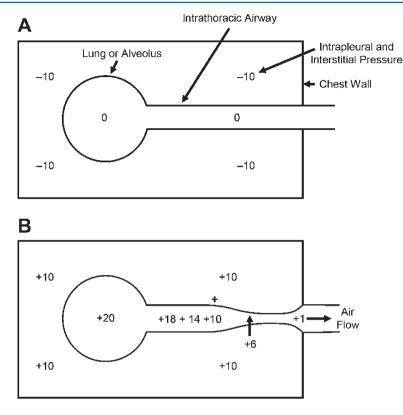
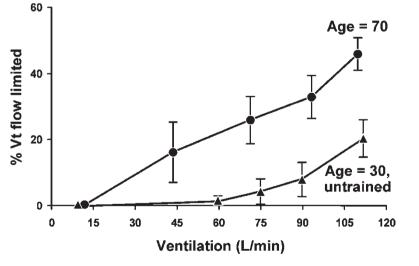


Fig. 12.5 Effects of pleural pressure on airway diameter at rest (**a**) and during expiration (**b**). Units shown are cmH2O. Intrapleural pressure is -10 cmH2O at rest but increases to +10 cmH2O during exhalation. This change in intrapleural pressure compresses the alveoli which increases the airway pressure. During exhalation this increased intrapleural pressure compresses the airways narrowing their lumen and resulting in increased flow resistance. This results in decreasing airway

pressure downstream from the alveoli. The point where pleural pressure equals intraluminal bronchiolar pressure is called the "equal pressure point" and results in airway narrowing with airflow limitation. The lung volume at which this occurs to a significant extent is called the closing volume (Reprinted from Shields et al. [161]. With permission from Wolters Kluwer Health)

Fig. 12.6 Flow limitation with progressive maximal exercise in 30-year-old untrained adults and in 70-year-old adults. At a given minute ventilation, the incidence of flow limitation during tidal breathing is greater in the elderly than in the young (Adapted from Johnson et al. [32]. With permission from Elsevier)



ference for oxygen $(A-aDO_2)$ is between 5 and 10 mmHg. An increase in the $A-aDO_2$ occurs with age because of an increase in ventilation/perfusion heterogeneity, thought to be caused by a decrease in alveolar surface area and increase in closing volume [39]. Additionally, increased body mass index, as seen with obesity, that frequently accompanies aging, can contribute to the widening of $A-aDO_2$. After 75 years of age, arterial oxygen tension remains relatively stable at around 83 mmHg [40]. The diffusing capacity of the lungs decreases with aging [41] at a rate between 0.2 and

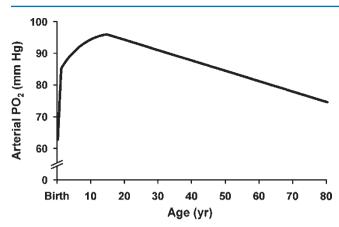


Fig. 12.7 Arterial oxygenation (Po2) as a function of age from birth to 80 years. Note the decline in arterial Po2 after the age of 20 (Reprinted from Murray [19]. With permission from Elsevier)

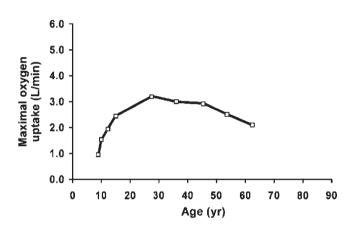


Fig. 12.8 Maximal oxygen uptake (VO_2 max) measured during maximal exercise as a function of age. Note the decline in VO_2 max starting near 30 years of age (Reprinted from Murray [19]. With permission from Elsevier)

0.3 mL/min/mmHg/year [19], with this decline being more pronounced after the age of 40. This deterioration is attributed to an increase in ventilation/perfusion mismatching, decline in pulmonary capillary blood volume [41], and/or the loss of the alveolar surface area [42].

Aging and Exercise Capacity

Age is a significant factor determining maximal O_2 uptake $(VO_2 \text{ max})$. VO_2 reaches a peak between 20 and 30 years of age and then decreases at a rate of 9% per decade (Fig. 12.8) [19, 43]. The VO_2 max decrease is more pronounced in sedentary elderly subjects than in the physically active [44]. In elderly individuals who maintain athletic exercise, the decline in VO_2 max is slowed. Factors that limit the VO_2 max in the elderly include a decrease in maximal minute ventila-

tion, decrease in the maximum arterial-venous O_2 content difference, decrease in O_2 extraction by the tissues, and reduced peripheral muscle mass. The decrease in O_2 transport capacity during senescence is also linked to an agerelated decrease in cardiac output. The O_2 cost of breathing (i.e., proportion of O_2 consumption by respiratory muscles) is higher than in younger subjects. Also, compared with younger individuals, the elderly are more responsive to CO_2 during exercise; for a given CO_2 production, the ventilatory response increases with aging, unrelated to oxyhemoglobin desaturation or increase in metabolic acidosis [44].

Regulation of Breathing

In humans, ventilation is adjusted by inputs from different chemoreceptors that respond to metabolic factors and by inputs from mechanoreceptors that provide feedback from the chest wall, lungs, and airways. Minute ventilation at rest is similar in young and elderly subjects, but tidal volumes are smaller and respiratory rates are higher in the elderly [45]. The mechanism is not fully understood, but it may represent an adaptation to decreases in chest wall compliance, as well as changes in the function of central chemoreceptors and peripheral mechanoreceptors in the chest wall and lung parenchyma [46]. Compared with younger subjects, elderly individuals have approximately 50% and 60% reduction in the ventilatory response to hypoxia and hypercapnia, respectively [47]. Moreover, studies have shown that the average increase in ventilation in response to an alveolar pressure of oxygen of 40 mmHg in older men is 10 L/min, in contrast to 40 L/min for younger individuals [48]. Responses to normocapnic hypoxemia during sleep can be even more depressed. For example, elderly individuals may not arouse from the REM phase of sleep until their oxyhemoglobin saturation decreases below 70%. Although in elderly subjects the ventilatory response to hypercapnia is blunted compared with younger subjects, the ventilatory response to exercise is actually increased: for a given CO₂ production during exercise, the ventilatory response increases with aging compared with younger individuals [44]. This cannot be explained by either increased anaerobiosis or oxyhemoglobin desaturation, but it seems that increased ventilation in the elderly compensates for increased inefficiency of gas exchange, allowing for the maintenance of normocapnia during exercise [49].

Other respiratory control mechanisms may be altered in the elderly because of reduced efficiency in distinguishing respiratory stimuli and/or altered integration of perception of stimuli within the central nervous system [50–52]. The elderly also have a lesser ability to perceive methacholineinduced bronchoconstriction [41]. The loss of important protective and adaptive mechanisms, which may result in lesser awareness of disease and delayed diagnosis of pulmonary dysfunction in the elderly, is influenced by the blunted response to hypoxia and hypercapnia and a lower ability to perceive disease states such as bronchoconstriction.

Upper Airway Dysfunction

Hypotonia of the hypopharyngeal and genioglossal muscles predisposes elderly subjects to upper airway obstruction, and the prevalence of sleep-disordered breathing increases with age [53]. Studies have found that up to 75% of subjects over 65 years old have obstructive sleep apnea (OSA) [54, 55]. Some of the consequences of chronic hypoxemia associated with OSA may include cognitive impairment, personality changes, and hypertension [55]. OSA may be even more prevalent in elderly obese individuals, who may have increased postoperative risk of respiratory complications [56].

The protective mechanisms of cough and swallowing are altered in elderly individuals, which may lead to ineffective clearance of secretions and increased susceptibility to aspiration. Mucociliary transport is also impaired in the elderly. Coughing is also less efficient in terms of volume, force, and flow rate. The loss of protective upper airway reflexes is presumably attributable to an age-related alteration in peripheral signaling together with decreased central nervous system reflex activity [58]. In addition, elderly individuals have an increased prevalence of neurologic diseases that may be associated with dysphagia and an impaired cough reflex leading to the increased likelihood of pulmonary aspiration [57] and pneumonia [58], which may have a significant impact on perioperative morbidity and mortality.

Perioperative Pulmonary Complications in the Elderly

With increased longevity, more elderly patients are potential candidates for major surgical procedures. For example, in 1997 in the United States, the Agency for Healthcare Policy and Research reported 1,350,000 major procedures in the 65-to 84-year-old age group and 233,000 procedures in the 85 and older age group [59]. Postoperative pulmonary complications, including atelectasis, pneumonia, respiratory failure, and exacerbation of underlying chronic lung disease, have a significant role in the risk for anesthesia and surgery [60]. These complications have been reported in 5–10% of the general patient population [61] and usually prolong the hospital stay by an average of 1–2 weeks [62]. Pulmonary complications in nonthoracic surgery are as prevalent as cardiovascular complications and contribute in a similar manner to morbidity, mortality, and length of stay [63, 64].

Numerous factors may contribute to the development of postoperative pulmonary complications in the elderly (Table 12.2) [65]. Advanced age is a significant independent predictor of pulmonary complications even after adjustment for various comorbid conditions [60, 63, 66]. Age increases the risk of pulmonary complications with an odds ratio of 2.1 for patients 60–69 years old and 3.0 for those 70–79 years old compared with patients younger than 60 years [60, 63, 67]. Older age represents the second most common identified risk factor for pulmonary complications after the presence of chronic lung disease [60, 66, 68]. A multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery [69] showed that age above 70 conferred a 2.6-fold increase in the risk of years old.

Factors contributing to an increased risk of pulmonary complications in the elderly are (a) decreases in chest wall compliance and muscle strength (increasing the work of breathing and the risk for respiratory failure); (b) changes in lung mechanics (including increased tendency for small airway closure which may impair gas exchange and promote atelectasis); (c) increased aspiration risk secondary to swallowing dysfunction; and (d) alterations in the control of breathing, including impaired responses to hypercapnia and hypoxia and increased sensitivity to drugs used during anesthesia (especially opioids) [70].

Intraoperative alterations in chest wall function lead to atelectasis, which forms within minutes after the induction of anesthesia and is an important cause of intraoperative gasexchange abnormalities. Chest wall dysfunction persists into the postoperative period because of pain (which limits the voluntary actions of the chest wall muscles), reflex inhibition of the respiratory muscles, and mechanical disruption of respiratory muscles (surgery in the thoracic and abdominal cavities). Consequently, after thoracic or upper abdominal surgery, FRC and VC decrease, and breathing becomes rapid and shallow, all of which may contribute to the development of pulmonary complications [71]. These effects apply to all ages but may be of special significance in the elderly patient with reduced respiratory reserve.

Older, nonanesthetized individuals have less efficient gas exchange compared with younger subjects [36]. Upon assuming the supine position, there is a decrease in FRC and hence an increase in airway resistance, which is more marked in the elderly (especially those who are obese) [36]. Alveolar gas exchange during anesthesia is less efficient in the elderly, and there is an inverse relationship between increased age and arterial Po₂ in spontaneously breathing anesthetized patients [37, 39]. After the induction of anesthesia, atelectasis develops in dependent lung regions and may produce significant shunting. However, both the amount of atelectasis and pulmonary shunting do not increase significantly with age [72, 73]. A similar phenomenon occurs in patients with

Table 12.2 Risk factors for postoperative pulmonary complications

Open thoracic surgery	
	General anesthesia
Cardiac surgery	High respiratory driving pressure $(\geq 13 \text{ cm H}_2\text{O})$
Open upper abdominal surgery	High inspiratory oxygen fraction
Major vascular surgery	High volume of crystalloid administration
Neurosurgery	Erythrocyte transfusion
Urology	Residual neuromuscular blockade
Duration of surgery >2 h	Nasogastric tube use
Emergent surgery	
(]]]	Open upper abdominal surgery Major vascular surgery Neurosurgery Urology Duration of surgery >2 h

Reprinted from Guldner et al. [65]. With permission from Wolters Kluwer Health

Respiratory driving pressure is defined as inspiratory plateau airway pressure minus positive end-expiratory pressure

ASA American Society of Anesthesiologists, COPD chronic obstructive pulmonary disease, Hb hemoglobin concentration, Spo₂ oxygen saturation as measured by pulse oximetry

chronic obstructive pulmonary disease (COPD); after the induction of anesthesia, there is less formation of atelectasis and less shunting compared with normal patients, which is explained by changes in the chest wall secondary to hyperin-flation that prevents alveolar collapse [74].

Decreased respiratory muscle strength, combined with diminished cough and swallowing reflexes (e.g., neurologic disorders, stroke), may diminish clearance of secretions and increase the risk of aspiration in the elderly [75, 76]. This risk is even higher in the presence of gastroesophageal reflux, which is also more prevalent in the elderly. Selective, rather than routine, nasogastric tube decompression after abdominal surgery has been proposed to improve the return of bowel function and reduce the risk of postoperative pulmonary complications, specifically a lower rate of atelectasis and pneumonia [77, 78]. Interestingly, the aspiration rate was not lower in patients with selective nasogastric decompression [78]. Finally, age-related changes in control of breathing, increased sensitivity to anesthetic agents, and diminished response to gas-exchange abnormalities predispose elderly patients to postoperative respiratory failure. Elderly patients also have a higher incidence of postoperative sleep apnea episodes [70, 79].

General Health Status

Multiple measures of functional status and general health predict the risk of postoperative pulmonary complications. An American Society of Anesthesiologists Physical Status Classification above II, poor exercise capacity, the presence of COPD, and congestive heart failure are all associated with increased risk of pulmonary complications in the elderly [63, 80, 81]. COPD is more prevalent in the elderly population and is the most important patient-related risk factor for the development of postoperative pulmonary complications, producing a three- to fourfold increase in relative risk [66, 81, 82]. Although obesity is prevalent in elderly patients and is associated with decreased perioperative arterial oxygenation, obesity is not a significant independent predictor of risk [63, 80, 83].

Decreased functional status, which may accompany aging, is an independent risk factor for pulmonary complications [63]. Objective measurement of exercise capacity in geriatric patients demonstrated that inability to perform 2-min supine bicycle exercise and an increase in the heart rate to above 99 beats/min were the best predictor of perioperative cardiopulmonary complications in patients older than 65 years undergoing elective abdominal or noncardiac thoracic surgery [84]. Patients with better exercise tolerance by self-report, better walking distance, or better cardiovascular classification had lower rates of postoperative pulmonary complications [85].

Strategies Used to Minimize Pulmonary Risk in Elderly Patients: Preoperative Considerations

Preoperative Testing

The value of routine preoperative pulmonary function testing is controversial. For lung resection surgery, the results of pulmonary function testing, including measurement of arterial blood gases, have proven useful in predicting pulmonary complications and postoperative function; however, spirometry does not predict postoperative pulmonary complications after abdominal surgery [85, 86]. The degree of airway obstruction assessed by spirometry does not represent an independent risk factor for postoperative respiratory failure, even in smokers with severe lung disease [87]. Spirometry, chest radiograms, and arterial blood gases should be obtained as indicated from the history and physical examination as a part of this evaluation, but should not be routinely ordered [78].

There is a high prevalence of unrecognized OSA in the surgical population [88]. In 2006 the American Society of Anesthesiologists published guidelines recommending a thorough preoperative evaluation for all surgical patients [89]. Overnight polysomnography is the gold standard to make the diagnosis of OSA but is impractical for widespread screening of all surgical patients [90]. Overnight pulse oximetry can be used as a screening tool but lacks diagnostic accuracy [91]. A practical option, being adopted by an increasing number of practices, is the use of a preoperative screen to assess OSA risk. The STOP BANG (snoring, tiredness, observed apneas, high blood pressure, BMI >35 kg/m2, age > 50 years, neck circumference > 40 cm, and male sex, with a score of 3 positives indicating moderate/high risk of OSA) OSA assessment tool has been widely used with positive and negative predictive values of 81.0 and 60.8% for OSA and 31.0 and 100% for severe OSA, respectively [92]. Anesthetic management of elderly patients with a history or positive screen of OSA can be tailored to decrease postoperative respiratory depression (see below).

Preoperative Therapies

To minimize postoperative pulmonary complications in elderly patients, it is important to optimize the respiratory status, beginning with a careful assessment of general physical status and particular attention to the cardiopulmonary system. Specific therapy should be instituted preoperatively if such treatment is likely to result in improved functional status, so long as the therapeutic benefit outweighs any risk from surgical delay (Fig. 12.9). For example, obstructive sleep apnea (OSA) is prevalent and often undiagnosed in elderly patients because aging may be blamed for many OSA symptoms (i.e., snoring, tiredness, unintended napping) [93]. Identification of these undiagnosed OSA patients and starting continuous positive airway pressure (CPAP) therapy preoperatively may improve respiratory function and outcomes [94]. Interestingly, the use of CPAP in nonsurgical \geq 65-yearold patients with recently diagnosed severe OSA improves cognitive function (episodic and short-term memory, speed of mental processing, and mental flexibility) compared to conservative care [95]. Whether perioperative CPAP

improves cognitive function in aging surgical patients with OSA has not been explored.

Preoperative spirometry should be used only to monitor the degree of therapeutic response to treatments such as bronchodilators used to treat reactive airway disease. Patients with a reversible component of airway obstruction must be treated with bronchodilators and/or corticosteroids. Antibiotics must be given if a pulmonary infection is suspected. Preoperative smoking cessation may decrease postoperative pulmonary complications, and all patients who smoke should be given help to quit [96, 97]. Past studies have been interpreted as demonstrating that quitting within a few weeks of surgery actually increases pulmonary complications by stimulating mucous production [98]. However, careful review of these studies and more recent data show that, although it may take several weeks of abstinence before pulmonary outcomes are improved, brief abstinence does not worsen outcomes [97, 98]. Thus, this consideration should not prevent practitioners from promoting preoperative abstinence from smoking, even for a brief period before surgery.

Strategies Used to Minimize Pulmonary Risk in Elderly Patients: Intraoperative Considerations

Surgical Considerations

The surgical site is the most important risk factor for the development of postoperative pulmonary complications and outweighs other patient-related risk factors [67, 69]. There is a higher likelihood of pulmonary complications with incisions closer to the diaphragm because of diaphragmatic dysfunction, splinting, and decreased ability to take deep breaths. For example, pulmonary complications caused by upper abdominal surgeries range from 13% to 33% as compared with lower abdominal surgeries that range from 0% to 16% [80]. Duration of surgery also has a significant role in the development of pulmonary complications, and surgeries that last more than 3 h have an increased risk of pulmonary complications [99]. When surgically feasible, laparoscopic techniques should be considered; however, significant respiratory dysfunction can occur even after laparoscopically performed operations [78], and whether laparoscopic procedures may reduce the risk of clinically important pulmonary complications is not clear. Nonetheless, other considerations such as reduced postoperative pain and length of stay often favor the use of laparoscopic techniques. Placement of an aortic stent instead of an open aortic aneurysm repair may be desirable in patients with significant pulmonary comorbidity.

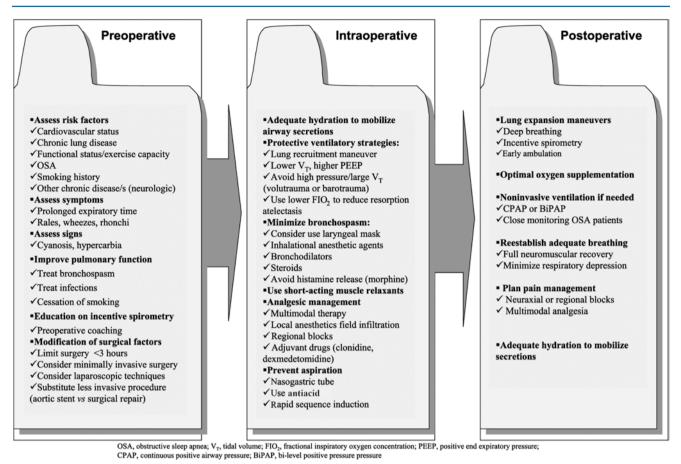


Fig. 12.9 Perioperative strategies used to minimize pulmonary complications

Induction of Anesthesia

Preoxygenation is recommended before the induction of general anesthesia. In contrast to younger patients, performing only four deep breaths before the induction may not be sufficient in elderly patients, who may require a full 3 min of 100% oxygen breathing to avoid oxyhemoglobin desaturation during rapid sequence induction [100]. In patients with intact oropharyngeal reflexes but significant reactive airway disease, avoidance of endotracheal intubation by using a laryngeal mask airway may be desirable.

Use of Muscle Relaxants During Anesthesia

In elderly patients, inadequate reversal of muscle paralysis may be an important factor for postoperative complications leading to hypoventilation and hypoxemia [86]. Pulmonary complications are three times higher among patients receiving a long-acting neuromuscular blocker than among those receiving shorter-acting relaxants [101]. Short-acting neuromuscular blocking agents should be used in the elderly to avoid prolonged muscle paralysis, and adequacy of reversal of neuromuscular block should be tested before extubation [78]. Reversal with sugammadex may reduce the risk of pulmonary complications in elderly American Society of Anesthesiologists physical status III–IV patients based on results from a retrospective single-center study [102].

Use of Regional Anesthetic Techniques for Surgery

Evidence is still unclear whether the use of regional techniques instead of general anesthesia will prevent postoperative pulmonary complications [78]. The primary respiratory advantage of regional anesthesia techniques in the elderly is avoidance of systemic opioids and mechanical ventilation [103, 104] The use of neuraxial anesthesia also has potential respiratory-related risks. For example, unintentional high anesthetic level during neuraxial anesthesia may be associated with paralysis of the chest wall (respiratory muscles) that may be poorly tolerated by the elderly, especially those with COPD. Regional techniques performed at the level of the neck (interscalene block, stellate ganglion block, axillary block) may be associated with paralysis of the phrenic nerve (diaphragm) and should not be performed bilaterally to prevent acute respiratory failure requiring urgent tracheal intubation. The level of intraoperative sedation should be appropriately adjusted in the elderly to assure anxiolysis and comfort but avoid decrease of respiratory function and airway protection reflexes.

Intraoperative Mechanical Ventilation

Evidence has accumulated that "protective ventilatory" strategies in high-risk patients can mitigate postoperative pulmonary complications [105–113]. A key feature that these strategies employ is the use of lower tidal volumes, usually defined as 6–9 mL/kg of predicted body weight (PBW). This practice of low tidal volume ventilation during general anesthesia is well accepted [65] and has been adopted by most academic medical centers [114, 115].

Ventilation strategies designed to minimize atelectasis with optimum lung recruitment appear to be beneficial to postoperative pulmonary outcomes, but the evidence is less clear [65, 116]. As discussed before, in contrast to younger patients, atelectasis may be a less important cause of intraoperative hypoxemia during general anesthesia in the elderly [72]; however, in elderly obese patients, atelectasis may have a significant role in deterioration of intraoperative arterial oxygenation [117].

The isolated use of positive end-expiratory pressure (PEEP) does not predictably reverse atelectasis or increase arterial oxygenation [118]. Ventilatory techniques (recruitment or vital capacity maneuver) employed to recruit and reexpand atelectatic lung regions to improve perioperative ventilation and oxygenation have garnered recent attention. Recruitment maneuvers require sustained lung insufflation (5-10 s long) with high inflation pressures $(35-40 \text{ cm H}_2\text{O or }$ more in cases of morbid obesity) to reliably open atelectatic lung fields [119–121]. Maneuvers must be paired with sufficient PEEP to maintain open alveolar units; otherwise, atelectasis readily redevelops [122]. Because recruitment maneuvers and PEEP increase intrathoracic pressure, preload is adversely affected and may lead to hypotension and resultant tachycardia. These hemodynamic changes may be poorly tolerated by elderly patients, especially with concomitant hypovolemia or cardiac comorbidities. Therefore, close monitoring of vital signs is paramount when deploying open lung strategies. In fact, hypotension was the most frequent adverse event reported in PROVHILO, presently the largest randomized control trial of the use of protective ventilation with open lung ventilation (the active arm employed low tidal volumes, moderate PEEP, and periodic recruitment maneuvers) [116]. Further, PROVHILO [116] found no benefit in pulmonary outcomes during general anesthesia in patients undergoing abdominal surgery and ventilated with either 12 cmH₂O PEEP or \leq 2 cmH₂O PEEP.

Because of concerns of hypotension and lack of solid respiratory benefits, current recommendations include initial ventilation with low PEEP, as reviewed by Guldner et al. [65] The ideal PEEP management that optimizes lung recruitment but avoids hypotension during general anesthesia is still not known. The concept of driving pressure ($\Delta P = pla$ teau pressure - PEEP) to guide intraoperative ventilation is an emerging alternative to the use of PEEP: lower ΔP achieved by adjustments in ventilator settings were associated with increased survival in patients with respiratory distress syndrome [123, 124]. In patients having surgery, high ΔP and changes in the level of PEEP that result in an increase of ΔP are both associated with more postoperative pulmonary complications [124]. Finally, guidance of mechanical ventilation settings using transpulmonary pressure (Ptp) has been established in the ICU setting [125], but is still not a routine practice in the operating room. In order to set a positive P_{tp} (and to endure that the lungs are "optimally" inflated), the clinician needs to estimate the value of pleural pressure, and this is done through measurement of end-expiratory esophageal pressures (Pes) measured with an esophageal balloon catheter placed in the mid-esophagus. P_{tp} is calculated as PEEP - end-expiratory esophageal pressure, and "proper" PEEP must be set to the value that achieves slightly positive end-expiratory P_{tp} (1 to 2 cmH₂O, i.e., PEEP = end-expiratory $P_{es} + 1$ to 2 cmH₂O).

Although controversial, an alternative approach for PEEP during general anesthesia is "intraoperative permissive atelectasis," when PEEP is kept relatively low and recruitment maneuvers are waived. This concept aims at reducing the static stress in lungs, which is closely related to the mean airway pressure, assuming that collapsed lung tissue is protected against injury from mechanical ventilation [65]. This type of ventilation may lead to deterioration in oxygenation and may require higher inspiratory oxygen fractions [65].

Strategies Used to Minimize Pulmonary Risk in Elderly Patients: Postoperative Considerations

Neuraxial Blocks for Pain Management

Good postoperative pain control is necessary in all patients. There is a longstanding debate regarding whether neuraxial techniques such as epidural analgesia reduce the frequency of pulmonary complications. It is clear that these techniques provide excellent analgesia, but their benefits regarding pulmonary outcomes are less clear [71]. In one meta-analysis [126], regional techniques reduced mortality by about a third with reductions of pulmonary embolism and pneumonia of 55% and 39%, respectively. However, many of the studies used in this and other meta-analyses have methodologic limitations. A recent unblinded, large clinical trial found few

differences in outcome between those receiving and not receiving epidural analgesia, with the exceptions that (1) respiratory failure was less frequent for some types of operations and (2) postoperative pain control was improved by epidural analgesia [127]. A prospective double-blind randomized trial performed by Jayr et al. [128] demonstrated that the use of epidural analgesia provided superior postoperative comfort without affecting the frequency of postoperative pulmonary complications. In addition, another blinded trial performed by Norris et al. [129] showed that in patients undergoing surgery of the abdominal aorta, thoracic epidural anesthesia combined with a light general anesthesia and followed by either intravenous or epidural patient-controlled analgesia offers no major advantage or disadvantage except for slightly shorter time to extubation. Postoperative pain management may include the use of a full range of adjunctive analgesia techniques, such as surgical field infiltration with local anesthetics, utilization of peripheral nerve blocks, nonsteroidal anti-inflammatory agents, clonidine, and dexmedetomidine [130]. This "multimodal approach" of using drugs that are associated with low potential for respiratory depression may be beneficial in elderly patients prone to developing postoperative respiratory depression.

Caution Regarding Perioperative Use of Opioids

Elderly patients may be especially sensitive to medications because of age-related altered pharmacokinetics and pharmacodynamics of drugs [70, 131]. Aging affects all pharmacokinetic processes, but the most important change is the reduction in renal drug elimination. At the same time, pharmacodynamic changes also occur at the receptor or signal transduction level or at the level of the homeostatic mechanisms [131]. This situation explains why the dosing of all anesthetic drugs should reflect the differences in pharmacokinetics and pharmacodynamics that accompany aging. Opioids are of particular concern in the elderly. Opioids reduce the respiratory response to chemical (hypoxemia, hypercapnia) load resulting in hypoventilation and hypoxemia. Given the fact that elderly patients may be particularly sensitive to opioids, they should be titrated carefully in order to avoid postoperative respiratory depression [70].

As discussed above, all surgical patients should have a thorough preoperative assessment for sleep-disordered breathing, which may include taking a history or a screening assessment tool [89]. Rates of hypercarbic respiratory failure requiring naloxone administration within 48 h of surgery have been found to be greater in patients with OSA [132]. Screening for signs of respiratory depression while patients are recovering from anesthesia in the postanesthesia recovery unit may help identify patients at higher risk for postoperative pulmonary complications [132, 133]. Patients deemed high risk for postoperative hypercarbic respiratory failure may benefit from higher levels of postoperative monitoring [134]. Traditional intermittent vital sign assessments in postoperative patients on standard surgical wards have been found to grossly underestimate the incidence and severity of postoperative hypoxemia [135]. The introduction to surgical wards of the use of continuous pulse oximetry combined with a mechanism to alert nursing staff of deteriorating vital signs has been shown to reduce rescue events for respiratory failure and intensive care unit transfers [136]. If such an approach would benefit elderly patients per se has not been specifically studied, but it is important to note that many patients in these studies were older.

Postoperative Respiratory Assistance to Maintain Lung Expansion

Decreased lung volumes and atelectasis attributable to surgery-related shallow breathing, bed rest, diaphragmatic dysfunction, pain, and impaired mucociliary clearance may be the first events in a cascade leading to postoperative pulmonary complications [78]. Postoperative use of lung expansion therapy such as incentive spirometry, chest physical therapy, effective cough, postural drainage, percussionvibration, ambulation, continuous positive airway pressure (CPAP), and intermittent positive pressure breathing is the mainstay of postoperative prevention of pulmonary complications in the elderly. Preoperative education in these maneuvers may reduce pulmonary complications more efficiently than when instruction is given after surgery [137, 138]. Lung expansion maneuvers, when performed appropriately, lower the risk of atelectasis by 50% [139]. No modality seems superior, and combined modalities do not seem to provide additional risk reduction [78]. Incentive spirometry may be the least labor intensive, whereas CPAP may be particularly beneficial for patients who cannot participate in incentive spirometry or deep-breathing exercises [78]. However, a most recent systematic review of randomized trials suggested that routine respiratory physiotherapy may not seem to be justified as a strategy for reducing postoperative pulmonary complications after abdominal surgery [140]. All patients with diagnosed OSA should have their status evaluated preoperatively, and, if they are CPAP dependent, they should receive the CPAP treatment immediately after tracheal extubation. In addition, they may require close postoperative monitoring (i.e., oxygenation and ventilation). Depending on the severity of OSA, type of surgery, and anesthesia, they may require higher levels of monitoring (see above).

Noninvasive Positive Pressure Ventilation (NIPPV)

Noninvasive positive pressure ventilation (NIPPV) is the delivery of mechanically assisted breaths without placement of an artificial airway, such as an endotracheal or a tracheostomy tube. Bi-level positive airway pressure (BiPAP) is a noninvasive ventilatory modality that seems to be more efficient than CPAP in supporting breathing. With BiPAP, continuous inspiratory positive airway pressure provides inspiratory assistance, and expiratory positive airway pressure sure prevents alveolar closure [130].

NIPPV may be used in patients with COPD exacerbations, cardiogenic pulmonary edema, hypercapnic respiratory failure caused by neuromuscular disease, and obesity hypoventilation syndrome and immunocompromised patients with respiratory failure. The role of nasal intermittent positive pressure ventilation (NIPPV) in hypoxemic respiratory failure attributable to other causes is still controversial and lacks adequate evidence support. The idea of utilizing NIPPV to manage patients with postextubation respiratory failure came from several trials demonstrating efficacy of NIPPV in postoperative respiratory failure, particularly when cardiogenic pulmonary edema was the etiology [141–145]. Immediately after extubation, elderly patients may need additional ventilatory support to maintain ventilation and oxygenation. CPAP has been successfully used to avoid tracheal reintubation in patients who developed hypoxemia after elective major abdominal surgery, and the use of CPAP was associated with lower incidence of other severe postoperative complications [146]. Outcomes of patients with postoperative postextubation hypoxemia treated by CPAP [146] may differ from that in the general intensive care population [147] or in patients with acute exacerbation of COPD [148, 149]. Thus, Esteban et al. [147] demonstrated that NIPPV does not prevent the need for reintubation and may be harmful in intensive care unit patients who develop respiratory failure after tracheal extubation. In contrast, in patients with acute exacerbation of COPD, comparing noninvasive ventilation with a standard intensive care unit approach in which endotracheal intubation was performed after failure of medical treatment, the use of noninvasive ventilation reduced complications, length of stay in the intensive care unit, and mortality [148]. The application of NIPPV has also been used successfully in the postoperative period with morbid obesity patients who were undergoing bariatric surgery [150, 151]. Prophylactic BiPAP used during the first 12-24 h after bariatric surgery resulted in significantly higher measures of pulmonary function, but did not translate into fewer hospital days or a lower complication rate [150].

Postoperative Mechanical Ventilation in the Elderly

An aging population is projected to substantially increase the demand for intensive care unit services during the next 25 years, including for postoperative care [152, 153]. The risk of respiratory failure requiring mechanical ventilation in response to a variety of physiologic insults, including surgery, is increased in the elderly because of underlying pulmonary disease, loss of muscle mass, and other comorbid conditions [154]. In patients that develop adult respiratory distress syndrome, older age is clearly associated with higher mortality rates [155, 156]. Ely et al. [157] prospectively studied whether age represents an independent effect on the outcomes in a cohort of patients requiring mechanical ventilation after admission to an intensive care unit. After adjustment for severity of illness, elderly patients, compared with younger patients, required a comparable length of mechanical ventilation. These effects could not be attributed to the differences in mortality; therefore, mechanical ventilation should not be withheld from elderly patients with respiratory failure on the basis of chronologic age [157].

Patients aged 65 years or older account for 47% of intensive care unit admissions [158]. With aging, there are several factors known to affect weaning from mechanical ventilators, such as decrease in lung elasticity, reduction in FVC, decreased respiratory muscle strength, and decreased chest wall compliance [159]. Kleinhenz and Lewis [160] reviewed the challenges of caring for elderly patients with chronic ventilator dependency. Long-term ventilator dependence, defined as need for mechanical ventilation for 6 h per day for more than 21 days, is disproportionately higher in patients over 70 years of age [160]. Long-term ventilator dependence complicates 9-20% of the episodes of mechanical ventilation treated in the intensive care units of acute care hospitals, and it is associated with an average mortality rate of 40% [160]. This is an important socioeconomic issue, and more research is needed regarding the causes that may lead to respiratory failure in elderly patients. There is an ongoing investigation of the effects of "protective ventilatory strategies" (lower tidal volume, higher PEEP, recruitment lung strategies, as well as effects of intraoperatively administered fluids and blood products) on postoperative pulmonary outcomes.

Significant Gaps in Our Knowledge

The ideal perioperative management for minimizing the risk of postoperative pulmonary complications in the elderly patient is multifactorial. Thus, further research should explore a combination of different approaches, from adequate intravenous fluid management (possibly involving a goal-directed fluid therapy) to opioid-free pain regimens, including optimized reversal of muscle paralysis. Prospective studies should be performed to confirm the suggested advantage observed retrospectively with sugammadex. Intraoperative protective ventilation with low tidal volumes should be considered standard of care, but the search for optimized lung recruitment that eludes hemodynamic adverse effects is still needed. Postoperatively, the benefit of CPAP therapy in elderly patients with confirmed or suspected OSA should be explored to improve both respiratory and cognitive outcomes.

Conclusion

Aging causes significant changes in respiratory function, which leads to ventilation perfusion mismatching and diminished efficiency of gas exchange. The perioperative period represents a time of increased functional demand on the respiratory system, and elderly patients with reduced respiratory function may be prone to developing pulmonary complications. These complications are a significant source of morbidity, mortality, and prolonged hospitalization. These pulmonary complications may be attributed to diminished protective reflexes, increased sensitivity to respiratory depressants, and altered responses to hypoxemia and hypercapnia. After identifying patients at risk for postoperative pulmonary complications, anesthesiologists must consider strategies to try to reduce the risk throughout the perioperative period. Besides optimization of underlying comorbid conditions, anesthesiologists and other perioperative physicians may utilize strategies that facilitate lung expansion such as deep-breathing exercises, incentive spirometry, and adequate postoperative pain control. Select patients may benefit from postoperative application of NIPPV.

Acknowledgments This chapter is dedicated to our great teachers, the late Drs. Joseph Rodarte and Robert Hyatt, who embedded in us a passion for pulmonary physiology and medical research in general. – Juraj Sprung and David O. Warner

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Renal, Metabolic, and Endocrine Aging

Sonalee Shah and Michael C. Lewis

Senescence or biological aging is the normal ongoing decline of function, characteristic of most complex life-forms. As such, aging is a normal rather than a pathological process. However, age is one of the strongest risk factors for a multitude of common diseases, such as diabetes mellitus, hypertension, and cancer.

Functional reserve is the body's ability to compensate for changes represented as physiological or pathological stress [1]. Adequate functional reserve is demonstrated when one could maintain homeostasis during increased physiologic demand. In contrast, decreased functional reserve is a decline in the ability to maintain a steady state during stress. Often this is due to the presence of comorbid disease. It is important to note that the effects of aging and therefore functional reserve vary significantly amongst individuals, and even within one individual all organ systems are not always affected to the same extent. Thus, both individual and interindividual variability can be significant and should be taken into consideration [2] when caring for older patients.

The complex geriatric syndrome resulting from a combination of decline in reserve and functional changes within physiologic systems leading to increased overall vulnerability is also commonly referred to as frailty syndrome. It is known that there are age-related changes in performance of regulatory biologic processes and, during stressful conditions, this can result in an inability to maintain homeostasis [3]. This phenomenon is especially marked in those individuals with decreased functional reserve, particularly in those with frailty syndrome, which predisposes to a catastrophic decline in health [2].

The biochemical underpinnings of aging are not entirely understood and certainly represent a complex and multifactorial process. One proposal is age-related changes in part occur as the result of constant exposure to free radicals generated as a product of mitochondrial oxidation. This

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Department of Anesthesiology, Pain Management, and Perioperative Medicine, Henry Ford Health System, Detroit, MI, USA e-mail: SSHAH2@hfhs.org ultimately leads to cumulative damage of intracellular molecules [4]. As every human being depends on oxidative mitochondrial respiration, all humans experience exposure to free radicals to some degree. However, differences in protective mechanisms may lead to significant variability in vulnerability between individuals.

In most Western countries, there is a shift toward a higher proportion of the population considered elderly. This increase reflects an increase in life expectancy due to improvement in living conditions and advances in medicine [5]. It is now predicted that by the year 2030, the populations of those 65 and 85 years of age and older will surpass 74 million and 9 million, respectively [6].

As a consequence of this growing aging population, a larger elderly surgical population is predicted, and it is estimated that almost half of those aged 65 will have a need to undergo surgery at least once in their lifetime [7]. This is important when considering outcomes, as overall a patient's age strongly correlates with operative outcome. For example, for noncardiac surgeries, 30-day mortality increases by the factor of 1.35 with every decade of age [8].

The increase in the volume of surgical procedures performed on the elderly population, with associated age-related changes, the increasing occurrence of frailty, and numerous other comorbidities create a challenge for anesthesiologists. Anesthesiologists must understand age-related changes in physiological processes and age-related comorbidities to provide individualized care to the older population.

An understanding of how basic age-related changes in physiology affect the pharmacokinetics and pharmacodynamics of elderly patents [2] is critical when caring for the older patient. Age alone is not a predictor of poor perioperative outcomes, but it is related to those comorbid conditions more commonly encountered in older patients that may be associated with poor outcome [7]. This chapter will focus on an introduction to some of the changes in the hepatic, renal, and endocrine systems and their specific effect on the pharmacokinetics and pharmacodynamics of drugs in the elderly.

Pharmacokinetics and Pharmacodynamics

Age-related metabolic changes have a direct effect on the pharmacokinetics and pharmacodynamics of anesthetic drugs. Such alterations are due to both specific anatomical changes of organs as well as a decrease in function.

Pharmacokinetics is the process by which a drug is absorbed, distributed, metabolized, and excreted. Absorption of a drug depends on the route of administration, and agerelated changes could impact absorption. For example, orally administered medications may be affected by decreases in gastric acid content, decreased motility and emptying, and even reduced blood flow to gastric tissue due to decreased cardiac output [3, 9, 10]. Although these alterations are commonly seen in the elderly patient, the clinical impact on altering orally administered drug dosage is minimal [3, 11].

The distribution of a drug within various bodily compartments is also altered, due to age-related changes in body composition [3, 9]. In general, there is a loss of lean body mass and total body water reducing the distribution volume for hydrophilic drugs. In contrast, the volume of distribution is increased for lipophilic drugs due to a relative increase in body fat [2, 3, 9]. The increase in total body fat favors deposition of drugs that are lipophilic, mainly impacting the terminal half-life of the decline in plasma concentration [2, 9]. An example of this phenomenon is observed with diazepam, a highly lipophilic benzodiazepine medication that is associated with a large volume of distribution. The terminal plasma half-life of diazepam increases gradually with age ranging from 20 h in the young to up to 90 h in 80-yearold individuals [12]. Drug clearance and plasma binding are unaltered, and the plasma concentrations of diazepam are not different between the young and the old. However, the increased volume of distribution increases the terminal half-life, prolonging drug effects. Data on other drugs such as fentanyl are contradictory in different studies. An explanation of the different findings between studies could be a large difference in body composition between individuals and other parameters in the aging population as shown in one study [13–15].

Changes in volumes of distribution are accompanied by a decrease in total body protein and a reduction in lean body mass, commonly termed sarcopenia [16]. Humans lose 0.5–1% of muscle mass per year after the age of 50; however, there is no cutoff measurement for the diagnosis of sarcopenia per se. The reduction in muscle mass is a major age-related change predisposing to clinical frailty.

In addition, there is a reduction in protein-related plasma transport mechanisms. Despite age-related changes in transport proteins, there is little clinical impact and many concerns remain mainly theoretical. Albumin is the primary transport carrier protein for most acidic drugs in plasma [2] and with aging, there is a 10–20% reduction in albumin production [17]. Decreased levels of albumin reduce the amount of bound drug, potentially increasing

the unbound and active form of the drug, increasing the risk of toxicity [9]. The quantity of alpha₁ acid glycoprotein, responsible for transporting basic drugs in the plasma, is unchanged or slightly elevated in the elderly [17]. This rise may be associated with an increase in inflammatory disease seen with aging [18]. A decrease in plasma cholinesterase production, especially in elderly men, may theoretically result in prolonged action of succinylcholine [5]. However, there is no evidence that this observation impacts clinical decision-making and care. Pharmacokinetics is further affected by age-associated decreases in hepatic metabolism and renal clearance (see below).

Pharmacodynamics refers to the pharmacological effects of the drug at the receptors of the target organs [19]. Pharmacodynamics is generally measured in terms of potency, efficacy, slope of the graph of efficacy range, and variability in concentration [20]. Aging affects pharmacodynamics, independent of any comorbid pathology [11], and these effects have been observed both at the receptor level and from diminishing functional reserve [19]. An illustration of this phenomenon is the attenuated response to beta receptor antagonists as the receptor expression decreases with age [19]. Another example is the increased response to propofol likely due to increased fluctuations in blood concentrations in older versus younger patients [11, 20, 21]. Therefore, a general practical recommendation is to reduce doses of anesthetic drugs in the elderly population due to changes in pharmacodynamics and pharmacokinetics [2, 20].

In addition to age-related or comorbidity-associated changes leading to altered pharmaco-physiology, polypharmacy can impact drug metabolism through drug-drug interaction, drugmetabolizing enzyme inhibition or induction. While drug-drug interactions are a general concern in medicine, there is a special need to pay attention to this issue in the elderly population [3].

Hepatic Function

Aging effects hepatic structure and consequently function due to several changes. Across the human life span, there is a reduction in liver size by 20–40% [22]. Cardiac output decreases by approximately 1% per year after the age of 30, leading to a parallel decline in hepatic blood flow of about 60% by the age of 90 [17]. Reduction in both splanchnic and hepatic blood flow seems to be a natural age-related process and likely accounts for the decrease of liver size and volume [3]. Liver size comprises 2.5% of bodyweight at 50 years and only 1.6% of bodyweight at 90 years [3, 17]. Although the overall organ mass declines, the volume of the individual hepatocytes is unaffected between 20 and 90 years of age [17]. Clinically, it still remains unanswered whether the decrease in liver size has any clinical relevance in the elderly patient [17]. Some studies have shown a correlation of decreased liver size with diminished drug clearance while others have shown no correlation, suggesting there may be other factors involved with drug clearance in the elderly [17]. There are no significant changes noted in relation to aging on liver function tests or other routine clinical tests of the liver, suggesting that overall hepatic drug metabolism in the elderly is relatively well preserved until at least 80 years of age [3, 19].

Drug metabolism by the liver occurs in two phases. Phase 1 reactions typically inactivate functionally active drugs to inactive metabolites by process of oxidation, reduction, and hydrolysis. This phase of metabolism is responsible for creating polar metabolites within enzymes such as the cytochrome P450 systems [3, 9]. These processes may also lead to functionally active metabolites derived from prodrugs [9]. There is some concern that the efficiency of phase 1 metabolism may be lessened in the elderly, leading to a prolongation of the half-life of drugs dependent on this phase of metabolism [9, 17]. There is also variability in the degree of reduction of drug clearance on those that are reliant on phase 1 metabolism, and this can result in up to a 30-50% reduction in clearance [11]. For example, lidocaine and midazolam will have less hepatic clearance as a result of this effect. The overall quantity of cytochrome P450 enzymes are reduced by approximately 30-50% in the elderly compared to their younger counterparts [23]. Although there are fewer enzymes available, changes within the hepatic endothelium are thought to be a cause for reduced metabolic clearance seen in the elderly, rather than the functional capability of these enzymes [23].

Phase 2 metabolism by the liver is responsible for converting the product of phase 1 metabolism to become more water soluble, facilitating excretion. It involves conjugation through addition of polar groups by a process of glucuronidation, methylation, sulfation, and acylation [3, 17]. Phase 2 metabolism appears to be relatively unaffected by aging [3, 17]. However, in elderly patients with a diagnosis of frailty syndrome, a reduced ability for conjugation might be present [11, 16].

In summary, most alterations of drug clearance in the elderly are the result of changes in hepatic blood flow, liver size, and not due to age-related changes in enzymes responsible for drug metabolism [11]. The decreased hepatic blood flow affects metabolism by decreasing the first-pass metabolism of drugs with high hepatic extraction ratios and reducing the clearance of hepatically metabolized drugs [11, 23]. The greatest effect is seen on those drugs with high extraction ratios, as their plasma concentration will be increased with the decrease in clearance for elimination [3]. The reduction in first-pass metabolism may also affect activation of prodrugs (e.g., tramadol or codeine) by having a reduced plasma concentration of drug available, leading to a decreased or delayed effect [11, 18]. See Table 13.1 for a categorization of drugs by hepatic ratio.

 Table 13.1
 Categorization of drugs by hepatic extraction ratio

High hepatic extraction ratio	Morphine Lidocaine Verapamil Propranolol Nitroglycerin Etomidate Propofol Ketamine Naloxone
Intermediate hepatic extraction ratio	Aspirin Codeine Hydromorphone Nortriptyline Diphenhydramine Etomidate
Low hepatic extraction ratio	Warfarin Phenytoin Diazepam Lorazepam Pentobarbital Carbamazepine Methadone

Renal Function

Age-related structural (e.g., number of glomeruli) and functional changes (e.g., glomerular filtration rate, renal blood flow, and tubular secretion) are associated with renal organ aging [24]. Decreased cardiac output leads to a reduction in renal blood flow and therefore renal size, as seen with the liver [24]. Structural renal alterations are decrease in weight, decreases in renal and cortical area, and number of glomeruli. Initially, until the age of 40-50 years, an increase in kidney size can be observed [24]. After age 50, there is a constant decline of organ size [24]. In addition to a decreased number of glomeruli, there is a multitude of generally agingassociated changes such as tubule-interstitial infarction, scarring, and fibrosis [24-26]. Scarring and fibrosis of glomeruli are most notably seen in the cortical zone, with a loss of functioning glomeruli of up to 50% by the age of 80 [5, 26]. Along with these changes in the number of tubules, there is a decrease in volume and length of tubule, as well as an increase in diverticula and atrophy [24, 25].

Reduced cardiac output as well as other concomitant diseases in the elderly leads to a decrease in renal blood flow. Along with the reduction of renal blood flow, there is a decrease in glomerular filtration rate (GFR) as well as creatinine clearance with increasing age [11, 24, 25]. A decline in GFR from approximately 130 to 80 mL/min can be seen between the ages of 30 and 80, with an acceleration of the decline after the age of 65 [25]. Creatinine clearance, often used as a measure of GFR, also declines in a similar fashion, even in the face of normal creatinine concentrations [11, 18, 27]. The decrease in GFR is not as great as the decrease in renal plasma flow, due to an increase in filtration fraction and a state of hyperfiltration [25, 26]. This can be seen more prominently in the deeper glomeruli and may be an adaptive compensation to help preserve function due to the reduced number of functional glomeruli [25].

Decreased renal plasma flow and GFR can affect the pharmacokinetics of drugs by reducing their elimination. These changes in metabolism may contribute to the increased adverse drug reactions noted in the elderly population [11]. For example, morphine-6-glucuronide, the active metabolite of glucuronidation of morphine by the liver, is renally excreted and may accumulate in cases of decreased renal function, leading to prolonged duration of analgesia and potentially adverse outcomes [16, 28]. Consideration for adjustments in dosing for medications excreted by the kidneys should also be made for drugs that will have prolonged half-lives (e.g., digoxin), taking longer to reach steady state [18].

Hypertension and diabetes are comorbid conditions that are often associated with worsening glomerulosclerosis and arteriolar sclerosis of the afferent, efferent, and cortical systems, potentially accelerating the negative impact of aging on renal function [24–26]. Comorbid conditions such as diabetes and hypertension can lead to an increase in mean arterial pressure, further causing a decline in GFR. However, these effects may not be clinically relevant until there is a critical decrease in functional renal reserve [24, 26].

Typically, under nonstressed conditions, aging has little effect on the kidney's ability to maintain fluid balance. Functional reserve of the kidney may be preserved in the healthy older adult, and electrolyte balance is maintained similar to their younger counterpart. However, in stressful states, as seen with surgery, the changes within the tubule lead to a decreased ability to retain sodium, concentrate urine, or even excrete free water [24, 25, 29–31]. Because the adaptive responses are lessened, there is often an inability to maintain sodium homeostasis resulting in dehydration in the elderly patient [24]. Dehydration is further aggravated due to the impairment of counteractive mechanisms, such as the thirst response, which is impaired in elderly and frail patients [30–32].

In the aging kidney, the remaining functional renal tubules become less responsive to autoregulation due to a reduced sensitivity to hormonal influence of aldosterone, vasopressin, and atrial natriuretic peptide (ANP) [24]. Increased ANP secretion is responsible for reduction in renin, and therefore aldosterone concentrations, contributing to dehydration and electrolyte dysfunction [30]. Suppression of renin compounded with downregulation of the renin-angiotensin system contributes to the hyponatremia and hyperkalemia often seen in the elderly [24]. Reduction in antidiuretic hormone (ADH) can also reduce the ability to concentrate urine in response to decreases in intravascular volume [30, 32].

Healthy older individuals generally maintain acid-base homeostasis under baseline conditions. However, due to an impaired ability to excrete hydrogen ion load, elderly patients

 Table 13.2
 Physiologic changes of aging and their pharmacokinetic consequences

Pharmacokinetic mechanism	Changes in the elderly	Consequence
Absorption	↑ gastric pH	
	↓ gastric motility and emptying	↓ absorption
	↓ gastric blood flow	
Distribution	↓ total body water	$\downarrow V_{\text{D}}$ of hydrophilic drugs
	↑ body fat	$\uparrow V_{\rm D}$ of lipophilic drugs
	↓ albumin	↑ free fraction of acidic drugs
	↑ α ₁ acid glycoprotein	↓ free fraction of basic drugs
Metabolism	↓ hepatic flow	↓ drug clearance
	↓ phase 1 metabolism	↓ biotransformation
Excretion	↓ renal flow	↓ elimination
		\uparrow adverse drug reactions

are more prone to metabolic acidosis [32] in stressful conditions.

The acute stress response to surgery includes secretion of ADH and increased water retention, as well as increased renin and aldosterone secretion contributing to additional water and sodium absorption. Thus, despite the often-blunted activity of the renin-angiotensin aldosterone system (RAAS) the elderly patient is still susceptible to retention of salt and water [30, 31]. In fact, the elderly might be particularly vulnerable in times of stress involving larger volume shifts. Even small changes in plasma volume might have deleterious effects due to, for example, reduced cardiac function or fluid overload leading to heart failure. Caution should be taken with fluid management in the perioperative setting, with close monitoring of fluid balance using blood pressure, pulse rate, and urine output as guides [29, 30].

A summary of the physiologic changes in pharmacokinetics due to aging can be seen in Table 13.2.

Endocrine

The endocrine system undergoes a multitude of changes with aging [33]. However, few of the observed natural changes with aging have an immediate effect on anesthetic considerations. However, the increase in incidence of insulin resistance, diabetes mellitus, and thyroid abnormalities as well as decrease in sexual hormone levels should be taken into consideration when evaluating elderly patients in the perioperative setting. Physiological aging-related endocrine changes, such as loss of muscle mass, particularly in males with andropause as well as the increased incidence of pathological endocrine abnormalities are a concern for the elderly patient [34, 35].

Probably the most prominent axis affected is the gonadal axis with a fairly sudden cessation of female hormone production around menopause and a slow decline of male sexual hormones with age (andropause). These hormonal changes lead to changes in general gene expression and a consequent decrease in muscle mass, further predisposing to sarcopenia, osteoporosis, and frailty [36]. These changes may also influence drug metabolism, but this is currently only a theoretical concern. In addition to the gonadal axis, there is an age-related decline in the activity of the somatotrope axis, decreasing insulin-like growth factor type 1 (IGF1) and growth hormone (GH) levels, which further predisposes to sarcopenia [37].

Dysfunction of the thyroid axis, including frank hypo- or hyperthyroidism, is more common in elderly [35]. TSH levels tend to be on average higher, particularly in the oldest of the old, and have been associated with longevity [38]. This needs to be factored in when making decisions on thyroid hormone replacement and TSH level targets for elderly patients, which may likely be higher than in the general reference population. However, it still remains a consensus that TSH levels >10mIU/l need to be evaluated for clinical hypothyroidism and possible hormone replacement. Frank symptomatic hypothyroidism in the elderly as well as biochemical hypothyroidism with elevated TSH and low thyroxine (T4) levels should definitely lead to initiation of replacement therapy. In the elderly, replacement therapy is ideally started with sub-physiological replacement doses and a slow increase guided by normalization of TSH levels to prevent stress on the cardiovascular system. However, a slightly increased TSH value in the setting of normal thyroid hormone levels and in the absence of symptoms can be accepted as normal in the elderly without the necessity for treatment.

Diabetes mellitus is by far more prevalent in the elderly population due to many of the metabolic changes associated with aging. Impaired glucose tolerance can be observed in 50% of individuals older than 80 years of age [39]. A decline in β-cell mass and insulin production and an increase in insulin resistance are responsible for the age-related increase in patients with impaired glucose tolerance and diabetes mellitus [40]. Although the interrelationship of sarcopenia and insulin resistance is not well understood, it is clear that muscle is a main organ of glucose disposal and muscle mass is reduced in sarcopenia. In addition, exercise increases insulinindependent glucose uptake and increases insulin sensitivity of muscle tissue. β -Cell function can decline by up to 25% by the age of 85. This decline, in combination with decreased glucose uptake by non-insulin-mediated receptors, may lead to an increase in glucose load for clearance by the renal system [41-43]. Renal clearance of glucose is reduced with aging, increasing circulating levels of blood glucose [41]. Gluconeogenesis, a homeostatic process by which cells are provided glucose in times of stress or food deprivation, may be upregulated causing an additional source of abnormally

high blood glucose levels [44]. Elderly patients are more prone to the development of stress-related hyperglycemia and intraoperative as well as postoperative temporary treatment with insulin might become necessary in these patients.

Adrenal hormone production and blood levels are also affected by aging. There is an age-related decline in adrenal androgens, such as DHEAS [45]. However, little is known about the physiological function of DHEAS, and therefore it does not impact clinical decision-making. While cortisol levels remain largely the same over the lifetime of humans, there might be some "local hypercortisolism" due to the increasing activity of 11 β -HSD, which converts cortisone to the active hormone cortisol, in some peripheral tissues, such as the bone, skeletal muscle, and skin causing glucocorticoidassociated catabolic effects, such as sarcopenia and osteoporosis [46].

Caring for the elderly patient, especially in the perioperative setting, can be challenging because of the numerous alterations of the metabolic systems of the body combined with comorbid conditions often associated with aging. Caution must be used when creating an anesthetic plan for this subset of patients, as the functional reserve may not be preserved, particularly in the frail elderly patient. As discussed in this chapter, a comprehensive understanding of the basic metabolic changes will help with management of the different pharmacokinetic and pharmacodynamics alterations associated with aging, in order to minimize adverse outcomes.

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Musculoskeletal and Integumentary Systems

Itay Bentov and May J. Reed

Introduction

The musculoskeletal and integumentary systems account for most of the tissue mass in healthy humans: the skin, muscle, and bone account for about 80% of lean body weight [1]. The main functions of the skin are to protect the body from external stressors, maintain temperature, and prevent fluid loss. The main functions of the muscle and bones are to provide posture and mobility. All of these functions are impaired in the aged and are particularly disrupted during the perioperative period. Anesthesia and surgery (which commonly starts with a skin incision) or positioning of the patient during surgery directly affects the musculoskeletal and integumentary systems and exposes the patient to potential risks of nerve injury, pressure ulcers, and surgical site infection. Anesthesiologists providing care for older adults should be mindful of age-related changes to the musculoskeletal and integumentary systems and implement interventions to minimize adverse outcomes.

Age-Related Changes to the Skin

Age-related changes to the skin (Fig. 14.1) [2] are related to environmental and genetic factors and are often the first (and most visible) signs of aging. Wrinkles and sagging skin are accompanied by graying and loss of hair. Histologically, there is a decline in epidermal and dermal thickness and composition and a reduction in the number of most resident cell types [3]: A reduction in the number and function of the

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pigment-producing melanocytes leads to a pale, translucent skin, and sun exposure leads to lentigines ("age spots"). The dermal-epidermal junction is flattened, and loss of connective tissue and subcutaneous fat leads to thinner and more fragile skin. Age-related changes to the skin affect not only the appearance but also negatively impact different protective functions of the skin. Blood flow through arterioles, capillaries, and venules (microcirculation) in the skin is diminished [4]. Reduced microcirculation impairs perfusion, fluid hemostasis, and delivery of oxygen and other nutrients. Reduced microcirculation can also disrupt temperature regulation and the inflammatory response [5]. Maximal skin blood flow in response to local heating is reduced in the aged, limiting the ability to transfer heat from the skin [6]. At rest, blood flow to the skin is reduced by 40% between the ages of 20 and 70 years [7].

Aging and the Incisional Wound

Age is an independent risk factor for postoperative surgical site infection (SSI) in the aged [8] even when accounting for other comorbidities that are common in the aged (diabetes, obesity, and malnutrition). Advanced age is considered to be an independent risk factor for SSI (as well as other risk factors such as comorbidities, frailty, and surgery complexity) [9]. Notably, a large cohort study in adults found that the risk of SSI increased with age and peaked in the 65-year-old age group but was reduced in older cohorts [10]. When SSI develops in the aged, it is associated with doubling of the healthcare cost and a fourfold increase in mortality [11].

Wound healing is a process that includes inflammation, tissue formation, and remodeling [12] (Fig. 14.2). Each of these processes is affected by aging (see below), leading to roughly a 30–40% delay in the healing process; however, given sufficient time, models of aged animals suggest that eventually, the aged catch up to their young counterparts with respect to most aspects of tissue repair [13].

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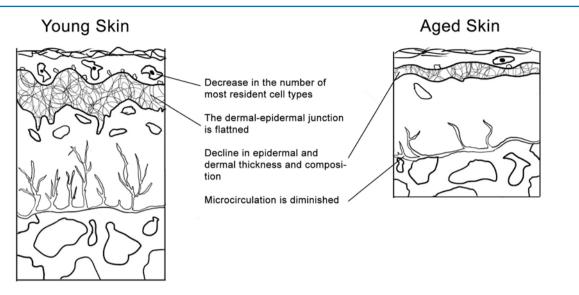


Fig. 14.1 Changes in skin with age contribute to impaired wound healing (Reprinted from Bentov and Reed [2]. With permission from Wolters Kluwer Health)

Inflammation

Skin incision leads to a local response that is intended to stop the bleeding and recruit the immune system to the injured site. Blood vessels constrict, and, at the same time, platelets attach to the endothelium and aggregate and release their granules to form a fibrin clot. During this process, several mediators of cell proliferation, extracellular matrix synthesis, and angiogenesis are released. Transforming growth factor beta 1 (TGF-B1) and platelet-derived growth factor (PDGF) elicit rapid chemotaxis of neutrophils, monocytes, and fibroblasts to the injured area, which stimulates generation of additional cytokines. The latter include the angiogenic factor vascular endothelial growth factor (VEGF) and the pro-inflammatory molecules tumor necrosis factor alpha and interleukin 1 beta [14].

Age-related changes in the inflammatory response result in alterations in cell adhesion, cell migration, and cytokine production. The production of most chemokines (measured by messenger RNA levels) declined with age by 20-70%, although levels of some pro-inflammatory cytokines are increased [15]. Total leukocyte and neutrophil counts are slightly lower in samples from older individuals [16]; however, granulocyte adherence is greater in aged subjects, especially women [17]. Phagocytosis is decreased in neutrophils from old, compared with young, healthy donors, potentially secondary to reduced neutrophil CD16 expression in the aged [18]. Aging is sometimes associated with a persistent pro-inflammatory state. At the same time, there is a reduction in the ability to generate an acute inflammatory response during injury. This paradox can result in disrupted wound healing due to lack of synchronization between pro- and anti-inflammatory

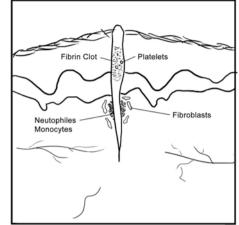
responses. Interestingly, adult men (mean age 61 years) who exercised before an experimental wound showed a reduction in stress-related neuroendocrine responses that was accompanied by accelerated wound healing [19], suggesting that targeted preoperative intervention may be of benefit.

Proliferation and Tissue Formation

Several hours after skin closure, re-epithelization begins [20]. Epidermal cells separate from neighboring cells, move from the dermis into the margins of the incisional area, and start to degrade extracellular matrix proteins. Epidermal cells express integrin receptors, produce collagenase, and activate plasmin by plasminogen activator. The cells proliferate about 1 or 2 days after the injury and produce a scaffold of basement membrane proteins from the margins inward. During this process, mediators and cytokines (interleukins, α -, and β -chemokines) that regulate angiogenesis are released [21]. Several days after the injury, macrophages, fibroblasts, and blood vessels simultaneously invade the wound [22]. Macrophages produce growth factors, such as TGF-B1 and PDGF. Fibroblasts synthesize a new matrix (first a provisional matrix of fibrin, collagen III, fibronectin, and hyaluronic acid; later a structural matrix of primarily collagen I replaces the provisional matrix). Blood vessels supply oxygen and nutrients, which is essential to sustain the newly formed granulation tissue. As an example, the deposition of collagen relies on proline hydroxylase, an oxygen-dependent enzyme [23].

In healthy human volunteers, superficial, split-thickness wound epithelization is delayed in subjects over 65 years **Fig. 14.2** The stages of wound healing are a sequential chain of events that includes inflammation, proliferation, and tissue formation and ECM and tissue remodeling. *ECM* extracellular matrix (Adapted from Bentov and Reed [2]. With permission from Wolters Kluwer Health)

A. Inflammation



C.



Proliferation and

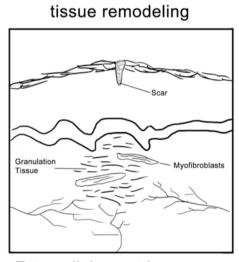
tissue formation

Β.

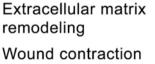
Degranulation Phagocytosis Infiltration

Extracellular matrix formation Angiogenesis

Angiogenesis



ECM and



old when compared to the control group (18–55 years old) [24]. Impaired endothelial cell function and reduced VEGF expression are possible mechanisms of age-related deficits in angiogenesis, which has an adverse effect on the development of an effective microcirculation [25]. In an explant model, age-related deficiencies in angiogenesis were reversed, in part, by stimulation with angiogenic growth factors [26].

Extracellular Matrix and Tissue Remodeling

During the last phase of wound healing, the extracellular matrix begins to remodel, and the incision undergoes further contraction. Fibroblasts assume a myofibroblast phenotype characterized by bundles of alpha smooth muscle actin-containing microfilaments. Synchronized collagen reorganization occurs by synthesis and catabolism (although at a much slower rate than in previous stages), which allows the granulation tissue to turn into a scar. Deposition and remodeling of collagen are slower in aged animals resulting in less scar formation [27]. Moreover, the collagen deposited has a looser, more disorganized matrix that has decreased tensile strength. The changes in aged collagen matrix reflect decreases in circulating factors, in particular reduced levels of TGF- β 1 – a potent stimulator of collagen synthesis [28]. Of note, dermal fibroblasts from aged and young donors exposed to exogenous TGF- β 1 exhibit similar biosynthetic and contractile properties [29].

Perioperative Interventions to Improve Wound Healing

In general, interventions provided weeks before elective surgery (pre-habilitation) appear to provide more benefit than comparable interventions provided after surgery (rehabilitation) [30]. Low patient adherence is a major obstacle of preoperative conditioning to improve clinical outcomes after surgery [31]. A number of perioperative measures may help reduce the risk of SSI and improve wound repair. Some of these measures include lifestyle changes that should probably be implemented well ahead of surgery and therefore have direct applicability to the perioperative surgical home.

Smoking Cessation

Smoking can accelerate aging by promoting oxidative stress [32] and telomere shortening [33]. Clinical assessment of skin wrinkling/aging in an aged cohort revealed that smoking one pack/day is equivalent to a decade of chronological aging [34]. It is disappointing that the aged are less likely to receive smoking cessation advice and support than younger adults [35]. Smoking decreases endothelial-dependent vaso-dilation and reduced blood flow to the skin due to activation of circulating leukocytes and platelet aggregation [36]. Smoking cessation for at least 4 weeks before surgery reduces the incidence of surgical site infection [37].

Physical Activity

Despite the documented reduction in mortality and improvement of quality of life produced by physical activity, the molecular and cellular changes that occur during physical activity are still being elucidated [38]. Regular physical activity can, in part, abrogate age-induced endothelial dysfunction [39]. Increased blood flow to the skin was observed in aged male individuals who exercised regularly for a decade when compared to sedentary matched controls [40]. In a nonsurgical group, a short training schedule (three times per week for 1 month) was shown to improve wound healing [41].

Glucose Management

Patients with diabetes mellitus are at increased risk of SSI, and perioperative hyperglycemia is a risk factor for postoperative infection, even in nondiabetics [42]. An intensive perioperative glycemic control with insulin has been recommended in high-risk surgical patients as it decreases mortality [43] and wound infections [44]. It is reasonable to assume that tight blood sugar control may be beneficial for wound healing in the aged population because it affects many pathways that regulate wound healing [45]. Several lines of evidence suggest that this line of reasoning is not straightforward. A trial of long-term intensive therapy of hyperglycemia in diabetic patients in the community reduced the risk of developing microvascular complications; however, the benefit was mainly in younger patients at early stages of diabetic complications, and the trial was stopped due to increased mortality in the intensive treatment group [46]. Intensive perioperative glycemic control did not demonstrate significant outcome differences compared with conventional glycemic control and resulted in an increase in hypoglycemic episodes [47]. Concerns regarding hypoglycemia are important because the aged are less likely to manifest clinical signs of severe hypoglycemia than the young [48]. Current recommendations suggest that perioperative insulin treatment of patients suffering from diabetes who are older than 70 years old should be more careful (similar to patients suffering from renal disease with a GFR < 45 ml/min) [49]. The role of glycemic control, blood sugar targets, and the duration of perioperative treatment that is required to reduce SSI (and other complications) still needs to be elucidated for the general surgical population. The results should be interpreted with caution in the aged population.

Antibiotic Administration

The Centers for Medicare and Medicaid Services implemented a project of prophylactic antimicrobials to decrease the morbidity and mortality associated with SSI. An agreement exists regarding the need for antibiotics in several types of surgeries (coronary artery bypass grafting, vascular, colorectal, hip/knee arthroplasty, and hysterectomy [50]) that are commonly performed on older adults. Underscoring the importance of antibiotic prophylaxis for the older population is data demonstrating that preoperative antibiotics administration is associated with reduced 60-day mortality in aged patients undergoing general surgery [51]. In carriers of nasal Staphylococcus aureus, decolonization with a topical application of an antibiotic that is effective against Gram-positive bacteria reduced any healthcare-associated wound infection [52] and SSIs [53].

Oxygen Administration

Wound healing is dependent upon adequate levels of oxygen [54]. Oxygen interacts with growth factor signaling and regulates numerous transduction pathways necessary for cell proliferation and migration [55]. It is also an indispensable factor for oxidative killing of microbes [56]. Low oxygen tension in the wound bed is considered to be a predictor of the development of infection [55], particularly when subcutaneous tissue oxygenation (measured by a polarographic electrode) falls below 40 mmHg [57]. Meta-analyses of supplemental oxygen therapy to reduce SSI suggest a beneficial effect [58], although not for all types of surgeries [59]. While most authors suggest that supplemental oxygen during surgery is associated with a reduction in infection risk [60, 61], others propose it may be associated with an increased incidence of postoperative wound infection [62]. A prospective trial randomizing patients to either 30% or 80% supplemental oxygen during and 2 h after surgery did not find any difference in several outcome measures including death and wound healing [63]. Of note, the administration of oxygen to the aged may be limited by the finding that although arterial oxygen tension does not decrease with age, there is a reduced steady-state transfer of carbon monoxide in the lungs [64]. This indicates that oxygen transport could be diffusionlimited in older subjects, especially when oxygen consumption is increased. Furthermore, longitudinal studies of five healthy men over three decades showed impaired efficiency of maximal peripheral oxygen extraction [65], suggesting that tissue oxygen uptake is reduced in the aged [66]. Consequently, the potential benefit of increasing tissue oxygen tension during surgical wound repair in older patients should be further evaluated.

Fluid Management

Clinical signs of intravascular volume status are often difficult to evaluate in older persons [67]. Moreover, the repercussions of extremes of intravascular volume have harmful sequelae. As an example, hypovolemia decreases tissue oxygen concentrations [68], while excessive fluid administration increases tissue edema, which can adversely affect healing [69]. In residents of nursing homes who are at a higher risk of impaired hydration (and subsequently reduced tissue oxygenation) [70], supplemental oral fluid intake did not reverse these deficits nor improve wound healing [71]. The need for more accurate determination of volume status is underscored by studies that show judicious use of fluids improves outcomes in the older population more than in the young population [72]. In a group of patients undergoing repair of femoral fractures (mean age 75 years old), using goal directed therapy shortened the hospital length of stay [73].

Consequently, a strategy of administering fluids in a manner that maintains optimal hemodynamics and end-organ perfusion is recommended.

Anemia is common in the older population. Over 8% of men and 6% of women greater than 65 years of age, and without severe comorbidities, have anemia as defined by hemoglobin levels below 10 g/dl [74]. Perioperative anemia in the aged population is associated with worse outcome [75]. However, an increase in red blood cell transfusions is correlated with increased SSI [76]. The optimal strategies to treat anemia preoperatively and to appropriately transfuse during surgery and postoperatively in order to maximize surgical wound healing in older adults have yet to be elucidated.

Temperature Management

Mild perioperative hypothermia is common not only during general anesthesia but also during regional anesthesia [77]. Age is an independent risk factor for development of hypothermia during anesthesia [78]. Mild hypothermia during the intraoperative period increases the risk of surgical wound infection, even after clean procedures such as hernia, breast, and varicose vein surgeries [79]. Thermoregulatory responses are decreased in the aged [80], mostly due to altered regulation of skin blood flow in the setting of a reduced microcirculation [81]. During general anesthesia with isoflurane [82] and sevoflurane [83], the threshold for thermoregulatory vasoconstriction is reduced in the aged more than the young. The aged are at additional risk of perioperative hypothermia because clinical signs (such as shivering) are absent at the same time thermoregulation is impaired [84]. Rewarming of the older patient takes significantly longer than younger adults, reflecting the same physiology that predisposes older adults to hypothermia [85]. Consequently, it is prudent to maintain euthermia for every aged patient during the intraoperative and postoperative period, regardless of the type of anesthesia. Strategies that use multiple modalities, for example, prewarming with the use of warmed fluids and forced-air warming devices, are more effective in maintaining euthermia, specifically in prolonged surgeries and in the older population [86].

The Effect of Anesthetic Technique: General Versus Regional

It is often assumed that the best anesthetic technique for older adults will result in reduction of the stress response while maintaining other compensatory responses. Numerous studies have evaluated the effects of different anesthetic techniques on markers of stress, metabolism, and inflammation. Administration of typical doses of volatile or intravenous agents does not suppress the endocrine response [87]. In contrast, regional anesthesia (most notably neuraxial blockade) blunts the endocrine stress response to surgery [88]. Thoracic epidural anesthesia increases peripheral tissue oxygen tension, even outside the dermatomes affected by the block [89]. Continuous lumbar plexus and sciatic nerve blocks did not affect cortisol levels but attenuated the postoperative inflammatory response (lower C-reactive protein) [90]. In a study of regional block after knee arthroplasty, clinical signs of inflammation were reduced although there were no detectable changes in levels of measured cytokines [91]. Although these clinical and theoretical perceptions often advocate for regional anesthesia rather than general anesthesia in older patients, there is no difference in various outcome measures [92, 93]. Studies that document a lower risk of SSI after neuraxial anesthesia than after general anesthesia (e.g., in a retrospective analysis of total hip or knee replacement [94]) are often lacking methodologically (e.g., the groups are dissimilar; the general anesthesia group was older with more comorbidities than those who received neuraxial anesthesia). Future studies will need to elucidate the effect of anesthetic technique (as well as the effects of different anesthetic medications such as opioids) on postoperative wound healing.

Local Anesthetics

The effect of local anesthetic infiltration on wound healing has been studied in numerous models with conflicting results. Some suggest that exposure to local anesthetics enhances wound repair, others propose no effect or a negative impact [95]. Local anesthetics may positively influence wound healing by reducing the stress response and alleviating pain [96]. Intra-articular lidocaine, used to achieve pain management after knee surgery, increased oxygen tension in the subcutaneous tissue [97]. Conversely, local anesthetics can be detrimental by delaying the synthesis of collagen [98], by an antiproliferative effect on mesenchymal cells [99], and, specifically in the aged, by regulation of growth factors [100]. Dose-dependent properties of lidocaine may be pronounced in aged tissues; a longer drug half-life in older individuals is probably the result of age-related decreases in hepatic blood flow and clearance [101].

Positioning

Positioning of elderly patients during surgery can be challenging. Incorrect operative positioning can lead to the development of pressure ulcers and nerve injuries and age is a risk factor for both of these adverse outcomes. Positioning of the patient should involve the entire operative team in an effort to prevent these complications. Although it has been suggested that most pressure ulcers are avoidable, some are related to non-modifiable factors such as hemodynamic instability that is worsened with physical movement and inability to maintain nutrition and hydration status [102]. Similarly, clinical data does not support the notion that post-operative neuropathy is completely preventable [103]. Nevertheless, it is important to recognize that the older patient is at greater risk of positioning injuries.

Pressure Ulcers

In a retrospective observational study of pressure ulcers that developed in the operating room, age was an independent risk factor, but there was no association with the duration of surgery, hypotension, or vasopressor use [104]. Current evidence in the general nonsurgical population supports the use of strategies to prevent pressure ulcers (use of support surfaces, repositioning the patient, optimizing nutritional status, and moisturizing sacral skin [105]). It is reasonable to apply these interventions in the operating room, although the efficacy of specific measures is still under investigation [106].

Sarcopenia and Nerve Injury

A closed claim analysis found that age is a risk factor for ulnar neuropathy after anesthesia [107]. The median age of individuals who experience postoperative ulnar and peroneal postoperative neuropathy is 50 years [108]. Potential mechanisms include age-related vulnerability of nerves (e.g., a deceleration of the ulnar nerve conduction velocity with age [109]), but global age-related microvascular and musculoskeletal changes probably play an important role. Aging is associated with sarcopenia (loss of skeletal muscle mass and function). Loss of muscle fiber begins at approximately 50 years of age, and by age 80, healthy individuals have lost about 30–50% of their muscle mass [110]. There is substantial variability between individuals in rates of sarcopenia that can be explained by gender, genetics, and lifestyle; however, much of the variability among individuals remains unexplained. The loss of muscle is accompanied by an increase in adipose tissue that results in a reduction of total body water [111]. These changes may predispose the nerve to compression from pressure against hard surfaces or bone, because there is a reduction in cushioning around the nerve. Sarcopenia leads to reduced mobility and is an important factor in the development of frailty, a state of extreme vulnerability to adverse events [112]. Results of trials that examined the benefits of exercise and dietary supplementation to improve muscle mass and physical performance in

the aged are inconsistent [113]. Over 15 years ago, the ASA published a practice guideline aimed "to prevent or reduce the frequency of occurrence or minimize the severity of peripheral neuropathies that may be related to perioperative positioning of patients" [114]. While age is identified as one of the specific preexisting conditions that may predispose a patient to develop peripheral neuropathies (other predisposing factors that were identified are smoking, diabetes, vascular disease, and extremes of body weight), no age-specific preventive strategies were offered. At the minimum, strategies used in the operating room for the general population (support surfaces, repositioning) should be applied to older patients as well.

Osteopenia and Osteoarthritis

Age-related osteopenia (bone mass loss that is less severe than osteoporosis) is considered a condition primarily affecting postmenopausal females; however, older males (as well as those treated by glucocorticoids or with androgen deprivation therapy for prostate cancer) are also at increased risk for osteopenia. Sarcopenia and osteopenia may also contribute to the development of osteoarthritis [115]. About one third to half of adults older than 65 years suffers from osteoarthritis. Osteoarthritis is a degenerative process of joint cartilage and the underlying bone [116]. Aging makes the joint more susceptible to the effects of abnormal biomechanics, joint injury, genetics, and obesity. Clinically, osteoarthritis usually presents as pain and stiffness of joints. The most commonly involved joints are in the bones of the hand, but involvement of joints in the neck, lower back, knees, and hips can have ramifications for surgical positioning. Induction in a supine position with the head elevated may need to be modified in a patient with severe osteoarthritis of the neck, not only because of potential for a difficult airway but also because it may be difficult for the patient to lie supine with the head elevated on a pillow. Placing a patient in lithotomy position may be impossible in patients with severe hip and knee arthritis.

Future Directions

The Association of Specialty Professors, with the National Institute on Aging and the Wound Healing Society, held a workshop to identify and explore research challenges relating to the study of age-associated changes in chronic wound healing. This led to establishment of research questions that need to be addressed in the future. One of the questions that were raised is: "During surgery, what steps can anesthesiologists take to mitigate risk for chronic or nonhealing wounds?" [117].

Conclusion

Older adults are at increased risk for surgical site infections, perioperative nerve injury, and pressure ulcers. Most of the perioperative interventions that are implemented in the care of the aged are similar to those that are offered for the general surgical population. Age-related changes in the skin, muscle, and bone, superimposed on concurrent comorbidities (such as diabetes), influence the response of the older patient to perioperative interventions. The clinician should be familiar with age-related changes to improve the quality of care of this vulnerable population.

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Perioperative Thermoregulation in the Elderly

Daniel I. Sessler

Perioperative thermal disturbances are common and there is considerable evidence that these disturbances are especially frequent in the elderly. The most common perioperative thermal disturbance-hypothermia-is both more likely and more severe in the elderly than in younger patients. Anesthetic drugs impair thermoregulation in all patients, and insufficient thermoregulatory defenses are the primary causes of hypothermia in most patients. Excessive hypothermia in the elderly is mainly due to disturbances in central and efferent thermoregulatory controls. Perioperative hypothermia has long been associated with complications including decreased drug metabolism and postoperative shivering. Even mild hypothermia may worsen perioperative outcomes by augmenting blood loss and transfusion requirement, decreasing resistance to surgical wound infections, and prolonging hospitalization. The elderly are especially susceptible to complications associated with hypothermia because of normal age-related changes in organ function and because many have substantial underlying diseases. However, thermal management for the elderly does not substantially differ from that for younger patients.

Normal Thermoregulation

Core body temperature is among the most jealously guarded physiologic parameters and is justifiably considered one of the "vital signs." The major thermoregulatory defenses are behavior [1, 2], sweating [3], precapillary vasodilation [4], arteriovenous shunt vasoconstriction [5], nonshivering thermogenesis [6], and shivering [7]. Each can be characterized

D.I. Sessler (⊠) Department of Outcomes Research, Cleveland Clinic, Cleveland, OH, USA e-mail: DS@OR.org by its threshold (triggering core temperature), gain (intensity increase with further core temperature deviation), and maximum intensity [8]. Temperatures between the first autonomic warm response (sweating) and the first autonomic cold defense (vasoconstriction) define the interthreshold range; these temperatures do not trigger autonomic thermoregulatory defenses [9].

Precise control of core temperature is maintained by a powerful thermoregulatory system incorporating afferent inputs, central control, and efferent defenses [10]. Efferent defenses can be broadly divided into autonomic responses (i.e., sweating and shivering) and behavioral responses (i.e., closing a window, putting on a sweater). Autonomic responses depend largely on core temperature and are mostly mediated by the anterior hypothalamus. In contrast, behavioral responses are mostly determined by skin temperature and are controlled by the posterior hypothalamus. Figure 15.1 presents a general model of thermoregulation in humans [11].

Afferent Input

Temperatures are sensed peripherally and throughout the body by various receptors and nerves, with transient receptor potential (TRP) proteins being the most important. The TRPV1 receptor was identified in 1997. Since then, ten TRP channels (TRPV1, TRPV2, TRPV3, TRPV4, TRPM2, TRPM3, TRPM4, TRPM5, TRPM8, and TRPA1) have been reported to be highly temperature sensitive. Five of them— TRPV1, TRPV2, TRPM3, TRPM8, and TRPA1—are expressed on human sensory neurons. Some thermo-TRP channels are probably either the prime or sole molecular thermosensors responsible for the reception of peripheral temperature [12–14].

Warm afferent signals are conveyed by unmyelinated C-fibers, as is pain. In contrast, cold signals traverse myelinated A-delta fibers; both C-fibers and A-delta fibers are widely distributed [15]. Most thermal input is conducted along the spinothalamic tracts, although both afferent and

The author consults many companies that make temperature management and measurement devices and serve on several advisory boards. However, all related fees are donated to charity.

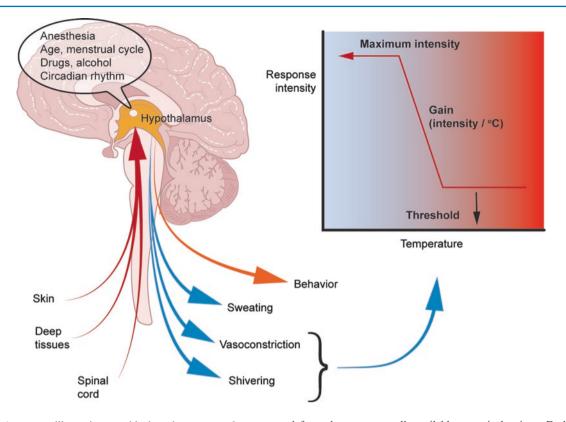


Fig. 15.1 A cartoon illustrating roughly how humans regulate temperature. Temperature is sensed at the skin surface, deep tissues, the spinal cord, the brain, and the hypothalamus. Integration of thermal input occurs at various levels, but the hypothalamus is the most important controller in mammals. The most important efferent autonomic responses are sweating, arteriovenous shunt vasoconstriction, and shivering. Behavioral responses (volitional activity) are by far the strongest

defenses but are not usually available to surgical patients. Each response is characterized by its *threshold* (triggering core temperature), *gain* (increase in response intensity with further deviation in core temperature), and *maximum response intensity* (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2017. All Rights Reserved)

efferent thermal signals are diffusely distributed within the neuraxis [16].

The central thermoregulatory control system accepts thermal input from tissues all over the body. The relative contributions of most tissues have yet to be determined in humans. However, animal studies suggest that the hypothalamus, other portions of the brain, the spinal cord, and deep thoracic and abdominal tissues each contribute very roughly 20% [8, 17-19].

The mean skin temperature contributes 5-20% as much as core temperature (deep central tissues and brain) to control sweating and active vasodilation; furthermore, the relation between mean skin and core temperatures at response thresholds is linear [4, 20–23]. That is, a 1 °C increase in skin temperature reduces the sweating and active capillary vasodilation thresholds (expressed in terms of core temperature) by 0.05–0.2 °C. Arithmetically, this relation takes the form

Thres_{MBT} =
$$\beta T_{skin} + (1 - \beta) T_{core}$$

where Thres_{MBT} is the sweating or vasodilation threshold in terms of physiologic (rather than anatomic) mean body temperature, T_{skin} is the mean skin temperature, and T_{core} is the core temperature, all in degrees centigrade.

The proportionality constant, β , in this case is 0.05–0.2. The skin surface contributes 20% ± 6% to control of vasoconstriction and 19% ± 8% to control of shivering; the contribution in linear (Fig. 15.2) [19]. Regional sensory contributions to thermoregulatory control have not been specifically evaluated in the elderly. However, there is little reason to believe that temperature sensation fails in the elderly or that integration differs markedly.

Central Control

Thermal afferent signals are integrated at numerous levels within the neuraxis, including the spinal cord and brain stem. The dominant controller in mammals, however, is the hypothalamus. (Interestingly, the spinal cord dominates in birds.)

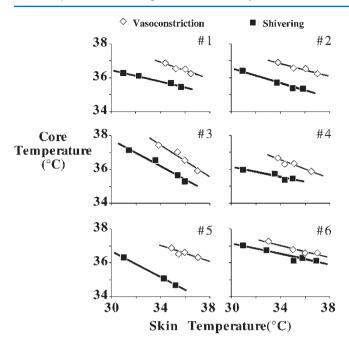


Fig. 15.2 The relative contribution of mean skin temperature to control thermoregulatory vasoconstriction and shivering in six men. The threshold (triggering core temperature) for each response is plotted vertically against mean skin temperature. Core and skin temperatures at the vasoconstriction and shivering thresholds were linearly related. The extent to which mean skin temperature contributed to central thermoregulatory control (β) was calculated from the slopes (S) of the skin temperature versus core temperature regressions, using the formula: $\beta = S/(S - 1)$. Cutaneous contribution to vasoconstriction averaged 20% ± 6%, which did not differ significantly from the contribution to shivering: 19% ± 8% (Reprinted from Cheng et al. [19]. With permission from Wolters Kluwer Health, Inc.)

Although core temperature varies with a daily circadian rhythm [24], body temperature is normally controlled to within a few tenths of a degree centigrade almost irrespective of the environment [22]. Such precise control is maintained by a powerful thermoregulatory system incorporating afferent inputs, central control, and efferent defenses.

The thresholds triggering thermoregulatory defenses are uniformly about 0.3 °C greater during the follicular phase in women [25], who then have core temperatures an additional ≈ 1 °C greater than men during the luteal phase [26]. However, men and women regulate core body temperature with comparable precision, usually maintaining core temperature within a few tenths of a °C of the target temperature (Fig. 15.3).

The major autonomic warm defenses, sweating and active vasodilation, are triggered at about the same temperature and seem to operate synchronously [27]. In contrast, vasoconstriction is the first autonomic response to cold [25]. Only when vasoconstriction is insufficient to maintain core temperature in a given environment is nonshivering thermogenesis or shivering initiated. In humans, nonshivering thermogenesis is

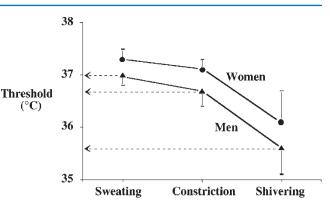


Fig. 15.3 The thresholds (triggering core temperatures) for the three major autonomic thermoregulatory defenses: sweating, vasoconstriction, and shivering. Temperatures between the sweating and vasoconstriction threshold define the interthreshold range, temperatures *not* triggering autonomic responses. The thresholds are uniformly about 0.3 °C greater during the follicular phase in women than in men and would be an additional ≈ 0.5 °C greater during the luteal phase. However, men and women regulate core body temperature with comparable precision. Results are presented as means ± SD (Reprinted from Lopez et al. [25]. With permission from Wolters Kluwer Health, Inc.)

restricted to infancy; infants use this defense in preference to shivering [28]. In contrast, nonshivering thermogenesis is of little importance in adult humans [29–31], although it is the most important cold defense in small animals.

When one efferent response is inadequate to maintain core temperature in a given environment, others are activated. Similarly, secondary defenses compensate for those working poorly. For example, when arteriovenous shunt vasoconstriction is defeated by administration of a vasodilating drug, core hypothermia will initiate shivering. Because autonomic responses are to some extent compromised in the elderly, behavioral responses are probably more important in this population—although this theory has yet to be formally evaluated.

Efferent Responses

Sweating is mediated by postganglionic cholinergic nerves that terminate on sweat follicles [32]. These follicles apparently have no purpose other than thermoregulation. In this regard, they differ from most other thermoregulatory effectors which are co-opted by the thermoregulatory system but continue to have other important roles, for example, vasomotion in blood pressure control or skeletal muscles in postural maintenance.

Heat exposure can increase cutaneous water loss from trivial amounts to 500 mL/h. Losses in trained athletes can even exceed 1 L/h. In a dry, convective environment, sweating can dissipate enormous amounts of heat—perhaps up to ten times the basal metabolic rate. Sweating is the only thermoregulatory defense that continues to dissipate heat when environmental temperature exceeds core temperature.

Active precapillary vasodilation is mediated by a factor, probably nitric oxide [33, 34], released from sweat glands, and thus occurs synchronously with sweating. Active dilation can increase cutaneous capillary flow enormously, perhaps to as much as 7.5 L/min [35]. The purpose of this dilation, presumably, is to transport heat from muscles and the core to the skin surface where it can be dissipated to the environment by evaporation of sweat.

Active arteriovenous shunt vasoconstriction is adrenergically mediated. The shunts are 100-µm-diameter vessels that convey 10,000 times as much blood as a comparable length of 10-µm capillary (laminar flow increases by the fourth power of vessel radius) [5]. Anatomically, they are restricted to the fingers, toes, nose, and nipples. Despite this restriction, shunt vasoconstriction is among the most frequently used and important thermoregulatory defenses. The reason is that the blood traversing shunts in the extremities must flow through the arms and legs, thus altering the heat content of these large tissue masses.

Shivering is an involuntary, thermogenic tonic tremor [7]. Typically, it doubles metabolic rate [36, 37], although greater increases can be sustained briefly. The shivering threshold is normally ≈ 1 °C less than the vasoconstriction threshold, suggesting that it is activated only under critical conditions and is not the preferred means of maintaining core temperature. One reason may be that shivering is a relatively inefficient response. Although shivering effectively transfers metabolic energy into heat, the heat is largely produced in the peripherally produced heat to a cold environment is further accentuated by the metabolic needs of shivering muscle and the resulting vasodilation.

Impaired Thermoregulation in the Elderly

There is considerable epidemiologic evidence that the elderly often fail to adequately regulate body temperature. Accidental hypothermia is especially likely in three populations: drug abusers (especially alcoholics), people suffering from extreme exposure (such as cold-water immersion), and the elderly [38]. While extreme—and usually prolonged—cold exposure is required to produce clinical hypothermia in young, healthy individuals, serious hypothermia is common among alcohol abusers even with mild exposure [39]. Hypothermia in these patients presumably results from drug-induced inhibition of thermoregulatory defenses. The extent to which alcohol impairs autonomic defenses remains controversial [40–43]; however, at minimum, alcohol signifi-

cantly impairs appropriate behavioral responses to cold exposure.

Hypothermia in the elderly can occur in moderately cold environments and is typically not associated with drug use [38, 39]. This observation suggests that hypothermia in the elderly may result from age-induced thermoregulatory failure. Supporting this thesis is the work of MacMillan et al. [44] who demonstrated in 1967 that elderly victims of accidental hypothermia responded abnormally to cold challenge. Subsequent studies have demonstrated that cold exposure produces more hypothermia in the elderly than in younger subjects [45, 46]. Cold tolerance is also poor in elderly rats [47].

Excessive hypothermia in the elderly presumably results from inadequate activation or efficacy of thermoregulatory defenses. Consistent with this theory, several features of thermoregulatory control in the elderly are known to differ from those in younger subjects. Sweating thresholds remain normal to the age of \approx 70 years; however, the sweating rate is reduced in the elderly. Age-relative reduction in the sweating rate seems to depend on fitness level [48]—although fitness level may itself depend on overall health. Decreased gain results from reduced sweat production per activated gland, rather than recruitment of fewer glands [49]. Sweating is also less effective in children than in adolescents [50]. Other studies, however, failed to identify age-related differences in sweating [51].

Vasoconstriction in response to cold exposure is reduced in the elderly [45]. This is a clinically important observation because vasoconstriction is the primary autonomic response to cold exposure. Similarly, the shivering threshold is reduced in the elderly [52]. Interestingly, abnormally reduced thresholds were not apparent in subjects younger than 80 years of age, and even then they were apparent in only a fraction of the population (Fig. 15.4). These data suggest that agerelated thermoregulatory impairment may not be common at ages less than 80 years. The data further suggest that impairment is not a linear function of age but instead occurs unpredictably in a fraction of the elderly population.

Altogether, there are surprisingly few studies evaluating age-related thermoregulatory changes in humans, especially in subjects exceeding 80 years of age. Even fewer of the studies are recent and use modern methods of controlling (or compensating) for changes in skin temperature. Most do not distinguish altered thresholds from reduced gain or maximum response intensity. The ethical and practical difficulties of conducting controlled physiologic evaluations in the elderly are apparent, and these difficulties are magnified in extremely old subjects who are most likely to have impaired responses. Nonetheless, as a large fraction of the US population enters this age bracket, greater understanding of agedependent thermoregulatory inhibition is clearly required.

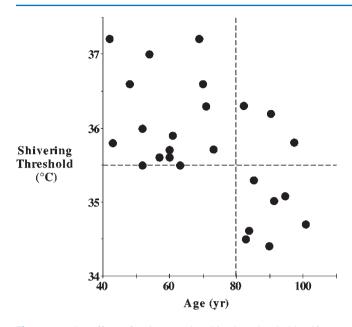


Fig. 15.4 The effect of aging on the shivering threshold. Fifteen patients aged <80 years (58 ± 10 years) (mean ± SD) shivered at 36.1 ± 0.6 °C; in contrast, ten patients aged ≥80 years (89 ± 7 years) shivered at a significantly lower mean temperature, 35.2 ± 0.8 °C (p < 0.001). The shivering thresholds in 7 of the 10 patients aged more than 80 years was <35.5 °C, whereas the threshold equaled or exceeded this value in all the younger patients (Reprinted from Vassilieff et al. [52]. With permission from Wolters Kluwer Health, Inc.)

Thermoregulation During Anesthesia

Thermoregulatory Defenses During Anesthesia

General anesthetics and most sedatives slightly increase the threshold for warm-defense responses. But these drugs also markedly decrease cold-response thresholds, thus increasing the interthreshold range 10–20-fold to \approx 4 °C at typical doses of common anesthetics. Because temperatures within this range do not trigger autonomic thermoregulatory defenses (by definition) and because behavioral compensations are unavailable in anesthetized patients, body temperature perturbations are common during anesthesia.

The first thermal problem identified with surgery was hyperthermia [53]. Hyperthermia resulted in part from the frequent use of ether, a drug associated with substantial sympathetic nervous system activation and thus peripheral vasoconstriction. More importantly, however, hyperthermia resulted when anesthetic-induced thermoregulatory impairment was combined with a warm operating environment. This mechanism continues to produce clinically important hyperthermia in some developing countries, although ether has largely been supplanted by halothane. Hyperthermia in developed countries gave way to hypothermia, however, with the introduction of air conditioning. Hypothermia is now by far the most common perioperative thermal disturbance and

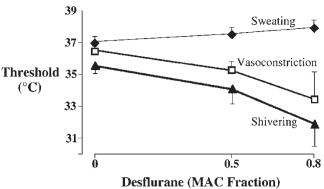


Fig. 15.5 Thermoregulatory response thresholds during desflurane anesthesia. The sweating threshold increased linearly, but slightly, during desflurane anesthesia. Desflurane markedly—although nonlinearly—reduced the vasoconstriction threshold. Consequently, the interthreshold range (temperatures *not* triggering autonomic thermoregulatory defenses) increased enormously during desflurane administration. In contrast, the vasoconstriction-to-shivering range remained essentially unchanged. Results are presented as means \pm SD. MAC minimal anesthetic concentration (Reprinted from Annadata et al. [57]. With permission from Wolters Kluwer Health, Inc.)

results from anesthetic-induced inhibition of thermoregulatory defenses combined with a cold surgical environment.

Sedatives and general anesthetics, with the exception of midazolam [54], markedly impair thermoregulatory control. For example, the sweating threshold is linearly increased by propofol [55], alfentanil [56], isoflurane [27], and desflurane [57]. Reduction of the vasoconstriction and shivering thresholds is also a linear function of propofol [55], dexmedetomidine [58], meperidine [59], and alfentanil [56] concentrations. Desflurane and isoflurane, however, produce a nonlinear reduction in the major cold-response thresholds, reducing the vasoconstriction and shivering thresholds disproportionately at higher anesthetic concentrations (Fig. 15.5) [57]. The result is that clinical doses of all anesthetics and most any "balanced" combination of anesthetics and opioids markedly increase the interthreshold range—thus substantially impairing thermoregulatory defenses.

Anesthetic-Induced Thermoregulatory Impairment in the Elderly

Intraoperative hypothermia is more common and severe in the elderly [60]. Because a major cause of intraoperative hypothermia is anesthetic-induced inhibition of thermoregulatory responses, these two observations suggest that anesthetics impair thermoregulation more in the elderly than in young patients. This thesis is supported by the observation that the vasoconstriction threshold is approximately 1 °C lower in elderly surgical patients than in younger ones (Fig. 15.6) [61].

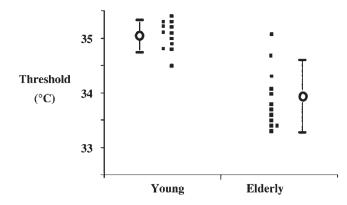


Fig. 15.6 The effect of aging on thermoregulatory vasoconstriction during general anesthesia. The vasoconstriction threshold was significantly less in the elderly (33.9 ± 0.6 °C, mean \pm SD) than in younger patients (35.1 ± 0.3 °C) (p < 0.01). Filled squares indicate the vasoconstriction threshold in each patient; the open circles show the mean and standard deviations in each group (Reprinted from Kurz et al. [61]. With permission from Wolters Kluwer Health, Inc.)

Intraoperative hypothermia is not only more common in the elderly, but it lasts longer postoperatively [62]. It is also associated with less shivering when compared to younger patients [60, 63], and what shivering does occur is at a lower intensity [64]. Prolonged hypothermia without shivering suggests that thermoregulatory defenses are not being activated, which is consistent with reduced perioperative vasoconstriction [61] and shivering [52] thresholds in the elderly.

An additional factor to consider is the age-dependent effects of anesthetic drugs. Renal and hepatic function is often reduced in the elderly. Consequently, clinically important plasma concentrations are likely to persist longer and at higher levels in the elderly. Equally important, any given plasma concentrations of many drugs produce a greater effect in the elderly. The minimum alveolar concentration of volatile anesthetics, for example, decreases about 25% in the elderly [65, 66]. Similarly, the effect of midazolam is markedly age dependent [67]. Combined pharmacokinetic and pharmacodynamic augmentation of anesthetic drug effects is thus likely to further impair thermoregulation in the elderly.

Perioperative Heat Balance

Both physical and physiologic factors contribute to perioperative hypothermia. Hypothermia would be unlikely without anesthetic-induced inhibition of thermoregulatory control because thermoregulatory defenses would normally be sufficient to prevent core temperature perturbations even in a cool operating room environment. However, most anesthetics markedly increase the range of temperatures *not* triggering thermoregulatory defenses [68]. Within this interthreshold range, body temperature changes are determined by patients' physical interactions with their immediate environments. Larger operations and colder rooms are thus associated with greater hypothermia. Once triggered, however, thermoregulatory vasoconstriction usually prevents further hypothermia—no matter how large and long the operation might be [69].

Despite multiple modalities of heat loss, each described by different (and mostly nonlinear) equations, cutaneous heat loss in patients is a roughly linear function of the difference between skin and ambient temperatures. The physical laws and equations characterizing heat transfer are comparably valid for all animate and inanimate substances and, of course, apply equally in young and elderly patients.

Mechanisms of Heat Transfer

There are four types of heat transfer: radiation, convection, conduction, and evaporation [70]. Among these, radiation and convection are by far the most important during surgery, together accounting for approximately 85% of the total loss [71]. Fractional losses via each route are, however, determined by numerous physical and physiologic factors including incision size, amount of administered (cold) intravenous fluid, and thermoregulatory vasoconstriction.

Radiative losses are mediated by photons and do not depend on any intervening media. Losses via this mechanism are related to surface properties (emissivity) and the difference of the fourth power of exposed skin and wall temperatures (in degree Kelvin). Radiative losses are thus not directly influenced by ambient temperature, although ambient temperature indirectly influences both wall and skin temperature. Radiation probably contributes about 60% to total heat loss [71, 72].

Conduction is defined by direct transfer of heat energy between opposing surfaces. It is related only to the insulating properties of the surfaces (or of an intervening layer) and the temperature difference between the surfaces. It is unlikely that conduction contributes more than about 5% to overall heat loss in the perioperative period. The reason conduction contributes so little is that only a small fraction of the body surface area is in direct contact with another solid surface and that surface is likely to be the operating table mattress which is a good insulator. The body heat required to warm cold intravenous fluids is probably best considered as a conductive loss. Loss via this route usually exceeds conventional surface-to-surface heat transfer.

Convection, which is often termed "facilitated conduction," contributes considerably more than conduction, perhaps about 25% of the total loss. Normally, there is essentially no conduction into air because still air is an excellent insulator and because a small layer of still air is maintained adjacent to the skin surface. But when warm air next to the skin is pushed away, it is replaced by cool air from the surrounding environment. This air is itself warmed by extracting heat from the skin, only in turn to be replaced by additional cool air. The equation describing convection is similar to that characterizing conduction, with the addition of a factor for the square root of air speed. Convection is the basis for the familiar "wind chill factor."

The heat of vaporization of water is among the highest of any substance: 0.58 kcal/g. Evaporation of large amounts of water thus absorbs enormous amounts of heat, which is why sweating is such an effective defense against heat stress. But except in infants, insensible cutaneous water loss is negligible [73, 74], and evaporative heat loss constitutes only a tiny fraction of the total in non-sweating individuals. Evaporative loss contributes to surgical hypothermia during skin preparation when the skin surface is scrubbed with water- or alcoholbased solution that is subsequently allowed to evaporate. Because skin preparation is usually restricted to a relatively small area and because evaporation is permitted for only a brief time, heat loss from skin preparation is not usually clinically important [75].

Water is also vaporized and lost from the lungs when they are ventilated with dry, cold gases. Numerous clinical studies [76, 77] and thermodynamic calculations [78] indicate that respiratory heat loss in adults is less than 10% of the total heat loss. Other studies identify effects of airway heating and humidification on core temperature that seem difficult to reconcile with thermodynamic calculations of heat transfer [79–81]; in some cases, these aberrant results are attributable to study design flaws. In contrast, respiratory losses are somewhat more important in infants and children than in adults [82, 83].

Finally, heat is lost when water evaporates from exposed surfaces within surgical incisions. The extent of this loss in humans remains unknown, although clinical experience suggests that it may be substantial because patients undergoing large operations become considerably more hypothermic than those having smaller procedures. Evaporative loss from large incisions may be up to half of the total heat loss in animals [84], although this ratio is likely less in humans.

Distribution of Heat Within the Body

Intraoperative hypothermia develops with a characteristic three-phase pattern. The first is a rapid, 1–1.5 °C decrease in core temperature occurring during the first hour after induction of anesthesia [85]. This is followed by a slower, nearly linear decrease in core temperature lasting 2–3 h [86]. And finally, core temperature reaches a plateau and does not decrease further [69]. Each portion of this curve has a different etiology.

The initial, rapid decrease in core temperature after induction of general anesthesia results from core-to-peripheral redistribution of body heat. Redistribution results when anesthetic-induced inhibition of tonic thermoregulatory vasoconstriction allows heat to flow from the relatively warm core thermal compartment to cooler peripheral tissues. (Surprisingly, anesthetic-induced vasodilation increases cutaneous heat loss only slightly [87].) Although redistribution, by definition, does not alter body heat content, it does markedly decrease core temperature. Internal redistribution of body heat is a major cause of core hypothermia in most patients (Fig. 15.7) [85]. Redistribution is also a major cause of hypothermia during epidural anesthesia.

The 2–3-h-long linear decrease in core temperature results simply from heat loss exceeding heat production [76]. In part, this results from an $\approx 30\%$ reduction in metabolic heat

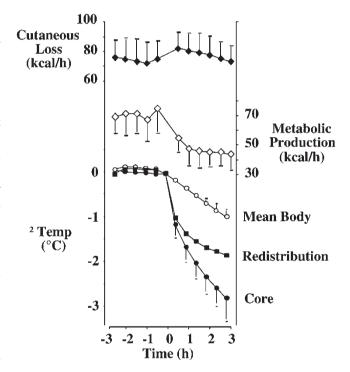


Fig. 15.7 Changes in body heat content and distribution of heat within the body during induction of general anesthesia. Heat loss and metabolic heat production were initially similar. Overall heat balance was thus near zero before induction of anesthesia (at elapsed time zero), but subsequently decreased by \approx 31 kcal/h. The contributions of decreased overall heat balance and internal redistribution of body heat to the decrease in core temperature were separated by multiplying the change in overall heat balance by body weight and the specific heat of humans. The resulting change in mean body temperature ("mean body") was subtracted from the change in core temperature ("core"), leaving the core hypothermia specifically resulting from redistribution ("redistribution"). After 1 h of anesthesia, core temperature had decreased by 1.6 ± 0.3 °C, with redistribution contributing 81% to the decrease. During the subsequent 2 h of anesthesia, core temperature decreased an additional 1.1 ± 0.3 °C, with redistribution contributing only to 43%. Redistribution thus contributed 65% to the entire 2.8 ± 0.5 °C decrease in core temperature during the 3 h of anesthesia. All results are shown as means ± SD (Reprinted from Matsukawa et al. [85]. With permission from Wolters Kluwer Health, Inc.)

production during general anesthesia [85]. Metabolic heat production is nearly constant during anesthesia and minimally influenced by anesthetic technique [69, 88]. Respiratory heat loss (even with a nonrebreathing circuit and unwarmed, dry gases) is simply a linear function of metabolic rate. In contrast, cutaneous heat loss is determined largely by surface insulation and ambient temperature and can therefore be altered by anesthetic management. The slope of this second phase of hypothermia curve depends on the difference between metabolic heat production and cutaneous and respiratory heat loss. While typically negative, the slope can be positive when heat loss is reduced to below metabolic heat production by high ambient temperature, sufficient insulation, or effective warming systems.

After 3–4 h of anesthesia, core temperature usually reaches a plateau and does not decrease further. This plateau is generally associated with arteriovenous shunt vasoconstriction. Vasoconstriction contributes to the plateau via two distinct mechanisms. The first is simply decreasing cutaneous heat loss [89]. The second is by constraining metabolic heat to the core thermal compartment, thus re-forming the normal core-to-peripheral temperature gradient that was obliterated by the initial redistribution hypothermia. Because heat loss may continue to exceed heat production during the core temperature plateau, body heat content often continues to decrease during this period—even though core temperature is constant (Fig. 15.8) [69]. For further discussion of perioperative heat balance, readers are referred to a detailed review [89].

Benefits of Mild Hypothermia

Severe hypothermia (i.e., core temperatures near 28 °C) has been known for decades to be protective against cerebral ischemia [90]. The basis for this protection was thought to be a decrease in the cerebral metabolic rate to about half of normal levels [91]. Although decreased metabolic rate surely contributes to hypothermic protection, there is increasing evidence that other mechanisms contribute. These include decreased release of excitatory amino acids (such as glutamate) and free fatty acids [92, 93], inhibition of calcium-/ calmodulin-dependent protein kinase II [94], preservation of the blood–brain barrier, [95, 96] reduced synthesis of nitric oxide [97] and ubiquitin [98].

More than 100 animal studies in virtually every ischemic model demonstrate that just 1–3 °C brain hypothermia provides substantial protection against ischemia [93, 99–102]. In each case, the protection seems to far exceed that resulting simply from reduced metabolic rate. There is also evidence that mild hypothermia protects the spinal cord and liver against ischemia [103]. Furthermore, mild hypothermia

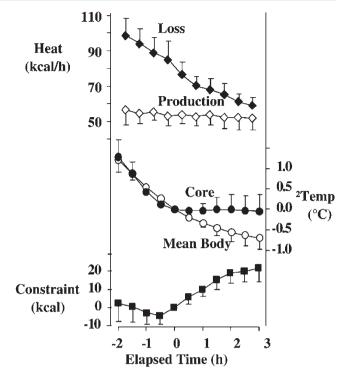


Fig. 15.8 Changes in body heat content and distribution of heat within the body during the core temperature plateau in anesthetized subjects. Vasoconstriction decreased cutaneous heat loss by ≈ 25 kcal/h. However, heat loss exceeded heat production throughout the study. Consequently, mean body temperature, which decreased at a rate of \approx 0.6 °C/h before vasoconstriction, subsequently decreased at a rate of ≈ 0.2 °C/h. Core temperature also decreased at a rate of ≈ 0.6 °C before vasoconstriction but remained virtually constant during the subsequent 3 h. Because mean body temperature and body heat content continued to decrease, constraint of metabolic heat to the core thermal compartment contributed to the core temperature plateau. That is, vasoconstriction reestablished the normal core-to-peripheral temperature gradient by preventing metabolic heat (which is largely generated in the core) from escaping to peripheral tissues. Constrained heat is presented cumulatively, referenced to the onset of intense vasoconstriction defined as time zero; data are expressed as means ± SD (Reprinted from Kurz et al. [69]. With permission from Wolters Kluwer Health, Inc.)

seems protective during spinal cord ischemia [104] and is beneficial during hypoxia and shock.

The extent to which mild hypothermia ameliorates cerebral ischemia in humans remains unclear. The best documented indication is neonatal asphyxia [105–108]. Two major trials suggested that mild hypothermia improves neurological function after cardiac arrest [109, 110]. However, a subsequent much larger trial showed no benefit whatsoever [111]. Trials have failed to show benefit from therapeutic hypothermia for aneurism surgery [112], brain trauma [113], and acute myocardial infarction [114]. All these trials, though, had substantial limitations, and negative outcomes in the studied contexts do not necessarily mean that the general concept of hypothermic brain protection is flawed. Hypothermia clearly reduces intracranial pressure, but a randomized trial of hypothermia in patients with critically elevated intracranial pressure did not improve long-term outcome [115]. Major trials on mild hypothermia are in progress for stroke, sepsis, and various other conditions. Assuming benefit is eventually demonstrated, it seems likely that the elderly will be at greater risk of ischemia because of age-related vascular compromise while simultaneously being at greater risk of hypothermia-related complications. In the absence of specific data, clinicians may have to make difficult risk–benefit judgments in elderly patients.

Complications of Hypothermia

Coagulopathy and Allogeneic Transfusion Requirement

Hypothermia decreases platelet function [116], apparently by decreasing the release of thromboxane A_2 [117]. This effect on platelet function seems to be entirely related to local, rather than core, temperature. (This is a factor that should be considered when interpreting a bleeding time.) Hypothermia also directly inhibits the enzymes of the coagulation cascade [118, 119] The effects of hypothermia on bleeding have generally not been appreciated by clinicians, in large part because coagulation tests are performed at 37 °C, irrespective of patients' actual temperatures.

