Difficult Decisions in Surgery:
An Evidence-Based Approach

Vassyl A. Lonchyna *Editor*

Difficult Decisions in Cardiothoracic Critical Care Surgery

An Evidence-Based Approach

Springer

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Series Editor

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The complexity of decision making in any kind of surgery is growing exponentially. As new technology is introduced, physicians from nonsurgical specialties offer alternative and competing therapies for what was once the exclusive province of the surgeon. In addition, there is increasing knowledge regarding the efficacy of traditional surgical therapies. How to select among these varied and complex approaches is becoming increasingly difficult. These multi-authored books will contain brief chapters, each of which will be devoted to one or two specific questions or decisions that are difficult or controversial. They are intended as current and timely reference sources for practicing surgeons, surgeons in training, and educators that describe the recommended ideal approach, rather than customary care, in selected clinical situations.

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"Cuore" by Maxo Rennella (Barcelona) (2016)

To my parents, Bohdan and Orysia, who prepared me for life's journey,
To my wife and best friend, Roksolana, with whom I share life's journey, and
To my daughters, Melania and Inna, who sweeten this journey.

Foreword

This volume is one in a series entitled "Difficult Decisions in Surgery," all published by Springer Verlag. The series was started in 2014 as a project of the Department of Surgery, University of Chicago, and all of the Volume Editors are University of Chicago faculty surgeons. The aim of the series is to identify challenging questions in a surgical specialty that are focused and clearly defined and for which useful information exists. Useful information, for purposes of the series, is evidence-based and provides insights into dealing with a posited question. Volumes have thus far been published in the fields of thoracic surgery, vascular surgery, pancreatic and hepatobiliary surgery, colorectal surgery, and endocrine surgery. The useful lifespan of a volume is up to 8 years, because new information is always replacing old concepts, and methods of clinical management evolve over ever-shortening periods of time. The aim of the series is to create a new volume in a specialty area every 5–6 years so that the content remains fresh and clinically useful.

As the Series Editor, it is my responsibility to select a specialty theme for the volumes in the series. I choose an editor for each volume who is knowledgeable in the field and well enough organized to produce a finished product in 12 months from concept to publication. This rapid schedule enables the contents to be up to date, which is essential in a publication meant for use in board review and in making decisions at the point of care. The Volume Editor must be acquainted with potential authors, each of whom is internationally recognized as an expert on a specific topic, is capable of exercising equipoise when addressing the topic, and is able to produce their chapter in 3 months from invitation to completed manuscript.

Authors are tasked with performing a focused literature search, identifying relevant articles, analyzing the content of the articles, and making recommendations based on the evidence. They are also asked to go beyond their systematic review and objective conclusions to provide the reader with insights as to their personal approaches to the question. This gives readers a balanced, clinically useful overview that combines experience and data.

In designing the current volume, Dr. Lonchyna has succeeded in achieving his objectives admirably. The topics and questions he outlined for the authors span the range of controversies that are commonly encountered in the CT ICU. The author

list reads like a who's who of CT critical care. The final product will be very useful to trainees, critical care nurses, CT surgeons, and critical care physicians from all specialties. Dr. Lonchyna has created an insightful, informative, and invaluable resource that will be a welcome addition to the literature.

Chicago, IL, USA Mark K. Ferguson, MD

Preface

Why write a book about cardiothoracic critical care?

Critical thinking and following evidence-based medicine (EBM) are of paramount importance in the daily care of critically ill surgical patients. While clinical experience is invaluable, one must also be of the mindset that we have to strive to always improve our clinical thinking, reasoning, and actions. What is gospel today may be heretical tomorrow. This can only happen by the use of appropriate data and studies that give evidence to the conclusions reached.

Publius (100 BC) said: "A rolling stone gathers no moss." The mind must be exercised. For all of our actions, we should ask: what is the evidence that this is beneficial? We should know that there are various types of evidence, and so we have to be able to examine the source and type of evidence and its currency.

This book is divided into a number of sections grouping together problems often encountered in the cardiothoracic ICU. We begin with quality and value, palliative care, and ethics in the ICU. We then discuss major topics such as resuscitation, hemodynamics (alterations in and treatment of), pulmonary support (especially the use of ECMO), mechanical assist devices, dilemmas following thoracic transplantation, attention to nutrition and glycemic control, coagulopathy, acute kidney injury, and, finally, catastrophes that we all face in the ICU.