Hip arthroplasty is among the most common operations in the elderly, and it is a procedure associated with substantial blood loss. Just 2 °C core hypothermia substantially increases perioperative blood loss during total hip arthroplasty, and also increases the requirement for allogeneic blood transfusion, as shown in some [120, 121] but not all [122] studies (Table 15.1). A meta-analysis summarizes available trial results [123], and a large observational study indicates that transfusion requirements increase with hypothermia [124].

 Table 15.1
 Mild intraoperative hypothermia increases blood loss during hip arthroplasty

	Normothermic	Hypothermic	p value
Final intraoperative core temperature (°C)	36.6 ± 0.4	35.0 ± 0.5	< 0.001
Blood loss (L)	1.7 ± 0.4	2.2 ± 0.6	< 0.001
Allogeneic blood (mL/ patient)	10 ± 55	80 ± 154	< 0.02

Note: Mild hypothermia (<2 °C) significantly increased blood loss and the requirement for allogeneic blood transfusion in patients undergoing total hip arthroplasty. As is typical for this procedure, the patients were elderly, averaging 63 ± 10 years of age (Based on data from Schmied et al. [120])

Surgical Wound Infections and Duration of Hospitalization

Wound infection is a common and serious complication of anesthesia and surgery. In patients having colon surgery, the risk of wound infection ranges from 3 to 22% [125]. Infections typically prolong hospitalization by 5–20 days per infection and substantially increase cost [126, 127]. Hypothermia facilitates perioperative wound infections in two ways. First, sufficient intraoperative hypothermia triggers thermoregulatory vasoconstriction [128] and postoperative vasoconstriction is universal in hypothermic patients [129]. Vasoconstriction decreases tissue oxygen partial pressure which reduces resistance to infection [130, 131]. Second, mild core hypothermia directly impairs numerous immune functions [132, 133].

Finally, vasoconstriction-induced tissue hypoxia also decreases wound strength independently of its effect on resistance to infection. Scar formation requires proline and lysine hydroxylation, permitting the cross-linking between collagen strands that provides wound tensile strength [134]. The hydroxylases catalyzing this reaction are oxygen tension dependent [135]. Collagen deposition is thus proportional to arterial PO₂ in animals [136] and to wound tissue oxygen tension in humans [137].

Consistent with these in vitro data, mild hypothermia during anesthesia reduces resistance to *Escherichia coli* and *Staphylococcus aureus* inoculations in guinea pigs [138, 139]. Furthermore, just 2 °C core hypothermia tripled the incidence of wound infection in patients having colon surgery (Table 15.2) [140]. The adverse effect of hypothermia on infection, especially non-wound infections, is supported by a recent retrospective analysis of compliance with thermal management guidelines. Compliant patients proved to have a significantly lower risk of hospital-acquired infection, shorter hospitalizations, and reduced mortality [141].

Hypothermic patients also require significantly longer hospitalizations in a trial from 1996 [140]. However, a recent observational analysis suggests that with current shorter hospitalizations, hypothermia is not an important factor [124].

Postoperative Shivering

It is common in reviews and book chapters to include the following logic: (1) shivering increases metabolic rate "up to 400%"; and (2) increased metabolic rate could be detrimental to elderly patients having cardiovascular disease [142, 143]. However, postoperative shivering in elderly patients is relatively rare [64] and usually of low intensity when it does occur. On average, postoperative shivering in young patients doubles oxygen consumption (although higher values may occasionally be sustained) [144, 145], whereas metabolic

Duration of hospitalization (days)

< 0.01

	Normothermic	Hypothermic	p value
Final intraoperative core temperature (°C)	36.6 ± 0.5	34.7 ± 0.6	< 0.001
Infections/number of patients	6/105	18/95	< 0.01

 11 ± 4

Table 15.2 Mild intraoperative hypothermia increases the incidence of surgical wound infections and the duration of hospitalization

Note: Mild hypothermia (<2 °C) tripled the incidence of surgical wound infections and prolonged hospitalization by 25% in patients having elective colon resections (Based on data from Kurz et al. [140])

rate increases only $\approx 20\%$ in the elderly [64]. Thus, there seems to be little support for the theory that elderly patients who become hypothermic subsequently develop shivering-induced myocardial ischemia.

Some patients, nonetheless, shiver during recovery from general anesthesia. At the very least, shivering is uncomfortable and remembered by many patients as one of the worst aspects of their surgical experience. Most postoperative shivering-like tremor is thermoregulatory [129], and therefore, can be completely prevented by maintaining intraoperative normothermia [146]. However, there is a small incidence of low-intensity tremor that is not thermoregulatory [147], a tremor that correlates with inadequate treatment of surgical pain [148]. A similar non-thermoregulatory shivering-like tremor can be observed during epidural analgesia for labor [149].

Shivering can be treated using a variety of techniques. The least invasive is skin-surface warming. Because mean skin temperature contributes $\approx 20\%$ to control of shivering [19], cutaneous warming decreases the shivering threshold proportionately. A typical forced-air warmer increases mean skin temperature by ≈ 3 °C, thereby reducing the shivering threshold to ≈ 0.6 °C. If a shivering patient's core temperature is within 0.6 °C of the shivering threshold, cutaneous warming can thus increase the threshold sufficiently to stop shivering [150].

Numerous drugs have also been proven effective for the treatment of postoperative shivering. The prototypical drug for this purpose is meperidine, which is far more effective than equianalgesic doses of other opioids [151]. For example, meperidine reduces the shivering threshold twice as much as equianalgesic concentrations of alfentanil [56]. Furthermore, meperidine markedly reduces the gain of shivering, whereas alfentanil does not [152].

The special anti-shivering activity of meperidine was thought to result from its kappa-receptor activity [153], but kappa opioids do not share disproportionately to reduce the shivering threshold [154]. Meperidine's central anticholinergic activity also fails to explain this drug's special antishivering activity [154]. Clonidine [155–157] and ketanserin [157] are also effective treatments for postoperative shivering, as are magnesium [158] and doxapram [159–161]. The efficacy of various anti-shivering treatments has been the subject of a recent meta-analysis [162]. For further discussion of perioperative shivering, readers are referred to a detailed review [163].

 14 ± 4

Impaired Drug Metabolism

The pharmacokinetic effects of mild hypothermia are poorly documented. Nonetheless, the duration of action of vecuronium, for example, is doubled by just 2 °C core hypothermia [164]. Hypothermia prolongs the duration of action of atracurium less, $\approx 70\%$ with 3 °C reduction in core temperature [165], perhaps because Hoffman elimination is relatively temperature insensitive compared with enzymatic degradation. Antagonism of the neuromuscular block is not compromised with either drug [164, 165]. Finally, steady-state plasma concentrations of propofol (during a constant rate infusion) were increased to $\approx 30\%$ by 3 °C core hypothermia [165].

The pharmacokinetic effects of hypothermia in the elderly have yet to be studied. However, drug metabolism in the elderly is often already compromised. It seems likely that hypothermia-induced prolongation of drug action combined with age-related deficiencies in drug metabolism may result in prolonged duration of action of anesthetic drugs in elderly, hypothermic patients. These pharmacokinetic effects will, in many cases, be confounded by pharmacodynamic effects. Although the magnitude of these effects has yet to be quantified, it would seem prudent to prevent hypothermia in the elderly and use the lowest required drug doses to minimize drug-induced thermoregulatory impairment.

Myocardial Ischemia and Arrhythmias

Myocardial infarction remains one of the leading causes of perioperative mortality. About 4% of surgical inpatients over the age of 45 years will have myocardial injury (as indicated by troponin elevation) [166]. Among those who do, 4% will be dead within a month—making myocardial injury and consequences the leading cause of the 30-day mortality [167].

Perioperative ischemia presumably requires underlying coronary artery disease, a predisposition that would be unusual in young patients but is typical in the elderly. The elderly are thus more susceptible to perioperative ischemia and have the most to benefit from maintenance of perioperative normothermia.

Even mild hypothermia increases circulating catecholamine concentrations and provokes tachycardia and hypertension [168, 169]. One might thus assume that hypothermia would provoke myocardial injury in fragile surgical patients, but harm has yet to be convincingly demonstrated. There is a single randomized trial that compared mild hypothermia and normothermia on myocardial outcomes in 300 vascular surgical patients [170]. Because the study was conducted before troponin became available, the investigators relied on continuous electrocardiographic analysis. They identified only one myocardial infarction in the entire study (a tiny fraction of the expected number) and thus were unable to adequately test their hypothesis. The extent to which mild hypothermia contributes to postoperative myocardial injury thus remains essentially unknown.

Thermal Management

The combination of anesthetic-induced inhibition of thermoregulatory defenses and cold exposure makes most surgical patients hypothermic. Hypothermia produces complications in both young and elderly patients, and the severity of these complications appears worse in the elderly. Consequently, active thermal management is especially important in elderly patients. The physical principles of heat transfer, however, apply equally in all patients. Thus, the same warming techniques proven effective in the general surgical population will also apply to the elderly. For a discussion of patient warming techniques, readers are referred to a detailed review [171].

Ambient Temperature, Passive Insulation, and Cutaneous Warming

Heat loss is a (very) roughly linear function of the difference between skin and environmental temperature. Typical intraoperative skin temperature is near 34 °C, which is ≈ 14 °C above ambient temperature. Consequently, each 1 °C increase in ambient temperature reduces heat loss $\approx 7\%$. Patients become hypothermic most rapidly during the initial 30 min after induction of anesthesia, and this is the period when patients are most likely to be undraped. But, counterintuitively, core hypothermia during this period results from internal redistribution of body heat, not primarily from heat loss to the environment [85]. Increasing ambient temperature for the brief period before and after induction of anesthesia therefore has little impact on patient temperature [172]. A single layer of passive insulation decreases cutaneous heat loss to $\approx 30\%$. However, the type of insulation makes little difference, with the efficacy of cotton blankets, plastic bags, cloth or paper surgical drapes, and "space blankets" all being comparable [173]. Patients who remain normothermic during surgery while covered only with a single layer of insulation require no additional thermal management. But increasing the number of layers makes relatively little difference, reducing loss by a total of only 50% with three layers; furthermore, warm and cold blankets provide similar insulation (Fig. 15.9) [174]. It is thus unlikely that progressive intraoperative hypothermia will be successfully treated simply by providing additional layers of insulation. Instead, active cutaneous warming will be required.

Circulating-water mattresses remain a common method of thermal management, despite evidence that these devices are nearly ineffective [175] and cause pressure-heat necrosis ("burns") [176, 177]. The efficacy of circulating water is restricted because relatively little heat is lost from patients' backs into the foam insulation covering most operating tables [76]. Instead, most heat is lost by radiation and convection from patients' anterior surfaces, loss that cannot be prevented by a water mattress. Newer posterior warming systems that incorporate pressure-relief materials warm patients effectively [178, 179]. Forced-air warming is effective, easy to use, inexpensive, and remarkably safe and is by far the most commonly used active warming system [175]. Recently developed circulating water garments transfer even more heat than forced air but are considerably more expensive [180–183].

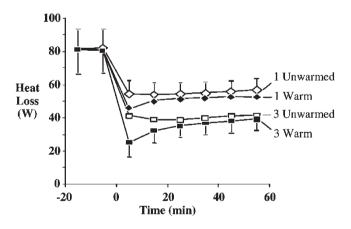


Fig. 15.9 Mean cutaneous heat loss during the control period (-20–0 elapsed minutes) and when the volunteers were covered with a single warmed or unwarmed blanket ("1 warm" or "1 unwarmed") or three warmed or unwarmed blankets ("3 warm" or "3 unwarmed"). There was no clinically important difference between warmed and unwarmed blankets. Increasing the number of layers from one to three slightly decreased heat loss, but the decrease was unlikely to be sufficient to prevent further intraoperative hypothermia (Reprinted from Sessler and Schroeder [174]. With permission from Wolters Kluwer Health, Inc.)

Fluid Warming

It is not possible to warm patients by warming intravenous fluids. Fluid warming alone is thus unlikely to maintain perioperative normothermia because it will not compensate for redistribution hypothermia, much less heat loss from the skin and from surgical incisions. However, it is certainly possible to cool patients by administering fluids much below body temperature.

The amount of cooling is easy to calculate: in an averagesized adult, 1 L of fluid at ambient temperature decreases mean body temperature at 0.25 °C. One unit of blood at refrigerator temperatures causes a similar decrease in body temperature [184]. Fluid warming should thus be restricted to patients who are already being warmed with some effective surface technique such as forced air *and* in whom large amounts of fluid (>1 L/h) is being given. Cooling of fluid in tubing between warmers and patients is clinically unimportant except in the occasional neonate who requires large amounts of fluid [185].

Prewarming

Internal core-to-peripheral redistribution of body heat is among the most important causes of hypothermia in most patients [85]. Because the internal flow of heat is large, it has proven difficult to treat with surface warming [76]. An alternative is to prevent redistribution. One method of minimizing redistribution is to produce drug-induced peripheral vasodilation well before induction of anesthesia. Because central thermoregulatory control remains normal before induction of anesthesia, behavioral compensation protects core temperature. The result is a constant core temperature, accompanied by increased peripheral tissue temperature. Because heat flows down a temperature gradient, induction of anesthesia is associated with little redistribution because the core-to-peripheral temperature gradient is small. This concept has been demonstrated using nifedipine [186], phenylephrine [187], and ketamine [188], all of which support the importance of redistribution hypothermia.

An alternative method of minimizing redistribution hypothermia is to actively warm peripheral tissues before induction of anesthesia. Even just 30 min of forced-air "prewarming" increases peripheral tissue heat content to ≈ 69 kcal, and 1 h of prewarming transfers nearly 136 kcal [189]. Either amount should be sufficient to minimize redistribution. The benefits of prewarming have been demonstrated in both volunteers [190] and surgical patients [146, 191, 192] (Fig. 15.10). Assuming intraoperative forced-air warming is anticipated, there is no additional patient cost to prewarming because the same disposable cover can be used before and during surgery. In typical clinical environments, prewarming reduces the amount of

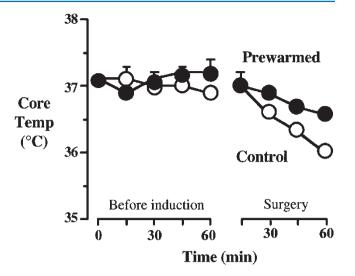


Fig. 15.10 Core temperatures during the preinduction period did not change significantly in the control group (*open circles*) or patients prewarmed with forced air (*solid circles*). After induction of anesthesia, core temperature in the control group decreased at nearly twice the rate of that in the prewarmed patients. After 1 h of anesthesia, core temperatures were 0.6 °C greater in the prewarmed patients than in the control group. Results presented as means \pm SEM (Reprinted from Camus et al. [191]. With permission from Elsevier)

redistribution by about 0.5 °C—which may or may not be clinically important.

Summary

Normal thermoregulatory control is impaired in the elderly, as is thermoregulation during general anesthesia. A major factor influencing intraoperative core temperature changes is internal core-to-peripheral redistribution of body heat that results from anesthetic-induced inhibition of thermoregulatory control. Many of the identified complications of mild perioperative hypothermia are likely to be more common and more severe in the elderly. Similarly, the core temperature plateau results from reemergence of thermoregulatory control, which may be impaired in the elderly. In contrast, the physical factors influencing heat loss do not differ much in young and elderly patients, and thermal management strategies are similar in young and elderly patients.

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Part III

Pharmacology

Inhalational Anesthetics

Gary R. Haynes

16

General anesthesia with inhalational anesthetic agents is the most common method of surgical anesthesia. Although regional and neuroaxial anesthetics are preferred in some circumstances, the use of general anesthesia with inhalational agents remains widespread. Total intravenous anesthesia has greater acceptance in Europe where it accounts for approximately 40% of general anesthesia cases. However, only a small portion of general anesthesia cases in the United States use this technique.

General anesthesia in older adults with inhalational agents compares favorably to intravenous anesthesia [1]. However, there are many gaps in our knowledge of volatile anesthetic drug effects in the elderly. Many of the most comprehensive studies on inhalational anesthetics were done in young adults. Clinical drug trials demonstrating their safety, dosing, and efficacy frequently involve younger patients. When clinical trials enroll subjects over a range of ages, they frequently do not stratify patients into age groups. Consequently, it is often impossible to make statements describing any differences between younger and older patients.

The focus of past clinical studies investigating inhalational anesthetic agents was their immediate effects and short-term outcomes. The control of cardiovascular responses and time for emergence from general anesthesia are typical examples. There is only limited information on the immediate perioperative outcome of elderly patients and even fewer reports regarding their long-term outcomes. When the concern is the elderly patient, there are often more questions than answers.

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The Pharmacokinetics of Inhalational Agents in the Elderly

The pharmacokinetic aspects of inhalational anesthetic agents include the absorption, distribution, and metabolism of these drugs. Profound age-related changes occur in the pharmacokinetics of intravenous drugs, so it is anticipated that age will also change inhalational anesthetic behavior. However, there are few studies describing how their pharmacokinetics change with age.

Advancing age modifies every aspect of systems controlling the movement of these drugs. Consequently, the assumptions based on the behavior of inhaled anesthetics in younger patients may not hold when administered to older individuals. Some insight comes from the results of studies in middleaged adults or from studies in the elderly conducted for some purpose other than examining pharmacokinetics.

The pharmacokinetics of volatile anesthetics can be studied in one of two ways. Under laboratory conditions, subanesthetic doses of several agents can be administered in combination to a single subject. This approach has the advantage of limiting the variability between individuals while measuring the kinetics of each drug. The drawback of this method is the inability to measure the pharmacologic effect specific to each drug [2, 3]. The other method is to administer a single agent and track it in an individual subject. These studies require validation in many subjects. Frequently, the design of such studies does not address the issue of age.

Influence of the Aging Pulmonary System

Uptake of anesthetics begins when the fresh gas inflow from the anesthesia machines carries a volatile agent into the patient. The uptake of an inhalational agent is simply the difference between the inspired and expired concentrations multiplied by the alveolar ventilation. The total gas flow passing through the vaporizer determines the rate of inhalational agent consumption [4]. In young subjects, saturation is most rapid with desflurane. Saturation is next most rapid with sevoflurane. High fresh gas flow (>3 L/min) will consume volatile agents more rapidly than when using low flows, and anesthetic drug cost can be reduced by using a low-flow technique. With the low-flow technique, fresh gas flow rate is reduced to less than half the patient's minute ventilation, usually to less than 3.0 L/min. Monitoring of inspired and expired gas concentrations is mandatory. At a low flow rate, consumption of an insoluble agent, such as desflurane, depends on fresh gas flow whereas halothane does not. Consumption of isoflurane and enflurane vary with minimal and low fresh gas flow rates [5].

Do anesthetic agents control the response to surgical stimulation in the same manner at low flows? The partial pressure of agents in pulmonary arterial blood that have a low blood/gas solubility should change rapidly with changes in vaporizer settings. Desflurane provides faster control of hemodynamic responses at 1 and 3 L/min flows, and its use requires fewer incremental increases to control acute responses to surgical stimulation. At fresh gas flow rates of 1 L/min, more interventions are necessary to control blood pressure in older patients receiving isofluane compared with desflurane [6].

The respiratory changes characterizing advanced age have been thoroughly reviewed by others [7–11]. The principal anatomic changes include lung atrophy and a loss of pulmonary elasticity. There is a loss of alveolar walls, a depletion of the connective tissue elastin, and an increase in interstitial fibrous tissue. The histopathologic change in the senescent lung is sometimes termed "senile emphysema," and it refers to the atrophic changes and dilatation of the alveoli that mimic mild emphysema (Fig. 16.1).

The destruction of alveolar walls results in small alveoli coalescing to form larger sacs. Consequently, the lungs have

less elasticity and less natural recoil to hold small airways open as lung volumes change with respiration [12, 13]. Airways from the level of bronchioles to the alveolar ducts lack a cartilaginous support. Without a semirigid structure to keep them open during passive exhalation, these airways depend on the elastic recoil of the lung parenchyma to prevent collapse at low lung volumes (Fig. 16.2). There is an age-related decrease in the diameter of small bronchioles from the fourth decade that is consistent with decreased compliance [14]. In the older patient, these dependent airways close at a higher lung volume than in younger subjects. The physiologic consequence of these changes is increasing ventilation perfusion (V/Q) mismatching with advancing age. A progressive hypoxemia develops as the number of alveoli gradually decreases and anatomic dead space increases [15].

The increased closing volume makes it more likely an older patient will experience hypoxia at some time in the perioperative period. Older patients experience hemoglobin desaturation at a faster rate because of greater V/Q mismatching. In the operating room, the transfer of oxygen is not as efficient when using positive pressure ventilation in the supine position as it is when breathing spontaneously. The combination of altered ventilatory response to hypoxia, sedation from residual inhalational agents, and analgesics increases the risk of hypoxia after general anesthesia. The likelihood of hypoxia is further compounded if pulmonary disease is superimposed on age-related changes.

An age-related mismatching of pulmonary ventilation and perfusion may influence the uptake of volatile anesthetic agents. Areas of the lung that are well ventilated but with less perfusion will contribute more anesthetic gas and can be expected to cause a more rapid increase in the ratio of alveolar (F_A) to inspired (F_I) agent concentrations. However, there is little evidence to confirm this. In the absence of grossly abnormal pulmonary function, the small increase in the F_A/F_I

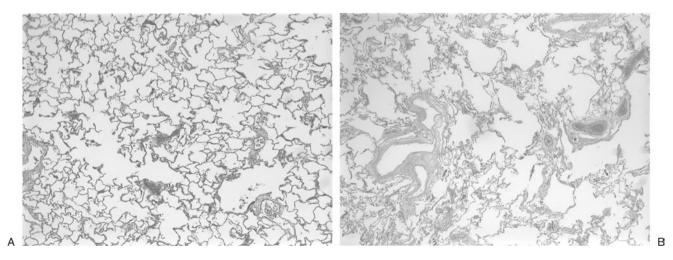


Fig. 16.1 Histologic sections of normal lung from a nonsmoking (a) 22-year-old homicide victim, and (b) a 75-year-old individual (hematoxylin and eosin stain, 2×)

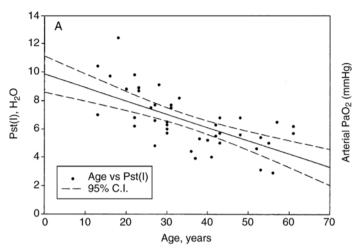
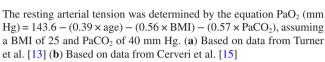


Fig. 16.2 (a) The change in static recoil of the lung measured at 60% of total lung capacity. The decrease in recoil with age is apparent. Atrophy of pulmonary parenchyma results in less elastic recoil to hold open small airways at low tidal volumes. (b) Increasing ventilation-perfusion mismatching occurring with age leads to lower resting PaO₂.



40

50

Age, years

60

70

80

110

100

90

80

70

60

50

0

20

30

В

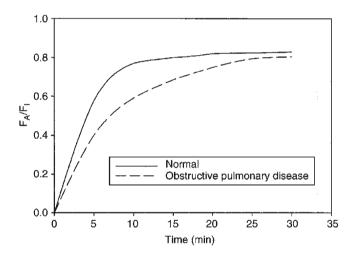


Fig. 16.3 The effect of pulmonary disease on the increase of alveolar concentration (F_A) compared with inspired concentration (F_1) versus time. The increase in F_A/F_1 is slower in subjects with pulmonary disease (Adapted from Gloyna [166]. With permission from Wolters Kluwer Health)

ratio caused by a progressive V/Q mismatch is probably offset by a lower metabolic rate, and hence lower ventilation and perfusion per kilogram body weight in the elderly. It is difficult to demonstrate any difference in anesthetic uptake attributable to age alone in normal patients (Edmond Eger, personal communication, 2005). However, patients with chronic pulmonary obstructive disease from emphysema, chronic bronchitis, or asthma will have a slower increase in the alveolar concentration (F_A) of volatile anesthetic agents (Fig. 16.3). There is no evidence that an obstruction to diffusion of anesthetic agents develops with age. Alveolar thickening from unusual disorders such as idiopathic pulmonary fibrosis or common problems such as lung congestion from cardiac failure should slow diffusion of anesthetic gases, but it is not likely that this results in a slower increase in the partial pressure of the inhalational agent in pulmonary venous blood.

Any change in V/Q mismatching has a more pronounced effect on inhalational agents with low blood/gas partition (B/G) coefficients [16]. This includes sevoflurane, desflurane, and the inorganic compound nitrous oxide (Table 16.1). Lu et al. [17] measured sevoflurane concentration in arterial and jugular venous blood samples in patients during cardiac surgery. Their study population consisted of 10 patients between the ages of 51 and 73 years who received a constant 3.5% inspired sevoflurane concentration for 1 h. It took 40 min before the concentration of sevoflurane in venous blood became equal to the arterial blood. The arterial sevoflurane concentration was also approximately 40% less than the end-tidal expired sevoflurane. Thus, the end-tidal sevoflurane concentration did not reliably reflect the parallel concentration of sevoflurane in the brain. The equilibration between arterial blood and brain tissues takes four times longer than predicted and sevoflurane uptake in the brain takes approximately 1 h [17]. Because of the changes slowing uptake, it should also be anticipated there will be slower elimination of inhalational anesthetics from altered pulmonary function [18].

Alveolar ventilation does not change with age. However, there are changes that lead to degrees of V/Q mismatching and changes in the control of minute ventilation in response to hypoxia and hypercarbia. The normal partial pressure of carbon dioxide in arterial blood is 4.6–5.3 kPa (34.5–

	Molecular	Boiling ^a	Vapor	Partition coefficient			Recovered as
Agent	weight ^{a, b} (g)	point (°C)	pressure ^{a, c}	Oil/gas ^a	Blood/gas	Fat/blood ^d	metabolites ^e (%)
Halothane ^{Br} F	197.4	50	243	224	2.3	51	11–25
$F \xrightarrow{F} F \xrightarrow{F} F$ Enflurane	184.5	57	172	98.5	1.91	36	2.4
Isoflurane F	184.5	49	238	90.8	1.4	45	0.2
Desflurane F F	168	24	669	19	0.45	27	0.02
$F \xrightarrow{F} O \xrightarrow{F} F$	200	59	157	53.4	0.60	48	5.0
-0 'N Nitrous oxide	44	-88	38,770	1.4	0.47	2.3	0

Table 16.1	Physical properties of	f inhalational agents including nitrous oxide

Note: Values are based on measurement at 37 °C unless otherwise noted For individuals aged 30–60 years "Data from Stevens and Kingston [158] bData from Eger et al. [159] cAt 20° C, in mm Hg

^dData from Eger [160]

^eData from Carpenter et al. [77]

39.8 mm Hg) in older patients [19, 20]. With advancing age, the control of ventilation is less sensitive. The normal response to hypercarbia is an increase in the minute ventilation. In young individuals, there is a profound response, about 2–5 L/min per torr carbon dioxide [21, 22]. Where the response to rebreathing carbon dioxide is 3.4 L/min in men whose average age is 26 years, the response is only 1.8 L/min in men who are about 70 years of age [23]. The likelihood of respiratory acidosis from impaired ventilation after general anesthesia is, therefore, greater but it is not documented.

The ventilatory response to hypoxia greatly diminishes with advanced age [23]. When combined with the sedative effect of inhalational anesthetics, the profoundly impaired drive to increase minute ventilation in response to hypoxia leaves the elderly patient at risk for hypoxia. This may contribute to the numerous instances of respiratory complications in the recovery period including hypoxia hypoventilation and atelectasis [24]. Therefore, less-soluble inhalational anesthetic drugs for elderly patients are reasonable choices. Transporting elderly patients with supplemental oxygen from the operating room to the postanesthesia care unit (PACU) is prudent. Generous use of supplemental oxygen and close monitoring while in the PACU are imperative.

Influence of the Aging Cardiovascular System

The major cardiovascular changes occurring with age include impaired pump function and atherosclerotic changes in the vasculature. These changes occur independently of diseases that can affect the heart and peripheral vasculature. The most common cardiovascular problems are hypertension, arteriosclerosis, atherosclerotic vascular, and coronary disease. Angina pectoris and myocardial ischemia leading to myocardial infarction are frequent myocardial events [25]. The incidence of cardiac arrhythmia increases with age, the most common conduction abnormalities being ventricular conduction defects, first degree atrial-ventricular block, atrial fibrillation, ST-T wave abnormalities, major O-wave and QS-wave abnormalities and in addition, evidence of left ventricle hypertrophy [26]. Heart failure is a common problem in the elderly, the incidence and prevalence increasing with age. The incidence of heart failure in individuals older than 65 years is increasing with 20-30 cases per 1000 persons older than 80 years of age [27, 28]. Approximately half of congestive heart failure cases occur in patients with preserved systolic function, a problem now recognized as diastolic dysfunction [29]. Diastolic dysfunction is common and is as predictive of eventual death as systolic failure. This problem is found frequently in association with coronary artery disease and ventricular hypertrophy [30]. This is likely due to aggravating subendocardial myocardial ischemia. The association of diastolic dysfunction with common cardiac disease, and its association with aging is an additional factor that may affect hemodynamic responses to fluid shifts, anesthetics, and other perioperative drugs.

Aside from being the frequent target of disease, the cardiovascular system experiences a decline in function with age. Measuring cardiac performance during exercise is often used as a surrogate for surgical stress. One general measure of cardiac function, the maximum oxygen transport or VO_{2max}, decreases at the rate of approximately 1% per year after age 30 [31–33]. It is tempting to rely on cardiac output as a way of assessing the effect of age. However, changes in cardiovascular function are variable and not easily attributed to a single cause. Cardiac output has several determinants, and, as a single index, it is not an adequate measure to understand anesthetic effects in the elderly.

In healthy older subjects, the peripheral flow of blood decreases and peripheral vascular resistance increases in comparison to younger counterparts. Physical conditioning does not alter these changes [34] (Fig. 16.4). Increasing vascular resistance may explain some decrease in cardiac output, but decreases in cardiac output may also result from decrement in the chronotropic response, systolic, and diastolic function. There is general agreement that the maximum heart rate response decreases with age. The maximum cardiac stroke volume does not change very much as a result of age alone, but it may decrease for several reasons, such as ventricular hypertrophy, stiffening of the ventricular wall, lower preload, and higher afterload. By carefully matching the physical abilities of older master athletes with younger competitive runners, Hagberg et al. [35] demonstrated that the decrease in VO_{2-max} occurring with age is attributable only to a decreased maximal heart rate. There was no change in the stroke volume and arterial-venous oxygen difference to account for lower cardiac output [35]. The influence of age on cardiac function is seen when normal subjects are stressed. The left end diastolic volume index (LEDVI) does not normally decrease with age, and exercise or stress increases LEDVI via β -adrenergic stimulation. This is the Frank–Starling mechanism and with advanced age, increasing the end-diastolic volume, and thus the stroke volume and cardiac output, compensate for diminished ability to increase the heart rate (Fig. 16.5) [36].

Cardiac output is determined by the heart rate and stroke volume. Altered uptake and distribution of inhalational anesthetic agents result when cardiac pump function decreases. Patients with decreased cardiac output have a slower systemic circulation time that is matched with a slower circulation through the pulmonary circuit. During general anesthesia, slower pulmonary circulation provides more time for volatile anesthetic agents to diffuse into the blood. Pulmonary venous blood can attain a higher partial pressure of anesthetic gas under these circumstances than anticipated. Thus, the effect of lower cardiac output is greater delivery of anesthetic drug to the myocardium and the central nervous system. Generally, this effect occurs with the more soluble anesthetics such as halothane and enflurane. The action of low cardiac output increasing uptake is attenuated by anesthetics with a lower B/G solubility. This favors the use of low-solubility agents such as desflurane and sevoflurane.

A slower systemic circulation also slows delivery of anesthetic agents to target tissues including the central nervous system (Fig. 16.6). The clinical result is a slower onset of anesthesia. However, with the most soluble inhalational agents, a lower cardiac output means arterial blood will convey a higher partial pressure of anesthetic agent to the central nervous system, and, consequently, with greater drug delivery, the anesthetic effect may be more profound. Low cardiac output in patients with cardiac disease exaggerates this effect. Volatile anesthetic agents can cause a cycle of myocardial depression leading to increased uptake, increased alveolar concentration, and further depression of cardiac output. Therefore, the potential cardiac depressant effect of volatile anesthetics is significant.

Anesthetics may decrease stroke volume by depressing contractility or slowing the rate. Bradycardia is encountered in many clinical situations and it is often a simple problem to treat. An advantage of newer volatile anesthetics is that they generally cause little change in heart rate or they tend to increase it slightly at higher concentrations (Fig. 16.7). In younger patients, tachycardia results from abrupt increases in desflurane administration above 1 minimal alveolar concentration (MAC) (Fig. 16.8). A similar but less-pronounced response also occurs with isoflurane [37]. The depression of myocardial contractility by anesthetic agents is a more important consideration. Global cardiac depression is most likely with halothane, enflurane, and to some extent, isoflurane. These drugs are more soluble in blood than either

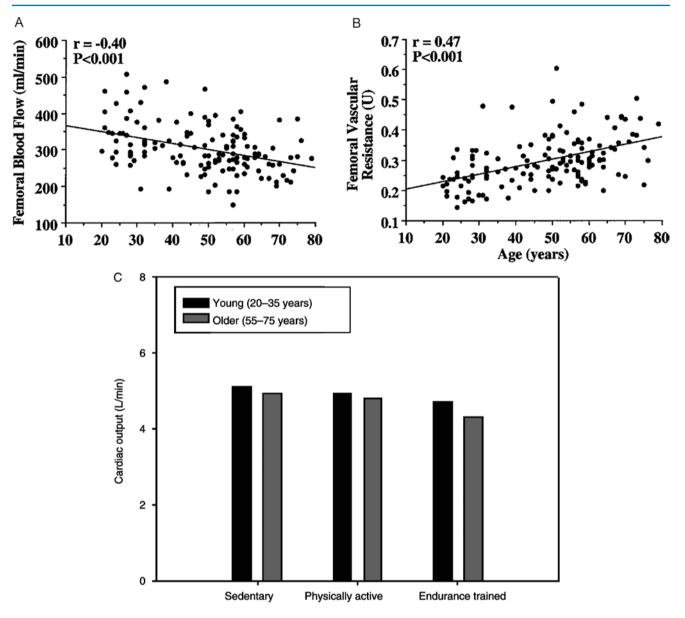


Fig. 16.4 Cardiovascular changes occurring with age in healthy male subjects. Femoral blood flow decreases (**a**) and peripheral vascular resistance increases (**b**) with age. The effect of age on these variables is not influenced by exercise conditioning. (**c**) Age-related changes in car-

diac output are minor ((a, b) Reprinted from Dienno et al. [34]. With permission from John Wiley and Sons, (c) Based on data from Dienno et al. [34])

desflurane or sevoflurane and can have a greater effect for this reason (Table 16.2).

Predicting how patients with combined pulmonary and cardiac disease will respond during general anesthesia with volatile anesthetics is difficult. Clinicians can expect slower induction and longer emergence from inhalational anesthesia. It is also likely these patients will have greater hemodynamic instability during anesthesia.

Influence of Body Composition Changes

A primary factor influencing inhalational agent pharmacokinetics is the change in body composition. These include a reduction in the skeletal muscle mass and an increase in the total body fat content [38]. Although there is considerable variation, the general trend is for an increase in the percentage of body fat (Fig. 16.9). The change in body composition is greater for men, with about 25% of their total body mass

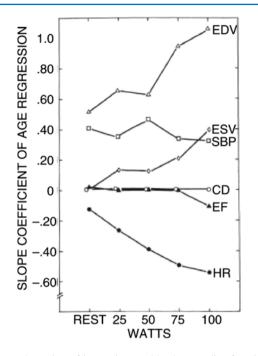


Fig. 16.5 The action of increasing workload on cardiac function as a function of advancing age. Each point is the slope of a coefficient for each physiologic parameter measured in a group of normal subjects ranging in age from 25 to 79 years. The subjects performed stationary bicycle work while hemodynamic measurements were taken and worked to the point of exhaustion. An increase or decrease in the slope coefficient with increasing workload indicates an increasing or decreasing effect of age. *CO* cardiac output, *EDV* end-diastolic volume, *ESV* end-systolic volume, *SBP* systolic blood pressure, *EF* ejection fraction, *HR* heart rate (Reprinted with permission from Rodeheffer et al. [118]. With permission from Wolters Kluwer Health)

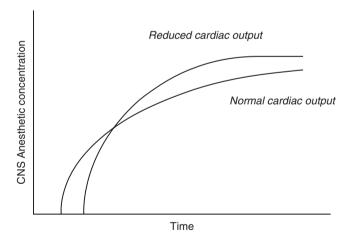


Fig. 16.6 Reduced cardiac output results in slower pulmonary circulation and allows for the diffusion of more anesthetic agent into the blood. This results in a more rapid increase in the partial pressure of agent in the blood, greater delivery to the central nervous system, and a more profound onset of anesthesia. This is more likely with the very soluble anesthetic agents. However, the onset of action may be delayed compared with patients with normal cardiac output (Adapted from Gloyna [166]. With permission from Wolters Kluwer Health)

being fat. For older women, the total body fat content averages 35% [39]. As total body fat increases with age, the proportion of total body water also decreases.

Fat tissue has a great capacity to retain lipid-soluble drugs. For those inhalational agents with greater lipid solubility, the volume of distribution increases (Tables 16.1 and 16.3). Fat acts as a reservoir for volatile agents, resulting in the accumulation of inhalational agents during maintenance and delaying emergence. Depending on many variables, including the lipid solubility of the agent, less blood flow to fat tissue than other tissues, and the duration of anesthesia, an increase in the proportion of body fat may prolong emergence. Although the changes in body fat composition are greater in men and women have a greater percent body fat at all ages, there is no indication of a gender difference with the pharmacokinetics of inhalational anesthetic agents.

The lipid-soluble drugs redistribute slowly from fat tissue so their effect may be prolonged. The loss of skeletal muscle mass has a significant impact on drug pharmacokinetics because this tissue receives a large portion of the blood supply. As the body fat content increases, a smaller part of each circulating blood volume perfuses this tissue and it diminishes the volume of distribution for the agents that are not very lipid soluble.

Most body fat resides in subcutaneous and abdominal areas. However, body fat may be heterogeneous and various anatomic fat stores may differ in their capacity to act as a reservoir for lipid-soluble drugs [40]. Subcutaneous fat that develops from excessive eating may function differently from the epicardial or mesenteric fat that is present even in very lean individuals. How this might affect the uptake and retention of lipid-soluble inhalational agents is yet to be determined.

The steady-state volume of distribution, V_{dss} , is greatest [41] for isoflurane and least with desflurane (Table 16.3). The movement of volatile agent from the central to peripheral compartments is fastest for desflurane and intermediate for sevoflurane, whereas isoflurane is the slowest. It is not just the greater solubility of isoflurane that accounts for its V_d being six times that of desflurane. Isoflurane increases blood flow to tissues such as skeletal muscle, a tissue with large storage capacity [41, 42].

The partial pressure of anesthetic permitting wakefulness, the MAC-awake value, determines the emergence from general anesthesia. The MAC-awake value for all volatile anesthetics is about one-third the MAC value. A slow, continued release of volatile agent from fat tissue can maintain a partial pressure of agent in the blood causing excessive sedation, respiratory depression, and contribute to postanesthesia delirium. This action may contribute to a greater incidence of postoperative complications and prolonged stays in the PACU.

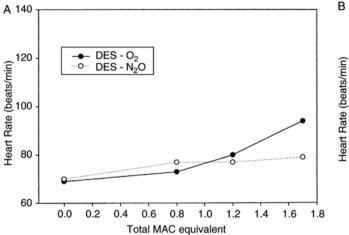
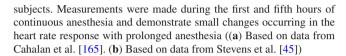
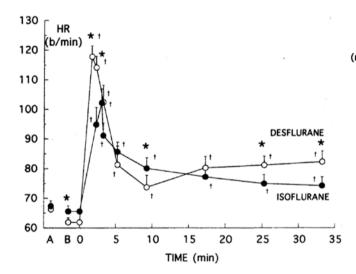


Fig. 16.7 (a) Hemodynamic effects of desflurane (DES) during controlled ventilation in young volunteer subjects. The subjects received no other drugs. *MAC* minimal alveolar concentration. (b) Hemodynamic effects of isoflurane during controlled ventilation in young volunteer





125 MAP (mmHg) 100 75 DESFLURA 50 Β Ο 10 15 20 5 25 А 30 35 TIME (min)

Fig. 16.8 A transient increase in heart rate, blood pressure, and sympathetic activity occurs with isoflurane and desflurane when the concentrations are increased rapidly to more than 1 minimal alveolar concentration. Several interventions have been described to effectively

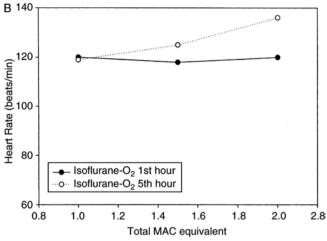
counter this occurrence, including avoiding the "over pressuring" technique. *HR* heart rate, *MAP* mean arterial pressure (Reprinted from Weiskopf et al. [37]. With permission from Wolters Kluwer Health, Inc.)

Table 16.2 The influence of halothane or enflurane on myocardial contractility, EES, in a canine model and during coronary artery bypass surgery

	Canine model			
	Halothane $(n = 7)$	Enflurane $(n = 7)$	CABG surgery	
Control	10.1 ± 0.6	15.2 ± 0.4	Control	11.5 ± 2.0
1%	6.7 ± 0.4	12.3 ± 0.6	60% N ₂ O	9.0 ± 2.2
2%	4.2 ± 0.5	9.3 ± 0.5	0.5% halothane	8.1 ± 2.4

Based on data from Van Trigt et al. [161]

 E_{ES} (mm Hg/mm) = slope of the end-systolic pressure-diameter relation, a sensitive index of contractility unaffected by volume loading; *CABG* coronary artery bypass graft



А

100

80

60

40

Total body fat (kg)

Fat-free Mass (kg)

Body fat (%)

·O···

Fig. 16.9 The change in body composition occurring with age. Data from the Fels Longitudinal Study including men (**a**) (n = 102) and women (**b**) (n = 108) for subjects not selected because of any known criteria related to body composition. Women have a greater percent of body fat than men at all ages. Men have an increasing trend in body weight and percent body fat. Women tend to lose fat-free mass as they become older (Based on data from Guo et al. [38])

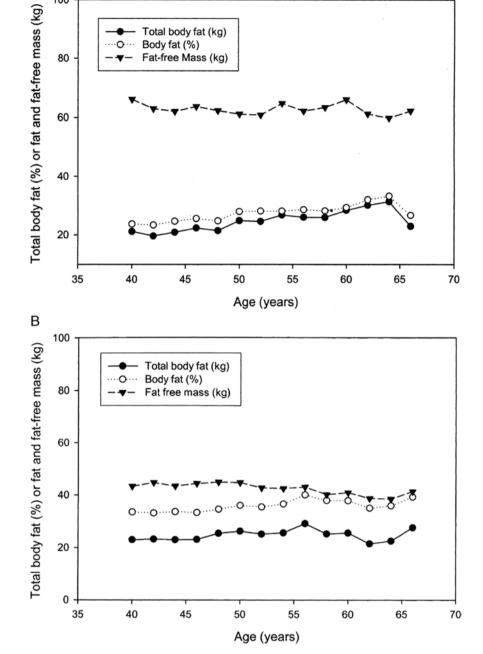


Table 16.3	Pharmacokinetics of newer volatile anesthetic agents
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Agent	MAC	B/G ^a	FGF ^b	k_{12} (min ⁻¹)	$Cl_{12}^{c}(mL_{vapor} kg^{-1} min^{-1})$	$v_{dss}{}^{c}\left(mL_{vap}\!/kg_{bw}\right)$
Sevoflurane	2.1	0.69	2	0.117 (0.070-0.344)	13.0 (9.8–22.4)	1748 (819–8997)
Isoflurane	1.2	1.4	<1	0.158 (0.065-0.583)	30.7 (15.9-38.7)	4285 (1509–9640)
Desflurane	6	0.42	<1	0.078 (0.029-0.186)	7.0 (4.4–11.1)	698 (408–1917)

MAC minimal alveolar concentration, B/G blood gas partition, k_{12} = microconstant for transport from central to peripheral compartment, Cl_{12} = transport clearance from central to peripheral compartment, V_{dss} = total volume of distribution during steady state ^aData from Eger [160]

^bData from FDA Product Prescribing Information: Desflurane and Sevoflurane

^cData from Wissing et al. [41]

The increasing proportion of body fat suggests an advantage with the less-soluble volatile anesthetic drugs. Emergence from general anesthesia has been studied by comparing desflurane and isoflurane anesthesia in elderly patients. Compared with isoflurane anesthesia, signs of early recovery and endotracheal tube removal occurred in approximately half the time with desflurane. Emergence was also faster than with intravenous anesthesia [43]. For short procedures (less than 2 h), patients reached signs of early recovery and experienced endotracheal tube removal sooner with desflurane compared with [44] sevoflurane.

Influence of Renal Changes

Renal atrophy occurs with age, mainly through the loss of cortical nephrons. The kidney loses about 20% of its mass by age 80, and functional changes accompany renal atrophy. Most subjects experience a decrease in renal blood flow, glomerular filtration rate (GFR), and creatinine clearance. The reduction in renal blood flow probably results from cardiovascular changes in addition to renal changes [45]. However, the Baltimore Longitudinal Study of Aging showed that a decline in the GFR is not inevitable because 30% of healthy individuals have no decrease in GFR with age [46]. The plasma creatinine level varies with the muscle mass and with age-related changes in body composition accompanying the aging process. Thus, it is better to evaluate renal function in the elderly using the Cockroft-Gault formula $[(140 - age) \times weight (kg)/Cr \times 72]$ than simply using the plasma creatinine value [47] (Fig. 16.10).

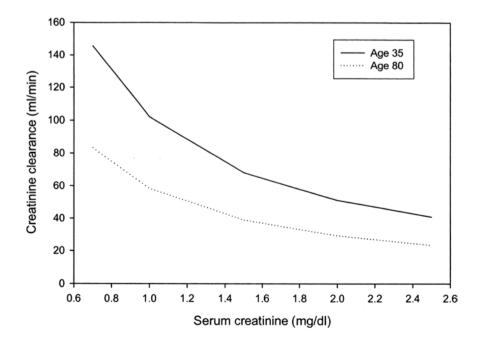
All volatile anesthetic agents in clinical use are fluorinated ether compounds. The constellation of renal changes may place the older patient at greater risk for [48] fluoride toxicity (Table 16.1). Inorganic free fluoride ions form during metabolism of these agents by the hepatic cytochrome P-450 enzyme system. Toxic levels of free fluoride produce a high output, vasopressin-resistant form of acute renal failure [49]. This disorder was first reported with methoxyflurane in 1966.

The only inhalation agents used today that can produce enough fluoride to be of concern are enflurane, isoflurane, and sevoflurane [50–52]. The threshold fluoride level for causing mild defects in renal concentrating ability is 50 μ mol/L [53]. Experiments with cultured collecting duct cells indicate mitochondria may be the target of the free fluoride ion [54].

Whether fluoride toxicity results from the use of modern inhalational anesthetics is in doubt. Concern surrounded the use of sevoflurane because about 5% of it is metabolized by the cytochrome P-450 2E1 isoform [55]. Of that, 3.5% appears in the urine as free fluoride ion [56]. This is less than the fluoride production from methoxyflurane metabolism but more than that seen with either enflurane or isoflurane.

The likelihood of fluoride toxicity has been questioned because fluoride levels greater than 50 μ g/L were reached in studies comparing sevoflurane and enflurane administration in humans, yet they did not demonstrate nephrotoxicity [57]. The mean fluoride level in patients receiving sevoflurane was 47 μ mol/L, twice the 23 μ mol/L level in patients that received prolonged enflurane anesthesia. More than 40% of subjects having prolonged sevoflurane anesthesia had plasma

Fig. 16.10 The relationship between serum creatinine and creatinine clearance by age. The glomerular filtration rate (GFR) decreases most individuals after age 30 but a decline in GFR is not inevitable. The graphs are standardized for a 70 kg male with values calculated using the Cockroft–Gault formula (Based on data from Hughes et al. [39])



fluoride levels greater than 50 μ mol/L, with no impairment of renal concentrating ability. The results of this study should be cautiously extrapolated to the elderly because it included only young volunteers in their mid-twenties [58]. Neither enflurane nor halothane produced a further decrease of renal function in patients with moderate renal insufficiency [59]. Enflurane is now used infrequently for general anesthesia. There are no clinical reports that actively assert that enflurane should be avoided in elderly patients with renal insufficiency.

A toxic fluoride threshold more likely will be met with prolonged exposure to isoflurane than halothane. The peak plasma level of fluoride occurs 24 h after an average 10-h administration of isoflurane. This is equivalent to 19.2 MAC hours of isoflurane exposure. With this level of exposure, 40% of patients studied had fluoride levels slightly greater than 50 μ mol/L. In contrast, similar exposure to halothane produced lower fluoride levels with the highest plasma levels occurring at the end of the surgical cases. Among elderly patients with renal insufficiency, no further deterioration of renal function resulted with the use of isoflurane, enflurane, or sevoflurane anesthesia [60]. Desflurane poses very little risk to patients with renal insufficiency because so very little of it is metabolized [61].

Sevoflurane breaks down in the alkaline environment of the carbon dioxide absorber to form fluoromethyl-2,2difluoro-1-(trifluoromethyl)vinyl ether, or Compound A. This happens particularly at low total gas flows. Like free fluoride ions, compound A is also nephrotoxic. The production of Compound A is increased with greater production and absorption of carbon dioxide because the degradation of sevoflurane increases with absorber temperature [58–64]. The combination favoring production of Compound A includes not only increased CO₂ absorption but also absorber temperature, decreased CO₂ washout, and high levels of sevoflurane [23, 65, 66]. Compound A is clearly nephrotoxic in the laboratory, but it is not certain whether any instances of renal failure occurred from using sevoflurane. In patients with normal renal function and ranging in age from 30 to 69 years, Compound A accumulated during anesthesia with 1 LPM gas flows. Yet, there was no difference detected in clinical or biochemical markers of renal function when those patients were compared with subjects receiving isoflurane anesthesia [67]. Compound A does not accumulate in breathing circuits or carbon dioxide absorbers when gas flows are 5 L/min, but because of the potential for Compound A formation, sevoflurane is not recommended for use at less than 2 LPM fresh gas flow [68]. Nevertheless, no differences in biochemical markers were noted among patients receiving sevoflurane at low-flow (1 L/min), high-flow (5-6 L/min), or low-flow isoflurane anesthesia, and no evidence of renal

toxicity exists [69]. Furthermore, in older patients with moderately impaired renal function, sevoflurane anesthesia does not cause apparent injury to the renal tubules [70], and low-flow anesthesia with sevoflurane does not result in any greater change in blood urea nitrogen, creatinine, or creatinine clearance than isoflurane [71].

Influence of Hepatic Changes

There is a similar atrophy of the liver that is accompanied by a reduction in hepatic blood flow [72–74]. Decreased hepatic blood flow results in diminished metabolism of drugs that rely on hepatic clearance. The decrease in hepatic blood flow seems responsible for the decreased hepatic metabolism of drugs and not changes in hepatic enzyme activity [75].

The newer inhalational agents are not extensively metabolized. Of all the volatile agents, halothane is the most extensively transformed with approximately 20% of it metabolized in the liver [76]. The other agents in common use are metabolized to a much lesser extent. Approximately 5% of sevoflurane, 2.4% of enflurane, 0.2% of isoflurane, and 0.02% of desflurane are metabolized [16, 77–79] (Table 16.1). Metabolism of halothane, isoflurane, and desflurane produces trifluoroacetic acid. The amount of this metabolite produced is lowest with desflurane [76, 80–83].

The hepatic-function changes associated with aging are probably important only for halothane and sevoflurane because the other agents undergo only minimal transformation. The loss of hepatic tissue with age may be associated with decreased metabolism of the volatile agents, but this is not documented. If decreased metabolism of these drugs occurs, it is probably not clinically significant.

Volatile anesthetic agents have a variable effect on liver function. Sevoflurane decreases production of fibrinogen, transferrin, and albumin in cultured hepatocytes more than exposure to halothane, isoflurane, or enflurane does [84]. However, enflurane causes greater depression of albumin synthesis than sevoflurane. The effects of desflurane on hepatic synthesis are not known. It is not anticipated that it would have much effect because so little of it is metabolized [85].

Many drugs bind to plasma proteins, and several intravenous anesthetic drugs are carried in the blood bound to plasma proteins. Albumin is a carrier for many drugs, and low blood concentrations of albumin are frequently encountered in elderly patients. This probably contributes to the exaggerated effects of many drugs in older subjects because of the greater fraction of unbound free drug. There is no evidence suggesting that volatile agents rely on protein binding for transport or that the increased sensitivity to volatile anesthetics works through this mechanism.

The Pharmacodynamics of Inhalational Agents in the Elderly

The introduction of halogenated ethers with progressively lower solubility characterizes the era of modern agents. As the solubility of newer agents approaches that of nitrous oxide, the result is a more rapid uptake and faster elimination of the drug. Theoretically, low solubility and faster uptake also allow greater control of anesthetic blood levels during the maintenance phase of anesthesia. Faster elimination with low-solubility agents should provide for a rapid emergence from anesthesia. Inhalational agents used for general anesthesia include isoflurane, sevoflurane, desflurane, halothane, and enflurane. For practical purposes, the first three warrant most consideration because they represent the majority of volatile agents used. The properties of the inhalational agents are found in Table 16.1.

Aging and the MAC

The classic expression of pharmacodynamic effect for volatile anesthetic agents is the MAC. MAC is the minimal alveolar concentration of a volatile drug at 1 atm that prevents movement in 50% of subjects following surgical incision [86]. The concentrations of volatile agents defined by MAC values are usually not enough for adequate anesthesia during surgical cases. Frequently, about 1.3 times MAC, or essentially an ED₉₅ dose of anesthetic, is needed [87].

For adult subjects, the MAC is 1.15% for isoflurane, 6% for desflurane, and 1.85% for sevoflurane. As patients age, MAC decreases for all the volatile drugs, generally occurring at approximately 6% per decade [88]. The decrease in drug requirement does not follow a linear relationship but accelerates after 40-50 years of age. This phenomenon also applies to intravenous anesthetic drugs in which the pharmacokinetics of injected drugs changes substantially with age [89]. Guedel [90] was the first to note that inhalational anesthetic requirements decrease with age. This has subsequently been documented for halothane [91], isoflurane, [92] enflurane, desflurane [93, 94], and sevoflurane [95]. The mathematic relationship of MAC, age, end-expired concentration of anesthetic agent, and the contribution by nitrous oxide has been determined [96]. A nomogram for estimating agerelated changes in MAC is available (Fig. 16.11).

Martin et al. [97] reviewed the use of the most common anesthetic drug combinations for general anesthesia. When controlling for the synergistic interaction of intravenous and inhalational agents, the authors demonstrated a decrease in drug requirements for 80-year-old patients. The decrease was not the same for drugs of different classes. The utilization of intravenous drugs decreased 30–50%, whereas the requirement for isoflurane decreased only 11–26% (Fig. 16.12). Although older patients do not require as much anesthetic drug, there is little known that explains the decreased requirement of inhalational anesthetics.

MAC is a value that provides a way to compare the potency of inhalational anesthetic agents on a specific endpoint. Depth of anesthesia is one endpoint of interest. Other endpoints have received less attention in the aged patient. This is generally one third the MAC value except in the case of halothane, for which MAC_{awake} is 0.55 MAC. MAC_{awake} decreases with age [98]. The MAC-BAR is the MAC of agent that inhibits a sympathetic nervous system response such as tachycardia or hypertension when subjects are stimulated. It is expressed as a multiple of the MAC (Table 16.4). However, there is no information on the concentration of volatile agent needed to attenuate autonomic reflexes (MAC-BAR) with increasing age.

There are several possible explanations of how age decreases the inhalational anesthetic requirements. Several changes contribute to this change: an increase in body fat; reductions in metabolism, reduced cardiac output, decreased drug clearance; and atrophy of organ systems, particularly the central nervous system [99]. A combination of factors probably accounts for the decreased dose of hypnotic drugs needed for loss of consciousness and shifting the electroencephalogram pattern [100–102]. Several factors associated with increasing and decreasing MAC are listed in Tables 16.5 and 16.6. Factors not associated with a change in MAC are listed in Table 16.7.

Drugs frequently used in the elderly influence the effective dose of volatile agents. These include calcium channel blockers [103] and clonidine [104]. Some drugs may affect MAC by depletion of neurotransmitters [105, 106]. Benzodiazepines and opioids have an additive effect with volatile anesthetic agents [47].

Slow emergence and prolonged sedation in the recovery room are usually regarded as detrimental for elderly patients. Postoperative sedation occurs in approximately 10% of elderly general surgery patients. Among elderly patients, the incidence of postoperative sedation after general anesthesia can be as high as 61% for those having emergency surgery. Intraoperative hypotension and anesthetic drugs contribute to postoperative sedation and longer hospitalization [107].

The physical properties of the inhalational anesthetics contribute to the speed of action and resolution of these drugs. The blood level of agents with low blood/gas and blood/lipid solubility changes rapidly in response to varying the administered dose. With emergence from general anesthesia, the resolution of the hypnotic effect resolves faster with these agents. Faster emergence from general anesthesia is an important way to minimize postoperative complications in the elderly. Reports indicate faster emergence from anesthesia and shorter time spent in the PACU with desflurane [32].

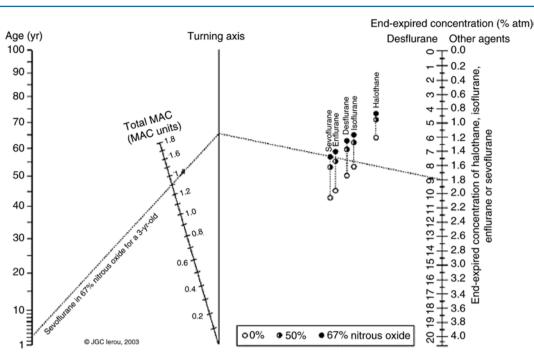


Fig. 16.11 Nomogram relating age, total minimal alveolar concentration (MAC) expressed in MAC units, and end-expiratory concentrations of volatile agent and nitrous oxide. A result is found by drawing two straight lines. Example (*dotted lines*): if the measured end-expired concentrations of sevoflurane and nitrous oxide are 1.8% and 67% (at

1 atm), respectively, then the total age-related MAC is 1.3 in a 3-yearold. Reverse example: a total MAC of 1.3 in a 3-year-old, when using sevoflurane and nitrous oxide 67% in oxygen, requires an end-expired sevoflurane concentration of 1.8% (Reprinted from Lerou [96]. With permission from Oxford University Press)

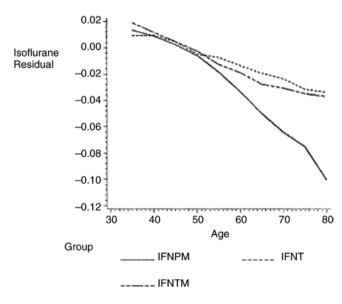


Fig. 16.12 The trend in reduction of isoflurane concentration with age. Compared with maximum values at age 30, there is an 11–16% reduction in isoflurane requirement by age 80. *IFNTM* isoflurane, fentanyl, nitrous oxide, thiopental, midazolam, *IFNPM* isoflurane, fentanyl, nitrous oxide, propofol, midazolam, *IFNT* isoflurane, fentanyl, nitrous oxide, thiopental (Reprinted from Martin et al [97]. With permission from Elsevier)

Neurodegenerative Changes in the Elderly and Inhalational Agents

Dementia in the elderly is common clinical challenge. The incidence of one form of dementia, Alzheimer's disease, is estimated to be 50% of the population greater than 85 years. Dementia can result from several causes, is sporadic and frequently idiopathic, but the disease process is often associated with cerebral atrophy. The main causes of dementia are Alzheimer's disease, dementia that is vascular in origin (i.e. multi stroke dementia), and occurring in association with Parkinson's disease. Deterioration of cognitive function is common to all form of the disease and the Minimum Mental State Examination (MMSE) is the research tool commonly used to assess cognitive changes in clinical studies [108]. The onset of dementia is insidious, slowly progressive and is associated with reduced life expectancy. Survival is highly variable but reported to range from 3 to 13 years from the time of diagnosis. However, about 13% of patients die within 2 years from the time of diagnosis, principally those with the non-Alzheimer's types of dementia [109].

The characteristic neuropathologic lesions found in Alzheimer's disease are extracellular plaques of beta amyloid protein (amyloid-A β) and the intracellular accumulation of tau protein which form neurofibrillary tangles. While there

	MAC [atm, (%)]	MAC [atm, (%)] at various ages ^a				MAC DAD			
	2-5 years ^b	36-49 years ^b	65 years ^b	MAC _{awake}	MAC _{awake} /MAC	MAC-BAR			
N ₂ O		1.04		0.68	0.64	-			
Halothane				0.0041	0.55	1.3			
Isoflurane	0.0160 (1.6)	0.0115 (1.15)	0.0105 (1.05)	0.0049	0.38	1.3			
Desflurane	0.0854 (8.54)	0.0600 (6)	0.0517 (5.17)	0.025	0.34	1.45			
Sevoflurane	0.0250 (2.5)	0.0185 (1.85)	0.0177 (1.77)	0.0062	0.34	2.24			

Table 16.4 Clinical properties of volatile anesthetic agents in routine use

MAC minimal alveolar concentration

^aData from Eger et al. [159]

^bVolatile agent delivered in oxygen without nitrous oxide

^cValues for subjects aged 20–60 years

^dData from Stevens and Kingston [162]

Table 16.5 Factors that increase minimal alveolar concentration

Increased central neurotransmitters
Monoamine oxidase inhibitors
Acute dextroamphetamine use
Cocaine ingestion
Ephedrine
Hyperthermia
Chronic ethanol abuse
Hypernatremia
Based on data from Ebert and Schmid [163]

may be a genetic contribution to this onset of Alzheimer's disease, contribution of environmental, diet, and the contribution by medical problems is thought to play a role in the pathogenesis of the disorder. Because much of the population have been exposed to general anesthesia with inhalational anesthetic agents at some time in their lifetime, and with the increasing likelihood of surgery in older individuals, the role of inhalational anesthetics promoting the deposition of amyloid protein in neurons is of concern. Halothane and isoflurane have been shown to enhance the dose-dependent oligiopolymerization of amyloid- β protein. This action is specific for the amyloid protein, and these inhalational agents accelerate this reaction in vitro at concentrations that are achieved in clinical practice [110].

Because geriatric patients will more likely develop additional cognitive impairment after surgery and anesthesia, understanding how detrimental influences can be minimized is vitally important. Inhalational agents have not shown a detrimental effect on cerebral oxygenation when compared to other anesthetic techniques. No difference in cerebral oxygenation could be detected when comparing sevoflurane and nitrous oxide anesthesia to spinal anesthesia [111]. When comparing to intravenous anesthesia older patients require slightly more time for early phase emergence (time to eye opening and time to endotracheal extubation) when sevoflu-

Table 16.6 Factors that decrease minimal alveolar concentration

Metabolic acidosis
Hypoxia (PaO ₂ < 38 mm Hg)
Hypotension (mean arterial pressure < 50 mm Hg)
Decreased central neurotransmitters (alpha methyldopa, reserpine,
chronic dextroamphetamine use, levodopa)
Clonidine
Hypothermia
Lithium
Hypoosmolality
Pregnancy
Acute ethanol use
Ketamine
Pancuronium
Physostigmine (10 times clinical doses)
Neostigmine (10 times clinical doses)
Lidocaine
Opioids
Opioid agonist-antagonist analgesics
Barbiturates
Chlorpromazine
Diazepam
Hydroxyzine
Δ -9-tetrahydrocannabinol
Verapamil
Based on data from Ebert and Schmid [163]
L 3

rane is the primary anesthetic. Postoperative mental status exam results are lower as the sevoflurane exposure is greater, and S100- β , a protein biomarker of acute brain injury when present in the circulation, is elevated when patients exposed to sevoflurane, but not with propofol anesthesia [112]. When comparing desflurane and sevoflurane in patients over 65 years, the early phase emergence was faster when patients received desflurane, but the postoperative MMSE scores were not different [113].

 Table 16.7
 Factors that do not reduce minimal alveolar concentration

Duration of anesthesia
Type of stimulation
Gender
Hypocarbia (Paco ₂ to 21 mm Hg)
Hypercarbia (Paco ₂ to 95 mm Hg)
Metabolic alkalosis
Hyperoxia
Isovolemic anemia (hematocrit to 10%)
Arterial hypertension
Thyroid function
Magnesium
Hyperkalemia
Hyperosmolality
Propranolol
Isoproterenol
Promethazine
Naloxone
Aminophylline
Based on data from Stevens and Kingston [164]

Based on data from Stevens and Kingston [164]

Cardiovascular Actions of Inhalational Agents in the Elderly

The elderly patient's heart and vascular system are anatomically and functionally different from younger patients. The most striking are a decrease in the maximum heart rate response to exercise, decreased sensitivity to catecholamines, increased pulmonary artery, and left ventricular diastolic filling pressures [114–117]. Determining whether these changes are a direct result of aging and if they can be modified are current issues. Both mechanisms of aging in the cardiovascular system and lifestyle undoubtedly have a role in these changes [118].

The physiologic response of elderly patients during anesthesia must be evaluated carefully because impressions about how elderly patients will respond may be incorrect. For example, Joris et al. [119] found that cardiac index decreases significantly in young patients when abdominal insufflation impairs venous return to the right side of the heart. Because cardiovascular changes inevitably occur with age, it is reasonable to expect greater hemodynamic changes in elderly patients. However, the response of elderly patients may be better than expected. In patients over age 75 years, the cardiac function decreased with induction of general anesthesia with isoflurane and nitrous oxide. But during laparoscopic cholecystectomy, the cardiac performance increased and blood pressure returned to preanesthetic levels with the onset of surgery. Surprisingly, elderly patients tolerated the decreased preload and increased afterload from abdominal insufflation rather well [120].

Hemodynamic changes during general anesthesia in sicker American Society of Anesthesiologists (ASA) physical status 3 and 4 patients are similar to changes in healthier ASA 1 and 2 patients [121–127]. Inhalation anesthesia produces a dose-dependent decrease in blood pressure and depression of the cardiovascular system [128–131]. Volatile anesthetics reduce blood pressure by reducing cardiac output and vasodilatation.

Inhalation anesthetics affect cardiac systolic function. Depression of myocardial contractility in the elderly varies with the inhalational agent. Isoflurane does not maintain the cardiac output in older patients as it does in younger individuals during anesthesia [130]. The addition of nitrous oxide to isoflurane helps maintain the cardiac index; however, its ability to maintain myocardial contractility is inconsistent. There are reports suggesting nitrous oxide both helps maintain [132] and depresses [133] myocardial contractility when combined with halothane.

Inhalational anesthetics also affect diastolic function. Myocardial relaxation has two components: an energydependent active component and a passive component, influenced by myocardial stiffness. In patients over the age of 60, halothane and isoflurane decrease the early, energydependent component of left ventricle relaxation, and the effect is greater with isoflurane [134]. Volatile anesthetic drugs may improve diastolic dysfunction by resulting in a shorter isovolumic relaxation time and higher peak diastolic velocity measured at the mitral annulus. This effect is not seen during propofol anesthesia. The cardiac status of the elderly patient is a significant factor in determining the response to inhalational anesthetics [135]. For instance, healthy elderly surgical patients with well-controlled hypertension tolerate inhalational induction of general anesthesia with sevoflurane. Whether receiving sevoflurane as a rapidly delivered bolus (8% for 3 min) or in a graded manner (8% initially with 2% incremental decreases until reaching 2%), patients with good pump function tolerate the induction with no change in heart rate, no electrocardiographic evidence of ischemia, and moderate decreases in blood pressure. The decrease in blood pressure when using incremental decreases of sevoflurane compared with maintaining the same concentration throughout the induction was less than that encountered when using low-dose sevoflurane and propofol in combination [136].

Blood pressure decreases significantly with the administration of inhalational anesthetics to patients with diminished cardiac function [137]. In patients with congestive heart failure, blood pressure and cardiac index decrease during isoflurane anesthesia. The decrease is greater with halothane in those patients with poor left ventricle function [138]. The catecholamine blocking effect of the inhalational agents may have a role in the hypotension encountered in these settings.

The inhalational anesthetics have a variable effect on heart rate. Isoflurane decreases systemic blood pressure in both young and old subjects. However, isoflurane decreases the cardiac index and heart rate in elderly subjects whereas it increases the heart rate and leaves the cardiac index unchanged in young individuals. Thus, isoflurane seems to maintain the cardiac index in younger patients through increases in heart rate whereas this does not happen in older patients. Sevoflurane produces a dose-dependent increase in heart rate when given to normal, healthy volunteers [139]. In contrast, the heart rate shows no significant change during induction with either 4% or 8% sevoflurane [140]. Halothane and enflurane have little effect on heart rate in elderly patients [141]. There is no difference in the heart rate during the initial period after induction of anesthesia when using halothane. With isoflurane anesthesia, elderly patients have a lower heart rate compared with younger subjects [130, 142].

Inhalational anesthetics also influence the cardiovascular system indirectly through actions on the autonomic nervous system. Rapid increases above 1 MAC in the inspired concentration of isoflurane and desflurane trigger transient sympathetic stimulation. There is a brief period of hypertension and tachycardia that is more pronounced with desflurane [37]. This action is apparently mediated through rapidly adapting airway receptors. Fentanyl and alpha- and beta-adrenergic blocking drugs easily block the effect [143, 144]. Although this phenomenon was studied in subjects in their early twenties, elderly patients have a higher state of sympathetic nervous system activity and it is likely this action may be more pronounced.

Many anesthetic drugs affect the QT interval, the measure of ventricular depolarization and repolarization. Advancing age is also a common factor promoting drug induced QT prolongation [145]. Examining the effect of age on the QT interval in patients receiving sevoflurane anesthesia, older patients (70+ years) had a significantly prolonged corrected QT (QTc) interval compared to younger subjects (20-69 years) [146]. In a prospective analysis of nearly 500 elderly patients for noncardiac surgery, 80% of study subjects had QTc prolongation while 18% showed decreases in QTc. Increases of more than 30 msec were attributed to isoflurane in 54% of patients, while 40% were attributed to nitrous oxide, 39% to sevoflurane, and 38% with desflurane anesthesia [147]. In another prospective study, different types of anesthesia were used in patients 61-75 years undergoing transurethral prostatic resection. The QTc was prolonged in more than half the patients under general anesthesia. While the study did not define a protocol for general anesthesia, most patients received sevoflurane or desflurane for maintenance and experienced QTc prolongation between 30 and 60 msec [148].

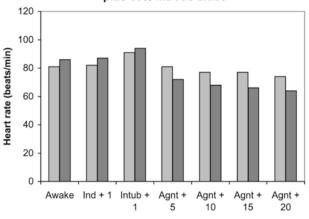
Inhalational anesthetics may have a delayed inhibition of hemodynamic control. Patients having a carotid endarterectomy with isoflurane anesthesia required more phenylephrine for blood pressure support and needed more labetalol during emergence to manage hypertension than did patients receiving propofol for general anesthesia. More significantly, although there was no difference in hemodynamic stability between patients anesthetized with isoflurane or propofol, patients anesthetized with isoflurane experienced significantly more frequent myocardial ischemia [149].

Volatile anesthetics typically cause peripheral vasodilatation. The expected consequence is greater blood flow if cardiac output can be maintained or increased. However, there is a distinct, age-related difference in peripheral blood flow between young (18-34 years) and healthy elderly (60-79 years) subjects during the induction of general anesthesia. When receiving either isoflurane or halothane in combination with 66% nitrous oxide, there is a slight difference in changes of heart rate or mean blood pressure between the age groups. The perfusion of skin and muscle, assessed by forearm blood flow, decreases along with the mean arterial blood pressure during anesthesia with halothane, and there is no age-related difference. However, with isoflurane anesthesia, the peripheral perfusion is maintained in young patients even though the blood pressure decreases whereas the perfusion decreases in the elderly (Fig. 16.13) [150].

Assessing beneficial or detrimental actions of volatile anesthetics on the aged cardiovascular system requires evaluating both intraoperative effects and the postoperative outcome. Sevoflurane may protect against myocardial ischemia and preserve cardiac function better than propofol [151, 152]. Sevoflurane anesthesia was shown to preserve cardiac function in minimally invasive, off-pump coronary artery graft surgery by comparing cardiac performance before and after clamping of the left anterior descending coronary artery [153]. When compared to propofol anesthesia both desflurane and sevoflurane preserve left ventricular function after cardiopulmonary bypass, and postoperatively following coronary artery bypass surgery in comparison to propofol anesthesia [154, 155]. When used as primary anesthetics in cardiopulmonary bypass surgery desflurane and sevoflurane are also associated with shorter ICU length of stay [156]. A beneficial effect is also seen when continuing sevoflurane into the immediate post-operative period. Soro et al. demonstrated lower cardiac troponin I levels and shorter length of stay when patients are sedated with sevoflurane rather than propofol. Their results also suggested greater hemodynamic stability and less reliance on vasopressor agents [157].

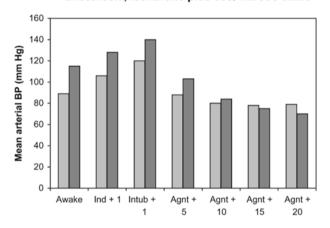
Gaps in Our Knowledge

Much of the clinical literature on inhalational anesthetic agents during the past decade focused on trying to demonstrate the superiority of one agent over another. The clinical issue is not that one agent is clearly better than another in all instances. Each agent can control the response to surgical stimulation during general anesthesia. The issues that matter are which drug is best, given the disease or pathophysiology

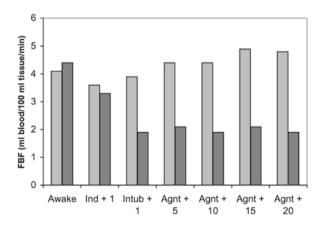


Heart rate during induction of anesthesia, isoflurane plus 66% nitrous oxide

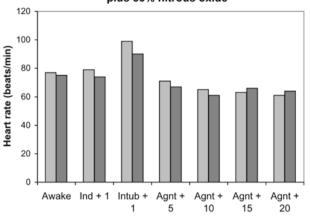
Mean arterial blood pressure during induction of anesthesia, isoflurane plus 66% nitrous oxide



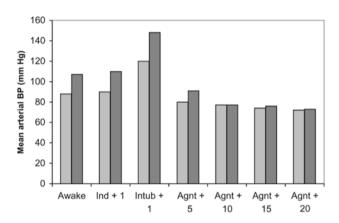
Forearm blood flow during induction of anesthesia, isoflurane plus 66% nitrous oxide



Heart rate during induction of anesthesia, halothane plus 66% nitrous oxide



Mean arterial blood pressure during induction of anesthesia, halothane plus 66% nitrous oxide



Forearm blood flow during induction of anesthesia, halothane plus 66% nitrous oxide

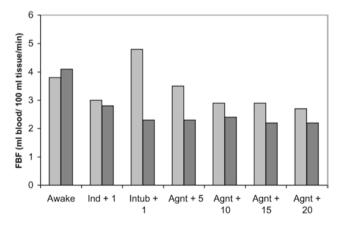


Fig. 16.13 Heart rate, mean arterial blood pressure, and forearm blood flow measured following the induction of general anesthesia in healthy young and elderly subjects. Patients received isoflurane (0.8-1.2%) or halothane (0.7-1.0%) and nitrous oxide (66%) after induction with etomidate and endotracheal intubation. Little difference in the change of heart rate or blood pressure was found between subject groups.

Forearm blood flow decreased in older and younger patients receiving halothane whereas it was much greater in young patients receiving isoflurane. Mean values are shown. *Light gray* bars = young (18–34 years), *dark gray* bars = elderly (60–79 years). Time units are in *minutes* (Based on data from Dwyer and Howe [150])

of the patient, and to what degree do we suppress consciousness and autonomic responses. The growing interest in the relationship of depth of anesthesia to long-term survival raises the possibility that we should use cardiovascular drugs as adjuncts to control heart rate and blood pressure.

Because of the limited number of publications describing how age affects anesthesia, extracting age-related data from studies that compare intravenous and inhalational agents is useful. In reviewing the anesthesia literature of the past decade, it is apparent there is a growing interest in the relationship between aging and general anesthesia. However, the limited knowledge regarding the influence age has on anesthesia is a cause for concern.

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Intravenous Sedatives and Anesthetics

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Introduction

The use of hypnotic agents in the perioperative period can range from light sedation in a nonoperating room (OR) procedural suite or an intensive care unit (ICU) to general anesthesia in the OR. While the intravenous medications used to induce sedation or anesthesia in the elderly population are typically the same as those used in the young, the doses that are needed can significantly vary because of alterations in pharmacokinetics (PK) and pharmacodynamics (PD) changes with aging. As such, this chapter will present the uses as well as cautions regarding the administration of propofol, thiopental, midazolam, ketamine, dexmedetomidine, and etomidate. Each intravenous hypnotic agent will be discussed, including the age-related effect on the PK/PD of each medication and current knowledge about appropriate dosing in the elderly population.

Propofol

Propofol was first investigated in Europe in the 1980s. Initially, the drug was suspended in a solvent that caused anaphylactoid reactions in some patients. It was reformulated in a different preparation and since then has gained widespread use. Owing to its quick onset of action, fairly predictable dose response, and quick termination of action, propofol has become the most widely used drug for intravenous induction of general anesthesia [1].

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Currently, propofol is the focus of a tremendous amount of research in target-controlled infusion techniques, both in the OR and in the non-OR anesthesia.

Pharmacology: Structure/Action

Propofol (2,6-diisopropylphenol) is a hypnotic drug of the class of alkylphenols that principally works at the gammaaminobutyric acid A (GABA_A) receptor site in the central nervous system (CNS) [2, 3]. Propofol is composed of a phenol ring with two isopropyl groups attached to it. It is not water soluble and is thus prepared in an oil-water emulsion consisting of soybean oil, egg lecithin, and glycerol [4]. This preparation is important because it can support the growth of bacteria, even though it contains disodium edetate to retard bacterial growth. Owing to this unique preparation, propofol is not considered to be antimicrobially preserved under United States Pharmacopeia specifications. Thus, the current recommendations are that sterile technique should be used when handling and administering this drug, as for all intravenous anesthetics, and that any propofol withdrawn from a vial should be used within 6 h and any vial that is spiked and used as an intravenous infusion should be completely used within 12 h. Any amount remaining after these durations should be discarded [5].

Pharmacodynamics

Central Nervous System Effects

Propofol has favorable effects on CNS parameters, as it lowers cerebral metabolic rate of oxygen (CMRO₂), cerebral blood flow (CBF), and intracranial pressure (ICP) (Table 17.1) [6, 7]. If a large bolus is given, propofol does have the ability to lower the mean arterial pressure (MAP) considerably, possibly lowering cerebral perfusion pressure (CPP) below a critical level (<50 mm Hg). This latter

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	Cardiovascular	a	Respiratory ^a		Cerebral ^a		
Agent	HR	MAP	Vent	B'dil	CBF	CMRO ₂	ICP
Propofol	0/↓↓	$\downarrow\downarrow\downarrow\downarrow$	$\downarrow\downarrow/\downarrow\downarrow\downarrow$?	$\downarrow\downarrow\downarrow\downarrow$	$\downarrow\downarrow\downarrow\downarrow$	$\downarrow \downarrow \downarrow \downarrow$
Thiopental	<u> </u>	$\downarrow\downarrow/\downarrow\downarrow\downarrow$	$\downarrow\downarrow/\downarrow\downarrow\downarrow$	\downarrow	$\downarrow\downarrow\downarrow\downarrow$	$\downarrow\downarrow\downarrow\downarrow$	$\downarrow \downarrow \downarrow \downarrow$
Etomidate	0	0/↓	$\downarrow/\downarrow\downarrow$	0	$\downarrow\downarrow\downarrow\downarrow$	$\downarrow\downarrow\downarrow\downarrow$	$\downarrow \downarrow \downarrow \downarrow$
Midazolam	1	$\downarrow\downarrow$	$\downarrow\downarrow/\downarrow\downarrow\downarrow$	0	$\downarrow\downarrow$	$\downarrow\downarrow$	$\downarrow\downarrow$
Ketamine	<u> </u>	↑ ↑/↑	0	<u> </u>	$\uparrow\uparrow$	$\uparrow\uparrow$	1
Dexmedetomidine	\downarrow	\downarrow	0	0		0	0

 Table 17.1
 Cardiovascular, respiratory, and cerebral effects of several intravenous hypnotic agents

Based on data from Morgan et al. [6]

0 = no change, $\uparrow/\downarrow =$ minimal change in corresponding direction, $\uparrow\uparrow/\downarrow\downarrow =$ moderate change in corresponding direction, $\uparrow\uparrow\uparrow/\downarrow\downarrow\downarrow =$ marked change in corresponding direction, *HR* heart rate, *MAP* mean arterial pressure, *Vent* ventilation, *B'dil* bronchodilation, *CBF* cerebral blood flow, *CMRO*₂ cerebral metabolic rate of oxygen, *ICP* intracranial pressure

^aWhere there is a difference between the young adult and the geriatric patient, the first set of arrows indicates the response in the young adult and the second set of arrows indicates the response in the geriatric patient

consideration is of prime importance in the elderly patient population because they are more apt to have critical carotid or aortic valvular stenosis, and their range of cerebral autoregulation may significantly alter if they are a patient with chronic hypertension. This is particularly true in candidates presenting for carotid endarterectomy and/or aortic valve replacement, as even moderate afterload reduction can threaten cerebral perfusion because the cerebral autoregulation curve is shifted to the right such that the baseline hypertension in these patients is required to perfuse the brain beyond these fixed stenotic lesions [8].

Propofol induces a biphasic pattern of electroencephalogram (EEG) activation that slows with increasing doses. After the initial activation, EEG slowing is dose related and proceeds to burst suppression and then to complete electrical silence [9]. During induction, patients older than 70 years reach significantly deeper EEG stages than younger patients, need a longer time to reach the deepest EEG stage, and need more time until a light EEG stage is regained [10]. The EEG changes described above cause a shorter duration of seizure in the patient on electroconvulsive therapy (ECT), but they also allow for a blunted hypertensive and hyperdynamic response that is often seen in these patients [11]. Although propofol often allows for seizures of a clinically acceptable duration [11], many psychiatrists prefer methohexital for ECT. Although methohexital does allow for longer seizure duration, it does not block the hypertensive response to ECT as much and thus is not as ideal in the geriatric patient who is likely to have cardiac disease.

The brain becomes more sensitive to propofol with increasing age. Schnider et al. [12] reported that geriatric patients were approximately 30% more sensitive to the PD effects of propofol than younger patients, as measured by EEG changes. This was found to be true for both induction doses and infusions. Thus, it seems that increasing age causes changes in the brain that increase the effective potency of propofol for the geriatric patient.

Respiratory Effects

Propofol causes dose-related depression of ventilation and is thought to produce some bronchodilation, although this is controversial (Table 17.1) [13, 14]. In standard induction doses, propofol causes apnea [15]. However, when compared with thiopental, respirations are lost later and recovered earlier [15]. With intravenous infusions for sedation, propofol causes increasing levels of respiratory depression, mainly by affecting the tidal volume. Furthermore, airway reflexes are depressed more so with propofol than with equivalent doses of thiopental or etomidate, and this effect is greatly enhanced by the addition of opioids [16]. Also, although propofol does not inhibit hypoxic pulmonary vasoconstriction, it does seem to blunt both the hypoxic and hypercapnic ventilatory responses [15, 17–19].

All of these changes described above have particular relevance for the elderly patient. Because of increases in closing capacity with increasing age, which will exceed functional residual capacity (FRC) even in the upright position in a 65-year-old individual, desaturation can occur at a faster rate. In the elderly, this occurs as a result of an increase in shunt fraction rather than a reduced FRC, as is seen with the obese individuals or in patients with restrictive lung disorders [20]. The elderly also have a decreased cough reflex and thus a decreased ability to clear secretions [21]. This inherently decreased cough reflex in the elderly patient combined with the suppression of this reflex from propofol puts the elderly person at higher risk for aspiration during its use. Furthermore, the elderly patient already has a blunted hypoxic and hypercapnic ventilatory response compared with the average adult patient [21]. These changes call for great vigilance when administering propofol to an elderly patient for minimal alveolar concentration (MAC) anesthesia or even light sedation. Ventilation should be closely monitored, particularly if supplemental oxygen is used, because the hypercapnic ventilatory response will become the primary regulator of respiration. This is important because supplemental oxygen could prevent hypoxemia, but allow for a progressive hypercapnia that could be dangerous to the patient. Finally, all of these effects are increased with the concurrent use of opioids, thus requiring even greater attention in operative and procedural situations when the elderly patient is maintaining oxygenation and ventilation through spontaneous respirations without a secure airway or endtidal carbon dioxide monitoring. However, all of the evidence cited thus far would suggest that increased PD sensitivity in the elderly patient moves in a parallel manner for respiratory depression and sedation/hypnosis; that is, the patient is not fully awake and merely experiencing decreased respiratory drive. Thus, in the spontaneously ventilating patient, the gradual titration of propofol matched with a vigilance attentive to signs of adequate respiration and level of sedation should provide for a safe and effective anesthetic.

Cardiovascular Effects

Propofol causes little change in heart rate but can cause profound changes in MAP when given in induction bolus doses (Table 17.1) [22]. These changes are caused by a reduction in systemic vascular resistance (via inhibition of sympathetic vasoconstriction) and preload, as well as direct effects on myocardial contractility. This hypotension is more pronounced than what is seen with the administration of thiopental, etomidate, or midazolam. In the normal adult patient, this hypotension is well tolerated and it is readily reversed during the stimulation of laryngoscopy and intubation. However, studies have shown that the degree of hypotension is increased and an adequate hemodynamic response to a bolus induction is decreased in the geriatric patient. This occurs by several mechanisms. First, propofol impairs the arterial baroreceptor reflex to hypotension, which is already decreased in the geriatric patient [23]. Second, the geriatric patient is more likely to have ventricular dysfunction. A decrease in preload in these patients may result in a significant decrease in cardiac output. Third, these patients are often taking beta-blockers and diuretics or other therapies that cause hypovolemia in the perioperative period. The former reduces the magnitude of any baroreceptor-mediated reflex tachycardia to a decrease in blood pressure, whereas the latter tends to make the patient more sensitive to changes in systemic vascular resistance and preload secondary to being relatively intravascularly hypovolemic [23]. Finally, it is possible for a profound decrease in preload to result in a vagally mediated reflex bradycardia [24]. Practically speaking, these concerns can be clinically applied in two general categories. First, for the geriatric patient with significant cardiac disease, it is best to avoid a rapid bolus induction with propofol. Second, many of the untoward effects noted above

can be greatly minimized if a slower infusion induction is performed with laryngoscopy being performed after reaching a PD endpoint, such as a bispectral index (BIS) value of less than 60 (see discussion in sections further) [25].

Other Effects

Two unique beneficial effects of propofol are noteworthy. Propofol has both antiemetic and antipruritic properties [26, 27]. Thus, its intraoperative and perioperative use has the potential to reduce the need for traditional antiemetic and possibly antipruritic medications in the postoperative period. This is particularly important in the geriatric patient who may be more susceptible to the untoward effects of drugs that work at cholinergic and dopaminergic sites in the normal treatment of nausea and pruritus [28].

Metabolism and Disposition (Pharmacokinetics)

The PK of propofol involves a very large volume of distribution, rapid redistribution, and rapid elimination via hepatic and extrahepatic routes (see Table 17.2). Owing to high lipid solubility, it has an onset of action of one arm-to-brain circulation time (almost as fast as thiopental). Rapid awakening from a single bolus is the result of extensive redistribution to non-CNS sites throughout the body. Its initial distribution half-life in a healthy adult patient is approximately 2 min [29–32].

There are various changes in the PK of propofol in the elderly patient. The central volume of distribution is less, systemic clearance is reduced, and intercompartmental clearance is reduced. During a propofol infusion, the plasma concentration of the drug is about 20% higher in the elderly patient as compared with the average adult [30]. Furthermore, the context-sensitive half-time changes with increasing age. Studies have shown that the time required for a 50% reduction in effect-site concentration (50% effect-site decrement time) is significantly prolonged with advancing age in an exponential manner. For propofol infusions less than 1 h, there is little difference in the recovery time of the young adult and the elderly patient. However, after a 4-h infusion, there is a doubling of the 50% effect-site decrement time in an 80 versus a 20-year-old patient, and this difference becomes even greater with infusions of 10 h and longer [30]. This fact is of particular importance because this assumes that there have already been dosage adjustments for other PK parameters such that the plasma concentration is the same in both the patients. Thus, even at reduced infusion rates, the elderly patient will take longer to emerge than the young patient.

	Vdss (1 k/g)	Cl (ml/kg/min)	t _{1/2} el (h)	CSHT1 (min)	CSHT3 (min)	F (%)
Dexmedetomidine	2–3	9–30 (↓)	2–3	~20	~40	94
Etomidate	2–5	12–25	3–5	5	8	76
Ketamine	1–3	11-18	2–3	5	22	50
Midazolam	1–2	6–11 (↓)	2–3	32	60	95
Propofol	2-10	20-30	4–7	10	21	98
Thiopental	1–3	3–5	7–17	80	120	75

 Table 17.2
 Pharmacokinetic parameters for commonly used intravenous nonopiates

Where (\downarrow) indicated effect of age on variable, from [29–31]

Table 17.3 Uses and doses of commonly used nonopiates drugs

		Induction/Maintenance		
	Sedation (iv)	Bolus	Infusion	Elderly (% reduction)
Dexmedetomidine	0.5–1 µg/kg ^a	0.5–3 µg/kg ^a	0.1–2.5 µg/kg/h	30–50
Etomidate		0.2–0.4 mg/kg	n/a	20–50
Ketamine	0.2–0.5 mg/kg	1–2 mg/kg	10-20 µg/kg/min	?0
Midazolam	0.02 mg/kg	0.025–0.1 mg/kg	0.3-1.5 µg/kg/min	20
Propofol	10-50 µg/kg/min	1.0–1.5 mg/kg	75-150 µg/kg/min	20
Thiopental		2–5 mg/kg	n/a	20

Where (\downarrow) indicated effect of age on variable, from [29, 33–37] ^aOver 10–20 min

Indications

Propofol, as noted in the previous section, is routinely used for induction and maintenance phases of general anesthesia, as well as for various levels of sedation in OR and non-OR anesthesia [1], and also in the ICU.

Dosing in the Elderly

When the PK and PD changes are considered together, the current literature suggests a 20% reduction in the induction dose of propofol, if given as a bolus (see Table 17.3) [33–37].Practically, this has been reported as a reduction of the bolus dose from 2.0–2.5 to 1.5–1.8 mg/kg [31]. Of note, it is the authors' clinical experience that if the induction dose is titrated to a neurologic endpoint (such as BIS or PSA4000) or given slowly to account for the effect-site hysteresis time (k_{e0}), this dose is reduced to as low as 0.8–1.2 mg/kg in the elderly, which corresponds with the findings of Kazama et al. [25]. Furthermore, numerous reports have shown that there is less hemodynamic instability if this bolus is given over a longer period of time in the elderly patient than one fast bolus [25, 30, 32].

Dosing requirements during an infusion are even less for the elderly patient. Schüttler and Ihmsen [32] have shown that for continuous low plasma level infusions, such as those used during the maintenance phase of an anesthetic for sedation (plasma concentration 1 μ g/mL), a 75-year-old patient will require approximately 30% less drug than a 25-year-old patient to maintain the same level of drug concentration. However, this only takes into account the PK changes with age (Fig. 17.1) [32]. The age-related decline in the amount of propofol required for the same level of anesthesia becomes even more profound when one considers the PD data along with the PK data. For a surgical level of anesthesia, Shafer proposes an age-adjusted dosing guideline based on the compilation of several PK and PD studies (Fig. 17.2) [12, 31]. This PD change is also illustrated in Fig. 17.3, which shows that a 75-year-old patient will require a 50% lower propofol plasma concentration than a 25-year-old patient to have the same likelihood of being asleep after a 1-h infusion [12]. Additionally, as aforementioned, it must be noted that a prolonged propofol infusion should be stopped earlier in the elderly patient to have recovery at the same time as the younger patient (Fig. 17.4) [32].

Adverse Effects and Contraindications

The major adverse effect of propofol, a significant decrease in blood pressure, has been already mentioned. If proper dosage adjustments are made, propofol is a well-tolerated induction and infusion medication in the elderly. However, in the patient with significant ventricular dysfunction or hemodynamic instability, it may be best to use etomidate or thiopental for bolus induction. It is also of note that propofol routinely causes pain on intravenous injection. However, this is normally brief and mitigated by lidocaine admixture or pretreatment [30]. 0.12

0.10

0.08

0.06

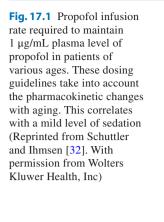
0.04

0.02

0.00 + 0

20

Propofol infusion rate [mg/kg/min]



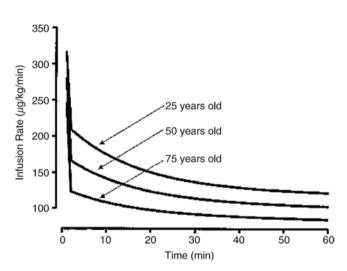


Fig. 17.2 Propofol infusion rate required to maintain adequate surgical anesthesia in patients of various ages. These dosing guidelines account for the changes with age in propofol pharmacokinetics and pharmacodynamics (Reprinted from Shafer [31]. with permission from Elsevier)

Future Considerations

One potential benefit of the use of propofol in the elderly population is its speculated anti-inflammatory and antioxidant properties [38–41]. Ongoing research supports that a propofol infusion for the maintenance of anesthesia decreases the magnitude of the rise of inflammatory markers in the elderly patient when compared with volatile anesthetic agents. This is of particular importance when it is viewed in light of the research showing that increases in inflammatory markers, such as interleukin (IL)-6, tumor necrosis factoralpha, C-reactive protein, and myeloperoxidase, are associated with increased rates of cardiovascular mortality and morbidity and postoperative cognitive dysfunction [42, 43].

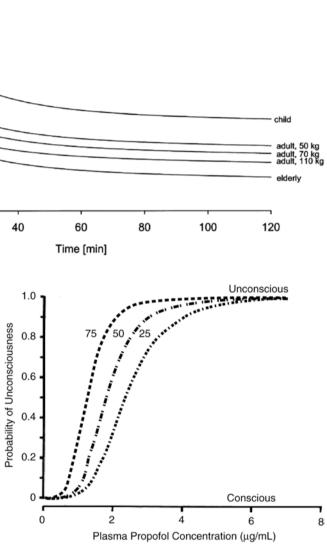
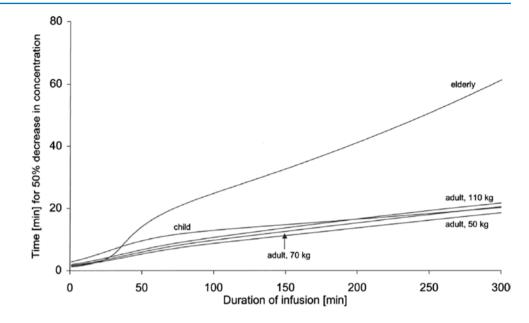


Fig. 17.3 Effect of age on propofol pharmacodynamics. This logistic regression shows the age-related probability of being asleep after a 1-h infusion of propofol. A 75-year-old patient is 30–50% more sensitive to propofol than is a 25-year-old patient (Reprinted from Schnider et al. [12]. With permission from Wolters Kluwer Health, Inc.)

Thiopental

Barbituric acid, a combination of urea and malonic acid that is lacking in sedative properties, was first synthesized in 1864 by J.F.W. Adolph von Baeyer, a Nobel prizewinning organic chemist [44]. The thiobarbiturates were first described in 1903. However, because of fatal experiments in dogs, their use was not further explored until the 1930s [45– 47]. In 1935, Tabern and Volwiler synthesized a series of sulfur-containing barbiturates, of which thiopental became the most widely used. Thiopental was clinically introduced by Ralph Waters and John Lundy, and became the preferred agent clinically because of its rapid onset of action and short **Fig. 17.4** Context-sensitive half-time of propofol in patients of various ages. Altered pharmacokinetics in the elderly become clinically significant after a 1-h infusion (Reprinted from Schuttler and Ihmsen [32]. With permission from Wolters Kluwer Health, Inc.)



duration, without the excitatory effects of hexobarbital [48]. In 2011, the American manufacturer of thiopental announced that it would stop production of thiopental not only in the USA but also at its Italian plant (because it was a supplier to the USA), because of its objection of thiopental use for lethal injection.

Pharmacology: Structure/Action

Thiopental is a hypnotically active drug that works at GABA_A receptor sites in the CNS [49]. Thiopental is of the class of thiobarbiturates, which is defined by having a sulfur substituted at the position C2. Substitutions at the 5, 2, and 1 positions of the barbiturate ring confer different pharmacologic activities to the barbiturate nucleus. Substitutions at position 5 with either aryl or alkyl groups produce hypnotic and sedative effects. A phenyl group substitution at C5 produces anticonvulsant activity. An increase in length of one or both side-chains of an alkyl group at C5 increases hypnotic potency. Substitution of a sulfur at position 2 produces a more rapid onset of action, as seen with thiopental [50].

Pharmacodynamics

Thiopental produces sedation and sleep. Sufficient doses produce a CNS depression that is attended by loss of consciousness, amnesia, and respiratory and cardiovascular depression. The response to pain and other noxious stimulation during general anesthesia seems to be obtunded. However, the results of pain studies reveal that barbiturates may actually decrease the pain threshold in low doses, such as with small induction doses of thiopental or after emergence from thiopental when the blood levels are low [51]. The amnesic effect of barbiturates has not been well studied, but it seems decidedly less pronounced than that produced by benzodiazepines or propofol [52].

Central Nervous System Effects

Barbiturates, similar to other CNS depressants, have potent effects on cerebral metabolism. Several studies in the 1970s demonstrated the effect of barbiturates as a dose-related depression of the CMRO₂, which produces a progressive slowing of the EEG, a reduction in the rate of adenosine triphosphate consumption, and protection from incomplete or focal cerebral ischemia [53, 54]. When the results of the EEG became isoelectric, a point at which cerebral metabolic activity is approximately 50% of baseline, no further decrements in CMRO₂ occurred [55]. These findings support the hypothesis that metabolism and function are coupled. However, it must be noted that it is the portion of metabolic activity concerned with neuronal signaling and impulse traffic that is reduced by barbiturates, not that portion corresponding to basal metabolic function. The only way to suppress baseline metabolic activity concerned with cellular activity is through hypothermia. Thus, the effect of barbiturates on cerebral metabolism is maximized at a 50% depression of cerebral function in which less oxygen is required as CMRO₂ is diminished, leaving all metabolic energy to be used for the maintenance of cellular integrity

[55]. This may be of importance to the elderly patient undergoing neurosurgery for aneurysm clipping or carotid endarterectomy in which focal ischemia may occur.

With the reduction in CMRO₂, there is a parallel reduction in cerebral perfusion, which is seen in decreased CBF and ICP (Table 17.1). With reduced CMRO₂, cerebral vascular resistance increases and CBF decreases [56]. However, for thiopental, the ratio of CBF to CMRO₂ is unchanged. Thus, the reduction in CBF after the administration of barbiturates causes a concurrent decrease in ICP. Furthermore, even though the MAP decreases, barbiturates do not compromise the overall CPP, because the CPP = MAP – ICP. In this relationship, ICP decreases more relative to the decrease in MAP after barbiturate use, thus preserving CPP. This is in contrast to propofol, which has a greater likelihood in the elderly patient of decreasing MAP to an extent that may compromise CPP, as noted above [57].

Onset of Central Nervous System Effects

Barbiturates produce CNS effects when they cross the blood-brain barrier. There are several well-known factors that help to determine the rapidity with which a drug enters the cerebral spinal fluid (CSF) and brain tissue. These factors include the degree of lipid solubility, degree of ionization, level of protein binding, and the plasma drug concentration. Drugs with high lipid solubility and low degree of ionization rapidly cross the blood-brain barrier, producing a fast onset of action. Approximately 50% of thiopental is nonionized at physiologic pH, which accounts in part for the rapid accumulation of thiopental in the CSF after intravenous administration. Protein binding also affects the onset of action in the CNS. Barbiturates are highly bound to albumin and other plasma proteins. As only unbound drug (free drug) can cross the blood-brain barrier, an inverse relationship exists between the degree of plasma protein binding and the rapidity of drug passage across the blood-brain barrier.

The final factor governing the rapidity of drug penetration of the blood-brain barrier is the plasma drug concentration. Simply because of concentration gradient, higher levels of drug concentrations in the plasma produce greater amounts of drug that diffuses into the CSF and the brain. The two primary determinants of the plasma concentration are the dose administered and the rate (speed) of administration. The higher the dose and the more rapid its administration, the more rapid is the effect. This is of particular importance in the elderly patient who may have a reduced central volume of distribution and thus require a reduced dose of thiopental to reach the same plasma concentration as a younger adult [58].

Cardiovascular System

Cardiovascular depression from barbiturates is a result of both central and peripheral (direct vascular and cardiac) effects [59]. The hemodynamic changes produced by barbiturates have been studied in healthy individuals and in patients with heart disease. The primary cardiovascular effect of barbiturate induction is peripheral vasodilation that results in a pooling of blood in the venous system. A decrease in contractility is another effect, which is related to reduced availability of calcium to the myofibrils. There is also an increase in heart rate. Mechanisms for the decrease in cardiac output include (1) direct negative inotropic action, (2)decreased ventricular filling because of increased capacitance, and (3) transiently decreased sympathetic outflow from the CNS. The increase in heart rate (10-36%) that accompanies thiopental administration probably results from the baroreceptor-mediated sympathetic reflex stimulation of the heart in response to the decrease in output and pressure. Thiopental produces dose-related negative inotropic effects, which seem to result from a decrease in calcium influx into the cells with a resultant diminished amount of calcium at sarcolemma sites. The cardiac index is unchanged or is reduced, and the MAP is maintained or is slightly reduced [59]. Thiopental infusions and lower doses tend to be accompanied by smaller hemodynamic changes than those noted with rapid bolus injections; however, their use in current practice is exceedingly limited if not gone altogether [25].

The increase in heart rate encountered in patients with coronary artery disease anesthetized with thiopental (1-4 mg/ kg) is potentially deleterious because of the obligatory increase in myocardial oxygen consumption (MVO₂) that accompanies the increased heart rate. Patients who have normal coronary arteries have no difficulty in maintaining adequate coronary blood flow to meet the increased MVO_2 [60]. When thiopental is given to hypovolemic patients, there is a significant reduction in cardiac output (69%) as well as a substantial decrease in blood pressure [45-48]. Patients without adequate compensatory mechanisms, therefore, may have serious hemodynamic disturbance with thiopental induction. All of these concerns are of particular importance in geriatric patients, because they are more likely to have clinically significant coronary artery disease, are more likely to be intravascularly hypovolemic, and their compensatory mechanisms to maintain heart rate and blood pressure may be reduced because of age-related alterations and pharmacologic treatments such as beta-blockers or calcium channel blockers. Thus, it is of prime importance in the elderly patient to understand proper dose reduction (discussed further) and the effects of the rate of administration of an induction bolus. If these are not heeded, it becomes common to have significant hypotension in the geriatric patient with the need to administer vasopressors after induction, a practice that can be avoided if a proper understanding of the above principle is gained.

Respiratory System

Barbiturates produce dose-related central respiratory depression. There is also a significant incidence of transient apnea after their administration for induction of anesthesia [15]. The evidence for central depression is a correlation between EEG suppression and minute ventilation [61]. With increased anesthetic effect, there is diminished minute ventilation. The time course of respiratory depression has not been fully studied, but it seems that peak respiratory depression (as measured by the slope of CO₂ concentration in the blood) and minute ventilation after delivery of thiopental 3.5 mg/kg occurs 1-1.5 min after administration. These parameters rapidly return to predrug levels, and within 15 min the drug effects are barely detectable [62]. Of note, respirations are lost sooner and return later than that seen with propofol. Patients with chronic lung disease are slightly more susceptible to the respiratory depression of thiopental. The usual ventilatory pattern with thiopental induction has been described as "double apnea." The initial apnea that occurs during drug administration lasts a few seconds and is succeeded by a few breaths of reasonably adequate tidal volume, which is followed by a longer apneic period. During the induction of anesthesia with thiopental, ventilation must be assisted or controlled to provide adequate respiratory exchange. This is of particular concern in the elderly patient who will have an increased closing capacity, which will produce a shorter time to become hypoxemic, as compared with the young adult patient [21].

Metabolism and Disposition (Pharmacokinetics)

Thiopental PK has been described in both physiologic and compartmental models. These models basically describe a rapid mixing of the drug with the central blood volume followed by a quick distribution of the drug to the highly perfused, low-volume tissues (i.e., brain) with a slower redistribution of the drug to lean tissue (muscle). In these models, adipose tissue uptake and metabolic clearance (elimination) have only a minor role in the termination of the effects of the induction dose because of the minimal perfusion ratio compared with other tissues and the slow rate of removal, respectively. Both of these PK models describe rapid redistribution as the primary mechanism that terminates the action of a single induction dose [31, 63]. Awakening may be delayed in older patients mainly because of a decreased central volume of distribution relative to younger adults [64]. The initial volume of distribution is less in elderly patients when compared with that in young patients (80 versus 35-year-old patient), which explains a 50–75% lower dose requirement for the onset of EEG and hypnotic effects [58, 64]. However, except in disease states, the clearance of thiopental is not reduced in the elderly, and thus, awakening should only be prolonged in the elderly with a bolus administration and not with a constant infusion.

Indications

Although supply has been limited in many countries in recent years, thiopental is an excellent hypnotic drug for use as an intravenous induction agent and continues widespread use in low and middle-income countries [62]. The prompt onset (15-30 s) of action and smooth induction make thiopental a reasonable choice, as long as the cardiovascular limitations and dangers noted above are taken into account. The relatively rapid emergence, particularly after single use for induction, has also been a reason for the widespread use of thiopental in this setting. Thiopental does not possess analgesic properties and therefore it must be supplemented with analgesic drugs to obtund reflex responses to noxious stimuli during anesthesia induction, intubation, and surgical procedures. Thiopental can be used to maintain general anesthesia, because repeated doses reliably sustain unconsciousness and contribute to amnesia. However, the ease of using propofol for light sedation and total intravenous anesthesia has supplanted the use of thiopental for this purpose and relegated it mainly for use in the induction portion of an anesthetic.

Dosing in the Elderly

In contrast to propofol, numerous studies have shown that the brain of the elderly patient is not intrinsically more sensitive to the effects of thiopental than that of the younger patient [58]. Further studies concluded that the need for a reduction in the induction dose of thiopental in the elderly is attributable to a reduction in the central volume of distribution [65]. Shafer [31] collated the results of several studies to suggest that the optimal dose in an 80-year-old patient is 2.1 mg/kg, which is approximately 80% of the dose needed for a young adult. However, it should again be noted that slower bolusing of the induction dose will generally result in less-acute hemodynamic alterations. Furthermore, monitoring of an EEG-related endpoint during a slow induction can guide the amount of drug given and may allow for a more individualized dosing regimen [66].

Adverse Effects and Contraindications

The effects of barbiturates on various organ systems have been extensively studied. There are several side effects that occur in unpredictable, varying proportions in patients, whereas the cardiovascular and pulmonary side effects are dose related [67]. The complications of injecting barbiturates include garlic or onion taste (40% of patients), allergic reactions, local tissue irritation, and, rarely, tissue necrosis. An urticarial rash may develop on the head, neck, and trunk that lasts a few minutes. More severe reactions such as facial edema, hives, bronchospasm, and anaphylaxis can occur. Treatment of anaphylaxis is to stop any further administration of the drug, administer 1-mL increments of 1:10,000 epinephrine with boluses of intravenous fluids, give inhaled bronchodilators, such as albuterol, for bronchospasm, and then administer histamine antagonists, such as diphenhydramine and famotidine.

Studies have shown pain on injection to be 9% and phlebitis to be approximately 1% with thiopental use [50]. Tissue and venous irritation are more common if a 5% solution is used rather than the standard 2.5% solution. Rarely, intraarterial injection can occur. The consequences of accidental arterial injection may be severe. The degree of injury is related to the concentration of the drug. Treatment consists of (1) dilution of the drug by the administration of saline into the artery, (2) heparinization to prevent thrombosis, and (3) brachial plexus block. Overall, the proper administration of thiopental intravenously into a briskly running IV is remarkably free of local toxicity [67]. However, it should be noted that thiopental can precipitate if the alkalinity of the solution is decreased, which is why it cannot be reconstituted with lactated Ringer's solution or mixed with other acidic solutions. Examples of drugs that are not to be coadministered or mixed in solution with the barbiturates are pancuronium, vecuronium, atracurium, alfentanil, sufentanil, and midazolam. Studies have shown that in rapid-sequence induction, the mixing of thiopental with vecuronium or pancuronium results in the formation of precipitate that may occlude the intravenous line [50].

Midazolam

The first benzodiazepine found to have sedative-hypnotic effects was chlordiazepam in 1955 [68]. Diazepam was synthesized in 1959 and became the first benzodiazepine used for sedation and anesthesia induction. Subsequently, a number of benzodiazepines have been produced including lorazepam and the antagonist flumazenil. The benzodiazepines produce many of the elements important in anesthesia. They produce their actions by occupying the benzodiazepine

receptor, which was first presented in 1971 [69]. In 1977, specific benzodiazepine receptors were described when ligands were found to interact with a central receptor [70]. The most frequently used benzodiazepine in the elderly is midazolam. Fryer and Walser's 1976 synthesis of midazolam produced the first clinically used water-soluble benzodiazepine [71]; it was also the first benzodiazepine that was produced primarily for use in anesthesia [72].

Pharmacology: Structure/Action

Midazolam is water soluble in its formulation, but highly lipid soluble at physiologic pH [72]. Midazolam solution contains 1 or 5 mg/mL midazolam with 0.8% sodium chloride and 0.01% disodium edetate, with 1% benzyl alcohol as a preservative. The pH is adjusted to 3 with hydrochloric acid and sodium hydroxide. The imidazole ring of midazolam accounts for its stability in solution and rapid metabolism. The high lipophilicity accounts for the rapid CNS effect, as well as for the relatively large volume of distribution [73].

Pharmacodynamics

Central Nervous System Effects

All benzodiazepines have hypnotic, sedative, anxiolytic, amnesic, anticonvulsant, and centrally produced muscle relaxant properties. The drugs differ in their potency and efficacy with regard to each of these PD actions. The binding of benzodiazepines to their respective receptors is of high affinity, stereospecific, and able to fully saturate the receptors; the order of receptor affinity (thus potency) of the three agonists is lorazepam > midazolam > diazepam. Midazolam is approximately three to six times as potent as diazepam [74].

The mechanism of action of benzodiazepines is reasonably well understood [75–77]. The interaction of ligands with the benzodiazepine receptor represents an example in which the complex systems of biochemistry, molecular pharmacology, genetic mutations, and clinical behavioral patterns are seen to interact. Through recent genetic studies, the GABA_A subtypes have been found to mediate the different effects (amnesic, anticonvulsant, anxiolytic, and sleep) [78]. Sedation, anterograde amnesia, and anticonvulsant properties are mediated via *a1* receptors [78], and anxiolysis and muscle relaxation are mediated by the *a2* GABA_A receptor [78]. The degree of effect exerted at these receptors is a function of plasma level. By using plasma concentration data and PK simulations, it has been estimated that a benzodiazepine receptor occupancy of less than 20% may be sufficient to produce the anxiolytic effect, whereas sedation is observed with 30–50% receptor occupancy and unconsciousness requires 60% or higher occupation of benzodiazepine agonist receptors [78].

Agonists and antagonists bind to a common (or at least overlapping) area of the benzodiazepine portion of the GABA_A receptor by forming differing reversible bonds with it [79, 80]. The effects of midazolam can be reversed by use of flumazenil, a benzodiazepine antagonist that occupies the benzodiazepine receptor, but produces no activity and therefore blocks the actions of midazolam. The duration of reversal is dependent on the dose of flumazenil and the residual concentration of midazolam.

The onset and duration of action of a bolus intravenous administration of midazolam largely depends on the dose given and time at which the dose is administered; the higher the dose given over a shorter time (bolus), the faster the onset. Midazolam has a rapid onset (usually within 30-60 s) of action. The time to establish equilibrium between plasma concentration and EEG effect of midazolam is approximately 2–3 min and is not affected by age [81]. Like onset, the duration of effect is related to lipid solubility and blood level [82]. Thus, termination of effect is relatively rapid after midazolam administration. But some physicians have a general sense that midazolam is associated with the production of confusion even after the termination of sedation. This has been reported in prior studies and case reports [83, 84]. However, a more recent study suggests that this might not be the case, particularly at lower doses [85]. Taken together, these data seem to suggest that single, lower doses of midazolam (0.03 mg/kg) will not cause confusion, whereas higher doses (0.05-0.07 mg/kg) along with an infusion of midazolam will have a greater association with confusion in the geriatric patient, as opposed to that seen with the use of a low-dose propofol infusion [83-85].