The authors pose questions to which there may be readily available quality answers and some that may not have excellent quality of evidence or no evidence at all [1].

While we strive to find the best answers via studies available, sometimes there are none available. Perhaps this is because there are no studies of a RCT that definitively show that, e.g., a bleeding vessel must be controlled to stop the loss of blood, but there may be abundant studies that may show the superiority of ligation over cauterization or titanium clips over catgut ligatures. Thoughtful reading of these chapters may inspire a young investigator to find a problem that is lacking in good evidence for the treatment and carry out a study that could produce the evidence needed to bring about a high level of evidence with a strong recommendation for a particular therapy.

Surgeons have always been at the forefront of giving exemplary and innovative care to their postoperative patients.

One of the earliest books on postoperative care was *Principles of Surgical Care: Shock and Other Problems* by Alfred Blalock of Vanderbilt University (1940) [2].

Here he addressed first and foremost the problem of circulatory shock, a most dreadful complication in those years as it is today. Through his clinical observations and experimental work in the laboratory, he defined the etiology of shock and gave substantiated grounds on how to deal with this problem. He astutely also recognized that one cannot write a monograph on shock by itself but must explore a whole host of other physiologic factors that go into the care of these patients. Hence, the book contains chapters on anesthesia, treatment of wounds, heart disease, thromboembolic disease, disorders of the circulatory system (shock), and its treatment with vasoconstrictive drugs, fluids, and blood. He goes on to describe metabolic and nutritional disturbances, pulmonary complications, abdominal complications, and renal complications. The topics are similar to those covered in this and any other current textbook of surgical critical care, save for neurologic complications and the use of modern devices for cardiopulmonary support.

Francis D. Moore continued this tradition with his encyclopedic single-authored work based on experimentation and evidence in *Metabolic Care of the Surgical Patient*. He recognized that it is not enough for the surgeon to be able to cut, but he must be able to take care of all of the metabolic perturbations of his sick patient. This was in a time before the intensive care unit with its many consultants was current therapy:

> The surgeon, not his consultants, joins the two in his own right: clinical judgement and a nice balance between operative skill and metabolic wisdom are needed; metabolic care is a part of surgery, not a separate consideration. Therefore, the first rule of metabolic care is to understand the disease itself. [3]

There are many texts written by surgeons that deal with the care of the surgical patient and their complications. There are, likewise, plenty of critical care texts written by pulmonologists and anesthesiologists, our brethren in the care of our surgical patients in the ICU. Surgeons, however, have a unique perspective on surgical disease and therefore may have a different slant on the critical care of surgical patients. This book has mostly surgeons as authors although there are also experts chosen for their expertise in the nonsurgical aspects of care in the ICU.

This book is meant for cardiothoracic surgeons, residents, fellows, and every member of the multidisciplinary team taking care of the postoperative cardiothoracic patient. Rather than being a how-to-do-it text, although one cannot help but digress there when needed, it is a text meant to stimulate thought about why and how we treat our patients, question our routines, and always be open to new ideas as studies present data to support them. Every question asked is answered by evidence that is then graded according to its value and recommendations given based on the quality of the data.

In going into the future, more surgeons should do formal training in surgical critical care and become board certified in this subspecialty. If surgeons are to participate fully in the care of their patients in the intensive care unit, their training must be commensurate with that of other specialties.

I wish to thank Mark K. Ferguson, MD, for the invitation to create and edit this textbook. At the Springer Nature Publishing House, I thank Vignesh Iyyadurai

Suresh, my Project Coordinator, who kept a fire burning to submit the chapters in a timely fashion. I thank my editors at the London office for their help and support: Melissa Morton and Wyndham Hacket Pain.