Respiratory Effects

Midazolam, like most intravenous anesthetics and other benzodiazepines, produces dose-related central respiratory system depression. The peak decrease in minute ventilation after midazolam administration (0.15 mg/kg) is almost identical to that produced in healthy patients given diazepam (0.3 mg/kg) [86]. Respiratory depression is potentiated with opioids and must be carefully monitored in elderly patients getting both. The peak onset of ventilatory depression with midazolam (0.13–0.2 mg/kg) is rapid (about 3 min), and significant depression remains for about 60–120 min [63, 87]. The depression is dose related. The respiratory depression of midazolam is more pronounced and of longer duration in patients with chronic obstructive pulmonary disease, and the duration of ventilatory depression is longer with midazolam (0.19 mg/kg) than with thiopental (3.3 mg/kg) [63].

At sufficient doses, apnea occurs with midazolam as with other hypnotics. The incidence of apnea after thiopental or midazolam when these drugs are given for induction of anesthesia is similar. In clinical trials, apnea occurred in 20% of 1130 patients given midazolam for induction and 27% of 580 patients given thiopental [72]. Apnea is related to dose and is more likely to occur in the presence of opioids. Older age [88] debilitating disease and other respiratory depressant drugs probably also increase the incidence and degree of respiratory depression and apnea with midazolam.

Cardiovascular Effects

Midazolam alone has modest hemodynamic effects. The predominant hemodynamic change is a slight reduction in arterial blood pressure, resulting from a decrease in systemic vascular resistance. The hypotensive effect is minimal and about the same as seen with thiopental [89]. Despite the hypotension, midazolam, in doses as high as 0.2 mg/kg, is safe and effective for induction of anesthesia even in patients with severe aortic stenosis. The hemodynamic effects of midazolam are dose related: the higher the plasma level, the greater the decrease in systemic blood pressure [90]; however, there is a plateau plasma drug effect above which little change in arterial blood pressure occurs. The plateau plasma level for midazolam is 100 ng/mL [90]. Heart rate, ventricular filling pressures, and cardiac output are maintained after induction of anesthesia with midazolam.

The stimulation of endotracheal intubation and surgery are not blocked by midazolam [91]. Thus, adjuvant anesthetics, usually opioids, are often combined with benzodiazepines. The combination of benzodiazepines with opioids and nitrous oxide has been investigated in patients with ischemic and valvular heart diseases [92–95]. Although the addition of nitrous oxide to midazolam (0.2 mg/kg) has trivial hemodynamic consequences, the combination of benzodiazepines with opioids does have a synergistic effect [96]. The combination of midazolam with fentanyl [93] or sufentanil [95] produces greater decreases in systemic blood pressure than does each drug alone.

Metabolism and Disposition (Pharmacokinetics)

Biotransformation of all benzodiazepines occurs in the liver. The two principal pathways involve either hepatic microsomal oxidation (*N*-dealkylation or aliphatic hydroxylation) or glucuronide conjugation [97, 98]. The difference in the two pathways is significant, because oxidation is susceptible to outside influences and can be impaired by certain population characteristics (specifically, old age), disease states (e.g., hepatic cirrhosis), or the coadministration of other drugs that can impair oxidizing capacity (e.g., cimetidine). Of the two, conjugation is less susceptible to these factors [97]. Midazolam undergoes oxidation reduction, or phase I reactions, in the liver [99]. The cytochrome P450 3A4 is primarily responsible for metabolism [100]. The fused imidazole ring of midazolam is rapidly oxidized by the liver, which accounts for the high rate of hepatic clearance. Neither age nor smoking decreases midazolam biotransformation [101]. Chronic alcohol consumption increases the clearance of midazolam [102].

The metabolites of the benzodiazepines can be important. Midazolam is biotransformed to hydroxymidazolams, which are active metabolites, and when midazolam is given in prolonged infusions, these metabolites can accumulate [103]. These metabolites rapidly conjugate and are excreted in the urine. The 1-hydroxymidazolam has an estimated clinical potency of 20–30% of midazolam [104]. It is primarily excreted by the kidneys and can cause profound sedation in patients with renal impairment [105]. Overall, the metabolites of midazolam are less potent and normally more rapidly cleared than the parent drug, making them of little concern in patients with normal hepatic and renal function. However, they may be a consideration in elderly patients with impaired renal function.

Midazolam is classified as a short-lasting benzodiazepine. The plasma disappearance curves of midazolam can be fitted to a two or three-compartment model. The clearance rate of midazolam ranges from 6 to 11 mL/kg/min [101]. Although the termination of action of these drugs is primarily a result of redistribution of the drug from the CNS to other tissues after bolus or maintenance use for surgical anesthesia, after daily (long-term) repeated administration or after prolonged continuous infusion, midazolam blood levels decreases more slowly.

Factors known to influence the PK of benzodiazepines are age, gender, race, enzyme induction, sepsis-related organ dysfunction, and hepatic and renal disease [106, 107]. Age reduces the clearance of midazolam to a modest degree [104]. Among the PK parameters of midazolam that vary significantly with age, it is clearance which does so most consistently [105]. In healthy adults, midazolam clearance is high, approximating 50% of hepatic blood flow [106]. However, with advanced age, there is a loss of functional hepatic tissue and a decrease in hepatic perfusion such that clearance is reduced in the elderly by as much as 30% from that of a young adult; recent modeling has predicted a 27% reduction in metabolic clearance in older versus younger patients [108]. The decreased clearance is not a result of agerelated changes in CYP3A4 enzymatic activity in the liver which is unaffected by age [106]. As a result of the normal

decline in lean tissue mass and concomitant increase in percent body fat in the aged, a slight increase is also observed in volume of distribution [107]. Moreover, according to one study, advanced age is in itself enough to cause the mean elimination half-life of midazolam to double [43]. Neither oral bioavailability nor midazolam protein binding are affected by age, despite reduced hepatic albumin synthesis and lower serum albumin concentrations in the elderly [105]. Finally, there appear to be no significant differences in PK variables between repeated bolus and continuously infused midazolam when used in ICU sedative doses [109].

Midazolam PK is affected by obesity. The volume of distribution is increased as drug goes from the plasma into the adipose tissue. Although clearance is not altered, elimination half-lives are prolonged, because of the delayed return of the drug to the plasma in obese individuals [104]. This can be of concern in elderly obese patients. Although the PK of midazolam is clearly affected by age, they are, with the exception of total clearance, not consistently altered to statistical significance. These PK changes with age do not explain [103] the increased sensitivity of the elderly to midazolam discussed above. There are PD factors that are yet to be fully understood that make midazolam more potent in the elderly than the young.

Indications

Intravenous Sedation

Midazolam is used for sedation as preoperative premedication [110], intraoperatively during regional or local anesthesia, and postoperatively for sedation. The anxiolysis, amnesia, and elevation of the local anesthetic seizure threshold are desirable benzodiazepine actions for regional anesthesia. It should be given by titration for this use; endpoints of titration are adequate sedation or dysarthria and maintained ventilation. The onset of action is relatively rapid with midazolam, usually with peak effect reached within 2-3 min of administration. There is an excellent correlation within individuals of sedation score to blood level, but between individuals there is considerable variation in blood level and sedation [107]. The duration of action primarily depends on the dose used. There is often a disparity in the level of sedation compared with the presence of amnesia (patients can be seemingly conscious and coherent, yet they are amnesic for events and instructions). The degree of sedation and the reliable amnesia, as well as preservation of respiratory and hemodynamic function, are better overall with midazolam than with other sedative-hypnotic drugs used for conscious sedation with the possible exception of propofol [88]. However, in elderly patients, inadvertent overdose for sedation during endoscopy has been reported

to cause a decline in cognitive function [111]. Also, in a small percentage of patients (1.4%), a paradoxical reaction successfully treated with flumazenil has been reported during endoscopy resulting in agitation rather than sedation [112]. When using midazolam for sedation, a sedation score such as the Ramsay Sedation Scale is commonly used whereas the BIS in elderly patients might result in less-reliable sedation monitoring [113]. When midazolam is compared with propofol for sedation, the two are generally similar except that emergence or wake-up is more rapid with propofol [88]. Midazolam and propofol require close medical supervision because of potential respiratory depression and hypotension [108, 109]. Despite the wide safety margin with midazolam, respiratory function must be monitored when it is used for sedation to prevent undesirable degrees of respiratory depression [63, 114, 115]. This is especially true in the geriatric patient and when opioids are also given [88, 116]. There may be a slight synergistic action between midazolam and spinal anesthesia with respect to ventilation [117]. Thus, the use of midazolam for sedation during regional and epidural anesthesia requires vigilance with regard to respiratory function, when these drugs are given with opioids. Sedation for longer periods, for example, in the ICU, is accomplished with benzodiazepines. Prolonged infusion will result in accumulation of drug and, in the case of midazolam, significant concentration of the active metabolite. The chief advantages are the amnesia and hemodynamic stability, and the disadvantage, compared with propofol, is the longer dissipation of effects when infusion is terminated.

Induction and Maintenance of Anesthesia

With midazolam, induction of anesthesia is defined as unresponsiveness to command and loss of the eyelash reflex. When midazolam is used in appropriate doses, induction occurs less rapidly than with thiopental or propofol [72], but the amnesia is more reliable. Numerous factors influence the rapidity of action of midazolam. These factors are dose, speed of injection, degree of premedication, age, American Society of Anesthesiologists (ASA) physical status, and concurrent anesthetic drugs [72, 110]. In a well-premedicated, healthy patient, midazolam (0.2 mg/kg given in 5-15 s) will induce anesthesia in 28 s. The BIS may be used to monitor depth with midazolam and adjuvant drugs during anesthesia [118, 119]. Emergence time is related to the dose of midazolam as well as the dose of adjuvant anesthetic drugs [72]. Emergence is more prolonged with midazolam than with propofol [120, 121]. This difference accounts for some anesthesiologists' preference for propofol induction for short operations. The best method of monitoring depth with midazolam is use of the BIS [122]. Over the years since its introduction into practice, midazolam has become much less used for induction and maintenance of anesthesia in part because of the delirium found with higher doses of the drug [123].

The amnesic period after an anesthetic dose is about 1-2 h. Infusions of midazolam have been used to ensure a constant and appropriate depth of anesthesia. Experience indicates that a plasma level of more than 50 ng/mL when used with adjuvant opioids (e.g., fentanyl) and/or inhalation anesthetics (e.g., nitrous oxideand volatile anesthetics) is achieved with a bolus loading dose of 0.05–0.15 mg/kg and a continuous infusion of 0.25–1 µg/ kg/min [124]. This is sufficient to keep the patient asleep and amnesic but arousable at the end of surgery. Midazolam when compared with dexmedetomidine MAC sedation during endoscopic nasal surgery produces more amnesia than dexmedetomidine [125]. Lower infusion doses almost certainly are required in elderly patients and with certain opioids.

Effects of Age on Pharmacology

Elderly patients require lower doses of midazolam than younger patients to reach various standard clinical endpoints of sedation, such as response to verbal command (Fig. 17.5) [126]. The usual induction dose of midazolam in elderly premedicated patients is between 0.05 and 0.15 mg/kg. Some studies show that patients older than 55 years and those with ASA physical status higher than 3 require a 20% or more reduction in the induction dose of midazolam [72]. However, Shafer, who collated the results of numerous PK and PD studies, recommends a 75% reduction in dose from the 20 to the 90-year-old patient. Thus, there is definitely a graded decrease in the amount of drug needed as a result of aging [31]. In a recent comparative study of midazolam and propo-

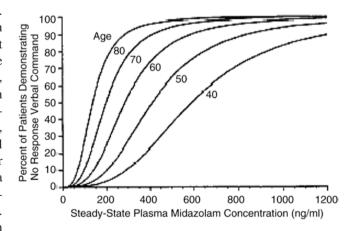


Fig. 17.5 Response curves to verbal commands in patients of various ages at varying plasma levels of midazolam. This demonstrates a pharmacodynamic change associated with aging in response to midazolam (Reprinted from Jacobs et al. [126]. With permission from Wolters Kluwer Health Inc.)

fol in elderly patients (65–93 years old) having hip surgery under spinal anesthesia, midazolam and propofol were similar with regard to hemodynamic and most ventilatory effects, but midazolam prolonged recovery time [127]. Finally, when midazolam is used with other anesthetic drugs (coadministration), there is a synergistic interaction [124, 128, 129], and the induction dose is less than 0.1 mg/kg. The synergy is seen when midazolam is used with opioids and/or other hypnotics such as thiopental, propofol, and etomidate.

Awakening after midazolam anesthesia is the result of the redistribution of drug from the brain to other, less wellperfused tissues. The emergence (defined as orientation to time and place) of young, healthy volunteers who received 10 mg of intravenous midazolam occurred in about 15 min [128], and, after an induction dose of 0.15 mg/kg, it occurred in about 17 min. The effect of age on emergence has not been well studied, but it likely is prolonged compared with younger patients because of greater potency in the elderly.

Adverse Effects and Contraindications

Midazolam is a remarkably safe drug. It has a relatively high margin of safety, especially when compared with barbiturates. It is also free of allergenic effects and does not suppress the adrenal gland [129]. The most significant problem with midazolam is respiratory depression. It is free of venous irritation and thrombophlebitis, problems related to aqueous insolubility, and requisite solvents in other drug formulations [72]. When used as a sedative or for induction and maintenance of anesthesia, midazolam can produce an undesirable degree or prolonged interval of postoperative amnesia, sedation, and, rarely, respiratory depression. These residual effects can be reversed with flumazenil.

Etomidate

Pharmacology: Structure/Action

Etomidate is a hypnotic drug that is structurally unrelated to all other induction medications. It contains a carboxylated imidazole ring that provides water solubility in an acidic milieu and lipid solubility at physiologic pH. It is dissolved in propylene glycol, which often causes pain on injection. Etomidate works by depressing the reticular activating system and enhances the inhibitory effects of GABA by binding to a subunit of the GABA_A receptor and thereby increasing its affinity for GABA. However, unlike the barbiturates, which have global depressant effects on the reticular activating system, etomidate has some disinhibitory effects, which accounts for the 30–60% rate of myoclonus with administration. Interestingly, one study has shown that this unwanted side effect can be reduced with pretreatment, similar to a defasciculating dose of neuromuscular blocking drugs (NMBDs) [130].

Pharmacodynamics

Central Nervous System Effects

Etomidate induces changes in CBF, metabolic rate, and ICP to the same extent as thiopental and propofol. However, because this is not the result of a large reduction in arterial blood pressure, CPP is well maintained [130]. This is of particular importance in the elderly person who is at risk for ischemic stroke secondary to carotid occlusion. Etomidate has EEG changes similar to thiopental with a biphasic pattern of activation followed by depression. However, etomidate has been shown to activate somatosensory evoked potentials [57]. Additionally, etomidate causes myoclonic movements after induction, a disturbing effect of unknown significant, in approximately 75% of patients but this is not evidence of an insufficient induction dose [131]. Of note, etomidate does have a higher rate of postoperative nausea and vomiting associated with it than with the other intravenous induction drugs [132]. Finally, there are no PD changes with age with respect to etomidate as measured by EEG [130].

Cardiovascular Effects

Unlike propofol, etomidate has minimal effects on the cardiovascular system. There is a slight decline in the arterial blood pressure secondary to a mild reduction in the systemic vascular resistance. Etomidate does not seem to have direct myocardial depressant effects, because myocardial contractility, heart rate, and cardiac output are usually unchanged [133]. Etomidate does not cause histamine release. These aspects of the PD of etomidate make it very useful in the patient with compromised intravascular volume, coronary artery disease, or reduced ventricular function, as is often encountered in the elderly patient.

Respiratory Effects

Etomidate causes less respiratory depression than benzodiazepines, barbiturates, or propofol in induction doses. In fact, even an induction dose of etomidate often does not cause apnea [61]. This fact, combined with its minimal cardiovascular effects, makes etomidate a very useful drug in the setting of a hemodynamically brittle elderly patient with a possible difficult airway and little respiratory reserve.

Endocrine Effects

Induction doses of etomidate temporarily inhibit the synthesis of cortisol and aldosterone, lasting approximately 12–18 h after a single bolus dose [134]. However, the clinical significance of this has been debated in septic patients. Some studies have shown an increased mortality with a single bolus dose in septic patients, whereas others have not [135]. Alternatively, long-term infusions or closely repeated exposures can lead to adrenocortical suppression, which may be associated with an increased susceptibility to infection and an increased mortality rate in the critically ill patient [136].

Metabolism and Disposition (Pharmacokinetics)

Etomidate is used only in intravenous formulations and is generally used for the induction of general anesthesia. Etomidate is similar to thiopental in its distribution and onset of action. Although it is highly protein bound, etomidate has a very rapid onset of action because of its high lipid solubility and its large nonionized fraction. Redistribution to noncentral compartments is responsible for its rapid offset of action. Hepatic microsomal enzymes as well as plasma esterases rapidly hydrolyze etomidate to its nonactive metabolites. This rate of biotransformation is five times greater than that of thiopental, but less than that of propofol.

The volume of distribution is slightly larger than that of the barbiturates and the elimination clearance is greater. However, the elimination clearance is still less than propofol. Thus, the elimination half-life of etomidate is faster than thiopental, but longer than propofol. Both of these parameters are decreased in the elderly, which causes a higher plasma concentration of etomidate for any given dose. Furthermore, to our knowledge, no study has ever shown an increased brain sensitivity to etomidate with increasing age. Therefore, like thiopental, any dose reduction in the elderly is attributable to PK, not PD, changes [33].

Indications

Etomidate is used for the intravenous induction of anesthesia. It has been used as an intermittent bolus technique for short procedures, but less commonly described. Typically, 25% of the induction dose is given every 15–30 min to maintain surgical anesthesia. Etomidate is not approved in the USA for maintenance infusions.

Dosing in the Elderly

The standard induction dose of etomidate is intravenous 0.2–0.4 mg/kg. However, the elderly may only require 0.1 mg/kg. This change in dosage is attributable only to PK parameters, and not PD [33].

Adverse Effects and Contraindications

Etomidate has a high incidence of side effects, most of which are minor. As mentioned in the previous section, etomidate has a higher rate of postoperative nausea and vomiting than either propofol or thiopental. The incidence of myoclonic movements on induction is reported to be as high as 60%. This effect as well as pain on injection can be reduced with a slow injection into a rapidly running intravenous carrier line, preferably in a large vein. When etomidate is injected into veins in the hand, the incidence of pain is reported to exceed 40%. Furthermore, because of the propylene glycol solvent, studies have shown that 10–20% of patients experience venous sequelae after its use [34].

Ketamine

History

Ketamine was first developed by the Parke-Davis and Company in the early 1960s as a fast-acting general anesthetic [35]. The initial clinical trials were conducted in the mid to late 1960s [36]. It received FDA approval in 1970 and was first used primarily in children undergoing a variety of diagnostic studies such as cardiac catheterization and radiology imaging [37] wherein it proved particularly useful [137]. Because the airway was maintained, it found use for repeated administration in burned patients requiring debridement and skin grafting [138]. It was found to be as good or better than morphine for the newly emerging operation, coronary artery bypass grafting [139], but because of the tachycardia associated with it and the contemporaneous emergence of highdose fentanyl [140], this use was short-lived. Use of ketamine as an anesthetic fell out of favor in the 1980s and 1990s largely because of its severe emergence delirium and its recreational abuse, as it had gained popularity as a club or "rave" drug and also used for date rape [141]. In 1999, ketamine became a federally controlled substance in hopes of limiting its recreational use [141]. The history of ketamine's early use has been recorded elsewhere [142, 143]. In recent years, it has seen a resurgence in the medical community, namely among anesthesiologists and emergency department physicians, because of its low cost, safety profile, and versatility.

Pharmacology: Structure/Activity

Ketamine is a phencyclidine which possesses sedative and dissociative amnestic properties rather than inducing a generalized depression of the CNS [143]. It is also known to be a potent analgesic. Its primary mechanism of action is noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonism in the thalamocortical and limbic centers of the CNS; however, opioid receptor (delta, kappa, and mu) blockade, GABA inhibition, increased release, and decreased uptake of norepinephrine, serotonin, and dopamine are other welldescribed actions of ketamine [144, 145]. It is partially water soluble and 5-10 times more lipid soluble than thiopental. Only 12% is bound to plasma proteins and is 93% bioavailable after parenteral administration [146]. It is a racemic mixture of the isomers R(-)-ketamine and S(+)-ketamine, with the S(+)-isomer being three to four times more potent and possessing fewer pyschomimetic side effects [146, 147]. Ketamine's wide dosing safety margin, the availability of S(+)-ketamine (only racemic mixture available in the USA), recent studies highlighting ketamine's modulation of central sensitization at subanesthetic doses, and a desire for multimodal, opioid-sparing anesthetic techniques have contributed to renewed interest [148].

Pharmacodynamics

CNS Effects

Historically, the CNS effects of ketamine were widely believed to be deleterious on ischemic brain tissue because of an increase in CMRO₂, increase in CBF, and increase in ICP [149]. Although on the surface these unfavorable changes might lead one to avoid ketamine in patients at risk for cerebral ischemia, more recent evidence suggests that use of ketamine is neuroprotective because of its ability to inhibit excitotoxic signaling of glutamate and aspartate, reduce neuronal apoptosis, attenuate the systemic inflammatory response to tissue injury, and maintenance of CPP via increased sympathetic nervous system activation, all of which may offset the detrimental effects on CBF and metabolism, especially when arterial carbon dioxide tension is controlled through mechanical ventilation [150, 151]. Ketamine's ability to attenuate the systemic inflammatory response to tissue injury is via suppression of nuclear factor kappa B (NF-kB) expression thereby decreasing transcription of inflammatory mediators such as IL-6, IL-8, and tumor necrosis factor (TNF)-a. Ketamine inhibits neuronal cell death by blockade of NMDA receptors-mediated influx of Ca²⁺ via voltage-gated channels and glutamate release initiated by ischemia.

Subanesthetic doses of ketamine have been shown to assist with neuroplasticity in treatment-resistant depression [152].

Ketamine boosts dendritic spinal density and neuronal spine maturation via rapid protein synthesis and activation of intracellular pathways [153].

Of particular importance to the elderly, several studies in the past decade have shown a decreased incidence of postoperative delirium after cardiopulmonary bypass (CPB) in anesthetized elderly patients treated with ketamine (0.5–1 mg/kg) compared with placebo [150, 154]. This may be at least partially related to ketamine's effectiveness in treating depression which is a known risk factor for postoperative delirium. Inhibition of HCN1 receptors, which regulate states of consciousness and are upregulated by inflammation, are also thought to play a critical role in prevention and treatment of delirium and neuropathic pain through inflammatory cascades [155, 156]. It is unknown if the ketamine-related decrease in delirium post-CPB can be extrapolated to all patients; however, there is a large international, multicenter, randomized control trial currently underway to assess postoperative cognitive function after other major surgeries [157].

Additionally, ketamine has been described to increase theta and beta activity on the EEG; therefore, increases in BIS may be observed in monitoring [137]. This is not particularly alarming, however, given ketamine's cortical NMDA antagonism. The BIS monitor reflects cortical activity rather than level of consciousness which is predominately a function of the thalamus and reticular activating system [158].

Due to the excitation properties of ketamine and reports of seizure-like activity early in the history of ketamine's inception, there was previous concern that ketamine might have proconvulsant activity. Investigations into patients with documented seizure histories given ketamine, and a subset with epileptic discharge present during initiation of monitoring, have shown either no worsening or an elimination of EEG discharges therefore supporting an anticonvulsant effect of ketamine [159, 160]. In fact, recent studies have shown that a subanesthetic dose of ketamine during induction with etomidate can decrease the rate of myoclonic, seizure-like movements by two-thirds [131].

Respiratory

Other notable advantages of ketamine are its ability to provide anesthesia while preserving spontaneous respiration and airway reflexes. In the absence of large bolus doses, ketamine is also less likely to produce respiratory depression than other intravenous anesthetics. The retention of protective airway reflexes with ketamine use, without depressing respiratory function makes the drug particularly appealing for patients that need to be kept spontaneously breathing during induction of anesthesia [161, 162]. Ketamine also has been shown to lower airway resistance [163] with decreased peak inspiratory pressures and increase lung compliance via an increased in chest wall compliance which can be particularly useful in patients with severe or refractory bronchospasm [164]. Although a few studies have shown ketamine to reduce respiratory rates, they showed no changed in minute ventilation but it did increase Pao₂ [165]. Maintenance of FRC is another unique feature of ketamine contributing to its beneficial respiratory profile [145].

Cardiovascular

In contrast to other intravenous sedatives and anesthetics, ketamine has a more favorable effect on the cardiovascular system, particularly in hypotensive patients. It is commonly referred to as a sympathomimetic drug and facilitates adrenergic transmission by inhibiting reuptake. Transient increases in heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and cardiac output do occur during ketamine use but return to baseline within minutes [166]. It is unclear whether these effects occur in patients who are catecholamine deplete. Titrated doses appear to be safe in elderly patients, including the critically ill, but should probably be avoided in patients who have conditions that might be exacerbated by acute increases in blood pressure, such as active myocardial ischemia or decompensated heart failure.

Metabolism and Disposition (Pharmacokinetics)

Ketamine has a large volume of distribution because of its lipophilicity, ranging anywhere from 5 L/kg in healthy patients to 16 L/kg in critically ill patients. It exhibits bicompartmental behavior and its elimination half-life is 4.9 h in critically ill patients versus 3 h in healthy patients [167]. It is metabolized hepatically via cytochrome p450 *N*-demethylation and hydroxylation to the inactive metabolite, norketamine which is approximately one-third as potent as the parent drug [145]. Decreased clearance is to be expected when given with p450 inhibitors. The metabolite, norketamine, is renally excreted; thus, dosing should be reduced in patients with reduced glomerular filtration [168].

Indications

Induction of anesthesia in elderly hypotensive patients without decompensated heart failure or active myocardial ischemia is probably the best-described indication for ketamine use. Another important indication for ketamine use is in patients with a known difficult airway and need for spontaneous respirations prior to securing of airway, though hypersalivation may somewhat limit its utility in this situation. Analgesia and sedation "analgosedation" in the ICU is one of the newer indications for ketamine use. Patients receiving ketamine infusion for analgosedation tend to have higher MAPs, fewer vasopressor requirements, and improved pain control as compared to patients receiving fentanyl infusion [169].

Ketamine is also effective for preemptive analgesia. It has been shown to inhibit the "wind up" phenomenon of pain mediated through inhibition of long-term potentiation via NMDA receptor antagonism in the dorsal horn neurons in the spinal cord [170].

Ketamine is also useful for the treatment of refractory bronchospasm. It has most successfully been used in children but there is sufficient evidence that it can be used to treat adult bronchospasm, specifically in the ICU [171].

Dosing in the Elderly

Minimal data exists regarding ketamine in the elderly and suggested dosing adjustments; however, it appears that no dosing adjustments are required based on the few studies that address dosing in elderly patients. A study in the early 1980s used ketamine as a sole anesthetic in eight elderly patients (mean age 83 years) presenting for repair of hip fracture. Cardiovascular and metabolic effects were checked at multiple time intervals (before premedication, end of procedure, 15 min postprocedure, and 2 h postprocedure). Patients were kept spontaneously breathing and induced over 2 min period until they were unable to react to verbal command. The mean induction dose was $1.75 (\pm 0.14)$ mg/kg and mean maintenance dose was 88 (± 14) mcg/kg/min, as compared to 1-2 mg/kg standard induction dosing for all patients. Transient changes were noted in SBP, cardiac index (CI), left ventricular stroke work index (LVSWI), and O₂ consumption but had returned to preoperative levels 15 min after anesthetic was stopped with no noted adverse reactions [172]. Another study in elderly patients (mean age 67) undergoing major abdominal surgery used 2 mg/kg for induction and 40 mcg/ kg/min titrated to sedation, again with only transient increases in heart rate, SBP, DBP, CO, and Pao₂. These returned to baseline within minutes after induction, and no adverse neurologic consequences were noted postoperatively [166]. Ketamine dosing as adjunctive analgesia in the elderly has been described as 0.5 mg/kg bolus, which is similar to analgesic dosing suggestions for the general population [173]. It does not induce hemodynamic changes at this dose.

Adverse Effects and Contraindications

There are a number of adverse effects of ketamine worth mentioning. As previously mentioned, ketamine is a sympathomimetic and can transiently increase heart and blood pressure, especially in bolus doses; thus, it should be avoided in patients with heart failure, cardiogenic shock, and myocardial ischemia. Careful titration of induction doses should be considered in patients presumed to be catecholamine deplete as it may cause hypotension in this population. Ketamine should be cautiously in patients with pulmonary hypertension as it has been reported in at least one study to increase pulmonary artery pressures [174].

Hypersalivation, which may also occur with ketamine use, can be easily treated with an anticholinergic such as glycopyrrolate. Other anticholinergics which have also successfully been used, such as atropine, should probably be avoided in the elderly population because of their deliriogenic effects. Another described adverse effect of ketamine which is of importance in the elderly population is an increase in intraocular pressure and thus should be cautiously used in patients with glaucoma, though a recent study of elderly patients receiving ketamine for ophthalmic surgery has refuted an increase in intraocular pressure [170, 175].

Dexmedetomidine

Dexmedetomidine is a highly selective α_2 -adrenergic agonist that was released for clinical use by the FDA in 1999 [176, 177]. It is the pharmacologically active *S*-enantiomer of medetomidine, a veterinary drug [178]. Dexmedetomidine is approved for use as an intravenous sedative and analgesic [176]. It is related to clonidine, another α_2 -adrenergic agonist approved for clinical use, but has eight times greater affinity for the α_2 -adrenergic receptor than clonidine [178–180]. This selectivity accounts for its greater sedative and analgesic actions than clonidine whose main uses are as an antihypertensive, alcohol withdrawal, and for treatment of attention deficit hyperactivity disorder (ADHD) in children. Unlike most sedative and analgesic compounds, it has minimal respiratory-depressant effects.

Pharmacology: Structure/Action

Dexmedetomidine is an imidazole derivative that comes in a water-soluble formulation with a pKa of 7.1 [181], and is recommended to be given by infusion in a concentration of 4 μ /mL of 0.9% sodium chloride [176]. It is a α_2 -adrenergic agonist that acts peripherally and centrally [182]. Alpha 2 receptors are found peripherally in vascular smooth muscle involved in regulating the autonomic and cardiovascular systems wherein they inhibit norepinephrine release thus leading to reduction in peripheral vascular resistance and thereby blood pressure. These receptors are also in the CNS and when occupied by an agonist inhibit the release of norepinephrine; this leads to sedation and a central vagatonic

action causing slowed heart rate. Finally, the α_2 -adrenergic receptors are found in the dorsal horn of the spinal cord wherein they inhibit pain pathways providing both analgesia and opioid sparing when combined with opioids used for analgesia [176, 178, 183, 184]. Thus, through the several agonist actions at the α_2 -adrenergic receptors, dexmedetomidine produces central sedation with some vagal-mediated slowing of the heart rate, and peripherally mediates analgesia and slight hypotension.

Pharmacodynamics

Central Nervous System Effects

Sedation, anxiolysis, analgesia, and hypnosis (sleep) with dexmedetomidine are dose-related [185, 186] CNS effects mediated by the α_2 -adrenergic, especially the 2_A subtype. The inhibition of neurons in the locus ceruleus in the brainstem is considered the primary central site of action. It produces these effects with minimal effects on respiration, unlike most sedative/hypnotics that modulate GABA or opiate receptors. Human EEG studies and animal laboratory studies [187, 188] have shown that the sleep induced by dexmedetomidine is more like normal sleep than seen with barbiturates, propofol, or benzodiazepines. The central actions of dexmedetomidine have been labeled "arousable sedation" [178] because patients are more easily awakened than when sedated with benzodiazepines or propofol [189]. Unlike midazolam, "amnesia" is not produced by dexmedetomidine except at high doses [186].

"Analgesia" is primarily mediated by the α_2 -adrenergic receptors in the dorsal horn of the spinal cord [182, 190] and is dose related [186]. Activation of these receptors inhibits the transmission of pain further centrally and work alone or in concert with coadministered opioids to produce analgesia. When combined with opioids for analgesia, less opioid is required to achieve desired analgesia and this is termed "opioid sparing." [191–193]. The analgesic advantage of dexmedetomidine over opioids is lack of CNS-mediated respiratory depression. Dexmedetomidine given intrathecally augments the analgesia from intrathecal or neuraxial administration of local anesthetics [194, 195].

Delirium prevention is an important new area for pharmacologic intervention because of the clinical importance and prevalence (11–43%) of delirium in surgical populations, especially in the elderly [196–198]. Delirium is associated with patient morbidity, mortality, and added length of stay and hospital costs [196, 199]. Dexmedetomidine centrally reduces hypothalamic–pituitary–adrenal activity thought to play a causative role in delirium [196, 200]. Clinical trials comparing dexmedetomidine with other sedatives in the ICU and incidence of delirium are discussed in sections further.

Respiration

Dexmedetomidine infusion in healthy volunteers produces mild dose-related respiratory depression and apnea [185]. Central apnea was not observed. Spo₂ remained above 95% in all patients given doses varying from 0.25 to 2.0 µg/kg, and peak decreased ventilation occurred 60 min after cessation of infusion of 2.0 µg/kg dose (highest) falling from 8.7 to 6.3 l/min with Paco₂ rising from 42 to 46 mmHg 10 min after administration. Response to inspired carbon dioxide was minimally impaired. As reported in another healthy volunteer study [186], there was little change in respiratory rate and overall the respiratory effects were mild and did not require assisted ventilation. Similar findings in patients given incrementally higher dosing of dexmedetomidine produce little respiratory effects [201]. Nevertheless, in frail individuals, the respiratory effects could be detrimental, and certainly when dexmedetomidine is administered with respiratory depressant sedatives and opioids, the need for vigilant respiratory monitoring is necessary.

Cardiovascular

Bradycardia or heart rate slowing is a common side effect of dexmedetomidine, centrally mediated by the α_2 -adrenergic agonist actions that cause a vagal-mediated cardiac slowing [182]. There is generally a biphasic blood pressure response to dexmedetomidine with an initial, short-lived (5–10 min) mild increase [177, 202] followed by decreases in blood pressure and heart rate [176, 203]. Cardiac output drops in a dose-related fashion along with heart rate [186]. Clinically significant sinus arrest has been reported with the use of dexmedetomidine [176] which means it should be used with caution in patients with heart block. The hemodynamic effects of dexmedetomidine tend to be more pronounced in elderly patients and this means dosing should be reduced or administered more slowly [178].

Stress Response to Surgery and Intensive Care Unit

Dexmedetomidine has been studied in surgical patients undergoing a variety of operations and in intensive care settings and found to ameliorate the stress response usually observed in these patients [204–206]. Serum IL-6, IL-8, and TNF- α levels are reduced when dexmedetomidine is given to patients. The adrenocortical function to stress is preserved. In normal volunteers, there is a significant reduction in epinephrine and norepinephrine [186].

Metabolism and Disposition (Pharmacokinetics)

Dexmedetomidine is biotransformed almost completely after administration. It undergoes direct N-glucuronidation as well as cytochrome P450-mediated metabolism in the liver [176]. Approximately 80–90% is excreted in the urine with 5-13% found in feces [182]. The metabolites are inactive. The hepatic clearance may be decreased by as much as 50% with severe liver disease [177]. Pharmacokinetics are presented in Table 17.2, and most studies have used a two or three-compartment model to describe the PK [176, 207]. Clearance is diminished by low cardiac output and increased age [207, 208]. The PK of dexmedetomidine are similar to midazolam and propofol, but the context sensitive half-time of propofol is shorter than either dexmedetomidine or midazolam which explains at least part of the reason that patients emerge more rapidly from sedation with propofol than the other drugs. Note that older patients have a reduced clearance of dexmedetomidine and this along with the apparent greater sensitivity to it in older patients mean that dosing in the elderly should be reduced compared to younger patients.

Dosage and Administration

The dosage of nonopioid drugs for sedation and induction/ maintenance of anesthesia and sedation are in Table 17.3. Dexmedetomidine when used for sedation and light monitored anesthesia care (MAC) is 1 µg/kg given slowly over 10–20 min [176]. The dose to bolus load for heavier sedation is 0.5–1 µg/kg followed by an infusion over hours of 0.2– 1.0 µg/kg/h [209]. Note that the dose in older patients should be reduced between 30 and 50% and the drug should be titrated to desired sedation level with adjustments in dosing based on the level of sedation required.

Indications

Dexmedetomidine has two rather restrictive FDA-approved indications: (1) for sedation in the ICU not to exceed 24 h, and (2) for sedation during procedures [176]. The actual uses are broader than this and are expanding especially for use in frail [210] and elderly patients because dexmedetomidine produces less respiratory depression compared to other drugs and reduces disturbing side effects in the elderly such as shivering and delirium. However, the drug should be judiciously used in patients with heart block and hypovolemia because of its cardiovascular effects [203].

Sedation Preoperatively and During Monitored Anesthesia Care

Dexmedetomidine has been clinically evaluated for preoperative sedation [211, 212], as an adjunct during surgery and during monitored anesthesia care (MAC) [213]. It proved an effective anxiolytic and safe when given intramuscularly $(2.5 \,\mu\text{g/kg})$ as a premedication [211]. Dexmedetomidine has also been used for sedation during nonsurgical procedures and compared to midazolam and propofol. In one randomized trial for sedation during fiberoptic nasotracheal intubation, demedetomidine (1.0 µg/kg/ over 10 min) was compared with propofol (1.9 mg/kg total infusion) and produced a more favorable comfort socre, fewer adverse airway events and more stable hemodynamics [214]. In a colonoscopy sedation study [215] two groups received fentanyl 1 µg/kg and one got dexmedetomidine (1 µg/kg over 10 min and followed by 0.5 µg/kg/h) and the other midazolam (0.5 mg/kg). The dexmedetomidine group had superior hemodynamic stability, sedation and satisfaction scores. However, in another sedation study using similar dosing, midazolam was found superior to dexmedetomidine for colonoscopy because of stable heomodynamics and time to discharge [216]. It is difficult to reconcile these two conflicting studies of the use of dexmedetomidine and midazolam for sedation for colonoscopy.

Dexmedetomidine is used as a component of MAC, usually with an opioid or another sedative. In a well-controlled early study of dexmedetomidine compared with propofol for MAC during regional anesthesia, dexmedetomidine produced similar sedation but onset and offset was slower [191]. The blood pressure was lower with propofol, but respiratory variables were similar. The dexmedetomidine patients experienced lower postoperative pain scores and required less morphine postoperatively. MAC dexmedetomidine produced similar sedation to propofol for lithotripsy, but patients had less pain with dexmedetomidine and higher Spo₂ values despite a slower respiratory rate [217]. When dexmedetomidine (0.2 µg/kg/h) was used with remifentanil during atrial fibrillation catheter ablation procedures, it produced better sedation and ventilation than a comparative group given midazolam (1-2 mg) and remifertanil [192]. It can be argued that the midazolam dose was too low to make a good comparison, but the opioid-sparing effects of dexmedetomidine are consistent with known actions.

When used during surgery for coinduction and maintenance (1 µg/kg over 10 min load followed by infusion of 0.5 µg/kg/h) in patients also getting propofol and remifentanil, the doses of propofol and remifentanil are significantly ($P \le 0.02$) reduced to maintain a predetermined BIS surgical level [193]. Also first requirement for analgesia postoperatively was significantly later in the dexmedetomidine group. There was no difference in the hemodynamics or recovery time between groups. Dexmedetomidine has been used as an infusion $(1 \ \mu g/kg \text{ over } 20 \ \text{min})$ at the end of surgery to facilitate emergence from anesthesia [218]. The emergence was rated smoother in the patients randomized to dexmedetomidine, and when used similarly reduces analgesic requirements in patients who have undergone colectomy [219]. One striking postoperative effect of dexmedetomidine administered during surgery is reduced shivering [220, 221]. Although the mechanism is unclear, the reduction of shivering is a possible indication for dexmedetomidine, especially in older patients. Overall, dexmedetomidine is a useful intraoperative adjunctive drug to other intravenous drugs used for general anesthesia.

Sedation Postoperatively and Intensive Care

Dexmedetomidine has been used postoperative analgesia as a component in postoperative patient-controlled analgesia (PCA). In a meta-analysis of seven trials comparing opioid alone or combined with dexmedetomidine, patients given the combination had significantly lower pain scores, required less opioids for pain, and had lower incidence of postoperative nausea, vomiting, and pruritus [222]. Patient satisfaction was also higher when dexmedetomidine was combined with opioids as a PCA treatment regimen. Dexmedetomidine has been extensively studied as a sedative/hypnotic and anxiolytic in intensive care patients for long (\geq 24 h) [207, 223] and short (\leq 24 h) periods of infusion [202, 224, 225]. The Society of Critical Care Medicine suggests that dexmedetomidine or propofol may be preferred for sedation in mechanically ventilated patients to benzodiazepines [199]. Light levels of sedation with regular arousal of patients are also recommended. Sedation should be monitored by one of a number of scores but the two most robust are Richmond Agitation-Sedation Scale (RASS) [226] and the Sedation-Agitation Scale (SAS) [227]. These are reliable and valid measures of sedation level [228]. In general, in ventilator-dependent patients, dexmedetomidine has been found superior to benzodiazepines because of less delirium [229], shorter times for extubation, and more arousable patients [230]. Compared with propofol sedation is similar, however propofol has shorter times for extubation, but more delirium. Depressed ventilation is less prominent with dexmedetomidine than propofol or midazolam. Dexmedetomidine produces some analgesia and thus when it is used for sedation in the setting of pain it reduces the dose of opioids as part of the sedation cocktail [204].

Xia and coinvestigators [231] performed a meta-analysis comparing clinical trials for ICU sedation of dexmedetomidine and propofol. The combined studies involved 1202 patients. Dexmedetomidine was associated with a significantly reduced length of ICU stay and incidence of delirium. There was more hypertension in the dexmedetomidine patients. Duration of intubation and mortality were similar with both the drugs. A consortium of 68 medical centers was formed to study dexmedetomidine or midazolam in a randomized trial involving 375 patients randomized to either drug for sedation. Both drugs achieved and maintained RASS set ranges and had similar duration of ICU stays. Prevalence of delirium was higher in the midazolam group (76.6 vs 54% P < 0.001) as was the incidence of tachycardia. The median time to extubation was 1.9 days shorter in the dextmedetomidine patients (P = 0.01). Dexmedetomidine patients had more bradycardia and less hypertension. However, Adams and coauthors reviewed six studies comparing dexmedetomidine with midazaolam and found no conclusive advantage to either [232]. There is information to support the conclusion that midazolam confers significantly (P = 0.015) more amnesia [233] and dexmedetomidine spares opioid [232] and adjuvant midazolam use [229].

One surgical population that stands out with dexmedetomidine is cardiac surgery in which the drug's salutary effects on delirium and other parameters are most promising. Compared to propofol for ICU sedation, dexmedetomidine provides shorter (P < 0.001) times for extubation significantly better patient satisfaction scores [234]. In a separate study of cardiac surgical patients above 60 years of age, dexmedetomidine had significantly less delirium than propofol used for sedation [235]. The difference in delirium was half that of propofol or midazolam in another cardiac surgical sedation study, and required less financial resources [236]. In a large (n = 1134) retrospective cohort study, dexmedetomidine when used for sedation compared to patients given other sedatives during immediate postoperative care had less mortality, overall complications, and delirium [123]. It seems from these studies that use of dexmedetomidine ICU sedation could be an important step in optimizing results after cardiac surgery.

Although the benefits of dexmedetomidine in the ICU have been clearly demonstrated, until recently, there was no evidence that pharmacologic prophylaxis of delirium improved outcomes. As previous studies compared dexmedetomidine to other sedatives, it was not clear if the beneficial effects of dexmedetomidine on delirium should be attributed to the increased deliriogenic effects of the other sedatives or if it played a role in pharmacologic prophylaxis. Additionally, all of the aforementioned ICU studies were in mechanically ventilated patients, which is a risk factor for delirium. In a recently published trial by Su et al. [237], noncardiac postsurgical patients over 65 years of age (n = 700) were randomized to receive low-dose dexmedetomidine (1 mcg/kg/h) or placebo within 1 h of admission to the ICU, with half of the patients in each group requiring mechanical ventilation at the time of admission to the ICU. Delirium was assessed starting on postoperative day one using the

Confusion Assessment Method in the ICU (CAM-ICU). The dexmedetomidine group had a significantly lower incidence of delirium in the first seven postoperative days as compared to placebo (9 vs 23%). Even when stratified by mechanical ventilation versus nonmechanically ventilated patients, the decreased incidence of delirium remained (29 vs 12% and 15 vs 6%, respectively). The dexmedetomidine group had a shorter duration to extubation in those mechanically ventilated on admission (6.9 vs 4.6 h). There were no increased adverse events in the dexmedetomidine group, such as bradycardia or hypotension, but there was a significantly reduced incidence of tachycardia and hypertension requiring treatment in this group. Interestingly, however, there was no difference in ICU length of stay or hospital length of stay. Long-term implications of this study remain to be elicited but its results of prophylactic dexmedetomidine on delirium prevention in the elderly are exciting.

Adjunct to Local Anesthesia

Dexmedetomidine given intrathecally [194] or intravenously potentiates the block of local anesthetics. It may be used as a sedative during spinal anesthesia and compared to patients given midazolam during spinal anesthesia raises the extent of dermatomal block, prolongs the senory block, but has no effect on duration of motor block [238]. This needs to be considered if dexmedetomidine is to be used for sedation in patients having either spinal or epidural anesthesia. Dexmedetomidine has been used intrathecally (3 μ g) in elderly patients given low-dose bupivacaine (6 mg) spinal anesthesia for transurethral prostatectomy [194]. Patients given dexmedetomidine had faster onset of block and longer duration of the block, but prolonged motor block in these elderly patients.

Effects of Age on Pharmacology

Few studies have compared the effects of dexmedetomidine in old versus younger patients, but there are three particularly instructive studies [212, 239, 240]. In a study of premedication prior to MAC anesthesia in renal failure elderly patients (\geq 65 years), dexmedetomidine premedication patients required significantly less propofol for sedation during the orthopedic surgery with spinal anesthesia [212]. Kim and coworkers found that the dose of dexmedetomidine to produce prescribed sedation(Observer's Assessment of Alertness/Sedation of 4/3) during prostatectomy surgery was 33% less in the older (65–78 years) patient group than the younger (45–64 years) [239]. This supports the recommendation that dosage be reduced when treating older patients. The third study examined the effect of adding dexmedetomidine or saline to total intravenous anesthesia with propofol/ remifentanil or sevoflurane in patients over 65 having orthopedic surgery [240]. Dexmedetomidine significantly reduced the Ricker's Agitation-sedation scores and patients were judged more calm on emergence and had less "dangerous emergence." As orthopedic patients constitute a significant percentage of the geriatric anesthesia practice and emergence in the elderly can be problematic, this study shows promise for the adjunctive administration of dexmedetomidine during general anesthesia.

Adverse Effects and Contraindications

Dexmedetomidine can cause hypotension and bradycardia, particulary if the bolus loading dose is given quickly. There also may be a short, transient period of elevated blood pressure with loading. The drug has produced sinus arrest and should be given with great caution to patients with varying degrees of a–v nodal conduction block or with sinus arrest. Otherwise, the dexmedetomidine is remarkably free of adverse effects. In the elderly, dosing should be reduced and hemodynamic and ventilator monitoring must be employed. The drug is given by continuous infusion for sustained effect and there may be some prolonged sedation after cessation of the infusion.

Gaps in Knowledge

- The advantages, if any, of the reduction in stress-related markers with dexmedetomidine need to be explored with regard to organ preservation and perioperative complications.
- The advantages in the frail elderly population should be more fully elucidated.
- The interaction of dexmedetomidine with other drugs in the elderly needs further study to characterize better the interactions of age and drug combinations.
- The effect of intraoperative ketamine on postoperative delirium in patients is not subjected to stress of CPB.
- Long-term cognitive effects of elderly patients receiving ketamine as analgosedation in the ICU.

Summary

This chapter has surveyed the pharmacology of frequently used intravenous hypnotic agents in the geriatric patient. There is substantial evidence of significant changes in the PK and PD behavior of propofol, thiopental, midazolam, ketamine, dexmedetomidine, and etomidate in this

population. A few final points remain when considering the general changes for each of these hypnotic agents. First, practitioners should perform a thorough review of the cardiopulmonary status of all geriatric patients, because an absence of complaints in a review of systems may merely be a function of a sedentary lifestyle. A more extensive history may elicit findings that would alter the method of induction or the combination/doses of drugs used for anesthesia. Second, a full review of the current medical management of systemic disease should be performed, because the elderly population often presents for surgery with outpatient polypharmacy. Particular attention should be given to current use of antihypertensive, diuretic, antidepressant, anti-Parkinsonian, and erectile dysfunction agents, with vigilance given to careful blood pressure monitoring when using the induction agents reviewed in this chapter in patients who are taking one or several of these medications. Third, a thorough understanding of the changes in the PK and PD of opioids in the geriatric patient is critical when combining them for sedation or general anesthesia in this population. Finally, unless a rapid sequence induction is indicated, a slow and careful titration of the induction of anesthesia using smaller doses of hypnotic agents and some form of an EEG monitor will prevent overdosing, subsequent hypotension, and delayed awakening in this population.

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The Pharmacology of Intravenous Opioids

Stephanie Whitener, Matthew D. McEvoy, Steven L. Shafer, and Pamela Flood

General Observations

Opioids are among the most effective and the most dangerous of the drugs administered by anesthesiologists. With the growing epidemic of opioid abuse and overdose in the general population, it is important to review the specific consideration for prescribing them in the elderly population. In the United States, between 1993 and 2012, opioid overuse has more than doubled with the elderly population showing some of the largest rates of increase. The World Health Organization proposed a three-step analgesic ladder for the treatment of chronic pain. They recommended starting with acetaminophen and nonsteroidal analgesics, progressing to opioids of intermediate strength, such as codeine, and treating severe pain with strong opioids such as morphine [1]. The Agency for Health Care Policy and Research (now called the Agency for Healthcare Research and Quality) has issued similar guidelines [2]. Particular care must be taken when using opioids in elderly patients. It is nearly tautological that elderly patients are more likely to suffer from chronic diseases than their younger counterparts. Some fortunate individuals remain physically vigorous until very late in life, whereas others seem to deteriorate physically at younger ages. Additionally, the cumulative effects of smoking, alcohol, and environmental toxins can accelerate the deterioration of aging in exposed individuals. Thus, it is not surprising that variability in physiology increases throughout life [3]

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S.L. Shafer • P. Flood Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University, Palo Alto, CA, USA (see Chap. 1). Increased physiologic variability results in increased pharmacokinetic and pharmacodynamic variability in elderly subjects. The clinical result of this increased variability is an increased incidence of adverse drug reactions in elderly patients [4]. Thus, elderly patients require more careful titration and, where possible and appropriate, therapeutic drug monitoring [5].

The Opioid Receptor

The existence of an opioid receptor was long suspected because of the high potency and stereoselectivity of pharmacologic antagonists. The biochemical discovery of opioid receptors was independently reported in 1973, by laboratories of Pert [6], Simon [7], and Terenius [8]. The finding of stereoselectivity led to an intense search for endogenous ligands, with identification of encephalin in 1975 [9]. Other endogenous peptide ligands were isolated subsequently [10, 11]. The fact that endogenous opioid ligands differed in their structure and binding sites suggested the existence of different opioid receptor types [12]. Three classes of opioid receptors were identified pharmacologically in the 1980s: μ (mu) [13], δ (delta) [14], and [15] κ (kappa).

Activation of the μ receptor is responsible for both the analgesic efficacy of the frequently used opioids and, unfortunately, for the majority of opioid toxicities. Shortly after characterization of the μ receptor, Pasternak and colleagues [16] demonstrated that there were two populations of opioid receptors: a high-affinity site, associated with analgesia and blocked by naloxazone, and a lower-affinity site, which was not blocked by naloxazone and seemed responsible for morphine lethality. It was subsequently demonstrated that morphine-induced analgesia was mediated by a population of receptors blocked by naloxonazine, which were termed μ_1 receptors, whereas morphine-induced ventilatory depression was blocked by a population of receptors that were not affected by naloxonazine, which

were termed the μ_2 receptors [17, 18]. To further complicate matters, a selective morphine-6-glucuronide antagonist was identified, 3-O-methylnaxtrexone, which had little effect on morphine analgesia [19]. This suggested that there was variability within the μ_1 receptor itself. Although identification of a specific μ_1 antagonist led to the hope that a μ_1 -specific agonist could be developed, no such agonist has ever been identified.

Additional evidence for μ receptor subtypes comes from the clinical observation of incomplete cross-tolerance among the opioids in patients [20], so that if a patient is switched from an opioid to which the patient has become tolerant to an "equianalgesic" dosage of another opioid, the potential exists for serious overdose [21]. Additional evidence for multiple μ receptor subtypes comes from variance in the potency for analgesic efficacy and toxicity among patients, such that there is no single opioid that has the best therapeutic window for all patients [21]. An extreme example of differential response to opioids is found in the CXBK mouse, which is insensitive to morphine but has normal sensitivity to fentanyl and morphine-6-glucuronide [22].

The μ opioid subtypes have unique distributions within the body [23]. Specifically, μ_1 is expressed in the brain, whereas μ_2 is expressed in the brain, gastrointestinal tract, and the respiratory tract [24]. Activation of both μ receptor subtypes acts to decrease calcium and potassium conductance and intracellular adenosine 3',5'-cyclic monophosphate (cAMP). The recently discovered μ_3 receptor is expressed on monocytes, granulocytes, and the vascular endothelium, where it acts to release nitric oxide [25]. Some of the vasodilatation that is associated with opioid administration that has been attributed to histamine release may be attributable to the activation of the μ_3 receptor.

The μ receptor is encoded by a single gene *Oprm*, located on chromosome 10 in the mouse [26, 27] and on chromosome 6 in the human [28]. A variety of polymorphisms of *Oprm* have been identified in humans, as recently reviewed by Lötsch and Geisslinger [28]. The polymorphism that has generated the most interest has been the substitution of an aspartate for an asparagine in the 118 position, which is abbreviated as the 118A > G SNP. This polymorphism has been associated with a decreased analgesic response to morphine. However, it does not reduce sensitivity to opioidinduced ventilatory depression [29].

The *Oprm* gene gives rise to a family of μ receptors through selective splicing of the mRNA into μ opioid receptor subtypes [30]. In 1993, the first μ receptor was cloned, MOR-1 [31, 32]. Since then, at least 15 different splice variants of MOR-1 have been identified in mice, all derived from the same *Oprm* gene [24]. Several splice variants have been identified in humans as well [33]. Splice variants likely give rise to pharmacologically identified subtypes of μ receptors based on the exons that are translated. Unfortunately, mapping between individual splice variants and pharmacologically identified μ subtypes is incomplete. The currently identified splice variants are insufficient to explain the pharmacologic groupings, although this would likely become clearer as additional splice variants are discovered and characterized pharmacologically.

All opioid receptors so far identified are coupled to G_i proteins [34]. At the cellular level, the opioid receptors have an inhibitory effect. When the receptors are occupied by opioid agonists, intracellular cAMP content is reduced. Reduced levels of cAMP both increase the activation of K⁺ channels and reduce the probability of voltage-gated calcium channels being open. These changes cause hyperpolarization of the membrane potential and thus reduce neuronal excitability [35].

The last 15 years have seen a resurgence of interest in the molecular basis of opioid signaling, driven by the discovery that opioids couple with β -arrestin-2 as well as with G_i proteins. [36] It appears that analgesia is mediated by the G_i pathway, while tolerance, addiction, constipation, and respiratory depression are mediated by the β -arrestin-2 pathway. [37] This discovery led to the search "biased ligands," opioids that preferentially signal through the G_i pathway, providing analgesia, with reduced signaling through the β -arrestin-2 pathway, mitigating toxicity [38]. Several opioid agonists with minimal activation of the β -arrestin-2 pathway are in active drug development [39, 40]. Initial clinical studies with oliceridine suggest that it has efficacy similar to morphine in a surgical pain model. [41]If these novel "biased" opioids are eventually approved for clinical use, their enhanced safety may render the opioids discussed in this chapter obsolete.

Aging and Opioid Receptors

End-organ sensitivity to various ligands changes with age. Part of this change is from differences at the level of the drug receptor-effector mechanism. For example, Ueno and colleagues [42] examined opioid receptors in young, mature, and aged mice. Aged mice had reduced µ receptor density but increased µ receptor affinity. Hess et al. [43] also observed decreased µ receptor density in rats with advancing age, associated with decreased sensitivity to pain. Similarly, Petkov and colleagues [44] observed decreased enkephalin receptors in aged rats, as well as decreased sensitivity to enkephalin. Aging may induce changes downstream of opioid receptor binding. In studies on opioid receptors in polymorphonuclear leukocytes, Fulop and colleagues [45] have shown that whereas cAMP was reduced on binding in cells from young adult animals, it was increased in cells from aged animals. Hoskins and Ho [46] have shown age-induced changes in the basal activities of adenylate cyclase, guanylate

cyclase, cAMP phosphodiesterase, and cyclic guanosine monophosphate phosphodiesterase.

Smith and Gray [47] examined the analgesic response to opioids in young and aged rats. They applied noxious stimulus at two different stimulus intensities. At the low-intensity stimulus (immersing the tail in 50 °C water), there was a trend toward increased sensitivity to opioids in the aged rats, but the difference was not significant. However, when subjected to high-intensity stimulus (immersing the tail in 55 °C water), the aged rats were about twice as sensitive to opioids as the young rats, an effect that was significant.

Other investigators have reached quite different conclusions using similar experimental paradigms (tail flick after immersion in hot water). Van Crugten and colleagues [48] looked at morphine antinociception in aged rats and found no difference in antinociception between aged and adult animals. Hoskins and colleagues [49] found that aged mice were about half as sensitive to morphine as mature adult mice.

In summary, the overall evidence in animal models shows decreased numbers of opioid receptors in aged brains. However, the story about the antinociceptive response to morphine is less clear in animal models, with studies showing increased sensitivity, decreased sensitivity, or no change in sensitivity with advancing age.

Aging and Pain Perception

Pain is a part of daily life for many elderly patients, with about 50% of elderly patients in a community setting having chronic pain with the prevalence being higher among elderly patients in long-term care facilities [50]. Elderly patients are particularly more prone to chronic pain than younger people [51, 52]. However, clinically it seems that pain in elderly subjects is indistinguishable from the experience of pain in younger subjects [53].

There are some interesting differences between young and older subjects in their response to experimental pain. There is some evidence that older patients are more sensitive to experimental pain [54], which may be explained by a reduction in the endogenous analgesic response to pain [55, 56], possibly mediated by reduced production of β -endorphin in response to noxious stimulation [57]. Older patients experience a more prolonged hyperalgesia after capsaicin injection compared with younger subjects [58]. Additionally, older patients seem to also require a higher intensity of noxious stimulation before first reporting pain [56].

Some of the differences between studies may also depend on exactly which pain pathways are activated during the assessment. Chakour and colleagues [59] demonstrated that pain transmission via C fibers was unchanged in young versus elderly subjects. However, there was a substantial reduction in pain transmission via $A\delta$ fibers. Thus, the relative perceptions of pain in elderly subjects versus younger subjects were influenced by the extent of pain transmission via $A\delta$ fibers.

Aging and Risk of Opioid-Related Side Effects

While pain is a common occurrence in the lives of the elderly population, and certainly is of concern in the perioperative period, care must be taken in providing analgesia with opioids because of the alterations in the risk of respiratory depression. In their secondary analysis of a retrospective cohort study, Cepeda and colleagues [60] noted that the risk of opioid-induced ventilatory depression increased with increasing age, with patients 61–70 years of age having 2.8 times the risk of ventilatory depression compared with patients 16–45 years old. Interestingly, in their analysis, they converted all of the opioids into morphine equivalents, and the conversion did not account for the increased potency of opioids in the elderly that will be described subsequently.

Although the risk of respiratory depression from opioids is greater in older people, the same is not true for all opioid side effects. Opioids are among the major causes of postoperative nausea and vomiting, increasing the risk nearly fourfold [59]. In the study by Cepeda et al., age was not a risk factor for nausea and vomiting [60]. In fact, age may actually decrease the risk of nausea and vomiting. Sinclair and colleagues [61] observed a 13% decrease in the risk of postoperative nausea and vomiting with each additional decade of life. This finding is consistent with the findings of Junger and colleagues [62].

The Onset and Offset of Opioid Drug Effect

Onset

The onset of opioid drug effect is determined by the route of delivery, the delivered dose, the pharmacokinetics of the opioid that determine the plasma concentrations over time, and the rate of blood–brain equilibration between the plasma and the site of drug effect. Table 18.1 shows adult pharmacokinetics of fentanyl [63], alfentanil [63], sufentanil [64], remifentanil [65], morphine [66], methadone [67],¹ meperidine [68],² and hydromorphone [69]. Table 18.1 also shows k_{e0} , the rate constant for blood–effect-site equilibration, fentanyl [63], alfentanil [63], sufentanil [70], remifentanil [65],

¹Data extensively reanalyzed to obtain volume and clearance estimates. ²Original data provided by S. Bjorkman and fit using population model to create estimates in Table 18.1.

	Fentanyl	Alfentanil	Sufentanil	Remifentanil	Morphine	Methadone	Meperidine	Hydromorpho
Volumes (L)								
V_1	12.7	2.2	17.8	4.9	17.8	7.7	18.1	11.5
V_2	50	7	47	9	87	12	61	115
V_3	295	15	476	5	199	184	166	968
Clearances (L/min)								
Cl_1	0.62	0.20	1.16	2.44	1.26	0.13	0.76	1.33
Cl_2	4.82	1.43	4.84	1.75	2.27	2.19	5.44	3.45
Cl ₃	2.27	0.25	1.29	0.06	0.33	0.38	1.79	0.92
Exponents (min ⁻¹)								
α	0.67	1.03	0.48	0.96	0.23	0.50	0.51	0.51
β	0.037	0.052	0.030	0.103	0.010	0.025	0.031	0.012
γ	0.0015	0.0062	0.0012	0.0116	0.0013	0.0005	0.0026	0.0005
Half-lives (min)								
$t_{1/2}\alpha$	1.03	0.67	1.43	0.73	2.98	1.38	1.37	1.35
$t_{1/2}\beta$	19	13	23	7	68	28	22	59
$t_{1/2}\gamma$	475	111	562	60	548	1377	271	1261
Blood-brain equilibration								
$k_{e0} (\min^{-1})$	0.147	0.770	0.112	0.525	0.005	0.110	0.067	0.015
$t_{1/2}k_{e0}$ (min)	4.7	0.9	6.2	1.3	139	6.3	10.	46
T _{peak} (min)	3.7	1.4	5.8	1.6	93.8	11.3	8.5	19.6
VD peak effect (L)	76.9	6.0	94.9	17.0	590.2	30.9	143.3	383.3

Table 18.1 Pharmacokinetic parameters for frequently used opioids

Note: The references for the pharmacokinetic parameters are given in the text

VD volume of distribution

morphine [66], methadone [71], meperidine [70],³ and hydromorphone [72].⁴ Based on these data, it is possible to predict the time course of concentration change in the plasma following an intravenous bolus, as seen in Fig. 18.1. The upper graph in Fig. 18.1 shows the concentration during 24 h following a bolus injection, whereas the lower graph just shows the first 30 min. In both cases, the curves have been normalized to start at 100%, which permits direct comparison of the pharmacokinetics despite differing potencies. As seen in the upper graph, the extremes of plasma elimination are remifentanil, which is ultra fast, and methadone, which has the longest half-life. Alfentanil has the second-shortest half-life among the eight opioids. Fentanyl, meperidine, sufentanil, hydromorphone, and morphine are all clustered in the middle. In particular, note how similar hydromorphone and morphine are when one examines the plasma pharmacokinetics. Approximately the same trend is observed in the first 30 min, although the initial distribution phase of hydromorphone takes it nearly as low as remifentanil in the first 10 min. As will be seen shortly, this is significant in terms of recovery.

The plasma is not the site of drug effect, and thus the time course of concentration seen in Fig. 18.1 will not reflect the time course of effect-site concentration or behavioral activity. By incorporating the plasma-effect-site equilibration delay into our calculations, we can examine the time course of the onset of drug effect, as shown in Fig. 18.2. In this case, we have normalized the effect-site concentrations to peak effect concentration [73] to again permit comparisons of the time course of drugs independent of the differences in potency. Alfentanil and remifentanil both reach a peak about 1.5 min after bolus injection, although the overall remifentanil drug effect is more evanescent. The peak fentanyl concentration occurs about 3.5 min after bolus injection, whereas the peak sufentanil effect is about 6 min after bolus injection. Methadone and meperidine are nearly indistinguishable following bolus injection, each reaching a peak about 12 min after a bolus. The peak for hydromorphone is 15-20 min after the bolus. Morphine is the outlier in terms of onset. Five minutes after a bolus injection, morphine is at 50% of the peak concentration. However, morphine reaches its peak concentration in the effect site about 90 min after the bolus injection. Table 18.1 shows the time to reach peak concentration for each of the opioids, as well as the volume of distribution at the time of peak effect, which is useful for calculating initial loading doses [74-76].

³Based on a time to peak of 8.5 min in goats ()! It is not great, but it is the best onset data available.

⁴Based on a time to peak effect of 15-20 min.

Fig. 18.1 The time course of plasma concentration following a bolus of fentanyl, alfentanil, sufentanil, remifentanil, morphine, methadone, meperidine, and hydromorphone, based on the pharmacokinetics shown in Table 18.1. The y-axis is the percent of the initial concentration, which by definition is 100% at time 0, permitting display of the relative time courses of these opioids independent of the dose administered

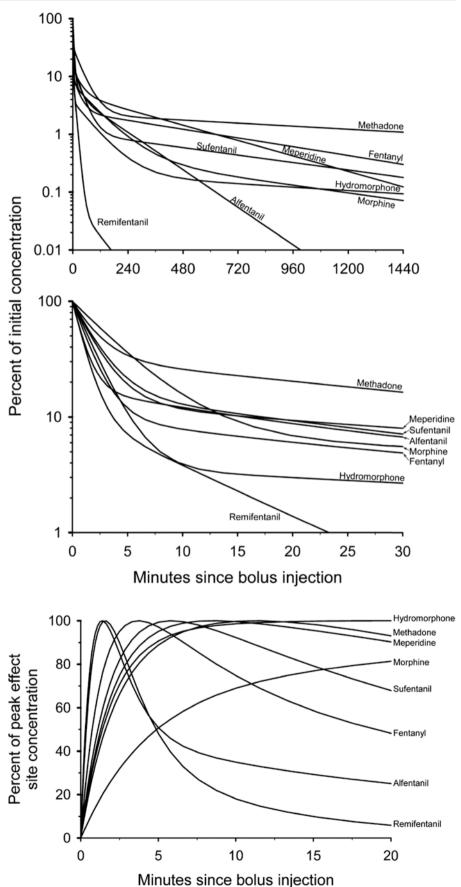


Fig. 18.2 The time course of effect-site concentration following a bolus of fentanyl, alfentanil, sufentanil, remifentanil, morphine, methadone, meperidine, and hydromorphone, based on the pharmacokinetics and rate of plasma-effect-site equilibrium shown in Table 18.1. The curves have been normalized to the peak effect-site concentration, permitting comparison of the relative rate of increase independent of dose. The times to peak effect correspond to those shown in Table 18.1

	Fentanyl	Alfentanil	Sufentanil	Remifentanil	Morphine	Methadone	Meperidine	Hydromorphone
MEAC (ng/mL)	0.6	14.9	0.056	1.0	8	60	250	1.5
Equipotent bolus dose at:	(µg)	(µg)	(µg)	(µg)	(mg)	(mg)	(mg)	(mg)
Peak effect	50	92	5.5	17	4.9	1.9	37	0.6
10 min	50	197	4.4	72	5.3	1.4	28	0.4
30 min	50	174	3.9	282	2.0	0.9	17	0.2

 Table 18.2
 Relative potency of frequently used opioids, based on the time of the observed effect

One clinical applications of the time course of drug effect following bolus injection is to guide programming of the lockout of PCA devices. A 10-min lockout for hydromorphone and methadone is a logical choice, because patients are able to make a decision to redose themselves after reaching peak drug effect. The slower onset of morphine is somewhat problematic, because patients will administer another dose while the prior dose is still reaching peak effect, creating the possibility of stacking bolus doses.

Considerable attention is given to "equianalgesic dosing" of opioids. The calculation of the equianalgesic dose is complicated by the relative intrinsic potency of the opioids, the different pharmacokinetic profiles, and the large differences in the rate of blood-brain equilibration. Table 18.2 shows equianalgesic doses of frequently used opioids, based on the "minimum effective analgesic concentrations" or "MEAC" (also called "MEC") of fentanyl [77], alfentanil [78], sufentanil,⁵ remifentanil,⁶ morphine [80],⁷ methadone [81], meperidine [82], and hydromorphone [72, 83].⁸ Reflecting anesthesiologists' familiarity with fentanyl, all of the calculations have been made using fentanyl as the reference opioid. The calculation of an equianalgesic bolus dose depends on when the observation of drug effect is made. For example, because fentanyl has a very rapid onset, and morphine has a very slow onset, 5 mg of morphine has the same effect at 10 min as 50 µg of fentanyl, whereas 60 min after the dose, 1 mg of morphine has the same effect as 50 μ g of fentanyl. Similarly, because the drugs accumulate during infusions at different rates, the relative potencies of the opioids change depending on how long the infusion has been running, as shown in Table 18.2.

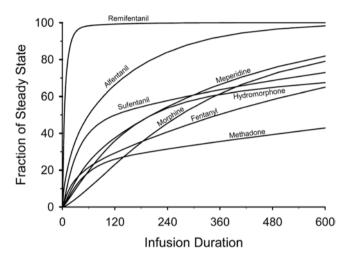


Fig. 18.3 The increase to steady state during an infusion of fentanyl, alfentanil, sufentanil, remifentanil, morphine, methadone, meperidine, and hydromorphone, based on the pharmacokinetics and rate of plasma–effect-site equilibrium shown in Table 18.1. The curves have been normalized to the steady-state effect-site concentration, permitting comparison of the relative rate of increase independent of infusion rate. Only remifentanil and alfentanil are at steady state after 10 h of continuous infusion

Figure 18.3 shows the increase in effect-site concentration during a continuous infusion for each of these opioids. As expected, remifentanil increases the fastest, whereas methadone increases the slowest. Note, however, that even after 10 h of drug administration, most of these opioids are only at 60–80% of the eventual steady-state concentration. This speaks to the problem of background infusions for PCA. Even after many hours, patients are not at steady state, and the increasing drug concentration from the background infusion may expose a patient to toxicity 12–24 h after initiation of the infusion. Given the increased sensitivity of elderly patients to the effects of opioids, background infusions are likely a particularly poor choice in this population.

Offset

The offset of drug effect is a function of both the pharmacokinetic behavior and the rate of blood–brain equilibration. The "context-sensitive half-time" [73, 84] is a useful way to consider the plasma pharmacokinetic portion of the offset

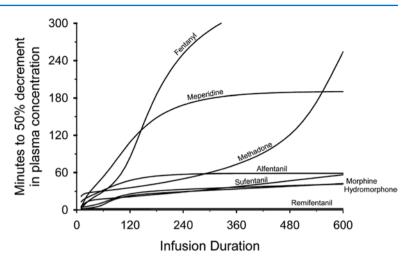
⁵Scaled to fentanyl based on relative electroencephalogram (EEG) potency of fentanyl [63] and sufentanil [79].

⁶Scaled to fentanyl based on the relative EEG potency of fentanyl and remifentanil [65].

⁷he MEC range given by Dahlstrom was 6–31 ng/mL, with a mean of 16 ng/mL. We chose 8 ng/mL, at the lower end of the reported range, because the average value of 16 ng/mL predicted equianalgesic morphine that seemed excessive.

⁸This was the most difficult potency to determine from the literature. Hill and Zacny documented a tenfold bolus dose potency difference versus morphine, which was the final basis for calculating this number and is similar to the value suggested by the Coda paper.

Fig. 18.4 The "contextsensitive half-time" (50% plasma decrement time) for fentanyl, alfentanil, sufentanil, remifentanil, morphine, methadone, meperidine, and hydromorphone, based on the pharmacokinetics shown in Table 18.1. Remifentanil shows virtually no accumulation over time with continuous infusions, whereas the offset of fentanyl changes considerably as it is administered to maintain a steady plasma concentration



time, as shown in Fig. 18.4. The *x*-axis on Fig. 18.4 is the duration of an infusion that maintains a steady concentration of drug in the plasma. The *y*-axis is the time required for the concentrations to decrease by 50% after the infusion is terminated. Remifentanil's pharmacokinetics are so fast that the context-sensitive half-time blurs right into the *x*-axis. Perhaps surprisingly, fentanyl is the outlier here. Fentanyl accumulates in fat, and so an infusion that maintains a steady concentration in the plasma winds up giving patients a large dose of fentanyl, resulting in slow recovery. Meperidine similarly shows long recovery. Note that for infusions of less than 10 h, morphine, hydromorphone, and sufentanil are nearly indistinguishable based on the plasma pharmacokinetics.

Once again, we have to consider that the plasma is not the site of drug effect. Therefore, we must consider the 50% effect-site decrement time [73, 85], as shown in Fig. 18.5. Because fentanyl and remifentanil have very rapid plasmaeffect-site equilibration, they have changed little between Figs. 18.4 and 18.6. Note, however, the huge change for morphine and hydromorphone. One might have thought from Fig. 18.4 that these drugs would result in rapid offset of drug effect following a continuous infusion. This is clearly not the case, because the blood-brain equilibration delay results in these drugs having far slower offset than alfentanil or sufentanil. The "surprise" here is methadone. One would rarely think of methadone as a reasonable choice for infusion during anesthesia, but the pharmacokinetics of methadone suggest that it might be a reasonable choice for anesthetics of 4 h or less.

Figure 18.6 shows the 20% effect-site decrement curve for these eight opioids. Figure 18.6 speaks to how often one might expect to redose a patient with chronic pain who is titrating the analgesic level to a just-adequate concentration. Because of its slow blood–brain equilibration, morphine would need to be given approximately every 2 h. Hydromorphone, fentanyl, and methadone would need to be given approximately every hour.

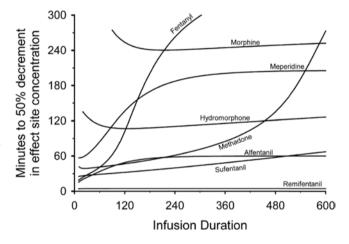


Fig. 18.5 The 50% effect-site decrement curves for fentanyl, alfentanil, sufentanil, remifentanil, morphine, methadone, meperidine, and hydromorphone, based on the pharmacokinetics and rate of plasma– effect-site equilibrium shown in Table 18.1. For drugs with rapid plasma–effect-site equilibrium, the 50% effect-site decrement curve closely follows the context sensitive half-time curve. However, for drugs with slow plasma–effect-site equilibration, a 50% decrement in effect-site concentration is considerably slower than a 50% decrement in plasma concentration (e.g., morphine)

Specific Opioids

Morphine

Morphine has three unique aspects among the opioids frequently used in anesthesia practice: it is an endogenous ligand of the μ receptor, has an active metabolite, and has a very slow onset of effect. Morphine was initially identified in the brains of mice that had never been exposed to exogenous morphine [86]. It has subsequently been found in the brains of cows [87], rats [88], and humans [89]. Codeine has also been identified as an endogenously synthesized substance. However, because codeine is mostly an inactive prodrug of

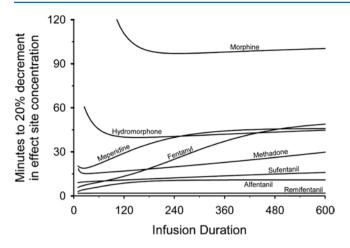


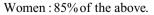
Fig. 18.6 The 20% effect-site decrement curves for fentanyl, alfentanil, sufentanil, remifentanil, morphine, methadone, meperidine, and hydromorphone, based on the pharmacokinetics and rate of plasma– effect-site equilibrium shown in Table 18.1. The effect-site levels of all opioids, except morphine, will decrease by 20% quickly when an infusion is terminated. The slower decrease for morphine is because of its slow plasma–effect-site equilibration

morphine, its presence in the brain does not diminish morphine's distinction as the only endogenous ligand of the μ receptor that is also a frequently administered drug.

Morphine is metabolized by glucuronidation into two metabolites, morphine-3-glucuronide, which is mostly inactive, and morphine-6-glucuronide, which is itself a potent analgesic [90]. Although the potency of intrathecal morphine-6-glucuronide is 650-fold higher than that of morphine [91], morphine-6-glucuronide crosses the blood-brain barrier very slowly, so slowly that it is unlikely that it contributes to the acute analgesia provided by morphine [92, 93]. However, with chronic administration, the levels of morphine-6glucuronide will increase to pharmacologically active concentrations [94].

Morphine-6-glucuronide is eliminated by the kidneys [95]. Creatinine clearance is reduced with advancing age, as shown in the often-cited equation of Cockroft and Gault [96]:

Men : Creatinine clearance (mL / min)= $\{ [140 - age(years)] \times weight(kg)] \}$ [72 × serum creatinine (mg%)]



This reduction means that the creatinine clearance of an 80-year-old patient will be about half that of a 20-year-old patient. Thus, morphine-6-glucuronide will accumulate more in elderly patients, necessitating a reduction in the dose of chronically administered morphine. Of course, if the

patient has renal insufficiency, it might be better to select an opioid without an active metabolite.

The second unique aspect of morphine is the slow onset of effect. The peak effect following a bolus dose of morphine occurs approximately 90 min after the bolus. This has been demonstrated using pupillometry [97–99], ventilatory depression [98], and analgesia [99] as measures of morphine drug effect. The likely explanation for this is that morphine is a substrate for P-glycoprotein, which actively transports morphine out of the central nervous system [100].

Figure 18.7 shows a simulation of the analgesic (y-axis > 1) and ventilatory (y-axis < 1) effects of three different morphine doses: a bolus of 0.2 mg/kg, a bolus of 0.2 mg/kg followed by an infusion of 1 mg/70 kg per hour, and repeated boluses of 0.1 mg/kg every 6 h [101]. The solid line is the median prediction, whereas the shaded area represents the 95% confidence bounds. As seen in Fig. 18.7, the time course of analgesia and ventilatory depression is similar, although the analgesia wanes somewhat faster than the ventilatory depression.

It is important to appreciate the slow onset of morphine when titrating to effect. Aubrun and colleagues [102, 103] have advocated postoperative titration of morphine in elderly patients by administering 2–3 mg boluses every 5 min. This is not logical for a drug with a peak effect about 1.5 h after bolus injection. It is surprising that Aubrum and colleagues did not see any toxicity with this approach, given the potential for accumulation with repeated titration of small doses of morphine to effect. However, it does explain why their study is unique in finding that elderly patients require the same amount of opioid as younger patients.

Meperidine

Meperidine, also called "pethidine," has little role in the management of pain. Meperidine is still a popular drug because of the familiarity of its use, particularly among surgeons and obstetricians. Meperidine is unique among opioids in that it has significant local anesthetic activity [104, 105]. Meperidine has been used as the sole analgesic intra-thecally for obstetric anesthesia, but its benefit over a combination of local anesthetic with another opioid is unclear. The only unique perioperative role for meperidine is the treatment of postoperative shivering, in which doses of 10–20 mg are typically effective.

The problems with meperidine are its complex pharmacology and its toxic metabolite. Holmberg and colleagues [106] examined the pharmacokinetics of an intravenous meperidine bolus in young and elderly surgical subjects. They found that elderly patients had reduced meperidine clearance, resulting in a longer half-life for meperidine.

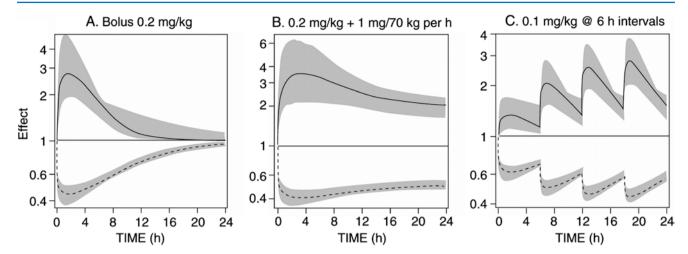


Fig. 18.7 Simulated analgesic (y > 1) and ventilatory (y < 1) effects of three different doses of morphine: 0.2 mg/kg (**a**), 0.2 mg/kg plus an infusion of 1 mg/70 kg/h (**b**), and a bolus of 0.1 mg/kg every 6 h (**c**). The analgesic and ventilatory effects peak concurrently, about 90 min after

the morphine bolus. Because the concentration versus response relationship is steeper for analgesia than ventilatory depression, the analgesic effect dissipates before the ventilatory depression (Reprinted from Dahan et al. [101]. With permission from Wolters Kluwer Health, Inc.)

There was minimal change in the initial volume of distribution. The clinical implication is that the initial dose of meperidine in elderly subjects should not be reduced based on pharmacokinetics, but meperidine will accumulate in elderly subjects with repeated administration. This makes meperidine a particularly poor choice for administration by PCA in elderly patients [107].

A worrisome aspect of meperidine is the toxic metabolite, normeperidine (or "norpethidine"). In a subsequent study, Holmberg and colleagues examined the renal excretion of both meperidine and normeperidine in elderly surgical patients [108]. Renal excretion was reduced in elderly patients, particularly for normeperidine. The result is that normeperidine will likely accumulate with repeated doses in elderly patients. Because normeperidine is highly epileptogenic, meperidine is probably a poor choice for PCA or other forms of continuous opioid delivery in elderly patients.

Meperidine has several other unique aspects to its pharmacology. It is the only negative inotrope among the opioids [109]. Meperidine also has intrinsic anticholinergic properties, which can result in tachycardia. Elderly patients with coronary artery disease are clearly at risk of adverse events if given drugs that have negative inotropic or positive chronotropic effects.

Last, meperidine is associated with several unusual reactions, including the potential for acute serotonergic syndrome when combined with monoamine oxidase (MAO)-A inhibitors and a significant increase of delirium in elderly patients compared to other opioids [110]. Fortunately, the classic MAO-A inhibitors, phenelzine (Nardil), tranylcypromine (Parnate), and isocarboxazid (Marplan), are now rarely used. Selegiline, often used in Parkinson's disease, is a weak MAO-B inhibitor and has been implicated in one nonfatal interaction with meperidine [111]. However, given the polypharmacy common in elderly patients, it would seem wise to avoid using meperidine when opioids with more selective pharmacology and inactive metabolites are available.

Hydromorphone

Hydromorphone in many aspects acts as a rapid-onset morphine. However, it lacks the histamine release associated with morphine and does not have active metabolites. There are no studies explicitly examining the role of age in hydromorphone pharmacokinetics or pharmacodynamics. In fact, there are surprisingly few studies examining the perioperative use of hydromorphone. Keeri-Szanto [112] found intraoperative hydromorphone to be approximately eight times more potent than morphine, with a half-life of 4 h versus 5 h for morphine. Kopp et al. [113] investigated whether 4 mg of hydromorphone provided any evidence of preemptive analgesia and found that it did not.

Rapp and colleagues [114] compared hydromorphone PCA to morphine PCA in postoperative patients following lower abdominal surgery. They found that hydromorphone PCA was associated with better mood scores, but with increased incidence of nausea and vomiting. They found that 1 mg of hydromorphone was approximately equianalgesic with 5 mg of morphine. This is about half as potent as suggested by Hill and Zacny [72], who determined that hydromorphone was tenfold more potent than morphine. Although Rapp and colleagues did not specifically study the effects of age, one would expect this ratio to be independent of age in the immediate postoperative period. Because morphine has an active metabolite that accumulates and hydromorphone does not, the apparent potency of morphine relative to hydromorphone may increase with chronic administration.

Lui and colleagues [115] compared epidural hydromorphone to intravenous hydromorphone, both administered by PCA in a double-blind/double-dummy protocol. They found more pruritus in patients receiving epidural hydromorphone, but no differences in postoperative analgesia, bowel function, or patient satisfaction. Overall, hydromorphone in the epidural group was half of that in the intravenous group, indicating that hydromorphone is acting spinally when administered via the epidural route. Hydromorphone and morphine both reach their peak concentrations in the cervical cerebrospinal fluid about 60 min after epidural administration [116], suggesting they have similar potential for delayed ventilatory depression after epidural administration. In a study of obstetric patients, Halpern and colleagues [117] found 0.6 mg of hydromorphone to be clinically indistinguishable from 3 mg of morphine, consistent with the 1: 5 relative potency reported for intravenous hydromorphone and morphine in the postoperative period.

Fentanyl

Fentanyl is among the "cleanest" opioids in terms of pharmacology. It has a rapid onset, predictable metabolism, and inactive metabolites. It is (obviously) the first of the "fentanyl" series of opioids, notable for their rapid metabolism and selective μ potency. It is the only one of the opioids that is available for transdermal and transmucosal delivery, although these methods of administration are being investigated for sufentanil as well.

Bentley et al. [118] studied aging and fentanyl pharmacokinetics in young and elderly groups of patients. They found that fentanyl clearance was decreased among the elderly, resulting in a prolonged half-life.

Scott and Stanski [63] used high-resolution arterial sampling during and after a brief fentanyl infusion to characterize the influence of age on the pharmacokinetics of fentanyl. These investigators did not find any effect of age on the pharmacokinetics of fentanyl or alfentanil, except for a small change in rapid intercompartmental clearance.

The minimal influence of age on the pharmacokinetics of fentanyl was subsequently confirmed by Singleton and colleagues [119]. These investigators found no change in the dose-adjusted concentration of fentanyl between young and elderly patients, except for a transient increase in concentration in elderly individuals at 2 and 4 min after the start of the infusion. These findings are consistent with the decreased rapid intercompartmental clearance reported by Scott and Stanski. 60

Age (years)

80

70

90

14

12

10

8

6

4

2

0

20

30 40

C₅₀ (ng/ml)

S. Whitener et al.

Fig. 18.8 The influence of age on the 50% maximal effective dose (C_{50}) of fentanyl, as measured by electroencephalogram depression. Although there is considerable variability, overall there is about a 50% reduction in C_{50} from age 20 to age 80, reflecting increased brain sensitivity. This has been shown for alfentanil [66] and remifentanil [68] and appears to be a class effect of opioids (Adapted with permission from Scott and Stanski [63]. With permission from American Society for Pharmacology and Experimental Therapeutics)

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Scott and Stanski used the EEG as a measure of drug effect to estimate the potency of fentanyl [63, 120]. They observed a decrease of approximately 50% in the dose required for 50% of maximal EEG suppression (C_{50}) from age 20 to age 85, as shown in Fig. 18.8. Because the pharmacokinetics of fentanyl seem nearly unchanged by age, it is likely that elderly patients require less fentanyl because of intrinsic increased sensitivity to opioids. Put another way—the elderly brain is twice as sensitive to opioids as a younger brain. This predicts that elderly patients require half of the fentanyl that younger patients require. Because the pharmacodynamics of fentanyl (i.e., the C_{50}) is affected by age, and not the pharmacokinetics, the offset of fentanyl drug effect in elderly patients who receive an appropriately reduced dose of fentanyl should be as fast as it is in younger patients.

The 50% reduction in fentanyl suggested by Scott and Stanski's integrated pharmacokinetic/pharmacodynamic model is in reasonable agreement with an analysis by Martin and colleagues [121] of intraoperative fentanyl utilization. Using the automated electronic record system in place at Duke University Hospital, they found that intraoperative doses of fentanyl decreased by about 10% per decade after age 30.

Other Fentanyl Delivery Systems

Fentanyl is also available in two unique dosage forms: oral transmucosal fentanyl citrate and transdermal fentanyl. Holdsworth and colleagues [122] studied pharmacokinetics and tolerability of a 20-cm² transdermal fentanyl patch in young and elderly subjects. Plasma fentanyl concentrations were nearly twofold higher in the elderly subjects compared with younger subjects, reflecting either increased absorption or decreased clearance. Given that fentanyl clearance seems

unchanged in the elderly, the likely explanation is that transdermal fentanyl absorption is more rapid in elderly patients, possibly because the skin is thinner and poses less of a barrier to fentanyl absorption. The increased concentrations in elderly subjects were associated with increased adverse events—so much so that the patch was removed for the study in every elderly subject, whereas none of the patches were removed in younger subjects.

Davis and colleagues [123] also noted that the time course of absorption of fentanyl through the skin is delayed in the elderly, with subcutaneous fat acting as secondary reservoir leading to prolonged release even after the removal of the patch.

Kharasch and colleagues [124] examined the influence of age on the pharmacokinetics and pharmacodynamics of oral transmucosal fentanyl citrate (the fentanyl "lollipop"). They found no change in the pharmacokinetics of fentanyl with age, including the absorption characteristics of the buccal mucosa. Perhaps unexpectedly, they also found no increase in sensitivity to fentanyl, as measured by pupillary miosis. Thus, in their view, the data do not support reducing the dose of oral transmucosal fentanyl citrate in elderly patients.

Alfentanil

The relationship between opioids and age becomes more complex when we consider alfentanil. Scott and Stanski [63] reported similar findings for alfentanil as previously described for fentanyl. In particular, they did not find any effect of age on the pharmacokinetics of alfentanil, except for a small change in the terminal half-life. Shafer et al. [125] also reported no relationship between age and alfentanil pharmacokinetics. Sitar and colleagues [126] reported a modest decrease in alfentanil clearance and central compartment volume in elderly subjects. In a study that used historical control data, Kent and colleagues [127] also reported a modest decrease in alfentanil clearance with advancing age. Lemmens et al. [128] observed that the pharmacokinetics of alfentanil in men (as studied exclusively by Scott and Stanski) were unaffected by age, whereas the pharmacokinetics in women showed a clear negative correlation between age and clearance.

In an effort to sort out these modestly conflicting results, Maitre et al. [129] pooled alfentanil concentration data from multiple prior studies and performed a population pharmacokinetic analysis to estimate the influence of age and gender on the pharmacokinetics of alfentanil. Maitre et al. found that clearance decreased with age and that the volume of distribution at steady state increased with age, the net effect being a longer terminal half-life with increasing age. That might sound like the end of the story, except that Raemer and colleagues [130] prospectively tested the Maitre et al. pharmacokinetics in two groups of patients, young women and elderly men, using computer-controlled drug administration. In this prospective test, the pharmacokinetics reported by Maitre et al. did *not* accurately predict the observed plasma alfentanil concentrations. However, pharmacokinetics reported by Scott and Stanski, which predict no influence of age or gender on alfentanil pharmacokinetics, accurately predicted the concentrations in both young women and elderly men. From these results, we can conclude that pharmacokinetics of alfentanil does not change in a clinically significant manner with age.

Although they found no change in pharmacokinetics with age, Scott and Stanski demonstrated that the C₅₀ for EEG depression with alfentanil decreased by 50% in elderly subjects, nearly identical to the increased potency of fentanyl in elderly subjects [66]. This would suggest that, based on pharmacokinetic alterations with age, the dose of alfentanil in elderly patients should be about half of the dose that would be used in younger patients. Unfortunately, subsequent studies by Lemmens et al. [131-133], based on clinical endpoints, found no influence of age on the pharmacodynamics of alfentanil. However, Lemmens et al. [134] observed that the alfentanil dose required to maintain adequate anesthesia, when administered by target-controlled infusion, was decreased by approximately 50% in elderly subjects. Thus, Lemmens et al. saw a similar change in dose-response relationship, in that the elderly required half as much opioid as younger subjects, but could not explain it as a pharmacodynamic difference. However, it is a bigger difference in concentration than any of the pharmacokinetic studies would have predicted, and there was no control group-the control group was a historical control group.

Where this leaves us is that there are many studies suggesting that the alfentanil dose in elderly subjects is about half of the dose in younger subjects. The available data suggest that the change is probably pharmacodynamic, but there may be a pharmacokinetic component to the increased sensitivity as well. If the change is mostly pharmacodynamic, perhaps, with a modest change in terminal half-life in elderly subjects, then the offset of alfentanil should be as fast in older subjects as it is in younger subjects, provided the dose has been appropriately reduced.

Sufentanil

Sufentanil is the most potent of the available opioids, with its potency approximately tenfold greater than fentanyl. [79] Age has, at most, only a modest influence on sufentanil pharmacokinetics. Helmers and colleagues [135] found no change in sufentanil pharmacokinetics between young and elderly subjects. Similarly, Gepts and colleagues [136] found no effect of age on sufentanil pharmacokinetics in a complex

population analysis. Matteo and colleagues [137] found that the central compartment volume of sufentanil was significantly decreased in elderly patients. This modest pharmacokinetic difference in elderly subjects would be expected to increase the effects of sufentanil in the first few minutes after a bolus dose and not subsequently. However, the elderly patients in Matteo's study were far more sensitive to sufentanil than the younger subjects. Six of seven elderly patients required naloxone at the end of this study, whereas only one of seven young patients required naloxone. Matteo et al. concluded that elderly patients had increased sensitivity to a given concentration of sufentanil, similar to the increased sensitivity to fentanyl and alfentanil in elderly patients described by Scott and Stanski.

Thus, based on the twofold increase in brain sensitivity to opioids demonstrated for fentanyl and alfentanil in elderly patients, one might expect similar increase in brain sensitivity to sufentanil in elderly patients. Thus, it is surprising that Hofbauer and colleagues [138] did not observe any influence of age on the sufentanil requirement of mechanically ventilated patients in the intensive care unit.

Remifentanil

Remifentanil has the fastest and most predictable metabolism of any of the available opioids. Remifentanil was introduced into clinical practice under Food and Drug Administration guidelines that mandated explicit pharmacokinetic and pharmacodynamic analysis for special populations, including elderly subjects. Thus, the influence of age on remifentanil pharmacokinetics and pharmacodynamics was established in high-resolution trials about three times larger than the trials for fentanyl, alfentanil, or sufentanil. The pharmacokinetic and pharmacodynamic models for remifentanil were reported by Minto and colleagues. [65] In a companion article, Minto et al. [139] used computer simulation to examine the implications of the complex age-related changes on remifentanil dosing. The pharmacokinetics of remifentanil changes with age, as shown in Fig. 18.9. With advancing age, V₁, the volume of the central compartment, decreases about 20% from age 20 to 80. Concurrently, clearance decreases about 30% from age 20 to age 80. Figure 18.10 shows the age-related changes in remifentanil pharmacodynamics. As also observed for fentanyl and alfentanil, the C_{50} for EEG depression is reduced by 50% in elderly subjects, suggesting that remifentanil has about twice the intrinsic potency in elderly subjects as in younger subjects. The $t_{1/2}$ k_{e0} , half-time of plasma-effect-site equilibration, is also increased in elderly subjects. In the absence of other changes, this would mean that the onset and offset of remifentanil drug effect will be slower in elderly patients.

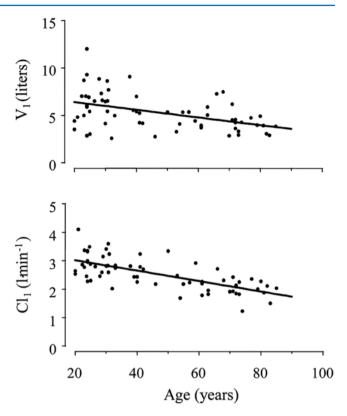


Fig. 18.9 The influence of age on remifentanil pharmacokinetics. With advancing age, the volume of the central compartment decreases by 50% from age 20 to age 80, and the clearance decreases by 66% (Adapted from Minto et al. [65]. With permission from Wolters Kluwer Health, Inc.)

Figure 18.11 uses computer simulations to examine the time course of blood concentration (solid lines) and effectsite concentration (dashed lines) after a unit bolus of remifentanil. The blood concentrations are higher in elderly subjects because of the smaller central compartment concentration. However, the slower $t_{1/2} k_{e0}$ in elderly subjects results in less-rapid equilibration. As a result, the effect-site concentrations in elderly individuals do not increase higher than the effect-site concentrations in young individuals. However, the onset and offset are slower in elderly individuals. For example, in a young individual, the peak drug effect is expected about 90 s after a bolus injection. In an elderly individual, the peak effect is expected about 2–3 min after bolus injection.

Figure 18.12 shows the influence of age and weight on remifentanil dosing. As seen in the top graph of Fig. 18.12, elderly subjects need about half of the bolus dose as younger subjects to achieve the same level of drug effect. This is not because of the change in pharmacokinetics. As shown in Fig. 18.11, the peak effect-site levels after a bolus of remifentanil are nearly identical in young and elderly subjects. Rather, the remifentanil bolus is reduced in elderly subjects because of the increased sensitivity of the elderly brain to

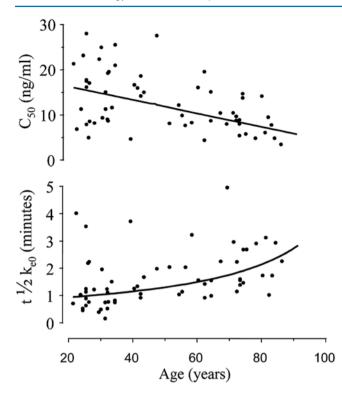


Fig. 18.10 The influence of age on remifentanil pharmacodynamics. With advancing age, the 50% effective concentration (EC₅₀) declines, reflecting a nearly identical increase in intrinsic potency as seen with fentanyl and alfentanil. Additionally, half-time of blood–brain equilibration ($t_{1/2} k_{e0}$) increases (Adapted from Minto et al. [65]. With permission from Wolters Kluwer Health, Inc.)

opioid drug effect, exactly as reported for fentanyl and alfentanil. The bottom graph in Fig. 18.12 shows that elderly subjects require about one-third as rapid an infusion as younger subjects. This reflects the combined influences of the increased sensitivity and the decreased clearance in elderly individuals.

As seen in Fig. 18.12, the influence of weight on remifentanil dosing is considerably less than the influence of age. We point this out because anesthesiologists reflexively adjust remifentanil infusions to body weight, but seem reluctant to make an adequate reduction in infusion rate for elderly individuals.

Figure 18.13 shows the time required for decreases in effect-site concentration of 20%, 50%, and 80% as a function of remifentanil infusion duration. These would be the "20% effect-site decrement time," the "50% effect-site decrement time," and the "80% effect-site decrement time," respectively. For each decrement time, the expected relationship is shown for a 20-year-old patient and an 80-year-old patient. Figure 18.13 suggests that elderly patients can be expected to recover from remifentanil about as fast as younger subjects, provided the dose has been appropriately reduced (e.g., Fig. 18.12).



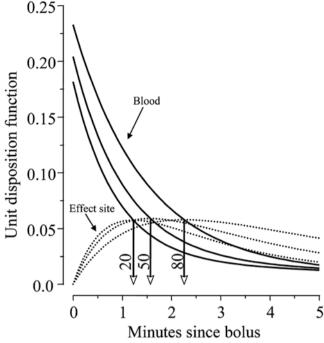


Fig. 18.11 Simulations showing the effect-site concentration from identical bolus doses in a 20-, 50-, and 80-year-old subject. The concentrations are highest in the 80-year-old subject because of the reduced size of the central compartment. However, because of the slower blood-brain equilibrium in the 80-year-old subject, the peak effect-site concentration is almost identical in the three simulations. Thus, the smaller V_1 is offset by the slower plasma–effect-site equilibration. However, a bolus of remifentanil takes about a minute longer to reach peak effect-site concentrations in elderly subjects (Adapted from Minto et al. [139]. With permission from Wolters Kluwer Health, Inc.)

The unique features of remifentanil are its rapid clearance and rapid k_{e0} , resulting in a rapid onset and offset of drug effect. It is tempting to speculate that these characteristics will make remifentanil an easy drug to titrate and that clinicians will not need to consider patient covariates such as advanced age when choosing a dosing regimen. However, the rapid onset of drug effect may be accompanied by rapid onset of adverse events such as apnea and muscle rigidity. The rapid offset of drug effect can result in patients who are in severe pain at a time when the anesthesiologist is ill-equipped to deal with the problem, for example, when the patient is in transit to the recovery room. It is thus important that anesthesiologists understand the proper dose adjustment required for the elderly. By adjusting the bolus and infusion doses, the anesthesiologist can hope to avoid the peaks and valleys in remifentanil concentration that might expose elderly patients to risk. When the proper adjustment is made, the variability in remifentanil pharmacokinetics is considerably less than for any other intravenous opioid. This makes remifentanil the most predictable opioid for treatment of the elderly.

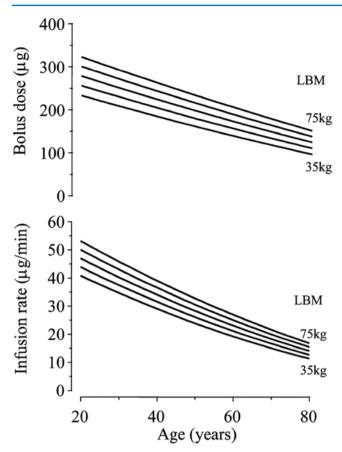


Fig. 18.12 The influence of age and weight on remifentanil bolus dose and infusion rates. Bolus doses should be reduced by 50% in elderly subjects, reflecting the increased brain sensitivity. Infusion rates should be reduced by 66%, reflecting the combined effects of increased brain sensitivity and decreased clearance. *LBM* lean body mass (Adapted from Minto et al. [139]. With permission from Wolters Kluwer Health, Inc.)

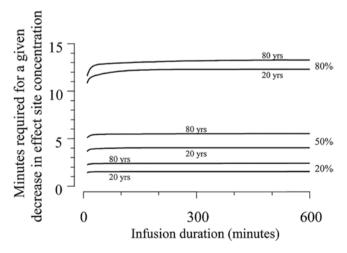


Fig. 18.13 The 20%, 50%, and 80% effect-site decrement curves for 20- and 80-year-old subjects. Provided remifentanil dose is adequately reduced, as shown in this figure, there should be little difference in the awakening time as a function of age

Methadone

Methadone has several distinguishing characteristics, including having the longest terminal half-life and being supplied as a racemic mixture with surprising stereospecific pharmacology. As shown in Table 18.1 and as evident in Fig. 18.1, the terminal half-life of methadone is approximately 1 day [66]. As a result, it will take nearly a week of methadone dosing to reach steady state. When methadone is used as a chronic analgesic, particularly in elderly patients, the patient and physician must be made aware that steady state will not be reached for several days, requiring vigilance for accumulation to toxicity during the "run-in" titration of methadone for analgesia. Also, adequate arrangements for rescue analgesia must be available during the period before steady-state levels.

Methadone's another unique feature is that it is supplied as a racemate with two enantiomers. L-Methadone is an opioid agonist, whereas D-methadone is an *N*-methyl-D-aspartate (NMDA) antagonist [140]. The potency of the D-methadone in blocking NMDA is such that, at clinically used doses, it may be effective in attenuating opioid tolerance and preventing central sensitization (hyperalgesia) [141, 142]. There are no specific studies examining the pharmacokinetics and pharmacodynamics of methadone in elderly subjects. However, as the increased brain sensitivity to opioid drug effect seems to be a class effect for opioids, it seems prudent to reduce methadone doses by about 50% in elderly patients compared with younger patients. Additionally, the NMDA-blocking activity of D-methadone may provide some analgesic synergy between the enantiomers.

The sustained effect of methadone and the combination of μ opioid agonism and NMDA antagonism suggest that methadone may be a good choice for postoperative analgesia. However, methadone must be used with great caution for the treatment of acute pain following surgery. The very long half-life may lead to delayed respiratory depression several days after surgery. Additionally, methadone is associated with QT prolongation, which may lead to fatal arrhythmia [143]. The risk of arrhythmia is particularly concerning with outpatient use of methadone, where the concentrations may be rising in an unmonitored setting. These concerns are highlighted in the black box warning on the methadone product insert. The risks and benefits of methadone for acute pain control following surgery must be carefully considered and likely limit the utility of methadone as an oral analgesic following hospital discharge.

Patient-Controlled Anesthesia

PCA devices are very effective means to provide postoperative analgesia in elderly patients (see Chap. 28). Lavand'Homme and De Kock [144] have reviewed the use of PCA in the elderly. They observed that poor pain management places elderly patients at risk of confusion and outright delirium, and this may be associated with poorer clinical outcomes. They emphasized that increased monitoring and individualization of dosage are essentials in PCA management of elderly patients. They also observed that elderly patients may need additional time to become familiar with PCA devices and that the devices will become ineffective if elderly patients become confused or agitated.

Macintyre and Jarvis [145] examined morphine PCA in elderly patients and observed that age is the best predictor of postoperative morphine requirements. They found that the average PCA morphine use in the first 24 h after surgery was approximately 100–age. However, they also emphasized that the dose needed to be individualized, because there was tenfold variation in the dose in each age category.

This is similar to the results of Woodhouse and Mather [146]. They found that elderly patients required significantly less fentanyl and morphine administered by PCA following surgery. They also identified a similar trend for meperidine, but it was less steep and characterized by higher variability. As seen in Fig. 18.14, elderly patients required about half as much morphine and fentanyl as younger subjects, consistent with the "50% reduction" suggestion at the beginning of the chapter.

Gagliese and colleagues [146] also found an approximately 50% reduction in PCA opioid use in elderly patients. In their study, patients in the younger group (average age = 39) expected more severe pain than those in the older group (average age = 67). However, both groups obtained similar efficacy from their PCA devices and expressed similar levels of satisfaction with PCA as a means of managing postoperative analgesia. The average 24 h dose of morphine (or morphine equivalents) in the younger patients was 67 mg at the end of day one and 44 mg at the end of day two. In the older patients, the average dose was 39 mg at the end of day 1 and 28 mg at the end of day 2. In an accompanying editorial, Ready [148] emphasized that patients must be able to understand and participate in their care, emphasizing the need to individualize therapy for elderly patients in whom a cognitive assessment might be appropriate before using PCA.

It is reasonable that other interventions, such as nerve blocks, infusions of local anesthetic, and adjuvant analgesic therapy, be combined with PCA to provide adequate analgesia at the lowest possible opioid dose in elderly patients (see Chaps. 19 and 28). Beattie et al. [149] have reported that ketorolac effectively reduces morphine doses in elderly subjects. In this case, the reduced opioid requirement must be balanced against the risk of gastric bleeding and fluid retention induced by ketorolac. However, in appropriate patients, one or two doses of ketorolac are associated with only modest risk and would be expected to provide significant synergy with morphine [150, 151].

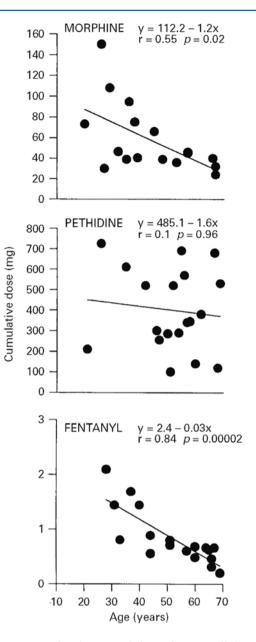


Fig. 18.14 Twenty-four-hour cumulative patient-controlled analgesia opioid administration as a function of age. Morphine and fentanyl both show the expected reduction in dose of about 50%, as predicted by the pharmacokinetic/pharmacodynamic modeling. Meperidine (pethidine) is more variable, perhaps reflecting its more complex pharmacology, or the stimulating effects of normeperidine (Reprinted from Woodhouse and Mather [147]. With permission from John Wiley & Sons)

Suggested Guidelines for Chronic Opioids in the Elderly

The subject of opioids in the management of chronic pain in the elderly has been extensively reviewed [152, 153]. A few basic principles will be emphasized here:

1. In general, opioids should be reserved for those elderly patients in whom less-toxic alternatives, such as

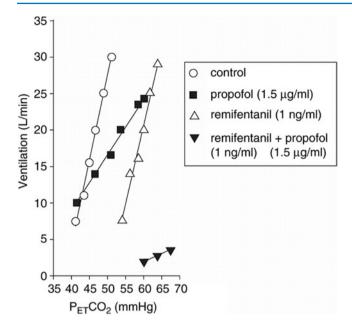


Fig. 18.15 The interaction between remifentanil and propofol on ventilation demonstrates a class effect for opioid/hypnotic synergy. In this figure, propofol very slightly changes the slope of the CO_2 versus ventilation curve, and remifentanil very slightly changes the apnea threshold without changing the slope. However, the combination of propofol and remifentanil (triangles, lower right) profoundly displaces both the slope and the apneic threshold (Reprinted from Nieuwenhuijs et al. [156]. With permission from Wolters Kluwer Health, Inc.)

acetaminophen and nonsteroidal antiinflammatory drugs, have proven ineffective.

- 2. It is best to start with the weaker opioids, such as codeine, and titrate to effect. The stronger opioids should be reserved for patients whose symptoms are inadequately treated by weaker opioids.
- 3. Careful monitoring during the initial dose titration is absolutely essential, particularly with opioids or delivery systems associated with long half-lives and time to steady state, such as methadone, oral sustained-release preparations, and transdermal fentanyl.
- 4. Opioid-induced constipation may be reduced by the use of a peripheral opioid antagonist, such as alvimopan [154] and methylnaltrexone [155].
- 5. Elderly patients are at increased risk of drug interactions (see Chap. 21). The risk of drug interactions particularly precludes the use of chronic meperidine in elderly patients. However, opioids should be used with great caution if combined with any drugs that decrease consciousness (e.g., benzodiazepines). Figure 18.15 shows the interaction between remifentanil and propofol on ventilation *in healthy volunteers* as reported by Nieuwenhuijs and colleagues [156]. Propofol and remifentanil individually have modest effects on ventilation; however, when combined (solid triangles), they demonstrate profound

depression of ventilation. This effect will be exaggerated in elderly patients because of the increased sensitivity to opioid drug effects.

- 6. Elderly patients are at increased risk of confusion in response to opioids.
- 7. Rotation of opioids may permit lower doses to be used, because of the incomplete cross-tolerance and individual differences in analgesic versus toxicity profiles among individuals.

Conclusion

Opioids are used for balanced general anesthesia and are appropriate for both acute and chronic pain in elderly patients, particularly when nonopioid analgesics have failed to provide adequate pain relief. Elderly patients, on average, need about half the dose of opioids as younger patients to achieve the same level of analgesic effect. The biologic basis for the increased brain sensitivity (pharmacodynamic increased potency) to opioids in elderly patients is not completely understood. Elderly patients have factors that place them at increased risk of opioid toxicity, including increased pharmacologic variability, frequent polypharmacy, noncompliance with dosage regimens, and impaired renal and hepatic function.

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Local Anesthetics and Regional Anesthesia

Sylvia H. Wilson and Michael Anderson

19

Introduction

Local anesthetics provide anesthesia or analgesia by disrupting nerve conduction in the central nervous system (CNS) or peripheral nervous system (PNS). In addition to reviewing basic nerve physiology, this chapter will discuss local anesthetic pharmacology, including mechanism of action, duration, metabolism, and systemic toxicity. Discussion will then focus on the implications of local anesthetic utilization in the geriatric patient.

Neural Anatomy

Peripherally, multiple tissue layers offer both protection to nerves and barriers to local anesthetics [1]. Nerves are bundled into fascicles composed of both afferent and efferent nerve fibers. Sympathetic fibers may also be present. Each fiber, or axon, is surrounded by a loose connective tissue containing glial cells, termed as endoneurium (Fig. 19.1). Groups of nerve fibers are bundled together, along with capillaries and fibroblasts, to create a fascicle. Each fascicle is further surrounded with the perineurium, a dense connective tissue layer. Fascicles are then bundled together and encased by another layer of dense connective tissue called the epineurium.

Peripheral nerves are classified by their conduction velocity, size, and function. Increased conduction velocity is associated with both increased nerve fiber diameter and myelin. Myelin improves nerve electrical insulation and expedites rapid impulse propagation through saltatory

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conduction. Similarly, myelinated nerve fibers commonly have a diameter exceeding 1 micron. Motor and sensory functions requiring critical speed are usually associated with large-diameter, myelinated fibers know as A-fibers [2]. A-alpha and A-beta fibers are the largest with rapid conduction velocities (2-33 micron diameter, 30-120 m/ sec). These fibers function for motor and proprioception providing both afferent and efferent innervation for muscles and joints. Slightly smaller A-gamma fibers are still fairly rapid (3-6 microns, 15-35 m/sec) and provide muscle tone through efferent innervation of the muscle spindle. Similarly, A-delta fibers (1-4 microns, 5-25 m/sec) provide afferent innervation to sensory nerves for pain, touch, and temperature. Autonomic functions are more commonly relayed by small-diameter fibers. The smallest myelinated fibers, B-fibers (<3 microns, 3-15 m/sec), provide preganglionic sympathetic innervation. C-fibers are the smallest fibers (0.3-1.3 microns) and the only unmyelinated fibers. They provide postganglionic sympathetic and afferent sensory nerve innervation for autonomic functions, pain, and temperature.