Chicago, IL, USA Vassyl A. Lonchyna, MD
September 6, 2018

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Chapter 1
Introduction

Vassyl A. Lonchyna

The mechanics of blood flow through the aortic valve and aortic root have only recently been described. However, the concept of how this flow shapes the movement of the anatomic structures in this part of the circulatory system was first described centuries ago by da Vinci:

> *The three-cusped valves of the heart were seen by Leonardo as a perfect example of mathematical necessity in the workings of nature. As blood was forced through the valve, eddies in the sinuses curved back into the cusps of the valve. When the flow ceased, these eddies opened the cusps against one another to form a perfect seal, preventing reflux.* (Fig. 1.1) [1]

This farsighted observation and musing by a thoughtful and inquisitive painter, sculptor, scientist, architect, engineer, anatomist, inventor and physiologist took almost 500 years to be proven correct [2]. Not only is he a true "Renaissance man" but he could be considered the father of "Evidence Based Medicine." His above described conclusion came after multiple observations (such as the movement of spikes driven through pig's hearts at their slaughter), multiple human cadaver dissections and laboratory experiments duplicating blood flow through the aortic valve:

> *…he described and drew a way to make a glass model of the heart. When filled with water, it would allow him to observe the way blood would swirl as it passed into the aorta. He used a bull's heart as a model, filling it with wax using the sculptor's technique he had used in creating a model of the brain. When the wax hardened, he made a mold to build a glass model of the heart chamber, valve and aorta. By sprinkling in grass seeds, he made the flow of water more visible.* [3]

The original version of this chapter was revised. The correction to this chapter can be found at https://doi.org/10.1007/978-3-030-04146-5_46

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Fig. 1.1 DaVinci Aortic valve. (RCIN 919082). Leonardo da Vinci. 1512–13. University of Illinois / © Her Majesty Queen Elizabeth II 2018. [1]

Evidence Based Medicine

Acute observations, an inquisitive mind, honesty, and knowledge are all traits that have served scientists and experimenters well in promulgating discovery. Medical therapeutics has likewise evolved over the centuries due to the works of notable physicians and scientists. Change, or improvement, is proceeding at breakneck speed in current times. Although one might say that we as clinicians have always practiced medicine based on research and data, this has crystallized more in the late 1990s and is the mantra of the current generation of physicians.

Evidence based medicine (EBM) consists of identifying a clinical problem or question, doing a focused search in the literature for relevant studies, choosing the most pertinent studies, and critically evaluating them for guidance as to the right answer to the initial clinical question. The guru of EBM, Dr. David L Sackett of Oxford University, described this succinctly in an editorial in 1986 that resonates even today:

> *Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. By individual clinical expertise we mean the proficiency and judgment that individual clinicians acquire through clinical experience and clinical practice.*
>
> *Increased expertise is reflected in many ways, but especially in more effective and efficient diagnosis and in the more thoughtful identification and compassionate use of individual patients' predicaments, rights, and preferences in making clinical decisions about their care.*
>
> *By best available external clinical evidence we mean clinically relevant research, often from the basic sciences of medicine, but especially from patient centered clinical research into the accuracy and precision of diagnostic tests (including the clinical examination), the power of prognostic markers, and the efficacy and safety of therapeutic, rehabilitative, and preventive regimens.*
>
> *External clinical evidence both invalidates previously accepted diagnostic tests and treatments and replaces them with new ones that are more powerful, more accurate, more efficacious, and safer.* [4]

EBM is a continuum. It relies on investigators challenging the status quo and creating trials and experiments that will test sometimes time-honored precepts of medicine or new concepts. Through structured studies, the gold standard of which is the randomized controlled trial (RCT), one can produce data that can confirm or dispute current thinking, a hypothesis or the benefits of a therapeutic regimen.

Is it possible to reverse our medical thinking? Prasad and Cifu in their 2015 book "Ending Medical Reversal" show with multiple examples how traditional, widely practiced therapeutic regimens have been "reversed" based on good quality studies, be they an RCT or a meta-analysis of multiple studies. In fact, the authors go out on a limb to say that a good deal of what doctors do is wrong. Our treatments are often widely instituted before there are good studies to show the benefits or harms to the patient. The reversal occurs when robust clinical studies prove ineffectiveness of certain therapeutic regimens [5].

A History Lesson

The Death of George Washington

George Washington died in the late evening hours of December 14, 1799 (Fig. 1.2). His terminal illness was quick but he suffered terribly. The day after riding for five hours at his farm in Mt. Vernon in inclement wet snowy weather, the President developed a sore throat, chills, fever, and difficulty swallowing and breathing. Summoned to his bedside, his long time personal physician, Dr. James Craik, bled him (as was the norm in those days for respiratory illnesses) twice (about 600 ml each time). He summoned consultants Dr. Brown and Dr. Dick. After their arrival, another 950 ml of blood was bled. In addition, Washington was given purgatives and enemas, which contributed to his dehydration. He remained conscious but had labored breathing. The younger Dr. Dick suggested a new procedure he had just learned, tracheostomy, to relieve his breathing. He was overruled by his older colleagues. The tremendous "therapeutic" loss of blood along with dehydration caused his death from hypovolemic shock that was hastened by the suffocation caused by his inflamed epiglottis [7].

Fig. 1.2 Washington on his deathbed. Junius Brutus Stearns. 1851. (Courtesy Wikimedia Commons) [6]

Bloodletting as Therapy

The physicians of the ancient world, most notably Hippocrates, considered humans to have four basic humors: blood, phlegm, black bile and yellow bile. Disease was considered to cause an imbalance of these humors, so a readjustment was conceived of: bloodletting [8]. Bloodletting was the therapy for many maladies, especially pneumonia and other infections. It was also used prophylactically in the spring and autumn to reinvigorate the human body.

At the time of Washington's death, there were physicians who saw the danger and ineffectiveness of bloodletting. One of the most staunch supporters of this therapy, however, was the noted signer of the Declaration of Independence, Dr. Benjamin Rush. During the yellow fever epidemics of 1793 and 1797 he pushed his "depletion therapy" of vigorous purgatives and aggressive bloodletting. He was challenged in Philadelphia on his results and poor record keeping by a publisher, William Corbett, which resulted in public feuding and such editorializing as, "The times are ominous indeed when quack to quack cries purge and bleed" (Porcupine's Gazette, Sept 19,1797) [9].

Meanwhile, in Edinburgh, two physicians likewise took opposite sides in the usefulness of bloodletting. Dr. William Alison was stubborn in keeping with his clinical experience and empirical observation in defending this age old practice. The younger Dr. Hughes Bennett was more progressive in that he relied upon newer methods in pathology and physiology to prove or disprove effectiveness of therapy. Central to his argument was that he observed an improved outcome in patients with pneumonia as the incidence of bloodletting diminished [8]. Here, in the middle of the nineteenth century, was the beginning of the use of statistics and an epidemiological approach to the study of the effectiveness of therapy as well as a more scientific study of disease [10].

Unfortunately, it would take almost another century to fully debunk the use of bloodletting. Even the esteemed physician Sir William Osler, in his first edition of "Principles and Practice of Medicine" (1892), described several indications for bloodletting, including timely venesection in cases of pneumonia [11]. This recommendation continued well after his death, as noted in the 14th edition (1942) of his classic textbook [10]. Finally, bloodletting, after a run of several millennia as a widely accepted and practiced therapy, was abandoned when its ill effects (hypotensive shock) and its ineffectiveness and harmfulness as a therapy was finally recognized and accepted. Perhaps George Washington could have been saved from his ultimate acute illness of epiglottitis if he were not bled and purged into hypovolemic shock (four times for total of more than 2.1 l). Here, then, is an example of medical reversal upending a sacred medical practice. In the last hundred years, the red tide has turned and we are infusing blood as rapidly and frequently as physicians of yesteryear bled them of massive amounts for any and every condition that offendeth man.

With Washington's breathing difficulty, what should have been done to rescue him from his symptoms of epiglotitis? Tracheostomy in 1799 was not yet a common procedure in the armamentarium of the physician. The history of tracheostomy goes back to the beginning of mankind. It was, however, during the Renaissance that this procedure was utilized in resuscitation, in drowning and choking victims, and in animal experiments. Despite knowledge of this procedure, its implementation was haphazard until well into the middle of the nineteenth century with the discovery of anesthesia and the usefulness of endotracheal intubation for airway control.

Dr. Dick dared to suggest this intervention at the bedside of George Washington, but was overruled or intimidated into not trying it by the other more senior physicians at the bedside. "I proposed to perforate the trachea as a means of prolonging life, and for affording time for the removal of obstruction to respiration in the larynx… It was received at first, at least by one of the physicians, with a seeming acquiescence…and finally a firm opposition to the measure" (letter written by Dr. Dick on January 10, 1800 and published in 1917 in The Medical Record [12]).