With advanced age, changes occur to both the CNS and PNS. The spinal vertebral bodies are brittle and may stimulate bone overgrowth. This results in vertebral disc space loss. These changes may lead to increased pressure and compression on both spinal cord and spinal nerve roots as they exit to the periphery. Peripherally, while some atrophy occurs with time, peripheral nerve impulse conduction is primarily slowed due to myelin degradation. Myelin degradation is attributed to multiple factors including bone overgrowth causing nerve compression and decreased blood flow to the nerve. Additionally, chronic medical conditions, such as diabetes, may exacerbate nerve injury. While peripheral nerve axons have some capacity to repair themselves in younger patients when the proximal nerve cell body is unharmed, this repair process is decreased and often incomplete in the geriatric population. CNS changes may create balance instability, decreased strength, and radiculopathy, while PNS changes are associated with delayed reflexes and decreased sensation [3].

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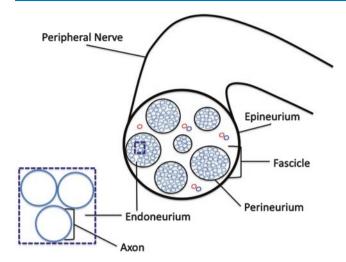


Fig. 19.1 Groups of nerve fibers are bundled together, along with capillaries and fibroblasts, to create a fascicle. Each fascicle is further surrounded by the perineurium, a dense connective tissue layer. Fascicles are then bundled together and encased by another layer of dense connective tissue called the epineurium

Basic Neuronal Physiology

Stimulation of sensory nerves by a thermal, chemical, or mechanical stimulus will trigger receptors at the distal ends of sensory nerves. Sufficient stimulus will create an electrical current known as an action potential. Action potentials are momentary, localized episodes of depolarization in which a positive charge is conducted along nerves by the movement of sodium ions across the nerve membrane down both electrical and chemical gradients. This creates a reversal in the electrical polarity of the membrane generating electrical current.

At rest, ion channels establish electrical and chemical gradients across the nerve membrane (Fig. 19.2). Active Na⁺/ K⁺ ATPase channels pump sodium ions out of the cell and potassium ions into the cell, with a 3:2 ratio, respectively [4]. This creates a chemical gradient with a high intracellular potassium concentration and a high extracellular sodium concentration. Concurrently, passive ion channels allow free movement of ions across membranes, facilitating extracellular movement of potassium along a concentration gradient. In addition to this chemical gradient, the active pumping of positive ions (sodium) out of the cell combined with the passive extracellular leakage of positive ions (potassium) creates an electrical gradient. This results in a resting electrical potential difference with the inside of the cell having a negative charge (-70 to -90 mV) compared to the outside cell.

In addition to passive and active ion channels, voltagegated sodium channels located on the nerve membrane open and close in response to the membrane potential difference. These voltage-gated sodium channels consist of an α -subunit and one or two β -subunits [5]. Nerve membrane stimulation

triggers the α -subunit to go through multiple conformational changes, including four functional states (resting, activated, inactivated, and deactivated). Simplistically, the channel can be considered to have two functional gates, an inner gate (h) and outer gate (m). When the nerve membrane is at *resting* potential (-70 to -90 mV), the outer m-gate is open and the inner h-gate is closed. With activation, the outer m-gate opens creating a rapid influx of sodium ions (electrical and chemical gradients) and the membrane potential increases. If sufficient sodium channels open to raise the membrane potential greater than -60 mV, a widespread opening of sodium channels is triggered resulting in an even more rapid influx of sodium ions. If the membrane potential bypasses neutral to reach +20 mV, the inner h-gates close and the sodium channels become inactivated, preventing further ion movement [6]. The membrane depolarization creates a potential difference, relative to adjacent areas, generating an electrical current and elevating the membrane potentials of contiguous areas. This triggers a wave of depolarization of the adjacent nerve membranes in unmyelinated nerves and adjoining nodes of Ranvier in myelinated nerves.

After the membrane depolarization peaks (+50 mV), sodium influx stops, potassium efflux ensues, and repolarization reverses the membrane potential. The nerve is refractory to further stimulation during the *inactivated* and *deactivated* states, preventing rapid depolarization of the axonal section and inhibiting retrograde impulse conduction. During the *inactivated* phase, sodium ions do not move through the voltage-gated channels. However, they are shifted to the extracellular space by the Na⁺/K⁺ ATPase pump. Movement of potassium through the passive ion channels further helps restore the membrane potential. As the membrane reaches -60 mV, the outer m-gate opens and the voltage-gated sodium channel is reactivated.

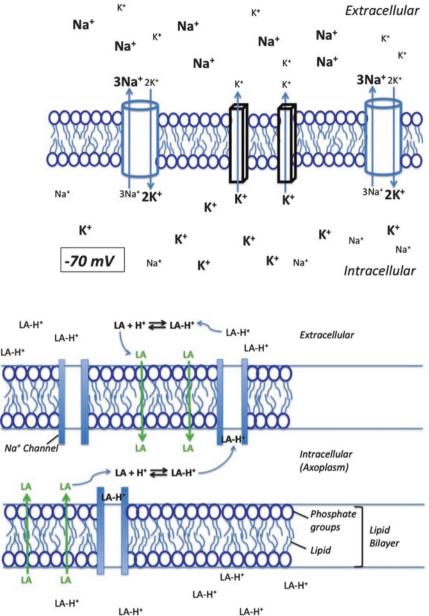
Pharmacology

Mechanism of Action

Local anesthetics are most commonly thought to block nerve conduction by reversibly binding with one or more α -subunits on voltage-gated sodium channels at an intracellular location (Fig. 19.3) [7]. Local anesthetics are typically manufactured as water-soluble salts (usually hydrochlorides) in an acidic solution. They must be converted into a non-ionized, lipidsoluble form in order to diffuse across a lipophilic lipoprotein membrane and enter the cell. The proportion of local anesthetic transformed to the non-ionized form is correlated with both tissue pH and drug ionization constant (pKa). After the local anesthetic moves into the intracellular space, a decreased intracellular pH regenerates the ionized form, which binds to the α -subunit and blocks the sodium channel.

Fig. 19.2 At rest, electrical and chemical gradients across the nerve membrane are established by ion channels. Active Na⁺/K⁺ ATPase channels pump sodium ions out of the cell and potassium ions into the cell with a 3:2 ratio, respectively. Passive ion channels allow potassium movement out of the cell (concentration gradient). Active pumping of sodium combined with passive leakage of potassium ions out of the cell creates an electrical gradient, resulting in a resting electrical potential difference with the inside of the cell having a negative charge (-70)to -90 mV

Fig. 19.3 Injected local anesthetics exist in an ionized, water-soluble (LA-H⁺) quaternary form. In order to transverse the lipid bilayer, it must change to the nonionized, lipophilic (LA) tertiary form. The drug then changes back into the ionized form (LA-H+) in order to bind to the voltage-gated sodium (Na⁺) channels



If enough sodium channels are interrupted, threshold potentials are not achieved and impulse conduction is obstructed. Intracellularly, ionized local anesthetic may also further disrupt the intra-membrane portion of the sodium channel, and this may be augmented by blockade of potassium channels, calcium channels and G-protein-coupled receptors [8-10]. Other theorized mechanisms of local anesthetic action exist. Local anesthetics may alter conduction by disrupting surface membrane charge. The Meyer-Overton theory proposes that local anesthetics result in cell membrane expansion which then impedes sodium conductance.

Local anesthetic affinity varies with the state of the sodium channel. Affinity is highest when the sodium channel is opening (activated or inactive). Affinity is least when the

channel is closed (deactivated or resting). Consequently, a resting nerve is less sensitive to local anesthetic than a nerve that is frequently stimulated.

As small nerve fibers are more vulnerable to blockade compared to large fibers, neural blockade is first noticed for the sensation of pain and temperature followed by touch, deep pressure, and last motor. Interrupting conduction is faster in smaller fibers due to shorter axonal length. Large fibers (touch, pressure, and motor) require higher concentrations to produce adequate blockade compared to small myelinated fibers (pain). However, local anesthetics block myelinated fibers more rapidly than unmyelinated fibers since drug pools near the axonal membrane. Consequently, C-fibers, which are small and unmyelinated, are difficult to

block. Unfortunately, these afferent postganglionic fibers of the autonomic nervous system carry information about pain, touch, and warmth and are associated with neuropathic pain when damaged.

Lastly, local anesthetics differ in their affinity for the receptor. Lidocaine binds and dissociates rapidly, while bupivacaine dissociates slower. This is related to chemical differences between various local anesthetics.

Local Anesthetic Types and Metabolism

Local anesthetics are composed of a lipophilic aromatic ring connected to a terminal amine by either an ester or amide linkage (Fig. 19.4). Local anesthetics are classified as either esters or amides based on this intermediate chain (Table 19.1).

The intermediate chain also determines the mechanism of metabolism and elimination. Esters are hydrolyzed in plasma by pseudocholinesterase, and pseudocholinesterase deficiencies will prolong neural blockade. The type of substitution and location on the aromatic ring determines the rate of hydrolysis. Consequently, procaine is hydrolyzed four times faster than tetracaine. Conversely, amides are metabolized by the liver in a dealkalization reaction. Hepatic function and blood flow determine amide clearance, and decreases in these will increase the elimination half-life.

Decreases in lean tissue mass, albumin, and hepatic blood flow associated with aging have been hypothesized to alter local anesthetic metabolism and elimination. While an increase in fatty tissues was observed to increase local anesthetic volume of distribution in one study with lidocaine, this

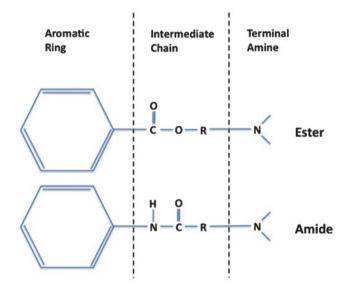


Fig. 19.4 Local anesthetics are composed of a lipophilic aromatic ring connected to a terminal amine by either an ester or amide linkage. Local anesthetics are classified as either esters or amides based on the intermediate chain

finding was not supported by later studies examining intravenous lidocaine infusions [14, 15]. Similarly, while albumin levels decrease with aging, plasma protein binding of local anesthetics remains largely unchanged as alpha-1 acid glycoprotein levels are minimally altered [16]. Likewise, despite a 20–40% decrease in hepatic blood flow in geriatric patients, local anesthetic hepatic metabolism remains unaltered [17]. Consequently, local anesthetic metabolism remains largely unaltered with aging unless complicated by significant liver disease.

Potency and Onset

Local anesthetic potency is primarily due to lipid solubility. The aromatic ring and its substitutions and additions to the terminal amine determine lipid solubility. Specifically, the terminal amine may exist in a quaternary form (four bonds, positive charge, water soluble) or tertiary form (three bonds, neutral, lipid soluble). The ratio of drug's solubility in a nonpolar solution (n-octanol) may be used to describe lipophilicity. This is known as the octanol-water partition coefficient, and the increased lipid solubility is associated with greater values [11, 18] (Table 19.1).

Local anesthetic onset is determined by the drug ionization constant (pKa). In order to stabilize local anesthetic bases in solution, clinical solutions are produced in a hydrochloride salt (pH 4–6). This converts them into a watersoluble (quaternary) state. Consequently, the onset is related to conversion to the tertiary (lipid soluble) form on exposure to physiologic pH (7.4). This conversion is determined by pKa, a pH that leads to 50% ionized and 50% non-ionized local anesthetic molecules. As local anesthetics are weak bases, their pKas are greater than 7.4. The greater the pKa of the drug, the greater the proportion in the quaternary form and the slower the onset.

Other factors can also impact the onset. Physiologic factors, such as increased tissue acidity caused by inflammation, can increase drug ionization and further delay quaternary to tertiary conversion. This is one explanation for the difficulty in anesthetizing infected tissue [12, 19]. The rate of diffusion can also be expedited by increased concentration. However, the relationship between onset and concentration is not linear but logarithmic. Therefore, doubling the concentration only marginally expedites block onset; however, it will provide denser blockade. This is commonly utilized with the ester local anesthetic chloroprocaine. Although it has a high pKa (8.9), it can be administered in high concentrations and high doses for rapid anesthesia onset. This is permissible due to its rapid metabolism by pseudocholinesterases. Local anesthetics are prepared in a range of concentrations to assist in the onset for less potent medications. For example, bupivacaine is very lipid soluble and therefore

			Lipid	Partition		Protein		
Medication	рКа	Onset (minutes)	solubility ^a	coefficient ^b	Potency	binding	Duration (hours)	
Amides								
Lidocaine	7.7	10-20 Fast	2.9	43	Intermediate	64	2-5 Intermediate	
Mepivacaine	7.8	10-20 Fast	0.8	21	Intermediate	77	2-5 Intermediate	
Prilocaine	7.9	10-20 Fast		25	Intermediate	55	2-5 Intermediate	
Etidocaine	7.7	10-20 Fast	141	800	Intermediate	94		
Articaine	7.8	10-20 Fast		-	Intermediate	95	2-5 Intermediate	
Bupivacaine	8.2	15-30 Intermediate	28	346	High	95	5-15 Long	
Levobupivacaine	8.1	15-30 Intermediate		346	High	96	5-15 Long	
Ropivacaine	8.0	15-30 Intermediate	3	115	High	94	5-15 Long	
Esters	Esters							
Procaine	9	Slow		1.7	Low	6	0.5-1.5 Short	
Chloroprocaine	9.3	10-15 Fast	0.14	810	Intermediate	-	0.5-1.5 Short	
Cocaine	8.7	Slow		-	High	98	Long	
Benzocaine	3.5	Slow		-	-	-	-	
Tetracaine	8.6	Slow	4.1	221	Intermediate	76	Long	

Table 19.1 Local anesthetics: classifications and characteristics

Based on data from Refs. [2, 11-13]

^aN-heptane/pH = 7.4 buffer

^bPartition coefficients with h-octanol/buffer

often utilized in lower concentrations (0.25-0.5%, 2.5-5 mg/ml) compared to lidocaine (1-2%; 10-20 mg/ml), which is less soluble.

Duration

Duration is generally described as short, intermediate, or long. Local anesthetic duration has classically thought to be directly related to protein binding. Factors keeping the drug near the nerve (increased lipid solubility, decreased tissue vascularity, presence of vasoconstrictors) may be of importance as well in prolonging duration of action.

In an effort to maximize onset and duration of the local anesthetics, it was often a common practice to combine short- and long-acting local anesthetics (e.g., mepivacaine and bupivacaine). However, evaluation of this practice revealed surprising results. When comparing interscalene blocks with mepivacaine, bupivacaine, or an equal mixture of each; the onset times for each group were nearly identical. Conversely, duration of the block was significantly decreased when compared to bupivacaine alone [20]. These results have been confirmed in other brachial plexus blocks [21]. Moreover, this effect was preserved whether local anesthetics were given as mixed or sequentially [22]. Therefore, if increased block duration is important, a mixture of different local anesthetics should be avoided. Conversely, mixing of nonlocal anesthetic perineural adjuncts (Table 19.2) has been described to increase anesthetic or analgesic duration. While epinephrine is the most common perineural additive, it has only been demonstrated to prolong the duration of shortacting local anesthetics (e.g., lidocaine); however, it serves a

valuable role as a marker for intravascular injection. Clonidine is another well-studied additive for both peripheral and neuraxial regional anesthesia techniques [24]. While clonidine is thought to act centrally through alpha-2 receptor stimulation, its peripheral mechanism is attributed to inhibition of the hyperpolarization-activated cation currents [26]. If clonidine doses exceed 100–150 mcg, sedation and hypotension become more common which may be of greater concern in the geriatric population [31]. While considered an accepted practice for both peripheral and neuraxial blockade, perineural clonidine remains an off-label use. Similarly, other adjuvants are considered off-label and experimental until further literature is available. With the success of clonidine, studies have recently examined dexmedetomidine, a more specific alpha-2 agonist, as a peripheral nerve block additive. Peripheral analgesic effects of dexmedetomidine are also attributed to inhibition of the hyperpolarizationactivated cation currents [25]. The addition of 100µg of dexmedetomidine has been postulated to be the ideal dose. This has shown to nearly double the duration of interscalene nerve block and prolong supraclavicular nerve blocks [32, 33]. While dexmedetomidine has known side effects of sedation, hypotension, and bradycardia, when comparing IV and perineural dexmedetomidine to placebo, no difference in the incidence of significant adverse events was noted [34]. Similarly, dexamethasone has been reported to prolong brachial plexus blocks in numerous reports, with low perineural doses (1–2 mg) being as effective as higher doses (4–8 mg) [27]. Whether the improved analgesic outcome of dexamethasone is a local or systemic effect has been greatly debated. However, the studies comparing systemic and perineural administration have only examined large doses of

Medication	Mechanism of action	Potential concerns	Sites studied	Prolonged duration ^a	Dosing
Buprenorphine [23]	Debated	Pruritis	Axillary, sciatic	Variable	0.3 mg
Clonidine [24]	Inhibition of hyperpolarization-activated cation currents	Bradycardia, hypotension, sedation	Numerous	2 h	30–300 µg (often 150 µg)
Dexmedetomidine [25]	Inhibition of hyperpolarization-activated cation currents [26]	Bradycardia, hypotension	Interscalene, axillary, posterior tibial	4–5 h	100 µg 150 µg 1 µg/kg
Dexamethasone [27–29]	Debated	Toxicity concerns with high doses [30]	Interscalene supraclavicular sciatic	4–10 h	1–10 mg
Epinephrine	Vasoconstriction	Potential neurotoxicity [30]	Numerous	0 h	2.5–5 µg/ml

Table 19.2 Summary of perineural additives examined in the literature

aIncreased analgesia duration compared to a long-acting local anesthetic

dexamethasone approaching the systemic analgesic doses (0.1 mg/kg); this question continues to stimulate debate [28, 29]. Buprenorphine is another additive where it is unclear whether the mechanism of analgesia is systemic or peripheral when administered perineurally [23]. While buprenorphine's use has shown improved analgesia in patients undergoing sciatic and axillary nerve blocks, its utility is limited by drug-associated nausea [23, 35]. Importantly, as neuronal toxicity is a concern with the use of perineural additives, basic science work has indicated that the most neurotoxic agent is often the local anesthetic [30]. Prolongation of local anesthetic duration can decrease the need for systemic analgesics which may be beneficial in elderly patients who are more susceptible to systemic opioids. While local adjuvants can help prolong local anesthetic duration, they are not without side effects, and the benefit of prolonged blockade should be weighed against possible adverse reactions.

Minimum Effective Volumes

The increased popularity of ultrasound guidance has helped to decrease both the incidence of vascular puncture and the onset time of regional anesthesia [36]. It has also allowed for extremely precise deposition of local anesthesia and decreased local anesthetic volumes for a given regional block. This last point contrasts with nerve stimulation techniques in which nearly 40 ml of local anesthetic was often recommended to ensure block adequacy.

Decreasing the volume of local anesthetics administered can allow for a larger margin of safety and allow for multiple regional blocks while still remaining under a toxic dosage of local anesthetics. Most studies have shown a similar onset time for the lower volumes. While mixed results have been found for block duration, most decreases in volume result in a shorter duration.

Toxicity

Local anesthetic protein binding is concentration dependent and influenced by the pH of the plasma. As pH decreases, the percentage of bound drug decreases. As acidosis develops, as can occur with hypoventilation, seizures, or cardiac arrest, the percentage of free (unbound) local anesthetic increases. As the percentage of bound bupivacaine changes from 95 to 75%, the percentage of free drug is amplified fivefold (5–25%), although the total drug concentration remains the same. This increase in free local anesthetic drugs with acidosis renders bupivacaine distinctly toxic.

Local Anesthetic Systemic Toxicity (LAST)

Local anesthetics absorption into the systemic circulation may lead to local anesthetic systemic toxicity (LAST). Signs of LAST classically occur on a spectrum. The standard description of LAST begins with CNS excitation, tinnitus, agitation, metallic taste, or perioral numbness. This rapidly progresses to seizures and CNS depression. Neurologic signs are followed by cardiac manifestations beginning with hypertension and arrhythmias and escalate to conduction blockade, bradycardia, and asystole.

In the classic presentation of LAST, symptoms rapidly begin following the administration of local anesthetics, likely reflecting direct intravascular injection. Slower presentations can also manifest several minutes following local anesthetic administration secondary to delayed absorption or partial intravascular injection in the distal periphery. Because of the possibility of delayed presentation, the American Society of Regional Anesthesia (ASRA) suggests a minimum of 30 min of monitored care following administration of large doses of local anesthetics [37]. Despite the classic LAST manifestations, multiple symptoms can occur simultaneously or cardiac arrest can be the presenting sign.

Treatment of LAST depends on the presenting symptoms. ASRA has published a checklist to promote comprehensive treatment. In all scenarios, calling for help and lipid emulsion to the bedside should occur first as symptoms may rapidly progress. For the initial CNS signs, supportive care with prevention of hypoxemia and acidosis is the main goal. Should seizures ensue, symptoms must be rapidly controlled to prevent physical trauma and acidosis. Benzodiazepines are the preferred pharmacological treatment for seizure abolition because of the lack of cardiac depressant effects. While thiopental and propofol have been used, they should be considered second line drugs and slowly titrated to minimize cardiac depression. If cardiac symptoms develop, management of the airway to prevent hypoxemia and worsening acidosis can help to lessen LAST severity. This should be quickly followed by CPR and ACLS; however, epinephrine dosing should be decreased (1 µg/kg) and vasopressin, calcium channel blockers, and intravenous lidocaine should all be avoided. Lipid emulsion (20%) should be bolused (1.5 ml/ kg) and then an infusion initiated (0.25 ml/kg/min). Additional boluses should be given in the setting of prolonged cardiovascular collapse and the infusion increased (0.5 ml/kg/min) if hypotension persists. The lipid infusion should be continued for a minimum of 10 minutes following return to cardiovascular stability [38]. These recommendations do not differ for the geriatric population.

Basic Principles and Blocks for Regional Anesthesia

Regional anesthesia may be used as the primary anesthetic or for postoperative pain management in the geriatric population. Patients receiving peripheral nerve blocks as the primary anesthetic have demonstrated decreased rates of postoperative sedation, nausea, and vomiting with improved pain control and expedited discharge times compared to patients receiving general anesthesia [39]. Further, regional anesthesia has been associated with decreased rates of chronic pain in certain surgical populations [40].

Both neuraxial and peripheral nerve blocks can be challenging in geriatric patients due to arthritis and decreased flexibility, leading to difficulty with positioning. While ultrasound guidance can ameliorate some positioning obstacles, ultrasound utilization is often greater with peripheral than neuraxial techniques.

Spinal and Epidural Blockade

Neuraxial anesthesia may be safely performed in geriatric patients; however, it can present challenges that are different compared to younger patients. As the body ages, the neur-

axial anatomy degenerates, leading to multiple possible spinal abnormalities. Elderly patients develop osteoporosis, compression fractures, herniated disks, and many other changes at increased rates compared with younger cohorts. Degenerative changes can lead to loss of intervertebral height or rotational distortion of the spine. Spinal stenosis, an anatomic change leading to narrowing of the spinal canal, has an incidence of approximately 14% in patients at the age of 40 years. This incidence increases to nearly 40% as patients approach 60 years of age [41]. These anatomic changes, leading to decreased epidural space potential volume, may be partially responsible for increased dermatomal spread of epidural injectate. It has been shown that an equal dose and volume of local anesthetic will have a slower onset time in the elderly patient but will provide a higher block height when compared to middle-aged patients [42]. In fact, some advocate decreasing epidural medication volumes because of the increased segmental spread [43]. Calcification of spinal ligaments, also associated with aging, can lead to an inability to access the neuraxis via the midline, often requiring a paramedian approach [44]. Geriatric patients are also more likely to have had spinal surgery leading to epidural adhesions, scarring, gross anatomic modifications from instrumentation or bone grafting, and damage to spinal ligaments [45]. These anatomic changes can alter the spread of local anesthetics in the epidural space leading to patchy or inadequate blocks. Aging also leads to changes in CSF volume and production levels. The total CSF volume increases with age, mostly compensating for the loss of brain volume [46]. While there is an increase in volume, CSF production slows with increasing age [47].

Despite these anatomical changes, neuraxial anesthesia is commonly utilized in multiple geriatric surgeries including lower extremity orthopedic procedures and joint arthroplasty, urologic procedures, and certain vascular cases. As people continue to age, there is a known decline in parasympathetic activity which leads to predominant sympathetic tone; this leads to increased blood pressure lability, elevated dependence on preload, and decreased responsiveness to chronotropic and inotropic medications. These clinical changes in the autonomic nervous system may complicate hemodynamic stability regardless of anesthetic choice and should be monitored closely. In patients with hip fractures requiring surgical intervention, the superiority of regional anesthesia to general anesthesia for multiple postoperative outcomes ranging from postoperative delirium and decreased hospital stay to pneumonia and death is continuously debated [48, 49]. While studies continue, regional anesthesia is at least as safe as general anesthesia and may have multiple benefits for the geriatric hip fracture patient.

Ultrasound can be utilized to facilitate neuraxial block placement. Even the less experienced sonographer can use ultrasound guidance to help identify midline structures (e.g., spinous processes) in cases of scoliosis or obesity [50, 51]. Specific studies do not exist regarding the use of ultrasound in geriatric patients. However, the routine use of ultrasound mapping could potentially aid in faster placement and less needle manipulation in the aging patient due to the increased incidence of dural ossification and spinal osteophytes which can complicate placement [52].

Brachial Plexus Blocks

Interscalene

The *interscalene approach* targets the C5–C7 nerve roots and is used to anesthetize the shoulder and proximal one-third of the humerus. It is inappropriate for more distal procedures, as it is associated with ulnar nerve sparing. Common side effects include nearly 100% ipsilateral phrenic nerve block and recurrent laryngeal nerve block [53]. This side effect may contraindicate an interscalene block in geriatric patients after prior phrenic or vagal nerve injury from prior cardiac, thoracic, or otolaryngologic surgery. Patients with reduced functional pulmonary reserve, such as chronic obstructive pulmonary disease, may also be poor candidates.

Ultrasound identification of the interscalene block can be accomplished by tracking the nerve roots proximally from the brachial plexus at the supraclavicular level. To find the C5–C7 nerve roots, ultrasound identification of the internal jugular vein and carotid artery should be obtained. These vessels should be tracked to the clavicle and then the ultrasound probe moved laterally identifying the subclavian artery. Just lateral to the subclavian artery lies the brachial plexus. The nerves are easily tracked by sliding the ultrasound probe cephalad and identifying the nerve roots between the anterior and middle scalene muscles (Fig. 19.5).

Supraclavicular

The *supraclavicular block* targets the nerves as they transition from trunks to cords above the first rib and lateral to the subclavian artery. This block has been dubbed as the "spinal of the arm" for its compact nerve arrangement and superficial location. It can be associated with ulnar sparing. Possible complications include ipsilateral pneumothorax (increasingly rare but historically 0.5–6% using a landmark technique), phrenic nerve blockade (36–67%), and recurrent laryngeal nerve block [54–56]. To identify the brachial plexus at the supraclavicular level, one should begin by identifying the carotid artery and internal jugular vein. The ultrasound probe is then moved caudad until coming in contact with the clavicle. Once the clavicle is reached, the probe is tilted to view under the clavicle and then moved laterally to

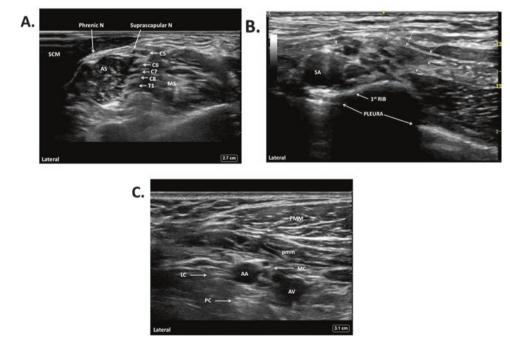


Fig. 19.5 Ultrasound images of anatomy for brachial plexus nerve blocks (A.) Interscalene. Nerve roots (C5-T1) are visualized between the anterior (AS) and middle (MS) scalene muscles. The suprascapular nerve and phrenic nerves are also visualized. *SCM* sternocleidomastoid muscle, *AS* anterior scalene muscle, *MS* middle scalene muscle. (B.): Supraclavicular brachial plexus block. The plexus lies lateral to the subclavian artery (SA) and superior to the first rib (FR) and pleura of the

lung. SA subclavian artery, FR first rib. (C.) Infraclavicular. The plexus is deep to the pectoralis major (PMM) and minor (pmm) muscles. The lateral (LC), posterior (PC), and medical (MC) cords surround the axillary artery (AA). PMM pectoralis major muscle, PMM pectoralis minor muscle, LC lateral cord, PC posterior cord, MC Medical cord, AA axillary artery, AV axillary vein

identify the subclavian artery. The brachial plexus is located lateral to the subclavian artery and superior to the first rib (Fig. 19.5).

Infraclavicular

The *infraclavicular block* targets the cords of the brachial plexus below the pectoralis major and minor muscles and lateral to the axillary artery and vein. Because of the more distal delivery of local anesthesia, the incidence of phrenic nerve paralysis is reduced to 0-26% [57, 58]. The most common approach to the infraclavicular block is the lateral technique and can be attempted with the arm adducted or abducted and externally rotated. The coracoid process should first be palpated and the ultrasound placed just inferior to this landmark. The ultrasound probe can be moved caudally to identify the axillary artery surrounded by the lateral, posterior, and medial cords, named in relation to the artery looking for caudal spread of the injectate (Fig. 19.5).

Axillary

Finally, in the *axillary approach*, local anesthetic is deposited near the musculocutaneous, median, ulnar, and radial nerves in proximity to the axillary artery and vein in the axilla. Because of the distal location of local anesthetic placement, the axillary block is not associated with phrenic nerve paralysis. Ultrasound axillary nerve block is performed using a linear probe held vertically in the axilla to reveal a short axis view of the axillary artery. Three nerves surround the artery. The radial nerve lies deep and posterior, the ulnar nerve medial, and the median nerve anterior-lateral in relation to the axillary artery. The musculocutaneous nerve has left the brachial plexus at this level and most frequently travels in the fascial layer between the biceps and coracobrachialis muscles. Local anesthetic should be deposited near all four nerves for a successful block.

Lower Extremity Blocks

Femoral Nerve Block

The femoral nerve originates from the L2–L4 nerve roots of the lumbar plexus. The femoral nerve provides motor and sensory control to the anterior compartment of the thigh as well as sensory innervation in the saphenous nerve distribution below the knee. The femoral nerve block has been frequently utilized to provide analgesia to the anterior knee, most frequently for patients undergoing total knee arthroplasty and anterior cruciate ligament repair.

The femoral nerve can be identified using ultrasound guidance by first identifying the femoral artery and vein at the level of the inguinal crease. The nerve sits lateral to the femoral artery, below the fascia lata and iliaca and on top of the iliopsoas muscle (Fig. 19.6).

As both the obturator and lateral femoral cutaneous nerves also originate from the lumbar plexus, the classic three-in-one femoral nerve block attempts to block all three nerves of the lumbar plexus. While it is often successful in blocking the lateral femoral cutaneous nerve, the obturator nerve is spared in the majority of blocks [59]. While providing excellent sensory blockade, the femoral block is also associated with significant quadriceps muscle weakness, and caution should be maintained in mobile patients. Consequently, the adductor canal block has gained recent popularity in place of femoral nerve blockade.

Adductor Canal Block

The adductor canal block is a newer approach to provide primarily sensory blockade to the anterior knee. This approach primarily blocks the saphenous nerve. However, the nerve to the vastus medialis is also often anesthetized and may lead to minor motor blockade. Both the anterior and posterior branch of the obturator nerve have been reported to occasionally run in the adductor canal [60]. The adductor canal block has gained popularity because of the equivalent analgesia it delivers when compared to the femoral nerve block [61, 62]. The major benefit of this approach is motor sparing of the quadriceps muscles allowing for better participation in physical therapy and maintenance of balance [63]. As falls are a concern in any geriatric patient postoperatively necessitating fall precautions, the potential preservation of quadriceps function is a huge advantage for this technique and the primary reason adductor canal blocks have grown in popularity over femoral nerve blocks.

This block is accomplished by ultrasound identification of the adductor canal in the mid-thigh, halfway between the patella and anterior superior iliac crest. After positioning the patient supine with the knee bent and externally rotated ("frog-legged"), the ultrasound probe is placed on the ventral thigh. Once the femur is identified, the ultrasound probe is moved medially to identify the vastus medialis muscle, which serves as the lateral border of the canal. The sartorius muscle forms the anterior border and the adductor muscles (adductor magnus and brevis) the posterior-medial border (Fig. 19.6).

Sciatic Block

The sciatic nerve originates from the sacral plexus at the L5 to S3 levels of the spine. The nerve exits the pelvis at the sciatic notch and continues to run posterior to the femur. Proximal to the popliteal fossa, the nerve bifurcates to become the tibial and common peroneal nerves. The sciatic nerve block is utilized to provide anesthesia and analgesia to nearly all of the lower leg and foot with the exception of the saphenous nerve, which provides sensation to an anterior-medial portion of the leg. It is often used for foot and ankle procedures, Achilles tendon repair, and providing analgesia

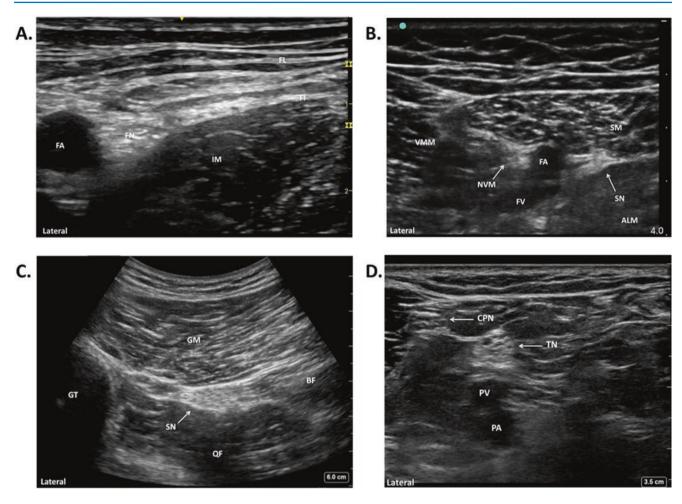


Fig. 19.6 Ultrasound images of anatomy for lower extremity nerve blocks (**A**.) Femoral nerve block. The femoral nerve (FN) is lateral to both the femoral artery (FA) and femoral vein (FV). *FA* femoral artery, *FI* fascia iliac, *FL* fascia lata, *FV* femoral vein. (**B**.) Adductor canal block. The adductor canal lies deep to the sartorius muscle (SM), medial to the vastus medialis muscle (MVV) and superior lateral to the adductor muscles. It contains the branches of the femoral vessels, the saphenous nerve (SN), and the nerve to vastus medialis (NVM). *SM* sartorius muscle, *VMM* vastus medialis muscle, *FA* superficial femoral artery, *FV* superficial femoral vein, *NVM* nerve to vastus medialis, *ALM* adductor longus muscle. (**C**.) Sciatic nerve block, subgluteal location.

The sciatic nerve (SN) is lateral to the greater trochanter (GT), medial to the origin of the biceps femoris muscle (BF), deep to the gluteus maximus muscle (GM) and superficial to the quadratus femoris muscle (QF). *GT* greater trochanter, *BF* biceps femoris muscle, *GM* gluteus maximus muscle, *QF* quadratus femoris muscle. (**D**.) Sciatic nerve block, popliteal location. In the popliteal fossa, the tibial nerve (TN) is identified superficial (dorsal) to the popliteal vessels. The common peroneal nerve, *TN* tibial nerve, *PV* popliteal vein, *PA* popliteal artery

to the posterior knee. While a sciatic nerve block reliably provides analgesia to the lower portion of the leg, the posterior cutaneous nerve of the thigh can be spared with even proximal blockade of the nerve, thus often maintaining sensory innervation to the posterior thigh [64]. The sciatic nerve can be blocked at multiple points ranging from the proximal parasacral approach to the more distal popliteal approach.

Ultrasound identification of the nerve can be easily accomplished with a subgluteal approach. Here, the sciatic nerve sits in the fascial layer between the greater trochanter and ischial tuberosity, below the gluteus maximus and above the quadratus femoris muscle (Fig. 19.6) [65]. Another simplistic technique, the popliteal approach, is the method most utilized for sciatic blockade. Performed with the patient supine, lateral, or prone, the popliteal artery is first identified at the popliteal crease with the tibial nerve lying superficial to the artery. The ultrasound probe is then moved cephalad, tracking the tibial nerve until it combines with the common peroneal nerve to form the sciatic nerve (Fig. 19.6).

Other Considerations

Anticoagulation

As patients continue to age, many medical conditions arise that require the use of hemostatic altering medications. It is estimated that nearly 2% of patients over 65 years of age suffer from atrial fibrillation, and the incidence increases with age [66]. Additionally, many elderly patients require percutaneous coronary intervention, valve replacement, or treatment for venous thrombosis or stroke. All of these chronic diseases are treated with prolonged anticoagulation or antiplatelet medications. While regional anesthesia has been proven safe in the average patient, the escalated propensity for epidural hematoma development has been noted specifically in anticoagulated patients. Because of the catastrophic sequelae of neuraxial bleeding, ASRA developed a consensus statement to help provide guidelines in patients receiving hemostatic altering medications. These recommendations provide expert opinion for the timing of drug cessation prior to neuraxial techniques, maintenance of neuraxial catheters, and timing for starting medications after a neuraxial technique or removal of indwelling neuraxial catheter [67, 68]. For drugs altering the coagulation cascade, a five half-life abstention should be considered in light of no published recommendations. If the medication alters platelet function, a longer time may be required and should be individualized based on specific platelet inhibition. Further, the mechanism of drug elimination and clearance should be taken into account as many of these medications rely on renal clearance and have prolonged action in patients with reduced renal function (Table 19.3).

While the ASRA neuraxial recommendations are often applied to deep plexus blocks, they do not apply to superficial peripheral nerve blocks. Because of the expandable compartments that superficial nerve blocks are performed in, the major risk in the anticoagulated patient is blood loss and not neural ischemia. Therefore, the decision to proceed with a peripheral nerve block should involve a risk/benefit assessment.

Falls

While regional anesthesia, specifically neuraxial and lower extremity peripheral nerve blocks, can significantly improve postoperative analgesia, it can also be associated with motor blockade and raise concerns for postoperative falls. Lumbar plexus blocks have been the most well studied in this regard with catheters associated with a 2.2% risk of falling and single injection with a 1.7% risk [69]. A separate study evaluating continuous femoral nerve catheters for total knee arthroplasty found a 2% incidence of falls [70]. Although evaluation of fall risk in healthy volunteers found no impairment with the adductor canal block [54], at least two case reports of profound and prolonged quadriceps weakness have been published. In the report by Veal et al., fluoroscopy revealed that injection of 2 ml of contrast in the adductor canal catheter resulted in retrograde spread to the femoral nerve [71, 72].

The average hospitalized patient has a 1.6% chance for an inhospital fall. While motor blockade from regional anesthesia may play a role in falls, the risk remains nearly identical to the average hospitalized patient, even with continuous blockade by perineural catheters. Pain, perioperative medications, concomitant comorbidities, intraoperative blood loss, and surgical factors also play a role in perioperative fall and must be evaluated to help minimize the risk [73]. Unfortunately, fall rates increase with age. Patients aged 56-70 years and over 70 years fall 1.45 and 1.78 times more frequently than patients under 55 years of age or less [74]. Similarly, another study examining falls after arthroplasty found that patients aged 68 years or more were more likely to fall [73]. While no single intervention has been proven to decrease falls, staff and patient education, assistance to the bathroom, and out of bed assistance with all patient interventions have shown to decrease falls in hospitalized patients [75].

Hypotension

Neuraxial anesthesia with local anesthetics is well known to lead to decreased SVR and blockade of the sympathetic nervous system. In the elderly patient, this leads to an increased blood volume sequestered in the legs, mesentery, and kidneys which is associated with approximately 30% decrease in systemic blood pressure [76]. Even in a younger cohort, spinal anesthesia can frequently lead to arrhythmia. Sinus bradycardia occurs in approximately 5% of cases, followed by first-degree and second-degree AV block at 3% and then frequent PVCs in 1.5% of patients receiving spinal anesthesia for cesarean section; the only identifiable risk factor was increased age in this group of patients [77]. While intravascular fluid administration is the first-line treatment for spinalassociated hypotension, pre-hydrating prior to spinal administration has not been found effective in preventing hypotension in elderly patients [78]. For significant hypotension following spinal anesthesia, the vasopressor of choice should be a direct acting alpha-1 agonist since indirect-acting agents can have unreliable vasoconstricting and ionotropic effects [79].

Hypothermia

The decrease in body temperature can be of particular concern in the elderly patient secondary to the possible significant increase in oxygen consumption associated with

Drug	Drug to neuraxial time	Indwelling catheter allowed	Neuraxial placement until drug	Catheter removal to drug	Specific considerations
Aspirin/NSAIDS	No restrictions	Yes	No restrictions	No restrictions	specific considerations
Heparin (prophylactic)	4–6 h	Yes	No restrictions	No restrictions	If prolonged therapy,
neparii (propriyractic)	4-0 11	105	no restrictions	No restrictions	check platelets
Heparin (therapeutic)	Normalized PTT	Yes	1 h	Normalized PTT	If prolonged therapy, check platelets. Neurologic checks with indwelling catheter
LMWH (prophylactic once-daily dosing)	12 h	Yes	12 h	4 h	If prolonged therapy, check platelets
LMWH (prophylactic twice-daily dosing)	12 h	No	12 h	4 h	If prolonged therapy, check platelets
LMWH (therapeutic)	24 h	No	12 h	4 h	If prolonged therapy, check platelets
Warfarin initiation (Coumadin)	INR <1.5	Yes	No restrictions	INR <1.5	
Warfarin discontinuation (Coumadin)	Normal INR 4–5 days	Yes	No restrictions	INR <1.5	
Clopidogrel (Plavix)	7 days	No	Unknown	6 h	
Ticlopidine (Ticlid)	14 days	No	Unknown	6 h	
Prasugrel (Effient)	7–10 days	No	6 h	6 h	
Ticagrelor (Brilinta)	5-7 days	No	6 h	6 h	
Apixaban (Eliquis)	3 days	No	6 h	6 h	Consider longer drug-free period with renal insufficiency
Rivaroxaban (Xarelto)	3 days	No	6 h	6 h	Consider longer drug-free period with renal insufficiency
Dabigatran (Pradaxa)	5 days	No	6 h	6 h	Consider longer drug-free period with renal insufficiency

Table 19.3 Recommendations for neuraxial techniques in patients receiving anticoagulant and antiplatelet medications

Based on data from Refs. [67, 68]

shivering. Specific patient risk factors that are associated with hypothermia following neuraxial anesthesia are increasing age and a higher level of blockade. On average core body temperature will decrease roughly by 1 °C within the first hour following a spinal anesthesia [80]. While the use of regional anesthesia does lead to vasodilatation in the affected region of the body, it has not been found to cause more hypothermia than general anesthesia. Conversely, the use of epidural anesthesia has been found to lead to smaller decreases in body temperature compared to general anesthesia in a cold operating room. These differences can be equilibrated if the operating room is heated to 24.5 °C [81].

Post-dural Puncture Headache (Spinal Headache)

Post-dural puncture headaches are one of the most frequently reported adverse events associated with neuraxial anesthesia. The incidence of headache in a middle-aged patient varies depending on the spinal needle gauge and needle tip with the highest frequency following the use of cutting needle tips. It has long been understood that headache risk is higher in younger patients, peaking in the third decade at a rate of 16% and falling in each subsequent decade. By the age of 60, the post-dural puncture headache risk decreases to 4% and continues to decline with increased age. This historical data also reflects the use of large (16–20 gauge) cutting tip needles [82]. More recently, a 2.6% incidence of headache was noted when utilizing a 22 gauge Quincke needle in the geriatric population [83]. This rate may be even lower with utilization of pencil point needles.

Significant Gaps in Our Knowledge and Future Directions

New or Novel Local Anesthetic Formulations

The majority of local anesthetics used today have been commercially available for many years. Despite having welltolerated medications, pharmaceutical corporations are actively trying to develop longer-acting or sustained released formulations to allow for prolonged local anesthetic effects.

Liposomal Bupivacaine

Liposomal bupivacaine is the newest local anesthetic that has become commercially available. This medication is composed of multivesicular liposomes impregnated with bupivacaine. Once injected, the liposomal matrix is slowly broken down, releasing a prescribed and continuous amount of local anesthetic. The current available formulation contains 266 mg of liposomal bupivacaine (1.33% in 20 ml vials), which is also the maximum daily dose. While this medication is expressed in milligram dosing, it is not directly equivalent to plain bupivacaine; rather, 266 mg of liposomal bupivacaine is equivalent to 300 mg of plain bupivacaine [84]. The purported benefit is prolonged analgesia due to the slow release of this medication over 72 h. While bupivacaine can be found in the plasma for up to 96 h after infiltration, its analgesic properties have not been found to be long acting. Studies comparing liposomal bupivacaine with non-liposomal local anesthesia have found no or limited benefit of liposomal bupivacaine [85, 86]. In patients undergoing total knee arthroplasty, periarticular injection of liposomal bupivacaine was compared to plain bupivacaine; however, no significant difference in analgesia was found [85, 87]. Liposomal bupivacaine is only approved for wound infiltration and infiltrative blocks such as transverse abdominis plane blocks. Additionally, the manufacturer is currently studying its use for peripheral nerve blockade and new indications may arise in the future. Currently, data is limited in its utilization and safety for peripheral nerve blocks. Notably, femoral nerve blockade with 266 mg of liposomal bupivacaine was found to have minor improvement in analgesia when compared to placebo [88]. Further high-quality studies are needed to determine if the added costs of liposomal bupivacaine are justified with its use. To date no specific studies have been performed evaluating the use of liposomal bupivacaine specifically in the geriatric population.

Saber Bupivacaine

Saber bupivacaine is another formulation currently under development as a sustained release local anesthetic. Bupivacaine is suspended in sucrose acetate isobutyrate. This leads to an extended release of local anesthetic over 72 h. As of November 2015, this formulation was undergoing phase 3 trials. The only published trial compared saber bupivacaine to placebo and found analgesic benefits for saber bupivacaine in patients undergoing open hernia repair [89]. There is no current data available to compare this new medication to plain bupivacaine at this time, and its use has not been approved by the FDA.

Proliposomal Ropivacaine

Proliposomal delivery systems are currently under development. In this formulation, liposomes are not created until the medication is reconstituted using aqueous media. The benefit of this formulation is that it extends the shelf life of the drug, making it stable at room temperature [90]. This medication has only been documented in one human study in healthy volunteers. This trial found the drug to nearly double anesthesia duration to pinprick (28 h vs 15 h) compared with plain ropivacaine [91]. Further studies and FDA evaluation will be required before this medication could become a therapeutic option.

Neosaxitoxin

Neosaxitoxin is a naturally occurring alkaline neurotoxin derived from shellfish. It acts by binding to the outer portion of some sodium channels. Its chemical structure does not permeate the blood-brain barrier and has poor affinity for cardiac sodium channels. Currently in phase 1 trials, it has been studied alone as well as combined with bupivacaine and epinephrine. During skin infiltration in healthy volunteers, neosaxitoxin provided roughly 6–9 h of sensory blockade compared to placebo [92]. Perineural use of this medication has been evaluated in the animal model. Sciatic nerve blockade was prolonged with a combination of neosaxitoxin and bupivacaine with and without epinephrine [93].

Other Future Directions

Patient Safety

With the invention of new local anesthetic formulations and regional techniques, concerns for patient safety will always need to remain under examination, specifically, concerns for neurotoxicity, nerve injury, and systemic toxicity with current local anesthetics, perineural adjuvants, and novel local anesthetic agents.

Regional Anesthesia and Outcomes (Short and Long Term)

Regional anesthesia and improved outcomes remain controversial subjects. While older publications showed a decrease in venous thrombosis following neuraxial anesthetics, the advent and implementation of pharmacologic prophylaxis have diminished this benefit. Consequently, disagreement exists on whether neuraxial anesthesia improves safety or outcomes compared with general anesthesia [94]. However, other benefits to regional techniques have been noted. A meta-analysis of over 360,000 patients undergoing lower extremity joint replacement found that neuraxial anesthesia was associated with a decreased incidence of postoperative surgical site compared to general anesthesia [95]. Additionally, regional anesthesia has also been associated with decreased rates of postoperative cognitive dysfunction but not postoperative delirium [96]. Unfortunately, while regional analgesia is excellent for intraoperative analgesia and postoperative pain, it has not been associated with improved functional outcomes several months postoperatively. While regional anesthesia may not reduce long-term morbidity, it has been associated with reductions in postoperative cardiac, pulmonary, neurological, and endocrine complications [97].

3D Ultrasound

While the majority of regional blocks are performed using 2D ultrasound technology, 3D ultrasounds do exist and have been used for placement of regional anesthetics [98]. The purported benefits of 3D ultrasound are better recognition of connective tissue planes that can obstruct local anesthetic spread and ability for more planes of tissue to be evaluated without significant probe manipulation [99]. Despite having been available for nearly 10 years, this modality has failed to gain popularity. This lack of utilization is likely secondary to cost and slower processing speed.

Regional Anesthesia and PACU Bypass

Peripheral nerve blockade can be a useful tool to provide excellent anesthesia with the possibility of quick recovery, allowing for bypassing phase 1 of the postanesthesia care unit. While this has been demonstrated in the general patient population [39], no specific study has evaluated this claim in the geniatric population [42].

Conclusions

Local anesthetic utilization for anesthesia has evolved considerably since cocaine was first isolated from the coca leaves during the 1860s. Since that time, numerous local anesthetics have been developed and much has been learned about their potential role in the perioperative period. Today, local anesthetics are widely utilized to provide anesthesia and analgesia. Our understanding of the mechanism of action for local anesthetics has also grown resulting in the development of novel formulations to prolong analgesic duration. However, research is still needed to better understand both neurotoxicity and systemic toxicity and examine the beneficial effects of regional anesthesia to improve perioperative care in the geriatric population.

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Neuromuscular Blocking and Reversal Agents

Cynthia A. Lien

Abbreviations

BChE	Butyrylcholinesterase
ED ₉₅	The dose that will cause, on average, 95% of
	neuromuscular blockade
NMB	Neuromuscular blockade
NMBAs	Neuromuscular blocking agents
PACU	Postanesthesia care unit
TOFR	Train-of-four ratio

Whether or not to maintain neuromuscular block in patients, young or elderly, is a matter of debate [1]. The decision is influenced in part by the type of anesthesia administered as well as the planned surgical procedure. When inducing and maintaining paralysis in a geriatric patient, special consideration must be given to the potential for altered pharmacologic behavior of neuromuscular blocking agents (NMBAs). A growing geriatric surgical population, coupled with constantly changing surgical trends and practices, mandates that nondepolarizing neuromuscular blocking and reversal agents, as well as anesthetics, are chosen based on their specific pharmacodynamic characteristics to optimize patient outcome.

Changes in the Structure of the Neuromuscular Junction

There are a number of changes that occur with aging that may affect the impact of neuromuscular blocking agents in geriatric patients. Because of skeletal muscle denervation, elderly patients have a decrease in generalized muscle

Department of Anesthesiology, Weill Cornell Medical College, New York, NY, USA e-mail: calien@med.cornell.edu strength and coordination. These changes coupled with decreased total body fluid and lean body mass, as well as decreased kidney function, cardiac output, and splanchnic blood flow may all affect the pharmacodynamics and kinetics of NMBAs.

In people over the age of 60 years, the neuromuscular junction undergoes continuous degeneration and regeneration. The reorganization is primarily initiated through a reduction in the number of motor neurons in the spinal cord [2] and the ventral root fibers [3]. The decrease in motor neurons is accompanied by a decrease in the number of motor units, which consist of a motor neuron and its innervated muscle fibers. Because reinnervation does not compensate for the progressive loss of neurons, muscle fibers degenerate and are replaced with fat [4] and fibrous tissue. The 25-35% decrease in muscle mass typically seen in the elderly [5] is thought to be the result of both a loss of muscle fibers and decrease in the size of primarily the fast-twitch fibers [6]. An increase in the size of the motor unit (innervation of more muscle fibrils by a motor neuron) partially compensates for the loss of motor units and results in an augmented twitch response when stimulating a single motor nerve [7] in the aged.

Aging is also accompanied by structural changes at the neuromuscular junction. Preterminal axons are increased in number and a greater number of the axons enter into a single endplate. The distance between the preterminal axon and the motor endplate is increased. Additionally, the motor endplate is composed of a greater number of smaller groupings of nicotinic acetylcholine receptors and is lengthened with increasing age. These changes are accompanied by a flattening of the folds of the endplate at the neuromuscular junction [8].

The extra junctional acetylcholine receptors that are frequently found in aged muscles [9] may be the result of the progressive denervation that accompanies aging. How the increased presence of extrajunctional receptors influences neuromuscular transmission in the elderly is not known. While proliferation of acetylcholine receptors, as is observed in disuse atrophy, leads to a relative resistance to

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neuromuscular blocking agents [10], elderly patients do not have an increased resistance to these agents.

There are age-related changes in acetylcholine storage and release at the neuromuscular junction in animals. In aged rats, the acetylcholine content of a single motor neuron at a neuromuscular junction of the diaphragm is less than that found in young adult rats. In these same neuromuscular junctions, though, an increased number of nerve terminals per endplate contributes to the release of greater amounts of acetylcholine at each endplate [11] and is likely responsible for maintenance of normal neuromuscular transmission in these rats. In spite of this observation, though, advanced age is associated with an overall decrease in the amount of acetylcholine released [8].

Despite all of the changes at the neuromuscular junction, changes in the pharmacodynamic behavior of the nondepolarizing neuromuscular blocking agents seem to be the result of alterations in their pharmacokinetics rather than altered interaction of the nondepolarizing compound and the motor endplate.

Dose-Response Relationships in the Elderly

There are a number of physiologic factors, with seemingly contradictory effects, that may have a role in the observed differences in the onset and duration of neuromuscular blocking agents in geriatric patients. The loss of muscle mass in the aged should result in an upregulation of acetyl-choline receptors [12] and relative resistance to nondepolarizing neuromuscular blocking agents. Conversely, decreases in lean body mass [13] and volume of distribution [14] would suggest that geriatric patients require smaller doses of neuro-muscular blocking agent to establish the same depth of paral-ysis that of a young adult. Similarly, the decrease in plasma proteins in the elderly should increase the bioavailability of NMBAs as less would be bound to proteins – resulting in a need for smaller doses to establish a specific depth of neuro-muscular block (NMB).

As demonstrated with both d-tubocurarine and metocurine, nondepolarizing neuromuscular blocking compounds are bulky, highly charged compounds that do not readily leave the central volume [15]. Following administration of a single bolus of the neuromuscular blocking agent to young and elderly patients, the older patients were found to have a decrease in the volume of distribution [15]. Results, with respect to volumes of distribution of other nondepolarizing compounds, have not been consistent and may be due to either study design or the dynamics of the NMBA. Pharmacokinetic study of the intermediate-acting agent, vecuronium, in patients over the age of 70 years demonstrated that both the initial volume of distribution and the volume of distribution after a single intravenous dose of 0.1 mg/kg were indistinguishable from what was found in younger patients [16].

Because nondepolarizing NMBAs are not highly protein bound [17], their bioavailability is the same in young and elderly adults [18] in spite of the decrease in plasm proteins found in the elderly. The available free fractions of long-, intermediate-, and short-acting compounds have all been shown, in vitro, to be the same in elderly and young adults [18].

With the structural changes in the neuromuscular junction found in the elderly, one could expect that sensitivity to nondepolarizing compounds would be increased in geriatric patients. Duvaldestin [19], however, found that after the administration of pancuronium, there was no difference in the plasma concentration-dose-response relationships in young and elderly patients. Similarly, the plasma concentration-dose-response relationships for both metocurine and d-tubocurarine were indistinguishable in elderly and young adult patients (Fig. 20.1) [15]. Similar results have been documented with the intermediate-acting nondepolarizing agents. Rupp et al. [20] found that the steady-state concentration of vecuronium at 50% neuromuscular block was the same in elderly and young adult patients. These results, consistent across different classes of NMBAs and varied durations of action, indicate that at the same plasma concentration of relaxant, elderly and young patients have the same degree of NMB and that sensitivity of the acetylcholine receptor is not increased in geriatric patients.

Although differences in pharmacokinetics influence the onset of effect and duration of action, the dose of relaxant that will generally produce 95% NMB (the ED₉₅) is the same in elderly and young adults. This has been found with the long-acting compounds, such as pancuronium [19], as well as the intermediate-acting NMBAs vecuronium [21], rocuronium [22], and atracurium [23].

Onset of Neuromuscular Block

The onset of effect of NMBAs is determined by, in addition to their potency, the time that it takes them to get to the neuromuscular junction. The speed with which they are delivered to the neuromuscular junction is influenced by circulation to the muscles and cardiac output. Once the neuromuscular blocking agent arrives at the muscle, it must diffuse into the neuromuscular junction and bind with the acetylcholine receptor to cause neuromuscular blockade. In geriatric patients, although there are some differences as to the extent (Table 20.1), increased age is generally associated with a slower onset of neuromuscular block when doses of $2 \times ED_{95}$ (two times the dose that causes, on average, 95% neuromuscular block) or greater are administered. Differences in onset are more apparent when doses that do

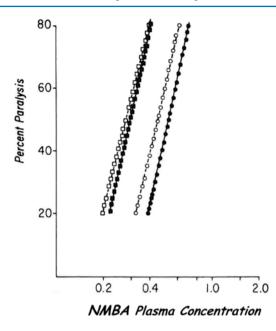


Fig. 20.1 The relationship between plasma metocurine (o-o) and d-tubocurarine $(\Box-\Box)$ in young and elderly patients and their depth of neuromuscular block. Values for the young are represented by the *unfilled symbols* (o and \Box) and those for the elderly by the *filled symbols* (• and \blacksquare). Differences between the young and elderly are not significant for either of the neuromuscular blocking agents (Adapted from Matteo et al. [15]. With permission from Wolters Kluwer Health)

not cause complete NMB are examined [24] (Fig. 20.2). The administration of doses causing complete paralysis allows only for the determination of the time required to achieve 100% neuromuscular block. Administration of smaller doses ($\langle ED_{95} \rangle$) allows the time required for the compound to actually have its maximal effect to be measured. While the greater time required for maximal effect in the elderly may be attributable to a decreased cardiac output, physically active, healthy geriatric patients do not necessarily have a decline in cardiac function [29, 30].

In a study in patients over the age of 65 years who were receiving oxygen-nitrous oxide-isoflurane anesthesia, cisa-tracurium (0.1 mg/kg) was administered after induction of anesthesia [31]. Onset of block was slower in elderly individuals than in young adults (3 versus 4 min, respectively). Pharmacodynamic modeling demonstrated that biophase equilibration was slower in the elderly than in young adults (0.06 versus 0.071, respectively), and the authors attributed the slower onset of neuromuscular block to the slower biophase equilibration. The relative contributions of decreased cardiac output and slower biophase equilibration remain to be determined.

The slower onset of NMB in geriatric patients may result in overdosing of the NMBAs. In an effort to shorten the onset of effect, larger or additional doses of NMBAs may be administered. The larger doses result in an increased duration of action of the neuromuscular blocking agent.
 Table 20.1
 Onset of maximal block in young and elderly patients following administration of nondepolarizing neuromuscular blocking agents

	Onset (minutes)			
Neuromuscular	Dose	Elderly	Young adult	
blocking agent	$(mg \cdot kg^{-1})$	patients	patients	Reference
Succinylcholine	1	1.58 [0.12]	1.18 [0.13]	[24]
Intermediate-acting n	ondepolarizing	neuromus	cular bloci	king agents
Vecuronium	0.1	4.92 [0.52]	3.70 [0.23]	[24]
	0.1	3.52 (1.11)	2.57 (0.66)*	[25]
Rocuronium	0.6	4.5 (2.4)	4.1 (1.5)	[26]
	1	1.33 (0.43)	1.04 (0.21)*	[27]
Cisatracurium	0.1	4.0	3.0*	[24]
	0.1	3.4 (1.0)	2.5 (0.6)*	[28]

Note: Data are mean (SD) or [SEM]

*Statistically significant difference when compared with elderly patients

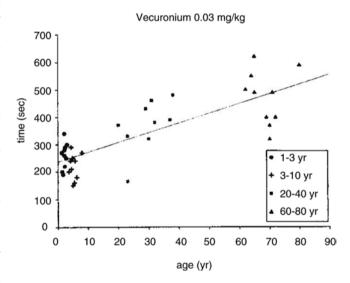


Fig. 20.2 The onset of maximal neuromuscular blocking effect of vecuronium 0.03 mg/kg in four different age groups. Onset of maximal effect is faster in the children and slowest in the most aged subjects. p < 0.00001 by linear regression (Reprinted from Koscielniak-Nielsen et al. [24]. With permission from Wolters Kluwer Health)

Furthermore, for those compounds that are eliminated through hepatic and renal mechanisms, the larger doses and administration of subsequent doses result in cumulation so that each subsequent dose lasts longer than those administered previously [32]. This progressive prolongation of effect occurs because recovery of neuromuscular function begins during redistribution of NMBAs, such as pancuronium or vecuronium, out of the plasma and into storage sites rather than during elimination of the compound from the body. With subsequent doses, the earlier doses are reentering the plasma for elimination. The drug effect, therefore, is a combination of the effects of the recently administered relaxant and a portion of the earlier doses as both contribute to plasma concentration. This effect is more pronounced with the longacting pancuronium than with the intermediate-acting vecuronium.

Pharmacokinetics and Duration of Effect

Aging, even in healthy elderly patients, is accompanied by decreases in hepatic and renal blood flow and function [33, 34]. Because the majority of nondepolarizing neuromuscular blocking agents are eliminated through some combination of these means, alterations in pharmacokinetics and duration of effect are to be expected. Alterations in the pharmacodynamics of nondepolarizing compounds as a result of changes in the pharmacokinetics associated with the normal process of aging may be difficult to distinguish from concomitant disease processes.

Long-Acting Agents

Of the long-acting neuromuscular blocking agents, pancuronium is the only one that is available for clinical use. These long-acting compounds generally depend primarily on the kidney for their elimination from the body (Table 20.2). It is not surprising, therefore, that they have a longer duration of action in geriatric patients. As found in the majority of studies of these compounds, their prolonged duration of action can be attributed to a prolonged elimination half-life and a decreased clearance, when compared to young adults (Table 20.3).

This is true for pancuronium, which, while still clinically available, is used relatively infrequently. McLeod [36] demonstrated a decrease in the clearance of pancuronium with increasing age. In a later study, Duvaldestin [19] studied the pharmacokinetics and dynamics of pancuronium in young and elderly adults and found that recovery intervals were prolonged by at least 60% in the elderly. The clearance of pancuronium was decreased more than 30% in the elderly, from 1.8 in young adults to 1.2 mL/min/kg (Fig. 20.3). Because the volume of distribution in the elderly was the same as in young adults, the decrease in clearance was accompanied by a doubling of the elimination half-life from 107 to 201 min.

Intermediate-Acting Agents

In contrast to the dependence of the long-acting NMBAs on the kidney for their elimination, the intermediate-acting compounds are eliminated from the body primarily through

 Table 20.2
 Means of elimination of nondepolarizing neuromuscular blocking agents from the body

Neuromuscular blocking agent	Means of elimination				
Long-acting compound	S				
Pancuronium	Kidney 85%, liver 15%				
Intermediate-acting con	npounds				
Vecuronium	Kidney 40-50%, liver 50-60%				
Rocuronium	Kidney 10%, liver 70%				
Atracurium	Kidney 10–40%, Hofmann elimination and ester hydrolysis 60–90%,				
Cisatracurium	Kidney 16%, Hofmann elimination >75%				
Short-acting compounds					
Mivacurium	Kidney <5%, butyrylcholinesterase >95%				

other mechanisms (Table 20.2). These include hepatic elimination, ester hydrolysis, and Hofmann degradation. In addition to decreases in renal function and blood flow, aging is associated with decreases in hepatic blood flow and hepatocellular function [26, 27, 37]. One would expect, therefore, that compounds relying on either of these means of elimination from the body would have altered pharmacokinetics. In contrast, clearance by Hofmann elimination is independent of end-organ function, and aging should have little impact on the pharmacokinetics of compounds eliminated through this mechanism.

Vecuronium was the first of the intermediate-acting nondepolarizing NMBAs to be introduced into clinical practice. Although it is eliminated primarily in the bile [38, 39], 20-25% of the compound is eliminated unchanged in the urine. The action of vecuronium in the elderly has been studied by four different groups of investigators [16, 20, 39, 40], and the results regarding pharmacokinetics and pharmacodynamics have not been consistent. d'Hollander and colleagues [39] examined the rate of recovery from vecuronium-induced NMB in geriatric patients. Recovery rates were compared to those in patients under the age of 40 and those between 40 and 60 years of age. The 10-25% and 25-75% recovery intervals, the time to recover from 10% to 25% and 25% to 75% baseline muscle strength, respectively, were significantly prolonged in the elderly patients. Additionally, less vecuronium was required to maintain 90% neuromuscular block for a period of 90 min in the elderly patients than it was in the younger individuals [39]. McCarthy [40] reported very similar findings with the clinical duration of action (the time from administration of an NMBA to 25% recovery of baseline muscle strength) of vecuronium being significantly prolonged in the elderly following administration of a bolus dose.

Rupp [20] studied the pharmacokinetics and dynamics of vecuronium in elderly patients in whom an infusion of the NMBA had been discontinued once 70–80% NMB had been achieved. The clearance and volume of distribution of vecuronium in patients older than 70 years of age were

Neuromuscular blocking agent	Patient age	$t_{1/2}\beta$ (minutes)	$Cl (mL \cdot kg^{-1} \cdot min^{-1})$	$V_d (L \cdot kg^{-1})$	Reference
Vecuronium	Young	78 ± 21	5.6 ± 3.2	0.49 ± 0.02	[16]
	Elderly	125 ± 55*	$2.6 \pm 0.6*$	0.44 ± 0.01	
	Young	70 ± 20	5.2 ± 0.8	0.24 ± 0.04	[20]
	Elderly	58 ± 10	$3.7 \pm 1.0^{*}$	$0.18 \pm 0.03*$	
Atracurium	Young	15.7 ± 2.5	5.3 ± 0.9	0.10 ± 0.01	[35]
	Elderly	$21.8 \pm 3.3^*$	6.5 ± 1.1	$0.19 \pm 0.06*$	
Cisatracurium	Young	21.5 ± 2.4	4.6 ± 0.8	0.11 ± 0.01	[28]
	Elderly	$25.5 \pm 3.7*$	5.0 ± 0.9	$0.13 \pm 0.02*$	
Pancuronium	Young	107 ± 24	1.81 ± 0.36	0.27 ± 0.06	[19]
	Elderly	$201 \pm 69*$	$1.18 \pm 0.39^*$	0.32 ± 0.10	

Table 20.3 Pharmacokinetics of nondepolarizing neuromuscular blocking agents in geriatric patients

 $t_{1/2}\beta$ half-life of elimination, *Cl* plasma clearance, V_d volume of distribution

*Statistically significant difference compared with younger adults

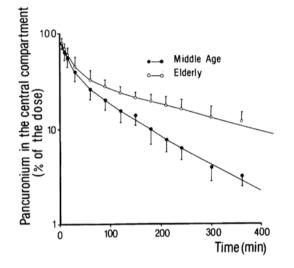


Fig. 20.3 The elimination of pancuronium from the plasma after administration of a bolus dose. Pancuronium disappears from the plasma significantly more slowly in elderly patients than in middle-aged adults (Reprinted from Duvaldestin et al. [19]. With permission from Wolters Kluwer Health)

approximately 30% less than what was found in younger adults. Elimination half-life and the 25-75% recovery interval, however, were similar in young adult and elderly patients. Lien [16] found that the 5-25% and 25-75% recovery intervals were approximately three times longer in elderly patients than in young adults following administration of a single intravenous dose of vecuronium. The clearance of vecuronium was half as fast in the elderly as it was in young adult patients (2.6 vs 5.6 mL \cdot kg⁻¹, respectively) and elimination of the compound was slower in geriatric patients (78 and 125 min for young adult and elderly patients, respectively). The authors concluded that the prolonged duration of action of vecuronium in elderly patients is attributable to its decreased clearance in this patient population, supporting the findings of d'Hollander and colleagues [39]. The decreased clearance is not inconsistent with the findings of Rupp et al. [20]

Like vecuronium, rocuronium is an intermediate-acting nondepolarizing NMBA with a steroidal structure. Similar to vecuronium, the kidney is not its primary means of elimination from the body. However, while it does not depend on the kidney for its elimination, clearance of rocuronium is decreased and its mean residence time is prolonged in patients with renal failure [37]. As with vecuronium, the behavior of this compound in aged patients has been studied by different groups of investigators [22, 26, 27]. In the case of rocuronium, however, the results are more similar across the studies. Baykara et al. [27] reported that recovery of the first response in the train of four after administration of 1 mg/ kg was slower in the elderly than in young adults. Bevan et al. [22] found, in a study of repeat bolus doses of rocuronium, that the clinical duration of action and the 25–75% recovery intervals were prolonged in elderly patients. With repeated doses of 0.1 mg/kg rocuronium administered at 25% recovery of twitch height, the duration of action increased in the elderly patients but not in the young adult patients. Matteo et al. [26] studied the pharmacokinetics and pharmacodynamics of rocuronium in geriatric patients following a 0.6 mg/kg dose and found that in patients between the ages of 70-78 years, clearance was decreased by 27%. Not unexpectedly, the 25-75% recovery interval was increased from 13 min in the young adults to 22 min in the elderly patients.

In contrast to NMBAs with a steroidal structure, atracurium depends on neither the kidney nor the liver as its primary means of elimination. It undergoes ester hydrolysis and the base and temperature catalyzed process of Hofmann elimination (Table 20.2). Because the elimination of atracurium is not end-organ dependent, the physiologic changes associated with aging would not be expected to affect its pharmacokinetics and recovery profile. As they had done with vecuronium, d'Hollander and colleagues [41] studied atracurium in patients over the age of 60 years. In this study, patients received an infusion of atracurium to maintain 90% depression of neuromuscular function for 90 min. The dose of relaxant required to maintain this depth of paralysis was calculated in the age groups studied (older than 60 years, 40–60 years, and younger than 40 years of age). There were no differences among the groups in either their 10–25% and 25–75% recovery intervals or the amount of relaxant necessary to maintain 90% twitch suppression.

Slight changes in the pharmacokinetics of atracurium in elderly patients, however, have been reported. Kent et al. [42] administered 0.6 mg/kg atracurium to elderly and young adult patients and found no difference in clearance and the volume of distribution between the two patient groups. There was, however, a small but significant difference in the elimination halflife. The elimination half-life of atracurium was prolonged by 15% in elderly patients, from 20 to 23 min. Kitts et al. [35] administered an infusion of atracurium to achieve 70% neuromuscular block. As described by Kent [42], elimination halflife was prolonged in the elderly. Because clearance was not affected by advanced age, the increase in elimination half-life was attributable to a larger volume of distribution in elderly patients. Most recently, Parker et al. [43] found that its elimination half-life was prolonged and clearance decreased in elderly patients. The results of Kitts, Kent, and Parker support the finding by Fisher et al. [44] that in addition to Hofmann elimination and ester hydrolysis, renal and hepatic mechanisms contribute to the elimination of the compound. Despite these pharmacokinetic differences in elderly patients, however, the dynamics of neuromuscular blockade with atracurium are not different in the young and elderly [35, 41].

Cisatracurium is one of the ten isomers that comprise atracurium. Similar to atracurium, it is eliminated primarily through Hofmann elimination. Renal clearance accounts for 16% of its elimination from the body [45]. As with atracurium, small changes have been found in the pharmacokinetics of this compound in elderly patients. Ornstein et al. [28] described a prolongation of its half-life of 4 min (21.5 versus 25.5 min in young and elderly patients, respectively) and an increase in its volume of distribution (108 versus 126 mL \cdot kg⁻¹ in young and elderly patients, respectively). Clearance was unchanged with advanced age. Sorooshian et al. [31] also found that clearance was unaffected by advanced age. The volume of distribution in the elderly, however, was larger. Both studies found no difference in recovery of neuromuscular function after administration of 0.1 mg/kg cisatracurium. In a later study, Pühringer et al. [46] also noted the lack of effect of small changes in pharmacokinetics of cisatracurium on the duration of action of the compound in the elderly. Patients received 0.15 mg/kg cisatracurium to induce neuromuscular blockade and 0.03 mg/kg boluses to maintain neuromuscular blockade. The clinical duration of action after the initial dose and the time to return to a train-offour ratio of 0.8 following the last dose of cisatracurium were the same in young adults and those older than 65 years of age.

Short Duration of Action

While no longer widely clinically available, mivacurium is the only available nondepolarizing neuromuscular blocking agent with a short duration of action that was used for a significant period of time. Like succinylcholine, it is metabolized by butyrylcholinesterase (BChE) and is dependent on neither hepatic nor renal function for its elimination. Recovery from mivacurium-induced block is prolonged in the elderly [47]. In this study, patients received either a bolus of 0.15 mg/kg mivacurium and were allowed to recover or, following the bolus, were given an infusion to maintain 90% suppression of neuromuscular response to stimulation. All recovery parameters were prolonged by approximately 30% in elderly patients. The amount of mivacurium required to maintain neuromuscular blockade was also reduced (3.7 versus 5.5 µg/kg/min in the elderly and young, respectively). Goudsouzian et al. [48] also found that elderly patients required a lower infusion rate to maintain a stable depth of block. A study of the kinetics of mivacurium in the elderly does not explain the prolongation of recovery observed in this patient population [49]. The investigators found that the half-life and clearances of the three isomers of mivacurium, cis-trans, trans-trans, and cis-cis, were not different in elderly patients. The volume of distribution of the relaxant was, however, larger in the elderly.

Plasma cholinesterase activity is reduced in the elderly [50] and mivacurium requirements are inversely related to BChE activity [51] in that patients with higher BChE activity require higher mivacurium infusion rates to maintain the desired depth of block than patients with lower BChE activity. When mivacurium is used in geriatric patients, lower infusion rates are required to maintain a stable depth of NMB and, if administered as repeated boluses, longer dosing intervals would be anticipated.

Postoperative Residual Neuromuscular Block

Residual NMB is a risk whenever a nondepolarizing NMBA is administered. The incidence of residual NMB, defined as a train-of-four ratio < 0.90, has been reported to be as high as 62% [52]. While it occurs in both young and elderly patients, residual neuromuscular block appears to be a more frequent occurrence in geriatric patients [53, 54]. An increased frequency of residual NMB in this patient population occurs because of a combination of factors including relative overdosing because of a slower onset of effect, a decreased clearance, decreased muscle mass, and increased variability in the duration of action of NMBAs [55–57].

Residual NMB is well recognized as being associated with adverse events [58–61]. One prospective trial of patient outcome after general anesthesia that included the use of

NMBAs (vecuronium, atracurium, or pancuronium) [58] demonstrated that elderly patients who received pancuronium were likely to enter the postanesthesia care unit (PACU) with a train-of-four ratio less than 0.7 more frequently than the vounger adult patients, regardless of the NMBA they received. Additionally, these patients were more likely to develop postoperative pulmonary complications than patients who had arrived to the postanesthesia care unit with a trainof-four ratio ≥ 0.7 . More recently, Pietraszewski [54] found that elderly patients were more likely to have hypoxia and inadequate recovery of neuromuscular function in the PACU. The one patient in this relatively small study who developed postoperative pneumonia was elderly, and the cause of the complication was determined to be residual paralysis. In a larger trial, Murphy [53] found that although younger patients received larger doses of rocuronium, residual NMB occurred more commonly in geriatric patients. Elderly patients with residual NMB were more likely to develop airway obstruction and hypoxemia before reaching the PACU and to report symptoms of muscle weakness than elderly patients who had adequate recovery of neuromuscular function. This finding is not unexpected as residual NMB interferes with the coordination of swallowing [62, 63] and the response of the carotid body chemoreceptor to hypoxia [64]. Consistent with the results of Berg's study [58], there was a trend toward longer hospital stays and more pulmonary complications in the geriatric population with residual NMB. Cedborg [65] found 1 year earlier that residual paralysis in geriatric volunteers resulted in an increase in both the severity and frequency of pharyngeal dysfunction.

Anticholinesterases

Because the duration of action of many nondepolarizing neuromuscular blocking agents is prolonged in the elderly, the impact of aging on the pharmacokinetics and pharmacodynamics of their antagonists is of interest. Even in young adults, anticholinesterases do not consistently and quickly facilitate recovery to a train-of-four ratio ≥ 0.90 . Inadequate dosing and reversal of too profound level of neuromuscular block commonly contribute to the incomplete recovery of neuromuscular function. The three anticholinesterases that have been available for use, edrophonium, neostigmine, and pyridostigmine, have prolonged durations of action and decreased clearances in the elderly (Table 20.4). The kinetics and dynamics of each in the elderly have been studied with vecuronium and many of the long-acting neuromuscular blocking agents. Edrophonium and neostigmine are more commonly used in clinical practice and will be discussed in this chapter.

Edrophonium

The clearance of edrophonium from the plasma depends primarily on the kidneys. As would be anticipated based on its means of elimination, the clearance of edrophonium (1 mg/ kg) is decreased and its elimination half-life prolonged in the elderly [67]. Because of its altered pharmacokinetics, dosing adjustments are not required for these patients. This has been demonstrated in two different dosing models. McCarthy et al. [68] demonstrated in a dose-response study that the dose of edrophonium required to antagonize 90% vecuronium-induced neuromuscular block, induced by a bolus of 0.08 mg/kg vecuronium, did not differ between the elderly and young adult patients. Similarly, Kitajima et al. [25] administered edrophonium, 0.75 mg/kg, to antagonize neuromuscular block that had been induced with 0.1 mg/kg, once the train-of-four ratio (TOFR) had returned to 25%. The authors found that there was no difference in the time required for the train-of-four ratio to recover to 75% in elderly patients (over the age of 70 years) and young adults. Matteo et al. [67] evaluated the ability of 1 mg \cdot kg⁻¹ edrophonium to reverse a deep, steady-state block produced by continuous infusion of metocurine in the elderly and younger adult patients. They found that there was no significant difference in the time to the maximum effect of the anticholinesterase in the two study groups (elderly 2.1 versus younger 1.7 min). In this model, the plasma concentration of edrophonium at any given point in recovery was greater in the elderly patients than in the young adults.

The change in the pharmacokinetic parameters of edrophonium in the elderly has no influence on its efficacy in antagonizing residual neuromuscular block in this patient population. Because its volume of distribution tends to be smaller and its clearance slower, the dose of edrophonium does not need to be adjusted to obtain the same degree of recovery as in younger adults.

Neostigmine

In a study designed similar to the kinetic studies of edrophonium in the elderly [67], Young et al. [66] studied the pharmacokinetics and dynamics of neostigmine in this patient population. Neostigmine was administered to patients receiving a metocurine infusion to maintain 90% neuromuscular block. The authors found that there was a slight, but not statistically significant, decrease in clearance of the anticholinesterase in the elderly and a decreased initial volume of distribution.

Dose-response studies of neostigmine are not as consistent as those involving edrophonium. They have demonstrated that the dose of neostigmine required for antagonism

Anticholinesterase	Patient group	$t_{1/2}\beta$ (minutes)	$Cl (mL \cdot kg^{-1} min^{-1})$	$V_{\rm i} \left({\rm L} \cdot {\rm kg}^{-1} \right)$	$V_{\rm d} \left({\rm L} \cdot {\rm kg}^{-1} \right)$
Edrophonium	Elderly	84.2 (17)*	5.9 (2)*	0.05 (0.02)	0.72 (0.3)
$(1 \text{ mg} \cdot \text{kg}^{-1})$ [25]	Young	56.6 (16)	121.4 (4)	0.2 (0.2)	0.81 (0.3)
Neostigmine	Elderly	16.7 (0.8)	23.5 (5)	0.068 (0.018)*	0.566 (0.13)
$(0.07 \text{ mg} \cdot \text{kg}^{-1})$ [66]	Young	18.5 (7)	33.5 (4)	0.1 (0.04)	0.549 (0.12)

 Table 20.4
 Pharmacokinetics of edrophonium and neostigmine, in elderly and young adults

Note: Data are shown as mean (SD)

 $t_{1/2}\beta$ half-life of elimination, Cl plasma clearance, V_i initial volume of distribution, V_d volume of distribution

*There is a statistically significant difference compared with younger adults

of residual neuromuscular block in elderly patients is either similar [69] or greater than [70] that required in younger adults. Slower spontaneous recovery from vecuroniuminduced block in geriatric patients during neostigmineantagonized recovery may be a cause of their apparent greater requirement for neostigmine. That being said, because of its decreased clearance in the elderly, the duration of action of neostigmine is also prolonged in these patients [71]. Additionally, the decreased initial volume of distribution of neostigmine [66] (Table 20.4) results in a greater plasma concentration of the anticholinesterase after administration of a single dose and may contribute to its prolonged duration of action. This is potentially advantageous because the duration of action of many nondepolarizing neuromuscular blocking agents is prolonged in the elderly.

Of note, the values reported for times to recovery to a train-of-four ratio of 0.7 are average values. As demonstrated by Kirkegaard et al. [72], there is a substantial degree of interpatient variability in the time required for neostigmine antagonism cisatracurium-induced neuromuscular block. This interpatient variability in young adults becomes even more pronounced when attempting to achieve recovery to a TOFR of 0.9, which is the new standard for complete recovery of neuromuscular function [73].

Adverse Effects of Anticholinesterases in Geriatric Patients

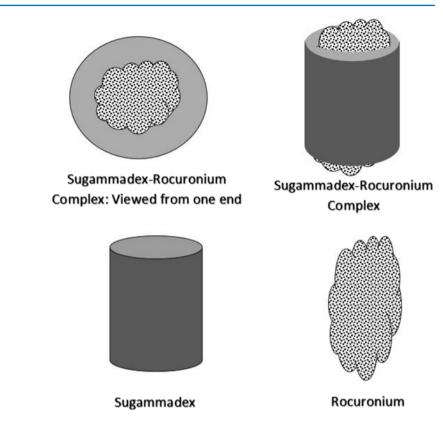
The cardiac muscarinic effects of anticholinesterase include dysrhythmias, such as bradycardia and conduction defects. Especially in the geriatric patient population, a large percentage of which has preexisting cardiovascular disease, anticholinesterase administration creates a greater risk of cardiac dysrhythmias [74]. Of the anticholinesterases, neostigmine is more likely to cause dysrhythmias than pyridostigmine (35% versus 14%, respectively) [75]. Antimuscarinic agents, such as atropine or glycopyrrolate, are always administered with anticholinesterases to counteract their bradycardic effects. Depending on the doses of the anticholinesterase and antimuscarinic chosen, tachycardia is frequently observed. In patients with cardiovascular disease, the resultant increase

in myocardial oxygen consumption may not be well tolerated and may lead to myocardial ischemia.

In addition, atropine is a tertiary amine and can, therefore, cross the blood-brain barrier. In the central nervous system, anticholinergic drugs are known to affect the central cholinergic pathway where they are a cause of deterioration in postoperative cognitive function [76]. Atropine has been shown to produce disorientation, hallucinations, and memory loss. Glycopyrrolate, which is a quaternary amine, does not readily cross the blood-brain barrier, and postanesthetic arousal times after its administration with neostigmine are shorter than those after the administration of atropine and neostigmine [77].

Sugammadex

Sugammadex is a selective relaxant binding agent that encapsulates steroidal neuromuscular blocking agents. One molecule of sugammadex binds to one molecule of rocuronium so that it is no longer able to bind to the neuromuscular junction (Fig. 20.4). Its mechanism of action is such that, unlike the anticholinesterases, it can effectively and quickly reverse even profound neuromuscular blockade when dosed appropriately. A recent study [78] demonstrated that the use of sugammadex to reverse rocuronium-induced neuromuscular block completely eliminated the occurrence of residual paralysis in the PACU. In contrast, 43% of patients receiving neostigmine in the same study had inadequate recovery of muscle strength on admission to the PACU. It is not simply the use of sugammadex that guarantees full recovery from neuromuscular blockade but its use as described in dosing guidelines [79]. The dosing guidelines are based on the response of the adductor pollicis to stimulation of the ulnar nerve. A dose of 2 mg/kg should be administered when there are two or more responses to train-of-four stimulation and 4 mg/kg administered when there is no response to train-of-four stimulation and the post-tetanic count is 1-2. The largest recommended dose of sugammadex, 16 mg/kg, should be used to reverse profound paralysis 3 min of administering 1.2 mg/kg. In order to follow these guidelines, depth of paralysis must be monitored. A recent **Fig. 20.4** A caricature demonstrating the interaction of sugammadex with rocuronium. Each molecule of the selective relaxant binding agent can bind with one molecule of rocuronium. The rocuronium-sugammadex complex is eliminated through the kidneys in the urine



study by Kotake et al. [80] demonstrated that introducing sugammadex into clinical practice reduced the incidence on incomplete recovery of muscle strength even when monitoring of neuromuscular blockade was not routinely used in the operating rooms. It did not, however, eliminate the possibility of a patient being partially paralyzed during tracheal extubation, the incidence of which remained at 4.3%.

As it does in young adults, sugammadex reverses rocuronium-induced neuromuscular block in geriatric patients [81-83]. While recovery occurred quickly following administration of rocuronium in each of these studies, recovery to a train-of-four ratio > 0.9 was slower in elderly patients than in young adults. In a study of reversal of rocuronium (0.6 mg/kg)-induced block with sugammadex (8.0 mg/kg) after ECT [84], time to recovery to a train-of-four ratio was on average 40 s slower in the elderly. The slower onset of effect was not related to cardiac index, suggesting that it is not age-related changes in cardiac function that account for its slower onset of effect. The results of a more recent dosefinding study suggest that elderly patients require larger doses of sugammadex to reverse profound neuromuscular blockade (post-tetanic count of 1-2) [85]. In this study, the ED₅₀ for sugammadex was approximately 1 mg/kg greater in the elderly patients than it was in young adults. If the absolute recovery time is of concern, administering a larger dose of sugammadex to an elderly patient may shorten the time to recovery of neuromuscular function.

Sugammadex and the sugammadex-rocuronium complex are eliminated through the kidneys [86]. The clearance of sugammadex is decreased, as expected, in elderly patients as their renal blood flow and function are decreased [81].

Summary

Although age-related changes in hepatic, renal, and cardiac function slow the onset and clearance of many nondepolarizing neuromuscular blocking agents in geriatric patients, extensive changes at the neuromuscular junction do not increase sensitivity to these compounds. Decreased clearance mandates that neuromuscular block be maintained and subsequent doses administered only after documentation of return of muscle strength with a monitor of neuromuscular blockade. Except in rare cases, antagonism of residual NMB will be required. Dosing of reversal agents, whether anticholinesterases or the selective relaxant binding agent, sugammadex, should, as it is with NMBAs, be based on the results of monitoring of neuromuscular function.

As the surgical population ages and surgical trends and practices evolve, neuromuscular blocking agents, like anesthetics, must be specifically chosen based not only on their pharmacokinetic and pharmacodynamic properties but also on the basis of patient age.

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Anesthetic Implications of Chronic Medication Use

R. David Warters and Tamas A. Szabo

Introduction

Elderly patients represent approximately 15% of the total population in the United States, yet they consume more than one-third of all medications [1]. The healthcare of older adults presents significant challenges including the increasing size of the age group, the biological process of aging, the increased potential for comorbidities and polypharmacy, and limited availability of appropriate evidence regarding drug effectiveness and safety in older patients.

Appropriate prescribing necessitates the understanding of geriatric physiology, pharmacokinetics, and pharmacology. Potentially inappropriate prescribing (PIP) is widespread in the elderly population. PIP occurs when the risks of a medication outweigh the potential benefits in a particular patient. PIP may occur when medications are prescribed with no clear evidence-based indication, in higher doses than necessary or in combination with other drugs that may lead to adverse drug-drug interactions. PIP also occurs when a patient does not receive the appropriate drug indicated for a certain disease or condition [2]. There were approximately 100,000 emergency hospitalizations for adverse drug events (ADEs) in elderly adults from 2007 to 2009 in the United States [3]. Avoiding PIP may decrease the risk of ADEs and improve geriatric care. A recent prospective cohort study, using data from a German insurance group, revealed an increased risk of 38% for all-cause hospitalizations in the first 180 days following the intake of potentially inappropriate medications (PIMs). Almost 6% of hospitalizations in the entire study population of elderly patients could have been prevented by eliminating PIMs [4].

In 1997, Beers devised a comprehensive set of explicit criteria for potentially inappropriate drug use in adults aged

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65 years or older [5]. Use of medications outlined in the Beers Criteria resulted in increased emergency room visits, increased risk of falls and fractures, and higher total healthcare costs [6, 7]. The Beers Criteria have been updated several times since their development, and the most recent version was published in 2015. The 2015 update added two new components to improve drug safety in the elderly: (1) drugs for which dose adjustment is required based on renal function and (2) drug-drug interactions [8]. Whereas the Beers Criteria are considered crucial in the optimization of pharmaceutical care in older adults in the United States, other screening tools exist as well. The STOPP/START (Screening Tool of Older Persons' potentially inappropriate Prescriptions/ Screening Tool to Alert doctors to the Right Treatment) are being used in Ireland [2, 9], the PRISCUS list [10] serves as a guide in Germany, whereas the NORGEP (Norwegian General Practice) criteria are used in Norway [11]. The European Union (EU) developed its own EU(7)-PIM list obtaining data from the United States, Canada, Germany, and France [12]. A recent descriptive study from Germany found a 28.3% prevalence of PIMs among the elderly [13]. An Italian study revealed that female sex, age > 79 years, chronic kidney disease, and hyperpolypharmacy were associated with the highest risk of multiple PIPs [14]. A Canadian retrospective cohort study showed that 28% of community-dwelling older adults in British Columbia filled one or more potentially inappropriate prescriptions in 2013. The prevalence was higher among women due to increased odds for prescriptions for benzodiazepines, tricyclic antidepressants (TCAs), and nonsteroidal anti-inflammatory drugs (NSAIDs) [15]. A higher prevalence of PIPs (81%) was found in older Korean adults. The most commonly prescribed medication classes were first-generation anticholinergic antihistamines (52.3%), pain medications (43%), and benzodiazepines (42.5%). Female sex, severity of comorbidities, and polypharmacy were associated risk factors for PIP [16].

The safe administration of anesthesia to elderly patients requires a thorough evaluation and understanding of chronic medications and the potential for interactions. The aim of

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this chapter is (1) to highlight frequently prescribed inappropriate medications in elderly patients, (2) to feature drugs that may have a potential interaction with medications used in anesthesia practice, and (3) to outline directions for future research.

Anticholinergics

Acetylcholine is the neurotransmitter for the entire parasympathetic nervous system and for parts of the sympathetic nervous system. Anticholinergic agents competitively block the effects of acetylcholine on the muscarinic receptors. In the central nervous system (CNS), acetylcholine is involved in several cognitive processes including attention, memory, and learning functions. Five different subtypes (M_{1-5}) of muscarinic receptors are present in the brain. Agitation, confusion, delirium, hallucinations, and cognitive decline suggest an anticholinergic effect in the CNS. In the peripheral nervous system, stimulation of muscarinic receptors results in bradycardia, miosis, stimulation of endocrine glands, bronchoconstriction, increased bladder tone, dilatation of blood vessels, and a decrease in blood pressure. Peripheral anticholinergic adverse effects include tachycardia, mydriasis, cycloplegia, dry mouth, constipation, urinary retention, nausea, impaired sweating, and bronchodilation.

Lipid-soluble tertiary amine anticholinergics such as atropine have more systemic side effects than lipid-insoluble drugs like tiotropium that have a quaternary ammonium structure. In addition to pure anticholinergics (e.g., atropine, tiotropium, scopolamine, glycopyrrolate, and oxybutynin), several other drugs possess anticholinergic properties and increase the risk of anticholinergic ADEs. Anticholinergic drugs are commonly prescribed for the elderly suffering from Parkinson's disease, behavioral problems, depression, psychotic symptoms, allergies, and urinary incontinence. Several medications are used for their anticholinergic properties (e.g., antiparkinsonians, antispasmodics, antimuscarinics), but there are drugs whose anticholinergic properties are not fundamental to their primary indication (e.g., antihistamines, antipsychotics, and antidepressants) [17].

The elderly are especially vulnerable to the central ADEs of anticholinergics. Aging reduces the number of muscarinic receptors in the brain; moreover, regions rich in muscarinic receptor density show a greater drop. The permeability of the blood–brain barrier may also be increased in many conditions that are common among the elderly (e.g., Alzheimer's disease (AD), Parkinson's disease, stroke, head injuries), potentially increasing the penetration of anticholinergics into the CNS. A cross-sectional study found that 27% of older adults with dementia were prescribed potentially inappropriate anticholinergics. Oxybutynin was the most frequently prescribed agent, accounting for 16.8% of the overall bur-

den. High prevalence was found for solifenacin (16.6%), paroxetine (10.4%), tolterodine (9.2%), promethazine (8.9%), and cyclobenzaprine (8.6%) as well. Self-reported anxiety, mood disorders, and "fair/poor" health status were associated with increased odds of receiving potentially inappropriate anticholinergics [18].

The most widely used test for quantifying anticholinergic load is called the serum anticholinergic assay (SAA). There is extensive variance in the published SAA results and SAA levels that cause cognitive dysfunction. The timing of blood sample may also influence results. Whereas SAA may reflect anticholinergic activity measured in the cerebrospinal fluid (CSF), penetration into the CNS varies between different drugs. Thus, relevance of their measurement from peripheral blood samples is controversial. Moreover, SAA activity has also been exhibited in patients not taking any known anticholinergics [19].

Antidementia Agents

According to the World Health Organization census in 2010, there were approximately 35.6 million people worldwide living with dementia. This number is expected to triple by 2050 [20]. Alzheimer's disease (AD), the most common form of dementia, is a large and growing problem which represents an increasing burden on healthcare. One-third of those over 85 years are affected, and the cost of care has been recently estimated at \$172 billion annually in the United States [21]. Several drugs have been approved by the Food and Drug Administration (FDA) for the relief of AD symptoms by regulating brain neurotransmitter levels. These drugs belong to two classes: cholinesterase inhibitors (ChEIs: donepezil, rivastigmine, and galantamine) and the N-methyl-D-asparticacid (NMDA) receptor antagonist memantine. Cholinesterase inhibitors inhibit the enzymatic breakdown of acetylcholine to maintain cholinergic neuronal signal transduction, whereas NMDA receptor antagonists modulate glutamate signal transmission. These drugs have proven effective in temporarily alleviating symptoms of AD. The resultant increase of acetylcholine at the neuromuscular junction may enhance the effects of succinylcholine and antagonize nondepolarizing neuromuscular blockade.

In general, ChEIs produce more frequent ADEs than NMDA receptor antagonists. Dizziness, headaches, nausea, vomiting, diarrhea, abdominal pain, and fatigue are the most common ADEs of ChEIs. Donepezil is usually well-tolerated, whereas rivastigmine is associated with having the highest frequency of adverse events. Dizziness, headaches, hypertension, somnolence, and constipation are the rare ADEs of memantine [22]. In a recent pharmacovigilance study, all ChEIs exhibited a significantly higher incidence of extrapyramidal symptoms, bradycardia, nausea, and vomiting compared to memantine.

Moreover, some ChEIs were more frequently reported for a variety of other ADEs such as generalized convulsions, gastrointestinal (GI) bleeding, diarrhea, obstructive pulmonary disease, and death. Stevens-Johnson syndrome was the only side effect that exhibited no obvious difference in reporting rate between memantine and ChEIs. Interestingly, concomitant use could neutralize the adverse effects of ChEIs, since the reporting frequencies of extrapyramidal symptoms, nausea, and vomiting among the patients using memantine and ChEIs in combination were no longer significantly higher than in patients using memantine alone [23].

A Cochrane Database study assessed the efficacy of rivastigmine in vascular cognitive impairment, vascular dementia or mixed dementia. A significant advantage in cognitive response was seen at 24 weeks compared to placebo. However, significantly higher rates of vomiting, nausea, diarrhea, and anorexia were noted in the participants randomized to rivastigmine [24]. The same author analyzed 13 trials to investigate rivastigmine in AD. Oral or transdermal rivastigmine offered some benefits compared to placebo at 26 weeks for cognitive function, activities of daily living, and the physician-rated global impression scales. No difference was found for behavioral symptoms. Patients on rivastigmine were about twice as likely to experience adverse events or withdraw from the trial before the end of the study. Limited evidence from one trial suggested that the transdermal patch had fewer side effects than the capsules but had comparable efficacy [25].

Hypertension is one of the strongest predictors of cognitive impairment. Diabetes mellitus, hyperlipidemia, smoking, and old age are other important risk factors known to increase the risk for AD-related dementias. Centrally acting angiotensin-converting enzyme inhibitors (CACEIs) were one of the first antihypertensives to be studied in AD. Secondary analysis of a multicenter, randomized control trial revealed that perindopril slowed disease progression in patients with established AD [26]. An observational case-control study compared the rates of cognitive decline in dementia patients receiving CACEIs with those not treated with CACEIs, and with those who started CACEIs during their first 6 months of treatment. The Quick Mild Cognitive Impairment screen demonstrated a small but significant reduction in the rate of cognitive decline in patients taking CACEIs. New CACEI patients showed a median improvement in Standardized Mini-Mental State Examination scores over the first 6 months of treatment. Compliance with antihypertensive treatment, however, may have accounted for the improvement in the new CACEI group [27].

Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs)

The renin angiotensin aldosterone system (RAAS) plays a crucial role in the maintenance of cardiovascular homeostasis. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) target the RAAS in different ways. Angiotensin-converting enzyme is responsible for the conversion of the decapeptide angiotensin I (ANG I) to the octapeptide angiotensin II (ANG II). Angiotensin II mediates its effects through angiotensin II type 1 (AT_1) and type 2 (AT₂) receptors. AT₁ receptor stimulation leads to vascular smooth muscle contraction and may also result in elevated levels of reactive oxygen species (ROS). Elevated ROS counteracts nitric oxide-mediated vasodilation. AT₂ receptor activation results in vasodilation via release of nitric oxide. ACEIs prevent ANG I \rightarrow ANG II conversion, whereas ARBs block the ANG II stimulation of the AT₁ receptor. Evidence in human primary monocytes shows that ANG II may promote atherosclerotic plaque rupture in an AT₂ receptordependent fashion [28]. ACEI-induced suppression of ANG II levels may blunt the direct toxic tissue effects of ANG II independent of blood pressure lowering. ACEIs also block the degradation of bradykinin, a vasodilator that plays an important role in ischemic preconditioning. Bradykinin, however, may also be responsible for common side effects including cough and angioedema. ACEIs are recommended for the management of heart failure, left ventricular dysfunction, left ventricular hypertrophy, myocardial infarction, carotid atherosclerosis, atrial fibrillation (AF), metabolic syndrome, and diabetic nephropathy by current American College of Cardiology (ACC) and American Heart Association (AHA) guidelines. ARBs are typically used in the elderly, who may not tolerate certain ACEI side effects, (e.g., coughing). ARBs are the most commonly used antihypertensives in the world. There is, however, conflicting evidence in the literature about the cardiovascular protection offered by ARB treatment.

The Evaluation of Losartan in the Elderly (ELITE) study and the ELITE II study yielded conflicting results regarding the cardiovascular benefits of ACEI versus ARB in older heart failure patients [29, 30]. In the ELITE study, treatment with losartan led to a significant risk reduction of all-cause mortality compared to captopril-treated patients. However, in the ELITE II study, there was no difference in all-cause mortality and sudden death between ARBs and ACEIs. A high-dimensional propensity score-matched study compared the effects of ACEIs and ARBs in elderly hypertensive patients [31]. Both drugs were found equally effective with regard to the risks of myocardial infarction, ischemic stroke, all-cause mortality, heart failure, acute kidney injury, and hyperkalemia.

A cross-sectional study compared the effects of ARB and ACEI on cardiovascular and cerebrovascular morbidity and mortality in elderly hypertensive patients. Age, drug type, history of cerebral infarction, and renal dysfunction were independent predictors of its primary endpoint (the composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke). The risk of a primary endpoint was significantly higher in the ARB group than in the ACEI group [32].

Several meta-analyses investigated the role of ARBs in the prevention of major cardiovascular events. When compared to active treatment or placebo, ARBs reduced the risk of stroke, heart failure, and new onset diabetes. They did not, however, decrease the risk of myocardial infarction [33]. A pooled analysis of 20 cardiovascular morbidity-mortality trials showed that RAAS inhibition by ACEIs was entirely responsible for the reduction of all-cause mortality. Treatment with an ARB offered no such benefits [34]. Another metaanalysis explored the efficacy of ACEI and ARB in the prevention of cardiovascular disease in patients with diabetes and hypertension [35]. ACEIs were found to significantly reduce the risk of all-cause mortality cardiovascular deaths and major cardiovascular events (including myocardial infarction by 21% and heart failure by 19%) in diabetic patients. In contrast, ARBs were only associated with a reduction in the risk of heart failure.

Whereas β -blockers and calcium channel blockers (CCBs) are typically continued in the perioperative period, ACEIs and ARBs are usually withheld due to the increased probability of severe intraoperative hypotension. A prospective randomized controlled trial evaluated the effects of preoperative continuation or discontinuation of ACEIs or ARBs in ambulatory surgery patients. Systolic, diastolic, and mean arterial blood pressures were not significantly different in the two groups in the preoperative holding area. The incidence of stage I and stage II HTN was similar in the postanesthesia care unit, as well. The above study, however, did not assess intraoperative hemodynamic changes [36]. Anesthetic technique and blood pressure management was standardized for carotid endarterectomy patients in another prospective study. There was no significant increase in phenylephrine requirements for patients taking β -blockers, CCBs, ACEIs, or ARBs. Total intraoperative vasopressor requirements were 75% higher in patients who were on a combination of three different classes of antihypertensives. Patients taking diuretics, either as a single antihypertensive or as a part of a multiple regimen, required significantly more phenylephrine intraoperatively, compared to those patients not on diuretics [37].

Digoxin

Digoxin has a complex pharmacokinetic profile, a narrow therapeutic range, and multiple potential drug interactions. It inhibits the cellular membrane Na⁺/K⁻ adenosine triphosphatase, which leads to an increase in the intracellular Na⁺ concentration, and by stimulation of Na⁺-Ca²⁺ exchange, an increase in the cytoplasmic concentration of Ca²⁺. Only a small percentage (16%) of digoxin is metabolized by the liver via hydrolysis, oxidation, and conjugation. The metabolism does not involve the cytochrome P450 system. Following intravenous administration, 50-70% of digoxin is excreted unchanged in the urine. Functional decline of hepatic and renal function in the elderly can alter digoxin metabolism. Hypomagnesemia, hypercalcemia, hypernatremia, and hypokalemia can alter the effects of digoxin on the myocardium, even when blood concentrations are within the therapeutic range. Exacerbations of chronic heart failure can lead to a reduced clearance of digoxin. Hypoxia and alkalosis in chronic pulmonary disease may precipitate digoxin toxicity. Manifestations of toxicity include gastrointestinal symptoms (e.g., abdominal pain, nausea, vomiting, diarrhea), neurologic symptoms (e.g., altered mental status, headache, hallucinations, convulsions), and a wide variety of arrhythmias (e.g., sinus bradycardia, AV conduction delays, and second- or third-degree heart blocks). Digoxin immune fab (DIF) use is indicated for the management of lifethreatening arrhythmias, for a serum potassium concentration over 5 mmol/l, whenever serum digoxin concentration exceeds 12 nmol/l or when acute adult ingestion of more than 10 mg of digoxin occurs [38].

Digoxin toxicity accounted for 5.9% of hospitalizations due to adverse drug events among patients \geq 85 years of age [39]. A retrospective cohort study found that the majority (88%) of patients admitted for digoxin toxicity were \geq 65 years or older, but only 20% of patients were administered DIF [40].

Coadministration of β -blockers, nondihydropyridine CCBs (e.g., verapamil and diltiazem), and dronedarone (a class III antiarrhythmic) may lead to advanced or complete heart block. Propafenone, amiodarone, and quinidine may double digoxin plasma concentrations [41].

Genetics—especially single-nucleotide polymorphisms (SNPs)—may crucially effect serum digoxin concentrations. The ATP-binding cassette B1 (ABCB1) gene is located on chromosome 7p21. ABCB1 is known to play an important role in the uptake, distribution, and excretion of many drugs. Since its discovery, several hundred SNPs have been identified in the ABCB1 gene. A statistically significant association was found between the common ABCB1 variants $1236C \rightarrow T$, $2677G \rightarrow T$, $3435C \rightarrow T$ and serum digoxin concentration in a cohort of elderly European digoxin users. An increase of $0.20-0.25 \mu g/l$ per additional T allele equals the

effect of a 0.25 defined daily dose (DDD) increase. Patients with two variant alleles have an increase in serum concentration of 0.4–0.5 μ g/l, similar to the effect of a dose increase of 0.5 DDD or 0.125 mg [42].

The effect of digoxin therapy on mortality remains questionable. Digoxin treatment was associated with an increased risk of all-cause mortality, vascular death, and sudden death in the post hoc analysis of the ROCKET AF trial (Fig. 21.1) [44]. Digoxin was associated with a 41% increase in all-cause mortality in patients with AF with or without heart failure in the AFFIRM trial [45]. A retrospective analysis of the LIFE trial assessed the relation of digoxin therapy and the risk of mortality in hypertensive patients with existing or new AF. Digoxin use was found to be a significant univariate predictor of allcause and cardiovascular mortality, but was no longer significantly associated with either after adjusting for AF risk factors and for a propensity score for digoxin use. These results suggest that the increased risk seen in univariate analyses may more strongly reflect a greater propensity to use digoxin in higher-risk AF patients than a true increased mortality risk from digoxin [46]. Current ACC, AHA, and Heart Rhythm Society (HRS) guidelines recommend the use of digoxin for rate control in patients with AF [43]. Digoxin should be avoided in elderly patients as first-line therapy for AF or heart failure. If used, dosages >0.125 mg/day should be avoided [8].

Dronedarone is a potent inhibitor of the P-glycoprotein (P-gp) transport system; therefore, it increases digoxin plasma concentration. A subgroup analysis of the PALLAS trial investigated the interaction of digoxin and dronedarone use on mortality outcomes. Patients randomized to dronedarone had significantly higher digoxin plasma concentrations at day 7 compared with those randomized to placebo. Among patients on digoxin at baseline, the dronedarone-digoxin interaction led to significantly increased cardiovascular mortality, especially arrhythmic death. In patients not on digoxin, dronedarone had no effect on mortality (Fig. 21.2). Apart from the obvious harmful pharmacokinetic interaction, it is possible that the combination of digoxin and dronedarone is proarrhythmic. On the other hand, concurrent digoxin use did not seem to increase the risk of developing heart failure from dronedarone [47].

Amiodarone

Amiodarone is an antiarrhythmic drug with predominantly class III effects, but it also has class I, II, and IV properties [48]. It is one of the most effective antiarrhythmic agents for the management of supraventricular and ventricular tachyarrhythmias. The Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) found that amiodarone was more effective at reducing AF recurrence rates at 1 year than sotalol or placebo (35% vs. 60% vs. 82%) [49]. Amiodarone was compared to

dronedarone in the DIONYSOS study and was superior in preventing recurrence of AF (42% vs. 63.5%) [50].

Adipose tissue is a major site of distribution for amiodarone. In obese patients, it will accumulate more in fat tissue, increasing the volume of distribution and lowering plasma amiodarone concentrations. Therefore, a smaller amount of drug will be available for accumulation in the myocardium. The large volume of distribution (60 l/kg) results in a delay in onset of action from days to weeks and a prolonged elimination half-life of weeks to months. The clearance of amiodarone is inversely related to age.

Amiodarone can prolong the QTc interval and may cause torsades de pointes, a life-threatening ventricular tachyarrhythmia. The proarrhythmic effects are accentuated with concomitant use of other QT-prolonging medications (e.g., sotalol, methadone, haloperidol).

Amiodarone is one of the most widely prescribed antiarrhythmic drugs for patients in AF and atrial flutter. A retrospective cohort study assessed the association of amiodarone use with mortality in patients with newly diagnosed AF and flutter. Amiodarone was not associated with increased hazard of death in multivariate and propensity-matched analyses. These results were consistent regardless of age, sex, heart failure, β -blocker use, estimated glomerular filtration rate, or warfarin use [51].

Pulmonary toxicity is one of the most serious, and potentially fatal, adverse effects of amiodarone. Pulmonary function tests with DLCO should be performed at baseline and for any unexplained cough or dyspnea. The most common clinical presentation of amiodarone-induced pulmonary toxicity is diffuse interstitial lung disease or immune-mediated hypersensitivity. The cumulative incidence was 10.6% at 5 years in a Japanese population receiving a low-mean maintenance dose. Older age, higher plasma monodesethylamiodarone concentration, and higher maintenance dose were found to be risk factors [52].

The high iodine content of the amiodarone molecule can affect thyroid function. Amiodarone inhibits the conversion of thyroxine to triiodothyronine in most tissues. Thyroid function tests (TSH, free T_4 , and free T_3) should be performed at baseline and at least every 6 months during therapy. Amiodarone may induce hypothyroidism in 5–25% of patients and hyperthyroidism in 2–10% of patients [53].

Dermatologic adverse effects (e.g., photosensitivity and gray-blue skin discoloration) and corneal microdeposits have been associated with long-term amiodarone use. A retrospective population-based cohort study demonstrated that after adjustment for age, gender, and medical comorbidities, amiodarone-treated patients had a twofold increased risk of optic neuropathy compared to controls. The mean interval between starting amiodarone and the development of optic neuropathy was 371 days [54].

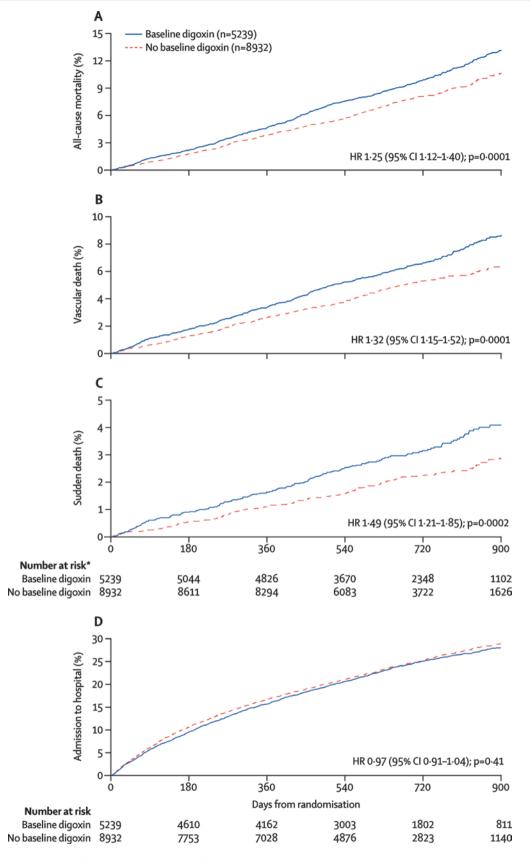


Fig. 21.1 Kaplan-Meier curves for (a) all-cause mortality, (b) vascular death, (c) sudden death and (d) admission of hospital in patients on baseline digoxin versus no baseline digoxin. *Applies to \mathbf{a} - \mathbf{c} . (Reprinted from Washam et al. [43]. With permission from Elsevier)

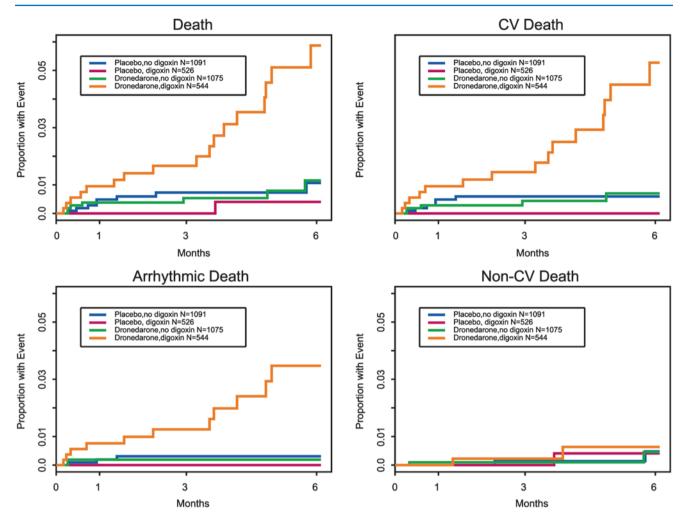


Fig. 21.2 Kaplan-Meier plots for mortality outcomes in patients on dronedarone and placebo with or without concomitant digoxin therapy (Reprinted from Hohnloser et al. [47]. With permission from Wolters Kluwer Health)

Amiodarone can accumulate at a faster rate in elderly patients as a result of the higher incidence of renal and hepatic dysfunction. However, no specific guidelines exist for dosing adjustments for this population. Elderly patients are also particularly sensitive to the cardiac effects of amiodarone, as well as thyroid dysfunction. The multiple adverse effects of amiodarone appear to be dose-related, so therapy should be initiated at the lowest effective dose. Maintenance doses of 100 mg/day are often effective [48]. Amiodarone may be reasonable first-line therapy in the elderly to help maintain sinus rhythm after myocardial infarction, with heart failure, left ventricular systolic dysfunction, left ventricular hypertrophy, or drug-refractory AF.

Dronedarone

Dronedarone, a class III antiarrhythmic drug, is a noniodinated benzofuran derivative related to amiodarone. Current ACC, AHA, and HRS guidelines recommend the use of dronedarone for maintenance of sinus rhythm after conversion from AF. It should not be used for rate control in permanent AF or in patients with severe or recently decompensated heart failure [43]. Currently, no dosage adjustments for dronedarone are recommended for the elderly. P-gp inhibition may increase the bioavailability of dabigatran if given concomitantly [55]. Dronedarone can also increase the INR in warfarin users, as well as the plasma levels of CCBs, ß-blockers, sirolimus, tacrolimus, and statins [43, 56].

Dronedarone is less lipophilic and has a much smaller volume of distribution and a shorter half-life than amiodarone. Dronedarone is associated with less organ toxicity than amiodarone as well. Adverse effects include bradycardia, QT-prolongation, nausea, diarrhea, rash, and abdominal pain. Some 150,000 patients had been prescribed dronedarone in the United States before two cases of rapidly progressing liver failure occurred which prompted the FDA to issue a warning about possible hepatic toxicity. Routine monitoring of hepatic serum enzymes should be performed before drug initiation, repeated at least once in the first 6 months of treatment and then yearly. From 2005 to 2014, 174 reports of acute renal failure and 144 reports of renal failure from dronedarone were reported to the FDA Adverse Event Reporting System (FAERS). Dronedarone may cause a specific partial inhibition of tubular organic cation transporters, leading to a limited increase in serum creatinine [57]. An Italian retrospective cohort study investigated the potential association between renal damage and dronedarone. The cumulative incidence of acute renal failure was 1.6% in the dronedarone group and 2.3% in the amiodarone group (p = 0.48). Moreover, neither the propensity score-matched model, nor the high-dimensional propensity score matched model could find any evidence of increased nephrotoxicity [58].

Dronedarone was associated with lower thyroid, neurologic, skin, and ocular side effects compared with amiodarone in the DIONYSOS trial. Premature drug discontinuation tended to be less frequent with dronedarone (10.4% vs. 13.3%) [50].

Switching between several antiarrhythmic drugs is relatively common in patients with AF. A post hoc analysis of data from the EURIDIS and ADONIS trials revealed that dronedarone was effective in maintaining sinus rhythm in patients who were previously treated with another antiarrhythmic agent, even if the drug was discontinued for lack of efficacy [59].

A Cochrane meta-analysis of four placebo-controlled dronedarone studies (EURIDIS, ADONIS, ATHENA, and DAFNE) revealed that dronedarone was associated with significantly lower AF recurrence, reduced risk of stroke, and more drug withdrawals due to adverse effects and proarrhythmia. There was no significant difference in overall mortality [60].

A multicenter, double-blind study evaluated the efficacy of dronedarone in patients with worsening heart failure and severe systolic dysfunction. The trial had to be terminated after a median follow-up of 2 months due to increased early mortality related to the worsening of heart failure [61].

A Swedish study evaluated real-world safety of dronedarone in patients with AF. Annualized mortality rates were significantly lower in the dronedarone group before and after propensity score matching (dronedarone vs. control population: 1.3% vs. 14% and 1.3% vs. 2.7%). Patients who were prescribed amiodarone and sotalol had the highest annual mortality rates, whereas dronedaroneand flecainide-treated patients had the lowest unadjusted mortality (Fig. 21.3). Contrary to the findings of the ANDROMEDA trial, heart failure patients on dronedarone had a significantly lower mortality as well. Newly diagnosed liver disease was also lower in the dronedarone group [62].

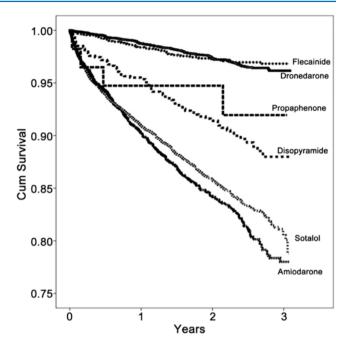


Fig. 21.3 Unadjusted annual mortality among users of different antiarrhythmic drugs. Note abbreviation of scale. *Cum* cumulative (Reprinted from Friberg [62]. With permission from Elsevier)

Pain Medications and Pain-Related Medications

Persistent pain commonly affects the elderly, and it remains one of the leading reasons why older people seek healthcare in the ambulatory setting. Prescription pain medication use is higher among patients aged >65 years than in the younger population. According to the CDC, there has been an almost fivefold increase in death rates involving opioid analgesics in those aged ≥ 65 years in the 12-year period leading up to 2011 [63]. The most prevalent types of pain in the elderly are low back or neck pain (65%), musculoskeletal pain (40%), peripheral neuropathic pain (40%), and chronic joint pain (20%). Chronic pain does not constitute part of the normal aging process, and its presence is associated with functional impairment, decreased appetite, impaired sleep, depression, and social isolation in older adults. The pain threshold increases, and pain tolerance decreases with aging. Moreover, the ability to mount an adequate physiologic response to stress associated with pain becomes attenuated with age.

Pain treatment plans should include both pharmacologic (PS) and nonpharmacologic strategies according to current American Geriatrics Society (AGS) recommendations. Nonpharmacologic management strategies including physical therapy, chiropractic care, exercise, TENS, magnets,

and acupuncture offer an alternative or complementary approach to pharmacologic pain management. A cohort study in elderly adults revealed that almost half of participants (49%) reported use of one or more PS to manage pain, with one quarter (27%) reporting daily use. One-third of older adults employed strategies that were consistent with American Geriatrics Society (AGS) recommendations to use both modalities to manage pain [64].

Acetaminophen

Acetaminophen is the most commonly used analgesic in the United States, and it remains the first-line treatment for older adults with persistent mild-to-moderate pain. Musculoskeletal pain, such as osteoarthritis and low back pain, should initially be treated with acetaminophen. It is less effective in relieving inflammatory conditions, such as rheumatoid arthritis. The FDA recommends a maximum daily dose of 3 g. Lower doses or avoidance altogether is recommended for individuals with liver disease [65, 66]. Compared with NSAIDs, acetaminophen is associated with less gastrointestinal (GI), renal, or cardiovascular toxicity, and no age-related differences exist in its clearance [67].

Nonsteroidal Anti-inflammatory Drugs

Nonselective NSAIDs are widely used to manage musculoskeletal and inflammatory pain conditions. NSAID use was responsible for 23.5% of ADE-related hospital admissions in elderly patients [68]. Prolonged NSAID therapy is associated with an increased risk of hospitalization, renal toxicity, myocardial infarction, stroke, and death in older adults [69-71]. Specific NSAIDs such as indomethacin, naproxen, oxaprozin, and piroxicam should not be prescribed for older adults (Table 21.1). The risk of GI complications triples in the elderly. The incidence of GI side effects appears to be more time-dependent, rather than associated with the specific drug used, but indomethacin may induce significant adverse effects within a week after initiation of treatment [72]. The combined use of thiazide diuretics and NSAIDs tripled the risk of hospitalization for congestive heart failure in elderly patients [73]. Concomitant administration of NSAIDs and aspirin increases the risk of GI bleeding [74]. Even cyclooxygenase-2 (COX-2) selective inhibitors increase the risk for GI adverse effects in older adults. Therefore coadministration of a proton pump inhibitor or another gastroprotective agent (e.g., misoprostol) is recommended when COX-2 inhibitors are taken for an extended period [74]. Topical agents primarily forgo the systemic adverse effects seen with their oral counterparts. Topical diclofenac demonstrated a superior effect on pain and func-

Table 21.1	Potentially	inappropriate	pain	and	pain-related	medica-
tions in olde						

Drug	Adverse effects
Non-COX-selective NSAIDs	
Aspirin > 325 g/day	Increased risk of gastrointestinal
Diclofenac	bleeding or peptic ulcer disease in
Etodolac	high-risk patients, including those aged
Ibuprofen	>75 years or taking corticosteroids, anticoagulants, or antiplatelet agents
Meloxicam	anticoagurants, or antiplatelet agents
Nabumetone	
Naproxen	
Oxaprozin	
Piroxicam	
Indomethacin	CNS adverse effects are more likely than with other NSAIDs
Ketorolac (including parenteral)	Increased risk of gastrointestinal bleeding, peptic ulcer disease, or acute kidney injury in the elderly
Opioids	
Meperidine	Renally cleared metabolite may cause seizures and death.
Pentazocine	Confusion and hallucinations possible
Antidepressants	
Amitriptyline	Highly anticholinergic, sedating, and
Amoxapine	cause orthostatic hypotension
Clomipramine	
Desipramine	
Doxepin >6 mg/d	
Imipramine	
Nortriptyline	
Paroxetine	
Protriptyline	
Trimipramine	
Skeletal muscle relaxants	
Carisoprodol	Highly anticholinergic, sedating, and
Chlorzoxazone	increase risk of fractures
Cyclobenzaprine	
Metaxalone	
Methocarbamol	
Orphenadrine	

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tion over placebo in several trials. Moreover, it proved to be as efficient as oral diclofenac, ibuprofen, and naproxen, but exhibited fewer GI complications. Topical diclofenac preferentially distributes to synovial fluid, leading to therapeutic concentrations in the target tissues [75].

Opioids

Patients with moderate-to-severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy according to the 2009 AGS guidelines [74]. Several studies have established the benefits of opioids in managing neuropathic, somatic, and visceral pain. Potent opioids are significantly more effective at providing pain relief than NSAIDs or TCAs [76]. They exhibit no ceiling effect and can produce profound analgesia by stepwise dose escalation. When long-acting opioids are prescribed, breakthrough pain should be anticipated and addressed. Most opioids, apart from morphine, hydromorphone, oxymorphone, and tapentadol, are primarily metabolized by CYP450 enzymes and have potential drug-drug interactions. Major metabolites of morphine and tapentadol undergo renal excretion; thus, care should be used when prescribing these drugs for older adults with compromised renal function. Chronic opioid use may be associated with fewer potential life-threatening adverse effects compared with long-term NSAID use but opioids have their distinct set of potential risks. Common opioid adverse effects include nausea, vomiting, sedation, respiratory depression, hyperalgesia, hypogonadism, pruritus, immune suppression, and cardiac dysrhythmias. Patients with a history of substance-use disorder may be prone to opioid diversion and abuse. The Opioid Risk Tool and the revised version of the Screener and Opioid Assessment for Patients with Pain are available for risk stratification for these patients [77, 78]. On the other hand, some experts suggest that underuse may be a larger problem among the elderly [74]. Older patients may use their opioid medication sporadically because of cost and fear of addiction. Meperidine should be avoided in patients with current or recent use of monoamine oxidase inhibitors (MAOIs) due to the potential of developing serotonin syndrome (symptoms: agitation, hyperthermia, diarrhea, tachycardia, sweating, tremors, and impaired consciousness). Tramadol is a centrally acting, synthetic μ -receptor agonist that also inhibits reuptake of serotonin and norepinephrine. It is used for managing acute and chronic, neuropathic and nonneuropathic pain conditions. The most common side effects of tramadol are sweating, nausea, constipation, pruritus, and dizziness. Concomitant administration with MAOIs, TCAs, or selective serotonin reuptake inhibitors (SSRIs) may result in serotonin syndrome.

Anticonvulsants

The potential risks of developing hyponatremia and syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH) limit the use of older anticonvulsants, such as carbamazepine and oxcarbazepine. Due to their more benign side-effect profiles and wider therapeutic windows, gabapentin and pregabalin are often used to manage neuropathic pain in older adults. Regardless, patients should be monitored for ataxia, dizziness, somnolence, weight gain, and edema. Drug–drug interactions do not limit the use of gabapentinoids as they do not inhibit any major CYP450 enzymes, although naproxen and morphine may increase systemic gabapentin levels. Pregabalin or gabapentin doses should be reduced or dosing intervals increased in patients with renal dysfunction. Pregabalin is effective for treating fibromyalgia, postherpetic neuralgia, diabetic peripheral neuropathy, and central neuropathic pain [79].

Antidepressants

TCAs are effective in treating neuropathic pain, but there are several safety considerations for using them in the elderly. Contraindications include concomitant use of MAOIs, uncontrolled narrow-angle glaucoma, hepatic disease, or heart block. TCAs may also be inappropriate for older adults with cardiovascular disease, seizure disorder, or an increased risk of falling. Tertiary TCAs such as amitriptyline, imipramine, and doxepin should be avoided in older adults due to anticholinergic effects and cognitive impairment. Secondary amines such as nortriptyline and desipramine have a more favorable side effect profile [80]. Duloxetine, a serotonin norepinephrine reuptake inhibitor (SNRI), is indicated for diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain. Duloxetine can have important drug-drug interactions with CYP1A2 inhibitors (e.g., fluoroquinolones, cimetidine), with CYP2D6 inhibitors (e.g., quinidine, ritonavir), and with CYP2D6 substrates (e.g., metoprolol, propafenone, tramadol, codeine, dextromethorphan, and ondansetron) [80]. Concomitant administration of duloxetine and NSAIDs increases bleeding risk. Duloxetine is contraindicated in endstage renal disease, chronic liver disease, and uncontrolled narrow-angle glaucoma. It should be discontinued before initiating treatment with MAOIs. It should be used cautiously in patients with hypertension, seizure disorder, and increased fasting blood glucose. Serotonin-norepinephrine reuptake inhibitors (SNRIs) or SSRIs should be considered in patients with comorbid depression and pain [81].

Skeletal Muscle Relaxants

Skeletal muscle relaxants include carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and orphenadrine. These drugs may relieve skeletal muscle pain, but their effects are nonspecific and not related to muscle relaxation. The 2015 Beers list does not recommend the use of most muscle relaxants due to their anticholinergic adverse effects, sedation, and increased fall risk in older persons. Baclofen, a γ -aminobutyric acid (GABA)type B agonist, is particularly effective in the management of paroxysmal neuropathic pain. It has been used in patients with severe spasticity as a result of central nervous system injury, demyelinating conditions and other neuromuscular disorders [82]. Discontinuation after prolonged use requires gradual tapering because of the potential for delirium and seizures [77, 78].

Benzodiazepines

Benzodiazepines enhance the activity of GABA, a major inhibitory neurotransmitter in the brain. They cause sedation, anterograde amnesia, anxiolysis, and muscle relaxation. They also possess hypnotic and anticonvulsant effects. All actions of benzodiazepines are generated by their interaction with GABA_A receptors. The benzodiazepine binding site is thought to be located at the interface between the α - and γ -subunits of the GABA_A receptors. The main adverse effects of benzodiazepines are CNS depression such as drowsiness, sedation, muscle weakness, and respiratory depression. Benzodiazepines should therefore be avoided in patients with preexisting CNS depression, obstructive sleep apnea, respiratory insufficiency, and myasthenia gravis and used with caution in those with chronic obstructive pulmonary disease [83, 84]. The 2015 Beers Criteria paper strongly recommends avoiding short- and intermediate-acting benzodiazepines in the elderly. Long-acting benzodiazepines may be appropriate for seizure disorders, benzodiazepine withdrawal, ethanol withdrawal, and generalized anxiety disorder [8]. Combined use of benzodiazepines and other CNSdepressants (sedative antidepressants, sedative antihistamines, antipsychotics, and opioids) may result in severe, or even life-threatening, respiratory failure. Paradoxical effects such as disinhibition, anxiety, and impulsivity further limit their use. Benzodiazepines may precipitate encephalopathy in patients with severe hepatic impairment.

Benzodiazepines have been associated with falls (odds ratio of 1.3–3.4) in several studies. Risk factors include female sex, short half-life benzodiazepines, duration of treatment, sudden dose increases, and concurrent use of multiple benzodiazepines [85].

A Canadian retrospective observational study investigated the extent and predictors of benzodiazepine and zopiclone (BZD-Z) prescribing in older adults with a history of a recent fall. In a 5-year time period, 21.6% of adults over the age of 66 had exposure to BZD-Z in the 100 days prior to admission. Of these, 74.2% continued to receive BZD-Z following discharge. The odds of being prescribed a BZD-Z following discharge were positively associated with female sex and negatively associated with increasing age [86].

Coabuse of opioids and benzodiazepines is a common phenomenon. In a recent time series study, the proportion of opioid recipients with a concomitant benzodiazepine therapy episode increased steadily from 7% in 2002 to 10% in 2014, representing a relative increase of 41% (Fig. 21.4). Concomitant use was considerably higher among chronic opioid users, women, and patients aged >65 years. Alprazolam, diazepam, and lorazepam were most commonly involved in concomitancy [87]. Multiple studies revealed that benzodiazepine consumption in France is among the highest in Europe. Concurrent use of benzodiazepines and opioid analgesics was observed in 23.6% of elderly patients in a French cross-sectional study. The highest rate of drugdisease interactions, comorbidities that could result in an increased risk of benzodiazepine ADEs, occurred in patients aged ≥ 80 years [84]. Chronic use of benzodiazepines was frequent (35.6%) in the oldest (≥ 80 years) Belgian community-dwelling subpopulation. Polypharmacy was present in 57.7% [88]. Almost half of elderly subjects were exposed to benzodiazepines 6 months before or after total hip replacement (THR). Exposure to benzodiazepines, zopiclone, and zolpidem lead to a significant increase in THR revision in a French population-based cohort study. Cumulative revision rates were 3% in the unexposed, 3.9% in the low dose, 4.4% in the medium dose, and 4.8% in the high dose groups (Fig. 21.5) [89]. Inappropriate benzodiazepine prescribing was identified in 43% of elderly psychiatric patients in a French retrospective study and has been associated with decreased daily functioning independent of age, gender, and psychiatric or somatic diagnoses [90].

Trazodone (a triazolopyridine antidepressant) and quetiapine (an antipsychotic) are medications with rapid onset and strong sedative effects due to antihistamine H1 properties and α_1 antagonist activity. A Canadian population-based cohort study found that benzodiazepine use has decreased significantly in the past 10 years in older adults in community (from 15.6% to 10.6%) and longterm care (LTC) (from 30.8% to 17.5%) settings. This change has occurred in parallel with significant increases in the prevalence of trazodone and quetiapine dispensing in both settings [91].

A large proportion of older people in Scotland are commonly prescribed benzodiazepines and Z-hypnotics. Overall, 12.1% of those aged \geq 65 years were prescribed one or more BZD-Z in a cross-sectional population-based study. In total, 28.4% of LTC residents and 11.5% of noncare home residents were prescribed BZD-Zs. Estimated annual BZD-Z exposure reduced with increasing age of LTC residents, whereas noncare home residents' exposure increased with age [92].

Benzodiazepines were among the ten most frequently prescribed drugs for elderly and very elderly (>79 years) patients in an Italian point-prevalence study. One-fourth of LTC residents and 22.2% of outpatients were prescribed BZDs [14].

Fig. 21.4 Nationally projected trends in the annual number of unique patients dispensed (a) opioids or (b) benzodiazepines in the United States between 2002 and 2014 (Reprinted from Hwang et al. [87]. With permission from Elsevier)

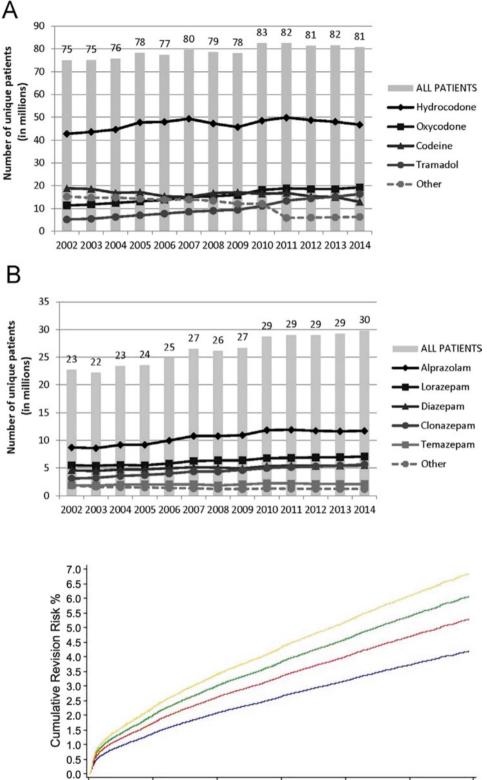


Fig. 21.5 Kaplan-Meier curves showing cumulative revision risk for total hip replacement in patients with different levels of benzodiazepine exposure (Reprinted from Beziz et al. [89]. With permission from PLoS One)

12 24 36 48 60 (237 466) (228 982) (164 977) (105 017) (50 159) Time Since Index THR, mo (Patients at risk) Unexposed Low cDDD/d Level of BZDs exposure Medium cDDD/d High cDDD/d

72

0

(246 940)

New Oral Anticoagulants (NOACs)

In the United States, 1% of the general population and 9% of people aged >80 years are affected by AF. It is the most frequently encountered cardiac arrhythmia and is associated with a fivefold increase in the risk of stroke. Vitamin K antagonists (VKA) have been used for decades in stroke prevention in patients with nonvalvular AF. Two classes of NOACs have emerged to overcome the limits of conventional anticoagulation. These synthetic and selective agents provide convenient, fixed-dose alternatives to VKAs with no need for laboratory monitoring. They have a rapid onset of action and few drug or food interactions (see Table 21.2).

Dabigatran is a direct thrombin inhibitor that inhibits the final step of the coagulation cascade, the conversion of fibrinogen to fibrin. Rivaroxaban, apixaban, and edoxaban directly inhibit factor Xa (Fig. 21.6) [93]. Fluctuations of creatinine clearance (CrCl) can increase dabigatran, rivaroxaban, and edoxaban plasma drug concentrations increasing predisposition to bleeding, especially in the elderly patient. The dose of apixaban does not need to be adjusted for hemodialysis patients or for patients with a CrCl <15 ml/ min [94]. Despite the elevated risk of bleeding, NOACs lower the risk of stroke, systemic thromboembolism, and mortality in AF.

In a nationwide propensity-matched cohort study, no significant difference was found between NOAC (dabigatran or rivaroxaban) and VKA in terms of hospitalization for bleeding or for arterial thromboembolic events during the early phase of therapy among new users with nonvalvular AF [95].

The relative safety and efficacy of rivaroxaban was comparable to warfarin in elderly diabetic and nondiabetic

patients, supporting its use as an alternative for prevention of stroke and systemic embolism in diabetic patients with AF [96]. These findings are consistent with results from a RE-LY trial subanalysis in diabetic patients which showed that diabetes does not seem to influence the relative safety and efficacy of dabigatran compared with warfarin [97].

In the RE-LY trial, in patients aged \geq 75 years, dabigatran 150 mg twice daily resulted in a similar reduction of stroke and systemic thromboembolism compared with warfarin. There was a trend, however, toward more major bleeding [98].

In the ROCKET-AF trial, in patients aged \geq 75 years, rivaroxaban was associated with a similar reduction of stroke and systemic thromboembolism compared with warfarin. There was a similar risk of major bleeding in rivaroxaban patients <75 years, but a trend toward more major bleeding in patients >75 years [99, 100].

In the ARISTOTLE trial, in patients aged \geq 75 years, apixaban led to a similar reduction of stroke and systemic thromboembolism compared with warfarin. Moreover, it was also associated with a lower risk of major bleeding in both patients <75 years and patients >75 years when compared to warfarin [101–103].

In the ENGAGE-TIMI trial, in patients aged >75 years. both edoxaban 60 mg daily and 30 mg daily provided a similar reduction of stroke and systemic thromboembolism compared with warfarin. Both edoxaban doses resulted in a lower risk of major hemorrhage in both patients <75 years and patients >75 years when compared to warfarin [104].

A meta-analysis including >70,000 patients from the RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48 trials demonstrated the beneficial risk-benefit profile of all

Table 21.2 Monitoring, reversal, and regional anesthesia recommendations for patients on New Oral Anticoagulants

Drug	Half-life	Coagulation tests	Reversal	Recommended interval between discontinuation of drug and pain procedure‡	Recommended interval between pain procedure ^a and resumption of drug
Dabigatran	13–18 h 28 h (renal impairment)	dTT ^b ECT ^b aPTT ^c	Idarucizumab APCC Activated charcoal Hemodialysis	4–5 days 6 days (renal impairment)	24 h
Rivaroxaban	11–13 h	Factor Xa ^b PT ^d aPTT ^d	Activated charcoal Andexanet alfa Ariprazine	3 days	24 h
Apixaban	13–15 h	Factor Xa ^b	Activated charcoal Andexanet alfa Ariprazine	3-5 days	24 h
Edoxaban	10–14 h	Thrombin generation	Andexanet alfa Ariprazine	No data available	No data available

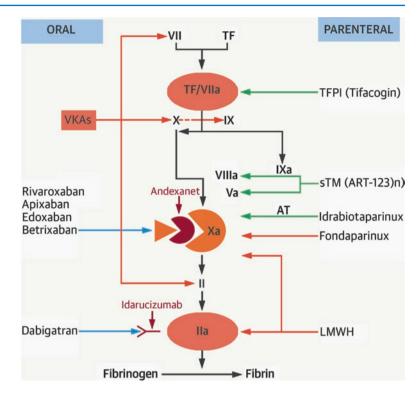
aPTT activated partial thromboplastin time, dTT diluted thrombin time, ECT ecarin clotting time, PT prothrombin time

^aMedium- and high-risk interventional procedures. For low-risk procedures, a two half-life interval may be considered. However, every case needs an individualized approach based on age, history of bleeding, concomitant use of other anticoagulants, and hepatic or renal impairment

^bQuantifiable dose-response °Provides estimate of effect

^dDose-dependent prolongation

Fig. 21.6 Mechanism of action of anticoagulant agents and of antidotes for new oral anticoagulants. The coagulation cascade and anticoagulant agents. Targets of anticoagulation and targets of the antidotes idarucizumab and andexanet. AT antithrombin, LMWH low-molecular-weight heparin, TF tissue factor. TFPI tissue factor pathway inhibitor, VKAs vitamin K antagonist. (Reprinted from Becattini and Agnelli [93]. With permission from Elsevier)



four NOACs when compared to warfarin. NOACs significantly reduced the risk of stroke and systemic embolic events by 19%. The benefit was mainly the result of a 50% reduction in hemorrhagic strokes compared to warfarin. Along with the reduction in hemorrhagic stroke, a substantial reduction in intracranial hemorrhage was observed. NOACs were, however, associated with increased GI bleeding. When compared to warfarin, NOACs resulted in a similar risk reduction in stroke or systemic thromboembolism and major bleeding in the subgroups of elderly patients [105].

Dabigatran 150 mg was associated with a 50% increased hazard of GI bleeding relative to warfarin in patients aged \geq 75 years [106–108]. Similarly, a retrospective, propensity-matched cohort study showed that the risk of GI bleeding was higher in dabigatran- and rivaroxaban-treated elderly AF patients (\geq 76 years) compared with warfarin [109].

In conclusion, NOACs exhibit a favorable risk-benefit profile when compared to warfarin for prevention of stroke and systemic thromboembolism in elderly patients. Caution is recommended with dabigatran 150 mg twice daily due to higher risk of major hemorrhage.

All NOACs are substrates of the transmembrane P-gp transport system. Strong P-gp inducers (e.g., carbamazepine, phenytoin, rifampin) can reduce NOAC plasma concentration and hence must be avoided. On the other hand, strong P-gp inhibitors (e.g., amiodarone, dronedarone, quinidine) can increase NOAC plasma concentration.

Emergent reversal of NOACs may be necessary in certain clinical situations (e.g., potential overdose, urgent surgery, or major hemorrhage). Neither fresh-frozen plasma nor vitamin K effectively reverses the effects of NOACs. Dabigatran can be dialyzed due to its low plasma protein binding; however, establishing dialysis access in a bleeding patient can be challenging.

Activated prothrombin complex concentrates (APCCs) are a mixture of nonactivated factors II, IX, X and activated factor VII. APCC has been the most reasonable alternative for reversing dabigatran effect until recently. Idarucizumab is a monoclonal antibody fragment indicated for specific reversal of dabigatran. It binds both free and thrombin-bound dabigatran with an affinity that is about 350 times higher than the binding affinity of dabigatran for thrombin. The safety and efficacy of idarucizumab were evaluated in a recent study. Idarucizumab was administered to elderly patients (median age 76.5 years) who had severe bleeding or who required an urgent procedure. In the interim analysis, 100% of patients achieved complete reversal based on an elevated dilute thrombin time and elevated ecarin clotting time at baseline. Normal or mildly abnormal hemostasis was seen in 97% of the patients [110]. And exanet alfa is designed to neutralize factor Xa inhibitors. It binds to factor Xa inhibitors and enhances the activity of endogenous factor Xa. It was able to reverse the anticoagulant effect of apixaban and rivaroxaban in healthy elderly volunteers [111].

Future Research

Given the high prevalence of comorbidities in the geriatric population and the resulting potential for polypharmacy, the risk for ADEs is greatly enhanced. Future research should focus not only on the development of specific agents to treat specific conditions, but must also examine the interaction of various agents. Due to the risks of polypharmacy, future research should also focus on nonpharmaceutical alternatives or adjuncts. For example, a multimodal approach to the management of pain, including pharmacologic and nonpharmacologic treatments that include physical and psychological therapies, has been shown to be quite effective in the geriatric patient [81]. The potential for cognitive decline further complicates the administration of medications in the geriatric population and should be considered when evaluating new drugs. For example, compliance with medication regimens can greatly affect the efficacy of drugs. Also, the risk of falling may complicate the risk profiles of some medications such as NOACs. Ongoing advances in biomedical research will continue to provide clinicians with a rapidly expanding armamentarium of pharmaceutical agents to treat a wide variety of conditions. The evaluation of any medication should focus not only on the particular target of action. but also on the overall effect on quality of life and cognition when administered concomitantly with other medications.

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Part IV

Special Concerns

Anesthesia for Common Nonoperating Room Procedures in the Geriatric Patient

22

George A. Dumas, Julie R. McSwain, and Sheila Ryan Barnett

Sedation and Monitoring

Sedation is often required for patients undergoing minor procedures. The increased availability of newer medications with short duration, rapid onset, and minimal side effects has led patients and physicians to expect comfort, amnesia, and good "operating" conditions for a multitude of minimally invasive procedures (see Chaps. 17 and 18). Given the increase in the elderly population, it is not surprising that there has also been a marked increase in procedures performed in extremely old patients. The skillful administration of sedation and analgesia for interventional procedures may allow these very elderly patients to avoid more invasive surgery and the consequent associated morbidity of surgery and prolonged hospitalization [1].

What Is Meant by the Term Sedation?

Both the American Society of Anesthesiologists (ASA) and the Joint Commission on Accreditation of Healthcare Organization describe four levels of sedation, from minimal or anxiolysis to general anesthesia [2, 3] (Table 22.1).

Minimal sedation or anxiolysis refers to a controlled state of diminished consciousness wherein the ability to respond to moderate verbal stimuli and the ability to maintain a patent airway are retained. There is little impact on the cardio-

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pulmonary status. Although this is popularly referred to as *conscious sedation* by many nonanesthesia specialties, an ASA task force on this practice recommends the use of *sedation and analgesia* rather than conscious sedation [2].

Moderate sedation or analgesia is a drug-induced state during which a patient may be less responsive than with anxiolysis but still respond to verbal commands appropriately, although sometimes requiring simultaneous light tactile stimulation. Spontaneous respiration is maintained and cardiovascular parameters are unchanged.

Deep sedation or analgesia is a drug-induced condition whereby the patient may be difficult to awaken but will respond purposefully to painful stimuli. With deep sedation, spontaneous respiration may not be adequate, and the patient may not be able to maintain a patent airway without assistance. Although controversial, in general, the ASA and many hospitals recommend the presence of anesthesia-trained personnel if deep sedation is anticipated or required to complete a procedure [2]. At a minimum, deep sedation requires the immediate availability of an individual trained in cardiopulmonary resuscitation and airway management.

Sedation is a continuum of consciousness, and the practitioner providing sedation should be ready to respond appropriately to the next higher level of sedation in addition to being comfortable at the current sedation level. This is particularly relevant when sedation is administered by nonanesthesiologists such as dental practitioners, radiologists, dermatologists, cardiologists, and gastroenterologists [4–9].

Why Is Sedation a Particular Concern in Elderly Patients?

The geriatric population is a heterogeneous group, and chronologic age does not always parallel physiologic age. Older patients present with multiple comorbidities, numerous medications, and less physiologic reserve [10, 11] (see Chaps. 4, 7, 8, and 27). They can be more sensitive to the sedative and depressant effects of the drugs used for sedation

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Table 22.1 Sedation depth					
Minimal	Patient responds appropriately to normal-volume verbal cues, through voice or action. The response is immediate				
Moderate	Patient responds purposefully to verbal or light tactile stimulus. The response is either verbal or physical, for example, opening eyes, turning head in a given direction, appropriate change in position				
Deep	The patient does not respond to either verbal or tactile stimulus, but responds appropriately to painful stimuli				

Table 22.2 Considerations for sedation in the elderly

1. Presence o	f multiple	comorbidities:	Coronary	disease,
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arrhythmias, prior cerebrovascular accidents

- 2. Positioning challenges
- 3. Chronic pain especially of the back and spine
- 4. Prevalence of chronic hypoxia and the need for home oxygen
- 5. Hearing and vision impairments that interfere with communication
- 6. Dementia and cognitive dysfunction

and are at increased risk from additive side effects when combinations of medications are administered. Although brief episodes of hypotension or desaturation may be insignificant in a young patient, the same episodes in an elderly frail patient may result in serious consequences, such as cardiac ischemia and arrhythmias [12] (Table 22.2).

Comorbid Conditions

Elderly patients carry a large burden of disease: In a study examining preoperative health status in elderly patients, more than 84% of 544 patients had at least one comorbid condition, with 30% of patients having three or more preoperative health conditions and 27% with two [10]. Disability restricting mobility is also prevalent: 73% of people older than 80 years have at least one disability. These conditions have an impact on the delivery of sedation and may limit the options available for sedation.

Cardiac conditions such as angina, hypertension, and congestive heart failure are all prevalent among elderly patients [13, 14]. The high incidence of coronary artery disease places older patients at high risk for myocardial ischemia during awake procedures, especially if the procedure is painful and/or anxiety provoking and it proves difficult to relieve the pain/anxiety without resorting to unacceptable levels of sedation. Similarly, hemodynamic instability, particularly hypotension, is more likely in older patients because of their sensitivity to hypovolemia and the increased sympathetic tone that could be reduced by sedation. However, hypotension is not a likely result if stage II sedation is not exceeded [2, 15].
 Table 22.3
 Practical considerations for the administration of sedation in elderly patients

- Allow extra time to explore the preoperative history including medications and comorbidities
- Provide written instructions in large type
- Provide extra copy of instructions to caretaker if applicable
- Allow extra time for changing clothes at the beginning and end of the procedure
- Be prepared to provide additional assistance transferring to and from procedure table
- Postoperative recovery facilities with monitoring should be available in the event of a slow postoperative recovery

Age-related pulmonary changes also affect the administration of sedation; changes in lung- and chest-wall compliance predispose the older patient to atelectasis with associated hypoxia that may not be amenable to treatment with supplemental oxygen [16]. Hypercarbia may also develop and produce hypoxia (if not on supplemental oxygen) and may produce undesired hypertension and tachycardia.

Renal disease may require alternations in medication dosing, and uremia can render patients very sensitive to the effects of sedation, especially the apneic side effects of narcotics. With the obesity epidemic in the United States, diabetes is becoming more prevalent and is very common in older patients. Glucose control can be problematic, and associated diabetic gastroparesis may result in a full stomach, even after 8 h of fasting.

Central nervous system aging renders older patients more sensitive to sedatives and analgesics, and patients with mild cognitive dysfunction are at particular risk of agitation and confusion with even small amounts of sedatives.

Challenges Encountered During Administration of Sedation

There are certain issues that are uniquely relevant to elderly patients that may impinge on the sedation plan [11, 17, 18] (Table 22.3).

Positioning

The accelerated loss of subcutaneous and intramuscular fat observed with aging may result in bony prominences that are at risk from skin breakdown and predispose elderly patients to accidental injury from seemingly benign positions. The loss of skin elasticity and slow healing further contribute to complex skin wounds and shearing injuries. Chronic pain, especially back pain, may limit the ability of an elderly patient to attain or maintain certain positions for long periods of time. Vertebrobasilar insufficiency may predispose an older patient to unexpected cerebral ischemia with neck extension; this may be particularly important if manipulation of the airway or neck is required. Cardiopulmonary compromise may occur secondary to positioning. For instance, the prone position or Trendelenburg may be less well tolerated in an elderly patient with significant cardiac disease.

Communication

Diminished visual acuity, blindness, deafness, or impaired hearing make it more difficult to communicate during a procedure. Furthermore, many common procedures such as colonoscopies and endoscopies take place in a darkened endoscopy suite, further reducing the sensory input to the older patient. Any written information should be easy to read, and extra copies should be available for patient's family, especially if the patient has any cognitive or communication issues.

Preprocedure Evaluation

Before administering sedation, an assessment of the patient's overall health including an estimate of the patient's reserve function of major organ systems is needed. At a minimum, this should include a medical history, a comprehensive list of medications, and a brief physical examination including an airway assessment. One of the guiding principles for the successful administration of sedation is cooperation; preprocedure assessment should include an evaluation of the patient's ability to cooperate at baseline. Patients who cannot cooperate because of dementia, sensory issues such as hearing or visual loss, or who are in extreme pain or disabled from arthritis and prior strokes and so on may not be suitable sedation candidates, and a deep sedation or a general anesthetic may be required [2, 11, 19, 20].

Scheduling and Information

The geriatric patient may have limited mobility and other issues that may result in the need for extra time to change and transfer from a chair to a stretcher. Therefore, additional time in between cases and arrangements to help with dressing and so on should be allotted.

All instructions should be written avoiding medical jargon and available in large easy-to-read print. In addition to preoperative instructions, written information should be given to patients and/or caregivers before discharge that clearly states what to expect postoperatively, whom to contact with questions, and how to arrange for emergency help if needed.

Sedation History

A history of sedation and anesthesia is invaluable. Difficulties with prior procedures under sedation, substance and alcohol abuse, and extensive pain medication use have been shown to predict difficulty in sedation administration. In addition, technically difficult or lengthy procedures also predict difficulty with sedation. In these instances, it may be preferable to schedule elective procedures for deep sedation or general anesthesia [2, 11, 19, 20] (Tables 22.4 and 22.5).

Consent

The patient should understand and agree with the specific plan for sedation and the risks involved. When the patient is significantly disabled or dependent, it is important to involve caregivers early. Aside from consent issues in these patients, caregivers are likely to be needed in the postprocedure care of the patient. Frequently, the surgical consent will include permission for sedation during the procedure, and separate consent for sedation is not always needed; however, specifics will depend on local administration and regulations within the hospital or facility.

Preoperative Fasting Guidelines

Both the ASA and the American Society for Gastrointestinal Endoscopy (ASGE) recommend restricting solid foods for 6–8 h and allowing only clear liquids until 2–3 h before

Table 22.4 Predictors of difficult sedation

History of:	
Substance abuse	
Heavy alcohol use	
Chronic narcotic use	
Difficulty with previous sedation case	
Anticipated prolonged or complex procedure	

Table 22.5 General anesthesia recommendations

General anesthesia is recommended in patients who are:

- Obtunded
- Intoxicated
- Septic
- Have active hematemesis
- Have significant cognitive impairment—e.g., dementia or are unable to cooperate secondary to confusion or anxiety
- At high risk from aspiration-e.g., obesity, reflux, or ascites
- Unable to lie still secondary to pain, confusion, or other medical conditions

the procedures. In the elderly person, it is useful to establish who is receiving these instructions and who is responsible to enforce them. In a more frail or demented patient, adherence to fasting guidelines is particularly important because it can be difficult to predict the reaction to sedation and there may be a need for conversion to a deeper sedation or a general anesthesia [19, 20].

Procedural Considerations

Monitoring

Guidelines for monitoring have been developed by the ASA [21]. At minimum, all sedated patients must be monitored throughout the procedure for level of consciousness. Standard monitoring includes heart rate monitoring via pulse oximetry, noninvasive blood pressure at regular intervals, respiratory rate, and oxygen saturation, and in the elderly population, electrocardiography is also recommended. Postprocedure vital signs should also be monitored periodically during the recovery period until the effects of all medications have worn off and the patient is ready for discharge.

The presence of a pacemaker requires the availability of a magnet if cautery is contemplated. Patients with a significant cardiac history, ongoing angina, congestive heart failure, or oxygen-dependent lung disease have almost little reserve function. These patients may not be suitable candidates for sedation because they may require additional monitoring.

Patients may maintain normal oxygen saturation despite significant hypoventilation and hypercapnia, and monitoring of ventilation is advisable whenever deep sedation is contemplated, especially during long procedures. Capnography can be used to monitor ventilation and to detect early increases in carbon dioxide [21]. Similarly, the bispectral index (BIS) monitor has been used to assess the level of sedation in patients receiving propofol for sedation [22].

It should be recognized that clinical monitoring of the elderly patient may be more demanding than that of the younger patient. During the procedure, a dedicated individual should be able to supervise the patient. This individual should not be performing the procedure but rather should be continuously monitoring the patient for responsiveness, cooperation, and vital signs. Because by definition a sedated patient should be responsive at all times, communication with the patient is one of the most valuable monitoring methods.

Emergency Resuscitation

When administering sedation, emergency resuscitative equipment should be available, and those providing sedation should ideally be trained in basic and advanced life support. Minimal emergency equipment should include dedicated oral suction, oxygen, a bag-valve-mask device, an oral airway, and anesthetic drug (agonist) reversal (antagonists) drugs [23, 24].

Oxygen

Elderly patients with limited pulmonary system reserve function are predisposed to hypoventilation and hypoxemia; this may be exacerbated by cardiopulmonary and other diseases. Studies in gastroenterology have described episodes of desaturation during endoscopic and colonoscopic procedures in both sedated and nonsedated patients, emphasizing the vulnerability of these patients [25, 26]. Supplemental oxygen provided via nasal cannula at 4 L/min has been successful in abolishing or attenuating episodes of desaturation. As stated, monitoring of ventilation is indicated because oxygen may mask the development of hypercapnia in sedated patients, especially those receiving supplemental narcotics [2, 19, 21].

Conclusions

Elderly patients should be offered the opportunity to undergo procedures and simple surgeries under sedation with minimal risk. Skillful administration of sedation may help avoid more morbid and complex surgeries and improve outcomes. Sedation in the older patient is safe, but requires additional vigilance and patience.

Gastrointestinal Endoscopy in the Elderly

Some of the most common nonoperating room procedures in the elderly are gastrointestinal endoscopies. The incidence of gastrointestinal disease increases with age. Endoscopic procedures are often utilized to diagnose and treat many of these conditions. Specifically, the elderly have higher rates of colorectal cancer, esophageal cancer, and gastric cancer. Biliary and pancreatic diseases are also more prevalent in the elderly [27]. Indications for upper endoscopy, colonoscopy, balloon-assisted enteroscopy, percutaneous endoscopic gastrostomy (PEG), endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasound (EUS) are essentially the same as for younger patients. However, screening colonoscopies have limited benefit after the age of 75 [28].

Aging and the Gastrointestinal Tract

Changes occur throughout the gastrointestinal (GI) tract during the aging process. Cellular changes include growth, differentiation, replication, and immunological changes [29]. Diverticular disease, malignancy, and GI motility issues are some manifestations of these changes [30, 31]. Dysphagia, diminished esophageal sphincter tone, decreased pharyngeal and supraglottic sensation, and diminished pharyngoglottal closure reflexes lead to increased incidence of aspiration and subsequent pneumonia or pneumonitis [32, 33]. Cholelithiasis and choledocolithiasis in the elderly may be influenced by increased gallbladder volume and altered gallbladder motor dynamics [34, 35]. Increased incidence of gastrointestinal bleeding is due to diminished protective mucosal function, changes in bicarbonate level, and higher use of bloodthinning medications including nonsteroidal antiinflammatory medications [31].

Preprocedure Evaluation and Concerns

Endoscopy is considered a low-risk procedure. Preoperative cardiac testing is unnecessary in asymptomatic patients. A 12-lead ECG is also unnecessary in patients with known cardiovascular disease scheduled for GI endoscopy [36]. Some patients may present with recent coronary interventions including bare-metal and drug-eluting stents. Consultation between the endoscopist, cardiologist, and anesthesiologist may be required. It should be noted that in therapeutic ERCP and some cancer-staging endoscopic ultrasound (EUS) procedures, the benefit of performing the gastrointestinal procedure prior to cardiac intervention may be warranted. Elderly patients presenting to the endoscopy suite are often taking anticoagulant and antiplatelet medications. These medications are usually continued unless symptomatic bleeding is ongoing or can be expected (planned sphincterotomy, polypectomy, or endoscopic mucosal resection). The risk of bleeding should be weighed against the risk of thrombotic complications. Appropriate guidelines and expert opinion may be required when making this decision.

Implanted cardiac devices should be evaluated preprocedure. Monopolar electrosurgical current may be used during sphincterotomy, snare polyp resection, hot biopsy forceps application, and argon plasma coagulation [37]. As such, precautions should be taken regarding pacemaker and internal defibrillator function. If electromagnetic interference is anticipated, cardiologist and manufacturer recommendations should be obtained regarding appropriate device setting, interrogation, and magnet use.

Dehydration is common in the elderly. This is more likely to occur in hot climates or when taking diuretic and antihypertensive medications. Fluid restriction and bowel prepara-

tions make patients very susceptible to hypotension and in orthostatic hypotension when standing. particular. Polyethylene glycol and sodium phosphate oral preparation solutions are commonly used for bowel preparation. Sodium phosphate preparations are contraindicated in elderly patients with renal insufficiency, heart failure, and volume overload. Sodium phosphate can result in hyperphosphatemia, hypokalemia, and hypernatremia [38]. Polyethylene glycol preparations have been associated with acute renal failure, particularly in geriatric patients [39]. Some patients may receive split-dose bowel preparation solutions. Improved bowel preparation is achieved with split-dose regimens as long as the "runaway time" or period of time since the second dose of bowel preparation solution was ingested does not exceed 5 h [40]. Split-dose preparations result in similar residual gastric volumes to the residual gastric volumes of when compared to those patients who received an entire single-dose solution the night before examination [41]. In most patients, a 2 h fasting period after the second dose of bowel preparation solution should suffice in maintaining standard nothing by mouth (NPO) conditions prior to sedation.

Prophylactic Antibiotics

Prophylactic antibiotic indications should be the same regardless of patient age for GI endoscopic procedures. Typically, antibiotics are not indicated for endoscopic GI procedures. The American Society of Gastrointestinal Endoscopy and the American Heart Association have issued guidelines [42, 43]. In patients with high-risk cardiac conditions and established gastrointestinal tract infections with enterococci, antibiotic coverage for prevention of infective endocarditis with an antibiotic targeting enterococci may be reasonable [42].

For prevention of infections other than infective endocarditis, antibiotics are also recommended in specific circumstances. Antibiotics are recommended for ERCP in patients with biliary obstruction with incomplete drainage or in patients with biliary strictures post liver transplantation. All patients should receive antibiotics prior to PEG tube placement. Antibiotic prophylaxis prior to aspiration of a mediastinal or pancreatic cystic lesion during EUS is suggested. In peritoneal dialysis patients undergoing lower GI endoscopy, antibiotic prophylaxis for prevention of peritonitis is suggested [43].

Upper Endoscopy

Upper endoscopy in elderly patients has a high diagnostic yield [44]. Elderly patients with a history of upper

gastrointestinal bleed (GIB) have the highest diagnostic yield (74%), while older patients with a family history of gastric cancer have the lowest yield (6%) [44]. The overall frequency of finding peptic ulcer disease and malignancy increases with age. Esophagogastroduodenoscopy (EGD) for indications other than emergency upper GIB is not associated with higher complication rates compared to younger patients [45]. It has been suggested that the use of an ultrathin endoscope (5–6 mm diameter vs. 8–11 mm) may allow for awake endoscopy or minimal sedation endoscopy due to the ease of insertion and less oropharyngeal irritation [46].

PEG tube placement is considered in patients expected to survive more than 30 days after placement. Postplacement mortality is high in the very elderly, but this is often related to the patient's underlying disease and comorbidities [47].

Various strategies have been described for upper endoscopy in the elderly. Sharing the airway of the anesthetized patient with the endoscopist can be challenging, and careful selection of anesthetic drugs and doses is required. Supplemental oxygen via a nasal cannula with carbon dioxide detection capability is usually placed. A nasal trumpet connected to a breathing circuit may also be considered. The patient is usually placed in the lateral position and insertion of the endoscope is typically the most stimulating part of the procedure.

The age-related reduction in pharyngeal sensitivity compared with younger patients is an advantage when performing a simple upper endoscopy. The elderly patient may not require much if any sedation. Aspiration is always a risk in sedated patients. However, the endoscopist is usually able to actively suction GI contents during the performance of upper endoscopic procedures. In the frail elderly patient, aspiration can be a morbid event [17, 48]. Studies of elderly patient sedation strategies for upper endoscopy have shown good outcomes with lower doses of propofol [49, 50]. In a study by Gotoda et al., average maintenance propofol dose for complex upper endoscopy was 85 mcg/kg/min in patients <70 years and 60 mcg/kg/ min in patients \geq 80 years [50]. Hypoxemia, which is more common in elderly patients with abnormal pulmonary function, can be lessened with a stepwise, judicious approach to upper endoscopy sedation [50, 51]. A prospective study of 720 older patients (60-80 years) showed that the use of etomidate for sedation in elderly patients at significant risk for hypotension can be considered [52]. This should result in better hemodynamic parameters when compared to propofol-based sedation during gastroscopy. Complications of excessive sedation in upper endoscopy are usually due to hypoventilation, hypotension, and hypoxia; however, inadequate sedation may lead to coughing, laryngospasm, and active regurgitation of gastric contents.

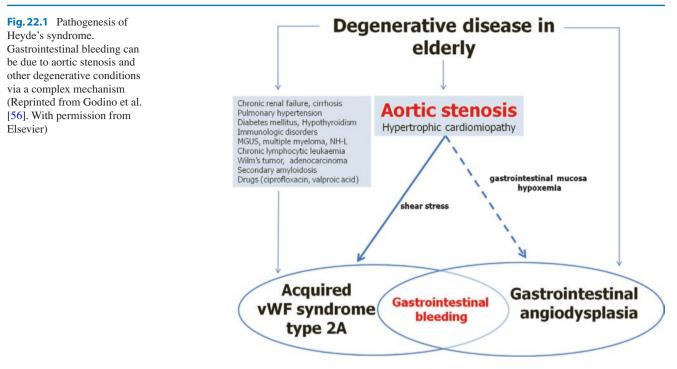
Colonoscopy

Colonoscopies are generally associated with considerable discomfort. A prospective study by Lukens et al. found that in octogenarians undergoing colonoscopy, poor colonic preparation was four times more likely in octogenarians than nonoctogenarians resulting in lower completion rates [48]. Hypoxemia was also more common during colonoscopy for octogenarians compared to nonoctogenarians (27% vs. 19%), and desaturations were associated with higher meperidine doses [48]. In a larger prospective study of 2000 patients, overall complication rates during colonoscopy were low regardless of patient age [53]. However, risk of perforation during colonoscopy does appear to increase with age [47]. Also, a meta-analysis of adverse events in elderly colonoscopies showed that cardiopulmonary events were more prevalent in patients 80 and older (28.9/1000) versus patients 65 and older (19.1/1000) and were related to sedation and higher patient comorbidities [54].

During colonoscopy, deeper levels of sedation are associated with increased risk of aspiration, splenic injury, and colonic perforation [55]. It is also known that sedation will facilitate the colonic endoscopic examination and increase patient comfort. Deeper levels of sedation may predispose to an increased rate of colonic perforations due to patient inability to show discomfort associated with the scope being advanced against resistance. Similarly, splenic injury may be more likely to occur secondary to increased patient tolerance to colonoscope loops stressing colonic to splenic attachments. Active or passive regurgitation of gastric contents may also occur. Endotracheal intubation may be indicated in patients determined to be at high risk for gastric aspiration during colonoscopy. Short-acting anesthetic agents such as propofol are preferred for rapid titration and ability to reduce the period of time in deep sedation. Titration of propofol and other anesthetic agents to EEG-based monitoring (e.g., BIS) can help providers reduce time spent in deep sedation [50].

Deep Small Bowel Enteroscopy

Obscure gastrointestinal bleeding and other small bowel disorders in the elderly patient are often identified via balloonassisted deep enteroscopy. The small bowel may be approached in either an anterograde or retrograde fashion. Heyde's syndrome, an angiodysplastic bleeding syndrome due to acquired type-2A von Willebrand factor, results from aortic stenosis [56] (Fig. 22.1). It is important that this association not be overlooked as deep levels of sedation or general anesthesia with an endotracheal tube are typically required to facilitate deep enteroscopy. A prospective review showed deep enteroscopy to have a high diagnostic yield and require lower levels of sedation in patients over 70 compared to younger patients [57].



Endoscopic Retrograde Cholangiopancreatography

Endoscopic management of pancreaticobiliary disease in the elderly is particularly advantageous as high-risk surgical procedures may be avoided. The high incidence of biliary tumors, cholelithiasis, and pancreatic head cancer in the elderly make this procedure common. Complication rates are low and safety has been demonstrated in multiple studies [47].

ERCP procedures may last an hour or more and adequate sedation is essential. The patient is usually placed in the prone position with the head turned to the side. A recent large retrospective study revealed that during ERCP, sedation-related adverse events (myocardial infarction, cardiac and/or respiratory arrest, arrhythmias, hypoxemia, hypotension, bradycardia, tachycardia) were more common in patients over 80 years [58]. Propofol, at lower doses, was the most commonly used agent in this study and highlights the need for expert care and the skillful management of sedation needed for ERCP in the elderly. In our practice, we often prefer general anesthesia with an endotracheal tube, particularly for longer and more complex cases. Another study of high-risk octogenarians undergoing routine ERCP demonstrated superiority of a propofol-based anesthetic compared to a midazolam/meperidine sedation [59]. Benefits of propofol included better patient cooperation, shorter recovery time, and significantly lower desaturation events in recovery.

Endoscopic Ultrasound

Endoscopic ultrasound is used to stage malignancies, evaluate the biliary tree, and evaluate extraluminal solid and cystic masses. In patients with suspected pancreatic cancer, endoscopic ultrasound is known to be particularly useful. This procedure is often utilized with fine-needle aspiration and combined with ERCP. Endoscopic ultrasound has demonstrated good safety in patients 75 years and older [60]. However, the echoendoscope has a more rigid tip than the standard endoscope may predispose the patient to an increased risk of perforation [61]. Similar to ERCP, sedation times are longer and a sedation strategy should be planned for accordingly.

Summary

GI endoscopic procedures in the elderly are useful both diagnostically and therapeutically. Sedation techniques are similar to those used in younger patients, although effective doses are lower. Hypoxia, hypotension, arrhythmias, and aspiration are more common in the elderly [38]. In the limited number of studies that evaluate sedation in the elderly for endoscopic gastrointestinal procedures, short-acting agents including propofol appear to offer advantages over traditional agents like midazolam and meperidine. Meperidine and midazolam, particularly at higher doses, may have prolonged effects and are associated with delirium [62]. As the elderly are more prone to orthostatic hypotension, care must be taken when allowing them to stand and ambulate after endoscopy. This is of particular concern in patients who have had bowel preparations or have been fluid restricted.

Electroconvulsive Therapy and the Elderly

It is estimated that approximately 12.5% of older people have some form of depression [63]. Major depression in adults over the age of 60 is estimated at 2% [64]. The rate is likely higher for those patients that are inpatient or in nursing facilities. There is evidence to suggest that major depression in the geriatric population may be related to concomitant cerebrovascular disease as well as underlying cognitive impairment [65]. In addition, depression that occurs later in life can lead to worsening cognitive deficits, and elderly patients undergoing electroconvulsive therapy (ECT) may suffer greater cognitive impairment when compared to younger patients [66]. However, this association is variable among patients, and the underlying biological mechanisms that lead to cognitive dysfunction (see Chap. 30) are not well defined [65].

Multiple studies suggest that ECT can be effective and well tolerated in the elderly, even for the "old-old" adults of over 75 years of age [66-71]. Advances in ECT over the past few decades, including the use of ultrabrief pulse treatments, have improved the safety of ECT and limited cognitive side effects, but have not necessarily improved the treatment efficacy for geriatric patients with major depression [72]. In addition, many of these studies were not randomized, typically small in sample size, and often retrospective in nature [68-70, 73]. In fact, a Cochrane Review published in 2003 highlighted the sparse randomized evidence on the safety and efficacy of ECT in the treatment of depression in geriatric patients [63]. In addition, randomized evidence on the effectiveness of ECT in elderly patients with concomitant neurodegenerative disorders such as pre-existing dementia, Parkinson's disease, and cerebrovascular disorders is absent [63]. However, elderly patients typically have more medical comorbidities requiring multiple medications. Polypharmacy, combined with age-related changes in drug metabolism, can make the elderly more prone to medication interactions and undesirable side effects with psychotropic medications used to treat depression. Thus, ECT may be the better option for treatment of major depression (Table 22.6). If untreated, severe depression in the elderly can also lead to loss of independence and a more frail state.

 Table 22.6
 Psychiatric diagnoses for which ECT has been alleged to be effective

- · Major depression, single or recurrent episode
- Bipolar major depression, depressed or mixed type
- Mania (bipolar disorder), mania or mixed type
- Schizophrenia
- Catatonia
- Schizophreniform or schizoaffective disorder
- Atypical psychosis
- Other conditions
 - Organic delusional disorder
 - Organic mood disorder
 - Acute psychotic disorder
 - Obsessive-compulsive disorder
 - Dysthymia
- Miscellaneous conditions
- Parkinson's disease
- Neuroleptic malignant syndrome
- Secondary catatonia
- Lethal catatonia

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Other Treatments for Depression in the Elderly

Subconvulsive neuromodulation therapies that can potentially improve mood disorders in the elderly include transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS). These treatments do not require anesthesia, nor do they provoke a seizure, which may make them less likely to affect cognition [72]. Other therapies approved for chronic depression in the United States include vagal nerve stimulation (VNS). Implantation of VNS typically requires general anesthesia to implant both the generator (usually around the left chest area) and the electrode (usually the left neck area near the vagus nerve) [72].

Preoperative Evaluation

Preoperative work-up for the geriatric patient undergoing ECT does not significantly differ from any other elderly patient. However, informed consent in a severely depressed patient who may also have cognitive comorbidities such as pre-existing dementia can present unique challenges. Many institutions provide these patients with educational materials such as videos, brochures, and classes to aid with the informed consent process.

Elderly patients have a higher prevalence of stroke, valvular disease, and atrial fibrillation as compared to younger populations. Thus, these patients may be taking anticoagulation medications when presenting for a course of ECT. The transient increase in blood pressure due to the sympathetic response to electrical stimulus can potentially increase risk of bleeding in patients who are chronically anticoagulated. Historically, oral anticoagulation was often held during ECT treatment; use of intravenous heparin as a bridge during ECT treatment has been described. There is very limited data to suggest how anticoagulants should be managed throughout the course of ECT treatment. Case reports and retrospective reviews of patients on long-term warfarin therapy have not demonstrated increased risk of intracerebral hemorrhage during ECT treatment [74-76]. There is one case report of a patient on chronic anticoagulation who then developed gross hematuria immediately after ECT treatment [77]. However, larger prospective evaluations are needed, especially given the expansion of oral anticoagulants such as direct thrombin inhibitors now on the market.

Elderly patients with underlying cardiac disease may also present with cardiac pacemakers and/or implantable cardiac defibrillators (ICDs). Unfortunately, there are no controlled trials that definitively outline the safest management for patients with these devices that undergo a series of ECT treatments. Analysis of multiple case reports and case series on this topic, however, suggest that ECT is safe in patients who have cardiac pacemakers, and the short duration of stimulus during ECT treatment does not have significant clinical effect on modern pacemakers [78]. In fact, the vast majority (80%) of patients in one retrospective pooled analysis had no modification to their pacemaker prior to ECT, while approximately 10% had their pacer changed to asynchronous mode. Risk of ventricular tachycardia (VT) or ventricular fibrillation (VF), however, still exists with conversion to asynchronous mode during ECT treatment, most likely due to the decelerationacceleration nature of heart rate related to the induced seizure [78]. However, for those patients with ICDs, nearly all had their ICD deactivated during the procedure [78]. Thus, it may be prudent to disable ICD devices prior to treatment, but allow pacemakers not associated with an ICD to continue to function as programmed.

Physiologic Changes during Electroconvulsive Therapy

The application of transcutaneous electrical stimulation to the brain can cause many physiologic perturbations. However, most of these changes are short-lived. The brain itself sees an increase in cerebral blood flow, as much as 133% above baseline, resulting in increased intracranial pressure [79, 80]. This increase in cerebral blood flow velocity may be attenuated but not completely eliminated by the administration of systemic antihypertensive medications [80]. Serious but rare cerebral side effects include intracranial hemorrhage, transient ischemic changes, and blindness.

 Table 22.7
 Common physiologic responses and side effects associated with electroconvulsive therapy

Variable	Response
Central nervous system	Increased blood flow velocity, intracranial pressure, and cerebral metabolism, dizziness, amnesia, confusion, agitation, and headaches
Cardiovascular system	Increased blood pressure, heart rate, and cardiac output, cardiac arrhythmias
Musculoskeletal system	Myoclonic-toxic contractions, bone fractures/dislocations, muscle and joint pain
Miscellaneous responses	Increased salivation, nausea and vomiting, dental damage, and oral cavity lacerations
Reprinted from Ding and White [79]. With permission from Wolters Kluwer Health	

Cardiovascular changes during and immediately after the electrical stimulus include an initial parasympathetic stimulus with resultant bradycardia or even asystole that can last for several seconds. This is immediately followed by sympathetic stimulation and catecholamine release leading to hypertension, tachycardia, and increased myocardial oxygen demand that can last for several minutes. In fact, up to a 20% increase in heart rate, 34% increase in blood pressure, and 80% increase in cardiac output has been reported in the literature [81]. However, these hemodynamic changes do not appear to directly correlate with the duration of seizure, as measured by motor or EEG activity [82]. There is also some suggestion that left ventricular systolic function transiently decreases after the seizure [83]. Rare but life-threatening cardiac side effects reported from ECT include ventricular dysrhythmias, conduction abnormalities, myocardial infarction, and even cardiac rupture [84–87] (Table 22.7).

Medications for Electroconvulsive Therapy

Older age is associated with elevated seizure thresholds [72]. In addition, the duration of the induced seizure is related to the efficacy of treatment. Thus, the anesthesiologist must balance the use of medications that often suppress seizure generation but still maintain an adequate general anesthetic state for several minutes. Mainstay sedative-hypnotic drugs for ECT include methohexital, thiopental, propofol, and etomidate. All have been described to be effective and safe in the use of ECT and confer individual advantages and disadvantages based on their pharmacokinetics, pharmacodynamics, and side effect profiles. In addition, there is no conclusive evidence to suggest that one agent is superior than another in terms of impacting depression scores [88]. Methohexital is often considered the best induction agent for ECT due to its epileptogenic effects, rapid onset, and short duration of action [79]. Propofol and thiopental tend to result in shorter seizure duration when compared to methohexital [88]. Etomidate has been associated with a statistically significant longer motor and EEG seizure duration when compared to propofol, methohexital, and thiopental [89]. Benefits of etomidate include rapid onset and cardiovascular stability. Side effects include pain on injection, adrenal suppression, and myoclonus [89]. Remifentanil, an ultra-short-acting opioid that does not increase seizure threshold, has also been used during ECT treatment. A recent meta-analysis suggests that the use of remifentanil as an adjunct to other induction drugs can significantly prolong seizure duration during ECT if the dose of the other induction drugs (such as thiopental or propofol) is decreased [90]. Also, the addition of remifentanil appears to significantly decrease the maximum systolic blood pressure [90]. Ketamine, in both sub-anesthetic and general anesthetic doses, may also be used in ECT, especially in treatment-resistant depression. There is emerging evidence that an infusion of ketamine has antidepressant effects and can improve mood in patients with treatmentresistant depression. In addition, ketamine has been shown to result in longer seizure duration as well as a faster improvement in mood after the first and second ECT treatment when compared to propofol [91]. In addition, there is recent evidence that ketamine infusions have antidepressant effects and can improve mood and could possibly emerge in the future as an alternative to ECT for patients with treatmentresistant depression [92].

Complications and Procedural Side Effects

Immediate Complications and Side Effects

Sympathetic response to the induced seizure leads to transient hypertension and tachycardia which often requires treatment in elderly patients who are at increased risk for myocardial ischemia. Several short-acting antihypertensives have been used during this period including nitroglycerin, nitroprusside, esmolol, labetalol, and nicardipine.

Given that patients are induced under general anesthesia and given a muscle relaxant, aspiration with bag mask ventilation is still a risk. While most providers verbally confirm NPO status, often depressed patients have difficulty communicating. Reported incidence of aspiration during ECT remains low, but it is still a possibility [93]. Providers should always be prepared to obtain a definitive airway and have quick access to suction and a ventilator at their physical location where ECT is performed.

Immediate postictal side effects include fatigue and weakness, amnesia, headache, confusion, and agitation [79]. Postictal agitation can be potentially harmful as the patient can injure themselves unintentionally. Administering small doses of benzodiazepines such as midazolam or atypical antipyschotics immediately upon termination of the seizure can be helpful in decreasing levels of agitation. Delirium is a little harder to diagnose in the immediate postictal state. It often presents as a hypoactive state that overlaps with many symptoms severely depressed elderly patients have prior to treatment [72].

Serious musculoskeletal complications such as fractures and joint locations have been reported [94, 95]. However, these reports are rare, especially now that muscle relaxants are routinely administered prior to the seizure stimulus. In addition, there are reports of safe use of ECT after fracture repair and joint replacement with higher doses of muscle relaxant used during ECT treatment [96, 97]. However, inadequate muscle relaxation as well as the muscle relaxant itself (typically succinylcholine) can result in postprocedure muscle aches and pains as well as place patients who have a high preprocedural risk for fractures (recent fracture, recent joint replacement, severe osteoporosis) at even higher risk for musculoskeletal complications.

Long-Term Complications and Side Effects

There have been case reports and chart reviews describing mechanical falls in the elderly during course of ECT treatment [98, 99]. However, mechanical falls can be quite frequent in the elderly at baseline. One proposed theory for increased fall risk during ECT treatment course is that patients may experience an increase in energy level as their depression improves, leading to more activity and mobility [98]. Another is that alterations in short-term cognition related to ECT or ECT-associated delirium can increase the fall risk as well. In general, there is very poor data to quantify or qualify the risks of ECT-associated mechanical falls. It is reasonable, however, to suggest that elderly patients undergoing ECT should be educated about the risks of falls and prevention strategies that they can implement in their surroundings to prevent falls.

Cataract Surgery in the Elderly

Cataract surgery is the most commonly performed operation in the geriatric population, and in economically developed countries, the overall rate of surgery is 4000–6000 operations per million people each year [100]. Good clinical outcomes have been shown to be attainable in very elderly patients despite multiple systemic and ocular comorbidities [101]. Cataract surgery is considered an "essential surgery" in the Disease Control Priorities due to high value and cost effectiveness where resources are limited [102]. In general, these are very low-risk outpatient surgeries performed with minimal sedation [103].

Cataracts

The majority of cataracts in the United States are senile or age-related cataracts and a major cause of blindness in the elderly [104] (Table 22.8). The exact pathogenesis of cataracts is not completely understood; however, the current evidence suggests that a photoxidative mechanism has a major role. The normal crystalline lens is composed of a very complex structure consisting of specialized cells arranged in a highly ordered manner; the high content of the cytoplasmic protein provides the transparency critical to the functioning lens. During aging, the epithelial cells are not shed as they are in other structures, and there is a gradual buildup of protein and pigment, forming the basis of the cataract. Risk factors include aging, smoking, alcohol consumption, sunlight, low education, steroids, trauma, and diabetes mellitus [105].

Modern Cataract Surgery

All cataract surgery involves removal of the cataract; key advances in the field have been the development of small foldable implantable lenses and the development of phacoemulsification techniques. The most popular approach to phacoemulsification cataract extraction is [106]. Ultrasonically driven oscillating needles are inserted through a tiny incision and used to emulsify the lens. A continuous irrigation/aspiration system is used to remove the fragmented lens. An artificial lens is inserted through the small incision. These tiny incisions frequently do not require sutures for closure, allowing for a rapid surgery and recovery (Table 22.9) [103, 105–108]. Femtosecond laser assisted cataract surgery is a new technique that may make cataract surgery safer and more reliable [105].

Intracapsular cataract extraction (ICCE) refers to the total extraction of the opacified lens and the capsule; a new lens is

Table 22.8 Most common causes of vision loss in the elderly

1. Cataract
2. Age-related macular degeneration
3. Glaucoma
4. Diabetic retinopathy

Tab	le 22.9	Complications	of cataract surgery
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1. Astigmatism
2. Wound leak or dehiscence
3. Prolapsed iris
4. Flat anterior chamber
5. Expulsive rupture of choroidal vessels
6. Strabismus
7. Secondary cataract

then inserted into the anterior chamber. This technique is rarely used. Extracapsular cataract extraction (ECCE) refers to the procedure during which the lens is removed but the posterior capsule is left intact. ECCE may be required for extremely hard, mature cataracts that are difficult to break up using phacoemulsification techniques. Both ICCE and ECCE procedures require relatively large incisions [105, 106].

Indications for Surgery

The key indication for surgery is visual impairment accompanied by deterioration in general function secondary to failing eyesight and a promising surgical prognosis for recovery of vision. Generally, prognosis depends on the presence or absence of other ocular comorbidities, such as glaucoma or retinopathy. Phacomorphic glaucoma and follow-up of diabetic retinopathy through regular funduscopic examinations are other indications for cataract extraction.

In older patients, even those with dementia, correction of vision may improve quality of life and allow for more independence [109, 110]. Vision loss has been associated with cognitive impairment and cognitive decline. Cataract extraction may slow cognitive decline or even improve cognition [111–113]. Depression has also been linked with cataracts in the elderly [114]. Cognitive impairment, vision related quality of life, and depression are related [115]. Depressive pseudodementia is cognitive impairment due to depression [116]. If poor vision from cataracts is causing depression and pseudodementia, cataract extraction may lead to improvement in these areas. Cognitive improvement and sleep enhancement may also result in the elderly due to improved blue-light transmission after cataract surgery [117, 118].

Poor vision and fall risk are increased in the elderly [119, 120]. Binocular vision plays an important role in preventing falls. If second eye cataract surgery is needed, it should be performed in a timely fashion to optimize binocular vision and help prevent falls or other accidents [121].

Preoperative Evaluation for Cataract Surgery

As stated, cataract surgery is very low risk. Cataract surgery patients have a 0.014% chance of dying [122]. Unfortunately, the preoperative assessment in these patients can still be problematic because patients have complicated histories and multiple illnesses. The preoperative assessment will need to identify patients that may need additional anesthesia, such as those with unstable medical conditions or conditions that may prohibit the patient from lying still during the procedure [123, 124].

The value of preoperative laboratory testing has been questioned, and a prospective trial evaluated preoperative testing in more than 18,000 cataract patients [124]. The trial found that preoperative testing (EKG, electrolytes, urea nitrogen, creatine, and glucose) did not affect outcomes for cataract surgery. A recent Cochrane Review showed that routine testing before cataract surgery does not increase safety, and costs are 2.55 times higher in patients who have routine testing [122]. In general though, a history and physical examination before cataract surgery is beneficial because these patients have complex medical histories.

Antithrombotic Therapy and Cataract Surgery

Management of antithrombotic therapies in older cataract patients involves weighing the risks of thrombotic complications against the risk of hemorrhagic complications. Discontinuation of anticoagulant or antiplatelet therapy substantially increases the risk of thromboembolic events. In patients with prosthetic heart valves, atrial fibrillation, or recent coronary stents, the risk is increased even more so [125, 126]. Cataract surgery is an avascular procedure and therefore at a very low risk for bleeding complications. When therapy levels are within the usual therapeutic window, needle blocks have been shown to be safe [125]. It most cases, it is recommended to continue antiplatelet and anticoagulant treatment for surgery. This includes retinal surgery under retrobulbar block [127, 128]. However, there is insufficient data regarding the safety of needle and cannula blocks for patients taking the newer antiplatelet medications (prasugrel, ticagrelor) and newer anticoagulant drugs (dabigatran, rivaroxaban, apixaban) [126]. Due to reduced clearance of these newer medications in elderly patients, special consideration may be needed before needle or cannula block.

Anesthesia for Cataract Surgery

Surveys and studies suggest that topical and intracameral anesthesia are the preferred anesthetic techniques, although there are areas in this country and the world where regional techniques are still used [129–133] (Table 22.10). This section describes the different types of anesthesia as well as the relative merits of each approach.

Table 22.10 Common anesthetic options for catara	act surgery
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- 1. Retrobulbar block
- 2. Peribulbar block
- 3. Sub-Tenon's block
- 4. Topical anesthesia
- 5. Topical anesthesia with intracameral injection

Regional Orbital Anesthesia

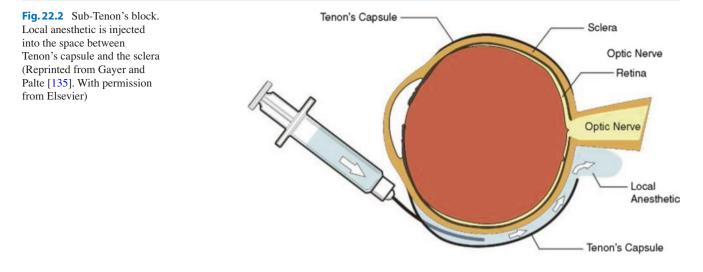
Regional anesthesia for eye surgery provides dense ocular anesthesia and akinesia; this may be advantageous in complex or prolonged cases. Retrobulbar and peribulbar blocks (needle blocks) are the most common regional techniques described [134]. The successful regional block requires a block of the optic nerve and the ciliary ganglion. Blockade of the ciliary ganglion results in a fixed, mid-position pupil. The surgery may also require paralysis of the orbicularis oculi muscle to prevent blinking; this muscle is innervated by the seventh facial nerve.

Retrobulbar and Peribulbar Anesthesia

Retrobulbar and peribulbar blocks are similar. The retrobulbar block involves the injection of local anesthetic agent behind the orbit within the muscular cone. The needle, typically 23 or 25 gauge and 38 mm in length, is introduced at the junction of the lateral and middle two-thirds of the lower lid above the inferior orbital rim. As the needle pierces the orbital septum, it remains parallel to the orbit floor; after reaching the globe equator, the needle is redirected upward to the apex of the orbit. The operator may feel a pop as the needle traverses the bulbar fascia, entering the muscle cone. Between 2 and 4 mL of local anesthetic is injected inside the cone of muscles, close to the optic nerve. During the injection, an awake patient is instructed to look straight ahead (a primary gaze), minimizing the chance of an intraneural injection. The peribulbar block is very similar; the needle is introduced as described for the retrobulbar block. However, the needle is kept parallel and lateral to the rectus muscle, and no effort is made to enter the bulbar fascia. As the needle reaches the equator, the local anesthetic is injected, i.e., around the muscle cone, not inside. For the peribulbar block, a larger volume of anesthetic is required to allow diffusiongenerally 4-6 mL. Additionally, it may take closer to 20 min to achieve the desired anesthesia. The peribulbar block may be accompanied by a second injection of 3-5 mL of local anesthetic injected medially in the superomedial orbit. A blunt-tipped needle of less than 31 mm in length is recommended to reduce the chance of a globe or neural puncture [129–131, 134].

Sub-Tenon's Block

Sub-Tenon's block is a combination block. Topical anesthesia is applied to the conjunctiva, and one quadrant of the sclera is exposed to reveal Tenon's capsule surrounding the sclera. A blunt catheter or needle is inserted into the sub-Tenon's space, and local anesthetic is infused [135] (Fig. 22.2). This provides excellent anterior anesthesia, but topical anesthesia is required for the cornea and conjunctiva. There is a small risk of global puncture with this type of injection, but in general, complications are lower than those described for retrobulbar blocks [131, 134].



Monitoring and Sedation

During the placement of the orbital block with sedation, the patient should be appropriately monitored. It is important that the patient remains still during the injection, and this may be achieved by the administration of short-acting sedative medication accompanied by supplemental oxygen. Multiple drug regimens have been described, and low-dose propofol (30-50 mg) is probably the medication of choice, offering excellent conditions with few side effects and a short duration [136–138]. In a study of elderly patients, Frey et al. found that the addition of ketamine (13.2+/-3.3 mg) to supplement propofol improved quality of sedation without prolonging recovery during retrobulbar block placement [139]. Midazolam is also frequently used, but has been linked to delirium in older adults. Short-acting narcotics can be used as well but have an increased risk of postoperative nausea and vomiting [140].

Combinations of a benzodiazepine, such as midazolam, and ketamine may result in improved patient cooperation [141]. The role for dexmedetomidine in cataract surgery is uncertain. A double-blind study comparing the use of midazolam to dexmedetomidine for sedation in cataract surgery under peribulbar block found that patient satisfaction was slightly higher with dexmedetomidine [142]. This advantage was offset by greater reductions in blood pressure and longer recovery time compared with the midazolam group. In a more recent study of patients 50–70 years, a lower loading dose of dexmedetomidine (0.25 mcg/kg) was used and compared to combination midazolam/fentanyl sedation for peribulbar block [143]. This provided stable hemodynamics and better surgeon satisfaction. Dexmedetomidine dosing should be decreased in the elderly ophthalmic patient.

In contrast to the requirements for block placement, minimal sedation during the case is generally sufficient. Shortacting opioids such as fentanyl, given at small doses, can

 Table 22.11
 Complications of retrobulbar/peribulbar anesthesia

- 1. Retrobulbar hemorrhage
- 2. Globe perforation
- 3. Neural injection of optic nerve
- 4. Vascular injection
- 5. Central retinal artery or vein occlusion
- 6. Brainstem anesthesia

provide analgesia with minimal sedation. Short-acting anxiolysis with midazolam can be used, particularly in patients with a history of alcohol abuse or benzodiazepine dependence. However, midazolam and meperidine may increase the risk of delirium. In a study of mostly elderly patients undergoing cataract surgery with topical anesthesia, dexmedetomidine infusion, without a loading dose, resulted in greater patient satisfaction and more stable hemodynamics compared to combination propofol and alfentanil sedation [144]. Other protocols have been described including patientadministration of propofol [145, 146]. controlled Unfortunately, abrupt changes in consciousness from propofol may result in undesirable head movement. Furthermore, any sedation must be balanced against the potential downside of disorientation and lack of cooperation in the patient during the procedure.

Side Effects and Complications of Intraorbital Anesthesia

Complications from intraorbital anesthesia are uncommon but the effects may be devastating, resulting in permanent visual damage or blindness (Table 22.11). Although the overall complication rate is low, this still has the potential to affect thousands of patients because of the huge number of patients undergoing cataract surgery. The most significant adverse events are described below. *Retrobulbar hemorrhage* occurs in 0.1–3% of needle blocks [147]. Hemorrhage occurs as a result of the inadvertent puncture of the ophthalmic artery as it crosses the optic nerve. Immediate signs of hemorrhage include proptosis, subconjunctival hemorrhage, and increased orbital pressure. Initial treatment is direct intermittent pressure to the eye. If the globe relaxes back (retropulsion) and intraocular pressure is normal, cataract surgery may be continued. If increased intraocular pressure or proptosis persists, then a lateral canthotomy is performed. If the intraocular pressure remains increased despite a patent canthotomy, then aqueous suppressants may be added. It should be noted that arterial fragility in hypertensive and diabetic elderly patients is a greater risk factor than clotting problems for retrobulbar hematoma [147].

Globe perforation is most common with a retrobulbar block, but may also occur during a peribulbar or sub-Tenon's block; the incidence varies from 0% to 1% of needle blocks performed [147]. Major risk factors for perforation include inexperience by the operator and staphyloma of the eye. The visual damage after a globe perforation will depend on the presence or absence of a retinal detachment and vitreous hemorrhage [131, 147] (Table 22.12).

Optic nerve damage is very rare after a retrobulbar injection [147].

Central Nervous System Complications

The optic nerve sheath communicates directly with cerebrospinal fluid, and inadvertent injection of local anesthesia into the sheath or directly through the optic foramen may result in immediate brainstem anesthesia. The incidence with retrobulbar blocks is 0.3–0.8% [147]. Similarly, intraarterial injection of local anesthesia may cause central nervous system toxicity and seizures.

Topical Anesthesia for Ocular Surgery

Topical anesthesia, mostly with lidocaine or tetracaine eye drops is popular with surgeons and patients [133, 148]. Topical anesthesia is often combined with an intracameral injection which involves a small incision and installation of local anesthesia into the anterior chamber. The intracameral injection reduces the discomfort during manipulation of the lens.

Advantages of Topical Anesthesia

There are several advantages to topical anesthesia (Table 22.13). The patient avoids the risk of retrobulbar hemorrhage and other complications, is able to see immediately, and the postoperative recovery is very speedy. Fewer adverse events have occurred when compared to needle blocks in several recent studies [132, 133]. Even complex cataract surgery may be performed under topical anesthesia. Jacobi et al. Table 22.12 Factors increasing risk of globe rupture

Uncooperative patient
Long eye axial length >26 mm
Staphyloma
Long needle used for the block

Table 22.13 Advantages of topical versus regional block

- 1. Eliminates risk of retrobulbar hemorrhage
- 2. Reduces risk to the optic nerve and other structures
- 3. Minimizes risk of strabismus postoperatively
- 4. Very short recovery time with immediate sight

found that surgical complications in complex surgeries were not different between patients receiving topical versus retrobulbar anesthesia [148].

The Role of the Anesthesiologist

There has been debate over the need for an anesthesiologist during cataract surgeries. Rosenfield et al. in a study of 1006 patients, found that in one-third of cases an intervention by an anesthesia team was required and that the need for an intervention was unpredictable [149]. The lack of predictability is perhaps one of the strongest arguments for anesthesia involvement. In an in-depth analysis of anesthesia management during cataract surgery, Reeves et al. found preferences for an anesthesiologist, sedation, and a block for the surgery. However, these results were highly dependent on the selection of a relatively small expert panel [150]. In contrast, the results of more recent surveys of ophthalmologists favor topical anesthesia. Anxiety, pain, and fear during cataract extraction result in lower patient satisfaction scores [151]. Thus, although not universal, anesthesiologists are still frequently involved in sedation and patient monitoring during cataract surgery.

Special Situations

There are some special circumstances in the elderly patient that may require alternative approaches. For instance, demented or uncooperative patients may require more sedation or even general anesthesia. Chronic pain patients may be unable to lie flat and be tolerant of medications. Significant kyphosis may make it difficult to position the patient so that the eye is directly below the microscope. Hypercapnia may result from sedation and the surgical drapes [152]. Providers must be prepared to manage airway complications, particularly upper airway obstruction which is common in patients with sleep apnea. Sometimes conversion to a general anesthetic is required and use of a laryngeal mask airway should be considered. The LMA provides smooth emergence conditions without concern of residual muscle paralysis.

Postoperative Considerations

Typically, there is no pain or only mild pain postoperatively [153]. In patients receiving blocks, an eye patch is common, and vision will take longer to return [154]. These patients may require additional help at home during convalescence.

Gaps in Our Knowledge and Future Directions

Sedation related adverse events are more common in elderly patients and in remote locations. Safety questions and research related to the best environment for nonoperating room procedures in the elderly needs to be examined. Studies that evaluate anesthetic strategies in elderly patients outside of the operating room are needed. These studies will examine different levels of sedation versus general anesthesia with and without a secure airway. Costs associated with performing various sedation strategies and procedures in nonoperating room settings must be analyzed. Also, the costs of not performing these procedures and subsequent deterioration in health will be an important consideration as the economics of healthcare tighten in this patient population. Questions regarding new techniques, including natural orifice transluminal endoscopic surgery, and new sedative agents, like remimazolam, and their effects on the elderly will need to be answered. Depth of sedation and EEG based brain monitoring during NORA and sedation cases in the elderly should remain fertile ground for future research. Finally, cognitive and overall health benefits of successful cataract surgery in the elderly have yet to be fully elucidated.

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Cardiothoracic and Vascular Procedures

Timothy L. Heinke and James H. Abernathy III

Cardiovascular disease is a predominantly geriatric disorder. There are an estimated 43.7 million people ≥ 60 years of age with cardiovascular disease (CVD) in the United States. In 2010, 51% of cardiovascular procedures were performed on patients 65 years or older. The prevalence of coronary artery disease, valvular heart disease, heart failure, atrial fibrillation, and vascular disease all increase with age. Men (84.7%) and women (85.9%) over 80 years of age have some form of CVD. Approximately 2/3 of all CVD deaths occur in people age >75 years [1]. Age-related changes to the cardiovascular system include advancing atherosclerotic disease in addition to changes in the fibromuscular skeleton of the heart, including myxomatous degeneration and collagen infiltration, termed sclerosis. Other age-related changes include calcium deposition on the leaflets of the aortic valve, base of the semilunar cusps, and the mitral annulus. Fibrosis with valve calcification is the most common etiology of valvular stenosis in the elderly. Valvular regurgitation often occurs as a result of ischemia or hypertensive disease, especially at the mitral valve [2]. The large burden of CVD has led to the development of novel therapies such as percutaneous left

atrial appendage closure devices and the continued evolution of minimally invasive techniques such as endovascular stent grafts and transcatheter valve therapies. Additionally, the probability that a male or female age >70 will be diagnosed with cancer of the lung and/or bronchus is 1 in 15 and 1 in 20, respectively [3]. Their presentation for lung resection surgery is becoming more common. This chapter summa-

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rizes new therapeutic options as well as provides up-to-date management strategies for cardiopulmonary bypass and lung resection surgery.

Percutaneous Cardiac Procedures

Transcatheter Aortic Valve Implantation (TAVR)

The first use of a percutaneously implanted aortic valve was described by Cribier et al. in 2002. Although the patient eventually succumbed to other medical conditions, the implanted aortic valve performed well, maintaining a mean gradient of 16 mm Hg and measured valve area of 1.5 cm² at 9 weeks post procedure [4]. This publication and the subsequent clinical adoption of transcatheter aortic valve technology fundamentally changed the treatment of valvular aortic stenosis (AS) in the geriatric population. The first randomized controlled trial, PARTNER, evaluated the use of the balloon expandable Edwards SAPIEN heart valve system. Cohort B of the PARTNER trial randomized 358 elderly patients (average age 83.1 years) with severe AS deemed not eligible for surgical aortic valve replacement (SAVR) to TAVR or conventional medical therapy including balloon valvuloplasty. The primary end-point, all-cause mortality at 1 year, was significant lower in the TAVR group compared to the medical therapy group (30.7% vs. 50.7%; p < 0.0001 [5]. Cohort A of the PARTNER trial randomized 699 elderly patients (average age 83.6 years) deemed high risk to TAVR or SAVR. The primary end-point, all-cause mortality at 1 year, was not significantly different between the TAVR and SAVR groups (24.2% vs. 26.8% p = 0.44). These results demonstrated non-inferiority of TAVR in the high-risk patient population. Other results from the PARTNER trial revealed an increased risk of stroke and major vascular complications in patients randomized to TAVR compared to SAVR (5.1% vs. 2.4%; p = 0.07 and

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16.1% vs. 1.1%; p < 0.001) at 1 year, respectively [6]. Similar results have been reported with other TAVR devices. The ADVANCE trial evaluated the self-expanding Medtronic CoreValve System in high-risk surgical patients and demonstrated 12-month all-cause mortality of 17.9% (15.2–20.5%) and stroke incidence of 4.5% (2.9–6.1%) [7]. These initial clinical trials demonstrated the safety and effectiveness of TAVR for severe aortic stenosis in the nonoperable and high-risk geriatric population. Recently, TAVR outcomes in an intermediate-risk patient population have been published. In patients (n = 2032) randomized to TAVR or SAVR, the rates of all-cause mortality and disabling stroke were similar. The TAVR group had less acute kidney injury, severe bleeding, and new-onset atrial fibrillation. The SAVR group had less vascular complications and paravalvular regurgitation [8].

Since the publication of the initial trials, clinician experience has grown and transcatheter valve technology has evolved. Analysis of 26,414 TAVR procedures performed in 2014 and recorded in the STS/ACC TVT Registry by Holmes et al. demonstrated several important trends. Specifically, the vast majority (~80%) of TAVR procedures are now performed via transfemoral access with 66.8% performed percutaneously. Vascular complications and stroke rates were 4.2% and 2.2%, respectively. The most common cardiovascular complication was the need for a new pacemaker or ICD post procedure (11%) [9]. Analysis of the same registry by Arsalan et al. revealed 3773 TAVR procedures were performed on patients ≥ 90 years old from 2011 to 2014. Compared to patients <90 years old, nonagenarians had higher STS-PROM scores (10.9% vs. 8.1%; p < 0.001) and higher 30-day (8.8% vs. 5.9%; p < 0.001) and 1-year mortality rates (24.8% vs. 22.0%; p < 0.001). Thus the ratios of observed to expected rates of death were similar between the groups. There were no differences in stroke rates, aortic valve reintervention, and myocardial infarction between the two age groups [10]. The preference for using CT angiography over transesophageal echocardiography (TEE) to determine valve size, decline in major complications, and the expanded use of percutaneous access has had a significant impact on anesthesiologists. With the aim of decreasing procedure time, ICU and hospital length of stay, and periprocedural vasopressor use, many TAVR procedures have been performed under moderate sedation. Large randomized trials comparing general anesthesia (GA) to local anesthesia/moderate sedation (MAC) have yet to be conducted. A review of 13 nonrandomized studies encompassing 6718 TAVR procedures found no significant difference in short- or long-term mortality between GA and MAC groups [11]. Smaller studies have not shown a difference in hospital or ICU length of stay [12, 13]. Reported rates of conversion from MAC to GA are as high as 17% [14]. When deciding to use GA or MAC, both patient comorbidities and procedural risks should be taken into account as well as the experience and preference of the heart valve team.

Percutaneous Mitral Valve Repair

Currently, MitraClip is the only FDA-approved percutaneous mitral valve repair (MVR) device. Its use is restricted to patients with degenerative \geq 3+ mitral regurgitation (MR), NYHA class III or IV symptoms, and prohibitive surgical risk [15]. The MitraClip functions similarly to the surgical technique described by Alfieri. In a series of 82 patients with Barlows's disease, 79 were successfully treated by Alfieri using an edge-to-edge MVR [16]. The MitraClip is a V-shaped clip that when closed affixes opposing segments of the anterior and posterior leaflets together creating a doubleorifice mitral valve. The clip is positioned inside the mitral valve orifice by accessing the left atrium via transseptal puncture. The procedure is dependent on TEE for septal puncture location, guiding device placement, and evaluation of leaflet attachment and residual MR. Due to the requirement for TEE, the MitraClip procedure should be performed under general endotracheal anesthesia. Although the EVEREST II trial demonstrated inferior outcomes when compared to surgery, subgroup analysis of high-risk patients revealed an improvement in NYHA functional class and improved survival at 1 year compared to historic controls [17, 18]. These results appear durable, with another trial reporting a 3-year survival rate of 61.4% compared to 34.9% managed medically [19]. The role of MitraClip in treating functional MR is undetermined. Currently there are two ongoing trials randomizing patients with >3+ MR and heart failure to MitraClip or medical management.

Percutaneous Left Atrial Appendage Occlusion

In patients over 80 years of age, 30% of all strokes are attributed to embolic events secondary to atrial fibrillation (AF) [20]. Anticoagulation with an oral medication is recommended for patients with AF and a CHA₂DS₂-VASC score ≥ 2 [21]. The use of anticoagulant medication is associated with annual risk of major bleeding of ~3.0% [22]. In patients with non-valvular AF, thrombus in LAA is responsible for >90% of embolic events [23]. There is a subset of patients with AF who are at high risk for stroke but are unable to be anticoagulated due to the risk of major bleeding. It is this group of patients that theoretically would benefit from LAA occlusion to reduce the risk of stroke. Several percutaneous LAA occlusion devices have been developed and can be divided into two categories, epicardial and intracardiac. Epicardial devices use a snare to close the LAA ostium. While intracardiac devices are delivered via a transseptal approach and use a self-expanding apparatus to occlude the ostium [24]. To date only the intracardiac WATCHMAN device has been evaluated by randomized controlled trials. The PROTECT AF trial demonstrated non-inferiority for prevention of ischemic or hemorrhagic stroke, cardiovascular or unexplained death, and systemic embolization of the device [25]. However concerns over device safety necessitated a second randomized trial, PREVAIL. The PREVAIL trial demonstrated an acceptable risk profile of the WATCHMAN device [26]. The WATCHMAN device is approved for patients with AF and at high risk of bleeding complications due to warfarin. TEE is vital for guiding placement of LAA occlusion devices and evaluating for incomplete LAA occlusion.

Conventional Heart Surgery

While procedures percutaneous have changed the management of some cardiac diseases in elderly patients, the standard of care for many cardiac lesions mandates conventional cardiac surgery such as coronary artery bypass grafts (CABG) and open valve replacement. Analysis of STS Cardiac Surgical Database consistently reveals increasing age as risk factor for perioperative morbidity and mortality. For isolated CABG surgery, patients \geq 75 years of age compared to those 65-74 years of age are at increased risk of mortality (4.7% vs. 2.4%), cerebral vascular accident (2.3% vs. 1.6%), renal failure (6.4% vs. 3.9%), prolonged ventilation (13.9% vs. 10%), reoperation (7.5% vs. 5.5), and prolonged length of stay (9.6% vs. 5.9%) [27]. This trend holds true for isolated valve procedures and combined valve-CABG procedures [28, 29]. Anesthesiologists and surgeons are faced with caring for older and sicker patients in cardiac operating room. As discussed in this book (see Chaps. 1, 4, and 5), elderly patients present with multiple organ system disease resulting in less physiologic reserve than their younger counterparts. They are more likely to have hypertension, diabetes mellitus, and cerebral and peripheral vascular disease. This section will focus on evidence-based strategies to minimize perioperative complications in the elderly population.

Cardiovascular

Atrial fibrillation (AF) is a morbid event occurring in up to 30% of elderly patients after cardiac surgery. Evidence supports the routine use of beta-blockers and statins to prevent postoperative AF [30, 31]. Additionally, their peripheral vascular system is more calcified and less distensible than younger patients. This increases their risk of aortic dissection and

embolization with cannulation and initiation of cardiopulmonary bypass (CPB). Severe aortic disease or lower extremity vascular disease may increase the risk associated with intraaortic balloon pump. Furthermore, poor coronary vasculature may predispose patients to incomplete revascularization and further ischemia after CPB. Ferguson et al. demonstrated that the internal mammary artery was underutilized in elderly patients (77% for elderly versus 93% for younger). Those elderly patients who received an internal mammary artery bypass had a lower operative and postoperative mortality, even after controlling for other causative factors [32].

Central Nervous System/Neurologic

Neurologic injury remains one of the largest sources of morbidity and mortality after cardiac surgery. Neurologic injury has been described in three forms: postoperative cognitive decline (POCD), delirium, and stroke. These topics are addressed in depth in other chapters of this text (see Chap. 30); however, their importance in cardiac surgery necessitates a review of pertinent information here. Suggested mechanisms of cerebral injury include global hypoperfusion, focal occlusion of the cerebral vasculature, or thermal injury on rewarming. It seems that, despite reductions in cerebral blood flow during CPB in the elderly, there is a concomitant reduction in cerebral metabolic rate of oxygen consumption keeping the difference in arterial-venous oxygen content normal [33]. POCD is simply defined as deterioration in one or more areas of cognitive function. Roach et al. studied adverse cerebral outcomes after CABG surgery in 2108 patients. Type I injuries were defined as death attributable to stroke or hypoxic encephalopathy, nonfatal stroke, transient ischemic attack, or stupor or coma at the time of discharge. Type II injuries were defined as new deterioration in intellectual function, confusion, agitation, disorientation, memory deficit, or seizure without evidence of focal injury. The predominant predictor of both type I and II injury was age: 6.1% of patients who were older than 70 experienced a type I injury, and 5.8% experienced a type II compared with 1.9% and 1.8%, respectively, for those patients younger than 70 years of age [34]. Newman et al. reported the incidence of cognitive dysfunction after CABG at 53% at discharge, 36% at 6 weeks, 24% at 6 months, and 42% at 5 years [35]. The authors concluded that cardiac surgery with cardiopulmonary bypass (CPB) contributed to cognitive decline. Subsequent studies including controls that did not undergo cardiac surgery or CPB failed to show an association between either and cognitive decline [36, 37] (Fig. 23.1).

Embolic phenomena have been blamed as the most likely culprit in central nervous system damage in the elderly. Using diffusion-weighted MRI, new ischemic events have been

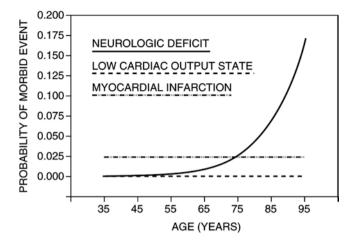


Fig. 23.1 Probability of incurring a morbid event during the perioperative cardiac surgical period and its association with age. Neurologic deficits increase dramatically beginning at age 65, whereas low cardiac output state and myocardial infarction remain relatively stable (Reprinted with permission from [76]. With permission from Elsevier)

detected in up to 43% of post-cardiac surgical patients [38]. Linking MRI findings to POCD has proven challenging, there are conflicting reports of the association between ischemic lesions found on MRI and POCD [38, 39]. Nonetheless, efforts to reduce embolic events have shown improved cerebral outcomes. Detecting ascending aortic atheroma either by surgical palpation or epiaortic ultrasound has been shown to reduce embolic events and improve post-bypass cerebral outcomes [40, 41]. pH management by either alpha-stat or pH-stat and the association with cerebral outcomes has been vigorously studied. pH-stat, through increased CO₂, is associated with increased cerebral blood flow, but alpha-stat preserves cerebral autoregulation [42]. Because some neurologic injuries are secondary to embolic phenomena, more cerebral blood flow may be detrimental. One small (n = 86) prospective, randomized trial failed to show a difference between alpha-stat and pH-stat management in adult patients [43]. Based on preserving autoregulation, alpha-stat blood gas management would be recommended in the elderly. No intervention, however, has been studied in a population exclusive to those aged more than 65.

Relative hypoperfusion and hypoxemia has also been implicated in POCD. Tissue injury due to inadequate perfusion/ oxygen delivery may not manifest itself until well after CPB has ended. A promising area of research revolves around the use of cerebral oximetry not only for monitoring cerebral perfusion but also as a surrogate for perfusion of other organs. Decreases in regional cerebral oxygen saturation (rSO₂) have been associated with not only neurologic dysfunction (postoperative cognitive decline and delirium) but also major organ dysfunction and ICU and hospital length of stay [44–48]. While ample literature supports the association between intraoperative decreases in rSO₂, there is inadequate evidence that reversing these decreases

positively impact outcomes. Proposed protocols to reverse decreases in rSO_2 include increasing mean arterial pressure, normalizing SaO_2 and $PaCO_2$, treating anemia, and ruling out causes of increased cerebral oxygen consumption [49]. However, randomized trials powered to validate these algorithms have yet to be conducted.

Renal

The prevalence of renal failure after cardiac operation varies from 2% to 15%, depending on the procedure and degree of preoperative renal dysfunction [23]. If it occurs, the mortality rate may be as high as 80%. Because the elderly have lower baseline glomerular filtration rate, are likely to have hypertension and an altered renal autoregulatory curve, and are more likely to have diabetes mellitus, they are at a higher risk of renal failure than their younger counterparts. The use of preoperative diuretics for those with depressed ejection fraction and radiopaque dyes often worsens preoperative renal function. Unfortunately, there has been no large investigation regarding the prevention of renal dysfunction in the elderly patient undergoing CPB. The most important principle might be that recovery of renal function after bypass is directly related to the recovery of cardiac function.

Cardiopulmonary Bypass Management

CPB provides many alterations to the normal physiologic milieu. The optimal mean arterial pressure, perfusion flow, mode of perfusion (pulsatile versus nonpulsatile), pH and CO₂ management, temperature, and hematocrit have not been established for the elderly patient undergoing CPB. As previously mentioned, aortic cannula sites should be carefully chosen with the assistance of epiaortic ultrasound scanning to minimize embolized atheromatous debris. Perfusion flows range from 1.2 to 2.4 L/min/m², with perfusion pressures varying from 30 to 80 mm Hg. No difference in outcomes has been demonstrated for flows within this range or for pulsatile versus nonpulsatile flows. Temperature management for CPB should be dictated by institutional preference. Grigore et al. demonstrated no difference in postoperative cognitive function between patients who underwent hypothermic CPB (30°C) versus normothermic CPB (35°C) [50].

The optimum hematocrit while on CPB and immediately after for the elderly patient has not been determined. The absolute safe level will depend on many variables, including adequacy of myocardial revascularization, myocardial function, and, possibly, the age of the patient. The adequacy of tissue oxygenation and perfusion as determined by the mixed venous oxygen saturation determines transfusion in most centers. Blood-sparing strategies such as cell salvage techniques and retrograde autologous prime should routinely be used to conserve hematocrit and decrease the need for transfusion. The elderly might be a group for whom a higher hematocrit is beneficial. Mathew et al. demonstrated that profound hemodilution (hematocrit 15–18%) during CPB was associated with a decline in cognition 6 weeks postoperatively [51]. However, transfusion delivers new risks, most of which are related to the inflammatory response. Increased sternal wound infection, longer intensive care unit stays, and increased renal failure associated with blood transfusion should be weighed against evidence of poor tissue oxygen delivery.

Anesthetic Management

The ideal anesthetic for cardiac surgery in the elderly provides hemodynamic stability, amnesia, analgesia, organ protection, and the ability for rapid emergence postoperatively. Although numerous studies have attempted to demonstrate the superiority of specific agents with mixed results, there are several key trends in the literature that are shaping current practice. The use of benzodiazepines for sedation should be minimized and/or avoided due to their association with postoperative delirium [52]. Dexmedetomidine should be used for postoperative sedation. When initiated in the post-CPB period, a dexmedetomidine infusion is associated with decreased delirium, postoperative atrial fibrillation, time to extubation, and mortality [53-56]. However, due to its lack of amnestic properties, volatile anesthesia should be continued until the procedure is complete and neuromuscular blockade has been reversed.

With admittedly little scientific evidence to support some of their assertions, some authors empirically recommend the following: [1] alpha-stat blood gas management, [2] higher perfusion pressures throughout the perioperative period, [3] higher mean arterial pressures while on CPB, [4] higher hematocrit before termination of CPB (>24%), [5] selection of the aortic cannulation site with the assistance of epiaortic ultrasound scanning, [6] the use of cerebral oximetry in high-risk patients, [7] avoidance of benzodiazepines, and [8] the use of dexmedetomidine for postoperative sedation.

Endovascular Abdominal Aortic Aneurysm Repair

The incidence of abdominal aortic aneurysm (AAA) in the United States is approximately 55,000 per year with an average age at presentation of 72.3 years [57]. An analysis of 25,576 patients from the NSQIP database revealed an annual increase in 30-day mortality of 6% for open repair (OAR)

and 4% for endovascular repair (EVAR) for each year increase in patient age [58]. In the randomized EVAR 1 trial, in which the average age at intervention was 74 years, EVAR was associated with less 30-day mortality than OAR (1.8% vs 4.3%) [59]. In patients >80 years old, the early postoperative survival benefit of EVAR vs. OAR is even more pronounced (30-day mortality 2.3% vs. 8.6%) [60]. Due to the early survival benefit, EVAR has become the treatment of choice for AAA in the elderly population [61]. Complex -juxtarenal aneurysms involving mesenteric and renal vessels are now repaired using endografts. A pooled analysis of 1725 patients undergoing juxtarenal AAA repair using open, fenestrated endovascular, or chimney endovascular technique showed no difference in 30-day mortality, although, open repair was associated with increased renal complications and chimney repair with increased stroke rate [62]. Due to the expanded use of endovascular repair techniques, regional and local anesthesia are now options for AAA repair. While randomized controlled trials do not exist comparing regional (RA), local (LA), and general anesthesia (GA) for EVAR, several retrospective studies have investigated this topic. An analysis of 1261 patients in the ENGAGE registry revealed no difference in perioperative morbidity and mortality among the three groups. Patients who received RA and LA had shorter procedure times and decreased ICU admission and hospital length of stay. Although patients with higher ASA classification were more likely to receive GA possibly confounding these results [63]. The choice of anesthetic technique should be based on patient comorbidities, the complexity and duration of the procedure, and the experience of the surgical and anesthesia teams.

Lung Resection Surgery

Due to the curative intent of surgical resection for lung cancer, age alone should not be a factor in evaluating a patient's surgical candidacy. Elderly patients should undergo risk stratification based on pulmonary function testing, cardiopulmonary reserve, and other comorbidities [64]. Recent analysis of the NSOIP database identified increasing age as a risk factor for increased complications and mortality following lobectomy [65]. There are evidence-based perioperative management strategies to reduce the rate of postoperative pulmonary complications. One lung ventilation (OLV) and surgical manipulation increase the risk of acute lung injury (ALI) during lung resection surgery. Protective lung ventilation strategies can reduce the rate of ALI during lung resection surgery. The use of low tidal volumes (<8 ml/kg), limiting peak inspiratory pressure (<35 cm H₂O), using PEEP (4-10 cm H₂O), and frequent recruitment maneuvers resulted in decreased incidence of ALI, atelectasis, and ICU admissions [66]. Additionally the use of volatile anesthetics

versus propofol during single-lung ventilation may be protective against ALI. A meta-analysis of eight randomized controlled trials encompassing 365 patients undergoing OLV demonstrated that volatile anesthetics were associated with decreased pulmonary complications and shorter hospital length of stay [67]. Intraoperative fluid management also plays a role in preventing postoperative pulmonary complications. The link between excessive fluid administration and pulmonary complications was first described by Zeldin et al. in 10 patients following pneumonectomy [68]. Similar results have described following less extensive resections [69, 70]. Current best practice dictates limiting fluid administration to <2 L in the intraoperative and early postoperative periods [71]. Pain control is another area in which anesthesiologists can positively impact outcomes following lung resection surgery. Multiple studies have demonstrated the benefits of regional anesthesia in preventing postoperative pulmonary complications following thoracotomy [72, 73]. Additionally, several studies have demonstrated paravertebral blockade can decrease postoperative pain scores following video-assisted thoracic surgery [74, 75]. Regional analgesia, thoracic epidural or paravertebral block, should be offered to all patients without contraindications undergoing thoracic surgery.

Important Gaps in Our Knowledge

Although advancements have been made in caring for elderly patients with cardiothoracic and vascular disease, there are still important questions to be answered. One high interest area of active research is the utility of the percutaneous procedures discussed above in different patient populations. There is an ongoing research evaluating TAVR in low-risk patients. MitraClip is being evaluated for the treatment of functional MR. Randomized controlled trials are being conducted evaluating cerebral oximetry treatment algorithms and their subsequent impact on cardiac surgical outcomes.

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Perioperative Management of Pacemakers and Internal Cardioverter-Defibrillators

24

G. Alec Rooke

Introduction

Permanent pacemakers and internal cardioverter-defibrillators (ICDs) comprise the vast majority of cardiac implantable electrical devices (CIEDs) and are especially common in older patients. Device function can be compromised by exposure to electromagnetic interference (EMI). In the operating room, monopolar electrocautery is the most common offender. It may suppress demand pacing, and in ICDs may also cause the device to deliver undesired overdrive pacing or shocks.

As is common in medicine, each field has terminology that sets it apart from other specialties, and this can be an issue when working with CIEDs. Table 24.1 lists the abbreviations used throughout the chapter, including the tables and figures. It is not clear whether such terminology is an impediment to understanding, but experience has shown that most anesthesiologists treat pacemakers and ICDs as "black boxes." Providers likely have rudimentary knowledge of how devices work, but not always enough to understand what to expect from the devices or to be able to correctly interpret what is observed on the electrocardiogram (EKG) monitor. However, with basic training, providers should be able to assess whether the device is working normally or not, to examine the degree of pacing by the device, and to make intelligent decisions about the management of these devices at surgery.

The ability of anesthesiologists to contribute to device management is important because current management is typically haphazard at best, in large part because no single group has taken ownership of this important task. The field technicians (company representatives) are knowledgeable, but their availability is often limited. Cardiologists may have little interest and limited availability to come to an operating room to evaluate and program devices, and unfortunately they may add to the confusion by suggesting the usual "just place a magnet" without further explanation or discussion. Anesthesiologists are better positioned to take on this task, given their emerging perioperative role as well as their presence in the operating room, but few anesthesiologists have been trained to evaluate and program devices.

Failure of ownership of CIED management can lead to suboptimal patient care. Not infrequently the anesthesiologist is left with a single therapeutic option: placing a magnet. In pacemakers, magnet use can prevent bradycardia, but it can also lead to an unwanted tachycardia from a competing rhythm (if a magnet is used inappropriately and both the patient and the device are generating rhythms), or the pacing rate associated with the magnet is high. For example, in St. Jude and Boston Scientific pacemakers, the magnet rate is typically 100. In ICDs, although a magnet is *supposed* to turn off detection of tachyarrhythmias and in so doing avoid accidental shocks, this particular magnet feature can be disabled in some devices. This is not common, but when it happens, it can lead to a false sense of security and potentially result in the patient receiving unnecessary defibrillation [1].

The primary goal of this chapter is to provide anesthesiologists with the knowledge necessary in order to take an active role in device (and patient) evaluation and management.

Basic Pacemaker Function

With respect to the pacing function of CIEDs, the three-letter code provides some basic information. In brief, the first letter indicates the chamber(s) where pacing can occur, and the second letter represents the chamber(s) where sensing occurs. For these first two letters, the options are atrium only (A), ventricle only (V), or both atrium and ventricle (D for dual). The third letter indicates the response of the device to

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a sensed beat. The options are inhibit (I), as in a sensed beat in a chamber will prevent the next scheduled paced beat; trigger (T), when a sensed beat will lead to a required depolarization of another chamber; and dual (D) for either I or T depending on the circumstances. To really understand pacing, it is easiest to start simple and progress to the more complex.

Single Chamber Pacing

The simplest pacemaker is a single chamber, asynchronous device. The device is usually implanted subcutaneously in

Table 24.1 Abbreviations used in this chapter

Term	Abbreviation
Cardiovascular implantable electronic device	CIED
Internal cardioverter defibrillator	ICD
Cardiac resynchronization therapy	CRT
Beats per minute	bpm
Electrocardiogram	EKG
Milliseconds	msec
Sinoatrial (node)	SA
Atrioventricular (node)	AV
Atrium or atrial	А
Ventricle or ventricular	V
Atrioventricular	AV
Inhibit	Ι
Trigger	Т
Dual (both atrium and ventricle, or both inhibit or trigger, depending on the position in the three letter code)	D
Atrial beat, spontaneous or paced	AS, AP
Ventricular beat, spontaneous or paced	VS, VP
Electromagnetic interference	EMI
Post-ventricular atrial refractory period	PVARP

Fig. 24.1 The end of a pacemaker lead. The tip electrode of the lead (here, a corkscrew design) ends up being buried in the cardiac muscle. The proximal electrode is the metal ring (*black*). The signal from the heart tissue that is observed by the device is the voltage difference between the two electrodes

the pectoral area, and the lead traverses the subclavian vein with the tip embedded in the chamber wall. Modern day leads are almost always bipolar, which means the signal picked up or delivered by the lead is the difference in voltage between the tip lead and the ring electrode 1-2 cm proximal (Fig. 24.1). Asynchronous pacing is designated as either AOO or VOO, for atrial and ventricular asynchronous pacing, respectively. Such a setting is not used in the long term, since most patients have some degree of intrinsic rhythm, even if it is just an occasional ectopic beat. The pacemaker must detect such events and delay the next pacing impulse accordingly. Inhibition of pacing when the patient is self-generating an adequate rhythm is called "demand" pacing. For a ventricular pacemaker, demand mode would be designated as VVI (demand pacing, where the ventricle is paced, sensing occurs in the ventricle, a sensed event inhibits pacing). There are only a few controls, specifically base rate, pulse amplitude, and pulse duration. The base rate, also referred to as the lower rate limit, will dictate the soonest a paced beat would occur. For example, a base rate of 60 beats per minute (bpm) means a paced beat would occur no later than 1000 msec after the last beat, regardless of whether that last beat was sensed or paced. If the device senses a spontaneous depolarization in the chamber before the timer times out, the timer resets and once again must wait the full interval before an impulse could be delivered. In this example, so long as a sensed beat always occurs before the 1000 msec ran out, there would never be a paced beat. Atrial-only pacing is typically used when there is sinoatrial (SA) node dysfunction, but the conduction system functions normally. Ventricular-only pacing may be found in ICDs when the patient normally has no need for pacing or if there is no point in monitoring or pacing the atrium, for example, if the patient is in chronic atrial fibrillation.



Dual-Chamber (Atrium and Ventricle) Pacing

Whenever possible, it is beneficial to maintain synchrony between the atria and the ventricles. The atrial "kick" contributes to ventricular filling, and if the SA node is functioning normally, it would be best to let its activity control the heart rate. This goal is achieved with leads in both the atrium and ventricle. The pacing mode is usually DDD, which requires some explanation. The device first "looks" for an atrial depolarization. If the device is counting down the time to a required ventricular depolarization, then the device expects to see an atrial depolarization no later than the AV delay time before the ventricular depolarization is expected. For example, with a base rate of 60, the device expects to see a ventricular depolarization by no later than 1000 ms after the last ventricular depolarization. If the AV delay is programmed at 150 ms, then the device expects to see a spontaneous atrial depolarization by 850 ms after the last ventricular depolarization. If no atrial depolarization is observed, then an electrical impulse is delivered to the atrium. Regardless of whether the atrium depolarized by itself or by a paced impulse, the device expects to see a ventricular depolarization by no later than end of the AV delay. If it does, the 1000 ms clock is reset and the whole process starts over. If no ventricular depolarization is seen, then an electrical impulse is delivered to the ventricle. Therefore, with a DDD device, there are four possible basic rhythms that could be observed (where A = atrium, V = ventricle, S = sensed, and P = paced; see also Fig. 24.2).

- AS-VS: The atrium depolarized on its own, and so did the ventricle (likely from the conduction system, e.g., normal sinus rhythm)
- AP-VS: The atrium was paced, but the ventricle depolarized on its own (likely from the conduction system, but a premature ventricular contraction would have the same effect)
- AS-VP: The atrium depolarized on its own, but the ventricle was depolarized by the device (normal AV conduction was too slow and exceeded the programmed AV delay time, or failed altogether)
- AP-VP: Both chambers were paced

The option of AS-VP is an example of "triggering," where a sensed beat (in the atrium) "triggers" a ventricular depolarization. AS-VP is also referred to as "tracking" because the pacing impulses to the ventricle follow, or track, the atrial activity. This pattern would be the norm in a patient with complete heart block but a normally functioning SA node. When this pattern is observed, practitioners can be confused because they may see the ventricle being paced at a rate much higher than the base rate. It is not device malfunction: the device is just trying to maintain AV synchrony. Tracking typically has an upper bound, a rate above which the atrial event will not lead to a paced ventricular beat. In an older, sedentary patient, that "upper tracking rate" might be as low as 120 but would be higher in a more active patient. The determination to pace the ventricle is made on a beat-to-beat basis. If the atrial rate exceeds the upper tracking rate, then the AV delay will be extended in order to pace the ventricle at the upper tracking rate for as long as possible. Eventually, though, an atrial beat will occur too early to permit a ventricular paced beat and the rhythm will mimic Mobitz type I block (pacemaker Wenckebach).

The Trouble with Triggering

Allowing a device to trigger a ventricular impulse after an atrial sense can lead to undesired tachycardias. Atrial fibrillation or flutter would cause very fast ventricular pacing if the device paced the ventricle after each atrial depolarization. Although the upper tracking rate described in the previous paragraph would limit how fast the ventricle was paced, a better strategy is to break the link between atrial activity and ventricular pacing. This goal is accomplished with a feature referred to as mode switching. If the device detects a very rapid atrial rate, then the device switches its pacing mode, typically to DDI. Note that the third letter indicates that a sensed beat can only inhibit pacing. There is no more "triggering." Of the four basic rhythms mentioned above, AS-VP is no longer an option. Assuming there is no intrinsic conduction to the ventricle, if the atrium is beating faster than the base rate, the ventricle will still be paced at the base rate (Fig. 24.3).

Another troubling event with the triggering feature is a phenomenon known as pacemaker-mediated tachycardia (PMT) or pacemaker-induced tachycardia (PIT). In the event a ventricular depolarization finds the conduction system in a non-refractory state, the depolarization could conduct in a retrograde fashion into the atrium. The ensuing atrial depolarization would be detected by the device, and in turn would lead to a ventricular pace after the AV delay (Fig. 24.4). By the time the ventricle depolarizes, the AV node/bundle of His would likely be non-refractory. The (paced) ventricular depolarization would once again conduct in a retrograde fashion to the atrium and the process would repeat. Given typical paced AV delay times, the time for the retrograde conduction and the time to detect the atrial depolarization, the entire cycle commonly takes about 0.5 s and so would result in a heart rate in the 120 bpm range. Prevention of PMT is primarily achieved by PVARP, a feature present in all dual-chamber devices. PVARP stands for post-ventricular atrial refractory period. During PVARP, the device will continue to monitor for atrial depolarization,

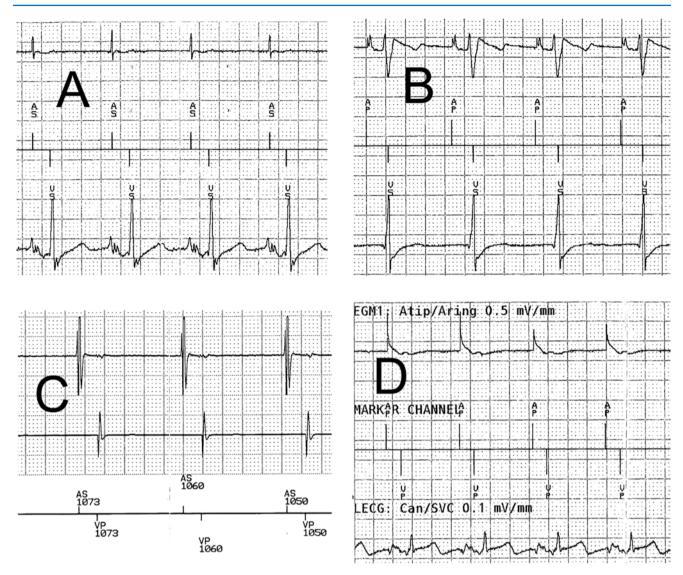


Fig. 24.2 Pacing options with DDD pacing. The four pacing options are illustrated. AS = sensed atrial depolarization, AP = paced atrial depolarization, VS = sensed ventricular depolarization, VP= paced ventricular depolarization. Panel **a** = AS-VS, which is a sinus rhythm at a rate higher than the base pacing rate. Panel **b** = AP-VS, where the atrium is paced but the patient's conduction system is intact and depolarizes the ventricle before the programmed AV delay time is exceeded. Panel **c** = AS-VP, where the patient's own atrial rate is faster than the base pacing rate, but the conduction to the ventricle is either absent or too slow to prevent a ventricular pacing impulse from being delivered.

This type of pacing is often referred to as tracking, because the ventricular pacing is tracking the spontaneous atrial rhythm. Panel $\mathbf{d} = AP$ -VP, where both chambers are being paced. All pictures are from strips generated by the interrogation box. All show channel markers that indicate whether the electrical events in the atrium and ventricle are sensed or paced. Atrial and/or ventricular electrograms show what the (bipolar) lead is actually observing. Also, in \mathbf{a} , \mathbf{b} , and \mathbf{d} there is a strip showing a signal that appears more similar to a surface EKG lead. These signals are generated by the voltage difference between an ICD coil and the device itself

but will not use an atrial depolarization to trigger a ventricular depolarization. A common programmed duration of PVARP is 250 msec. In the case shown in Fig. 24.4, the retrograde conduction was so slow that the tail end of the retrograde P wave fell just beyond the end of the PVARP, allowing for an atrial sense that could trigger a ventricular depolarization.

Rate-Response

When people exercise, the heart rate normally increases to enhance cardiac output. Patients with chronotropic insufficiency may have little or no increase in heart rate with exercise and therefore have significant exertional limitations. The rate-response feature of CIEDs is designed to sense patient

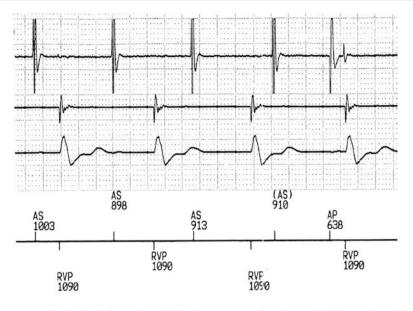


Fig. 24.3 DDI pacing. The top trace is the signal from the atrial lead, the next trace is the signal from the ventricular lead, and the third trace is the signal from the lead created by the ICD coil to the device. The bottom trace shows the markers indicating what events are paced or sensed. In this example, the patient had complete AV block and was temporarily converted from DDD at 60 bpm base rate to DDI at 55 bpm. The atrial rate is approximately 66 bpm, but because DDI mode eliminates tracking, the ventricular pacing is no longer linked to the atrial

events. In fact the ventricle is paced at the base rate of 55 bpm. The AV dissociation is apparent by the progressively longer period between an AS and a VP. Also illustrated is what happens when an AS happens to fall in a period after a ventricular event where the AS is noted but does not "count" as an event (labeled as "(AS)"). Because of this, an AP occurs before the next VP because in the apparent absence of intrinsic atrial activity, AV synchrony would occur if both chambers are paced

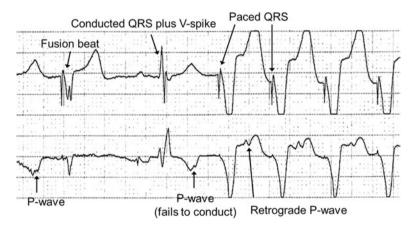


Fig. 24.4 Pacemaker mediated tachycardia (PMT). Two surface EKG leads are shown. The first two QRS complexes constitute fusion and pseudofusion beats, respectively (the latter is where the conducted ventricular depolarization fails to reach the RV lead in time to prevent the ventricular pacing spike). After the pseudofusion beat, there is a PAC that fails to conduct to the ventricles. Because the pacemaker is programmed to DDD, the PAC causes the pacemaker to pace the ventricle (see AS-VP example in Fig. 24.2). The long AV delay is deliberate in order to permit intrinsic conduction to occur as much as possible.

activity and ramp up the heart rate accordingly. There are several methods that can be used to sense when the patient is active. The most common method, the accelerometer, is found in almost all devices. A piezoelectric crystal in the Because the PAC failed to conduct, the conduction system is no longer refractory. The ventricular depolarization can now conduct in a retrograde fashion back to the atrium (retrograde P wave). The retrograde P wave extended just beyond the 240 msec PVARP and therefore the P wave "triggered" another ventricular depolarization. The process would repeat itself until something would interrupt the cycle. For example, placing a magnet on the pacemaker would change the mode to DOO and would break the cycle. The problem, of course, is that the next PAC would simply reinitiate the PMT

device detects movement in the form of acceleration and will increase the pacing rate to a value in proportion to the magnitude of the acceleration, but not above a programmed upper limit. As with all demand pacing, if the patient's intrinsic rate is higher than what is dictated by the rate-response, then pacing will be inhibited.

Another method for varying pacing rate with activity involves bioimpedance. The resistance (impedance) between a lead tip and the device itself will change with respiration because of the change in lung volume. This measurement provides respiratory rate, and the magnitude of the impedance change is used to reflect tidal volume, hence the method being labeled as a minute ventilation sensor. At present, only pacemakers made by Boston Scientific/Guidant have this specific feature. An alternative bioimpedance method is present in some Biotronik devices. Changes in sympathetic nervous system stimulation of the cardiac muscle cause small changes in lead impedance. These changes are used to increase the minimum pacing rate of the device, with programmable gain and upper rate limits just as with the other rate-response methods.

Rate-response is not used on every patient, but when it is, the three-letter code becomes a four-letter code with an "R" at the end. For example, VVIR would indicate ventricular demand pacing that includes a rate-response feature.

Cardiac Resynchronization Therapy (CRT)

The goal of CRT is to provide for a more synchronized contraction of the left ventricle. In severe left ventricular enlargement and muscle hypertrophy, the left bundle often fails. Left ventricular depolarization must now initiate in the right ventricle, reaching the septum first and then spreading around the left ventricle making the lateral (free) wall of the left ventricle the last to be depolarized. Septal contraction may cause the free wall to bulge out because the free wall is still relaxed. By the time the free wall is at its peak of contraction, the septum is relaxing so the septum bulges into the right ventricle. In short, each wall "ejects" partly into the other wall, and stroke volume is compromised. Placing a pacing lead on the free wall permits most of the left ventricle to begin contraction at the same time. In CRT, it is disadvantageous to permit the native conduction from the atrium to the right ventricle because it may lead to a pattern of depolarization different from one initiated by the right and left ventricular pacing leads. For this reason, the PR interval is deliberately set to a short duration so that the pacing spikes are delivered before any intrinsic activation occurs. The EKG or rhythm strip will reveal nothing but ventricular paced beats, but the observer should not automatically assume the patient is pacing-dependent. There may well be conduction to the right ventricle if the pacing is suppressed, but there is no way to tell just from looking at the EKG.

Basic ICD Function

The first important aspect of ICD function is that all ICDs possess essentially every feature that pacemakers have. Whether or not those pacemaker functions are utilized is another matter altogether. If a patient needs an ICD but has a normally functioning SA node and conduction system, the ICD is likely to be programmed to a nominal setting of VVI at a backup rate of 40. Nevertheless, the device can provide all the pacemaker functions already described if needed by the patient.

What distinguishes ICDs from pacemakers is their ability to treat ventricular tachyarrhythmias, specifically ventricular tachycardia and ventricular fibrillation. ICDs do not detect these arrhythmias as a clinician would with a rhythm strip; in fact, the overall morphology of ventricular depolarization is not "visible" to the device. Bipolar leads can only "see" the depolarization of a small portion of myocardium as the wave sweeps by the lead tip and the limited tissue view provides no data on overall myocardial electrical activity. For these reasons, the basic determination of ventricular tachycardia or fibrillation is made by heart rate. If the device sees a rate above a certain value, it considers the rhythm to be ventricular tachycardia. If the device sees a rate above a different (higher) value, it considers the rhythm to be ventricular fibrillation. Should there also be an atrial lead, then other checks for ventricular arrhythmia can be used for confirmation, such as a ventricular rate higher than the atrial rate.

Therapies are determined by what the device considers the rhythm to be. In the case of ventricular tachycardia, the device can be programmed to initially respond with several attempts of overdrive pacing. If unsuccessful, a series of synchronized cardioversions will likely be attempted. If the rhythm meets the criteria for ventricular fibrillation, overdrive pacing may be attempted while the device is charging for a defibrillation, but the primary treatment will be defibrillation. All therapies are limited to a maximum number of attempts. The energy associated with a shock is much less than with external shocks, on the order of 25–40 joules. As with modern external devices, the internal shock is bipolar. The current flow is well contained within the body, so there is no risk to someone touching the patient at the time of the shock.

Effect of EMI on CIEDs

To manage CIEDs appropriately during surgery, and properly interpret the rhythms observed during a procedure, it is important to understand how EMI can disrupt CIED function [2]. Monopolar electrocautery is the most common source of EMI, but at least a theoretical possibility of interference exists from other sources such as radiofrequency ablation. Less frequently encountered sources of interference include TENS units, spinal cord stimulators, and breast tissue expanders that contain magnets (and may act like a magnet over the device). Bipolar electrocautery does not interfere with CIED function. This chapter focuses on the effects of monopolar electrocautery.

Whether or not EMI is "seen" by the device depends on many factors, but the key issue is whether the amplitude of the EMI signal at the lead exceeds the minimum voltage used to define when a cardiac depolarization has occurred. The voltage detected at the lead will be influenced by the intensity and proximity of the EMI to the leads and the difference in distance between the electrodes and the source of the EMI. If the tip and ring electrodes of the lead are equidistant from the source, both electrodes see the same signal and the difference is zero (no detection of EMI). If one electrode is further from the EMI source, then the difference in amplitude between the electrodes may exceed the minimum voltage that defines a sensed depolarization. With bipolar sensing, the leads are only a centimeter apart and therefore EMI is less likely to generate a voltage difference between those two leads, especially as the source of the monopolar cautery gets further away from the leads. In fact, monopolar cautery applied below the umbilicus should not be detected by bipolar leads.

In contrast, monopolar sensing measures the voltage difference between the tip of the lead in the heart and the device, which usually means that monopolar cautery creates significantly different voltages at the two locations. This is why monopolar sensing is far more likely to detect EMI than bipolar sensing.

With bipolar cautery, current flow is between two electrodes in close proximity. The signals generated by each electrode are opposite in polarity. Consequently, they tend to cancel each other out when viewed from even just a little distance away. Bipolar cautery should not be detected by CIEDs, and therefore bipolar cautery will not inhibit demand pacing or trigger tachyarrhythmia therapies.

If EMI is sensed by a device, it is typically interpreted as a high rate of intrinsic activity of that heart chamber. As might be expected, detection of a high heart rate will suppress demand pacing and, in the case of an ICD, potentially cause the delivery of tachyarrhythmia therapy, including defibrillation. The consequence of suppressed pacing depends on what the heart will do on its own. The result could be a minimal slowing of the heart rate if the intrinsic rate is just below the minimum pacing rate, or it could be asystole if the heart has no intrinsic rhythm. Undesired shocks from an ICD appear to be rare in the operating room, but they can and do occur (Fig. 24.5) [1]. In order to prevent suppression of demand pacing by EMI, many CIEDs have a feature called "noise reversion." As mentioned, EMI often is interpreted as a very high heart rate. If the device recognizes that these "depolarizations" are occurring faster than can be explained by any physiological process, then the CIED assumes that what is being observed must be noise. Since the device can no longer determine if the heart is actually beating or not, the device starts pacing the heart as a safety measure. This could result in paced and intrinsic rhythms that compete with each other (Fig. 24.6)—but it is better to have competing rhythms than no rhythm at all. If noise reversion is not present, or if the EMI fails to trigger noise reversion, then detected EMI will suppress demand pacing (Fig. 24.7).

Monopolar cautery can cause other problems in the operating room. As mentioned previously, if EMI is interpreted as a high rate in the atrium but was not "seen" by the ventricle. the device would likely mode switch to DDI or DDIR. The change in mode could lead to an increase or a decrease in the heart rate. A decrease in ventricular rate could occur if, prior to the mode switch, ventricular tracking was present. That is to say, the patient had an atrial rate higher than the base pacing rate and the patient has heart block, so the ventricle was being paced based on the atrial rate (tracking). With the mode switch, tracking is eliminated, so the ventricle would likely now be paced at the base rate without AV synchrony. An increase in pacing rate could occur if the mode switch response included the rate-response feature (e.g., DDIR or VDIR) even though the base mode was DDD. If the rateresponse sensor happened to be activated at time of the mode switch, then the ventricle could get paced at a rate higher than the expected base rate, assuming that the ventricular pacing is not inhibited by the EMI. It is important for the anesthesiologist not to be alarmed by such transient rate or ORS width changes unless the rate is very low or very high.

A serious consequence of monopolar cautery can occur when the battery is wearing out and the cautery is applied relatively close to the device or leads: the EMI can cause a transient decrease in the battery voltage. If the voltage drops below a minimum value, the device shuts down. When the battery recovers, the device boots up but the programmable settings are the factory-set default values for the device. This phenomenon is known as *power-on reset*. Typically, the default settings are very basic, and the pacing parameters may not be adequate for the patient. Even worse, if an ICD had tachyarrhythmia detection programmed off for surgery, a power-on reset would restore tachyarrhythmia detections, and further EMI could result in defibrillation attempts by the ICD.

Decades ago, devices could be arbitrarily reprogrammed by high-intensity EMI. Although this is no longer an issue,

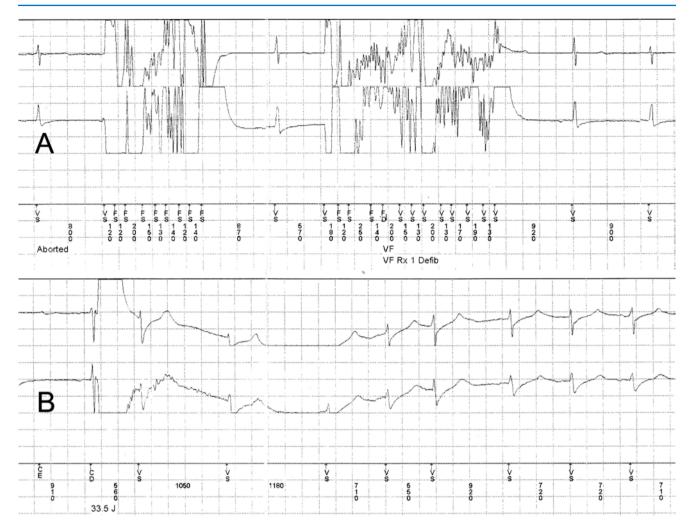


Fig. 24.5 EMI-induced ICD shock. Two portions of a download from an ICD are shown. Each portion shows the RV lead signal, the ICD coil to device can signal and the channel markers. The ICD is in the process of being removed and to do so, short bursts of monopolar cautery were used to cut through scar tissue around the device. Panel A illustrates the noise generated by cautery. Note the device detects "QRS"s at a very

fast rate (indicated as VS, FS, and FD on the channel markers). After a series such bursts, the device delivered a shock (see 33.5 J at the bottom of Panel B) even though just before the shock a normal rhythm existed. Brief bradycardia is noted after the shock, and several beats are required before the heart returned to a more normal rhythm. Download provided by Jordan Prutkin

should monopolar cautery be applied directly to the device, the electronics will be destroyed and the device will cease function.

Although some of the undesirable effects of EMI can be prevented by placing a ring magnet over the device, programming the device for surgery has several advantages. First of all, concerns over the magnet slipping and losing contact with the device are eliminated. In addition, other features that can be annoying in the operating room can often be dealt with, such as noise reversion or the rateresponse feature [3]. When programming for surgery is not available, magnet use is the only other option. Placing a magnet is recommended somewhat indiscriminately by cardiologists, however, there are distinct limitations to its use. Some pacemakers can be programmed to not respond to a magnet, including those from Boston Scientific, St. Jude and Biotronik. The magnet response in an individual pacemaker can be checked preoperatively by placing the magnet on the device for 30 s or so while monitoring the patient. If asynchronous pacing is continuously observed on the monitor at the expected pacing rate, then magnet use during surgery should be able to maintain an adequate rhythm. This maneuver also provides valuable information on the battery status as will be described later. With ICDs, magnet placement is expected to disable tachyarrhythmia detections in an ICD, but Boston Scientific and St. Jude ICDs may be programmed to ignore the magnet. Confirmation of disabled tachyarrhythmia detection is provided when tones are emitted by the device with magnet placement, but sometimes there is no way to determine if the magnet is being sensed by the device (Table 24.2). In all cases, it is imperative to know how the device will respond to the magnet; if the expected response is not observed, then the device should be interrogated.

Perioperative Management of CIEDs

Comprehensive management of CIEDs is a multistep process. Following proper identification of the device, the overall strategy entails ensuring that the device and leads are working normally and devising a plan for the operating



Fig. 24.6 Noise reversion. A photo of the monitor in the operating room is shown with two ECG leads and an arterial tracing. In this example, the pacemaker did not permit disabling of noise reversion. The cardiac rhythm just before the application of monopolar cautery was atrial pacing with normal conduction to the ventricles (AP-VS). The appearance of cautery is indicated by the frequent and erratic factitious "pacing spikes" on the screen as well as some noise in the signal. Electromagnetic interference (EMI) suppresses demand pacing, but when noise reversion is present the device can determine that the EMI is unphysiologic and truly "noise." The presence of "noise" changes the pacing mode to DOO. The presence of ventricular pacing is demonstrated by wide QRS complexes. When the cautery ceases, the rhythm returns to AP-VS

room that entails programming the device for surgery, using a magnet, or proceeding to surgery with no specific intervention other than watchful monitoring with a magnet at the ready.

Evaluation of CIEDs Prior to Surgery

Basic device information should be acquired in order to confirm that a CIED is functioning normally and to be able to establish an appropriate plan for device management during surgery (Table 24.1). The location of the surgery, the type of electrocautery (presumably monopolar) or other radiofrequency equipment that will be used, the extent of the EMI (frequency and duration of cautery bursts), and the patient's medical condition will influence the plan. For example, if monopolar cautery will only be applied below the umbilicus, the risk of the device being affected by the EMI is very low provided the device sensing is bipolar. In this situation, no programming of the device for surgery would be needed. If the cautery EMI is closer to the CIED and likely to be sensed by the device, then the need for programming depends on what the consequences would be of that sensing. Suppression of demand pacing would be anticipated, but even asystole might be acceptable if the EMI was applied infrequently and for only a few seconds at a time. Longer periods of a cauteryinduced inadequate heart rate could be managed with a magnet if the device is a pacemaker and if it is convenient to place and remove the magnet during surgery. One concern with magnet use on a pacemaker, however, is that the pacing rate could be as high as 100 bpm. Programming would be favored over magnet placement when monopolar cautery use will be more than brief, the cautery will be applied close to the leads, and the patient has an inadequate rhythm on their own. This would be especially important with ICDs, since the magnet does not switch an ICD to asynchronous pacing. However, a magnet would be an acceptable option in a patient with an ICD who is not pacing-dependent, assuming

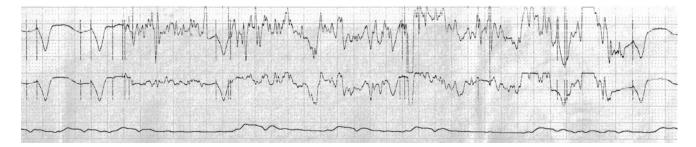


Fig. 24.7 Suppression of demand pacing. A rhythm strip obtained during cardiac surgery illustrates suppression of demand pacing during monopolar cautery. The top trace shows lead II, the middle trace shows V5, and the bottom trace is the arterial pressure. At baseline, the patient is AV paced at 75 bpm (DDD). The patient was pacing-dependent. The

presence of cautery is apparent from the noise in the EKG traces. The pulsations in the arterial trace become infrequent and irregularly timed during the cautery, indicating that much of the time the cautery noise is sensed as intrinsic cardiac activity with suppression of pacing. This device did not permit programming to asynchronous pacing

Table 24.2	Device manufacturer	contact information and	pacemaker battery response
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Company, website, technical support	Pacemaker response to magnet	ICD response to magnet
Biotronik biotronik.com 800-547-0394	Asynchronous pacing at a rate of 90 bpm, unless this feature is programmed off. ^a A magnet rate \geq 80 bpm is okay.	Suspends tachyarrhythmia sensing. No tones. In some models, after 8 h of continuous magnet placement, tachyarrhythmia sensing is restored (call company for details)
Boston Scientific/Guidant bostonscientific.com 800-227-3422	Asynchronous pacing at a rate of 100 bpm, but can be programmed to not respond to the magnet. Magnet rate \geq 85 bpm is okay	R wave synchronous beep indicates suspension of tachyarrhythmia sensing (beeps continue indefinitely). Magnet response can be programmed off
Ela/Sorin (now called LivaNova) livanova.sorin.com 877-663-7674	Asynchronous pacing at a rate \geq 80 bpm (gradual decrease from 96 bpm)	Always disables tachyarrhythmia sensing. Pacing rate changes to magnet rate but remains in demand mode
Medtronic medtronic.com 800-723-4636	Asynchronous pacing at a rate of 85 bpm, becomes VOO at 65 bpm at elective replacement	Always disables tachyarrhythmia sensing. Continuous tone for 10–30 s on initial magnet placement
St. Jude sjm.com 800-933-9956	Asynchronous pacing at a rate of at least 98.6 bpm, unless this feature is programmed off. Becomes VOO at <87 bpm at elective replacement	Suspends tachyarrhythmia sensing, but this feature can be programmed off. No tones

^aHold magnet for at least 10 beats as device could revert to normal pacing. If reversion to demand pacing occurs with the magnet still engaged, call the company for details

that the ICD is not programmed to ignore the magnet and that the magnet is easy to place and maintain its position. The decision about whether programming is needed for surgery is therefore a combination of the type of device, the location of the device relative to the surgical field, the ability to maintain contact with a magnet, the consequences of the EMI to that patient, how effective a magnet would be at preventing those consequences, and whether the base heart rate needs to be increased due to the severity of the surgery.

Management by Trained Professionals

Once a plan is established, the next challenge is identifying a provider capable of programming the device if programming is necessary. The options are often influenced by the size and location of the hospital or surgery suite and the cardiology services available on-site-in reality few institutions have robust systems in place. This exemplifies one of the reasons why perioperative anesthesiologists need to have a basic grasp of CIED management and be ready to lead the process. Cardiologists may not have the resources or interest in providing device management. Relying entirely on a representative from the device company is an alternative, but company representatives are not licensed providers and do not have hospital privileges. They should not be expected to evaluate the device and determine a plan. Consequently, many institutions send a form to the patient's cardiologist to obtain a plan for device management and then arrange for a company representative to perform any recommended programming on the day of surgery. This approach, while acceptable, is less than ideal. Representatives are busy and may not be available when needed, especially if significant

advance warning is not provided or the surgery is in a rural area. Secondly, cardiologists and anesthesiologists may have different goals for the patient during surgery. Often the cardiologist's primary concern is maintaining an adequate heart rate and avoiding accidental tachyarrhythmia therapy. In contrast, anesthesiologists may have additional concerns such as whether the baseline backup pacing rate is adequate for the surgery (assuming the patient is pacing-dependent) or whether other features such as the rate-response feature or noise reversion might affect the rhythm in the operating room. These ancillary functions may cause rhythm alterations that are distracting to the anesthesia caregiver but fortunately rarely have a significant adverse impact on the patient. Although it is not mandatory to disable rate-response, noise reversion, or other features, doing so may be helpful and easy to do so if the device is being programmed for surgery, but such changes may not be included in recommendations provided by a cardiologist.

To avoid having to depend on cardiologists or company representatives to come to the operating room area, a few hospitals now use anesthesiologists who are trained to evaluate and manage CIEDs [2, 3]. It appears that anesthesiologists can perform this task at least as well as (non-electrophysiology) cardiology fellows and offers the advantage that it is easier for the individual performing the programming and the anesthesia team to collaborate when everyone involved already knows each other [3]. Nevertheless, development of an anesthesiologist-based device service is not trivial. There is a lot to learn, and new situations continue to present themselves. Having access to a knowledgeable electrophysiologist or cardiologist who is willing to provide training and advice can be very helpful to a successful anesthesiology-based service. Regardless of who evaluates and programs the device for surgery, there should be a discussion between the anesthesia team and the programming individual so that concerns are addressed, and the anesthesia team understands what to expect from the device during surgery. It is particularly important that the anesthesia team should understand what magnet placement will accomplish if the decision is made to make no programming changes for the surgery. If the patient has an ICD and tachyarrhythmia detection is programmed off, then defibrillation equipment must be kept with the patient. If the patient has a history of defibrillation with the device, or if the surgical drapes will make pad placement difficult, then defibrillation pads should be placed prophylactically.

Management by the Anesthesiologist

There will be many situations when no trained professional is available, and the anesthesiologist must be prepared to evaluate the device and to decide how best to proceed with anesthesia and surgery.

 Table 24.3
 Information that should be obtained about a CIED prior to surgery

surgery	
Item	Desired result
Device type and why implanted	
Device check within 12 months (simple pacemaker) or 6 months (all ICDs or pacemaker with CRT)	Device is functioning normally (no alerts). No new worrisome rhythms detected. Tests of lead function are normal and stable
Battery life expectancy	At least 3 months at time of surgery (note: a more recent check than in last 6–12 months may be necessary if battery power is low)
Pacing mode and backup pacing rate	Which chambers? (atrium, right ventricle, left ventricle)
Rate-response	Is it turned on? If so, which method? (accelerometer, minute ventilation, tissue impedance) How high a rate can it provide?
ICD therapy	Lowest ventricular rate associated with therapy
Pacing dependency	What percent of the time is the patient paced?
Underlying rhythm (applies when the patient is paced a high percentage of the time)	What is the rhythm if pacing is temporarily suppressed?
Magnet response—pacemaker	Will async pacing result? At what rate?
Magnet response—ICD	Will tachyarrhythmia detection be suspended? Will the device emit any sounds with a magnet that confirms tachyarrhythmia suspension?

The first step is identification of the device type and manufacturer. Ideally, the patient should have a card that provides this information. If the patient does not know, then examination of a chest X-ray (CXR), if available, may provide the necessary information. Devices often have a signature icon visible by X-ray, and the shape and internal pattern of the device can provide clues as to the brand and manufacturer [4]. CXR findings can also help distinguish a pacemaker from an ICD; the presence of at least one large coil indicates that the device is an ICD, whereas if the leads are uniformly thin, the device must be a pacemaker. Another option is to call each company and ask if the patient has one of their devices. Each company maintains a registry of all patients with their devices and a technical support line that is staffed at all times (Table 24.3).

The next step is to determine *why* the device was implanted. This will help establish how likely the patient is dependent on the device for maintaining a satisfactory heart rate. For example, a patient with a history of third-degree heart block is likely to be pacing-dependent and need intervention, whereas someone whose device was placed for rare syncopal episodes may not need any modification of the device for surgery.

The patient should be asked *when* the last time the device was checked. The check could have been performed at a clinic visit or telephonically and should have been within 1 year for a pacemaker and 6 months for an ICD or a pacemaker with cardiac resynchronization therapy [2]. If a device has been routinely monitored, it is likely safe to assume that the device is functioning adequately. At the time of surgery, at least 3 months of battery life remaining is recommended. As a battery wears out, battery checks become more frequent, and hopefully the patient is aware of this circumstance. It may also be reassuring if the patient tells you that their cardiologist is aware of the upcoming surgery and is not concerned. If the device is a pacemaker, then a battery check can be performed with a magnet. Unlike early pacemakers where a magnet caused the device to pace at the base pacing rate, modern pacemakers change their pacing rate based on the status of the battery. As a battery loses charge, the pacing rate associated with magnet placement decreases, either gradually or in steps depending on the company. If you know what to expect for a magnet response, you can determine the status of the battery (Table 24.2). Unfortunately, you cannot perform a similar battery check on an ICD as the magnet does not affect the pacing rate, with the possible exception of ICDs manufactured by Ela/Sorin.

The rhythm should be examined carefully on a monitor. All monitors filter the EKG signal, and this process will prevent the actual pacing spikes from appearing on the screen. To "see" pacing spikes, a module within the monitor must be turned on in order for the monitor to specifically look for the characteristic appearance of a pacing spike. If the monitor

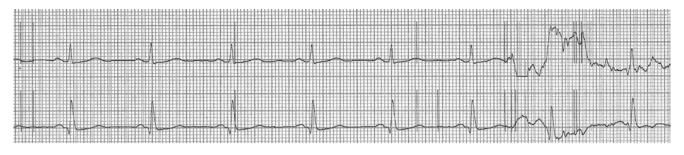


Fig. 24.8 Artifactual pacing spikes. A rhythm strip of leads II and V5 reveals a number of randomly appearing pacing spikes, especially toward the end of the strip where monopolar electrocautery was used. This patient did not have a CIED; therefore, all the pacing spikes are

sees what it considers to be a pacing spike, a vertical line is placed on the screen. It is important to recognize that the line you see on the screen or rhythm strip is not the actual electrical signal of the pacing spike, but rather an artificial "spike." Extraneous electrical noise can fool this module into "seeing" pacing spikes that do not exist. Therefore, a line on the monitor suggesting the presence of a pacing spike might be an artifact (Fig. 24.8). Continued observation of the monitor should permit determination of which pacing spikes are likely artifact and, from that, whether there are pacing spikes that do not cause depolarization or if there are pacing spikes when they should not be present. When pacing spikes are present (outside of the post-depolarization refractory period) but there is no chamber depolarization, then the concern is failure to capture. When pacing spikes are seen clearly after a spontaneous chamber depolarization, it suggests that the spontaneous depolarization was not sensed by the device (failure to sense). Both problems indicate serious malfunction. If no pacing spikes are observed at baseline, then placing a magnet on a pacemaker will commence asynchronous pacing. Each pacing spike should result in a depolarization, assuming the spike occurred after the refractory period.

A vital question is whether the patient is pacingdependent. Without adequate records, this can be difficult to impossible for the anesthesiologist to determine, which is why it is important to get information from the cardiologist who manages the device. If the patient or medical record review fails to provide answers, then a rhythm strip may provide clues. If P waves, a narrow QRS, and no pacing spikes are seen (e.g., normal sinus rhythm), then the patient is not pacing-dependent. If, on the other hand, pacing spikes are seen, then the patient may or may not be pacing-dependent. The presence of atrial spikes only proves that the patient's spontaneous atrial rate is lower than the pacing rate. Of course, how much lower is unknown. It could be anywhere from just slightly lower to asystole, and only formal interrogation would reveal the answer. The presence of ventricular pacing does not automatically guarantee pacing dependency. It might merely mean that the intrinsic conduction happens to be too slow to reach the ventricle before the device paces

artifacts. Hospitals and especially operating rooms are electrically noisy. The stray EMI can occasionally mimic the characteristic appearance of a pacing spike

the ventricle. In the case of biventricular pacing, the desire is to initiate both RV and LV contraction before the intrinsic conduction reaches the ventricles; therefore, the AV delay is programmed deliberately short. Of course, it is also possible for the patient to have complete heart block and need cardiac resynchronization therapy. In short, in many circumstances, it will be impossible for the anesthesiologist to determine pacing dependency simply from looking at the rhythm.

Given the difficulties described above, if pacing spikes are observed on the monitor, the safe approach is to assume the patient is pacing-dependent and therefore at risk if suppression of demand pacing occurs. The next step is to consider where the cautery will be applied and specifically will it be above or below the umbilicus. If monopolar cautery will be applied above the umbilicus, then a decision needs to be made ahead of time what to do if suppression of demand pacing leaves the patient with an inadequate heart rate. If the device is a pacemaker, then a magnet is an option, provided it can be placed without interfering with the surgery. It is also important to recognize that the magnet rate is typically high, and a decision needs to be made as to whether the patient could tolerate that rate. If use of a magnet is not a rational choice, then there needs to be a serious discussion with the surgeon about possibly delaying a case until the device can be evaluated and reprogrammed if necessary.

If the device is an ICD, the situation becomes more complicated. It is likely that the magnet will suppress tachyarrhythmia detection, and the presence of tones from the device after magnet placement is reassuring when present, but as noted previously, St. Jude ICDs may not respond to the magnet and do not provide any tones when a magnet is sensed. Given those caveats, as long as the magnet can be secured over the device safely, the risk of an inadvertent shock is low. Unfortunately, for all ICDs, there is no way to provide for asynchronous pacing other than by programming. Therefore, the triple storm is a pacing-dependent patient with an ICD having surgery with monopolar cautery above the umbilicus. There is nothing the anesthesiologist can do to prevent suppression of demand pacing. So again, a serious discussion with the surgeon is in order. The surgeon needs to be aware of the response to the cautery, and if that response is severe bradycardia or worse, the frequency and duration of monopolar cautery bursts may need to be limited.

Conduct in the Operating Room

The location of the cautery grounding pad on the patients is an important consideration. For monopolar cautery, electricity flows from the cautery tip to the ground pad. To the greatest extent possible, that current flow should be directed away from the device and the leads. For cautery applied below the chest, ground pad placement on the thigh or buttock is fine, but when the surgical site is higher than the abdomen, pad placement may need to be modified. For head and neck surgery, it would be best to place the ground pad on the deltoid opposite the device. For shoulder surgery on the same side as the device, ideally the pad would be further down the ipsilateral arm. If this is impractical, the ipsilateral back or flank is the next best choice.

A magnet should always be readily available in the operating room, especially if the device is still in demand pacing (pacemaker) or if tachyarrhythmia detections are still active (ICD). Even if a pacemaker is programmed to asynchronous pacing for surgery, the magnet will change the pacing rate to the magnet-associated rate.

Monopolar cautery typically interferes with EKG interpretation and continuous monitoring of the pulse is essential. The simplest method is to use the pulse oximeter. The tracing should be displayed on the screen because the "beep" is typically triggered by the EKG signal, not the pulse oximeter signal. Observation of the oximeter waveform during cautery will easily reveal any change in pulse rate. For example, if the device has been programmed to asynchronous pacing for surgery, no bradycardia should be observed during cautery. If the device is still in demand mode but the patient is currently being paced, then it is possible that the pulse will decrease and be erratic if the cautery inhibits pacing, and the patient's intrinsic rhythm is slower than the paced rate. If the pulse rate does decrease, it then becomes important to determine if the pulse is adequate for the patient. If the pulse is unacceptably low, then consider magnet placement if the device is a pacemaker. The alternative is to get the surgeon to use cautery as sparingly as possible to minimize the duration of bradycardia. This latter option is the only possible method to handle cautery-induced bradycardia when the patient has an ICD (other than programming to asynchronous pacing).

To reiterate, if the device is a pacemaker programmed to demand pacing, it is reasonable to wait and see what cautery does to the rhythm before placing a magnet. Even if pacing spikes were observed in holding, the patient may have a perfectly acceptable underlying rhythm or, even better, device function may not be affected by the cautery. Magnet placement on a pacemaker can also break PMT, should it occur in the operating room. If the device is an ICD and the tachyarrhythmia detection is still activated, then place a magnet from the very start. If the device is expected to emit tones, be sure you detect those tones as it indicates the device has sensed the magnet and disabled tachyarrhythmia detection. Even if the surgery is below the umbilicus, nothing is lost by placing a magnet over an ICD. Should a ventricular tachycardia occur, removal of



Fig. 24.9 Rhythm strip of pacemaker tracking. A two-lead rhythm strip is shown. The patient has a pacemaker programmed to DDD at a base rate of 60. Pacing spikes precede every QRS at a rate of nearly 100 bpm. At first glance, it would be easy to wonder why the heart is being paced at a high rate. Once it is recognized that the P waves are

native and not paced, then it should be clear that the device is merely ensuring that a QRS follows every P wave (tracking). In fact, this patient had complete heart block. The pacemaker is acting as the patient's conduction system and maintaining AV synchrony, exactly as it is supposed to do the magnet instantly restores full function, and the ICD would then treat the arrhythmia.

Lastly, a device programmed for demand pacing may have many features that can lead to a paced rhythm that is faster than the base pacing rate. The rate-response feature is a common example, but the most frequent cause of high rates of pacing is tracking, when the ventricle is paced as it matches the spontaneous atrial depolarizations after an appropriate AV delay (AS-VP; see Fig. 24.2c and also Fig. 24.9). There are other features that may lead to relatively brief periods of pacing above the base rate but generally for only a short time and rarely result in a dangerous tachycardia. The anesthesia caregiver is advised to ignore such seemingly unexplained periods of faster pacing.

Postoperative Management

If the device was programmed for surgery, then it should be evaluated and the original parameters restored prior to the patient leaving a monitored setting. If the device programming was not altered in any way for surgery, then it is recommended that the patient have the device checked within a couple of weeks. However, if there is any suggestion of device malfunction during surgery, or if untoward patient events occurred such as severe metabolic or hemodynamic disturbances occurred, or chest compressions or external defibrillation was applied, then the device should be checked before the patient leaves a monitored setting [2].

Significant Gaps in Our Knowledge

CIEDs are machines and therefore their response to the signal detected by the leads is predictable. In that respect, there are no gaps in our knowledge, but it is the rare anesthesiologist who knows every possible feature of every device. Because of that device complexity, manufacturers could do a lot better at designing CIEDs with an eye toward their operation during surgery. For example, it would be best if every device could be easily reprogrammed to the original settings after the surgery is completed. Currently, some companies permit the device settings to be stored in the programming box. Postoperatively, a simple push of the button should then program the device back to the stored settings. Unfortunately, even when this "restore" feature is present, it does not always return all settings to their original values [3]. Another problem is that devices sometimes utilize unusual features that can at least transiently alter the rhythm in the operating room, thereby confusing the anesthesia team. It would be good to have an "operating room" setting for devices left in demand mode that would simplify the programming by turning off these unusual features. Magnet response in ICDs could be improved. It would be useful for all ICDs to provide

an audible sound with magnet placement to indicate that tachyarrhythmia sensing has been disabled. If a magnet also caused ICDs to change to asynchronous pacing at a rate based on the battery status for a brief period, then it would be easier to confirm adequate battery life prior to surgery without requiring the use of a programming box.

Summary

Pacemakers and ICDs are complex devices whose function can be interfered by stray electromagnetic signals, most commonly in the form of monopolar cautery. It is important for anesthesiologists to understand basic device function, monitor the pulse in the operating room, and know how a magnet will affect the device. An effort should be made to determine if the battery has enough reserve which can be done with a magnet if the device is a pacemaker. Taking the time to understand what the device should be doing (baseline programming) and analyzing whether or not the patient is currently being paced is important to planning intraoperative management. If, for example, a patient is currently being paced and therefore could be pacing-dependent, a plan must be made in advance as to how cautery-induced bradycardia or asystole will be handled (magnet versus programming versus limiting cautery duration and frequency). If the device is an ICD, at a minimum, a magnet should be placed to inhibit tachytherapies and the presence of audible tones confirmed if such tones are expected. The anesthesiologist should recognize when their ability to control these devices may not be sufficient, with the worst-case scenario being a patient with an ICD, is pacing-dependent, and having intrathoracic surgery with extensive monopolar cautery use. There are some patients who really need to have their devices specifically programmed for surgery. Each institution should have a process whereby the necessary device information can be obtained, and a plan devised and placed in motion ahead of time so that everyone is not suddenly presented with an impossible situation right before surgery.

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Special Concerns of Intraoperative Management in Orthopedic Procedures

John P. Williams, Catalin Ezaru, and Lynn Cintron

Orthopedic Procedures

Total Hip Arthroplasty

Background

One of the most common procedures performed in the geriatric population is the total hip arthroplasty [1]. Depending upon the age range examined, it is either the second or the third most common procedure performed within the age range of 65–90+ years. In patients aged 18–64 years, it is not even in the top ten. In older females, the incidence of bone fractures is so common that it is higher than the aggregate incidence of stroke, breast cancer, and heart disease [2]. Further, 40% of those with hip fracture will require nursing care and 20% will be unable to return to normal ambulation.

With these statistics, it is little wonder that perioperative efforts are focused on either identifying preoperative risk modifiers or working to reduce known comorbidities [3]. While the definition of geriatric tends to focus on age alone, the last decade has seen an explosion in the understanding and need for further research to better quantify important modifiers of the aging process. Chief among these modifiers is the diagnosis of frailty [4–6].

While frailty is an easy concept to grasp, providing an exact definition is more tenuous and is beyond the scope of this chapter; however, we refer the reader to Chaps. 4 and 6 for a more thorough review of the concept of frailty and its

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application to perioperative care [4–8]. There are also several guidelines available to assist in the perioperative care of the geriatric patient for hip surgery both emergently and electively [7–11].

Finally, there are a few reviews that have examined the interaction or intersection of the Perioperative Surgical Home (PSH) as well as ERAS with the various Frailty scales and measures [12]. The application and expansion of the PSH as a concept has resulted in the development of several guide-lines and protocols for the management of hip fracture in the elderly most notably in the UK [13]; however, the propagation of these guidelines was assisted by the development of an active surveillance database in use for over a decade [14, 15].

Interestingly, the initial guidelines [14] were designed following a Cochrane Review of outcomes following emergent hip fracture surgery [16] and include a recommendation for regional anesthesia (specifically subarachnoid anesthesia) even though this same review noted, "The effect of the removal of the oldest trial (McLaren 1978), which has an excessive mortality in the general anaesthesia group, also shows the weakness of the evidence." Despite this comment as well as others suggesting that there were issues in the review, it served as the basis for the guidelines evaluated in two recent Anaesthesia Sprint Audits of Practice (ASAP) [13, 17]. While the exact guidelines may or may not be ideal suggestions, the framework of those guidelines act as an excellent roadmap for examining important aspects of anesthetic care for hip fracture patients.

Intraoperative Care

The ASAP practice standards outline twelve standards for anesthetic practice [13]. While the first standard is not relevant to this chapter, those from two onward are.

Standard 2 seems to be the most controversial of the standards suggested. The choice of either anesthetic category,

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Standard 2 – Spinal or epidural anaesthesia should be considered for all patientsStandard 11 – Hypotension should be avoided

general or regional, as a "safer" technique is not a universally accepted tenet. There are several papers and reviews regarding this subject that have been referred to previously, and almost all the reviews from the twenty-first century can find no difference in outcome regarding the selection of anesthetic approach. More importantly, whatever approach is chosen, it should be one that is familiar to the provider and provides for scrupulous attention to blood pressure management [17].

The management of blood pressure in the geriatric population is an important variable in determining outcome as has been suggested by a variety of studies throughout the last decade [18, 19]; however, there remains at least one major question. Regardless of the chosen level of hypotension (i.e., MAP < 55, MAP < 70, SBP < 20% below awake, etc.), the relationship between the chosen blood pressure and the chosen outcome (generally mortality, cardiac or neurological injury) has not been shown to be causal, only related. One possible hypothesis is that those patients with lesser hemodynamic reserves are the most likely to suffer hypotensive episodes and would also be more likely to suffer further insults over time. Developing hypotension in response to an anesthetic may simply be a biomarker for this poor reserve. Thus, while the avoidance of hypotension remains a paramount concern for anesthetic personnel, this may or may not reduce the likelihood of current or future events. This in no way should suggest therapeutic nihilism, but simply that we need to focus our attempts on examining the role of avoiding hypotension directly instead of looking for surrogate markers for poor outcomes.

Standard 3 – Spinal anesthetics should be administered using hyperbaric bupivacaine (< 10mg) with the patient positioned laterally (bad hip down)

Standard 4 – Co-administration of intrathecal opioids should be restricted to fentanyl

These standards suggest that if one wishes to use spinal anesthesia, reducing the dose of bupivacaine to less than 10 mg reduces hypotension [17, 20]. There is also a strong suggestion that hypobaric spinal techniques be avoided for the same reason (hypotension) [20, 21]. Adding fentanyl to the intrathecal mixture allows for improved postoperative analgesia with fewer issues of delirium, sedation, and respiratory depression. However, there is little direct evidence that fentanyl improves outcomes in hip fracture patients, so this recommendation represents a significant research opportunity. The Sprint Audit [13] demonstrated that fentanyl was used in only 32% of cases with the majority (~50%) adding diamorphine. Thus, it seems that many anesthetists do not follow this practice which suggests that there should be a room for further exploration.

Standard 5 – If sedation is required, this should be midazolam or propofol

The advantage of both propofol and midazolam lie primarily in their pharmacokinetic profiles and their wide safety margins when used in the geriatric population [22]. There is a general sense that geriatric patients tend to meet discharge criteria post sedation more quickly following propofol compared to midazolam; however, the data show small absolute differences (17.6 vs. 10.1 min for midazolam vs. propofol, respectively); thus, this may not be relevant clinically [22]. This finding is similar to that of their younger brethren (10.4 vs. 4.2 min for midazolam vs. propofol, respectively) [23]. Intraoperative amnesia is more complete following the use of midazolam [23], but whether this is a crucial outcome to the geriatric patient is not clear (patient satisfaction scores of 4.6 vs. 4.7 for midazolam vs. propofol, respectively) [22]. In the Sprint Audit [13], oversedation was common and may have contributed to hypotension; thus, tight control of sedation level is necessary to avoid this outcome. Further, the Audit also suggested that the use of propofol was associated with a reduced incidence of postoperative confusion compared to benzodiazepines and opiates [13].

Ketamine is frequently used for sedation during spinal anesthesia primarily for its salutary hemodynamic effects. Unfortunately, there is a fine line between the dosing for sedation and the avoidance of postoperative confusion [13]. It has been suggested that when combined with general anesthesia at a dose of 0.5 mg/kg, ketamine does not increase the incidence of postoperative cognitive dysfunction (POCD) at days 1 and 6 [24].

Standard 6 - Supplemental oxygen should always be provided

The use of supplemental oxygen is based on several observations. The first is that the implementation of spinal anesthesia is associated with sedation independent of anesthetic agents [25, 26]. In addition, regional oxygen saturation falls below baseline levels in patients receiving subarachnoid anesthetics with or without supplemental sedation [27]. Thus, the addition of supplemental oxygen seems both prudent and perspicacious. Further, because regional cerebral oxygen saturations are associated with that of peripheral oxygen saturations [28], the use of supplemental oxygen in concentrations higher than that obtained with nasal cannula is highly recommended.

Standard 7 – Inhalational agents should be considered for the induction of general anaesthesia.

This standard could be interpreted exactly as it is written, or with some license, it could also be interpreted as an admonition to avoid excessive administration of anesthetic agents and use a deliberate and watchful induction technique. These authors prefer the latter interpretation. Indeed, the outcome of the Audit suggests that most anesthetists also believe in the latter interpretation [13]. Fully 93% of those audited pursued an intravenous induction rather than an inhalational one. We are sure that if the question, "Did you consider the use of inhalational agents for induction?" was asked, most of that 93% would say, "Sure, I considered it for about 10 s and then reached for my trusted intravenous agent." Slow gentle inhalational inductions with sevoflurane are hemodynamically more stable than rapid intravenous inductions by both the nature of the rapidity of the transition from awake to anesthetized as well as the maintenance of spontaneous ventilation (see Standard 8). The important take away for the readers is that one should use the method most familiar to them with the caveat that there are well-established nomograms and guidelines for the reduction in dosing of anesthetic agents in the geriatric population [8, 29, 30].

Standard 8 – Spontaneous ventilation should be used in preference to mechanical ventilation

This is also a controversial recommendation as there are multiple reasons to select endotracheal management (ET) in preference to either LMA or mask supplementation. ET management reduces the risk of aspiration and allows for rapid control of the airway should the patient require urgent intervention. While spontaneous ventilation is not impossible with ET management, it increases both the work of breathing and the risk of hypoventilation for this reason (unless supplemented with pressure support). Spontaneous ventilation does allow for enhanced matching of ventilation and perfusion and is generally associated with decreased degrees of hypotension.

In the recent Audit [13], this recommendation was not as controversial as the previous standard but was clearly not followed in all or even most cases. Among those patients who received general anesthesia with an ET tube (44.2% of cases), 81% were paralyzed and mechanically ventilated, 9% were non-paralyzed but mechanically ventilated, 9% were not recorded or other, and in NONE of the cases, spontaneous ventilation was used. In those patients, whose airway was managed with an LMA (51% of cases), spontaneous ventilation was used in 73% of those cases, non-paralyzed but mechanically ventilated in 13%, and paralyzed and mechanically ventilated in slightly less than 9%. This suggests that less than half of all patients were allowed to breathe spontaneously.

Standard 9 – Consider intraoperative nerve blocks for all patients undergoing surgery

The use of peripheral nerve blocks (PNB) for all types of surgery and all ages including the geriatric group is increasing worldwide [31]. The chief advantage of these approaches is the reduction in the need for parenteral and oral opiates for managing analgesia. However, when they are placed immediately prior to surgery they also reduce the dose of anesthetic needed and can accelerate the rate of discharge from the PACU or ambulatory surgery [31]. Further, they can also

assist in positioning the patient for subarachnoid anesthesia if placed prior to administration.

In the Audit [13], PNBs were used in 56% of patients and most (54%) were administered without the need for either ultrasound guidance or nerve stimulation. This was due in part to the use of fascia iliaca block in 56% of patients, instead of the more traditional (in the US) 3-in-1 (lateral cutaneous, obturator, and femoral nerve) or psoas compartment block. The fascia iliaca block, while not providing comparable analgesia to the 3-in-1 block, is easier to perform using landmark techniques, and this may explain its more common appearance in the Audit. Ultrasound guidance was used in 26% of cases in the Audit. What is most interesting is the very wide variation in the use of PNBs in the hospitals audited [13], ranging from 8% to 92%.

Standard 10 – Neuraxial and general anaesthesia should not be combined

While this technique is frequently used in younger and healthier patients, it is not appropriate except under very select circumstances in the geriatric population. The incidence of hypotension is higher than with either technique alone [13]. The incidence of hypotension overall was very high depending upon the definition. The Audit analyzed hypotension using eight different definitions: fall in systolic blood pressure of greater than 20 or 30%, lowest systolic blood pressure greater than 20 or 30%, and mean arterial pressure of less than 70 or 55 mmHg.

Using these definitions, the combination of general anesthesia and subarachnoid anesthesia resulted in a prevalence of hypotension of 47–93%. With subarachnoid anesthesia alone, hypotension ranged from 22 to 85% compared to the prevalence rate for all anesthetics that ranged from 32 to 89%. The incidence of hypotension for the general anesthesia group was similar in both magnitude and direction compared to the combined group but it was not quite as severe, ranging from 40 to 92%. These data again reiterate the reasoning behind the preference for subarachnoid over general anesthesia as regards the avoidance of hypotension.

Standard 12 – Patients should be routinely assessed for the occurrence of Bone Cement Implantation Syndrome (BCIS)

The incidence of symptomatology compatible with the diagnosis of BCIS varies across hospitals and across countries [32]. A generally accepted definition of BCIS did not exist prior to this publication by Donaldson et al. [32]. Their definition includes "hypoxia, hypotension or both and an unexpected loss of consciousness occurring around the time of cementation, prosthesis insertion, reduction of the joint or, occasionally, limb tourniquet deflation in a patient undergoing cemented bone surgery" [32]. Their group also proposed a grading system for the severity of the reaction: Grade 1 is

characterized by a fall in SpO2 to less than 94% or a fall in systolic blood pressure of 20% or more. Grade 2 is characterized by fall in SpO2 to less than 88% or a fall in systolic blood pressure of 40% or more or an unexpected loss of consciousness. Grade 3 is characterized by cardiovascular collapse requiring CPR [32].

Using these criteria, a separate study from Sweden [33] performed a retrospective analysis in 1016 patients undergoing cemented hemiarthroplasty. The incidence rates of BCIS Grades 1, 2, and 3 were 21%, 5%, and 1.7%, respectively. More importantly, early mortality was related to the severity of the grade. Overall perioperative mortality was 2% which is similar to the range reported in other large studies (1.3–2.5%) [34, 35]. Although there was no difference between the absence of vs. Grade 1 symptoms (5.2% vs. 9.3%, respectively), early mortality with Grade 2 symptoms was 33% and with Grade 3, 88% [33].

However, the role or importance of the syndrome in the long-term outcome of patients is disputed [36, 37]. The primary reason for the dispute is that the functional outcomes for cemented prostheses are felt to be superior to that from the non-cemented version [36, 37]. Thus, many now focus on identifying those patients at highest risk for morbidity and mortality from BCIS as a critical step in improving the safety of hip surgery [38, 39]. Both articles have identified similar risk stratifications regarding BCIS: cardiopulmonary compromise, particularly focused on drugs that suggest compromised cardiac reserve (diuretics, beta-blockers, ACEi); age, frailty was not measured or assessed in these reports; male sex, possibly related to the size of the femoral medullary canal, ASA 3 or 4 status, which is likely a marker for comorbidities; and, finally, hypotension/hypovolemia immediately preceding the insertion of cement.

Providers (geriatricians, anesthesiologists, surgeons) should also discuss with each other plans for managing patients who present with these markers. Clearly discussing the influence each of these risk factors will have on the proposed surgical, anesthetic, and postoperative approach will insure the optimal outcome for each patient. Monitoring hemodynamic status more invasively, while not conclusively shown to change outcome, allows for faster diagnosis and a more tailored therapeutic approach. As the old saying goes, "forewarned is forearmed."

Monitoring

For most geriatric patients, it seems prudent to place an arterial catheter prior to the initiation of surgery. This serves the purpose of providing beat-to-beat analysis of blood pressure and the ability to rapidly assess the status of arterial blood gases if necessary. Some form of monitoring of cardiac output is also essential to tailoring treatment as most investigators report a drop in cardiac output with the onset of BCIS. The type of cardiac output monitor can take the form of an esophageal Doppler, transesophageal echocardiography, pulmonary artery catheter, or pulse contour devices [40]. Each of these approaches has advantages and disadvantages, but the chief defining characteristic is whether the device can be used in non-intubated, sedated patients (PA catheter and pulse contour devices). Of course, it should go without saying that all standard ASA recommended monitoring is in place prior to initiating the anesthetic.

Treatment

Treatment for BCIS is directed at the primary probable cause of the hemodynamic derangement. While the exact etiology is not clearly defined, a constellation of physiologic alterations result including: an increase in pulmonary vascular resistance, increase in pulmonary artery pressure, decrease in right ventricular function, decrease in cardiac output, decrease in stroke volume, decrease in SpO2, and an increase in V/Q mismatch [38, 39, 41]. While the putative cause of most problems is related to a combination of embolic phenomena of one sort or another (fat, cement, bone, air) and activation of a variety of vasoactive substances (histamine, complement, cytokines, etc.) acting primarily on the right side of the heart [38], treatment is directed at increasing systemic blood pressure, increasing stroke volume and cardiac output.

Preventive volume loading and augmentation of inspired oxygen concentration immediately prior to cementation in high-risk patients combined with monitoring with a CVP or PA catheter is essential to successful management [32]. Management of hypotension can be accomplished with a variety of vasoactive drugs including phenylephrine, norepinephrine, and vasopressin for increasing systemic vascular resistance; epinephrine and dobutamine for increasing cardiac output; and if a pulmonary artery catheter is in place, milrinone could be used for pure right ventricular overload and failure. The latter compound however is a significant vasodilator and should rarely be used in this scenario without evidence of isolated right ventricular overload (high CVP, tricuspid regurgitation or poor right ventricular function, and an under-filled left ventricle as imaged on echocardiography), and even then, it is best used in combination with a vasoconstrictive agent.

Transfusion

The use of blood and blood products has become more controversial over the last decade. Originally, a more liberal (definitions vary but generally means transfusion for hemoglobin concentrations of less than 10 gm/dl) policy was used in the elderly. The prevailing belief was that the higher incidence of comorbidities (primarily cardiovascular and pulmonary) and a desire to rapidly regain functional status required a higher oxygen-carrying capacity [42].

However, in 2011, a large multicenter study (FOCUS – Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair) from the NIH strongly suggested that this was not the case [43]. The study was carried out in 2016 patients over the age of 50 with a history of or risk factors for cardiovascular disease and a hemoglobin level of less than 10 gm/dl. Patients were then assigned to either a liberal (threshold of 10 gm/dl) or restrictive (threshold of less than 8 gm/dl) transfusion strategy. The primary outcome was mortality or inability to walk across a room without human assistance on 60-day follow-up. The average age of their participants was approximately 82 years and approximately one-quarter of the participants were male; there were no differences between groups regarding the type or extent of cardiovascular risk factors, type of fracture, type of anesthetic, or primary residence (approximately 88% in both groups were in a retirement home or at home). Likewise, there were no differences in hemoglobin prior to surgery (average of 11.3 ± 1.5) or at entry into the study (9.0 ± 0.8); however, blood loss was slightly and statistically (though not clinically relevant) greater in the restrictive group (209 ± 179) vs. 232 ± 257 , respectively).

Fifty-nine percent of patients in the restrictive group did not receive transfusions, while only 3.3% of patients in the liberal group were not transfused. Compared to 54.9% of patients in the liberal group, 16.6% of patients in the restrictive group received 2 or more units of red cells. There was no difference in the age of the units transfused or the use of leukoreduction. The primary reason for transfusion in the restrictive group was tachycardia or hypotension. At 30 days, 46.1% of patients in the liberal group and 48% of patients in the restrictive group met the criteria for the primary endpoint (death or inability to walk), a nonstatistically significant difference. At 60 days, the percentages had decreased (35.2% and 34.7%, respectively), but there remained no statistical difference between the two groups. Mortality rates for these same two time periods were 5.2% and 4.3% for the liberal vs. restrictive groups and 7.6% and 6.6%, respectively.

This same finding was confirmed by at least two further studies [44, 45]. The first trial examined functional outcomes in 305 patients, but did not prospectively group patients by a transfusion strategy, but rather measured their ability to walk in a predetermined amount of time (6 min), maximal hand strength, and two measures (SF36 and CR10) for QoL (Quality of Life) following either hip or knee arthroplasty [44]. Patients were assessed preoperatively and again on postoperative days 1–10 where they completed the SF36 form and were asked to walk as far as possible in 6 min. They were then asked to assess their level of effort during the walk on a CR10 scale [46], and finally their grip strength was measured in their dominant hand. Patients were grouped according to their hemoglobin value on the day of their post-operative visit into four groups: $\leq 8, 8-9, 9-10, \text{ and } \geq 10 \text{ gm}/$

dL. There were no differences in the four outcome variables across the four groups except for grip strength as the percentage of males in the ≥ 10 group was significantly higher (47% vs. 29%, 19%, and 32%, respectively). Most patients were examined postoperatively between days 4 and 5 (4.6 ± 1, 4.5 ± 1.5, 4.8 ± 1.5, and 4.6 ± 1.7 respective to Hgb group). While there were significant decreases over time in each of the groups, they all performed equally well compared to their preoperative states. Further, there were no significant differences between the groups with respect to adverse events (cardiac and respiratory), symptoms of anemia, length of stay, or incidence of prolonged hospital stay.

The second trial involved 603 patients who were prospectively randomized to a restrictive or liberal transfusion strategy [45] and followed for 14 days following operation. Outcome measures included complications (infectious, respiratory, neuropsychiatric, cardiovascular, and hemorrhagic), mobilization delay, QoL (FSI or Functional Status Index), and mortality. Demographic criteria were balanced across groups apart from a history of COPD which was higher in the restrictive group (incidence of 10.7 vs 4.6%). As expected, the number of transfused patients was smaller in the restrictive group (26.4% vs. 39.1%). There was no difference in hospital stay or median blood loss between groups. Infectious and respiratory complications occurred more frequently in transfused patients regardless of categorical assignment. Of those patients who developed infections, 66% had been transfused, while 70% of patients with respiratory complications were transfused. QoL scores were not affected by transfusion strategy.

Although these studies would appear to conclude the debate about where transfusion triggers should be set, a Danish study was published in 2016 that has reignited the debate [47]. This paper is a composite of three papers published as part of a thesis for PhD [48–50]. The three papers sought to examine the role that frailty and not simply age plays in responding to transfusion strategy following surgery for hip fracture in 284 patients.

The patients were drawn from two populations: one in nursing homes and the other in sheltered living facilities. The two groups were matched across a wide variety of demographic factors including but not limited to ADLs, gender, residence, comorbidity, dementia, age, and pre- and intraoperative transfusion. The only statistically significant difference was in age which was not clinically significant (85.7 vs. 86.9 for restrictive vs. liberal, respectively). The restrictive group was transfused at a level of 9.7 gm/dL and the liberal group at 11.3 gm/dL. This is an important distinction from almost all the other studies we have discussed. The restrictive group is being transfused at a level that would generally be "liberal" in almost all the other studies.

Thus, the first significant question to ask is to what degree are the results reflective of a comparison of essentially two different liberal transfusion strategies? Essentially, they created "more" and "less" liberal transfusion groups with a relatively small number of patients. They did find that their frailest patients were from nursing homes (interestingly, however, the incidence of dementia was not different between the two residency groups) and that these patients had the higher survival rate in the more liberal group (36% vs. 20% at 90 days). Further, 30-day mortality was significantly lower in all patients in the more liberal group (7% vs. 16%). There is a caveat to these findings, however, as they evaluated their outcomes with respect to both an intention to treat and on a per protocol basis.

The per protocol group was smaller than the intention to treat group with only 260 patients in total. While the 90-day mortality was higher in the restrictive group in both analyses, the 30-day mortality for all patients was only significantly different in the per protocol analysis. Also, they did not find an increase in infections with the more liberal group which other investigators have noticed. Overall, the most important findings from this study is the outcomes as related to frailty rather than simply age. Unfortunately, the use of relatively high values for the "restrictive" group made the ability to relate this study to so many others in the literature very difficult.

Thus, one is left with the impression that unless the patient has pre-existing coronary artery or severe pulmonary disease, the restrictive strategy appears to be as safe as the more liberal strategy. Further, if one lives or works in an environment where blood and blood products are expensive or difficult to locate, then the restrictive strategy can conserve these previous resources at no physiologic expense to the patient.

Total Knee Arthroplasty

Unlike total hip arthroplasty, there are few guidelines that suggest best practices. There are, however, ERAS pathways that are quite helpful in identifying areas on which one should pay attention. Almost all the ERAS protocols focus on alterations in behavioral, pharmacological, and procedural issues [51]. An example of a behavioral change is the education of both patient and staff about the principles of ERAS, while an example of pharmacological change is the addition of gabapentin on the evening prior to surgery and the use of tranexamic acid and IV acetaminophen prior to induction. An example of a procedural change is the removal of discharge from the surgeon's purview and instead being discharged when standardized criteria are met.

The development of ERAS pathways occurred much earlier outside the United States; thus, the larger trials and outcome measures are from outside the United States [51-54]. In the first of these papers [51], the ERAS pathway was introduced in 2008. The initial pathway included oral gabapentin 300 mg on the evening prior to surgery along with dexamethasone 10 mg. At the induction of anesthesia, an additional 4 mg of dexamethasone is administered. The preferred anesthetic technique was either low-dose subarachnoid anesthesia (2–3 ml of 0.25% plain or 2 ml of 0.5% heavy bupivacaine with no additional intrathecal opioids) or a propofol-based anesthetic with ketamine added as a single dose of 0.5 mg/kg. Acetaminophen is added with both techniques, and a Cox-2 inhibitor can be added. While there is no set fluid administration, a more restrictive protocol is encouraged with vasopressors as needed for blood pressure support. Tranexamic acid is administered on induction in a dose of 15 mg/kg but is withheld if there is a history of thromboembolism in the past 6 months.

Local anesthetic (levobupivacaine 0.125% is used in this pathway, but ropivacaine could be substituted) is injected into the joint capsule, muscle, fat, and skin in a total dose of 80 ml. A catheter like the one used for epidurals is placed in the joint exiting away from the incision, and a second dose of 20 ml is added following closure of the wound. The catheter is removed on the morning of the first postoperative day; however, prior to removal, three more 40 ml doses are administered at roughly 6-8 h intervals. Postoperative analgesia also includes gabapentin, 300 mg twice a day for 5 days and oxycodone as needed twice daily for 2 days followed by tramadol 50-100 mg, every 4-6 h. Patients are first mobilized 3-5 h postoperatively, and once the patient can walk with the assistance of external aids, the process for discharge begins. Once discharged, pain is managed with acetaminophen, weak opioids, and NSAIDs.

Using this protocol, 1500 hip and knee patients were compared to 3000 patients using a traditional pathway for the 4 years prior (2004–2008). There were minor differences in demographics with the ERAS group having a significantly higher incidence of hypertension, noninsulin-dependent diabetes, and COPD. There was a significant reduction in both 30- and 90-day mortality (0.5% vs. 0.1%, and 0.8% vs. 0.2%; traditional vs. ERAS). There were no differences in complications between the two groups, and overall length of stay (LOS) decreased from a mean of 8.5-4.8 days and a median of 6-3 days. Unfortunately, TKA was not differentiated from THA in this evaluation; however, it seems unlikely that there would be major differences in mortality between the two surgical groups (THA vs. TKA). This same cohort of 4500 patients was followed for an additional 2 years, and the significant difference in mortality between the two groups was maintained at both 1 and 2 years (2.1% vs. 1.3% and 3.8% vs. 2.7% for traditional vs. ERAS) [54].

The use of regional anesthesia in preference to general anesthesia is in keeping with what was already discussed in the THA section. Further, others have noted that subarachnoid anesthesia in elderly patients undergoing TKA is associated with improved outcomes, including lower incidence of delirium and sore throat and lower pain scores on postoperative days 3 and 4 [55]. Timing of antiplatelet inhibitors prior to and after surgery needs to be considered before neuraxial puncture. Although aspirin alone is considered safe in neuraxial anesthesia, the concurrent administration of other antithrombotic drugs significantly increases the risk of spinal hematoma, and the recommended safety times for each of these other drugs must be strictly followed [56].

Both remaining large comparisons are from the regions of Australia and New Zealand [52, 53], and again they both examine a combination of THA and TKA. The first study was completed in 2013 and their study enrollment was divided into three phases: a traditional phase from March to September of 2012, a training phase during September of 2012, and the ERAS pathway from October of 2012 to May of 2013 [53]. Total patient enrollment was 709 with 412 enlisted in phase 1 and 297 in phase 3. A patient was considered to have successfully completed the ERAS pathway if 11 or 16 predetermined criteria were met including coordinator counseling preadmission, preadmission review by a physiotherapist, clear oral fluids up to 2 h preoperatively, preoperative oral carb loading, no sedative premedication, subarachnoid anesthesia, local anesthesia (this could be either local infiltration or femoral (or adductor canal) nerve block - we will discuss which PNBs are most beneficial at the end of this section), less than 10 mg of IV morphine, fluid restriction to less than 1 L after accounting for blood loss, active intraoperative warming, antiemetic prophylaxis, multimodal oral analgesia through the 3rd postoperative day, oral carbohydrate supplementation in the PACU, mobilization within 24 h, and hospital discharge within 5 days.

As one can see, these are almost identical to the criteria used in the study discussed previously. Demographic data did not differ significantly between phases 1 and 3 with the exception of the rate of NSAID/COX-2 inhibitors' use preoperatively (26% vs. 37%, respectively). Overall implementation of the pathway was extremely good at 81%. Further, there was a significant reduction in the length of hospital stay (geometric mean of 5.3 (1.6) vs. 4.5 (1.5), phase 1 vs. phase 3) and a higher percentage of patients were discharged by day 5 (52% vs. 60%, phase 1 vs. phase 3). Like the previous study, local infiltration was the preferred method of local analgesia compared to PNBs (75% vs. 15%). Despite this, dynamic pain scores (with movement) were significantly better in phase 3 compared to phase 1 in PACU (0 (0-4) vs. 0 (0-7), median (IQR)) and at 24 h (mean knee flexion in degrees -57 (24) vs. 51 [18], phase 3 to phase 1). There was also significant improvement in time to weight bearing, oral food and fluid intake, and removal of drainage and urinary tubes. Six-week complication rates were similar as was the rate of hospital readmission while patient satisfaction was higher. Fifty-nine percent of patients in the ERAS pathway

were considered ready for discharge on day 3 vs. 41% of those in standard practice.

In the final assessment of ERAS, the traditional group was historical (June through August of 2012) and was compared to a prospective ERAS group (August through December of 2013). The ERAS pathway was like those described previously in all respects with a few exceptions. There was more attention to postoperative nausea and vomiting prophylaxis (ondansetron 4–8 mg around the clock for the first 24 h) and lesser reliance on PNBs and local infiltration for postoperative analgesia; 100 patients were included in both groups for analysis.

There were no differences between the two groups with respect to demographic criteria. The median LOS in the ERAS group was decreased by 1 day compared to traditional (4 vs 5 days). Complication rates did not differ between the two groups nor did overall mortality. There was a small but statistically significant reduction in overall costs associated with the ERAS pathway. Finally, 81% of patients in the ERAS pathway met their early mobility goals versus only 48% of the traditional group. Further, 82% of those in the ERAS pathway who met early mobility goals were discharged in 4 days or less. Readmission rates for both groups were similar.

In summary, the use of ERAS pathways that include most, if not all, of the approaches described here result in an improved outcome regarding mortality, LOS, and costs. Overall, there seems little reason not to adopt these strategies moving forward. The care of an aging population of orthopedic patients must be focused on providing the highest quality care for the least amount of fiscal resources to avoid either rationing of care or excessive medical (and ultimately societal) expenditures.

Peripheral Nerve Blockade

As noted, many (but not all) of the ERAS pathways suggest use of PNBs to reduce the need for intraoperative analgesia and anesthesia (if general anesthesia is used) or to enhance the postoperative analgesic management and reduce the reliance on opioids. The innervation of the skin around the knee and surrounding tissue comes from the femoral nerve, obturator nerve, and sciatic nerve (the last as two branches – the tibial and common peroneal nerves). The joint space is innervated by the femoral nerve anteriorly and the obturator and sciatic nerves posteriorly.

A very recent paper [57] has examined the use of a variety of different approaches for providing postoperative analgesia including PNBs, periarticular infiltration, and epidural analgesia. The authors identified 170 trials published between 1987 and 2016, encompassing over 12,500 patients and utilizing 17 different treatment modalities. They evaluated these modalities for three primary outcomes: acute postoperative pain during rest and movement, postoperative opioid consumption, and quality of early postoperative rehabilitation (range of motion combined with degree of flexion). Secondary outcomes included postoperative incidence of nausea, vomiting, pruritus, urinary retention, and DVT, LOS, and blood loss.

Approximately 59% of the trials (121) used some version of neuraxial anesthesia, but the clear majority of these (87 of 121) used only subarachnoid anesthesia. Of the 170 trials, 57 used general anesthesia (7 TIVA and the remainder volatile with 16 of the latter including N₂O). Seventy-one of the trials used acetaminophen with or without NSAIDs, while 9.4% used some form of gabapentin, and 24 trials (~14%) did not specify.

All forms of combined PNBs were superior to any single nerve block for analgesia. The cumulative ranking curves were different based on the primary outcome examined. The top five methods of analgesia for each primary outcome were summarized over the first 72 h: *pain at rest*, femoral/obturator, femoral/sciatic/obturator, lumbar plexus/sciatic, femoral/sciatic, and the fascia iliaca compartment block; *range of motion*, femoral/sciatic, femoral/obturator, femoral, lumbar plexus, and periarticular infiltration; *reduction in opioid consumption*, femoral/sciatic, lumbar plexus, and femoral/sciatic; and *pain with movement*, femoral/obturator, intrathecal morphine, femoral/sciatic, periarticular infiltration, and lumbar plexus/sciatic.

Secondary outcomes showed similarly disparate results depending upon the outcome examined. The incidence of nausea was lowest with auricular acupuncture followed by femoral/obturator, lumbar plexus/sciatic, femoral/sciatic, and adductor canal block. The *incidence of vomiting* on the other hand was lowest with liposomal bupivacaine followed by femoral/obturator, periarticular infiltration, femoral, and femoral/sciatic. Pruritus was lowest with the lumbar plexus/ sciatic block followed by auricular acupuncture, femoral, femoral/sciatic, and periarticular infiltration. Finally, the incidence of urinary retention was lowest with auricular acupuncture followed by lumbar plexus, lumbar plexus/sciatic, femoral/sciatic, and femoral. Length of stay was shortest with the adductor canal block followed by lumbar plexus/ sciatic, periarticular infiltration, liposomal bupivacaine, and placebo. Finally, the incidence of deep venous thrombosis was lowest with femoral/sciatic blocks followed by placebo, epidural anesthesia, adductor canal block, and periarticular infiltration.

Perhaps the most interesting finding in this meta-analysis is the fact that auricular acupuncture placed in the top two in three of the six secondary outcomes measures. In fact, it was the top performer in two categories, lowest incidence of nausea and urinary retention, and was second in pruritus. The only PNB that placed consistently in the top five was the femoral/sciatic, placing in five of the six secondary outcomes. The lumbar plexus/sciatic was a close second placing in the top five in four of six secondary outcomes as did periarticular infiltration.

The authors conclude by stating that the combination of femoral and sciatic PNBs appears to be the best choice overall, a finding that certainly makes sense when applied to the neural anatomy of the knee and knee joint. The addition of the obturator nerve to this block combination improves analgesia and opioid consumption but cannot supplant either block. The need for participation in rehabilitation immediately following or in proximity to surgery has altered the anesthetic landscape for TKA significantly. While epidural anesthesia was considered the gold standard, the need to preserve quadriceps function has significantly impaired the analgesia available from the block. This is due to the reduction in the local anesthetic component to a point where ineffectual analgesia results. The preservation of quadriceps function is also the likely reason for an increase in the use of the adductor canal block which is like a femoral block for pain control and opioid consumption but superior for length of stay (ranking first). Clearly, more work is needed to help define the role of PNBs in analgesia during rehabilitation.

Finally, while it may be tempting to suggest that the use of PNBs can help reduce the need for postoperative opioid use and thus the likelihood for chronic opiate abuse and misuse, a recent paper has cast doubt on this supposition [58]. Prolonged use of opioids after TKA occurs in 10-34% of patients [59]. In this paper, the authors examined slightly over 120,000 patient records from the years 2002-2012 and used billing data to identify the use of PNBs or neuraxial blocks in patients aged 65 or less. Chronic opioid use was defined as having filled >10 prescriptions or >120 days' supply of opioid in the first year after surgery (excluding the first 90 days). They used a multivariable logistic regression and adjusted for a large set of possible confounding variables (i.e., comorbidities, previous opioid use, alternative medication use, etc.). They found no association between peripheral nerve blocks in any of their three subgroups (opioid naive, intermittent opioid users, and chronic opioid users) and the chronic use of opioids after surgery.

There are however at least two major problems with this study. The first is that apropos of our previous discussion on the best approach for analgesia for TKA, there was no use of sciatic blocks in this study. Most of the patients received femoral blocks only (88.6% of patients) while much smaller numbers received either a lumbar plexus block (0.55%) or other types of blocks (3.61%). This suggests that analgesia in the early postoperative period was incomplete and may have contributed to the outcome. However, since the neuraxial group also demonstrated no relationship to chronic opioid use, this explanation seems less likely. The unadjusted incidence of chronic opioid use in the first year postoperatively was 1.78% vs. 1.81% (block vs. no block) in the naive group;

6.08% vs. 6.15% (block vs. no block) in the intermittent group, and 67.6% vs. 67.8% (block vs. no block) in the chronic group.

Thus, one is left with the finding that while the use of PNBs is clearly helpful in managing pain and reducing opioid consumption in the acute postsurgical period, there is minimal data supporting the ability of the PNBs to reduce the chronic use of opioids post surgery.

Spine Surgery

Cervical

Cervical spine surgery is most easily discussed along two main categories: emergent and elective. Elective surgical procedures include decompressive, disc, and stabilization procedures and are generally required for treatment of cervical myelopathy as the result of degenerative changes in the spine that occur and increase with age [60], and age is often considered a risk factor for pursuing surgery [61, 62]. This concern regarding age translates into different surgical approaches and associated comorbidities. For example, anterior approaches are generally favored over posterior in the geriatric age group and more levels are decompressed at the time of surgery compared to a younger cohort [63]. Meanwhile, ERAS has not been a significant factor in managing patients' surgical journey, even though these procedures offer many of the opportunities to improve LOS and rate of rehabilitation from which other surgical procedures have benefited [63].

In a recent meta-analysis [64] of 2868 patients across 18 studies, the authors found a lower functional recovery rate in an elderly (age greater than 65) group of patients (a finding that led many to suggest that advanced age results in worse outcomes); however, these same patients generally noted that the recovery was sufficient to reduce their dependence and improve their quality of life. This meta-analysis suggests that age is only a functional risk factor and that patientderived outcomes are more important than purely objective measures of functional recovery. The Swedish Spine Register has been ongoing since 1993 [65] and they report both surgical outcomes and patient-reported outcomes. They noted that the older patients were generally more satisfied with their experience than their younger counterparts. For those 65 and older, 92-93% of patients were satisfied with the treatment of their pain and discomfort vs. 84-89% of those between the ages of 16 and 64 [64].

There are other differences due to age and comorbidities. The LOS for elderly patients is generally prolonged; however, blood loss is generally less than that in their younger counterparts [63]. The most commonly reported complications and adverse events following surgery across all age groups were C-5 palsy, CSF leak, pneumonia, and delirium [63]. However, only delirium was statistically significantly different (higher) in the elderly age group. Thus, future focus for ERAS pathway development should include management of delirium as a principal component in addition to the usual components previously discussed. In a very recent analysis of outcomes in 10,232 patients aged 80–103 years [66], not only was LOS longer (3.62 vs 3.11 days), but also the incidence of in-hospital complications (11.3 vs. 7.15%), the rate of nonroutine discharge (33.7 vs. 16.2%), and inhospital mortality were all higher (0.31 vs 0.06%) in the elderly population.

Emergent cervical surgery in the geriatric age group is primarily two procedures: Type II odontoid fractures [67] and central cord syndrome [68]. Type II odontoid fractures are the most common cervical spine fracture in patients over the age of 65 [66]. In their systematic review of the treatment of these fractures, the authors identified 21 articles covering 1233 patients [66]. Overall, both short- (\leq 3 months) and long-term (\geq 12 months) mortalities were lower (odds ratio, 0.43 {0.3-0.63} and 0.47 {0.34-0.64}) with operative intervention compared to non-operative treatment. Further, there was no difference noticed regarding complications (1.01 $\{0.63-1.63\}$). Also, unlike the elective management of cervical myelopathy, there was a roughly even distribution between anterior and posterior approaches with no differences noticed regarding mortality (short- or long-term) or complications. Unfortunately, there were significant limitations to their study; most importantly, they had no way to adjust for selection bias, as individual comorbidities were not reported in most of the studies.

Central cord syndrome typically occurs in patients with pre-existing cervical spondylosis who are then exposed to a hyperextension injury and is the most common incomplete spinal cord injury [67]. In their review of national trends in the management of central cord syndrome, the authors assessed outcomes for 16,134 patients from 2003 to 2010. Overall, approximately 40% of patients were treated using a surgical approach; however, the rate of surgery was lower in those aged 65–79 (27.4%) and over 80 (7.8%). Mortality however was significantly associated with older age with those patients over the age of 79 comprising 34.8% of those experiencing mortality. Mortality was also associated with several comorbidities including congestive heart failure, weight loss, coagulation disorders, and diabetes mellitus [67].

Anesthetic Approach

One might surmise that general anesthesia with endotracheal intubation is the only approach for cervical surgery; however, there are in fact both regional and non-intubating approaches for surgery [69, 70]. We will review these two options first and then discuss approaches for general anesthesia.

The use of deep and superficial cervical plexus blocks (CPB) for anterior cervical discectomy and fusion (ACDF) surgery was investigated by a group from China [68]. They compared general anesthesia (GA) to CPB in 356 patients undergoing single-level ACDF and compared several characteristics including but not limited to preparation/induction time, hemodynamic changes, duration of surgery and recovery time, blood loss, and patient satisfaction. As might be anticipated, induction and recovery times were significantly shorter in the CPB group. Interestingly, the duration of surgery was also significantly shorter (though a clinically insignificant 4 mins) in the CPB group. Blood loss was identical between groups; but hemodynamic responses were less dramatic with the GA group. Analgesic need and treatment for PONV were significantly reduced in the CPB group, and the incidence of severe PONV was significantly higher in the GA group. Patient satisfaction was significantly worse in the CPB group with 29 of 187 (15.5%) patients saying that they would NOT select this technique again in the future compared to only 2 of 169 (1.2%) patients in the GA group. Finally, three patients developed cervical nerve palsy and two developed Horner's syndrome in the CPB group.

Interestingly, we could not identify any trials of the use of Laryngeal Mask Airway (LMA) in anterior cervical surgery; however, there is a report of their use in posterior cervical surgery [69]. This Danish study compared two groups: selfpositioning prone prior to surgery and introduction of an LMA following induction of anesthesia vs. standard general endotracheal intubation (GETA), followed by positioning in the prone position. However, most importantly, the exclusion criteria for the study included BMI greater than 35 kg/m², a Mallampati score of 3 or 4, surgical time of 2 h or more, and age greater than 70. This, to us, seems critical to the interpretation of the outcomes as those patients most likely to suffer from positioning and airway complications as well as almost all geriatric patients were excluded at the outset. One hundred forty patients were randomized and 131 patients were evaluated regarding time to readiness for X-ray, airway problems, sore throat, hoarseness, and myalgia/arthralgia. The LMA was designated as "correctly seated" once a gastric tube was in place and the seal was complete (three attempts were allowed before changing to GETA). No succinylcholine was used for placement of the endotracheal tube. Only two patients required conversion from LMA to GETA secondary to incomplete seal, and a third patient was canceled due to severe hypotension. There were no differences between the groups regarding duration of surgery, emergence, and LOS in PACU. There were slightly more patients with myalgia/arthralgia in the GETA group at 3 h, but these differences resolved prior to the 24-h analysis. Overall, it seems that this technique cannot be recommended for routine use in the United States.

No discussion regarding anesthesia for cervical spine surgery in the elderly would be complete without consideration of the use and type of intraoperative neurophysiologic monitoring. We have elected to combine these two discussions as one has important effects on the other.

Most authors agree that the use of intravascular arterial assessment is important in avoiding or treating episodes of hypotension. While both the spinal cord and the brain autoregulate, this is complicated and altered by the presence of hypertension, diabetes, and anesthetics [71, 72] in addition to the normal carbon dioxide and sympathetic influences. Further, if one is using motor evoked potential (MEP) monitoring, significant hypotension can alter MEP recordings; thus, the use of invasive monitoring for arterial blood pressure is crucial [73].

The choice of anesthetic can also be affected by the presence of MEP recording. The use of intravenous agents is broadly considered to be superior to inhalational agents including nitrous oxide [72, 74, 75]. However, inhalational agents have been used successfully with the admonition that the total dose be kept at or below 0.5 MAC [76]. Perhaps the most important aspect of anesthetic management is to maintain a stable anesthetic background on which the intraoperative monitoring is used. If MEPs are not contemplated or needed, there seems to be little reason to prefer one technique over another. Other patient-related aspects that can make for a difficult monitoring environment include both age and BMI [74].

In a recent single-site report regarding the usefulness of monitoring for cervical spine surgery [77], a group of investigators from the United States identified 200 patients' charts retrospectively to assess the effect of neuromonitoring in cervical surgery. Anterior (114), posterior [73], and combined [12] surgical approaches were used, and the average age was NOT in the geriatric age group (50.1 \pm 13.7 for anterior, 55.2 ± 13.4 for posterior, and 54.8 ± 13.7 for combined). Both SSEP and MEP were utilized in the study and a total of eight neurological alerts were detected. Three patients (2.6%) had SSEP alerts, two were related to arm malposition and one to hypotension. Five patients (4.4%) had MEP alerts, four by significant hypotension and one by bone graft compression. All were in the anterior approach group. Overall sensitivity for SSEP alone was 37.5% and for MEP alone, 62.5%; however, the sensitivity and specificity of the combination of the two modalities was 100%. The mean reduction in mean arterial pressure (MAP) at the time of alteration in the signal was 33.7%. Restoration of MAP restored normal signals within 5 min.

After considerations for intraoperative monitoring and positioning, the next most likely time for problems to occur is during airway management with different types of problems occurring at intubation and extubation [78, 79]. In their most recent review of closed claims regarding cervical spinal cord, root, and bony spine injuries, Hindman et al. noted that 54% of all cervical injury claims (26 of 48 patients) were related to cervical spine surgery [77]. Fully 96% of the patients were intubated under direct vision with fiber-optic intubation being rare. The authors concluded that,

"However, almost equally often, one or more nonsurgical factors may unfavorably affect the cervical cord, particularly in susceptible patients (pre-existing deficits). These factors appear to include head/neck position during surgery or intubation, and/or arterial blood pressure..."

Interestingly, in another review from one of the author's institutions [80], the overall incidence of new postoperative deficits was 2.4% while the incidence of SSEP changes was over twice that at 5.3% (27 patients). While the authors noted that the most common identifiable cause of SSEP changes was hypotension (11 patients), changes related to the surgical process (vertebral body decompression, disc distraction, retractor position, durotomy, graft dislodgement) were the leading cause of SSEP changes (13 patients). Patient positioning was responsible for SSEP changes in two patients, one related to head positioning and one related to taping of the arm. Although intubation has not been routinely associated with involvement with cervical injury, the possibility clearly exists and thus it seems a prudent approach to use some form of indirect visualization for intubation [81].

The postoperative airway issues principally involve laryngotracheal and laryngopharyngeal edema formation [78]. In a recent review article on this topic, several important facts emerge. First, the overall incidence ranges in the literature from 1.2% to 6.1% with the incidence increasing with increasing degrees of surgical intervention (multiple levels or combined anterior/posterior approaches) [82]. The etiology of airway compromise ranges widely from edema formation secondary to prolonged retraction to hematoma formation, abscess development, and construct failure. Risk factors for the development of airway issues include exposure of more than three vertebral bodies, exposures involving C2–C4 levels, blood loss over 300 ml, surgical time greater than 5 h, pre-existing myelopathy, and patients undergoing combined procedures [81].

There is no proven deterrent to the onset of airway compromise; however, there is a suggested risk stratification system that sounds rational and divides patients into three tiers: low, intermediate, and high risk [78]. Low- and intermediaterisk procedures without complicating patient factors (morbid obesity, OSA, etc.) such as one- or two-level decompression and reconstruction or a three-level discectomy and fusion can be extubated safely in the operating room. However, the intermediate group may require overnight monitoring to insure there are no delayed sequelae. The high-risk group which is constituted by complex repairs or combined approaches paired with difficult patient characteristics suggests the need for delayed extubation in the ICU for up to 36 h [81]. Following extubation, the patient should remain under close observation in the ICU for 4–6 h prior to transfer.

While the use of dexamethasone was originally suggested to prevent the onset of edema formation, one current prospective, randomized trial has failed to find an effect [83]. There were 66 patients in total and they received three doses of dexamethasone, 20 mg prior to incision and two doses of 10 mg each at 8 and 16 h later. The patients were all in the high- to intermediate-risk categories and as such were left intubated until the day following surgery, and this is likely why these investigators did not find a difference. Had they extubated these patients immediately after surgery, we suspect they may have found a difference. They did notice that there was a significantly higher fraction of females in those patients who had delayed extubation (11 patients were delayed in extubation and of whom 8 were female). There were no other significant differences except that those patients who had delayed extubation were kept in the hospital 1.5 days longer (4.27 vs. 5.63 days). Thus, while this trial on the surface appears to be negative for dexamethasone, the purposeful delay in extubation of 1 day may have obscured any true difference. It is also possible, however, that there are two separate mechanisms for airway compromise postoperatively: an early component related to physical trauma that is responsive to steroid therapy and a later component related to surgical inflammation that is less responsive.

Two further trials have been conducted regarding the use of steroids for anterior cervical spine surgery (ACDF). The first article examined the use of morcellized collagen sponge mixed with triamcinolone and applied to the retropharyngeal space prior to wound closure in 25 patients undergoing ACDF for 1 or 2 levels and compared them to 25 patients who did not [84]. Instead of assessing the incidence of significant airway issues, they measured the amount of prevertebral soft tissue swelling (PSTS) and the incidence of odynophagia. The PSTS ratios of the steroid vs. that of the control group were compared immediately, at 48 h, 4 days, and 2 weeks postoperatively. Those ratios were 58.2 vs. 74.3%, 57.9 vs. 84.1%, 56.3 vs. 82.9%, and 44.9 vs. 51.4%; all differences were statistically significant at all time periods. The incidence of odynophagia was also lower in the steroid group.

In the second study, 112 patients undergoing multilevel ACDF received either dexamethasone at a dose of 0.2 mg/kg at induction followed by four doses of 0.06 mg/kg at 6 h intervals vs. saline. Swallowing function was not assessed formally until 1 month following surgery [85]. Patients who became symptomatic with severe dysphagia or airway problems were given steroids for therapy. Evaluations were carried out both with and without these patients included in the analysis. Dysphagia was significantly reduced in the postoperative period for up to 1 month as were LOS and airway

difficulty. Seven of the 56 patients in the placebo group required steroids for dysphagia compared to only one of 56 in the steroid group. While airway compromise and need for intubation did not reach significance, it was extremely close (p = 0.057). Overall, there was 2.7% incidence of airway difficulty and three of the patients in the placebo group required intubation and further treatment with steroids compared to none in the steroid pretreated group. Although not related to this discussion, they also noted that the use of steroids delayed but did not decrease the incidence of successful fusion.

The management of postoperative pain has been addressed by several groups [86–89]. There is no protocol that is universally accepted across institutions, thus various approaches have been tried with good success. Both local anesthetics and infusion-based techniques have been used with good success. If the only parameter measured was reduction in opiate consumption in the postoperative period, then the intravenous techniques using either dexmedetomidine or low-dose ketamine seem preferable to the use of either liposomal bupivacaine or superficial cervical plexus block. The dose of dexmedetomidine used in the postoperative period (after use in the intraoperative period as well) was 0.2 mcg/kg/hr for the first 24 h, while the dose of ketamine was 1 mg/kg at induction followed by an infusion of 83 mcg/kg/hr for the first 24 h. Both groups noted significant reductions in the use of PCA opiates as well as improved patient satisfaction.

Finally, while there are no true ERAS pathways or guidelines for the management of anterior cervical spine surgery (ACSS) per se, there is a recent publication that has suggested best practices [90]. These recommendations are the product of a panel of five neurosurgeons, three anesthesiologists, one orthopedic spine surgeon, and a registered nurse. Further, the consensus statements are intended to be used for ambulatory ACDF (discharge within 4-8 h of admission). The panelists grouped all statements into five broad categories: patient selection, postoperative nausea and vomiting, pain management, surgery and discharge preparedness, and provider economics. The only patients that were to be excluded were those with severe cardiopulmonary comorbidities (ASA Grade 4 and above and NYHA Grade 3-4). Risk for PONV should be assessed prior to surgery and prophylaxis agents should be tailored. Interventions structured to reduce PONV include the use of nonopioid analgesia, aggressive hydration, dexamethasone or 5-HT3 antagonists, oral famotidine on arrival, and transdermal scopolamine for those patients with a history of motion sickness. Consensus was also reached for the development of an analgesic plan prior to surgery. Intravenous methocarbamol (Robaxin), if available, should be considered for us intraoperatively. Non-opioid analgesics such as acetaminophen instead of nonsteroidal analgesics and opiates should

be considered as first-line agents and titrated against a validated pain scale postoperatively. Patients and caregivers must be educated on all aspects of the procedure to include: aims of surgery, procedural details, and anesthetic-related issues. This should also include expectation with respect to postoperative care including smoking cessation (preferably 6 weeks prior to surgery), medication use, warning signs, and access to emergency care as well as an evaluation for thromboembolic risk. This preparation should also include counseling for those patients with low pain threshold or taking opiates chronically. Finally, all agreed that patients and caregivers should be made aware of the risk for hematoma/edema formation and recognize the signs of impending issues. All panelists also agreed that patients should be observed for at least 3 h post surgery as well as receiving a call from a nurse on the morning following surgery.

While none of these suggestions meet the standards required of an ERAS pathway or surgical guidelines, these are sensible suggestions if one is to move the use of ACSS surgery into the ambulatory arena.

Lumbar

Background

The United States has the highest rate of lumbar spine surgery in the world despite a similar incidence and prevalence of spine disorders worldwide, with large regional variations across the United States [91]. In 2007, Consumer Reports rated lumbar spinal surgery as number one on its list of overused tests and treatments [92], and questions have been raised about the appropriateness of surgical indications [93]. The population over the age of 65 is the fastest growing segment in the United States, and the need for spinal care is expected to rise further. The main concerns for geriatric patients undergoing lumbar spine surgery are (1) limited functional and cognitive reserve even in the absence of disease (the "healthy" elderly patient), (2) high likelihood of age-related comorbid conditions which may increase complications associated with invasive procedures, and (3) poor bone quality predisposing to fractures and spinal deformity which may lead to both repeat and more invasive procedures.

The Aging Spine

Physiologic changes associated with aging can affect all bony structures, articular facets joints, and intervertebral discs ultimately resulting in a stiffer yet weaker spine [94]. A number of degenerative diseases are prevalent in the elderly population. *Spinal stenosis* is a narrowing of the spinal canal leading to back and radicular pain, with neurogenic claudication being the classic presenting feature. Imaging studies do not correlate well with symptoms in elderly people, so diagnosis of spinal stenosis is based on the clinical syndrome. *Spondylolisthesis* is any displacement of the cephalad vertebral body in relation to the caudal vertebral body and posterior elements. Spondylolisthesis occurs most frequently at the L4–L5 levels and is usually accompanied by spinal stenosis at the corresponding vertebral level. *Vertebral fractures* may occur due to endocrine and metabolic changes associated with aging leading to osteoporosis and poor bone quality.

Geriatric Spine Surgery: Efficacy and Safety

Non-operative treatments are usually the first line of treatment unless the patient presents with acute neurologic deficits or worsening symptoms such as intractable pain. There is considerable controversy regarding the benefits of surgery compared to nonsurgical interventions for spine disorders, and the main culprit may be the lack of agreement between spine surgeons as to the best surgical treatment modality for various degenerative lumbar diseases. In a retrospective cohort analysis of Medicare recipients [95] undergoing surgery for lumbar stenosis between 2002 and 2007, the rate of complex fusion procedures increased 15-fold, from 1.3 to 19.9 per 100,000 beneficiaries despite the overall decline in surgical rates over that time period. More complex procedures were associated with increased risk of major complications, 30-day mortality, and resource use. The study could not clearly answer why more complex operations were performed as it seems very implausible that the number of patients with complex spinal pathology increased 15-fold in just 6 years.

Literature on geriatric clinical outcomes is generally poor due to lack of uniformity of basic definitions, absence of standards of care or standardized outcome measures, and small sample sizes. In a review of randomized control studies comparing lumbar fusion surgery to non-operative care for treatment of chronic back pain, Mirza and Deyo could not identify a clear advantage of surgery while stating that limitations of the trials prevented firm conclusions [96]. The Spine Patient Outcome Research Trial (SPORT) is a large, randomized multicenter trial which has examined surgical versus conservative therapy for three lumbar disorders: disk herniation [97], degenerative spondylolisthesis [98], and spinal stenosis [99]. While the trial did not look specifically at geriatric patients, the mean age of the participants in the degenerative spondylolisthesis study was 66 years. The authors reported that surgery was significantly superior to conservative treatment in pain reduction and functional improvement at 2-year and 4-year follow-up. A significant limitation of this study (like many other surgical trials) was the marked degree of nonadherence to randomized treatment (up to 40% crossover from conservative to surgical therapy) which reduced the power of the intention-to-treat analysis to demonstrate a treatment effect. Similar results and limitations were observed for the spinal stenosis (mean age of participants was 65.5) and disk herniation (mean age 42.3) cohorts of the trial with the differences between the groups diminishing over time.

Intraoperative Management

Spinal surgery includes a wide variety of procedures ranging from minimally invasive surgery such as micro discectomy to complex fusion surgery. Perhaps the most important consideration guiding management of the geriatric patients is understanding the invasiveness of the procedure as this can be associated with prolonged operative time in prone position, increased blood loss, and significant postoperative pain impeding functional recovery.

Choice of Anesthesia

General anesthesia is by far the most commonly used technique for lumbar spine surgery. Regional and neuraxial (spinal or epidural) anesthesia are increasingly being favored for other orthopedic procedures like hip or knee arthroplasty and may be associated with superior perioperative outcomes [100]. However, these potential benefits have to be weighed against significant drawbacks during lumbar spine surgery: inability to control the airway in prone position, titrate the duration of the anesthetic, or perform intraoperative neurophysiologic monitoring. Limiting the sedation level (presumably by choosing regional instead of general anesthesia) may offer additional potential benefits in the geriatric population such as decreased incidence of delirium [101] and postoperative cognitive dysfunction. A recent review of 11 studies that compared lumbar spine surgery patients receiving general versus regional anesthesia [102] found no evidence to suggest that morbidity, mortality, or long-term complication rates differ between the two approaches; secondary outcomes such as hemodynamic profiles and analgesic requirements appeared more favorable in the regional group. Ultimately, the anesthetic choice should be based on the patient's, surgeon's, and anesthesiologist's comfort with the technique.

Positioning

The vast majority of lumbar spine surgery is performed with the patient in prone position with all the potential associated caveats: airway edema, endotracheal tube dislodgement, eye injury, neck manipulation, abdominal pressure, upper and lower extremities, and positioning difficulties. The geriatric population can be especially vulnerable due to associated conditions like osteoporosis or undiagnosed cervical spine pathology. Advanced arthritis (not limited to the spine) may complicate positioning of the arms and shoulders. Great attention should be paid during turning (e.g., maintaining in-line neck stabilization) and also after achieving prone position (neutral neck position, extra padding).

Monitoring

Intraoperative monitoring in patients undergoing lumbar spine surgery focuses on two areas that are closely interrelated: neurophysiologic monitoring of the spinal cord to ensure integrity of neural pathways and hemodynamic monitoring to ensure adequate perfusion pressure to vital organs.

Intraoperative monitoring of the spinal cord includes somatosensory evoked potentials (SSEP), motor evoked potentials (MEP), and electromyography (EMG) which can be used alone or in combination. Numerous factors can attenuate evoked potentials including hypotension, hypothermia, anemia, and anesthetics. SSEPs and MEPs are more sensitive to inhalational agents, so typically an intravenous technique is preferred although low concentration of inhalational drugs (< 0.5 MAC) is acceptable. Regardless of technique and drug selection, maintaining a steady anesthetic state in addition to communication with the surgeon and neurophysiologist is paramount in order to establish adequate baselines and parameters for monitoring. As with many anesthetic drugs or techniques, *how* one uses it may be more important than *what* one uses.

Aging can significantly alter drug pharmacology. Pharmacokinetic changes include a reduced volume of distribution (due to decreased total body water), potential sequestration of lipid soluble drugs (due to increased body fat), and prolonged elimination time. Overall, geriatric patients are likely to be more sensitive to anesthetic drugs due to age-related pharmacodynamics changes in addition to the potentially decreased clearance.

The goal for hemodynamic monitoring is (in theory) simple: maintaining adequate perfusion of the vital organs. This is important for all patients but especially for the elderly as their limited reserve makes them susceptible to complications such as neurologic and cognitive deficits, renal failure, or myocardial ischemia. While this goal appears straightforward, monitoring the perfusion pressure of end organs is difficult in clinical practice. Generally, perfusion pressure is calculated as the difference between mean pressure (MAP) and end-organ pressure but this may be overly simplified and not take into account regional differences in blood flow and organ physiology. Both the brain and the spinal cord can autoregulate blood flow within a wide range of MAPs (typically 50–150 mm Hg), but newer research shows that the lower limit of autoregulation may be higher than previously believed [103]. In addition, other local factors (such as spinal stenosis, retractor pressure) can cause regional ischemia even at "safe" MAPs. In clinical practice, it is common to maintain MAP close to (or above) the baseline levels while paying close attention to changes in neurophysiologic parameters. This translates into use of multiple/ multimodal monitoring techniques, low threshold for placement of invasive monitors, higher likelihood of vasoactive infusions, and above all continuous vigilance as no single approach can be considered best for all patients.

Postoperative Visual Loss (POVL)

POVL is a rare yet devastating complication associated with spine surgery, and the American Society of Anesthesiologists established a registry in an attempt to delineate the causes [104]. Risk factors include prolonged prone positioning, obesity, significant blood loss, and anemia. Although advanced age has not been specifically linked to POVL, many elderly patients may have comorbidities such as vasculopathy and optic neuropathy that can contribute to POVL. Further, they can be exposed to prolonged surgeries that include significant blood loss due to age-related spine characteristics (poor bone quality).

Enhanced Recovery and Spine Surgery

There are wide variations reported in complication rates, length of stay (LOS), postoperative pain, and functional recovery after spine surgery which makes a strong argument for implementation of enhanced recovery pathways [105]. However, spine surgery lags significantly behind other orthopedic procedures like hip and knee replacement. Key among the reasons is that lumbar spine surgery encompasses different procedures with a wide range of indications. As mentioned before, standards of care for many lumbar diseases have not been established and different procedures have been shown to be beneficial for various pathologies.

As a result, spinal ERAS protocols are few, very recent, and applied to a small number of patients when compared to pioneering surgical specialties such as colorectal. Spinal ERAS is very much in its infancy; there are no spinal surgery protocols on the ERAS Society website. There is a paucity of research with the few relevant studies being nonrandomized and non-blinded. Fleege et al. [106] reported a reduction in hospital stay from 10.9 to 6.2 days in patients undergoing stabilization of one or two segments for degenerative lumbar spine pathologies. Blackburn et al. [107] described a spinal enhanced recovery program that included 21 clinical pathway interventions throughout the perioperative period. Intraoperative interventions included: use of minimally invasive techniques when possible, a standardized analgesic regimen aimed to reduce reliance on opioids, epidural and local infiltrations of local anesthetics, and blood loss prevention using tranexamic acid. After implementing this protocol, length of stay was reduced by 52% (from 6 to 2.9 days) and readmission rates decreased from 7% to 3%. Wang et al. [108] reported on 42 consecutive patients (mean age 66.1 ± 11.7 years) treated with a new minimally invasive trans-foraminal interbody fusion and showed a reduction in the hospital stay from 3.9 to 1.29 days compared to standard fusion technique previously used. While there were certain interventions that could be labeled as "ERAS components" such as the use of liposomal bupivacaine for analgesia in order to minimize opioid consumption, it appears that the change in surgical technique from

open to endoscopic/minimally invasive was mostly responsible for the improvement in outcomes reported. This view was tempered however as the authors concluded that their long-term follow-up data were insufficiently powered to draw definitive conclusions as to efficacy and safety of the fusion procedure.

Multimodal Pain Management in Spine Surgery

ERAS by its definition is a multimodal and multidisciplinary approach where small incremental gains lead to overall improvements in patient outcomes. Multimodal pain management is an integral component of ERAS and is almost exclusively the domain of the anesthesiologists. This is extremely important as spine surgery with fusion ranks very high on the surgical pain scores [109] particularly in the first three postoperative days. There is an increasing body of research on multimodal analgesia although it is mostly geared toward the general population and not toward elderly patients specifically. While the review of geriatric pain management is beyond the scope of this chapter, it is important to remember a few important principles: (1) pain perception is an inherently subjective experience and can be substantially altered in an older patient, (2) individuals may exhibit particular sensitivity to opioid analgesics, and (3) opioid-sparing techniques including regional and neuraxial can be particularly helpful in geriatric patients.

Opioids remain a mainstay of perioperative analgesia after major spine surgery, but their well-publicized potential for side effects (short- and long-term) has catalyzed the search for safe and effective alternatives and adjuvants. A recent review by Devin and McGirt [110] supports the multimodal approach while suggesting that chronic opioid use in the preoperative period may have a negative impact on outcomes following spinal procedures. The authors used the North American Spine Society grades of recommendation for reviews: Good evidence (Grade A) for Level I studies with consistent findings, fair evidence (Grade B) for Level II or III studies with consistent findings, and insufficient or conflicting evidence (Grade I) defined as inconsistent findings or lack of investigation. The authors found good evidence (Grade A) that acetaminophen, gabapentinoids, neuraxial blockade, and extended-release local anesthetics reduce postoperative pain and opioid requirements. One important caveat regarding extended-release local anesthetics (such as liposomal bupivacaine) is that the vast majority of research has been conducted in other types of procedures and not in spinal surgery. There is fair evidence (Grade B) that nonsteroidal anti-inflammatory drugs (NSAIDs) decrease postoperative pain without reducing bone healing and fusion rates. Caution is still advised as the benefits of these drugs should be considered against the risks of hemorrhage, gastric ulceration, and renal toxicity especially in the geriatric population. Last but not least, Devin and McGirt

concluded there was mixed/conflicting evidence that ketamine decreases postoperative pain or opioid usage after spine surgery, somewhat surprising and disappointing findings given the recent resurgence and newfound popularity of ketamine.

Dunn et al. [111] have also reviewed novel approaches to analgesia for major spine surgery and while they presented the evidence differently than Devin and McGirt, the findings were similar. Dunn et al. found high-level of evidence to support the use of opioids, acetaminophen, gabapentinoids, and N-methyl d-aspartate (NMDA) receptor antagonists for analgesia in spine surgery. There was promising, but limited evidence favoring the use of α -2 receptors agonists (dexmedetomidine) and intravenous lidocaine. The authors placed neuraxial opioids and NSAIDs in a third category; while they are useful analgesics, their use is limited due to concerns for infection and neurologic injury after surgery (neuraxial techniques) and bleeding and bone-healing risks (NSAIDs). It is important to highlight that other important nuances/differences were present within these broad categories. For example, in the NMDA receptor antagonist class (methadone, magnesium, ketamine), the data supporting methadone and magnesium was favorable but limited, especially for magnesium. Ketamine has been studied more extensively; however, the results are mixed and some studies showed no benefit, similar to data reported by Devin and McGirt; however, the authors still recommended it as a useful adjuvant in spine surgery. Also, a majority of the studies reviewed involved patients undergoing "minor" spine surgery (discectomy, single-level laminectomy) where pain patterns are likely to be different from patients undergoing more invasive surgeries.

Based on the available evidence supporting multimodal therapy, McDunn et al. have proposed a stepwise (ladder) approach for perioperative analgesia based on the type of surgery: minor (laminectomy, discectomy), moderate (1–2 level fusion), major (multilevel fusion). Patients undergoing minor surgery can be treated with opioids and acetaminophen. For patients having moderate surgery, ketamine and/or lidocaine can be added to the previous regimen. Finally, patients undergoing major procedures may benefit from preoperative gabapentinoids, intraoperative methadone, or neuraxial anesthesia in addition to previous modalities. While this approach can be seen as common sense, further research is needed as there is a lack of evidence regarding optimal perioperative protocols and pathways.

Summary

Aging populations and elderly patients' desire to remain active and maintain their independence are likely to increase the need for surgery, especially in orthopedics and spine. Enhanced recovery protocols can be especially important for the geriatric population. Lumbar surgery lags significantly behind (but ahead of cervical spine surgery) other surgical specialties. A better understanding of the preoperative chronic pain state, pharmacokinetic and dynamic changes, and individual differences is key for geriatric patients. It is paramount to address the heterogeneity of the surgical procedures with respect to this patient population in designing pathways to improve the perioperative process and improve outcomes.

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Geriatric Trauma and Emergent/Urgent Surgery

George Jospeh Guldan III

Epidemiology of Elderly Trauma

The most common mechanisms of trauma in the elderly are falls and motor vehicle crashes. Motor vehicle crashes are the second leading cause of trauma but accounts for the majority of trauma mortality [1]. It is estimated that around 25% of elderly motor vehicle crash victims receive chest injuries. This is significant as these injuries (most commonly rib fractures) can exacerbate preexisting cardiopulmonary disease and increase the rate of respiratory failure [2]. With vehicle crashes and all forms of blunt trauma, elderly patients are more likely to incur injuries (especially long bone fractures) compared to their younger cohort. Elderly patients account for the highest percentage of automobile versus pedestrian fatalities in the United States despite being behind children in numbers of incidents.

Falls are the most frequent cause of injury, occurring in over 50% of all geriatric trauma admits. In 2013, Maxwell et al. conducted a large retrospective review of over 25,000 geriatric trauma admits in the United States. Orthopedic injuries, especially to the long bones such as the femoral neck, were the most common injury. Intracranial injuries, specifically subdural hematomas, were the next most common injury type accounting for approximately 20% of injuries presenting to Level 1 trauma centers [3]. In general, Level 1 trauma centers are managing geriatric patients at highest risk for morbidity and mortality, while the majority of single injuries are managed by non-trauma centers [4]. The data, when compared to a previous population-based study from 1989, show that the age of trauma victims is increasing with those over 80 years of age having the largest increase (Fig. 26.1). The increasing age of trauma patients has a significant impact on morbidity and mortality because the amount of coexisting disease and possible medication complications also are higher in this cohort.

Epidemiology of Elderly Emergent Surgery

Emergency surgeries in the elderly are not all related to traumatic events. The need for emergency surgery increases with age and makes up approximately 20% of emergent/ urgent case volume [5]. Elderly patients with emergency surgical presentations have a mortality approaching 50% in some studies, but also carry a high risk of long-term dependence after recovery [6]. This makes understanding the particular challenges in this population essential to controlling outcomes as well as improving the financial and societal burdens of this patient group. The most significant emergent surgical procedures in the elderly due to high mortality and surgical workload are hip fractures, ruptured/leaking abdominal aortic aneurysms (AAA), and emergent laparotomy [7]. Specific pathologies and considerations of each procedure are given in detail later in the chapter.

Assessment in the Elderly

It is often difficult to assess the severity of injuries in the geriatric population due to age-related changes in physiology and coexisting disease states. For instance, acquiring an accurate medical history in an 80-year-old trauma patient with baseline dementia is challenging. Also, the admission of elderly patients with hip fractures and other single injuries does not always necessitate a trauma or critical care service despite the potential for a much higher morbidity and mortality in this age group [8]. This is in large part due to the lack of large-scale studies showing definitive differences in survival when elderly trauma patients are treated in trauma centers. However, there is an increasing movement toward standardized geriatric-specific protocols in trauma team activation, triage, and initial assessment. While the initial trauma assessment is the same in all patients, there are geriatricspecific physiologic considerations that must be taken into account (Table 26.1).

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Fig. 26.1 Percentage of geriatric traumas by year 1989 versus 2009 (Reprinted from [3]. With permission from Southeastern Surgical Congress)

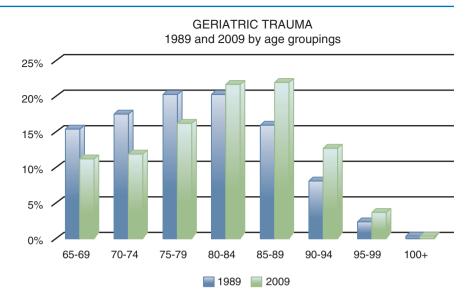


Table 26.1 Recommended geriatric trauma secondary assessment

Laboratory and testing	Comorbidities	Medications
Arterial or venous blood with base deficit	Hypovolemia/congestive heart failure (echocardiography)	Beta blockers
Serum electrolytes	Acute coronary syndrome (EKG)	ACE inhibitors
INR/PTT/PT	Pneumonia	ASA/clopidogrel/other antiplatelet agents
Renal function (BUN/Cr)	Stroke, TIA, preexisting dementia	Direct thrombin inhibitors
Toxicology screen	Septicemia (UTI, etc.)	Coumadin

- 1. *Airway evaluation*: Elderly patients have decreased esophageal tone which can increase the risk of aspiration. They often also have reduced mouth opening from temporomandibular arthritis and reduced neck mobility from osteoarthritis. These factors can increase the risk of airway difficulties.
- 2. Cardiopulmonary evaluation: Elderly patients have decreased systolic reserve and diastolic dysfunction which makes them sensitive to changes in end-diastolic volume. Age-related changes to the cardiac conduction system can lead to both tachycardic and bradycardic dysrhythmias. They also have a decreased response to catecholamines. Because of decreases in chest wall compliance, decreased FEV-1, and increases in closing volume, they are prone to increased ventilation-perfusion mismatch and hypoxia despite normal respiratory rates. Due to these changes, it is extremely important to provide supplemental oxygen early in the evaluation period. Decompensated heart failure in elderly trauma patients has been shown to increase mortality significantly, especially those taking beta blockers and anticoagulants [9]. Studies have shown vital signs can be inappropriately reassuring in elderly patients versus their younger counterparts as well. Hefferman et al. showed that elderly mortality increases with a heart rate > 90 beats per minute (bpm) and systolic blood pressure < 110 mmHg versus

younger patients who had no adverse effects until heart rates exceeded 130 bpm and systolic blood pressure fell below 95 mm Hg [10].

- 3. *Neurological evaluation*: Increased likelihood of preexisting strokes and dementia can make initial evaluation challenging. Changes to the structure of the dura and bridging veins along with frequent anticoagulant use make geriatric trauma patients more susceptible to subdural hematoma even after relatively minor impacts. Cerebral autoregulation also decreases with advanced age which increases the vulnerability during periods of hypotension [11]. This has been shown to compromise tissue perfusion in some studies even when blood pressures are within a "normal" range [12].
- 4. *Musculoskeletal evaluation*: Decreases in bone density make the likelihood of fracture much higher in this population, especially of the hip and ribs [13] [14].
- 5. Laboratory and imaging evaluation: In the elderly, hypoperfusion is often underappreciated on initial evaluation. Studies have shown that a base deficit of greater than -6 mEq/L on initial arterial blood gas is a surrogate of severe injury and is associated with a mortality approaching 60% in an elderly patient. In addition, a base deficit less than -5 mEq/L is equated to a 23% risk [15]. More elderly patients are taking an oral anticoagulant, antiplatelet agent, or both to decrease embolic events

associated with chronic cardiovascular disease. This has a significant impact on both post-insult bleeding as well as postsurgical care as noted in several studies [16–18]. Finally, elderly patients are at increased risk for electrolyte abnormalities as well as chronic kidney disease, so evaluation of renal function is important as well.

- 6. *Medication reconciliation*: Elderly patients are likely to be on numerous medications that either directly impair their response to injury, such as beta blockers and angiotensin converting enzyme (ACE) inhibitors, or drugs that increase the likelihood of complications such as warfarin and clopidogrel [19]. It is imperative to the care and ultimately the outcomes of these patients that these drugs are taken into account during early treatment and resuscitation.
- 7. *Legal wishes and advance directives*: Finally, there are other considerations that must be made in geriatric patients in regard to their baseline functional status and their wishes for care. It is common for elderly to have directives in regard to heroic measures, and many have health-care proxies in place.

Because of the challenges and failings of the traditional triage system, much effort has been put into geriatric indicators and scoring systems to rectify this shortcoming. There has been no shortage of scoring systems in the trauma world, but none have been specifically created to account for the unique geriatric population. The PALLIATE Consortium created and validated a

Table 26.2 Commonly used geriatric high-risk indicators

Assessments	Injury type	Medical comorbidities
ISS (injury severity score) > 16	Blunt/sharp chest trauma	Age > 75
Glasgow coma score < 14	Closed head injury	CHF/significant cardiac disease
Base deficit > -6 mmol/L	Open fractures	Pulmonary disease (COPD)
Systolic BP <110 mmHg	Hemoperitoneum	Cirrhosis
HR > 90	Long bone/pelvic fractures	Renal failure (Cr >1.8)

Triage

Triage in elderly patients is challenging because their initial physiologic response to trauma can differ from younger patients due to medications such as beta blockers and preexisting conditions such as poorly controlled hypertension. This can obscure early recognition of vital sign deterioration and delay triage and definitive treatment. These issues have made it difficult to apply general trauma assessment guidelines and algorithms to the geriatric population. In a retrospective review of 26,565 patients, Chang et al. showed that 49% of those over the age of 65 were under triaged [20]. The most commonly used metric for triage, the ISS (injury severity score), does not take into account age-related comorbidities. In addition, retrospective reviews have shown that trauma team activation occurs less often in elderly patients despite similar injury scores (ISS > 15) [21]. Taylor et al. also showed in a large retrospective analysis at 24 trauma centers that older patients had a significantly higher mortality at any level of severity by ISS [22]. Clearly there is a benefit to triaging geriatric trauma patients appropriately and getting them immediate care at large trauma centers with high volumes of geriatric patients. One retrospective cohort study showed that geriatric trauma patients had a lower rate of major morbidity and mortality when cared for at a trauma center with significant geriatric volume. The same study showed that the opposite effect occurred when centers cared for a large volume of younger trauma victims [23].

Given all these factors, it is reasonable to recommend that high-risk geriatric trauma patients be transferred to a center that has significant experience with geriatric patients. There new assessment tool known as the Geriatric Trauma Outcome Score (GTOS). The GTOS utilizes the commonly used ISS, the patient's age, and the performance of a blood transfusion within 24 h of admission to create a geriatric-specific score using a proprietary formula. They then validated their scores of predictive mortality versus the existing Parkland trauma data, which showed a high degree of accuracy [25]. While simple to utilize with commonly used existing indicators, the GTOS does not take into account other injuries and comorbidities that can affect outcomes. Table 26.2 shows a summary of some of the more commonly used indicators in geriatric trauma that correlate with increased negative outcomes.

Frailty

The newest indicator being studied is the effect of frailty in the geriatric patient. Frailty has been shown to play a major role in the higher mortality seen in geriatric trauma patients. Frailty is defined as "a condition or syndrome which results from a multisystem reduction in reserve capacity to the extent that a number of physiological systems are close to, or past the threshold of symptomatic clinical failure" [26]. Frailty therefore helps to better define the patient's physiological baseline state before an insult. This is much more useful than utilizing age alone as an estimate of overall physiologic condition and reserve. There are many different evaluation tools for frailty, but all of them have the following key factors [27].

Indicators of Frailty

- · Low physical activity
- · Slow walking speed
- · Unintentional weight loss
- Self-reported exhaustion
- Weakness (grip strength, ability to stand from a seated position)

The incidence of frailty in the geriatric community at large is in the 10% range, while those having emergency surgery are >50% range [28]. This is important because preinjury frailty has been independently associated with a greater 1-year mortality rate [29]. The validity of frailty as an index is clear, but the challenge for clinicians is the self- or family-reported nature of frailty indicators. The frailty index will be a useful addition to the current trauma assessment tools, but how to integrate them with current tools and reduce dependence on self-reporting needs further research.

Resuscitation and Initial Management

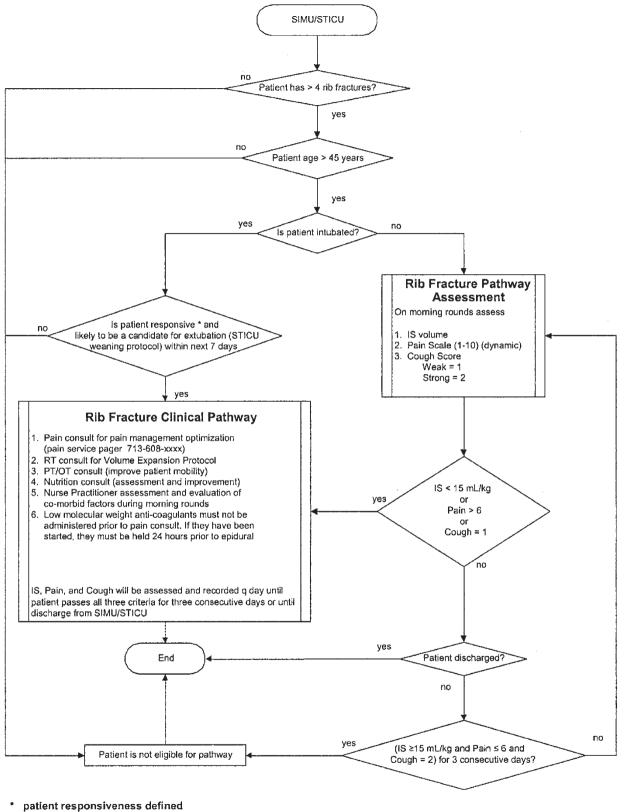
Initial resuscitation in elderly patients is more challenging due to their decreased physiological reserve. It is imperative for resuscitation to be timely and appropriately targeted. As vital signs may be unreliable in identifying early shock in the elderly due to preexisting hypertension and the presence of medications that blunt sympathetic response, early fluid and/ or blood administration is recommended if significant blood loss is suspected. While younger patients increase their cardiac index and oxygen delivery in response to trauma, elderly patients have lower levels to start with and cannot increase them [30]. As in any patient population, there is no ideal hematocrit, but transfusions should be targeted based on ongoing blood loss and signs of end-organ hypoperfusion such as low urine output, lactic acidosis, and increasing base deficit. Of these factors, base deficit has been the most studied as an end point of resuscitation. Davis et al. showed when the base deficit was reduced to less than -6 mEq/L, there was almost a 40% reduction in mortality risk [15]. Systolic blood pressure has been studied extensively as well. In three separate studies, a systolic pressure less than 90 mmHg was predictive for large increases in mortality [22, 31, 32]. Hashmi et al. pooled all available studies which included systolic blood pressures of 100 and 110 mmHg and found an overall increased odds of morbidity and mortality with systolic blood pressures less than 100 and 110, respectively [8]. Another indicator of poor tissue perfusion is serum lactate levels. Serum lactate levels of greater than 2.5 mmol have been associated with a twofold increase in mortality in elderly trauma patients. Furthermore, increased serum lactate levels were present in some geriatric patients without traditional vital signs that would suggest organ hypoperfusion

[33]. In any patient that does not respond to initial attempts at fluid and/or blood resuscitation, it is reasonable to pursue echocardiography to rule out systolic or diastolic heart failure complicating their treatment.

Hypoventilation is another acute issue in elderly trauma patients that has a high association with mortality. Thus, any signs of hypoventilation should be quickly treated with positive pressure ventilation. To better identify hypoventilation, end-tidal carbon dioxide should be utilized. Blunt trauma to the chest with multiple rib fractures greatly increases pulmonary-related morbidity in this patient population [14]. However, an aggressive multidisciplinary approach combining regional pain management with respiratory therapy, physical therapy, and nutrition can actually reduce pulmonary complications associated with rib fractures (Fig. 26.2) [34].

During stabilization of geriatric trauma patients, it is also important to consider the reversal of any previous anticoagulation as well as an evaluation by CT scan to assess for potential intracranial hemorrhage. Harm from radiation is less of a concern in patients of advanced age. Reversing coagulopathy from warfarin within 2 h of admission followed by rapid head CT has been shown to reduce mortality due to posttraumatic intracranial hemorrhage by 75% in elderly trauma patients [35, 36]. Reversal of warfarin protocols with FFP and vitamin K are now common with new prothrombin complex concentrate (PCC) reversals being utilized by some centers. The newest four-factor PCCs contain factors II, VII, IX, and X and can rapidly and completely reverse vitamin K antagonist effects. In addition, this therapy has the advantage of not volume overloading patients at high risk for heart failure. Unfortunately, with the advent of oral direct thrombin inhibitors (dabigatran) and Anti-Xa drugs (rivaroxaban), it is not always apparent by INR measurement whether patients are anticoagulated. While a normal INR should rule out therapeutic levels of dabigatran and rivaroxaban, the effects on laboratory values are not equivalent to therapeutic warfarin. PTT levels will only be slightly elevated by either direct thrombin inhibitors or Anti-Xa drugs. While there are no reversal agents for dabigatran, studies have shown that PCCs dosed at 25-50 units/kg can completely reverse rivaroxaban [37]. Another diagnostic option for anticoagulation status is the thromboelastogram (TEG) which will pick up all anticoagulant effects and is useful in detecting antiplatelet agents as well. There are no reversal agents for clopidogrel, so platelet transfusion should be utilized if clinical bleeding occurs after known exposure.

Given the challenges and high mortality rates in the geriatric emergency surgery population, there have been significant efforts to improve outcomes by creating treatment protocols and guidelines. In 2012, Calland et al. created a specific set of guidelines based on the available evidence to optimize triage, resuscitation, and medical decision making in this challenging patient population (Fig. 26.3) [38].



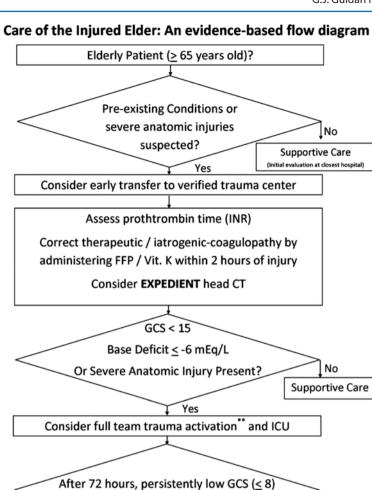
in non-intubated patients as GCS >= 13 in intubated patients as GCS components eyes =4 and motor = 6

Fig. 26.2 A protocol for treating elderly with multiple rib fractures. *SIMU* surgical intermediate care unit, *STICU* shock trauma intensive care unit, *IS* incentive spirometry, *RT* respiratory therapy, *PT* physical

therapy, *OT* occupational therapy, *GCS* Glasgow Coma Scale (Reprinted from [34]. With permission from Elsevier)

Fig. 26.3 Eastern Association for the Surgery of Trauma practice guidelines (Reprinted from [38]. With permission from Wolters Kluwer Health Inc.)

No





despite paucity of sedation?

**Evidence for benefit from full team activation derived from study of patients ≥ 70 y.o.

In addition, other groups have implemented protocols for geriatric emergency patients based on these guidelines and other evidence. Bradburn et al. initiated a protocol on all patients greater than 65 years old with at least one high-risk trauma indicator at a busy Level 2 trauma center. This protocol showed a significant improvement in overall mortality [39]. Their protocol included the following key features:

- 1. STAT ABG to evaluate for hypoventilation, base deficit, and lactate levels
- 2. Continuing ABGs every 4 h if base deficit is −6, until base deficit is decreased to less than −2 mmol/l to ensure complete resuscitation
- 3. Basic metabolic panel every 24 h to follow renal function and replace electrolytes
- 4. Checking INR PT/PTT every 24 h to assess for coagulopathy or medication effect

- 5. ICU admission with hourly neurological checks for 24 h to monitor mental status and GCS
- 6. Obtaining an echocardiogram for any unexplained hemodynamic stability to rule out systolic or diastolic heart failure, structural disease, or cardiac injury
- 7. Consulting geriatric specialist team to coordinate inpatient care and management

Other groups have gone one step further and created a full geriatric consult service. In this model, a core group of geriatricians with trauma training takes care of the patient once they enter the ICU phase of treatment. Their focus is more on the patient's comorbidities, with emphasis on baseline physical and cognitive function, mood, medications, and pain control. Fallon et al. studied the effects of implementing a geriatric trauma consult team and showed a reduction in inappropriate medications by 20%, while making changes to 65% of patient's medications and affecting dispositions in 49% of patients. The primary trauma team took at least one recommendation in 91% of patient cases [40]. What is clear is that knowledgeable geriatricians can positively impact patient care in this high-risk population.

Specific Injury Considerations and Outcomes

Head Trauma

Even minor head trauma can lead to higher morbidity and mortality in the elderly population [41]. Those who present with a Glasgow Coma Scale (GCS) of less than 9 have an 80% chance of death or permanent disability leading to loss of independence and institutionalization [42]. Most head trauma is the result of falls, and despite seemingly minor injuries, intracranial bleeding complications are the key complications associated with poor outcome. It is imperative to quickly obtain a head CT scan in elderly patients if their mental status decreases or if they are at high risk for intracranial bleeding. Studies have shown that elderly patients with normal neurological exams and minor injury mechanisms can still have significant subdural or epidural hematomas [43]. Coagulation should be assessed rapidly so appropriate correction of coagulopathy can be achieved. As mentioned earlier, it is important to also assess for the new oral anticoagulants as they are not always apparent on routine laboratory panels (Table 26.3).

Orthopedic Injury

Hip fractures are one of the most common and debilitating injuries in the elderly. There are more than 1.6 million hip fractures per year worldwide, with more than 300,000 occurring in the United States [44]. Some have even predicted that as the population continues to age, the incidence of hip fractures will exceeded 6 million per year [45]. Despite the straightforward nature of the surgery to repair hip fractures, elderly patients can have severe complications and poor outcomes after surgery. At the 1-year postoperative mark, elderly hip fracture patients have a 33% mortality rate with those surviving having significant effects on quality of life [44, 46]. Despite the push for several beneficial initiatives, including less invasive surgical techniques, preemptive antibiotics, early mobilization, and

 Table 26.3
 Common testing and reversal for anticoagulants

Anticoagulant	Laboratory testing	Reversal
Coumadin	INR prolonged	FFP, Vit K, PCCs 25–50 units/kg
Clopidogrel/ASA	TEG shows antiplatelet effect	Platelet transfusion
Dabigatran	INR slightly prolonged	No reversal
Rivaroxaban	INR slightly prolonged	PCC 25–50 units/kg

anticoagulation to reduce deep vein thrombosis, there has been a leveling off in mortality since the late 1990s [46]. The mortality rate is between 1-6% at admission, 10% at the 30 day mark, and 23% at 6 months [47]. The higher 6-month and 1-year mortality rates are multifactorial due to a complex interaction of preexisting comorbidities, frailty, and inflammatory and hypercoagulable states. The preexisting physiological state of the individual patient is thus important in how geriatric patients react to traumatic insults. Pugely et al. studied over 4331 patients who underwent hip fracture repair and found a 30-day mortality of 5.9% with morbidity during the same time approaching 30% [48]. They identified several risk factors that significantly increased the likelihood of adverse outcomes. In their study, patients with age greater than 80 had a mortality odds ratio of 2.41 with a morbidity odds ratio of 1.43. Male patients also had a significant increase with a mortality risk of 2.28. A higher ASA physical status classification was also a large risk factor, along with functional dependence, malignancy, cardiac disease, open versus percutaneous surgery, and operating time.

To date no prospective studies have shown that the type of intraoperative anesthetic has any significant effect on mortality. However, some observational studies have shown differences in outcomes with regional anesthesia. Neuman et al. in a large database analysis of 18,158 patients showed both a lower in-hospital mortality and a lower occurrence of pulmonary complications in patients receiving spinal anesthesia. However, a more recent observational analysis showed no benefit for regional versus general anesthesia choice [49]. Given the current literature, there is yet no clear benefit for anesthesia type, and the decision should be made on a patient by patient basis. The frequent presence of anticoagulants in this patient population, however, makes neuraxial techniques contraindicated in many instances.

Intraoperative management, specifically goal-directed therapy, has been proposed to improve outcomes after hip fracture surgery [50]. The challenge for this avenue of research is that the intraoperative period for hip surgery is such a brief time. Certainly, maintaining normal hemodynamics in a geriatric patient is advisable, but it may have less of an impact on outcomes than other measures which encompass more of the perioperative period.

A large meta-analysis of available studies totaling over 191,000 patients has recently shown that the timing of when surgery occurs is also a factor. Those receiving early surgery (24–48 h) had a significant risk reduction in mortality [51]. As with all retrospective studies, it does have limitations including the inability to determine if patients had a delay in surgery due to serious preexisting comorbidities which would obviously put them at higher risk. Other retrospective studies have also shown that complications (such as pressure ulcers) increase when surgery is delayed beyond 48 h [52]. There is also evidence that patients who undergo surgery early fair better due to less preoperative immobility. Al-Ani et al. showed hip fracture surgery performed within 36 h increased the

likelihood of patients returning to independence at the 4-month postoperative marker [53].

The type of surgical intervention is also under consideration, with the goals being early ambulation and weight bearing. Generally, arthroplasty is chosen for its advantages with early weight bearing and better results in geriatric patients [54]. There is a risk of fat/cement embolism, however, though this has been shown to be mitigated by intra-femoral vacuum during prosthesis insertion [55].

To address these facts, new strategies have been developed to improve outcomes in the elderly with hip fractures. The concept of orthogeriatrics has been created to combine orthopedic best practices with geriatric-specific postoperative care delivered by a multidisciplinary team (Fig. 26.4) [56].

In Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique Hôpitaux de Paris, they have implemented a system where all hip fracture patients are admitted to a geriatric unit and receive an orthopedic consultant. This approach, which puts the geriatric team as the primary postoperative decision makers, showed a sustained decrease in mortality and morbidity as well as an increase in post-op ambulation (Fig. 26.5) [56].

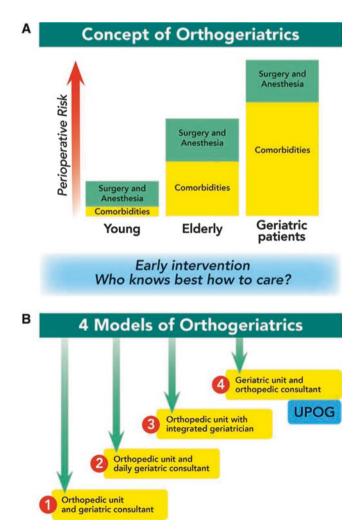


Fig. 26.4 Description of orthogeriatric principles (Reprinted from [44]. With permission from Wolters Kluwer Health, Inc.)

Regardless of the exact system utilized, a multidisciplinary approach to the care of these patients has now been shown to be effective. The following are the most important goals for elderly hip fracture and other trauma patients according to Boddaert et al. [44].

Key Factors

- 1. Early alert from the emergency department.
- 2. Consider hip fractures as emergency surgical cases. Complete < 24 h if possible.
- 3. Rapid transfer to a geriatric unit after surgery <48 h postoperatively.
- 4. Rapid transfer of stable patients to a rehabilitation unit.

Acute Abdomen

Diagnosis of acute abdomen in the elderly can be difficult due to confounding variables often present in geriatric patients. Previous strokes or baseline dementia can make communication of abdominal pain difficult. An elderly patient undergoing emergency laparotomy for any reason carries a high mortality rate which increases with age [57]. Mortality from emergency abdominal surgery increases with each decade of life, peaking at 50% for those over the age of 80 [58]. Stewart et al., in an assessment of emergency surgical mortality, showed that complicated peptic ulcer disease was the most frequent cause of death followed by AAA, bowel obstructions, biliary disease, mesenteric ischemia, peripheral vascular disease, soft tissue infections, and appendicitis [59].

Abdominal aortic aneurysm occurs most commonly after the seventh decade of life and carries a mortality rate of 75%. Elderly patients can be treated with endovascular aortic aneurysm repair (EVAR) which has the benefit of avoiding major open surgery [27]. The IMPROVE trial was a large multicenter cohort trial which studied patients with presumed ruptured aneurysms who received either open or endovascular repair [60]. The study found that a systolic BP of <70 was an independent predictor of mortality and that a local anesthetic EVAR was protective versus a general anesthetic in regard to survival. EVAR is now the preferred method for AAA repair in high-risk populations.

Bowel obstructions can be easily misdiagnosed in the elderly, and a detailed history must be obtained to evaluate for anemia, change in bowel habits, and potential hernias. It should also be noted that the incidence of colorectal cancer is higher in the geriatric population and should be ruled out as well. Springer et al. showed that non-operative management of patients who then required surgery had a mortality of 14% versus those who underwent immediate surgery of 3% [61].

Biliary disease is very common in the elderly with up to 50% of patients older than 65 years suffering from gallstones. Of note, up to 25% of patients have no pain and less than half

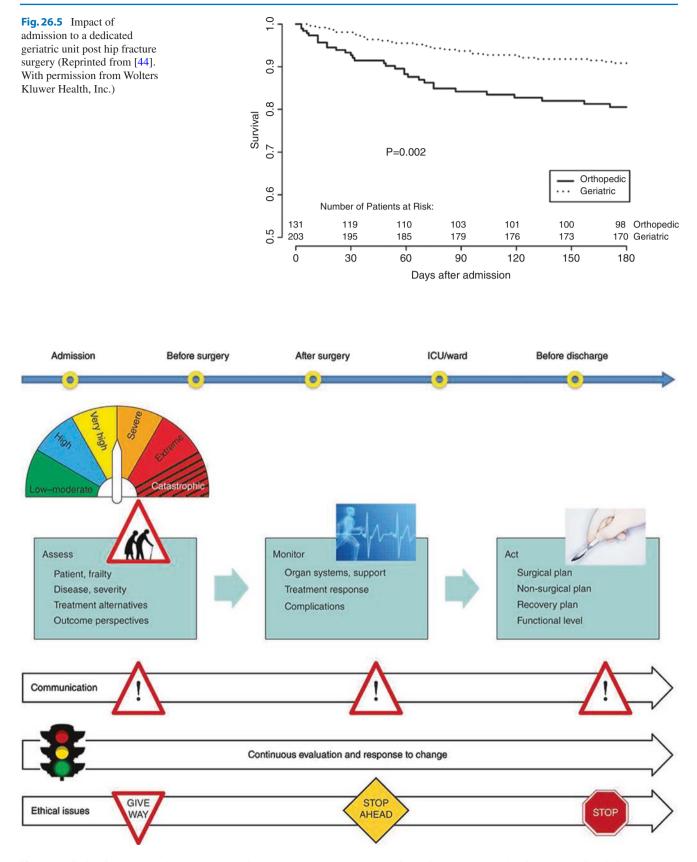


Fig. 26.6 Caring for the geriatric patient undergoing emergent surgery (Reprinted from [67]. With permission from John Wiley & Sons)

present with fever and leukocytosis. The mortality rate for acute cholecystitis in the elderly is 10% [62]. Delayed diagnosis can lead to gall bladder perforation, abscess formation, and sepsis. It is optimal for patients to receive treatment within 48 h of presentation to reduce complications. ERCP can be utilized for treatment of cholelithiasis in high-risk individuals, and the complication rate is quite low at 3% as elderly patients are less likely to develop post-procedural pancreatitis [63].

Mesenteric ischemia becomes increasingly common in the elderly and is secondary to atherosclerotic disease, emboli, or thrombosis [64]. Acute mesenteric ischemia has a severe adverse rate of complications with mortality approaching 60–80% if intestinal infarction has occurred or surgery is emergent [65]. Anesthetic management is complex and must account for the likelihood of concomitant cardiovascular disease and often will require large-volume fluid resuscitation and vasopressor support.

Peripheral vascular disease is also common in patients over 65 years and is a major cause of morbidity with amputation rates of 12% and mortality in 25% of cases [66]. Once again, the presence of cerebrovascular and cardiovascular disease along with diabetes and poor renal function commonly confound the care of these patients. The expansion of interventional radiology and endovascular procedures has increased the number of high-risk patients that can have interventions.

The elderly patient having any emergency surgery must initiate a complex process of considerations and decisions that should involve the patient, patient's family, and a multidisciplinary care team (Fig. 26.6) [67].

The ultimate goal is not only to improve outcomes but to make better perioperative decisions based on preexisting frailty and functional status.

Future Research

While it is difficult to perform prospective trials in emergent/ urgent surgery due to problems with consent and the urgency of the procedures, it is greatly needed in the elderly emergent surgery population. Elderly patients are underrepresented in clinical trials involving surgery, and the breadth of trauma outcome research has been retrospective [68]. Future research should include in the following areas:

- 1. Better understanding of frailty and incorporating it into existing evaluation criteria.
- 2. Study the utilization of geriatric protocols and geriatric services on a wide variety of injuries to attempt to reproduce the success seen with hip fractures.
- 3. More research into the necessity of aggressive treatment of medication-induced platelet dysfunction.
- 4. Assess different models of preoperative optimization prior to emergency surgery in the elderly.

5. Develop cost-effective strategies for different approaches in elderly patients presenting with emergent surgical pathologies.

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Perioperative Care of the Elderly Cancer Patient

B. Bryce Speer and Vijaya Gottumukkala

Demographics

The above age 60 demographic is the largest growing segment of our patient population in the USA. It is projected that 20% of the US population will be over 65 years of age by 2030. In 2016, an estimated 1.7 million new cancer cases will be diagnosed with approximately 600,000 cancer-related deaths [1]. Given that age is the single most important risk factor for cancer and the median age at diagnosis is over 60 years for greater than 50% of new cases, it is expected that 70% of cancers and 85% of all cancer-related deaths will occur in this patient population [2]. In 2014, cancer was the leading cause of death in all people in the USA ages 45-64 and second leading cause of death of all people in the USA over 65 years second only to heart disease [3]. Solid tumors are common in this patient population, and surgery in appropriate patients remains the mainstay for control of tumor burden. However, an age-related higher incidence of comorbid burden in this patient population and inability to rapidly recover from postoperative complications due to decreased physiologic reserve, frailty, altered drug pharmacokinetics/ pharmacodynamics, and higher incidence of postoperative delirium and cognitive abnormalities put these patients at higher risk for postoperative morbidity and mortality. Nevertheless, the current data on the operative mortality and morbidity after complex cancer surgery in older patient population is conflicting [4–6]. While some single-center studies of elderly patients undergoing major cancer surgery reported an operative mortality rate of less than 5% [7–10], a few larger observational studies reported a substantially higher risk for worse operative outcomes [11, 12]. Given the con-

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flicting data about operative outcomes in this age group, it is vital to understand the differences between the physiology of normal aging from the higher incidence of disease burden in older patients. In a recent report of major cancer surgery in the elderly, the authors report that older patients were more likely to have preoperative comorbidities and to receive intraoperative blood transfusions. Increased age was also associated with higher operative mortality (4.83% for >75 years vs. 1.09% for ages 40-55 years), a greater frequency of major complications, and more prolonged hospital stays-all of which persisted after multivariable adjustments. However, despite its strong association with 30-day operative mortality, the authors reported that the impact of older age was comparable to other preoperative risk factors predictive of short-term operative outcomes [13]. Age alone should therefore not be a reason to withhold adjuvant, neoadjuvant, curative, or palliative treatment options in this patient population.

Preoperative Assessment

A good understanding of preoperative, intraoperative, and postoperative factors that may contribute to outcomes in this patient population will help develop appropriate care strategies to minimize perioperative risk for adverse short-term operative outcomes. Despite its association with increased perioperative morbidity and mortality, chronological age alone is not a good gauge of the physiology of aging and its effects on perioperative outcomes in a particular patient. Due to significant interindividual variability in the biology of aging, comorbid burden, frailty, and functional status, the detailed assessment of each individual patient as well as establishing clear goals of therapy (curative intent or palliation of symptoms) becomes critical in the elderly patient with cancer. Elderly patients are less likely to undergo surgical treatments regardless of disease stage [3]. As with any surgical patient, medical optimization of comorbid burden is vitally important. It is also important to identify the patient's symptom burden prior to surgical intervention as these directly influence patient distress, quality of life (QOL), and survival [14]. Preoperative assessment of symptom burden may aid in optimizing intraoperative and postoperative management strategies aimed at returning the patient to his or her presurgical baseline. There are many tools available for the practitioner to administer in assessing a broad spectrum of symptom content. Each tool varies in psychometric validation [14].

Although the role of a geriatrician has not been established in surgical care of the cancer patient, many studies show preoperative geriatric assessment predicts postoperative mortality and morbidity as well as survival in geriatric oncology patients [15, 16]. A comprehensive geriatric assessment (CGA) is defined as "a multidimensional, interdisciplinary diagnostic process to determine the medical, psychological, and functional capabilities of an older person in order to develop a coordinated and integrated plan for treatment and long-term follow-up" [17]. In fact, some of the first studies of the relationship between CGA status and perioperative morbidity and mortality were performed in patients with cancer. Particularly telling were the assessments of instrumental activities of daily living (IADLs), degree of comorbidities, and polypharmacy. Recently there has been an increasing focus on actual testing of the patient rather than the use of questionnaires for functional assessment. Examples of performance-based measures of functional status are the "Timed Up and Go" test, the 6-minute walk test, and the grip strength. Despite this focus, additional studies are still needed to test the prognostic ability of performancebased measures of functional status as well as any statistical correlation between objective and subjective measures of functional status in the geriatric oncology patient. Understanding the functional capacity and fatigue level in the elderly oncologic patient may aid in determining candidacy for surgical intervention [6]. The Preoperative Assessment of Cancer in the Elderly (PACE) is a prospective, international study designed to determine if the fitness of elderly surgical patients with malignant tumors can be assessed accurately enough to permit individualization of treatment [6]. Overall, the burden of comorbidity is associated with worse survival in patients with cancer [18–22]. It is becoming evident that concomitant diseases impact not only overall survival but also the behavior of the cancer itself. For example, diabetes decreases the 8-year disease-free survival of stage III colon cancer patients to an extent similar in magnitude to the beneficial effect of fluorouracil/levamisole adjuvant therapy [18]. Similarly, hyperinsulinemia is associated with a worse disease-specific survival in patients with prostate cancer [19], colon cancer [20], and breast cancer [21]. Obesity is also associated with a worse progressionfree survival and worse overall survival in patients with ovarian cancer [22]. Nagle et al. demonstrated that overweight, obese, and morbidly obese women with ovarian cancer had worsened survival when compared with women of normal range body mass index (BMI). Furthermore, risk of death increased 3% for each five unit increase in BMI above 18.5 kg/m² [23]. The effect of obesity on cancer survival is not limited to women as it is a risk factor for prostate cancer in men and is associated with an increased risk of disease progression after confirmatory biopsy in men in low-risk prostate cancers [24-26]. IGF-1, a growth factor pathogenic in tumor development, is elevated in both obese and hyperinsulinemic patients and is implicated in part in the carcinogenesis in these patient populations [27]. When controlling for all comorbidities, obese, elderly patients have a 25% increased risk of readmission compared to nonobese, elderly patients [28]. BMI is directly proportional to the rate of readmission in elderly patients [28].

Although surgery alone may be curative for early-stage solid tumors, many elderly patients will require neoadjuvant therapy (chemotherapy, radiation therapy, or hormone therapy as a single intervention or the combination) to shrink tumor prior to surgical resection. It is therefore extremely important to understand the potential systemic side effects of such treatments in temporal relationship to the operative procedure. In a study of over 34,000 patients with non-small cell lung cancer, Hardy et al. demonstrated significant associations with the use of chemotherapy/radiation therapy and risks of developing cardiac toxicity. The risks of treatmentassociated ischemic heart disease or cardiac dysfunction were greatest among patients with left-sided lung tumors [29]. In addition, perioperative risk associated with neoadjuvant therapy increases with increasing age and increasing time from initial diagnosis. It is not clear if combination neoadjuvant therapy confers additional risk compared to a single-agent therapy [29–34]. Interestingly, radiation to the left chest carries greater risk for a patient to develop myocardial ischemia than radiation to the right chest [29]. Specific chemotherapeutic agents have known cardiac side effects regardless of single or multimodal therapy [35]. For example, anthracyclines are associated with acute heart failure, arrhythmia, and OT prolongation, whereas antibody-based TK inhibitors are known for LV dysfunction. Antimetabolites (5-fluorouracil, capecitabine) are associated with myocardial ischemia, acute myocardial infarction, and arrhythmia. Other chemotherapeutic agents are known for pulmonary toxicity including doxorubicin, methotrexate, bleomycin, and busulfan. Reported incidence of acute pulmonary toxicity with bleomycin is up to 40% with a fatality rate of 1.5%. The toxicity patterns can range from subacute progressive pulmonary fibrosis to hypersensitivity pneumonitis, organizing pneumonia or an acute chest pain syndrome. While the symptoms and signs usually develop during treatment and regress with discontinuation of therapy, they could be delayed in manifestation up to 6 months after completion of therapy and may not ever completely resolve. Hyperoxia may potentiate acute pulmonary toxicity from bleomycin and should therefore be avoided [36, 37]. One proposed mechanism is that the production of highly oxidized radicals may be increased with increased FiO2. Oxidative stress occurs when a cell cannot destroy the excess free radicals. These free radicals may exert toxicity on surfactant production increasing damage to alveoli as well as nuclear DNA which results in fibrosis as well as potentially increase risk for malignancy [36, 38]. Preoperative questioning of exposure to these medications, detailed history on the tolerance and course of therapy, as well as signs and symptoms of pulmonary toxicity from exposure are important for planning perioperative care strategies. For patients with a history of pulmonary toxicity to bleomycin, intravenous fluid therapy should be guided to avoid volume overload and perioperative pulmonary edema. In the absence of a history of bleomycininduced pulmonary toxicity, exposure to bleomycin in itself is not a reason to restrict higher FiO2.

Frailty is now widely regarded as an independent risk factor for poor outcomes in the elderly patient with cancer [39]. Phenotypic frailty, the most widely studied preoperative screening tool, uses five criteria including involuntary weight loss, exhaustion, slow gait, poor grip strength, and sedentary behavior [40]. Two separate investigations have concluded that frailty is an independent predictor of discharge to a supported facility, the number of complications, and length of stay [41, 42]. Both concluded that adding frailty index to either the ASA physical status or other indices of risk such as either the Lee or Eagle Index would improve the area under the receiver operating characteristic (ROC) curve to about 0.86 for prediction of surgical complications and discharge to an assisted or skilled nursing facility [43]. Most recently, Chen et al. demonstrated that frail and sarcopenic geriatric patients demonstrated increased postoperative complications after total gastrectomy for gastric cancer [44]. Unfortunately, despite these risk factors, it is difficult to find a frailty assessment index that can sufficiently cull patients needing further preoperative assessment [45].

Tahiri et al. have demonstrated that elderly patients who experience a greater number of more severe complications take longer to return to their preoperative functional status following abdominal surgery. However, assessing the overall contribution of the number and the severity of postoperative complications to outcomes has been a challenge. The comprehensive complication index (CCI), first developed by Clavien et al., is a tool which accounts for both the number and severity of complications and generates a numeric score on a scale of 0 to 100 with higher numbers indicating greater likelihood of taking longer to return to preoperative functional status [46]. Of all statistically significant predictors of recovery, the comprehensive complication index score was

the only potentially modifiable factor [47]. Instituting evidence-based perioperative care pathways to minimize symptom burden with a particular focus on pain control and delirium prevention; early rescue to prevent cardiovascular, thrombotic, pulmonary, renal, and infectious complications; and improving functional recovery by early mobilization (with adequate fall precautions) are key in this vulnerable patient population. One such pathway is the enhanced recovery pathway. This is a philosophy of care, which utilizes multidisciplinary interventions in the preoperative, intraoperative, and postoperative phases of care in order to expedite recovery of the patient to his or her baseline. An important component of the perioperative care continuum is patient preparation including advanced care planning (ACP) and optimization for surgery, with particular focus on prehabilitation programs. Advanced care planning occurs when the patient, while able to understand and make decisions for end-of-life care, discusses and makes known those desires with the physician and family members [48]. Wright et al. demonstrated that patients who did not have end-of-life discussions receive more aggressive end-of-life care than those who did designate their wishes. Further, patients' quality of life decreased as the number of aggressive interventions increased [49]. A discussion with the patient and his or her loved ones regarding advanced care planning is essential in the management of any oncologic patient.

Intraoperative Management

Perioperative care of the elderly patient requires recognition of special considerations of the contracted intravascular volume status, higher vascular tone (sympathetic dominance), left ventricular hypertrophy, and diastolic dysfunction, all of which lead to higher risk for hypotension at induction of anesthesia. Furthermore, they are dependent on both heart rate and adequate ventricular filling pressures to maintain their cardiac output secondary to diastolic dysfunction. A large retrospective [50] as well as a case-controlled [51] study has independently reported an increased incidence of 30-day mortality and postoperative ischemic stroke, respectively, with intraoperative hypotension. While in the former study, there was a relationship between the area under threshold (AUT) for blood pressure deviations based on the population and individual patient-related baseline data, the later study demonstrated hypotension best defined as a decrease in mean blood pressure relative to a preoperative baseline value. Extension of the importance of avoiding intraoperative hypotension is perhaps the concept of "triple low." The triple low condition consists of mean arterial pressure (MAP) <75 mm Hg, BIS <45, and an end-tidal volatile anesthetic concentrations in minimum alveolar concentration (MAC) equivalents of <0.8. Cumulative duration of triple low was

shown to be associated with perioperative mortality [52]. In a subsequent study, patients enrolled in the B-Unaware, in the BAG-RECALL, and in the Michigan Awareness Control Study were evaluated for cumulative concurrent duration of MAC less than 0.8, MAP less than 75 mmHg, and BIS less than 45 (triple low) [53]. Triple low in this study was independently associated with an increased risk of 30- and 90-day postoperative mortality even after controlling for patient comorbidity through propensity matching. It could be speculated that perhaps triple low identifies patients who are sensitive to anesthesia secondary to poor cerebral reserve (age, frailty, systemic disease and illness) and possibly at risk of brain hypoperfusion.

Other intraoperative management strategies aimed at reducing postoperative complications include those within an enhanced recovery after surgery program. Enhanced recovery after surgery was first introduced by Henrik Kehlet in the early 1990s. It is a multimodal approach which utilizes strategies in all phases of the perioperative period to attenuate the surgical stress and as a result decrease length of stay and reduce postoperative complications [54–57]. Within the intraoperative phase, key components are fluid management and opioid-sparing analgesia as well as minimizing indwelling catheters, drains, and nasogastric tubes. Goal-directed fluid therapy (GDFT) and hemodynamic optimization based on regulating vascular content, tone, and integrity may have value in patients undergoing complex surgery with risk for major blood loss [58]; however, the data is conflicting [59– 61]. Specific oncologic procedures coupled with diseasespecific variations in the pathophysiology may show different results based on potential complications directly related to intraoperative fluid management. For example, Colantonio et al. demonstrated the use of GDFT in patients undergoing cytoreductive surgery, and hyperthermic intraperitoneal chemotherapy improves outcomes as measured by systemic postoperative complications and length of stay as compared to standard fluid therapy [62]. Another prospective study examining malignant ascites in epithelial ovarian cancer revealed that fluid demands steadily increase in patients with high-volume malignant ascites which can be treated using GDFT coupled with cardiac output monitoring [63]. Conversely, GDFT did not improve clinical outcomes in patients undergoing major elective rectal surgery as opposed to colonic resection [64], again supporting that physiologically distinct processes coupled with individual patient characteristics [65] may be an explanation for applicability in GDFT. Nonetheless, intraoperative hemodynamic stability is a crucial piece in maintaining end-organ perfusion and reducing postoperative complications.

Perioperative blood transfusion in patients with cancer is a complicated story. Fluid therapy, hemodynamic optimization, and anemia management are to be considered together in the perioperative period to maintain optimal tissue oxygen delivery. Frequently patients with cancer are anemic, undergo complex surgical procedures with major blood loss, and are frequently administered large amounts of intravenous fluids in the perioperative period. To maintain tissue oxygen delivery, these patients often receive allogeneic erythrocyte transfusions along with fluid therapy for hemodynamic optimization. There is a concern over the possible negative effects of erythrocyte products on cancer progression and recurrence due to the immunomodulation and inflammatory consequences of blood transfusions. There are relatively few randomized trials related to transfusions and cancer recurrence. Pooled estimates of the effect of perioperative blood transfusions on recurrence in colon resections for cancer resulted in an OR of 1.42 (95% confidence interval, 1.20-1.67) against transfused patients from randomized studies in a recent Cochrane review. Although heterogeneity was detected, stratified meta-analyses confirmed these findings by site and stage of disease, timing of administration of blood products, type of products administered, and volume of transfused products. However, given the heterogeneity and the inability to assess the effect of the surgical technique, the authors were not able to attribute a definite causal relationship [66]. In a recent randomized control trial of patients admitted to the ICU after major surgery for abdominal cancer, a liberal erythrocyte transfusion strategy using a hemoglobin threshold of 9.0 g/dl was found to be superior compared to a restrictive strategy with a hemoglobin threshold of 7.0 g/dl [67]. The decision to transfuse in these patients should therefore be carefully considered balancing the acute effects of untreated anemia on immediate postoperative complications and the long-term oncologic effects of erythrocyte transfusions. In those patients who are at risk of developing significant anemia during or immediately after surgery (hemoglobin <9 g/dl), an active blood and anemia management program consisting of preoperative administration of iron supplements or blood transfusions, minimal access surgical techniques, and intraoperative strategies to conserve and minimize blood loss may prove helpful. This is particularly important in the elderly patient population given their poor physiologic reserve and inability to tolerate inadequate tissue oxygen delivery with significant impact on morbidity and mortality.

Another key component of the enhanced recovery program is opioid-sparing analgesia while providing effective dynamic analgesia. In a retrospective review of over 300,000 patients, 12% had an opioid-related adverse event (ORADE) [68]. ORADE contributed to increased length of stay and increased likelihood for readmission [68]. An additional retrospective study examining greater than 100,000 patients undergoing abdominal surgical procedures demonstrated approximately 10% ileus in the postoperative period leading to increased readmission rate, increased length of stay, and increased total cost [69]. The pharmacokinetics of most opioids have significant variability. Due to changes in gut absorption, metabolism and clearance with aging, coupled with the pharmacodynamics of aging, generally cause opioids to be more potent and have a longer duration of action than compared to younger patients [70]. Multimodal opioidsparing analgesia can be effective in managing postoperative pain without the risk of opioid-related adverse events. Nonsteroidal anti-inflammatory medications and selective Cox-2 inhibitors consistently reduce postoperative opioid consumption [71]. Local and regional anesthesia also decreases postoperative opioid consumption when utilized as part of a multimodal strategy [72]. While minimizing ORADE contributes to improved outcomes in the elderly, it remains to be seen if wider adoption of nonsteroidal antiinflammatory drugs (NSAIDs) and Cox-2 inhibitors as part of the multimodal opioid-sparing regimen will result in other unexpected adverse events and morbidity. It is important to assess the patient's history and understand the planned surgical procedure when developing the plan of care.

Postoperative Considerations

Perioperative complications are directly related to poor surgical outcome in elderly patients [73]. Neurologic complications are the most common postoperative complication in elderly patients [74]. A spectrum of cognitive abnormalities occurs after major complex surgery in the elderly patient population. These range from delayed emergence, emergence delirium, postoperative delirium (24-72 h after surgery), and postoperative cognitive dysfunction (POCD). Postoperative delirium (POD) is seen in a significantly higher number of older surgical patients. Hempenius et al. have concluded that the preoperative level of cognition and the severity of the surgical procedure are independent risk factors for POD in elderly undergoing elective surgery for solid tumors [75]. Controlling postoperative pain is important in preventing delirium. Higher pain scores are associated with postoperative delirium in elderly patients undergoing noncardiac surgery [76]. While POD has been associated with higher incidence of postoperative complications, prolonged length of hospital stay, and increased risk for mortality [77], the level of functional impact of POCD is less clear. However, it is reported that POCD has an impact on functional outcomes such as ADLs (activities of daily living) and IADLs (instrumental ADLs) [78]. Postoperative cognitive dysfunction may resolve with time. Currently, it seems the incidence of initial cognitive decline in older patients is high (25% at 2-10 days) with gradual resolution (10% at 3 months, 5% at 6 months, 1% at 1 year). At 1 year, 429

the cognitive decline is indistinguishable from matched controls [79]. The observed link between exposure to anesthetics and development of clinical dementia in laboratory observations has not been clearly established in clinical practice [80]. There is some evidence to suggest that avoiding sedative medications, providing adequate pain relief, avoiding deep anesthesia, maintaining diurnal rhythms in sleep cycle, minimizing disruption to patient's usual daily routines as much as possible, maintaining contact with familiarity to friends and family, and early control of infectious and metabolic derangements can decrease the incidence of delirium [81]. Identifying patients at high risk for POD, employing perioperative measures to minimize POD, having a high index of suspicion, and instituting timely interventions in the postoperative period will help improve outcomes for this high-risk patient population.

Cardiovascular and pulmonary complications represent additional concerns in the elderly patient. Age alone remains a risk for pulmonary complications even after adjusting for comorbidities [82]. Despite this well-known fact, there are few studies examining therapeutic interventions to reduce pulmonary complication risk in elderly patients. Sieber et al. described risk factors for pulmonary complications to include long-acting neuromuscular blockade, poor lung expansion [83, 84], site of surgery, and aspiration. Hoeks et al. proved the Lee Risk Index is a prognostic factor in both late mortality and impaired health status [85]. Factors increasing risk for late mortality were cerebrovascular disease, insulin-dependent diabetes, and renal insufficiency. Factors increasing risk for impaired health status were ischemic heart disease, heart failure, cerebrovascular disease, insulin-dependent diabetes, and renal insufficiency. Awareness of the patient's comorbidities will aid in postoperative management and in reducing overall complications and improving outcomes and QoL (quality of life) in this high-risk patient population. Failure to rescue, defined as the number of patients who die from postsurgical complications divided by the total number of patients who develop complications, is a measure of an institutions ability to diagnose and treat postoperative complications [86]. In a prospective study utilizing the National Surgical Quality Improvement Project (NSOIP) database, Tamirisa et al. examined patients undergoing pancreatic resection and discovered that inhospital mortality was higher in patients 80 years of age or older as well as failure to rescue rates. Further, diabetes, COPD, and ascites were associated with increased risk of failure to rescue. "Failure to rescue" patients were associated with complications such as acute renal failure, septic shock, and pulmonary complications [86]. These data suggests that increased failure to rescue in the >80 years of age patient population correlates with increased mortality rate. It also suggests that timely intervention and, more importantly, early recognition of postoperative complications

may reduce postsurgical mortality in the elderly patient. Although elderly patients experience cardiovascular and pulmonary complications more frequently than non-elderly patients, the initial pulmonary or infectious complication is associated with a significantly higher failure to rescue rate [87]. Given that more than two thirds of patients with failure to rescue have multiple complications [88], attempting to identify patients who are at increased risk for postoperative complication may dramatically reduce morbidity and mortality in this age group.

Another measurable outcome new to surgical and anesthetic oncology is the time to return to intended oncologic therapy (RIOT). This is a metric that facilitates comparison of surgical and perioperative interventions, including enhanced recovery, to determine the amount of time required to begin postsurgical adjuvant therapy. It has been demonstrated that hypertension, multiple preoperative chemotherapeutic regimens, and postoperative complications may cause inability to RIOT [89]. Further, inability to RIOT correlates with shorter disease-free intervals and overall survival [89]. As cancer therapies become more available and effective, and the number of cancer survivors grows in this patient population, outcomes such as the length of time to RIOT, the quality of survival in addition to disease-free survival and overall survival will be important to measure. Recovery of functional status (IADLs in this patient population) is particularly important as it is one of the domains of recovery that takes the longest to return to baseline (preoperative) levels following surgery. Furthermore, this becomes all the more relevant in discussions pertaining to patient-centered outcomes and improving population health (triple aim) as many elderly patients value functional independence more than lifesaving therapy if it results in cognitive or functional impairment. Perioperative care of the elderly cancer patient is an intricate matter that requires attention to detail in all phases of care and must be congruent with the patient's goals for treatment.

Significant Gaps in Our Knowledge

- 1. What is the best way to prevent failure to rescue as measured by early recognition and decreased postoperative morbidity and mortality?
- 2. How can we minimize the time for return to intended oncology therapy in the elderly cancer patient?
- 3. Which screening tool is best to assess frailty as measured by sensitivity to predict risk of postoperative complications?
- 4. Do NSAIDS and Cox-2 inhibitors have an impact on morbidity and mortality when used in conjunction with multimodal opioid-sparing analgesic techniques?

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Part V

Postoperative Care

Pain Management

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The number of Americans aged 65 and older are projected to more than double from 46 million today to over 98 million by 2060, and the 65-and-older age segment of the total population will rise to approximately 24% from 15% [1] (http:// www.prb.org/Publications/Media-Guides/2016/aging-unitedstates-fact-sheet.aspx). Given these evolving demographics, it is anticipated that there will be a concomitant rise in the demand for a variety of surgical services [2]. Regional anesthetic and analgesic techniques are being utilized increasingly in the perioperative plan as a way to improve pain control, reduce opioids, and improve compliance and outcomes. Epidural anesthesia includes low doses of local anesthetic agents, which can result in sympathetic blockade that may be exaggerated in the elderly patients [3–5].

According to the latest data from the National Center for Health Statistics, the total number of inpatient procedures performed in US hospitals in 2006 was around 48 million and over 50 million ambulatory surgeries up from 40.3 and 31.5 million, respectively, in 1996 [6] and the elderly patients undergo a disproportionate number of surgical procedures compared with younger age groups. The increase in outpatient surgery has dramatically outstripped the increase in inpatient surgeries over the past few decades presenting special problems for providing appropriate pain management [7]. There is no doubt that acute pain secondary to surgery, either inpatient or outpatient, will continue to be a significant problem for physicians.

In addition, estimates are that 80%–85% of individuals over 65 years old have at least one significant health problem that predisposes them to pain. Epidemiologists at Brown

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University (reporting in JAMA, June 17, 1998) found that between 25% and 40% of older cancer patients studied had daily pain. Among these patients, 21% between the ages of 65 and 74 received no pain medication at all. Of those 75–84 years old, 26% received no pain medication, and for those older than 85, 30% were left untreated [8].

In northern California, Jury Verdict No. H205732–1 of the California Superior Court awarded \$5 million to the family of an elderly lung cancer patient in a civil suit in which the physician was found liable for recklessness and elder abuse for failure to prescribe adequate pain medication. This resulted in California Assembly Bill 487 that required all physicians in California to obtain 12 continuing medical education credits in pain management and palliative care over the next 3 years following the passage of the law in order to renew their licenses.

Currently, in California, for example, 50 contact hours must be completed every 2 years of continuing medical education of which 20% must be in the area of geriatric medicine if 25% of patients in the doctor's practice are older than 65 years old (but particularly for doctors with practices in Family and/or Internal Medicine). There remains the onetime requirement of 12 h in the subject of pain management and the appropriate care and treatment of the terminally ill. The Medical Board in California will accept courses or programs that address one or both topics. These requirements reinforce the need for better education of physicians in geriatric pain management. Other states have instituted similar recommendations, in part, to reduce the epidemic of prescription opioid abuse.

And so, as much as providing adequate pain management is a moral obligation, inadequate pain management has also become a liability. There are about 1.5 million frail elderly patients residing in 20,000 nursing homes in the United States. Forty percent are over the age of 85 years. Forty-five percent to 85% may have pain as compared with 25%–50% of community-dwelling elderly patients [9, 10]. A telephone poll, conducted by Cooner and Amorosi from Louis Harris

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and Associates of New York City in 1997, revealed that more than half of older adults had taken prescription for pain medications for longer than 6 months, and 45% had visited at least three physicians for their pain in the last 5 years [11]. New pain visits to physicians are most common in the 15- to 44 -year-old group, whereas the lowest are in the elderly patients. Persistent pain complaints, however, are most common in the elderly patients, and pain is the most common symptom noted by the consulting physician [12]. Yet elderly people and young children are often perceived by the health care delivery system as being insensitive to pain. And therefore, those who are most dependent on the health care system are most likely to receive the least optimal care for pain.

Pain is a highly subjective, variable sensory and emotional experience, with a pathophysiology composed of complex neuroanatomic and neurochemical processes [13]. Everyone has an intuitive idea of what pain is. Pain is always something that "hurts." But many things hurt. A broken arm hurts. This is an example of acute somatic pain. A heart attack hurts. This is ischemic pain. A kidney stone and appendicitis hurt, which are examples of visceral pain. An amputated leg may hurt; this is phantom limb pain. An individual may hurt in the arm or leg on the side affected by a stroke. Both of these are examples of central neuropathic pain. The death of a loved one "hurts." It is a "painful emotional experience" for which we use the same words of description as for physical injury. It is clear then that the perception of "pain" is always subjective and takes place in the brain. Tissue injury is perceived as nociception. But the site of the nociception does not necessarily correspond to the area of the body in which "the pain" is felt. Furthermore, the tissue injury may have actually healed while the perception of pain persists.

Three Pain Scenarios

It is quite clear from the above introduction that pain in the elderly patients follows one of three scenarios:

- 1. Acute pain results from surgery, cancer, fractures, medical conditions such as vascular ischemia, herpes zoster, etc.
- 2. Chronic pain results from various persistent medical and physical conditions. Specific chronic pain syndromes that are known to affect the geriatric population disproportionately include arthritis which may affect 80% of patients over 65, cancer, herpes zoster and postherpetic neuralgia, temporal arteritis, polymyalgia rheumatica, atherosclerotic peripheral vascular disease, diabetic neuropathy, and back pain syndromes [13]. In chronic pain states, there is often the absence of the "normal" physiologic indicators of acute pain such as tachycardia, hyper-

tension, and diaphoresis. Yet, there may be hyperpathia, allodynia, and hyperalgesia in the absence of any physical findings of tissue injury:

- Allodynia is pain elicited by a nonnoxious stimulus (clothing, air movement, and touch), mechanical (induced by light pressure), and thermal (induced by a nonpainful cold or warm stimulus).
- Hyperalgesia is exaggerated pain response to a mildly noxious (mechanical or thermal) stimulus.
- *Hyperpathia* is delayed and explosive pain response to a noxious stimulus.
- 3. Finally, there are those who are suffering from persistent pain who then experience a new acute injury or exacerbation of their primary condition that is superimposed on their primary pain state.

Elderly patients present special problems with respect to treating pain in each of these three scenarios.

Depression, Anxiety, and Pain

Associations between pain and depression are well documented in elderly patients [14-16].

Studies show that elderly subjects who are anxious and/or depressed voice more localized pain complaints than their nonanxious and nondepressed counterparts. Furthermore, anxious and/or depressed individuals report more intense pain [17, 18]. Clinical evidence suggests that cognitive impairment may be exacerbated by pain and/or its treatment, especially in the elderly patients. These patients may benefit dramatically from psychologic or psychiatric interventions. Common missed diagnoses or underdiagnosed diseases in the elderly patients that can cause pain include the following: endocrine disorders, neurologic disorders, major medical disorders including electrolyte imbalances, polypharmacy, dysphoria, sleep disturbances, and loss of appetite, etc. [13].

Assessment

Many older adults are afraid to report pain [19, 20]. There is often fear of losing independence because of chronic illness. If an older adult fears that reporting pain will lead to a debilitating diagnosis that may cause nursing home placement or further loss of physical independence, he or she may be less likely to report it. Or the patient may fear additional procedures, diagnostic tests, or medication prescriptions that may result from reporting pain. For acute postoperative pain, this is less of a problem unless the patient has dementia or other condition that prevents direct communication.

Elderly patients may present special problems in obtaining an accurate pain history. Failures in memory, depression, and sensory impairments may hinder history taking. They may tend to under report symptoms because they expect pain associated with aging and their diseases, or because they just do not want to be a bother to anyone. The inability to be aware of and to verbalize one's emotional state is called *alexithymia*. Patients with chronic pain have been found to have a significant incidence (33%) of alexithymia. This may be a factor in causing geriatric patients to express emotional distress more often through somatic complaints because they have been found to be more alexithymic [21].

Nociception Is Not Pain

Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a *psychologic state*. Although we appreciate that pain most often has a proximate physical cause, especially acute pain, activity in nociceptor systems is not equivalent to the experience of pain. The recognition that pain serves an important biologic function related to survival, raises the important question: To what extent do age-related changes in nociception affect the capacity of the pain experience to fulfill an "enteroceptive" function, such as thirst, hunger, and thermoception that constitute sensory indexes of the health of the body? [22].

Age does not seem to affect success of traditional interventions for the treatment of pain. Assessment and intervention for pain in the elderly patients should begin with the assumption that all neurophysiologic processes subserving nociception are intact. That is to say, tissue injury produces the same intensity of stimulus in an elderly person as in a young person. There are data to suggest that there is impairment of A δ fibers with aging and therefore of the early warning of tissue injury [22]. There are also data that suggest that widespread and substantial changes in structure, neurochemistry, and function occur in the dorsal horn of the spinal cord and central nervous system (CNS) with aging [22].

Multiple studies report reductions in the descending inhibitory modulating systems for nociception in the elderly patients. Gibson and Ferrell [22] conclude that the reduced efficacy of endogenous analgesic systems might be expected to result in a more severe pain after prolonged noxious stimulation. It is also possible that documented decline in afferent transmission pathways could be offset by a commensurate reduction in the endogenous inhibitory mechanisms of older persons, with a net result of little or no change in the perceptual pain experience [22]. They further conclude that any deficit in endogenous analgesic response (which is stimulus intensity-dependent) will become critical, thereby making it more difficult for persons of advanced age to cope with severe or persistent clinical pain conditions [22].

Although there is controversy over whether the number and integrity of nociceptors decreases with age, *the position* that age dulls the sense of pain is untenable [22]. It is the processing of the nociceptive information that may be altered in the elderly patients, and the elderly patients may be more sensitive to the side effects of medications that are used to treat pain. These observations thereby give the impression that the elderly patients are less sensitive to pain. But no physiologic changes in pain perception in the elderly patients have been demonstrated according to a recent five-state study [8]. One would not assume that a surgical incision in an elderly patient will "hurt" less and therefore does not need to be treated. Likewise, anyone who has observed an elderly patient with acute herpes zoster certainly can attest to the excruciating pain that these unfortunate patients report.

Pathophysiology of Types of Pain

Somatic Pain

A noxious stimulus in the periphery activates nociceptors. This results in a release of pain-producing substances, e.g., prostaglandins, leukotrienes, and substance P. Impulses travel via A δ and C fibers to the dorsal horn of the spinal cord. Somatic pain is well localized and gnawing. There is also often the presence of associated tenderness and swelling. Examples include fractures, bone metastasis, and postoperative pain. This type of pain is usually opioid-responsive.

Visceral Pain

When viscera are stretched, compressed, invaded, or distended, pain will result. The pain is poorly localized and may be referred to seemingly somatic areas distant from the viscera of origin. It is described as deep, squeezing, cramplike, or colicky. It is frequently associated with sympathetic and parasympathetic symptoms: nausea, diaphoresis, and hypotension. Examples include bowel obstruction and pancreatic cancer. This type of pain is also usually opioid-responsive.

Neuropathic Pain

Injury to neural tissues or dysfunctional changes of the nervous system from trauma, compression, tumor invasion, or cancer therapies result in this form of pain. The pain may be associated with sensory and motor deficits, but not always. The quality of the pain is often described as burning, squeezing, lancinating, or electrical. There can be associated sleep and eating disturbances, and significant patient emotional suffering. Examples include brachial and lumbosacral plexopathy, postherpetic neuralgia, neuromas, complex regional pain syndrome, diabetic neuropathy, and radiculopathies. Neuropathic pain is associated with opioid tolerance, termed "*apparent opioid resistance*." That is, patients with neuropathic pain often require higher than expected doses of opioids to obtain pain relief, and the pain relief is usually not complete.

Neuropathic Pain and Visceral Hypersensitivity

Injury of nerves innervating somatic structures enhances nociception from stimulation of viscera with convergent input from nearby dermatomes, suggesting that somatic neuropathic pain could be accompanied by an increased likelihood of visceral pain [23]. This raises the possibility that pain disorders such as fibromyalgia (FM), chronic fatigue syndrome, chronic pelvic pain, and chronic interstitial cystitis all represent visceral hypersensitivity pain syndromes of neuropathic origin. More recently, it is becoming apparent that the pain of FM seems to be accompanied by generalized central sensitization, involving the length of the spinal neuraxis. Thus, widespread central sensitization appears to be a hallmark of FM and may be useful for the clinical case definition of this prevalent pain syndrome [24].

Medication Management

Little is known of the neurophysiologic relationships between pain and age-related degenerative brain diseases. However, Fine [25] has reviewed the issues of pharmacologic management of persistent pain in older patients. In general, pharmacodynamics (what the drug does to the patient) is unaffected in the normal aging process. The molecular action of morphine is the same in all animals, although dose requirements to produce the same effect may change with age. However, because centrally acting drugs may interact with a preexisting disease state, care must be taken when treating pain in patients with CNS disease such as Parkinsonism, Alzheimer's disease, dementia, or stroke.

Pharmacokinetics (what the patient does to the drug) is frequently affected by aging processes, and disease states. Pharmacokinetic changes attributable to physical aging may complicate medication management [26]. There is decreased liver mass and blood flow, which prolongs opioid and acetaminophen metabolism. This is of concern, particularly with fixed combination drugs, such as hydrocodone or codeine with acetaminophen (Vicodin[®], Norco[®], or Tylenol[®] 3#) and opioids with active metabolites, e.g., morphine to morphine-3-glucuronide or meperidine to normeperidine.

There is decreased renal function which increases the risk of nonsteroidal anti-inflammatory drug (NSAID) nephrotoxicity and accumulation of metabolites of drugs such as meperidine. There is decreased plasma binding, which increases blood levels of active drugs, opioids, and NSAIDs (even the cyclooxygenase [COX-2] specific inhibitors, such as celecoxib [Celebrex[®]]) [27].

In the elderly patients, there is increased CNS sensitivity to opioids leading to enhanced sedation, analgesia, and side effects including delirium. But the experience of pain tends to counteract the sedative effects of opioids. Therefore, patients who have not received adequate doses of opioid analgesics and who are still experiencing pain do not suffer respiratory depression [28].

In acute pain situations or in a "pain crisis," rapid titration of opioids in elderly patients is safe. In a study of 175 elderly patients versus 875 younger patients who were treated with intravenous (IV) morphine for postoperative pain in the postanesthesia care unit, there was no increased incidence of adverse side effects noted when a strict titration to pain level protocol was followed. It was not necessary to change the protocol according to age [29, 30].

The use of an opioid is the strategy of choice for rapid titration to pain relief in most clinical situations. Opioid side effects are usually manageable if frequent assessments are made. The elderly patients, of course, may require more frequent assessments and smaller incremental doses in order to manage side effects. The exact timing of interval assessments must be dictated by the needs of the individual case.

The management of an acute pain crisis involves immediate control of the pain, maintenance of analgesia, and a longterm management plan. During the initial titration to pain relief, there is ample opportunity to evaluate the patient for the causes of the pain. The best way to gain control is to get the syringe and titrate to effect. The dose depends on the history of current use or whether the patient is opioid-naive and the familiarity of the physician with the different analgesics.

Opioids such as hydromorphone and meperidine reach maximum effective site concentrations 10–15 min after an IV bolus. Fentanyl reaches maximum effect in just over 3 min. Morphine reaches 50% of its effect in 5 min but may not reach full effect for another 60 min. Although fentanyl and its congeners are very potent and fast onset analgesics, they are less suitable as analgesics outside of the operating room. Bolus doses every 10–15 min of hydromorphone until the patient is comfortable, begins to become sedated, or has decreasing respiratory rate has become the most effective method of opioid analgesic loading.

Aubrun et al. report that acute pain control in the postanesthesia care unit is essential [29]. The protocol for rapid pain control includes titration of morphine even though they agree that it is not the most ideal agent for rapid IV administration. However, they did report that morphine titration can be used with caution in elderly patients, in children, or in obese patients. In practice, IV morphine titration allows the physician to meet the needs of individual patients rapidly and limits the risk of overdose making this method the first step in postoperative pain management [31].

After loading the patient and obtaining comfort, maintenance dosing must be ordered. Intramuscular or IV bolus dosing by the nursing staff on a PRN basis is a poor choice. The dose required to make the patient comfortable can be used as an estimate of the 3-h dose requirement for maintenance, e.g., when converting to IV patient-controlled analgesia (PCA).

Contraindications for IV PCA include patients who are unable to operate the device because of impaired mental status or physical limitations, and patients who are unwilling to use the technique, i.e., some patients do not want to push the button and want to be given their medication by the nurse. Patients with sleep apnea disorders pose a relative contraindication. Failure to achieve adequate analgesia without side effects after an appropriate trial is also a contraindication. If the patient chooses to have the nurse administer analgesia, it would still be advantageous to have a PCA set up, which would eliminate intramuscular injections that hurt and produce tissue injury in the elderly patients. Also, the medications can be titrated by the nurse using small doses at frequent intervals to achieve adequate analgesia.

Postsurgical Analgesia

As stated earlier, elderly patients undergo a high number of surgical interventions. The importance of adequate postoperative analgesia for reducing morbidity, and mortality in the elderly patients is undisputed [32]. Epidural analgesia and IV PCA are both excellent postoperative techniques. Physicians are often reluctant to use PCA in older patients [33, 34]. But PCA was found to be effective in this population with the caveat that the patient is physically or mentally able to operate the machine [35].

In a study of elderly patients after abdominal surgery, IV PCA versus patient-controlled epidural analgesia (PCEA) [36], the authors concluded that PCEA with local anesthetic and opioid provided better pain control, improved mental status, and better bowel function return than did traditional IV PCA morphine after general anesthesia. Orthostatic and mobility deficits were not a problem with the PCEA adjustments [36].

Carli et al. [37], in their study of patients for elective colon surgery randomized to an IV PCA group or epidural group, found that epidural analgesia enhanced functional exercise capacity and health-related quality of life indicators after colonic surgery. The results indicated that the epidural group had improved outcomes for pain control, mobilization, gastrointestinal motility, and intake of protein and calories. This may be a function more of the local anesthetic, facilitating bowel function, thereby causing less nausea, and more willingness to eat.

Decreased pain can also result in the same benefits, not just at rest but also with mobility, and less pain may ameliorate insulin sensitivity, hypercatabolism, and maintain muscle protein better. These benefits seemed to carry out to 6 weeks in the study of health-related quality of life indicators, leaving little doubt that epidural analgesia is even better than systemic opioids in the elderly patients [37].

Regional anesthetic techniques are also excellent for the elderly patients. Evidence is mounting that peripheral nerve blocks as the sole anesthetic or in combination with general anesthesia hold benefits. Surgical procedures that are particularly amenable to the addition of regional anesthetic techniques are hip replacements or fractures (lumbar plexus catheters or fascia iliaca catheters), knee replacements, Anterior Cruciate Ligament repair (femoral or adductor canal catheters ± sciatic catheters), shoulder surgery (interscalene catheters), upper extremity surgery (supraclavicular or infraclavicular catheters), thoracotomy or breast surgeries (paravertebral catheters), foot and ankle surgeries (lateral sciatic or popliteal catheters), abdominal surgeries (transabdominus plane block catheters), and rectus sheath block). For outpatient or short stay surgical procedures, peripheral nerve block catheters may be better than epidurals. Continuous infusion of low-concentration local anesthetics for 1-3 days postoperatively through a disposable pump with the patient removing the catheter at home [38-49].

Opioid Therapy

There is a large interindividual response to the analgesic effect of opioids and a relatively narrow therapeutic index [50]. Genetic factors contribute to the differential response to opioids by regulating their pharmacokinetics (metabolizing enzymes and transporters) and pharmacodynamics (receptors and signal transduction) [51]. In a study by Hwang et al., the *OPRM1* A118G opioid receptor gene variant polymorphism was associated with interindividual variability in postoperative response to opioids [52]. It seems evident that in the future physicians will be taking buccal swabs from their patients in order to determine genetic screening for opioid analgesic responsiveness.

Oral and transdermal medications should be used if possible. Opioids can be dissolved and put down a G-tube, and rectal preparations are available or can be compounded. Fast-onset and short-acting agents should be used for episodic pain, and long-acting agents for continuous pain. Meperidine should be avoided in elderly patients because of a higher potential for CNS effects [53]. Nausea and constipation should be treated prophylactically [20].

Opioid Addiction

The American Academy of Pain Medicine and American Pain Society define addiction as a compulsive disorder in which an individual becomes preoccupied with obtaining and using a substance for nonmedical reasons or reasons other than pain relief, the continued use of which results in a decreased quality of life. This does not seem to be a clinical issue in pain management for the elderly patients. Nonetheless, opioid phobia both on the part of the physician and the patient persists. It is even less of a problem in acute pain management postoperatively. Much of the problem is lack of knowledge about the differences among addiction, tolerance, physical dependence, and pseudoaddiction as described by Weissman and Haddox [54].

Any patient exposed to opioids for several days for the treatment of pain can experience withdrawal phenomena if the drug is stopped abruptly. This is not addiction and will occur with many different classes of drugs including betablockers, insulin, and various antihypertensive agents, etc. Likewise, the need to increase the dose of an opioid over time may be a measure of tolerance or worsening disease, neither of which equate with addiction. In pseudo-addiction, a patient who is prescribed an inadequate dose of an opioid may exhibit drug-seeking behavior in an attempt to obtain adequate analgesia. Drug seeking is frequently interpreted by medical staff as a sign of addiction. However, pseudo-addiction is an iatrogenically produced condition and careful monitoring of the patient will distinguish this from true drug addiction as defined above [54].

The new Centers for Disease Control and Prevention (CDC) opioid prescribing guidelines for primary care physicians have clearly set a national standard for opioid selection and dosing, cautioning prescribers to carefully assess and reassess the risks versus benefits of opioid therapy for each patient. Specifically, the guidelines note that primary care clinicians should avoid increasing a dosage beyond a threshold of 90 morphine milligram equivalents (MME) a day [55].

"Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediaterelease opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than 7 days will rarely be needed," the CDC guideline states [56]. The problem with these guidelines is that elderly patients frequently undergo painful surgical procedures and the pressures to discharge patients from the hospital earlier and require analgesic management at home or in rehabilitation facilities. Three to seven days of opioid therapy may not be adequate as the CDC guidelines maintain.

Titration of Opioids

Opioids are not generally considered to be "organ toxic," although data are accumulating that indicate that morphine has multiple other nonanalgesic-related effects such as apoptosis of nerve and brain cells in the presence of glial activation by inflammation. Morphine seems to have a multitude of opposite effects depending on acute small doses, chronic administration, or even single dose administration [57]. Furthermore, Bajic et al. have shown that repeated morphine administration in neonatal rats (PD1–7) is associated with increased supraspinal apoptosis in distinct anatomical regions known to be important for sensory (cortex) and emotional memory processing (amygdala) [58]. Brain regions are important for learning (hippocampus), and autonomic and nociceptive processing (hypothalamus and periaqueductal gray) were not affected.

Our knowledge of opioids is increasing rapidly. The classical view of opioid analgesia proposes (–)-opioid agonist isomers stereo-selectively bind to classical opioid receptors producing an inhibitory influence on nociceptive signal transmission. A growing body of literature suggests that the classical view of analgesia ignores an important nociceptive modulatory influence driven by opioid-induced glial activation resulting from opioid agonists binding to glial opioid binding receptors which in turn increase pro-inflammatory cytokines (such as interleukin-1) expression and release, leading to a decrease in opioid efficacy at the neuronal component [59].

Watkins et al. explain how (–)-opioid antagonists bind to both the neuronal and glial components resulting in blockade of any potential opioid analgesia and glial activation [59]. Due to the stereo-selectivity of neuronal opioid receptors only the (–)-isomer of opioid agonists and antagonists are able to bind. Therefore, when a combination of an opioid (+)-antagonist and an opioid (–)-agonist are introduced to this system, the (+)-antagonist is unable to bind to the stereoselective neuronal opioid receptor, but is able to block the non-stereo-selective glial site. The opioid (–)-agonist can act freely at the neuronal opioid receptor, but is unable to bind to the glial site due to its blockade by the (+)-antagonist. Therefore, this situation produces opioid receptor-mediated analgesia without the opposing force of opioid-induced glial activation, thereby potentiating opioid analgesia [59].

Chronic opioid administration modulates lymphocytes' functional capabilities increasing susceptibility to infectious diseases [60]. It is also becoming apparent that cytokines may cause depressive illness in man [61]. And so it is also becoming apparent that the use of opioids in pain therapy is much more complicated than once thought involving complicated relationships between the stress, endocrine, and immunological systems and the brain areas involved with

memory and mood (depression, anxiety). And yet all experienced pain physicians have treated or are treating a small subset of patients who seem to require high-dose, long-term opioid therapy, and remain functional.

So what is the correct dose of opioid analgesics? The "correct dose" is the dose that provides analgesia without producing intolerable and uncontrollable side effects. This was defined by Louis Lasagna and Henry Beecher in 1954 [62]. The same principle holds today, some 62 years later. There is no ceiling effect with opioids. Therefore when treating acute pain, if the pupils are not pinpoint, if the patient is responsive, if the respiratory rate is adequate and ventilation is effective, and if the patient is still in pain and is still free of other side effects, the patient is not receiving too much. *But care must be taken to prevent constipation*.

Opioid Conversions

Patients who are treated with epidural opioids or IV PCA opioids in the hospital are rarely able to leave the hospital without the need for continued analgesic therapy. The pressure applied to physicians by Medicare, Health Maintenance Organizations, and private insurers to reduce length of stay has made pain management a priority to allow earlier discharge. As mentioned earlier, regional perineural catheters with the continuous infusion of low-dose local anesthetics have certainly contributed to better postoperative analgesia with early discharge from the hospital.

However, if this is to be accomplished successfully, physicians must still have knowledge of equianalgesic equivalents of opioids. Equivalency charts can be found in many different texts. An excellent review can be found in a relevant article by Gammaitoni et al. [63]. In the experience of this chapter's authors, some simple conversions for chronic administration include the following:

- IV morphine 10 mg = 30 mg orally.
- IV morphine 1 mg = hydromorphone 0.2 mg IV.
- Oral morphine 30 mg = hydromorphone 6 mg orally.
- Oral morphine 30 mg = oxycodone 15–20 mg orally.
- IV morphine 60 mg/day = morphine orally 180 mg/ day = fentanyl transdermal patch of 100 μg/h.
- IV morphine 10 mg = hydrocodone 30 mg orally.

An example of a common mistake is the patient who is obtaining excellent pain relief from an IV PCA of 10 mg of morphine every 3 h. When the time for discharge arrives and the PCA is discontinued, the substitution is frequently hydrocodone/acetaminophen (Vicodin[®]) 5 mg/325 mg tablets or (Norco[®]) 10 mg/325 mg. The equivalency for analgesic effect for 10 mg of morphine IV is 30 mg of hydrocodone orally. Ten milligrams of morphine IV every 3 h would be eight doses per day of 30 mg of hydrocodone or 48 or 24 tablets of hydrocodone/acetaminophen per day, respectively. Of course, this would be a lethal dose of acetaminophen. It is unlikely that any patient would actually take 24–48 tablets per day, but the normal prescription of 1-2 tablets every 6 h PRN for pain might certainly be inadequate for someone requiring 10 mg of morphine IV every 3 h.

It therefore behooves the physician managing the patient to convert the patient to an acceptable oral medication several days before discharge to ensure adequate pain control and lack of side effects. In converting from IV morphine to transdermal fentanyl, the authors have found that 60 mg per day of IV morphine would require a 100 μ g/h transdermal fentanyl patch, which would be changed every 72 h. Because hydromorphone is approximately 5 times more potent than morphine, 60 mg per day of IV morphine would convert to 12 mg per 24 h of hydromorphone and again equate to a transdermal fentanyl patch of 100 μ g/h dose.

CYP 2D6 Enzyme and the Efficacy of Codeine and Codeine-Like Drugs

Codeine, dihydrocodeine (Tylenol[®] #2, #3, #4, Synalgos[®] DC), and hydrocodone (Vicodin[®], Lortab[®], Norco[®], etc.) are not fully active opioids. These opiates must be converted to morphine or hydromorphone by the enzyme CYP2D6 to become effective [64, 65]. Approximately 20% of the population is genetically deficient in this enzyme and so would report a poor analgesic response when prescribed these medications. Furthermore, many medications also inhibit the action of CYP2D6 that are frequently used by elderly patients; some of these are shown in Table 28.1.

Oxycodone is metabolized by CYP2D6; therefore, patients who are deficient in this enzyme will have a greater effect from oxycodone medications, such as oxycodone/ acetaminophen (Percocet[®]).

Table 28.1 Medications that inhibit the enzyme CYP 2D6

Amiodarone (Cordarone®)	
Fluoxetine (Prozac [®])	
Haloperidol (Haldol®)	
Paroxetine (Paxil®)	
Propafenone (Rythmol®)	
Quinidine	
Ritonavir (Norvir®)	
Terbinafine (Lamisil®)	
Thioridazine (Mellaril®)	
Based on data from Ref. [64]	

Opioids for Neuropathic Pain and "Broad-Spectrum Opioids"

Many elderly patients suffer from neuropathic pain which is poorly responsive to opioid analgesics that act primarily at the μ opioid receptor (Table 28.2) [66]. While affinity for μ , δ , and κ receptors of opioids are steric-dependent, the affinity of "l" and "d" forms are nearly equal with respect to nonopiate receptor actions such as *N*-methyl-D-aspartate (NMDA) antagonist and blockage of reuptake of serotonin and noradrenaline. Multiple actions of the broad-spectrum opioids seem to be synergistic with respect to analgesic action, similar to using narrow-spectrum opioids in combination with an NMDA receptor antagonist and a tricyclic antidepressant. As listed in Table 28.3, the opioids that have dual actions both for opioid receptors and NMDA receptors will be more effective for neuropathic pain than the narrow-spectrum opioids. These are shown as broad-spectrum opioids.

While methadone is widely used in opioid addiction medicine for either slow withdrawal programs or for methadone maintenance programs, it is also widely used in treatment of neuropathic pain because of its triple effect as described above. It is however a difficult drug for primary care physicians because of the complex conversion from other opioids to methadone or vice versa. Douglas et al. present a systematic review of the complexities of methadone conversions [67].

Levorphanol (levo-3-hydroxy-*N*-methylmorphinan) is a step 3 opioid first developed in the 1940s as an alternative

 Table 28.2
 Narrow-spectrum opioids acting only at opioid receptors

Morphine
Hydromorphone
Codeine
Fentanyl
Sufentanil
Oxycodone
Oxymorphone
Buprenorphine??? (may have benefit in neuropathic pain)

 Table 28.3
 Other actions of broad-spectrum opioids not at the opioid receptors

Broad-spectrum opioids acting	Broad-spectrum opioids acting also
also as antagonists to	as inhibitors of reuptake of
N-methyl-D-aspartate receptors	serotonin and norepinephrine
	(similar to the tricyclic
	antidepressants)
Methadone	Methadone
Ketobemidone	Levorphanol
Dextromethorphan	Dextromethorphan
Meperidine (pethidine)	Tramadol
Tramadol	Meperidine (pethidine)
Levorphanol	Tapentadol

to morphine. Levorphanol belongs to the morphinan opioid series. Levorphanol has greater potency than morphine and is a potent NMDA receptor antagonist. Levorphanol interferes with the uptake of norepinephrine (NE) and serotonin, which makes it potentially useful for neuropathic pain. Glucuronidation changes Levorphanol to Levorphanol-3-glucuronide with excretion by the kidney. Levorphanol has a long half-life and may accumulate with repeated dosing. Levorphanol can be administered orally, intravenously, and subcutaneously, and is therefore an ideal substitute for methadone. It should not be given together with Monamine Oxidase Inhibitors as it can lead to hypertensive crisis [68].

Because meperidine has a metabolite that acts in the brain of elderly patients and leads to confusion and even seizures, the only true broad-spectrum opioid analgesics available are methadone, Levorphanol, and to some extent tramadol. Tramadol is only a weak opioid agonist and weak NMDA receptor antagonist, and is only available for oral administration, as is Tapentadol [69].

End-of-Life Care

In 2004, for 67% of patients, the last place of care was an institution, with 38.4% dying in a hospital and 30.5% in a nursing home. Only 33% died at home; 49.3% of these were on home hospice care; 38.2% received no formal services; and 12.5% had home health care nursing services without hospice participation [70].

Reporting on the degree of satisfaction of bereaved family members with the care their loved ones received, hospice care at home received the highest level of overall satisfaction with 71% of respondents. Twenty-five percent of all patients with pain or dyspnea did not receive "any" or "enough" treatment. Inadequate pain management was 1.6 times more likely in a nursing home setting or with home health services and 1.2 times more likely in a hospital than with home hospice [70].

End-of-life pain management for patients who are being managed at home presents problems of assessment and administration of medication. Patients who are still able to swallow can be managed with oral medications. Rectal suppositories, transdermal medications, and transmucosal medications are available.

Morphine is available in multiple preparations. Kadian[®] and Avinza[®] are marketed as 24-h, single-dose sustainedrelease morphine preparations. Although their uptake properties differ, they both have the property of being packaged in a capsule that can be sprinkled as pellets onto applesauce or added to slurry for administration down an NG- or G-tube, while retaining the sustained-release characteristic. MS Contin[®] is an every 12-h sustained-release morphine preparation that cannot be broken open. Doing so destroys the integrity of the sustained-release capsule; the patient receives the entire dose as an immediate-release preparation. Oxy-Contin[®] is a 12-h sustained-release preparation of oxycodone that also cannot be opened or it too becomes an immediate-release preparation.

There is currently one preparation of extended release hydromorphone (Exalgo[®]) which is reported as a single dose 24 h preparation. Methadone is long acting but is not a sustained-release preparation. Fentanyl (Duragesic[®]) and Buprenorphine (Butran[®]) are the only commercially available transdermal opioids. Extended release Oxymorphone is marketed as Opana[®] and Tapentadol extended-release oral tablets are known as Nycenta[®]. Tramadol extended release has been available for some time as Ultram[®] ER. Zohydro[®] an extended release formulation of hydrocodone eliminates the limitation of dosage which is the result of combination of hydrocodone with acetaminophen products.

Fentanyl is available in a buccal absorption preparation. Transmucosal fentanyl citrate (OTFC) lozenge on a plastic handle; Actiq[®], was the first of its kind designed for rapid uptake of a powerful opioid analgesic. This has now been supplanted by an additional five such compounds (Effentora[®]/ Fentora[®], Abstral[®], Instanyl[®], Breakyl[®]/OnsolisTM, and PecFent[®]) concurrently approved in Europe and/or the US, and have documented efficacy in quickly relieving breakthrough pain episodes [71].

It is important to remember that sustained-release medications are encouraged for patients who have continuous pain. But it must also be remembered that activity will often increase the level of pain; patients must be prescribed rapidonset, short-acting medications to be used for such breakthrough pain [72]. Because patients vary tremendously in their requirements for pain medication, particularly in the senior population in which the margin for error is smaller, it is important to titrate patients with immediate-release medication to determine how to convert to sustained-release medication.

Although sustained-release morphine is available in capsules that are recommended for every-12-h dosing and every-24-h dosing, the absorption characteristics will determine whether a particular patient experiences adverse effects such as nausea or sedation, or "end-of-dose" failure. It is sometimes necessary to lower the dose and change to every-8-h or every-12-h dosing. And it is important to distinguish between "end-of-dose" failures of sustained-release medications from breakthrough or activity based pain [73].

Rarely in acute pain situations and more often in end-oflife care, patients' pain cannot be brought under control with opioid infusions alone. In such situations, optimum pain control with minimal side effects could be obtained with a combination solution of 1 mg/mL morphine and 1 mg/mL ketamine, with a lockout period of 8 min with an IV PCA [74]. These agents can both be given orally as well in the same ratio, e.g., 30 mg of immediate release morphine sulfate with 30 mg of ketamine every 3–4 h.

Sedation of Terminally III Patients

When patients are terminally ill and traditional analgesic regimens are unsuccessful at providing adequate analgesia and/or relief from suffering, the following solution can provide benefit [75]:

Ketamine (dissociative anesthetic, NMDA blocker) 2 mg/ mL $\,$

Midazolam (benzodiazepine, reduces incidence of hallucinations, sedative effects, and antianxiety) 0.1 mg/mL

Fentanyl (potent opioid, less nausea, less pruritus, less constipation, and enhanced effect combined with ketamine/midazolam) 5 μ g/mL

IV infusion should begin at 3–5 mL/h titrating to effect. Doubling the concentrations will allow reduction of the volume infused if needed. High concentrations can be used as subcutaneous infusion as long as the volume infused per hour remains less than 2 mL.

Regional anesthetic techniques can make an important contribution to end of life care by providing excellent analgesia or even anesthesia in an extremity, allowing for reduction in the amount of opioids. Supraclavicular brachial plexus blockade has been reported for treating the severe pain caused by a Pancoast tumor involving the arm of a terminal patient, allowing the patient relief of pain and increased mobility [76].

Neurolytic neuraxial blocks have been used for many years but no prospective randomized trials have been reported. Reports of effectiveness are based on small case report studies [77, 78]. However, celiac plexus neurolytic blocks for pancreatic cancer pain has been reported in larger patient groups [79].

Nonsteroidal Anti-Inflammatory Analgesics (NSAIDs)

The antiprostaglandin effect of NSAIDs can be beneficial during the acute phase of soft tissue injury. This biochemical effect may control the inflammatory response to injury and provide pain relief. The duration of an NSAID's analgesic effect may be different from its antiinflammatory effect. The antiinflammatory effect may last longer than the analgesic effect.

Chronic inflammatory disease pain such as arthritis may warrant chronic NSAID therapy. But some authors have expressed concern that NSAIDs may actually interfere with the later stages of tissue repair and remodeling, where prostaglandins still help mediate debris cleanup. This does not seem to be true for the cyclo-oxygenase 2 inhibitors (COX-2) specific inhibitors. Therefore, dosage, timing, and potential side effects of NSAIDs should be evaluated. It is not possible to predict patient response to a particular NSAID by chemical class or pharmacokinetics [80].

Some authors report that osteoarthritis may not be solely an inflammatory disease of the joints (peripheral sensitization) but may also be a disease of central sensitization [81]. This complicates treatment of elderly patients with osteoarthritis.

It must be remembered that COX-2 specific inhibitors do not affect platelet aggregation and therefore may pose a risk for myocardial infarction if a patient is taken off aspirin therapy. For the same reason, it is safe to continue COX-2 specific inhibitors with daily low-dose aspirin. COX-2 inhibitors also have a safer profile from the standpoint of gastrointestinal irritation, but care should still be taken in patients with borderline renal function [82, 83]. Baseline renal function tests should probably be obtained for elderly patients who are beginning a course of chronic coxib therapy or NSAID therapy. Drug holidays of 30–60 days every 4–6 months may also be advisable.

Tricyclic Antidepressants and Specific Serotonin Reuptake Inhibitors (SSRIs)

Tricyclic antidepressants are often used as adjuvants in treating neuropathic pain because of their inhibition of reuptake of serotonin and NE. The link between depression and pain may be both psychological and biological. The biological basis for depression has focused on dysregulation of the neurotransmitters serotonin (5-hydroxytryptamine, or 5-HT), NE, and dopamine [84].

There is fear that antidepressants will cause cardiac arrhythmias. Tricyclic antidepressants are safe for cardiac patients, except for several months after a myocardial infarction or if a conduction defect or persistent dangerous arrhythmia is already present [85].

Specific serotonin reuptake inhibitors (SSRIs) have safer cardiac profiles than tricyclic antidepressants. SSRIs are effective for depression. *SSRIs do not have analgesic effects like the tricyclics because they are only serotonin reuptake inhibitors and not norepinephrine reuptake inhibitors*. Both are necessary to modulate neuropathic pain. Tricyclics are more effective for pain and for sleep but may also cause sedation, cognitive changes, and dizziness. Elderly patients taking tricyclic antidepressants are at risk for falling, resulting in hip or other fractures. Again, titration and frequent reassessment are the key to successful treatment. In addition, many newer classes of antidepressants provide inhibition of reuptake of NE, serotonin, and dopamine without the associated sedation [86, 87].

Anticonvulsants for Neuropathic Pain

Gabapentin (Neurontin®) and Pregabalin (Lyrica®) are probably the most effective agents with the fewest side effects for the treatment of neuropathic pain [88]. Gabapentin is absorbed in the duodenum, not metabolized by the liver, not protein bound, excreted unchanged by the kidneys, and has no ceiling dose. It is nontoxic to the liver and kidney. The only significant side effects are sedation and cognitive impairment. Pregabalin is similarly relatively free of toxic effects, but both need to be reduced in the presence of renal insufficiency. Starting low and titrating to response again is the recommendation, but rapid titration upward is possible as Oxcarbazepine (Trileptal[®]), tolerated. lamotrigine (Lamictal[®]), and Topamax[®] are also effective substitutes.

Evaluation by a psychiatrist may yield information about clinical depression resulting in emotional suffering perceived as pain versus sadness, frustration, and isolation in response to inadequately treated pain. This would be valuable information in making a choice of treating with an SSRI versus a tricyclic or other agent with serotonin, NE, and/or dopamine reuptake inhibition effects.

With any of these medications, tricyclic or other antidepressants, anticonvulsants, etc., cognitive impairment caused by the medication must frequently be accepted or tolerated in the elderly patients in order to obtain pain relief.

Pain and Insulin Resistance

Acute, severe pain decreases insulin sensitivity. This would indicate that relief for acute pain is important for maintenance of normal glucose metabolism. Many elderly patients are diabetic, emphasizing the need for good pain relief [89].

Regional Analgesia

As indicated earlier, upper extremity surgeries are amenable to brachial plexus anesthesia and analgesia. Brachial plexus nerve blocks have a prolonged duration of action in the elderly patients, approximately 2.5 times longer. This would lead to a slower return of pain and therefore easier titration of postoperative medications [90]. However, elderly patients are frequently at risk for falls before surgery, so greater care must be taken in discharge criteria after a regional anesthetic to make sure they can maintain balance and that the caregiver with whom they will be discharged home is capable of protecting them from falls.

As indicated earlier, more and more elderly patients are having more and more surgeries as our population ages. Many of these procedures are orthopedic procedures especially amenable to regional analgesics techniques providing faster recovery, earlier mobilization, and faster discharge from the hospital. In this age of cost consciousness and patient satisfaction as well as improved outcomes, it is incumbent upon surgeons to request and encourage the incorporation of regional analgesic techniques into the care of elderly orthopedic surgical patients. This is particularly important in light of physicians' reluctance to prescribe opioids to patients, particularly elderly patients even though opioids can be prescribed safely [91].

Common Pain Syndromes

Chronic lumbar pain as a result of degenerative arthritis is very common. Osteoarthritis is the most common cause of nociceptive pain in the elderly patients. Inflammatory pain does respond well to analgesics such as antiinflammatory medications and opioids. But as indicated previously some authors report that osteoarthritis may not be solely an inflammatory disease of the joints (peripheral sensitization) but may also be a disease of central sensitization [81]. This complicates treatment of elderly patients with osteoarthritis.

Cancer pain, myofascial pain syndromes, postherpetic neuralgia, diabetic polyneuropathy, radiculopathy or amyotrophy, trigeminal neuralgia, peripheral vascular disease, and central poststroke pain (CPSP) syndrome are all common in the elderly patients. Furthermore, arthritis of the knee, hip, and shoulder are all common problems in the senior population, and surgical replacement is very advanced and highly successful. Diagnosis is easy and fairly certain to be correct. But appropriate pain management is essential for outcomes leading to improved quality of life. Chronic pain after total hip arthroplasty seems to be a significant problem in at least 12.1% of patients [92]. And 13% of patients report moderate to severe pain at 1 year post total knee arthroplasty in spite of an absence of clinical or radiologic abnormalities [93].

CPSP is a neuropathic pain syndrome characterized by constant or intermittent pain in a body part occurring after stroke. It is associated with sensory abnormalities in the painful body part. The incidence of CPSP is 8% within the first year, but pain may appear up to 3 years after the stroke. Sixty-three percent of those who develop pain had onset within the first month [94]. Two-thirds of those who develop pain experience moderate to severe pain. This 8% incidence of pain with 5% expressing moderate to severe pain is similar to other neuropathic pain syndromes such as phantom limb pain [95], central pain in spinal cord injury [96], and pain in diabetic neuropathy [97].

Back Pain

About two-thirds of adults have low back pain at some time. Of the 65 million people in the United States with low back pain, approximately 151,000 undergo fusion of

the lumbar spine each year [98]. The number of spinal fusion surgeries is increasing annually, in part, according to Deyo et al., because of widening indications, including the diagnosis of back pain made by discography [99, 100]. Allegri et al. offer us a comprehensive review of the problems associated with diagnosis and treatment of low back pain [101].

Because of the high rate of unsatisfactory results with open spinal surgery and the more tenuous physical condition of elderly patients to undergo and tolerate open spinal surgery, less-invasive techniques for treating discogenic pain have been developed. One such procedure is percutaneous diskectomy using coblation technology. This is a percutaneous technique to reduce the volume of internally disrupted disk material [102]. Spinal cord stimulation and intrathecal drug delivery has also been moderately effective for control of pain in unremitting low back pain and radicular pain [103–105]. For chronic zygapophyseal joint (spinal facet joint) pain, radiofrequency neurotomy of the medial branch of the posterior spinal nerve ramus has been found to be effective in both the cervical and lumbar regions [106, 107].

Although low back pain is a fact of life for a substantial proportion of the population at all ages, the aged have a greater prevalence and experience greater impact on their quality of life than the remainder of the population. At the same time, they are underrepresented in research [108]. Treatment protocols are poorly defined in the elderly patients. History and a comprehensive evaluation are necessary for an appropriate strategy [109].

Thoracic and Lumbar Compression Fractures

Epidural injections can be helpful for acute vertebral compression fractures, which are common in the elderly patients. Continuous epidural infusion of local anesthetic is also an option but requires hospitalization. Vertebroplasty is also an option. This involves a technique designed to consolidate pathologic vertebral bodies through the injection of orthopedic cement under fluoroscopic guidance [110–112]. This procedure has been shown to be safe in frail elderly patients and can improve quality of life [113].

Spinal Stenosis

Neurogenic claudication is frequently a presenting symptom of lumbar spinal stenosis. The patient complains of pain in the legs with walking which is relieved with rest. Epidural injections can sometimes be helpful in early disease. In advanced disease if surgery is not an option, spinal infusion therapy may be helpful as an alternative [114].

Herpes Zoster (AHZ, Shingles)

The word *herpes* stems from the Greek *herpein* which means "to creep," whereas *zoster* means "girdle." The disease infects 800,000 people in the United States each year, and the incidence increases with advancing age. The etiopathogenesis of herpes begins after chicken pox, when the varicella virus becomes dormant in a spinal nerve. When reduced cell-mediated immunity occurs, AHZ reactivates. Reactivation leads to infection down the nerve to the skin with the eruption of skin lesions. The inflammation can also travel to reach the spinal cord or the trigeminal brainstem complex [115].

The first sign of shingles is intense pain or itching, even before the lesions erupt on the skin. It is only along one nerve on one side of the body. Treatment should start as soon as possible with antiviral medication, pain medication, and steroids. Steroids are safe in acute herpes zoster because it is an immunoglobulin G-mediated immune response [115]. Epidural injections usually are helpful only in the first 3 days after eruption. Subcutaneous infiltration of local anesthetic and long-acting steroid can provide relief and accelerate healing. Stellate ganglion sympathetic and superior cervical sympathetic ganglion local anesthetic blocks can be helpful for zoster of the face in the trigeminal distribution. Manabe et al. [116] demonstrated that continuous epidural infusion of local anesthetic can shorten the duration of zosterassociated pain.

Postherpetic Neuralgia

Usually this disease is defined as pain that extends beyond the normal healing period of 6 weeks to 2 months. The pain takes on the characteristics of neuropathic pain with allodynia, and hyperalgesia. Moragas and Kierland [117] have reported on the frequency of persistent pain lasting less than 6 months and more than 12 months for various age groups. For patients less than 29 years old, the percentage of patients with persistent pain after "shingles" was 4% or less for less than 6 months and more than 12 months.

For the 30- to 69-year-olds, the frequency of persistent pain lasting more than 12 months ranged between 10% and 37%. But for patients over the age of 70 years the incidence of persistent pain for less than 6 months increased to almost 75% while persistent pain over 1 year was still almost 50%, and this continues to increase with increasing age. This is why aggressive treatment of acute herpes zoster is so important even though aggressive therapy will not prevent the development of postherpetic neuralgia. However, it will change the quality of the pain from the intense unsupportable pain syndrome to a more diffuse, deep aching pain that can be supported [118].

Treatment options for postherpetic neuralgia have not significantly improved over the years. Analgesics, even traditional opioid analgesics, offer little relief. Methadone can be helpful if the patient can tolerate it. It is a difficult medication to titrate in the elderly patients. Spinal cord stimulation can be beneficial in about 50% of cases of postherpetic neuralgia if the virus has not affected the dorsal horn of the spinal cord. Lidocaine 5% topical patches have been found to reduce the symptoms of postherpetic neuralgia about 30%– 40%. Kotani et al. [119] did report on the use of intrathecal methylprednisolone 60 mg administered with 3 mL of 3% lidocaine once per week for up to 4 weeks as being 70% effective in reducing pain. Pregabalin is also FDA approved for post herpetic neuralgia pain.

Currently there is considerable concern and uncertainty regarding the future effects of varicella and zoster (shingles) vaccinations [120]. The consensus view of mathematical modeling studies is that the overall varicella associated burden is likely to decrease in the long term, regardless of the level of vaccine coverage. On the other hand, recent evidence suggests that an increase in zoster incidence appears likely, and the more effective vaccination is at preventing varicella, the larger the increase in zoster incidence.

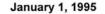
Case Examples

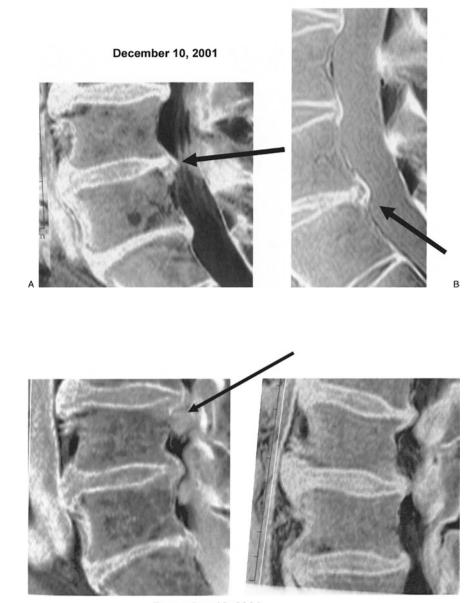
When assessing pain problems and making clinical decisions for therapy in the elderly patients, the situation is not always what it seems, and care must be taken to not go down the wrong path. Following are three cases that illustrate this problem.

Case 28.1. Lumbar Radiculopathy

A 67-year-old male physician presented with a sudden onset of back and leg pain, with a foot drop. A magnetic resonance imaging (MRI) scan showed a protruding disk with nerve root impingement corresponding to the side of the foot drop. The patient chose not go to a surgeon but instead requested that this author treat him with epidural steroid injection therapy. He received an initial lumbar epidural steroid injection followed by two caudal steroid injections over a 3-week interval. He experienced rapid resolution of all symptoms, including the foot drop, and returned to playing golf again with no return of the foot drop at 3 years after epidural injections. The MRI image is shown in Fig. 28.1a (December 10, 2001). Fig. 28.1b is a comparison MRI image (January 1, 1995) taken when the patient volunteered to have a scan done for a new scanner that needed calibration. The disk protrusion was present in 1995 but was asymptomatic until 2001. It is also clear that faced with the MRI image of 2001

Fig. 28.1 (a) MRI from December 10, 2001. The patient was symptomatic of the disk protrusion at L4–5 (arrow). (b) MRI from January 1, 1995. The patient was asymptomatic of the disk protrusion at L4–5 (arrow)





December 10, 2001

along with pain and a foot drop, most neurosurgeons would have considered this a surgical emergency (Fig. 28.2). It is clear that epidural steroid injections cannot dissolve away a disk protrusion. In this case, however, the problem was an acute nerve root irritation in the presence of a longstanding asymptomatic disk protrusion that did respond to epidural steroid injections.

Steroid injections are efficacious for different spine problems. Epidural steroid injections are being performed under image intensifier needle guidance both by the translaminar approach as well as the transforaminal approach to treat radiculitis and radiculopathy of the cervical as well as the lumbar nerve [121-123].

Case 28.2. Excessive Treatment in a Missed Diagnosis

An 85-year-old woman who was healthy, ambulatory, and living independently, upon getting out of bed one morning, experienced a sudden onset of right hip pain radiating down her leg. Nothing was done for a week, but she was not able to

Fig. 28.2 Significant disk protrusion noted (arrow)

B





Fig. 28.3 (a) A-P X-ray of the lower lumber spine and pelvis showing extensive discogenic and vertebral body degeneration with scoliosis to the left, osteophytes and endplate abnormalities on the left. (b)

Magnified view of the right acetabulum showing the small fracture (circled in black). The patient never complained of back pain

bear weight on that leg. After a week, she went to her primary doctor who immediately ordered an MRI scan of her lumbar spine. Based on the results of that scan, she was referred to a pain clinic where she underwent a series of three translaminar lumbar epidural steroid injections and a left-sided L3 and S1 transforaminal epidural steroid injection without benefit. She continued to be unable to walk. Surgery was recommended for her back, but fortunately the patient declined. After 6 months, she was referred to this author. Upon taking the history and performing an examination, it was clear that the most likely diagnosis was a fracture of the right hip. The patient never complained of back pain and never complained of left-sided leg pain. Her pain was always emanating from her right hip. A plain X-ray was ordered by this author that revealed a fracture of the pelvis close to the acetabulum on the right side. It is a wonder in looking at the X-ray, however, that the patient never did suffer from back pain (Fig. 28.3).

Case 28.3

A 56-year-old female complained of nagging left sided low back pain for 2-3 days. The pain suddenly escalated to 10/10 pain radiating from the mid lumbar left back down the buttocks on the left side to the left knee. The patient was afebrile, and she could not bear weight on the leg because of pain. She was seen by a pain management physician who performed an epidural steroid injection to provide some relief. An MRI and CT were obtained; and an IVP and abdominal ultrasound, and fortunately all were without pathology. The patient was admitted to the hospital for pain control and a presumptive diagnosis of Herpes zoster sine herpetica, which is acute herpes zoster without skin lesions in the left L3 nerve distribution [124]. She was treated with a continuous epidural infusion of local anesthetic for pain control, high-dose steroids, antiviral, and gabapentin. This was all based on the facts that imaging did not show any herniated disk, no kidney stone, no ovarian pathology, no outward signs of infection, no fever and no elevated white count. There are few conditions that can produce this severity of pain in a single nerve distribution. Twenty percent of acute herpes zoster patients present without skin lesions. Many weeks later this patient's cultures came back positive for Zoster and she did make a full recovery without post herpetic neuralgia. If her MRI had shown a herniated disk at L3–4 she most likely would have gone to surgery for the wrong reason, and the result would have been much different, the failed back surgery syndrome patient with unremitting neuropathic radicular back pain.

Conclusions

The major goal of geriatric care is often comfort and control of the symptoms of chronic disease [10]. The following guidelines are useful in approaching pain management in the elderly patients:

- 1. Always ask elderly patients about pain.
- 2. Accept the patient's word about pain and its intensity.
- 3. Never underestimate the potential effects of chronic pain on a patient's overall condition and quality of life.
- 4. Be compulsive in the assessment of pain. An accurate diagnosis will lead to the most effective treatment.

- 5. Treat pain to facilitate diagnostic procedures. Do not wait for a diagnosis to relieve suffering.
- 6. Use a combined approach of drug and nondrug strategies when possible.
- 7. Mobilize patients physically and psychosocially. Involve patients in their therapy.
- 8. Use analgesic drugs correctly. Start doses low and increase slowly. Achieve adequate doses and anticipate side effects.
- 9. Anticipate and attend to anxiety and depression.
- 10. Reassess responses to treatment. Alter therapy to maximize functional status and quality of life.
- Anticipate the level of pain associated with surgery, and other treatments, and incorporate regional anesthetic and analgesic blockade into a multimodal approach for pain management.

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ICU Management

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Introduction

Anyone practicing adult critical care medicine is likely to encounter elderly patients in a significant portion of their daily practice. In this sense, all intensivists practice "geriatric critical care." However, there are a number of complex considerations that often influence the care of this heterogeneous group of patients. In fact, it may be difficult to accurately define the practice of geriatric critical care. An understanding of the general principles of the normal physiology of aging, geriatric pharmacology, and common comorbidities discussed in Part II and Part III of this textbook is an excellent starting point for the management of elderly patients in the ICU. Beyond these basic principles, a simple framework for geriatric critical care should include the concept of patient- and family-centered care that meets the needs of older adults. This care should include a thorough and thoughtful consideration of age, comorbidities including the presence of common geriatric syndromes, and the best available medical evidence. It is important to define the goals for a given episode of care or proposed therapeutic intervention that include a realistic assessment of the expected outcome, understanding of the patients' and families' values, and an appreciation that aging is associated with an increase in the frequency and severity of iatrogenic complications as well as an increased risk of harm from any treatment. Intensive care professionals must appreciate that goals of care may vary significantly between patients based on their values and perception and may even vary within the same episode of care. For many elderly patients, important therapeutic goals will include the ability to improve or maintain function, preserve a level of independence, alleviate pain, and control symptoms. While there has been an increasing research emphasis on outcomes of interest for critically ill elders, there is often

Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, WA, USA e-mail: pauldr@uw.edu little well-established data on which to base treatment recommendations and offer prognostic expectations to patients and families. This chapter will explore the allocation and use of intensive care unit admission for elderly patients, intensive care outcomes for elderly patients including available information on the influence of geriatric syndromes, and review significant gaps in our knowledge in providing critical care for older adults.

Access to Care, Triage, and Outcomes

The most pressing question in providing critical care for elderly patients is the difficult and largely unknown problem of determining who is likely to benefit from the intensive care environment. What combination of patients and their medical conditions are most likely to achieve a good or acceptable outcome primarily due to the higher levels of nursing care, monitoring, or interventions available exclusively in the ICU? Alternatively, which patients admitted to the ICU will derive no demonstrable benefit but will generate increased costs or even experience harm? In considering these questions, it is helpful to understand underlying limitations in the evidence. The utility of ICU care for elderly patients is not easy to document. Trial design and chosen end points need to be carefully considered. There are few randomized controlled trials. Much of the published literature consists of cohort trials with inherent risk of bias and results that are best considered hypothesis-generating only. Older studies were chiefly concerned with ICU or hospital mortality. These end points are of limited value in measuring what matters most to elderly survivors of critical care who often consider the most important and meaningful outcome as a return to independence or return to their premorbid level of function. More recent studies have examined mortality following discharge from the hospital for variable periods of time, but these end points fail to capture the presence and extent of any functional disability. In addition to mortality, the elderly often have significant comorbidities that are present prior to their acute critical illness. These conditions have

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their own associated mortality over time making the consideration of control groups especially important. Some studies seek to compare the ICU cohort to age-adjusted hospital patients not admitted to the ICU to allow assessment of the effect of disease severity, while others compare ICU survivors to an age-adjusted cohort in the general population to provide an overall estimate of mortality compared to the community. Studies that seek to evaluate the effect of critical illness on disability are challenged by the contribution of premorbid disability. Some studies have sought to assess outcomes in terms of health-related quality of life (HRQOL) using validated survey tools. The results of these studies have been criticized on the basis of being particularly susceptible to survivor bias and proxy recall bias [1]. An increasing number of studies utilize administrative data sets with inherent limitations including the granularity of data available [2]. Other factors complicating interpretation of the literature include heterogeneity in the types of outcomes reported, types of ICUs, or types of patients included in the studies, methodological differences, varying definitions of aging, duration of data collection, and lack of separation of in-hospital (ICU) mortality versus long-term survival [3]. With these limitations and caveats in mind, the body of literature does suggest a number of important factors in the care of the critically ill elderly patient and provide suggested areas of further research.

Despite their modest percentage of the population, older adults occupy over half of all ICU beds in the United States [4]. The patterns by which elders access critical care resources, the decision to admit an elder to an intensive care unit, and the outcomes of that care are complex processes that are likely related in complicated and potentially unintuitive ways. Many factors may influence these processes including factors related to patients, families, surrogate decision-makers, critical care providers, regional and local practice patterns, and age-related bias [5, 6]. Important questions regarding outcomes related to specific disease states, the influence of comorbidities, the impact of geriatric syndromes, and the effect of advanced age on outcome remain. These complex issues are further affected by a considerable degree of variability in the frequently dynamic question of what outcomes are acceptable to patients and their families [7].

The currently observed and projected future increase in the elderly cohort has prompted the well-deserved concern that there will be a corresponding increase in utilization of healthcare resources and that an unprecedented increase in the demand for limited intensive care resources will be the result [8]. Specialty areas such as cardiovascular and cancer care have enjoyed therapeutic advances leading to decreased mortality and increased life expectancy for a number of related conditions that often affect older adults. These medical advances along with the rapid expansion of "minimally invasive" or "less invasive" interventions including transcatheter cardiac valve replacement, increasing options for endovascular treatment of complex vascular lesions, and laparoscopic or robotic approaches to various conditions have the potential to offer options for patients previously considered at too great a risk for surgery and push the demand for ICU beds even further. These concerns in part have driven an increase in critical care capacity in the United States with an observed increase in available critical beds from 67,579 beds in 2000 to 77,809 in 2010 [9]. Recent data, however, suggests that a relentless increase in the consumption of ICU resources by elderly patients might not be universal. Not surprisingly, the issue is considerably more complex.

Several available studies from different countries and healthcare systems suggest that an increase in the elderly patient population does not necessarily lead to a proportionate increase in the number of older patients admitted to intensive care units. Docherty et al. studied access to critical care among elderly patients in Scotland utilizing data from 2005 to 2009 [10]. They reported a significant decrease in admissions for older patients over the period of study. Interestingly, older patients admitted to ICUs had a comorbidity profile similar to that of younger patients suggesting that the extent of comorbidity might have influenced the triage decision. The authors also noted decreased use of organ support in the oldest cohort including less renal replacement therapy and highlighted high mortality rates for patients admitted with nonoperative underlying conditions. Despite the expected increased mortality among older patients, 25% of patients with admitting diagnosis of pneumonia and 45% of patients admitted for emergency abdominal surgery achieved survival with a reasonable rate of independence at 12 months. It is extremely difficult to know if the decrease in admissions as reported is related to accurate and appropriate triage, success of ICU care, or if it represents rationing of care based on age.

Sjoding et al. examined trends in critical care use in the United States and reported a 29.2% decrease in critical care admissions between 1996 and 2010 [11]. Admissions for cardiovascular diseases decreased, while admissions for infectious diseases became more prominent with sepsis becoming a major reason for ICU admission. This finding suggests an increasing importance of sepsis as a health concern for the elderly. These results are especially important as elderly survivors of sepsis appear to be at increased risk for adverse long-term outcomes [12]. In contrast to the findings in the Scottish study, organ dysfunction became more prevalent over the course of the study period, as did the use of organ-supportive therapies.

Although consensus statements on ICU triage have recommended that age alone should not be the only factor in triage decision-making, there is evidence to suggest that age may play a role [13]. An analysis of ICU admission for patients presenting to 15 emergency departments in France demonstrated considerable variability in the use of ICU resources [14]. A minority of elderly patients meeting possible criteria for ICU admission were actually admitted with rates ranging from 5.6% to 38.8%. Andersen et al. studied triage decisions for octogenarians in Norway reporting a 30% rate of refusal for ICU admission [15]. Evaluating physicians were asked to cite the primary reasons for refusal of admission. For patients refused admission, major factors included advanced age, low functional status, and severity of illness. For patients not triaged to ICU who were judged too well to benefit, major factors included age, male sex, university hospital care site, fewer comorbidities, and lower severity of illness. This study did, however, suggest a trend in providers that pursued admission to an ICU with prompt initiation of intensive care therapies while assessing the initial response to treatment and gathering more information followed later by limitation of care. In this study, 83% of nonsurvivors had documentation of limitation of care, and 64% of those died within 2 days after triage. This has been described by some as an "ICU trial" and may offer a clinical strategy when a triage decision is not immediately clear [16]. The Norwegian data also suggest a heavy use of intermediate care resources mainly at university medical centers. This could influence overall lower ICU admission rates for patients that otherwise may have been recommended for ICU transfer with implications for the ability to generalize this data to centers that do not utilize intermediate care environments. It has been suggested that age may be an important factor in decisions to refuse ICU admission when resource availability is limited [17]. The presence of advance directives may also influence the decision for ICU transfer with fewer patients considered for ICU admission [18]. A contrasting view to the reported trend in the decreasing use of the ICU by elderly patients is provided by a study noting an increase in ICU admission rates and resource utilization for the very old in Australia and New Zealand [19]. Very old patients were more likely to be admitted from chronic care facilities, have a greater burden of comorbidities, and have a higher severity of illness on admission but were less likely to receive mechanical ventilation. The very old cohort had a greater length of stay, had a higher ICU and in-hospital mortality, and were more likely to be discharged to a long-term care facility. A study of ICU admissions for nonagenarians in Germany reported ICU and hospital mortality of 18.3% and 30.9%, respectively, with a 1-year survival of 34.9%. Functional outcome parameters were not reported [20].

The relationship between ICU capacity, effect on patient acuity, and outcome for elderly patients with unplanned ICU admissions was examined by Fuchs et al. [(21).] This retrospective observational cohort study examined the effect of increased ICU capacity created by the opening of an additional medical unit. The bed increase resulted in increased ICU admissions, lower patient acuity and lower crude, and adjusted 28-day mortality. However, there was no change in one-year survival for ICU survivors.

Lerolle et al. reported on changes in the aggressiveness of therapies offered to older critically ill patients in a single academic mixed medical-surgical ICU in France [22]. Compared to the elderly patients admitted from 1992 to 1995, the elderly patients admitted from 2001to 2004 received a higher intensity in treatment and use of life-supporting therapy. Nevertheless, the two cohorts were not identical in that the 2001–2004 group had a higher acuity of illness at the time of presentation but had less premorbid functional limitation. ICU survival was 65% and 64%, respectively, but when survival was adjusted for the observed to expected mortality ratio, a significant survival benefit was evident for the second, more aggressively treated group. However, this does call into question the interplay and importance of illness severity and premorbid level of function on overall outcome.

As discussed previously, age may influence the decision to admit to the ICU, but age also appears to affect the course of care following intensive care admission. The pursuit of new limitations in life-sustaining therapy as noted in the study by Andersen et al. [14] is an obvious influence on the decision to pursue aggressive treatment including admission to intensive care. While such limitations may be extremely appropriate in the setting of serious comorbidities, chronic debilitation, and severe acute conditions, there is some evidence that advanced age alone may impact the decision to limit life-sustaining therapies. Turnbull et al. reported on a prospective cohort of elderly patients presenting with mild acute respiratory distress syndrome [23]. After controlling for prehospital functional status, comorbidities, initial severity of illness, and daily organ dysfunction scores, each 10 years of age was associated with a 24% greater likelihood of new limitations in life-sustaining therapy. This finding suggests that declining condition during the episode of acute illness likely impacted the decision to limit therapy but was not the only factor involved. A dynamic aspect of treatment decisions was also evident as none of the patients had treatment limitations in place at the time of admission. The decision to limit treatment was associated with outcome as those patients with new treatment limitations experienced a 14% survival to ICU discharge with almost 70% of deaths taking place in patients after the implementation of treatment limitation. Whether these findings are related to accurate assessment of clinical course by providers or represent an age-related bias on the part of caregivers and surrogates is unclear.

While it is generally accepted that increasing age is associated with increased mortality for many conditions, other age-associated factors may influence the provider's decision to admit an elderly patient to the ICU. Providers may not fully appreciate the patient's willingness to receive aggressive, invasive therapy [24]. In addition, some elderly patients may be willing to accept a greater degree of functional disability following critical illness, but this is not easy to predict prior to the onset of acute illness and the need for critical care [25]. It is clear from the above discussion that wide variability exists with regard to patient selection for ICU admission independent of disease severity. Geographic region appears to also play an important role. Tschirhart et al. found that the use of intensive procedures at the end of life is heavily influenced by regional differences as reflected by the Hospital Care Intensity Index (HCI). HCI is a calculation based on a ratio of the average number of hospital days and physician encounters experienced by patients in the referral region for each hospitalization compared to the national average [26]. Intensive procedures examined in this study included many common ICU-related interventions such as intubation, mechanical ventilation, gastrostomy tube insertion, enteral or parenteral nutrition, cardiopulmonary resuscitation, and tracheostomy. The HCI remained a significant factor after controlling for individual medical, social, and functional characteristics with patients in high HCI regions receiving more interventions during the last 6 months of life. Other variations in practice have been studied by Wunsch et al. They looked at the use of intensive care resources following elective surgery in Medicare beneficiaries undergoeither esophagectomy, pancreaticoduodenectomy, ing cystectomy, open abdominal aortic aneurysm repair, or endovascular abdominal aortic aneurysm repair [27]. Age was independently associated with ICU admission following esophagectomy, cystectomy, and pancreaticoduodenectomy but not open or endovascular AAA repair. It is unclear why age was not associated with ICU admission for AAA repair, but it may be related to routine use of ICU following certain types of procedures based on practice patterns. Age was related to an increase in complications and hospital mortality for all of these procedures. In a separate publication, the routine use of ICU resources postoperatively in this elderly surgical population did not lead to a mortality reduction [28]. Variability in the use of ICU resources is not limited to surgical populations. Admon et al. studied elderly patients with hospital admissions for congestive heart failure, acute myocardial infarction, stroke, pneumonia, chronic obstructive pulmonary disease exacerbation, or hip fracture treated with arthroplasty [29]. Hospitals in this study were classified as low, moderate, or high ICU facilities. The authors reported wide variation in ICU admission rates between hospitals for the various diagnoses, but utilization within hospitals was consistent suggesting that the hospital practice is the major contributor to the use of ICU resources. The authors suggested a number of factors that potentially contribute to local practice variability including hospital policies, practice norms, use of protocols, and possible financial incentives.

Additionally, factors such as perceived nursing skill level, nurse to patient ratios, and availability of step-down units may influence hospital practice trends.

The current understanding of factors influencing ICU outcomes for elderly patients has evolved from a focus on age alone as the greatest variable influencing risk to elucidating the effect of severity of illness at the time of presentation with a more recent emphasis on a variety of aspects of a patient's premorbid functional status. Djaiani and Ridley demonstrated significantly decreased survival at 1 year for those over 85 years of age compared to those 70-85 years [30]. In addition to age, the presenting diagnosis and severity of illness were also independent predictors of survival at 1 year. However, Somme et al. suggested that age is not the best predictor of short-term ICU survival [31]. They followed 410 elderly patients over the age of 75 for 2 years admitted to a single university intensive care unit in France. The study identified three subgroups: old (75–79 years), very old (80-84 years), and oldest old (over 85 years of age). ICU survival in these groups was 68, 75, and 69%, respectively. Three-month survival was 54, 56, and 51%. Patients surviving their ICU stay had far greater rates of mortality than agematched controls in the general population. These differences, however, decreased significantly by one year post discharge. Acuity of illness as assessed by APACHE II was the only variable associated with dying in the ICU. Age and limitation of activity before admission were the only identified determinants of long-term survival. These results are also supported by a study of 817 patients over 65 years of age who received at least 48 h of mechanical ventilation. In this study, age, functional status, and preexisting illness were associated with increased mortality at 2 months [32].

A review by Hennessy et al. underscores problems with heterogeneity across studies. They reviewed outcomes related to functional status and health-related quality of life (HRQOL) in 16 studies [3]. The overall results were mixed. Ten studies reported relatively good HRQOL, overall patient satisfaction with outcome, or no change from premorbid condition. Three studies demonstrated no significant difference in preadmission and post-discharge function. Two studies documented reduction in functional status but a preserved perception of quality of life in ICU survivors. One study that focused only on physical functioning found a reduction in HRQOL but did not include a subjective assessment.

Cuthbertson et al. followed 300 consecutive patients admitted to a single intensive care unit in Scotland for 1 year [33]. They employed a validated tool to assess HRQOL. Patients over 64 years of age comprised 36% of all study patients. Physical and mental component scores were reported for survivors over 64 years of age and suggested decline in function for the physical component at 3 and 6 months with a gradual return to premorbid levels at 1 year. The mental component score showed decline at 3 months with return to premorbid levels at 6 months. The scores for all patients admitted to the ICU were significantly lower than data for controls from the general population suggesting a lower level of function prior to ICU admission. As outlined above, quality of life is of central importance, but small decrements in objective performance may not necessarily translate to subjective dissatisfaction on the part of patients [25].

More recently published data has suggested that it may be useful to think about ICU admission for the elderly in terms of elective postoperative admissions compared to urgent or emergent medical or surgical admissions as outcomes appear to differ significantly between the two [8, 34]. Bagshaw et al. examined 120,123 admissions from 57 ICUs in Australia and New Zealand. In this cohort the leading indication for critical care admission of patients over 80 years of age was planned surgery. ICU mortality was 12% with a 25% hospital mortality. Seventy-two percent of survivors were discharged home [19]. A study from the Netherlands reported a 1-year survival of 57% in elderly patients having scheduled surgery with 75% of those living at home prior to surgery returning home [34]. It is important to note that elderly patients considered for elective surgical intervention may already represent a type of selection bias as they would have been deemed as acceptable candidates for the proposed procedure. In contrast, the results for acute medical diagnoses and unplanned surgical admissions are considerably worse with mortality rates in some series as high as 80% [34, 35].

The need for mechanical ventilation appears to be associated with adverse long-term outcome. Following high-risk surgery, older patients requiring mechanical ventilation beyond 96 h appear to have increased mortality at 1 year and high burdens of treatment with many experiencing prolonged hospitalization or transfer to a long-term acute care facility (LTAC) [36]. Barnato et al. studied the effect of use of mechanical ventilation on functional outcomes. Importantly, this study measured preadmission functional status and demonstrated that the need for mechanical ventilation in elderly ICU populations was associated with greater disability at 1 year compared to those not requiring mechanical ventilator support [37]. Medicare beneficiaries who survive critical care to hospital discharge appear to have an increased mortality in the first 3 years following discharge with risk highest in the first 6 months compared to hospitalized patients not admitted to the ICU surviving to discharge and matched controls in the general population. The mortality risk is increased for ICU survivors receiving mechanical ventilation and for all hospital survivors requiring skilled nursing care [38]. The mortality at 6 months was 14% for all ICU survivors but was 30% in those receiving mechanical ventilation. Survivors discharged to nursing facilities experienced a 6-month mortality rate of 26%. Moitra et al. studied the effect of length of stay in the ICU on mortality and not surprisingly reported an association between LOS in the ICU and 1-year mortality

[39]. Importantly, this effect was present for all patients independent of the need for mechanical ventilation. Further, critical care resources were consumed in a disproportionate fashion with 40% of all ICU days accounted for by 11% of patients requiring ICU stays of 1 week or greater.

Older survivors of severe sepsis have been reported to experience cognitive impairment and functional limitation at considerably higher rates than patients hospitalized for nonsepsis conditions [12]. It has been suggested that critical illness may accelerate the progression of disability associated with preexisting geriatric syndromes. In a study of sepsis survivors, Iwashyna et al. found increased rates of low BMI, falls, incontinence, vision loss, hearing loss, and acute pain. When the magnitude of these factors post-sepsis were compared to prospective pre-sepsis measurements, only low BMI was increased to a greater extent than would have been predicted by the rate of progression identified before the onset of sepsis [40]. This finding questions whether critical illness uniformly contributes to the acceleration of underlying deficits or if this is more indicative of the natural progression of disability. Therefore trajectories following critical illness may be important to consider when assessing associations between critical illness and exacerbation of preexisting conditions and underscore the importance of accurate assessment of functional limitation prior to the onset of acute illness and the complex relationship between baseline condition, acute illness, and long-term outcome.

The problem of predicting functional recovery from critical illness is important and is an area ripe for further research. It is widely appreciated that elderly ICU survivors often experience increased disability and that return to a premorbid level of both cognitive and physical function is not assured [41]. Recovery is often a long process [42]. Ferrante et al. followed 754 community-dwelling adults aged 70 or older over a 14-year period [43]. These individuals were screened monthly for 13 functional activities. Of this cohort, 302 subjects experienced ICU admission accounting for 388 separate ICU admissions. Of these, 186 patients (219 ICU admissions) survived to their first post-discharge assessment. Six months later, 114 (52.3%) were alive with functional recovery as defined by return to a disability count that was equal to or less than the pre-ICU disability assessment. Sixty-nine patients (31.7%) were alive with increased disability. Thirty-five patients (16.1%) died in the first 6 months following ICU discharge. Hearing impairment and vision impairment were strongly associated with a reduced likelihood of functional recovery. Greater functional self-efficacy and higher BMI were associated with a greater likelihood of functional recovery. It is unclear if interventions targeted at these factors can influence outcome.

Heyland et al. reported on the development of a clinical prediction model to estimate survival and functional performance 1 year following ICU admission [44]. Four hundred thirty-four patients aged 80 or older with an admission to one of 22 ICUs in Canada were followed with the Clinical Frailty Scale and Palliative Performance Scale scores for 1 year. In the first year post-ICU discharge, mortality was 50%, and only 29% had demonstrated recovery from critical illness as defined by a Palliative Performance Scale of greater than 60. Factors associated with recovery included being married, having a primary diagnosis of emergency coronary artery bypass or valve replacement surgery, and having a higher baseline Palliative Performance Scale score. Predictors of non-recovery included male sex, primary diagnosis of stroke, higher acuity of illness as measured by APACHE II, more extensive comorbidities as measured by Charlson comorbidity index, and greater frailty as assessed by the Clinical Frailty Scale. For many critically ill patients and their families, early palliative care consultation may be useful to facilitate communication, understand and discuss goals of care, assist in alleviating suffering, and support family members. Palliative care for the elderly is discussed in detail in Chap. 31.

Geriatric Syndromes

Geriatric syndromes are the result of a complex interaction between the physiology of normal aging, chronic medical conditions, and functional stressors in older adults. Commonly described syndromes include falls, urinary incontinence, frailty, impaired mobility, and cognitive impairment [45]. The current understanding is limited and is further complicated by varying definitions of specific syndromes and varying assessment methods [46]. In general, the presence and progression of a geriatric syndrome are associated with a declining quality of life and increasing dependency. This is further associated with increased vulnerability to stressors and adverse events such as critical illness, trauma, and surgery. An increasing amount of attention has been focused on the effect of geriatric syndromes with an emphasis on frailty as a predictor of outcome for a variety of clinical conditions [47]. This has been recently explored with regard to the impact on outcome in patients admitted to the ICU.

While definitions vary, frailty can be assessed based on common clinical presentations that include falls, delirium, and sudden immobility. Muscle weakness related to sarcopenia, polypharmacy, sensory impairment including decreased visual or auditory acuity, and cognitive impairment may be present. Frailty assessment in the community often involves assessment of gait speed or a timed get up and go test [45]. While these may be useful in preoperative assessment for elective surgery, they cannot be performed in the emergent environment of most ICU admissions. Domains often associated with frailty include nutritional status, physical activity, mobility, energy, strength, cognition, mood, and availability of psychosocial support. A number of assessment tools are available, but complexity of data collection required and the need for special training are barriers to implementation at the bedside. For example, the Frailty Index includes an assessment of 92 items. More abbreviated questionnaires such as the PRISMA 7, Canadian Study of Health and Aging Clinical Frailty Scale, or clinical assessment tools such as the phenotypic definition proposed by Fried et al. may be used [48-50]. Fried's assessment defines frailty as the presence of three or more elements that include decreased grip strength, self-reported exhaustion, unintentional weight loss, slow walking speed, or low physical activity [50]. In the critically ill patient population, surrogate assessments for frailty have been reported that include assessment of prehospital functional status, cognitive impairment, and nursing facility residence. A loss of skeletal muscle mass and strength is evident in about half of those over the age of 65. This is thought to be due to age-related changes and is known as sarcopenia. Sarcopenia has been correlated with frailty in several studies. Causes of sarcopenia are thought to include disuse atrophy, inflammation, nutritional deficiencies, and altered endocrine function. Functionally, sarcopenia is manifested by progressive weakness, fatigue, decreased gait speed, and difficulty walking longer distances. Critical illness is often accompanied by severe inflammatory processes, protein catabolism, and immobility leading to the risk for ICU-acquired weakness, a risk that appears to be increased in the elderly. Surrogate measurements for sarcopenia including radiographic assessment of muscle size have also been used to estimate frailty [51, 52].

Frailty has been associated with adverse outcome in many conditions encountered in the ICU population including noncardiac surgery, cardiac surgery, and unplanned ICU admission. Frailty has been associated with increased 30-day mortality, morbidity, and failure to rescue from postoperative complications in both endovascular and open abdominal aortic repair [53]. Frailty was present in 32.8% of patients admitted to six academic ICUs in Canada. Patients assessed as frail were older, more likely to be female, and had a greater number of comorbidities and more functional dependence than those who were not frail. Frailty was associated with increased in-hospital mortality and mortality at 1 year. Frail ICU patients experienced more major adverse events and were more likely to become functionally dependent [54]. A multicenter cohort study of over 1000 patients demonstrated an association between greater clinical frailty scores and increased 3- and 12-month mortality, a greater odds of disability in performing IADLs, and reported poorer HRQOL [55]. Interestingly, over half of those with clinical frailty in this study were under 65 years of age. Frail Medicare beneficiaries admitted to the ICU also have higher mortality rates compared to non-frail elders [56]. Clinical frailty scores may

be more accurate in predicting mortality than frequently used severity of illness scoring systems in critically ill elders or serve to augment the performance of conventional risk models [57, 58]. The presence of frailty implies a greater burden of disease and decreased life expectancy. For patients considered to be frail by Fried's frailty index measured within 4 days of hospital discharge, there is an associated increase in mortality within 6 months post discharge [59]. While outcomes for elderly patients admitted to the ICU after elective cardiac procedures appear good in comparison with other ICU patients, frailty is associated with increased mortality, morbidity, and functional dependence following cardiac surgery [60, 61]. Use of geriatric assessment including evaluation for frailty has been explored in some ICUbound patients and may be especially relevant to those facing elective surgical procedures [62, 63]. There is some evidence that exercise and nutrition can be of benefit in stabilizing frailty in community dwellers [64, 65]. Therapies targeting further muscle loss such as early mobility and early optimization of nutrition are attractive strategies to improve outcome when hospitalization and ICU admission are pursued.

Delirium

Postoperative delirium is discussed in detail in Chap. 30. This section will review aspects of delirium pertinent to the ICU. Delirium is characterized by an acute onset of altered cerebral function with fluctuating mental status, inattention, and either disorganized thinking or a disturbed level of consciousness [66]. The pathophysiology of delirium remains poorly understood. Current concepts suggest that imbalances between neurotransmitter systems involving the excitatory dopamine system and the inhibitory γ -aminobutyric acid (GABA) and acetylcholine systems contribute to the development of delirium [67]. In the setting of critical illness, other frequently encountered mechanisms associated with altered mental status may be contributory. These include the influence of inflammatory mediators, such as tumor necrosis factor and interleukin-1, decreased cerebral blood flow, hypoxemia, electrolyte and metabolic disturbances, and effects of centrally active medications including sedatives, hypnotics, analgesics, and anticholinergics. The development of delirium in critical illness is likely multifactorial with a combination of direct effects of disordered neurotransmitter function and decreased brain reserve manifested as increased susceptibility to a variety of pathologic or pharmacologic insults. For patients in the ICU, delirium is a common problem that affects up to 80% of adult patients on mechanical ventilation [68]. Delirium is manifest by three described motor subtypes. These include hyperactive, hypoactive, and mixed. Hyperactive delirium is associated with agitation, combative behavior, or frank hallucinations.

Patients with hyperactive delirium represent the minority of patients with delirium in the ICU [69]. Hypoactive delirium is the more common subtype in elderly patients. These patients typically appear quiet and peaceful but are actually more likely to exhibit disordered thinking and inattention. A third subset of patients may present with manifestation of both hyperactive and hypoactive forms. This has been defined as mixed delirium. A cohort study in medical ICU patients evaluating the prevalence of various forms of delirium found hyperactive forms present in 5% and hypoactive and mixed forms present in roughly 45% each. Different subtypes of delirium have been associated with different outcomes with one study suggesting a greater mortality rate for patients with hypoactive delirium admitted to the ICU after elective surgical procedures [70]. The diagnosis of delirium in the ICU can be challenging due to the waxing and waning nature of the clinical manifestations and the prevalence of hypoactive delirium that often may give the appearance of a comfortably resting patient. Systematic application of a screening tool is necessary to prevent missed diagnosis [71].

Delirium in the ICU is evaluated by the use of validated scoring systems. Preferred tools include the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDS) [68]. These assessment methods have been validated in ICU patients and can be employed in patients on or off of mechanical ventilation. They have demonstrated high inter-rater reliability and are sensitive and specific when compared to published diagnostic criteria from the American Psychiatric Association [72-74]. Delirium in ICU patients has been associated with a number of adverse outcomes including increased mortality, prolonged mechanical ventilation, hospital length of stay, cost of care, and long-term cognitive impairment. The presence and duration of delirium have been associated with mortality in a number of studies [75, 76]. A recent meta-analysis has suggested that this frequently reported association may need further study [77]. This study included randomized trails that evaluated measures to reduce delirium compared to standard care. A lower rate of delirium in the intervention group did not result in a reduction in short-term mortality. Prospective cohort studies have demonstrated an association between increasing duration of delirium and cognitive impairment lasting up to 12 months p [78, 79]. Milbrandt et al. reported a 40% increase in total cost of hospitalization for patients with one or more documented episodes of delirium. The severity of delirium was also associated with increasing hospital costs [80]. All episodes of delirium may not confer the same risk. There is evidence to suggest a difference in outcomes related to delirium that reverses quickly after the discontinuation of sedative medications [81]. In prospective cohort study of 102 medical ICU patients, Patel et al. reported lower ventilator, ICU, and hospital days and lower 1-year mortality rates in patients with

rapidly reversible delirium as compared to patients with persistent delirium [81]. Persistent delirium was defined as the presence of delirium as determined by CAM-ICU assessment that was present 2 or more hours after termination of sedative medication. Many risk factors for the development of delirium have been suggested [74, 82]. In general risk factors can be separated in predisposing patient factors and precipitating or acquired factors related to treatment in the ICU environment. The most significant baseline risk factors appear to be preexisting dementia, past history of hypertension or alcoholism, coma, and high acuity illness at the time of admission although a recent publication did not support severity of illness, alcohol use, or coma as contributory in increasing the risk of delirium [68, 83]. Surprisingly, age has not consistently been demonstrated to be a significant risk factor for delirium in ICU patients but has a strong association for patients outside of the ICU [68]. Treatment-related risk factors include the use of benzodiazepines, anticholinergic medications, and opioids [74]. The use of dopamine for vasopressor and inotropic support in shock states demonstrated a strong association with an increased incidence of delirium in one study, but multiple confounders were present [84]. The association, however, did remain after adjustment for severity of illness. It is important to note that the many adverse outcomes associated with delirium are associations without proof of causation. It is tempting to entertain the notion that decreasing the incidence or duration of delirium will lead to outcome benefit but that is far from proven. Nonetheless, understanding the effectiveness of interventions to prevent or treat established delirium appears to be prudent. In general, interventions to prevent or treat delirium can be divided in pharmacologic therapies and nonpharmacologic measures. The available data for ICU patients is mixed. A delirium prevention trial in noncardiac surgical patients using haloperidol infusions demonstrated a decrease in delirium in patients undergoing intra-abdominal surgery [85]. A study of ICU patients considered to be at risk for the development of delirium employing a preventive strategy with intermittent intravenous haloperidol also reported a decreased incidence and shorter duration of delirium in the treatment group [86]. A randomized controlled trial using higher doses of intermittent haloperidol did not demonstrate differences in days alive and free of delirium or coma in the treatment group [87]. A double-blind placebo-controlled trial of haloperidol in a mixed ICU population did not demonstrate benefit in preventing conversion to delirium in those with subsyndromal delirium [88]. Rispiradone has been studied in cardiac surgical patients as prophylactic agent to decrease the incidence of delirium and for early intervention in postoperative patients with subsyndromal delirium [89, 90]. These trials have reported significant reduction in conversion to delirium. In addition to the interest in prophylaxis for delirium prevention, other strategies for delirium

prevention include avoidance of therapies associated with the promotion of delirium. For ICU patients a frequent concern is the choice of analgesics and sedatives. Increasing evidence has implicated benzodiazepines and deep levels of sedation as therapies that increase the risk of delirium [74]. A study of 106 critically ill patients comparing lorazepam to dexmedetomidine demonstrated more delirium- and comafree days in the dexmedetomidine group [91]. A multicenter trial comparing midazolam infusion to dexmedetomidine also demonstrated a lower incidence of delirium in those receiving dexmedetomidine [92]. A meta-analysis examined seven randomized controlled trials comparing dexmedetomidine sedation to standard care that included benzodiazepines and propofol. There was high heterogeneity among the studies that limited interpretation. The analysis reported a lower incidence of delirium in the dexmedetomidine group that was not statistically significant [93].

Several studies have examined the effect of nonpharmacologic measures including early mobility in the ICU and improved sleep hygiene on the incidence of delirium. Schweickert et al. included delirium as a secondary outcome in a multicenter, randomized controlled trial of medical ICU patients with a treatment intervention consisting of combined daily interruption of sedation combined with physical therapy sessions. The intervention arm demonstrated a significantly shorter duration of delirium [94]. Sleep hygiene in the ICU is problematic due to the nature of the environment, the interruption of normal sleep architecture associated with acute illness, and the administration of sedative medication [95]. In this regard there may be an advantage for dexmedetomidine over propofol. Dexmedetomidine appears to preserve normal sleep architecture whereas propofol does not [96, 97]. It has been observed that normal circadian release of melatonin is altered in severe sepsis and lower melatonin levels have been reported in postoperative ICU patients with delirium compared to those without [98-100]. Administration of melatonin or melatonin antagonists is another approach to delirium prevention that attempts to address fragmented sleep as contributing factor. Data are mixed. Interestingly, the perception of quality of sleep appears to be incongruent with transition to delirium [101]. The interactions between sedatives, sleep, and the development of delirium are complex, and definitive data are lacking [102].

The treatment of established delirium is controversial, and once again the available data is conflicting. Current strategies include administration of typical antipsychotics such as haloperidol or atypical antipsychotics such as olanzapine, quetiapine, and ziprasidone [103–105]. Adverse drug reactions are not uncommon when antipsychotic medications are used in this setting [106]. Reported adverse reactions include QTc prolongation, drowsiness, drug-induced fever, neutropenia, and ventricular tachycardia. When pharmacologic strategies are employed, care must be taken to ensure that medications are not inappropriately continued post discharge from the ICU [107, 108]. Dexmedetomidine has been studied in patients with agitated delirium preventing extubation, suggesting efficacy in this clinical setting [109].

Post-ICU Care

Critical illness is associated with the development of new physical and cognitive impairments that can result in significant disability with long-term consequences. The term, postintensive care unit syndrome, has been suggested to describe new or worsening impairments in physical, cognitive, or mental health status that become evident after critical illness and persist beyond acute care hospitalization [110]. Physical impairment may include problems with pulmonary, neuromuscular, or physical function. Cognitive deficits may be related to executive function, memory, attention, or processing speed. Mental health issues such as anxiety, acute stress disorder, depression, or posttraumatic stress disorder may be present. As discussed previously, return to independence is frequently an important goal of hospital care for older adults. Loss of physiologic and functional reserve places the elderly at particularly high risk for disability in the setting of critical illness. Disability in the performance of activities of daily living (ADLs) and instrumental activities of daily living (IADLs) appears to be a major problem in ICU survivors. While disability appears to improve over time, considerable numbers report issues with performing ADLs at 1 year including a new ADL disability or worsening of a prior disability.

Patients with prolonged ICU stays are often considered to be "chronically critically ill" with altered physiology relating to factors including immunosuppression, healthcareacquired infections, malnutrition, endocrine dysfunction, ICU-acquired weakness, cognitive dysfunction, and posttraumatic stress disorder [111]. Prevalence of chronic critical illness increases with age with the greatest prevalence in those 75–79 years old [112]. The need for prolonged mechanical ventilation is a hallmark of chronic critical illness. Patients are often referred for tracheostomy to facilitate ventilator weaning and to advance the course of care. Treatment recommendations from physicians frequently require consent from surrogate decision-makers as critically ill patients are often not able to participate in medical decision-making. Unfortunately, surrogate decision-makers as well as care providers may have unrealistically optimistic expectations regarding survival, functional outcome, and quality of life following transfer to long-term care [113]. More importantly, communication between providers and family members regarding expected outcomes may not be ideal. Up to 20% of patients recovering from critical illness opting for continued support will require prolonged care due

to persistent organ failures or other factors. Many of these patients are now cared for in settings outside of the acute care hospital including skilled nursing facilities, rehabilitation facilities, and long-term acute care hospitals (LTAC). This includes a considerable number of older ICU survivors. While limited data exists on utilization of post-ICU care, what is known is concerning. Kahn et al. performed an epidemiologic study of LTAC utilization by Medicare beneficiaries from 1997 to 2006 [114]. They found increases in patients transferred to LTAC facilities from the ICU as well as increased usage of skilled nursing and rehabilitation facilities over the same period. Mortality rates were relatively unchanged, and a corresponding decrease in patient discharge to home was reported. The 1-year mortality for those discharged to LTAC was considerable at 48.2-52.2%. Higher mortality rates were observed in those patients requiring transfer with mechanical ventilator support. Suggested reasons for increased LTAC utilization include increased availability of LTAC beds during the study period and the possibility of financial incentive to discharge costly longstay patients from short-stay hospitals for complex care or ventilator weaning. This study, along with others, calls into question the efficacy of LTAC models in improving patient outcome. Ideally, long-term acute care could benefit the chronically critically ill elder by providing expert care in therapies that have potential benefit [115]. Identifying those most likely to benefit and the nature of specific interventions with the greatest likelihood to improve outcome remains problematic.

Significant Gaps in Our Knowledge

High-quality data to guide the care of the critically ill elders is limited. Extrapolation of data from general ICU populations with consideration of the physiologic changes of aging, decreased organ function, impaired organ reserve, altered pharmacokinetics, greater sensitivity to many medications related to changes in pharmacodynamics, and the interplay of baseline comorbidities often drives the treatment approach in clinical practice. Elderly patients have historically been excluded from many clinical trials calling into question the validity of applying results to older patients [116]. It has also been demonstrated that evidence-based therapies are frequently underutilized in the elderly [117]. Understanding how disease processes vary with age and if treatments directed at those differences can affect outcome is an important research goal that affects nearly every aspect of ICU care [117]. Development of improved tools to aid in appropriate triage of critically ill elders including an understanding of how geriatric syndromes such as frailty affect the response to treatment and influence long-term outcomes is needed to better counsel patients and families regarding functional

outcome. The answers to these questions may in turn inform the difficult question of identifying which elderly patients benefit from admission to a critical care unit. The bulk of the available data suggest that elderly ICU survivors frequently experience significant disability. Teasing out the relationships between aspects of ICU care or underlying conditions that are causally linked to adverse outcome, finding new alternatives, and discovering new therapies or interventions to promote recovery are areas in need of further research. This will be no easy task as it will require confirming causal relationships for many of the outcomes associated with various conditions. For example, if delirium were found to cause increased mortality, measures to prevent or treat the condition may improve survival. It is possible, however, that delirium is the result of decreased cerebral reserve and avoiding or shortening the course of an episode of delirium has no effect on survival. Two of the most significant disabilities following critical illness in the elderly are cognitive decline and impaired mobility. Identifying modifiable risk factors and effective therapies in this area has the potential to make a difference in outcomes that matter to elderly patients and their families [118].

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Postoperative Cognitive Impairment in Elderly Patients

Michelle Humeidan, Stacie G. Deiner, and Nicholas Koenig

Abbreviations

ACS	American College of Surgeons
ACS	American College of Surgeons
	Activity of daily living
AGS	American Geriatrics Society
ASA	American Society of Anesthesiologists
BIS	Bispectral index
CABG	Coronary artery bypass graft
CAM	Confusion Assessment Method
CAM-ICU	Confusion Assessment Method for the
	Intensive Care Unit
CCI	Charlson comorbidity index
CPB	Cardiopulmonary bypass
CRP	C-reactive protein
CVD	Cerebrovascular disease
DRS-98R	Delirium Rating Scale Revised 1998
DSI	Delirium symptom interview
DSM V	Diagnostic Manual of Diagnostic and
	Statistical Manual of Mental Disorders
ICD-10	International Classification of Diseases
	tenth revision
ICDSC	Intensive Care Delirium Screening Checklist
ICU	Intensive care unit
IL	Interleukin
IQCODE-SF	Informant Questionnaire on Cognitive
	Decline in the Elderly Short Form
MCI	Mild cognitive impairment

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MDAS	Memorial Delirium Assessment Scale
MMSE	Mini mental status exam
NIRS	Near-infrared spectroscopy
NSAIDS	Nonsteroidal anti-inflammatories
NSQIP	National Surgical Quality Improvement
	Program
Nu-DESC	Nursing Delirium Screening Scale
PAD	Peripheral artery disease
PCA	Patient controlled analgesia
PD	Postoperative delirium
POCD	Postoperative cognitive dysfunction
POD	Postoperative day
QOL	Quality of life
RCI	Reliable change index
SIRS	Systemic inflammatory response syndrome
TIA	Transient ischemic attack
TNF-α	Tumor necrosis factor-α

Introduction to Postoperative Cognitive Impairment

Individuals over the age of 65 years are the fastest growing segment of the population, and this will result in significant growth in the demand for surgical procedures by 2020 [1]. Postoperative cognitive impairment is a common and morbid complication preferentially seen in the elderly, which is further defined based upon timeframe of presentation. Usually occurring in the first 24-72 h after an operation, postoperative delirium (PD) is characterized by fluctuating disturbance of consciousness hallmarked by inattention and disorganized thinking. Occurring in the weeks to months following surgery, postoperative cognitive dysfunction (POCD) is characterized by decline in cognitive performance from a baseline exam and may be domain based (e.g., learning and memory, verbal abilities, perception, attention, executive functions, and abstract thinking) [2]. Incidence of PD varies widely from 4% to 7% after elective outpatient surgery, to excess of 65% after hip fracture repair or cardiothoracic surgery [3, 4]. Likewise a range of POCD rates have been reported (5.6–12.7%, 3-months post major noncardiac surgery [5], to 21–29%, 3-months after cardiac surgery) [6].

The consequences of developing postoperative cognitive impairment can be significant. Patients who experience PD stay in the hospital longer and have higher morbidity, mortality, and nursing home placement [7, 8]. Impairment of postoperative cognitive recovery and the associated complications equate to billions of healthcare dollars annually [9, 7, 10], emphasizing PD as a health concern for aging patients. Likewise, long-term consequences of POCD include increased mortality [5], withdrawal from the labor market, and dependence on social welfare [11].

Measures to improve outcomes in aging surgical patients are a major priority for healthcare policy and safety measures. Multidisciplinary panels including representatives from the American College of Surgeons (ACS), American Society of Anesthesiologists (ASA), and American Geriatrics Society (AGS) called the ACS Geriatric Surgery Task Force and the AGS Geriatrics-for-Specialists Initiative have compiled best practice guidelines on perioperative management of the geriatric patient which focus on the immediate preoperative, intraoperative, and postoperative periods [12]. The AGS Clinical Practice Guideline for Postoperative Delirium in Older Adults (AGS guidelines) [13] provides focused recommendations and guidance for management of patients at risk for postoperative cognitive problems. The ASA has launched the Brain Health Initiative with significant commitment to research and future development of additional best practice guidelines to avoid postoperative cognitive disorders. This chapter reviews the important contributions of these professional societies and provides an overview of PD and POCD screening, diagnosis, classification, and pathophysiology. Details of various risk factors associated with the patient, perioperative course, and perioperative management with a focus on prevention and treatment are also presented. Generally, PD recognition, prevention, and treatment are far better described in comparison to POCD for reasons we will discuss in detail. Though the impact of postoperative cognitive impairment is well known, a consensus about how to approach informed consent with patients requiring surgery has not been reached. However, information in this chapter will facilitate discussion about postoperative cognitive impairment with surgical patients.

Identifying High-Risk Patients and Postoperative Cognitive Impairment

Various screening assessments exist to facilitate recognition of individuals at risk for delirium and have been adopted in many different settings for daily postoperative evaluation of elderly surgical patients. The AGS guidelines recommend that health professionals caring for postsurgical patients should be trained to recognize and document signs and symptoms associated with delirium [13]. The most common delirium assessments include the *Diagnostic and Statistical Manual of Mental Disorders* (DSM V), *International Classification of Diseases tenth revision* (ICD-10), and the *Confusion Assessment Method* (CAM). There are many other tools which we will describe, although a full account is beyond the scope of this chapter. POCD is more challenging to assess in patients because diagnosis requires pre- and postoperative neurocognitive testing [14].

Validated Delirium Assessments

The ideal delirium screening assessment would be easy and quick to administer, identify the various subtypes of delirium, allow for repeated use over the waxing and waning course of delirium and be applicable in a variety of patients (medical, surgical, critical care). Though several different checklists and assessments have been used over the years [15], there exists today a core group of validated delirium assessments (Table 30.1).

Perhaps the most well-known delirium test is the Confusion Assessment Method (CAM). Inouye et al. developed a bedside assessment for delirium that could be administered quickly by nonpsychiatrists. The CAM exists as a diagnostic questionnaire (CAM Long) and a shortened screening algorithm (CAM Short). The CAM Long identifies acute onset and fluctuating course, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbance, abnormal psychomotor activity, and altered sleep-wake cycle. The CAM Short assesses only the first four components of the CAM Long, requiring presence of acute onset or fluctuating course and inattention, plus either disorganized thinking or altered level of consciousness for delirium identification. The CAM is validated as a sensitive, specific, reliable, and easy to use tool for delirium identification [13, 16]. Similar to the CAM Short, the CAM-ICU is a four-part assessment modified for ICU patients with difficulty communicating (on mechanical ventilation, presence of orogastric tubes, psychoactive medication, etc.) [17]. Additional validated delirium screening tools include the delirium symptom interview (DSI), NEECHAM Confusion Scale, Intensive Care Delirium Screening Checklist (ICDSC), and Nu-DESC (Nursing Delirium Screening Scale) (Table 30.1).

The DSM V diagnosis of delirium requires that symptoms develop quickly (typically hours to days) relative to baseline and classically fluctuate in severity over time. Hallmark features of delirium are (1) altered awareness (e.g., reduced orientation to the environment), (2) additional cognitive disturbances (e.g., memory deficit, altered language, visuospatial ability, or perception), and (3) inattention (e.g.,

Table 30.1 Validated delirium assessments

Tool	Clinical application	Additional information
Confusion Assessment Method (CAM) Sensitivity: 94–100% Specificity: 90–95% [13, 16]	General use in at-risk patients CAM Long: comprehensive questionnaire for nonpsychiatrist clinicians CAM Short: Assesses only the first four components of the CAM Long, used by clinicians and nursing	Can have a false-positive rate of up to 10%
Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) Sensitivity: 95–100% Specificity: 89–93% [17]	Adapted for quick administration by nurses and clinicians in the ICU to allow delirium assessment in critically ill patients with potential communication difficulties (i.e., mechanical ventilation, psychoactive medication, orogastric tubes)	Questionable effectiveness in demented patients
Delirium symptom interview (DSI) Sensitivity: 90% Specificity: 80% [18]	General use in at-risk patients, administered by clinicians and nurses	Information is gathered only from the patient. Acute onset and possible etiology are not part of the assessment
Nursing Delirium Screening Scale (Nu-DESC) Sensitivity: 85% Specificity: 86% [19]	General use in at-risk patients, used by nurses	Assesses psychomotor retardation (not agitation), 13% false-positive rate
Intensive Care Delirium Screening Checklist (ICDSC) Sensitivity: 99% Specificity: 64% [20]	Used for critically ill patients, used by clinicians and nurses	Does not focus on cognitive tasks

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reduced ability to sustain, shift, direct, and focus attention). To diagnose delirium, these symptoms must not be better explained by another preexisting neurocognitive disorder (e.g., dementia). Likewise, symptoms must not be a direct physiological consequence of another medical condition. Examples of conditions which contribute to acute confusion and may mimic postoperative delirium are listed in Table 30.2. Arguably hypoxia and ischemia are the two most important of these ten to rule out in a timely manner. In addition to evaluation of DSM V criteria (ICD-10, CAM), tools like the Delirium Rating Scale Revised 1998 (DRS-98R) and Memorial Delirium Assessment Scale (MDAS) can also be used for delirium diagnosis [13].

Emergence from anesthesia drugs (polypharmacy, withdraw, anticholinergics, antihistamines, barbiturates, and benzodiazepines)
Endocrine and metabolic disturbances (hypoglycemia, hypothyroidism, hyponatremia, hyperammonemia, etc.)
Mental disorders (dementia, depression, and anxiety)
Hypoxia and ventilation disturbances
Infection
Sensory deprivation or overload
Ischemia (TIA, CVA)
Intracranial neoplasm
Seizure disorder (postictal state)
Constant of Michaella Handiday, Staria C. Daines and Michaelas

Courtesy of Michelle Humeidan, Stacie G. Deiner, and Nicholas Koenig

Classification of Delirium Subtypes

PD is classified by duration and symptomatology. PD can be either acute or persistent according to its duration and time course (hours to days versus weeks to months, respectively) and can be further categorized as either hyperactive, hypoactive, or mixed based upon motor activity. Hyperactive delirium is characterized by increased psychomotor activity such as mood lability, agitation, and/or refusal to cooperate with medical care. Hypoactive delirium is characterized by decreased psychomotor activity such as sluggishness or lethargy approaching stupor. In mixed delirium, individuals may have features of both hyper- and hypoactive delirium at different points in their clinical course [21]. Longitudinal assessment of activity subtypes (no subtype, hyperactive throughout, hypoactive throughout, mixed throughout, variable over course) has shown that the majority of delirious patients are stable in their course of delirium, with less than 40% demonstrating subtype variability. The hypoactive subtype is associated with the worst overall prognosis [22].

Diagnosing POCD

The range of abilities associated with cognition is broad, including learning and memory, verbal abilities, perception, attention, executive functions, and abstract thinking [2], and there has been a lack of uniformity in the terminology and methodology used to report on POCD in the literature [23]. Self-reporting of cognitive problems correlates poorly with objective testing, so the diagnosis of POCD requires pre- and postoperative cognitive testing [24]. Generally a group of neurocognitive tests have been combined and administered as a battery, with verbal learning and working memory, episodic memory, processing speed, and set shifting emerging as the most sensitive cognitive testing domains. Some examples of these tests include the logical memory test, CERAD word list memory, Boston Naming Test, category fluency test, digit span test, trail-making test, and digit symbol substitution [2]. A change score using baseline cognition and postoperative performance may be used to identify POCD. POCD may be defined on the basis of significant decline on greater than or equal to two tests or a more subtle decline across the neuropsychological test battery [25].

In order to compare across studies and fit into the greater literature regarding cognitive disorders, a multidisciplinary work group including anesthesiologists, surgeons, geriatricians, neuropsychologists, neurologists, and psychiatrists has been assembled to provide consensus definitions and nomenclature for POCD by late 2016. The subjective component is not sufficient to define POCD; however, it may have some weight in future POCD diagnostic criteria [26].

Pathophysiology of Postoperative Cognitive Impairment

The pathophysiology of postoperative cognitive impairment is being investigated with basic, translational, and clinical research. There is emerging evidence that delirium may be the prodrome of long-term cognitive impairment [27]. Proposed mechanisms for PD and POCD have significant overlap, and current research implicates general health status, inflammation, oxidative stress, and disruption of the circadian clock. Ultimately altered neurotransmission and loss of cellular and regional communication within the CNS are likely responsible for the functional disturbances characteristic of PD and POCD [28].

Systemic inflammation manifesting with a cascade of proinflammatory events results from surgical trauma and/or infection. Baseline levels of circulating inflammatory mediators, including cytokines and acute phase proteins, increase severalfold with aging. Likewise, microglia in the aging CNS assume a "primed" phenotype, resulting in an exaggerated and pathologic response to stress or an immune challenge [29, 30]. Markers of immune activation, elevated levels of C-reactive protein (CRP), interleukin (IL)-6, IL-1RA, IL-10, IL-8, neopterin, S-100 beta (S-100 β), tumor necrosis factor- α (TNF- α), and cortisol have been reported in delirious patients and can be measured in a variety of tissues including plasma, urine, and CSF [29-31]. During a pro-inflammatory state, development of fever, sickness behavior, and activation of the hypothalamic-pituitary-adrenal (HPA) axis occur [32]. Immune activation ultimately results in CNS dysfunction secondary to altered blood-brain barrier, oxidative stress, and some degree of compromised neuronal and glial function [30].

Outside of the immune system, oxidative stress can occur with any condition where the body's ability to metabolize reactive oxygen species is overwhelmed. Fundamentally, reactive oxygen species are associated with energy imbalances and local ischemia that leads to excitotoxicity, apoptosis, and escalation of local inflammation. Poor tissue oxygenation has been associated with PD, and an intervention to remedy cerebral oxygen desaturations during major cardiac surgery resulted in decreased PD occurrence [33]. The use of near-infrared spectroscopy (NIRS) in other elderly surgical populations has shown significant position-associated changes in cerebral oxygenation (prone versus supine), but the impact of this on PD and POCD needs further study [34]. Preoperative identification of patients with regional cerebral desaturation prior to noncardiac surgery may identify those at high risk for PD, though trials showing benefit of intraoperative cerebral oxygenation monitoring are lacking [35, 36].

Disruption in circadian rhythms has been reported after minor and major surgery, which affects postoperative sleep quality and recovery. Sleep deprivation leads to decreased cognitive function and may predispose to postoperative delirium [37]; therefore, pharmacologic and nonpharmacologic maintenance of normal circadian rhythms may decrease or ameliorate PD. Melatonin is one drug investigated because of its sleep-wake cycle regulatory effects and also because of its anti-inflammatory and antioxidant properties [30]. Disruption in the endogenous rhythm of plasma melatonin and excretion of the urine metabolite on the first postoperative day have correlated with the duration of major surgery [38], and low postoperative melatonin has been reported in patients who develop PD [39]. However, a recent trial failed to demonstrate benefit of postoperative melatonin supplementation for prevention of PD in ICU patients after major elective surgery, and furthermore the rates of delirium subtypes (hypoactive versus hyperactive) were not altered by melatonin administration [40].

Decreased acetylcholine availability, excess of dopamine, norepinephrine, and/or glutamate release, and variable alterations in serotonin, histamine, and/or g-aminobutyric acid (GABA) may be implicated in PD. Neuronal network connectivity and receptor availability and function may also be implicated [29, 30]. Acetylcholine neurotransmission is vulnerable to dysfunction during immunologic stress and periods of altered synthesis and metabolism (e.g., surgery, ischemia, dehydration, severe illness). Exposure to anesthetics can alter cholinergic neurotransmission [41]. Based upon the pathophysiology of Alzheimer's disease, a cholinergic mechanism may contribute to increased risk of postoperative cognitive problems in patients with preexisting dementia [42, 43] (see Chap. 10).

Surgical stress, inflammation, medications, and altered perioperative hormonal regulation may play a role in both PD and POCD. More research is required to elucidate various mechanisms, which could vary with severity and type of cognitive compromise postoperatively.

Table 30.3 Preoperative risk factors for PD

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		Guenther et al. [69]	Cardiac surgery
		Tan et al. [70]	Cardiac surgery
Pol et al. [/1] Vascular surgery		Pol et al. [71]	Vascular surgery
Lee et al. [72] Hip fracture repair		Lee et al. [72]	Hip fracture repair

(continued)

Table 30.3(continued)

Risk factor	Study	Population	
Higher preoperative pain scores	Smulter et al. [52]	Cardiac surgery	
	Tan et al. [70]	Cardiac surgery	
	Behrends et al. [73]	Noncardiac major surgery	
Lower regional oxygen saturation levels in the brain	Schoen et al. [74]	Cardiac surgery	
	Morimoto et al. [35]	Abdominal surgery	
Depression (presenting with ongoing depressive episode)	Kazmierski et al. [56]	Cardiac surgery	
Depression (presenting with depressive symptoms)	Böhner et al. [48]	Vascular surgery	
	Leung et al. [75]	Noncardiac elective surgery	
History of depression	Stransky et al. [76]	Cardiac surgery	
Alcohol use	Litaker et al. [54]	Major elective surgery	
	Shah et al. [53]	Major head and neck cancer surgery	
	Patti et al. [77]	Colorectal surgery for carcinoma	
Drug abuse	Fineberg et al. [49]	Spine surgery (lumbar)	
Smoking history	Benoit et al. [78]	Abdominal aortic aneurysm repair surgery	
	Miyazaki et al. [51]	Cardiac surgery (CABG)	
Decreased functional capacity/preoperative frailty	Juliebø et al. [59].	Hip fracture repair surgery	
	Pol et al. [71]	Vascular surgery	
	Brown et al. [82]	Cardiac surgery patients	
Increased ADL dependence/reduction in ADLs	Leung et al. [83]	Noncardiac surgery	
	Hattori et al. [84]	Vascular, orthopedic, and GI surgery	
Poor preoperative nutritional status	Ganai et al. [85]	Abdominal surgery	
	Tei et al. [86]	Colorectal cancer surgery	
Dehydration	Harasawa & Mizuno [87]	Cerebrovascular surgery	
Fluid fasting	Radtke et al. [88]	Surgery	
Low BMI	Lee et al. [72]	Hip fracture repair surgery	
	Juliebø et al. [59]	Hip fracture repair surgery	
Benzodiazepine use	Do et al. [79]	Orthopedic surgery	
Psychoactive medications	Benoit et al. [78]	Abdominal aortic aneurysm repair surgery	
Polypharmacy	Goldenberg et al. [93]	Hip fracture repair surgery	
	McAlpine et al. [94]	Gynecologic malignancy surgery	

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Risk Factors for Postoperative Cognitive Impairment

Risk factors associated with the development of cognitive problems after surgery can be categorized as preoperative, intraoperative, or postoperative in accordance with the point at which they are first introduced during a patient's perioperative care. These factors are also often divided into predisposing factors (i.e., those factors that are present at baseline) and precipitating factors (i.e., those factors that occur during the patient's clinical course). Many predisposing factors, such as demographics and health history, are not modifiable, but other factors may improve with treatment or intervention.

Preoperative Factors

Certain unifying themes relate a number of reported preoperative risk factors: demographics, decreased "cognitive reserve," burden of illness, use of certain substances/ medications, psychosocial factors, and poor functional status. Advanced age, previous history of delirium, depression, multiple comorbidities, alcohol abuse, and preoperative ASA score (an assessment of systemic impact of comorbid disease) are the most consistently reported (see Table 30.3).

It has been suggested that the risk for PD in adults increases with each increasing year of life, and as a threshold, after 60 years of age, surgical patients are more likely to develop PD [44–52]. Decreased preoperative "cognitive reserve" and/or previous neurological insult is a major risk factor for PD as indicated by history of stroke, transient ischemic attack (TIA), dementia [53], delirium [54], subjective reporting of memory complaints [55], or performance below a pre-identified standard reference score on tests such as the MMSE [56, 58] or the Informant Questionnaire on Cognitive Decline in the Elderly Short Form (IQCODE-SF) [48, 53, 54, 59–61]. Despite the strong connection between preoperative cognitive deficits and risk of postoperative cognitive impairment, genetic markers of Alzheimer's disease have not been predictive of PD or POCD risk [62].

Burden of illness, as indicated by presence of various comorbidities such as diabetes [52, 56], peripheral artery disease (PAD) [56, 63], cerebrovascular disease (CVD) [56, 64], atrial fibrillation [65, 51], heart failure [44, 64], obstructive sleep apnea [66], and renal failure [67], has been associated with an increased risk of PD development. Research has also shown certain preoperative vascular factors, including preoperative carotid stenosis of 50% or greater [51] and atherosclerosis in the ascending aorta [63], to be significant predictors of PD in the cardiac surgery population. In general, a greater number of medical comorbidities, e.g., a higher Charlson comorbidity index (CCI), is widely recognized as a PD risk factor [68–72]. Higher preoperative pain scores have been associated with increased likelihood of developing PD [52, 70, 73], as have lower baseline regional oxygen saturation levels in the brain [35, 74].

Psychosocial factors also appear to play a role in development of postoperative cognitive deficits. Depression has been demonstrated as a risk factor for PD, whether the patient is presenting with an ongoing depressive episode [56], depressive symptoms [48, 75], or a history of depression [76]. Alcohol use has been associated with risk of PD [53, 54, 77], as well as drug abuse [49] and a history of smoking [51, 78]. One study indicated that patients unsatisfied with their level of social support were more likely to develop PD [79]. It has also been shown that patients with a greater amount of dispositional optimism (a behavior trait characterized by the tendency to react to situations with positive outcome expectations) are less likely to develop PD [80].

Decreased functional capacity and preoperative frailty are risk factors for PD [59, 71, 81]. A recent study in cardiac surgery patients over the age of 55 years reported that the prevalence of frailty was approximately 31%, and frail patients had significantly increased risk of PD compared to non-frail patients [82]. Preoperatively, increased dependence with respect to performing activities of daily living (ADLs) [83] and lower overall quality of life increase risk of developing PD [84]. Poor preoperative nutritional status [85, 86], dehydration [87] and fluid fasting [88], and low BMI have all been associated with PD [59, 72].

Avoidance of polypharmacy and appropriate medication use in elderly patients may decrease the incidence of PD. The AGS Beers Criteria List medications have been deemed inappropriate for geriatric patients for a variety of reasons, some of which are associated with cognitive issues [89, 90]. Beers Criteria medications which may be commonly administered to surgical patients include benzodiazepines, nonsteroidal anti-inflammatories (NSAIDS), antihypertensives, and sliding scale insulin. Anticholinergic medications are another example of Beers Criteria medications which are commonly used for their antihistamine, antispasmodic, and antiemetic properties [91, 92]. Likewise, prescribers should refrain from administration of corticosteroids and meperidine due to increased risk of PD [13, 90]. Polypharmacy is associated with PD, demonstrating importance of assessing a patient's medication exposure globally, in addition to avoidance of specific medications [93, 94] (see Chap. 21).

Many risk factors for PD have also been identified as risk factors for POCD, including advancing age, preexisting cognitive impairment (PD, MCI, dementia), diminished functional status, multi-morbidity, low level of education, history of alcohol abuse, coronary artery bypass grafting (CABG) surgery, and exposure to psychoactive medications [5, 43, 95–99].

Intraoperative Factors

Characteristics of intraoperative course and patient management contributing to risk for postoperative cognitive impairment include surgical variables, medication-specific risks, and hemodynamic stability (Table 30.4).

Emergency surgery is associated with the development of PD [45, 100, 101]. Duration of surgery has also been shown to be a significant factor for PD [53, 72, 102], as well as more invasive surgery [49, 58, 101, 103, 104].

Anesthetic medications and anesthesia depth have been investigated for association with PD. Some evidence exists that episodes of deep anesthesia increase the risk of PD [105]. One study reported that patients under light propofol sedation (i.e., targeting BIS of 80) have significantly lower prevalence of PD than patients under deep sedation (i.e., targeting BIS of 50) [106]. Though it is not clear if depth of anesthesia influences PD development, the literature consistently demonstrates that the mode of anesthesia (i.e., regional versus general) is not associated with PD [107–109].

Intraoperative use of long-acting opioids is a significant predictor for PD [88], and a number of studies have exhibited an association between fentanyl and the development of PD [88, 110, 111]. However, poor postoperative pain control is also associated with PD [112–114]. The use of midazolam as an anesthetic [79] and administration as postoperative sedation increases risk of PD [115].

Fluid management and patient hemodynamics have been associated with PD development. Greater intraoperative volume loads increase risk of PD [52]. Both patient blood loss [116] and blood transfusions have been linked to PD development [47, 117]. Likewise, intraoperative hypotension and low intraoperative body temperature are predictors [77, 118, 119]. Intraoperative use of cardiopulmonary bypass (CPB) may contribute to high rates of PD in cardiothoracic surgery patients, with one potential mechanism being increased embolic load to the brain during CPB [120, 121].

As with the preoperative risk factors, intraoperative risk factors associated with PD and POCD have some overlap. High-risk surgery, including cardiac and vascular cases, is associated with increased POCD. Patients who

Risk factor	Study	Donulation
	J	Population
Emergency surgery	Krzych et al. [45]	Cardiac surgery
	Kalisvaart et al. [100]	Hip surgery
	Koebrugge et al. [101]	Endovascular aortoiliac surgery
Longer duration of surgery	Shah et al. [53]	Major head and neck cancer surgery
	Norkienė et al. [102]	Cardiac surgery
	Lee et al. [72]	Hip fracture repair surgery
Invasive surgery	Fineberg et al. [49]	Spine surgery (lumbar)
	Koebrugge et al. [101]	Endovascular aortoiliac surgery
	Salata et al. [103]	Aortic aneurysm repair surgery
	Hudetz et al. [104]	Cardiac surgery
	Osse et al. [58]	Cardiac surgery
Fentanyl use	Radtke et al. [88]	Surgery
	Andrejaitiene & Sirvinskas [110]	Cardiac surgery
	Burkhart et al. [111]	Cardiac surgery
Midazolam use	Do et al. [79]	Orthopedic surgery
Greater intraoperative volume loads	Smulter et al. [52]	Cardiac surgery
Low intraoperative body temperature	Detroyer et al. [119]	Cardiac surgery
Blood loss	Marcantonio et al.	Major elective noncardiac surgery
Blood transfusions	Whitlock et al. [117]	Cardiothoracic surgery
	Gao et al. [47]	Spine surgery
Intraoperative	Patti et al. [77]	Colorectal surgery
hypotension	Tognoni et al. [118]	Urological surgery
· 1	rognom et al. [110]	croisgieur surgery

Table 30.4 Intraoperative risk factors for PD

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have undergone CABG have more cognitive dysfunction after 5 years than control subjects without coronary artery disease [122]. Though CABG surgery has a significant rate of POCD, avoiding the use of CPB was not protective against long-term cognitive decline (5-year outcomes) [123]. Perioperative factors like number of cerebral emboli, temperature, mean arterial pressure, and jugular bulb oxygen saturation have varying predictive power [99]. Prolonged duration and deeper levels of anesthesia, intraoperative hypotension, and cerebral oxygen desaturation may contribute to POCD although there is significant equipoise here [43, 96, 124]. Consistent effect of anesthetic type (regional versus general) has not been demonstrated [107]. For pharmacological prevention of POCD, no clear benefit to any single drug including atorvastatin, ketamine, propofol, lidocaine, or magnesium sulfate has been proven [125].

Table 30.5 Postoperative risk factors for PD

Risk factor	Study	Population
Pain	Vaurio et al. [112]	Major elective
		noncardiac surgery
	Leung et al. [113]	Major noncardiac surgery
	Nie et al. [114]	Hip fracture repair surgery
Administration of	Adunsky et al.	Hip fracture
meperidine	[126] Marcantonio et al.	repair surgery Major elective
	[127]	noncardiac surgery
	Morrison et al. [128]	Hip fracture repair surgery
Benzodiazepines	Marcantonio et al. [127]	Major elective noncardiac surgery
	Leung et al. [83]	Noncardiac surgery
	Takeuchi et al. [131]	Esophageal cancer surgery
Tramadol	Brouquet et al. [129]	Major abdominal surgery
Pneumonia	Loponen et al. [64]	Cardiac surgery (CABG)
	Takeuchi et al. [131]	Esophageal cancer surgery
SIRS	Guenther et al. [69]	Cardiac surgery
Low cardiac output syndrome	Norkiene et al. [46]	Cardiac surgery (CABG)
	Norkienė et al. [102]	Cardiac surgery
Higher postoperative body temperatures	Smulter et al. [52]	Cardiac surgery
Postoperative blood transfusion	Marcantonio et al. [116]	Major elective noncardiac surgery
Low postoperative hematocrit	Marcantonio et al. [116]	Major elective noncardiac surgery
Low postoperative oxygen saturations	Wang et al. [132]	Major head and neck surgery
Markedly abnormal postoperative levels of sodium, potassium, or glucose	Yildizeli et al. [133]	Thoracic surgery
Elevated levels of C-reactive protein	Burkhart et al. [111]	Cardiac surgery
	Dillon et al. [134]	Major elective surgery
Admittance to ICU	Pol et al. [71]	Vascular surgery
Significantly longer time on mechanical ventilation	Norkienė et al. [102]	Cardiac surgery
Significantly longer time on mechanical ventilation	Burkhart et al. [111]	Cardiac surgery

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Table 30.6	Summary of best practices in the prevention and treatment of PD ^a
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Perioperative phase of care	Best practice	Strength of recommendation	Quality of evidence
Preoperative (prevention)	Educational programs to improve understanding of epidemiology, assessment, prevention, and treatment	Strong	Low
Preoperative (prevention)	Multicomponent non-pharmacologic intervention program (e.g., cognitive reorientation, sleep enhancement, early mobility, adaptations for sensory impairment, nutrition, fluid repletion, pain management, adequate oxygenation, prevention of constipation)	Strong	Moderate
Postoperative (management/treatment)	Multicomponent intervention program (cognitive reorientation, mobility/exercise/ physical therapy, therapeutic activities/ cognitive stimulation, sensory adaptation, nursing education, and geriatric consultation)	Weak	Low
Postoperative (management/treatment)	Perform medical evaluation, make medication and/or environmental adjustments, order appropriate diagnostic tests, and obtain appropriate clinical consultations to identify and manage underlying PD contributors	Strong	Low
Preoperative/postoperative (prevention)	Provide regional anesthetic at the time of surgery and postoperatively to improve pain control	Weak	Low
Postoperative (prevention)	Optimize postoperative pain control with nonopioid medications if possible	Strong	Low
Postoperative (prevention)	Avoid medications that induce delirium (e.g., benzodiazepines, anticholinergics, sedative-hypnotics, meperidine)	Strong	Low
All (prevention and management)	Avoid newly prescribing cholinesterase inhibitors to prevent or treat PD	Strong	Low
Postoperative (management/treatment)	Use antipsychotics at lowest effective dose for the shortest possible duration to treat severely agitated or distressed patients (only if behavioral interventions have failed) – evaluate ongoing use daily	Weak	Low
Postoperative (management/treatment)	Avoid benzodiazepines as first-line treatment of agitated patient except when specifically indicated (i.e., treatment of withdrawal)	Strong	Low
Postoperative (management/treatment)	Avoid antipsychotics and benzodiazepines in older adults with PD who are not agitated (e.g., hypoactive PD)	Strong	Low

Based on data from Ref. [13] & Courtesy of Michelle Humeidan, Stacie G. Deiner, and Nicholas Koenig

^aTable excludes practices for which the American Geriatrics Society Expert Panel did not issue a recommendation for or against practices lacking sufficient evidence of efficacy

Postoperative Factors

Postoperative risk factors for cognitive dysfunction also exhibit categorical themes: postoperative pain and pain control, postoperative complications, and characteristics of postoperative management (Table 30.5).

Postoperative pain management is complicated by the increased risk for PD seen with both poorly controlled pain and use of opioids [112–114]. Administration of meperidine [126–

128] and tramadol [129] has also been associated with PD risk. Patient-controlled analgesia (PCA) is associated with more risk of PD than oral opioids [88–112]. For patients undergoing total hip arthroplasty, lumbar plexus block plus PCA has been shown to significantly reduce the risk of PD compared to PCA alone [130]. Generally, anesthesia practitioners should work with surgeons and pain management physicians when necessary to create an appropriate analgesic plan for geriatric patients before a major operation (see Chaps. 9 and 28). This plan should consider physiologic and metabolic changes in the elderly and incorporate opioid-sparing techniques like adjunctive medications (e.g., acetaminophen, gabapentin) and regional analgesia (e.g., peripheral nerve blocks and epidurals). Since narcotics decrease GI motility, a prophylactic pharmacologic bowel regimen should be started when appropriate [12].

A number of postsurgical complications beyond those associated with pain management are associated with PD [61, 131] including pneumonia [64, 131], systemic inflammatory response syndrome (SIRS) [69], and low cardiac output syndrome [46, 102]. While lower intraoperative body temperatures have been shown to be a risk factor [119], higher postoperative body temperatures have been associated with increased risk of PD, even though the patients were not febrile [52]. Postoperative blood transfusion is associated with PD development [116], as is low postoperative hematocrit [116]. Low postoperative oxygen saturations [132], markedly abnormal postoperative levels of sodium, potassium, or glucose [133] and elevated levels of CRP [111, 134] increase PD risk. Admittance to the ICU [71] and significantly longer time on mechanical ventilation [102, 111] have also been associated with PD.

Early postoperative cognitive impairment is associated with increased risk for long-term cognitive decline [98]. Medications like benzodiazepines and anticholinergics also increase POCD risk [127]. Complications such as anemia (hematocrit <30%), postoperative infections, and respiratory complications are likewise associated with POCD [43].

Treatment

If preventive efforts are unsuccessful, non-pharmacological and/or pharmacological strategies may be employed to treat PD. Non-pharmacological means primarily involve multicomponent treatment strategies and general health maintenance (i.e., managing the underlying contributors to delirium). Pharmacologic treatment consists of the careful administration of antipsychotics and review of all medications.

Comprehensive treatment of PD includes making environmental adjustments, ordering appropriate diagnostic tests, and obtaining clinical consultation as necessary (Table 30.6). Non-pharmacological interventions for treating PD typically consist of one or more of the following elements: mobility/exercise/physical therapy, cognitive reorientherapeutic activities, cognitive stimulation, tation. maintenance of nutrition and hydration, promotion of sleep hygiene, visual and hearing adaptations, nursing interventions, and geriatric medicine consultation. The most widely studied intervention for delirium in hospitalized nonsurgical patients is the Hospital Elder Life Program (HELP). Based upon the Yale Delirium Prevention Program, HELP provides

a standardized protocol targeted at six delirium risk factors (preexisting cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration) and has been shown to decrease delirium 14.4% in medicine inpatients, with an estimated cost savings of >\$1.2 million per year in a 500-bed community teaching hospital [135]. More recently, a modified HELP approach focusing on only early mobilization, nutrition and cognitive activities was applied to a surgical population, and 0 of 179 elderly patients experienced PD after elective abdominal surgery compared to a 16.7% incidence of PD in the control group of 77 patients [136].

When non-pharmacological approaches are unsuccessful, AGS guidelines recommend that pharmacological treatment with antipsychotics is only warranted if patients are severely agitated or distressed and are threatening substantial harm to self and/or others. The lowest effective dose and shortest duration of administration should be used, and daily inperson evaluation of the need for continued use should be performed. In tandem, medication adjustments (such as discontinuing or decreasing deliriogenic and extraneous medications if possible) should be instituted.

Several of the proposed perioperative interventions for decreasing PD risk may also decrease risk of POCD, but more research is necessary to develop treatment strategies for POCD. Postoperative infections should be aggressively managed. Medications should be regularly reviewed assuring cautious narcotic, benzodiazepine, and anticholinergic use, while adequately treating pain. Dehydration and electrolyte imbalances should be corrected [43]. The role of cognitive exercise in improving executive function has been shown in healthy patients [137], but whether this intervention will improve POCD will require more research [43].

Summary

PD and POCD are cognitive complications seen most commonly after surgery in the elderly. The burden on patients and the healthcare system is significant. Risk factors may or may not be subject to change and intervention. Recognition of key modifiable risk factors helps guide best practices for the care of patients at risk for PD and POCD. Screening patients for risk factors can identify patients who may require enhanced services before and after surgery. Both pharmacological and non-pharmacological treatments are currently used for PD and POCD, but to date the most promising intervention has been a use of a multidisciplinary team of providers to optimize perioperative care of geriatric surgical patients. One opportunity for healthcare providers to have a significant impact on the aging surgical population is in the area of medication management, with efforts like avoiding AGS Beers Criteria medications and aggressively targeting polypharmacy. Working knowledge of PD screening assessments and ability to recognize PD symptomatology is important for all who provide care for the geriatric surgical patient. A primary goal of leaders in POCD research is to unify nomenclature and diagnostic criteria to allow consistency across studies, and ultimately to promote recognition and evaluation of these patients clinically. In the future perioperative collaboration between geriatricians, surgeons, anesthesiologists, and nursing will facilitate cognitive recovery and health after surgery by providing optimal care to at-risk patients in the aging population.

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Palliative Care for the Anesthesia Provider

Allen N. Gustin Jr.

Introduction

The American population is growing older. Americans over the age of 65 years totaled 46.2 million in 2014 and represented 14.5% of the population (approximately one in seven Americans) [1]. By 2060, this number will increase to 98 million people over the age of 65 years and will represent almost 30% of the population here in the United States (USA) or one in three Americans [1]. As our population ages, so does the burden of serious illness. Almost two-thirds of patients older than 65 years have multiple chronic conditions [2]. Providing high-quality end-of-life care has become challenging because of multiple factors, including the increasing number of elderly patients, structural barriers to access of care for older patients, and a fragmented healthcare system [3, 4]. In 1997, a report by the Institute of Medicine that evaluated end-of-life care in the United States described significant patient and family suffering related to end-of-life care and emphasized the need for improvements (Table 31.1) [3]. Over the last 15 years, hospice use doubled, and palliative care guidelines have made improvements regarding quality measures for the care of elderly patients with chronic and/or severe illness [4-6]. A follow-up Institute of Medicine report in 2014 revealed that palliative care services are underused and are too frequently unavailable and that current providers should seek further skills training in palliative care (Table 31.1) [4, 7]. What is clear is that palliative care approaches can benefit geriatric patients, their families, and their healthcare providers not only in the course of general care but also anytime a geriatric patient presents to any perioperative setting.

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Palliative Care, Hospice, and End-of-Life Care

The term "palliative care" was first introduced by a Dr. Balfour Mount, a Canadian physician who had introduced "hospice-like" services into a number of Canadian hospitals [8]. The definitions of palliative medicine have since evolved over the years – this is detailed in Table 31.2 [4, 7, 9-12]. At first palliative care was epitomized as the care associated with patients dying from cancer. As the field evolved and the benefits of palliative care emerged, it was clear that this type of care could be provided to a broader range of patients with a vast array of serious illnesses, and the field expanded its opportunities and options for many different patient populations with both acute and chronic health issues. Currently, the most contemporary definition of palliative care involves the following three components: (1) aggressive, expert-based symptom management, (2) psychosocial support of both the patient and the patient's family, and (3) an expansive discussion of the patient's goals of care for his/her medical care [4].

While working toward achieving all three of these goals, palliative care prioritizes providing both the patient and his/her family with relief from the symptoms, pain, and stress of serious illness—whatever the diagnosis, wherever the location, and whatever the outcome. The ultimate goal of palliative care is to improve the quality of life for both the patient and the family. Palliative care can be initiated early in the course of treatment of any illness (regardless of severity) and may be delivered across the continuum of healthcare settings (including the home, the nursing home, the long-term acute-care facility, the acute-care hospital, the intensive care unit (ICU), any perioperative setting, the emergency room, or outpatient clinic) [4, 13–15].

Palliative care can be available when life-prolonging therapy begins, after life-prolonging therapy is withheld or withdrawn, and even during any bereavement period for the patient's family after the patient's death (Fig. 31.1) [16]. Figure 31.1a depicts the traditional model of palliative care where a patient first receives life-prolonging/life-sustaining therapy until it fails, and only then is palliative care offered
 Table 31.1
 Institute of Medicine recommendations and challenges for providing quality end-of-life care in America

1997 recommendations for end-of-life care

- 1. *Raise the issue*. People should think about, talk about, and learn about decisions they may face, as they or those they love approach death
- 2. *Raise expectations*. Dying people and their families should expect good, dependable care. They should expect their beliefs and wishes to be respected
- 3. *Do what we know helps.* Doctors, nurses, social workers, and others need to use what we already know how to prevent and relieve pain and other symptoms
- 4. Get rid of barriers to good care. Doing this will often require support of lawmakers, voters, the media, and healthcare managers
- 5. *Build knowledge*. The National Institutes of Health and other public/private groups should work together to find out more about end-stage disease and end-of-life care

2014 challenges for providing quality end-of-life care in America

- 1. Increasing number of elderly Americans, including those with some combination of frailty, significant physical and cognitive disabilities, multiple chronic illnesses, and functional limitations
- Growing cultural diversity of the US population, which makes it ever more important for clinicians to approach all patients as individuals, without assumptions about the care choices they might make
- 3. Structural barriers in access to care that disadvantage certain population groups
- A mismatch between the services patients and families need most and the services they can readily obtain
- 5. Availability of palliative care services has not kept pace with the growing demand
- 6. Wasteful and costly systemic problems, including perverse financial incentives, a fragmented care delivery system, time pressures that limit communication, and a lack of service coordination across programs
- 7. The resulting unsustainable growth in costs of the current healthcare delivery system over the past several decades

Table 31.2 Definitions for palliative care

World Health	Active total care for the patient whose
Organization, 1990	disease process is not responsive to cure
World Health Organization, 1993	The study and management of patients with acute, progressive far advanced disease for whom the prognosis is limited and the focus of care is quality of life
National Consensus Project, 2004	The prevention and relief of suffering and the support of the best possible quality of life for patients/the family regardless of the state of disease
World Health Organization, 2007	Palliative care as a pathway to improve the quality of life for patients and families with palliation and relief of suffering
Institute of Medicine, 2014	The care that provides relief from pain and other symptoms, supports quality of life, and focuses on patients with serious advanced illnesses and their families
Center to Advance Palliative Care	The specialized medical care for patients with serious illness

and provided [4, 10]. Many physicians feel the perioperative environment fits this paradigm as surgeons can sometimes be slow to consider palliative medicine until all efforts to restore the patients' health have failed. Figure 31.1b depicts an overlapping model where palliative care is gradually increased while the patient receives a gradual decrease in lifeprolonging therapy [4, 10]. Figure 31.1c depicts an integrated model where palliative medicine is delivered at the beginning of an illness and is provided concurrently with life-prolonging therapy [4, 10]. The amount of palliative care can increase and decrease depending on the preferences and needs of both the patient and the family [4, 10]. Figure 31.1d depicts an ICU individualized integrated model where the patient receives palliative care alongside ICU care [4, 10]. In the ICU, hospice care is not nor can it be integrated into critical care because, though palliative care can be provided concurrent to critical care, hospice care cannot. One should note that usual "life-prolonging" medical care in any care environment ends with the patient's death, whereas palliative care engagement and application peak at death and continue after death to address the bereavement needs and issues of the patient's family [4, 10].

Whether in the ICU, the emergency room, the perioperative care, or any patient care area, expert statements recommend coordinating palliative care with life-prolonging care. Life-sustaining medical/surgical care and palliative care can be complementary as long as the patient's medical/surgical condition and the patient's goals of care are in parallel and complementary. In 2013, the American Academy of Hospice and Palliative Medicine (AAHPM) "Choosing Wisely" initiative listed the top five initiatives that should be considered in any patient's care [16]. One of those top five items encouraged the idea that palliative care should be provided to patients with a serious illness and should not be delayed while the patient is being actively treated [16]. Overall, palliative care is appropriate at any age (pediatric to geriatric) and at every stage of any serious illness and can be provided concurrently with curative or other life-prolonging therapies [17].

Although palliative care can be integrated into the continuance of geriatric care, it is still underused in the United States [4, 17]. Despite national efforts to improve end-of-life care, reports of pain and other alarming burden of symptoms in the last year of life have been increasing over the last 10 years [18]. Moreover, advances in healthcare have transformed many previously lethal diseases (human immunodeficiency virus and AIDS, heart failure, chronic obstructive pulmonary disease, some forms of cancer, end-stage renal disease, and dementia) into chronic conditions where significant physical and psychological burdens exist for both the patient and their family [4]. To meet the growing need for palliative care, hospital-based, home-based, hospice-based, emergency room-based, and community-based palliative

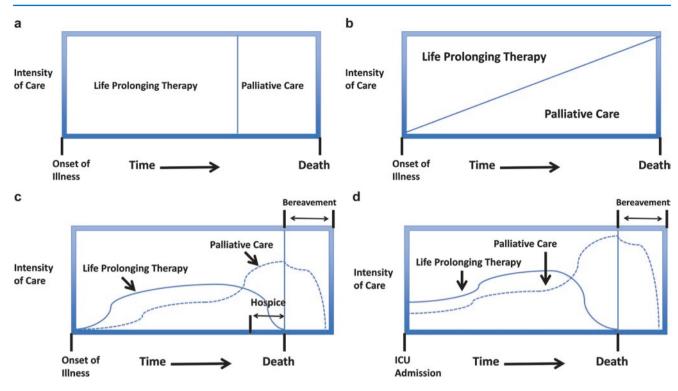


Fig. 31.1 (a) Traditional dichotomous model, (b) overlapping model of palliative care, (c) individualized integrated model of palliative care, (d) Individualized Integrated Model of Palliative Care (Reprinted with permission of the American Thoracic Society. Copyright © 2016

American Thoracic Society. Lanken et al. [10]. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society)

care programs are increasingly being developed and utilized in greater numbers each year [19]. However, there are still not enough trained specialized palliative care providers to meet public demand; the Center to Advance Palliative Care focuses on the fact that there is approximately 1 cardiologist for every 71 patients experiencing a myocardial infarction, 1 oncologist for every 141 newly diagnosed patient with some form of cancer, and only 1 specialized palliative care physician for every 1200 patients living with a serious or lifethreatening illness [4, 10].

Earlier in the evolution of hospice care in the United States, many healthcare providers and patients considered hospice and palliative medicine to be the same entity. Many healthcare providers are confused by the relationship or the distinctions between palliative care and hospice care. Simply stated, hospice care and the field of palliative care can be complimentary to one another, but differences do exist. Endof-life care has been used globally to refer to the process of addressing the medical, social, emotional, and spiritual needs of patients who are nearing the end of life. End-of-life care may include a broad range of medical, surgical, and social services, including disease-specific interventions and palliative/hospice care for those with advanced serious conditions who are near death [7]. More specific than palliative care, hospice is for the dying patient [4]. On the other hand, palliative care is based on the patient's or family's need, in contrast

to hospice care that is based on the patient's prognosis. Palliative care can be provided with every effort related to restoring the patient's health regardless of any life-sustaining treatment (including ICU care). Hospice care, however, tends to focus on the patient's goals of care at the end of life and cannot/usually is not typically provided concurrently with aggressive curative or life-prolonging treatment options [4]. Palliative care can be provided with no limitations to care – even with the use of cardiopulmonary resuscitation (CPR), intubation, and all other life-sustaining therapies [7]. Hospice tends to discourage life-sustaining options that do not support the patient's goals of care and highly encourages each patient or surrogate to consider having active Do Not Resuscitate/Do Not Intubate orders.

Palliative Care-Related Perioperative Issues

Cardiopulmonary Resuscitation (CPR)/Do Not Resuscitate (DNR) Orders/Do Not Intubate (DNI) Orders/Anesthesiology

CPR is provided approximately 800,000 times each year within the United States [4, 20]. It is the only medical intervention where no consent is required and where an explicit physician order is absolutely necessary for it to be withheld from a patient [4, 20]. In 1983, the President's Commission for the Study of Ethical Problems in Medicine clarified that

patients had a right to expect CPR as the standard of care in all situations of cardiac arrest [4, 21]. The only time that CPR should be withheld in only is if a note exists where a patient's wish was clearly documented to have CPR withheld [22]. During the 1980s, a patient's DNR orders were routinely rescinded when entering the perioperative area as perioperative personnel believed that routine anesthesia and surgical care in the operating room (e.g., volume resuscitation/administration and use of vasoactive medications) would be considered or confused with "resuscitation" [4, 21, 22]. During the last two decades, opinions have been evolving to consider that DNR orders should only apply to the actual delivery of CPR in the event of an actual cardiac arrest and all the medical treatments before the actual event of a cardiac arrest are actually not CPR (and so should not be affected by an active DNR order) [23]. Moreover, studies still support variation in practice concerning how to manage active DNR orders for perioperative patients who present for procedures whether in or out of the operating room. In one study, anesthesiologists were twice as likely as either other healthcare providers to assume that DNR patients would readily suspend their DNR order in the operating room [4, 24]. Furthermore, when comparing these providers with others, they were much less likely to discuss the implication of an active DNR order with their patients, more likely to refuse to provide care for a DNR patient, and more likely to ignore a patient's active DNR request even if the patient made his/ her wishes explicit after an informed discussion [4, 24].

The Patient Self Determination Act of 1990 established as law in the United States that a patient's right to selfdetermination was the supreme standard in medical ethics, taking precedence over beneficence [4, 9, 25]. Because of this act, routine suspension of an active DNR orders in the perioperative period is considered a violation of a patient's right of self-determination [4, 26-28]. As a result, the American Society of Anesthesiologists' (ASA) practice guidelines refute the required rescission of an active DNR order within the perioperative period and instead support the act of "required reconsideration" of a patient's active DNR status before proceeding with any surgical procedure and exposure to anesthesia [4, 29]. In this discussion with a patient, the anesthesiologist or surgeon should address the patient's goals of care and core values in the context of risks and benefits of either the anesthesia or the surgical procedure [21]. In this author's estimation, four possible outcomes of this DNR discussion exist. These outcomes are the following: (1) keep the DNR orders active throughout the perioperative periods, (2) fully rescind the DNR order completely with the idea of reactivating the DNR orders at some point after surgery, (3) agree to provide some aspects of resuscitation but deny other aspects of the DNR orders, or (4) allow for either the surgeon or the anesthesiologist to use substituted judgment for the patient based on the wishes of the

patient [4, 30]. Many anesthesiologists are uncomfortable with providing anesthesia to a patient with active DNR or DNI orders. As anesthesiologists titrate anesthesia to achieve the desired effect for patient comfort in order to tolerate a surgical procedure, patient safety concerns with possible needs to secure an airway or manage hemodynamic changes could be at odds with an active DNR/DNI order. As such, some anesthesiologists may be unwilling to proceed to the operating room with an active DNR/DNI order. On the other hand, having a truthful discussion with the patient can allow for the anesthesiologists to understand the true nature of the patient's active DNR/DNI orders. Many patients have the DNR order for times when patient would consider the situation to be futile or completely nonbeneficial. When the patient is informed of the nature of how anesthesia is delivered, this author has found that patients are quite reasonable and most of the time are completely willing to rescind the DNR/DNI orders for the duration of the anesthesia procedure and for a period of time after the surgical procedure. Clinical anesthesia and surgical care should be discussed with the patient while keeping the patient's overall goals of care as the centerpiece of the discussion. The healthcare team is not ensuring a particular outcome but rather ensuring that care is designed around the patient's individual goals of care and values and continues to be medically consistent with standards of care [4, 21].

But, what if the patient wants the DNR and the DNI orders maintained throughout any care provided within the operating room or procedural area? Based on the previous discussion, patients with active DNR/DNI orders can have none of, a portion of, or all of their DNR/DNI wishes maintained in the operating room and throughout the perioperative period. Managing these patients with care limitations and/or end-of-life issues can be psychologically and ethically challenging for some healthcare providers especially the anesthesiologists [4]. What is an anesthesiologist to do when presented with a clinical situation where he/she feels ethically uncomfortable to provide intraoperative care for a geriatric hospice or palliative care patient at the end of life? In those circumstances, the American Medical Association Code of Ethics does offer some assistance and states that a clinician should not be compelled to perform procedures or provide care that they view as inconsistent with their own personal values [4, 31]. Rather, the practitioner should involve a second clinician who is willing to comanage the patient by performing the desired procedure or provide the care desired by the patient [4, 31]. Consistent with this guidance, an anesthesiologist can refuse to provide care for a patient when he or she has fundamental ethical concerns of providing anesthesia care for this patient, but the anesthesiologist cannot abandon the patient and is required to promptly find another anesthesiologist who would be willing to provide the care to the patient. Similar to management of other

patients with care limitations (i.e., the Jehovah's witness patients who refuse blood transfusions), anesthesia care practices should consider developing individual practice guidelines to support and facilitate the care of any patients who wishes to maintain active DNR orders throughout the perioperative period [4].

Noninvasive Positive-Pressure Ventilation (NPPV)

Active DNR/DNI orders which are meant to limit active treatments are taken immediately on hospital admission to protect patients from possible interventions that both contradict their preferences and which could deprive them from any communication with their families, particularly during times near the end of life [32]. In particular, active DNI orders specifically limit the placement of endotracheal tubes during times when ordinary patients would be intubated. The role of noninvasive positive-pressure ventilation and highflow nasal cannula has been rising in the treatment of dyspnea or other symptoms of respiratory compromise (viz., hypoxemic respiratory failure or hypercarbic respiratory failure) [33, 34]. The problem is determining when the clinical practice of noninvasive positive-pressure ventilation (NPPV) or high-flow nasal cannula support is either appropriate or nonbeneficial [33, 34]. Indeed, some perioperative patients with treatment limitations may refuse endotracheal intubation outside the operating room but may accept NPPV or high-flow nasal cannula because it may forego intubation while potentially providing relief from suffering caused by forms of dyspnea. Some physicians caution that NPPV or high-flow nasal cannula may be inappropriate in the context of any end-stage disease because of an increased use of medical resources, prolongation of the dying process, and intensification of suffering [4, 35]. Yet, NPPV or high-flow nasal cannula may be beneficial for patients with progressive dyspnea, and the use of NPPV/high-flow nasal cannula should be tailored to each patient's situation and each patient's goals of care [4, 34, 35].

Percutaneous Feeding Tubes, Hydration, and Artificial Nutrition

Many cultural and religious variations exist among patients and create conflict between goals of care of the patient and the concerns about hydration/artificial nutrition for patients near or at the end of life. The AAHPM endorses the ethically and legally accepted view that artificial nutrition and hydration, whether delivered parenterally or through the gastrointestinal tract via a tube (including nasogastric tubes), are a medical intervention [4, 36]. This clarification of artificial hydration and nutrition beingc considered a medical intervention suggests that both can be withheld or withdrawn just as any other medical intervention, provided that the intervention does not meet the goals of care of the patient. The AAHPM recognizes that in some faiths and traditions, family members or surrogate decision-makers may consider artificial nutrition and hydration as a basic sustenance or as a symbolic importance, apart from any measurable benefit of the patient's physical well-being [4, 36]. Some national organizations have advocated to the avoidance of placement of percutaneous feeding tubes in particular patient populations who would not benefit from the use of artificial hydration and nutrition. In 2013, the AAHPM noted that percutaneous feeding tubes should not be placed into patients with advanced-stage dementia [16]. These feeding tubes were found to worsen delirium, increase fall risks, and increase risk of aspiration and did not aid in the healing of bed sores when placed in patients with advanced dementia [37]. The American Geriatrics Society released a position statement advocating for the avoidance of placing feeding tubes in patients with advanced dementia [38]. Such views should be explored, discussed thoroughly, fully understood, and respected in every way possible, in keeping with patient and family values, beliefs, and cultures [4, 36]. Members of the Roman Catholic faith tend to view the removal of artificial nutrition and hydration as passive euthanasia [4, 39]. Family members can feel distressed when nutrition or hydration is withheld because they may believe that the patient "is starying to death" or "will thirst to death" [4]. Thus, there may be equally good, ethical, and valid reasons for patients, particularly at the end of life, to either pursue or not to pursue palliative hydration and artificial nutrition [4]. Moreover, anesthesiologists may care for these geriatric patients in the operating room for placement of feeding tubes or other procedures for providing enteral nutrition. Consequently, involvement in these procedures typically is aided by careful discussion of the goals of care plans and goals with the entire clinician team as well as with the patient.

Palliative Surgery/Palliative Surgical Procedures/Palliative Proceduralists

Palliative surgery is not a new term and is similar to palliative medicine in that the focus is the relief of a patient's symptoms but achieves this goal through a surgical procedure or other noninvasive interventions. As a definition, palliative surgery can be defined as any surgical procedure aimed at the alleviation of a symptom with the aim of improving the quality of life for the patient, with minimal impact on survival as possible [40–42]. Palliative surgery is not the opposite of cure but has its own distinct indications/ goals that should be evaluated independently [42]. As techniques have improved, several palliative surgical procedures once managed solely by surgeons are being performed by the nonsurgical interventionist or the proceduralist. Examples of these procedures include placement of esophageal stents for advanced-stage esophageal cancer, colonic stents for advanced-stage colorectal cancer, and gastric stents for gastric outlet obstruction. The effectiveness of any palliative surgery/procedure should not be judged by either the surgeon's or proceduralist's evaluation or assessment of symptom resolution [42]. Rather, the effectiveness of any palliative surgery should only be judged by the presence and durability of patient acknowledgment of symptom resolution [42]. As the incidence of dyspnea has been increasing in the geriatric population, several palliative surgeries can be performed to aid in the management of any associated symptom burden. A few examples of these procedures include coronary artery bypass grafting for angina, lung transplantation for dyspnea secondary to end-stage lung disease, and the implantation of automatic implantable cardioverter defibrillators or the implantation of ventricular assist devices for dyspnea associated with advanced hear failure.

Palliative Sedation, Physician-Assisted Suicide, and Euthanasia

The concept of palliative sedation was first illustrated in the literature in 1991 in order to describe the practice of druginduced sedation for terminally ill patients [43]. The sedation was meant for the management of otherwise refractory symptoms leading to uncontrolled patient suffering [44]. Some critics claimed that this palliative sedation was actually "slow euthanasia" or mercy killing in disguise [45]. Recommendations, guidelines, and standards for the appropriate implementation of palliative sedation have been issued by both national and international organizations [8]. Supporters note that palliative sedation is "the intentional administration of sedative drugs in dosages and in combinations required to reduce the consciousness of a terminally ill patient as much as necessary to adequately relieve one or more refractory symptoms" [24]. This is in direct contrast to either physician-assisted suicide or euthanasia where the intent of palliative sedation is to relieve symptoms, not to end the patient's life [4, 8]. Palliative sedation has critical ethical and legal considerations that require a specific foundation of clear communication of all available treatment objectives among all the stakeholders (patient, family, nurses, doctors, clergy, and others). The incidence of palliative sedation is difficult to estimate from the literature (ranging somewhere between <1% and 30%) given the wide variation in definitions of the practice [43, 44]. Many groups advise that the ethical concept of proportionality is the key concept for palliative sedation as the depth of recommended sedation

should be proportional to the severity of the symptoms being treated [8, 45].

The American Academy of Hospice and Palliative Medicine (AAHPM) consensus statement regarding palliative sedation recognizes that one of the aims of palliative care is to relieve patient suffering (pain, suffering, and distress) associated with disease but that, unfortunately, not all symptoms associated with advanced illness can be controlled with pharmacologic, procedural, or other psychiatric interventions [4, 46]. Palliative sedation is defined by the AAHPM as the use of sedative medications to reduce patient awareness of any distressing refractory symptoms that are insufficiently controlled by symptom-specific interventions or therapies. The level of sedation is proportional to the patient's level of distress, and alertness is preserved as much as possible to minimize further distress [46]. The AAHPM also specifically defines the circumstance of "palliative sedation to complete unconsciousness." This occurs when the administration of sedation is pushed to the point of complete unconsciousness and can be considered when less sedation has not achieved sufficient relief of any distressing symptoms. This practice of sedation to unconsciousness is used only for the most severe, intractable suffering at the very end of life [46].

Currently, the ethical debate does support palliative sedation for the management and relief of refractory or intractable symptoms [4, 47-49]. The key ethical features are (1) the clinician's intent to relieve patient suffering, (2) the degree of sedation being proportional to the severity of patient suffering, and (3) that the patient (or surrogate) should give informed consent [4, 49]. The American Medical Association Statement on the End-of-Life Care advocates that patients should have "trustworthy assurances that physical and mental suffering will be carefully attended to and comfort measures intently secured" [50, 51]. Palliative sedation is legal in every state within the United States [4]. Palliative sedation has been reinforced as legal by the US Supreme Court in Vacco v Quill (521 US 793; 1997) and Washington v Glucksberg (521 US 702; 1997) [4, 50, 51]. Geriatric anesthesiologists may wish to familiarize themselves with the ethical issues associated with palliative sedation as drugs used for this practice include common anesthetics, such as ketamine, propofol, or barbiturates [4]. As drug shortages have been an issue of recent anesthesiology practices, agents in some hospitals that are used for palliative sedation may be restricted to anesthesia practitioner [4]. Thus, anesthesiologists may be asked at some point in the future to participate in the practice of palliative sedation.

At this time, euthanasia is illegal in the United States [52]. 20 years ago, no country on this planet allowed for euthanasia. However, three countries currently allow for certification for euthanasia. Those countries include the following: Belgium (legalized in 2006), Luxemburg (legalized in 2009), and the Netherlands (legalized in 2001) [52]. Certification process for euthanasia in each of these countries varies, but patients can gain certification for euthanasia with serious illness or as they approach the end of life. Also, patients can gain certification for euthanasia for existential suffering which can include severe depression and other psychiatric conditions. As for physician-assisted suicide, only one state within the United States allowed this practice approximately 10 years ago. That single state was Oregon. In 2016, the following states currently allow physician-assisted suicide as legal: Oregon, Washington, California, and Vermont. Montana allows for physician-assisted suicide as legal under a court ruling [52]. Nevada's law for physician-assisted suicide (one county) is under review by that state's supreme court [52]. Four other states (Tennessee, New York, Connecticut, New Jersey, and Maryland) have legislation under review for the consideration of the legalization of physician-assisted suicide [52]. Outside of the United States, Belgium (legalized in 2002), Canada (legalized in 2015), Columbia (legalized in 2015), Luxembourg (legalized in 2009), the Netherlands (legalized in 2001), South Africa, Germany, and France all have forms of physician-assisted suicide. As compared to other countries, it should be noted that South Africa, Germany, and France require more formal legal process to achieve the right to physician-assisted suicide [52].

Integrating Palliative Care and Perioperative Care for Geriatric Adults

As survivors of the intensive care unit (ICU) increase in number and are studied beyond their ICU stay, a new syndrome has been identified and is termed "the survivorship syndrome" or "post-intensive care syndrome" [4, 53, 54]. A broad array of physical and psychological symptoms (including impairments in function and cognition) impair the quality of a patient's life during and after the ICU [4, 18]. Patients may develop functional and neurocognitive deficits after surviving an ICU admission [55–61]. Not only do patients experience symptoms of survivorship, but the family members of critically ill patients can exhibit signs of anxiety and depression, along with signs of complicated grief and posttraumatic stress disorder [55, 56].

Many ICU patients are unable to participate in shared decision-making with the ICU team given their reasons for requiring the ICU resulting in decisions being made by the patient's surrogates [62, 63]. These discussions can be particularly difficult because surrogates can react to communications with ICU staff by focusing on details rather than the larger picture, relying on personal instincts or beliefs, and sometimes rejecting prognostic information [4, 64]. The need for specialist palliative care consultation is sometimes

justified in the ICU. Indeed, members of the ICU team should be providing basic palliative care at all times to all patients within the ICU. However, given that ICU personnel do not necessarily follow patients outside of the ICU, specialized palliative care involvement can aid in the continuity of care for these patients both inside and outside of the ICU (throughout recovery, hospital discharge, and at home) [4].

Unique barriers can exist for implementation of a formal palliative care program in any ICU [4]. These barriers can include unrealistic expectations for ICU therapies for the patient by the patient, family, ICU nursing staff, or ICU clinician, misperception that palliative care and critical care are not complementary and are not concurrent approaches, confusion of palliative care with end-of-life or hospice care, concerns that the institution of palliative care will hasten death, adding further demands on ICU clinician or team effort, no adequate rewards for evidence of palliative care excellence, and failure/inability to apply effective approaches for system or culture change to improve palliative care [4, 17]. Despite the presence of all these barriers, palliative care is increasingly accepted as an essential component of comprehensive ICU care for critically ill patients, regardless of the diagnosis or the prognosis [4, 18].

Implementation of any palliative care service in a surgical ICU can be especially challenging [4]. Some evidence suggests that surgeons have an exaggerated sense of accountability for patient outcomes and tend to do everything possible to avoid patient death [4, 65]. Surgeons have been shown to believe that they enter into a "covenantal" relationship with the patient (and by extension, the family or surrogate) and that patients and their families may consciously or unconsciously cede any sort of decision-making to that surgeon, particularly related to what the goals of care should be for the patient after a surgical procedure [4, 65]. In a national survey, many surgeons described conflict with ICU physicians and ICU nurses with respect to what is considered the appropriate goals of postoperative care [4, 66]. In addition, surgeons described difficulties in managing clinical aspects of poor outcomes of patients, communicating with the family and the patient about such poor outcomes, and coping with their own discomfort about these poor outcomes [4, 31]. Given the strong sense of responsibility for patient outcomes, surgeons can be resistant to any integrated palliative care program in the ICU, and further surgeon involvement/ approval may require additional encouragement from other specialties (including anesthesiologists) to consider possible palliative care options for patient care [4, 17, 66].

As the longer-term impact of intensive care on those patients who are surviving acute critical illness is increasingly documented, palliative care can definitely help to prepare and support each patient and each family for the challenges after ICU discharge [4, 18]. Key ICU quality markers for palliative care measures have been identified and implemented. The Care and Communication Bundle was developed and tested as part of national performance improvement by the Voluntary Hospital Association [4]. This bundle is triggered after a particular length of time has passed from admission to the ICU and involves identifying the medical decision-maker and resuscitation status before ICU day 2, offering both social work and spiritual care support before ICU day 4, and conducting an interdisciplinary family meeting not later than ICU day 5 [4, 67]. As chronic ICU patients tend to present repeatedly for procedures within the operating room, anesthesiologists can advocate for more engagement of palliative care services for perioperative patients within the surgical ICUs of their institutions [4].

Refractory Heart Failure, Mechanical Circulatory Support Devices, and Palliative Care Consultation

Over 80% of all heart failure patients are over the age of 65 years, and the management of these patients can be challenging [67]. Success with heart failure management in these patients has gradually improved over time; however, as our ability to manage these patients improve, so does the symptom burden experienced by this elderly group of patient [68]. This highlights the continued need for palliative care consultation in this patient group. For some patients, the heart failure will remain stable, whereas other patients will continue to advance. For those patients whose heart failure advances, progression to refractory heart failure may require the consideration of a mechanical circulatory support (MCS) device. Initial age concerns regarding candidacy for a MCS device have been shown to not be an issue. Though no formal "cutoff" age has been included in any of the clinical trials, two studies have shown that elderly patients have no increased rate of complications or different outcomes as compared to their non-geriatric cohorts [69, 70].

Both heart failure management and the use of mechanical circulatory support (MCS) for patients with advanced heart failure (which is refractory to medical therapy) have made tremendous progress over the past 15 to 20 years [4, 72]. Thousands of patients have had MCS devices inserted successfully as improvements in patient selection, surgical techniques, and postoperative management have occurred over these years [66]. MCS broadly includes devices implanted to improve cardiac output on a temporary basis (extracorporeal membrane oxygenation) or for longer periods of support (with the ventricular assist device being the most common) [4, 59–69, 71–75]. Compared with medical therapy alone, the placement of an MCS device has been shown to improve survival, quality of life, and the functional status in appropriately selected patients with advanced heart disease [76]. For a subset of patients with advanced heart failure, MCS device implantation can be performed until a heart transplant is available for the patient (referred to as a "bridge to transplant") [72]. Some patients may recover from their heart failure without ever needing a heart transplant (i.e., recovery from viral myocarditis or postpartum cardiomyopathy) where the MSC device can be successfully explanted without further issue (referred to as "bridge to recovery") [4, 72]. For patients who are ineligible for cardiac transplantation (patient preference, age, or comorbidities) and who are unlikely to recover their heart function to allow for explanation of the MSC, then, a MSC device can be placed with the intent that the device will remain in place for the duration of the patient's life (referred to as "destination therapy") [4, 72].

Because MSC devices are being placed more frequently as destination therapy, implantation is no longer restricted to the supply of transplantable hearts [4]. Moreover, destination therapy can add complexity to the patient's treatment options and decision-making during the course of the MSC device as the patient approaches the end of life [69]. Several analyses have concluded that in patients with an MSC device for destination therapy, the patients' goals of care are all too often undefined [68, 69]. Without defined goals or care or any advanced directives, destination therapy has the potential of merely maintaining circulation in a moribund patient, a situation sometimes referred to as "destination nowhere" [77]. Although the continuous-flow devices (i.e., HeartMate II or HeartWare) have shown improved morbidity and mortality, hospitalizations are still frequent. Complications are universal in all patients with MCS devices and can include the following: bleeding episodes (usually gastrointestinal), arrhythmias, infections (especially of the driveline), respiratory failure, renal failure, right heart failure, and cerebrovascular events [78, 79]. These adverse events can significantly affect a patient's morbidity and quality of life [4, 79, 80]. Because patients have the right to exercise his/her own autonomy, a patient or his/her family members may elect for deactivation of the MSC device if they believe that the goals of care are no longer being achieved with the MSC device [81]. Some healthcare providers are concerned that deactivation of the device is a form of physician-assisted suicide. However, deactivation is not physician-assisted suicide, and when a MCS device is deactivated, death is due to the underlying heart failure, rather than the act of deactivation of the device [81].

Given these complexities, experts and practitioners have suggested that proactive perioperative palliative care consultation may benefit patients considering MSC device placement. One study has shown feasibility of proactive palliative care in "preparedness planning" for all MSC patients [4, 74, 77, 82]. The 2013 International Society for Heart and Lung Transplantation Guidelines published practice guidelines that recommend specialist palliative care participation in the care of all patients being considered for an MCS device. The summary recommended that specialized palliative care be a component of the treatment of patients with end-stage heart failure during the evaluation phase for a MSC and that care goals and end-of-life preferences should be discussed with every patients receiving MCS as destination therapy [4, 72]. In addition, the International Society for Heart and Lung Transplantation recommends that palliative care specialists should be involved in the inhospital management of all MSC patients [4, 69, 72]. Accordingly, anesthesiologists and the cardiac anesthesiologist should recognize the need for greater involvement with palliative care specialists in the perioperative management of patients with MSC devices. Anesthesiologists and cardiac anesthesiologists should consider using these palliative care specialists more frequently when perioperative needs arise.

Automatic Implantable Cardioverter-Defibrillators (AICD) and Posttraumatic Stress Disorder (PTSD)

As patients with heart failure are living long, indications for the placement of AICDs have expanded further as left ventricular function declines. Unanticipated conditions are now being seen after the implantation of the AICD. Up to 40% of AICD recipients reached anxiety levels that needed pharmacologic therapy for control [83]. Up to 40% of AICD recipients reached levels of depression significant enough to require therapy [83]. As for those who had an AICD present for greater than 2 years, 31% of the patients developed PTSD [83]. The potential psychosocial distress regarding the depressive symptoms includes excessive sadness, anhedonia, and increased decreased appetite [83]. The PTSD symptoms exhibited by these patients tend to be seen as reexperiencing, avoiding, and hyperarousal. The anxiety component includes frequent worry, psychomotor agitation, and muscle tension. Risk factors for the distress in AICD patients include the following: age less than 50 years, female gender, premorbid psychiatric diagnosis, low social support, and greater than five defibrillations [83]. Given these symptom burdens, anesthesiologists should be aware of the increased symptom burden in patients with AICDs when these patients present to the perioperative area and should further consider these issues when involved in the care of the patient being considered for AICD placement.

Summary

The use and the roles of both palliative care and hospice programs are expanding throughout healthcare every year. As our population ages and as the symptom burden of chronic

disease/serious illness increases, the need for continued use and participation of palliative medicine practitioners throughout the spectrum of healthcare is obvious. Both palliative care and hospice can be used to meet the physical, emotional, and spiritual needs of elderly patients effectively and have addressed many of the concerns voiced by these patients when they face life-limiting illness [4, 84]. Subsets of patients do exist for whom conventional and customary approaches to pain and other symptom management by both anesthesiologist and surgeon do not provide adequate comfort [40]. In these cases, immediate consultation with a palliative care specialist who has the expertise in the management of these complicated patients and their complicated symptom burdens is appropriate [41]. A plan of care can usually be developed that safely, ethically, and legally coincides with each physicians duty to patient care [41, 85]. Despite palliative medicine and hospice being in their infancy just a short time ago, significant strides have been made as both fields continue into maturity. Palliative care and hospice have helped to shift the focus of patient care from a practitionercentered and institution-centered practice to a more familycentered, patient-centered, and evidence-based practice paradigm [4, 7, 21, 85, 86]. Palliative care allows for aggressive symptom management in the geriatric patients in the perioperative setting, even when a patient has chosen curative or life-prolonging therapies [18]. For patients who are at the end of life, palliative care and hospice allow the patient to die in peace rather than in a piecemeal fashion [4, 39]. For those who are not at the end of life, this approach to patient care offers the same hope: to live in peace, not piecemeal [4, 87].

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