Here was a technique that surely would have been of benefit yet, at the time, had not undergone enough scrutiny and study to be commonly accepted. One may question, however, the need for exhaustive trials to prove the worth of tracheostomy in a patient with respiratory embarrassment. To intervene could be lifesaving, to do nothing leads to suffocation. This is a lesson from history of a very difficult decision in the setting of critical illness; one could even argue of a surgical nature (to cut or not to cut…). The therapy afforded at that time, bloodletting, has, with appropriate studies, undergone medical reversal. The surgical procedure of tracheostomy, which could have been lifesaving, was not yet evaluated, studied and accepted widely enough to have become the standard of care.

The Book

This is a volume that is dependent upon evidence-based data to support the difficult decisions made in the course of treating critically ill patients in the ICU. The authors were tasked with developing their chapter themes by first structuring the questions to be asked according to the PICO (Patients of interest, the Intervention that was applied, Comparator patients with similar conditions but treated differently, and Outcomes of interest) model (Fig. 1.3) [13]. Examples of questions asked to focus the search strategy are listed in Fig. 1.4 [13].

Once the search strategy was formulated, a literature search in PubMed, Cochrane Collection, Google Scholar and other databases was performed. By focusing the search queries using PICO terms, the authors could optimize their efforts in finding the most relevant studies needed to support their chapter themes. Selected papers were evaluated as to the quality of the evidence presented. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) system for grading the evidence is used throughout this book. The authors were to develop recommendations for what is the best practice based on the published evidence. The strength of the recommendations likewise follows the GRADE system.

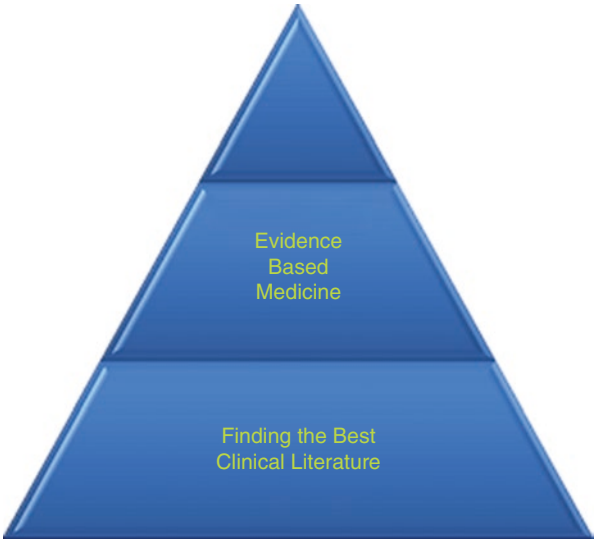

Fig. 1.3 PICO model. (Data from [13] with permission from the University of Illinois)

The P.I.C.O. Model for Clinical Questions

P	**P**atient, **P**opulation, or **P**roblem	How would I describe a group of patients similar to mine?
I	**I**ntervention, Prognostic Factor, or Exposure	Which main intervention, prognostic factor, or exposure am I considering?
C	**C**omparison or Intervention (if appropriate)	What is the main alternative to compare with the intervention?
O	**O**utcome you would like to measure or achieve	What can I hope to accomplish, measure, improve, or affect?
	What **T**ype of question are you asking?	Diagnosis, Etiology/Harm, Therapy, Prognosis, Prevention
	Type of **S**tudy you want to find	What would be the best study design/methodology?

Fig. 1.4 The PICO model for clinical questions. (Data from [13] with permission from the University of Illinois)

Grade

Guidelines that serve to provide clinicians with the most up to date recommendations about the diagnosis and treatment of various diseases and guiding them through alternative therapies have been created by various working groups and professional societies for several decades. The evaluation of the quality of evidence and the strength of the recommendations have been inconsistent because of the various different methodologies used. For the last 20 years the GRADE Working Group, based at McMaster University in Hamilton ON, but with an international

collaborative group, has developed a system that combines the best of all the systems for grading guidelines.

An advantage of the GRADE system over others is that there is clear separation between the grading of the quality of evidence and the strength of the recommendations. Other strengths are that outcomes of alternative management strategies are evaluated; there are precise methods and instructions on the upgrading and downgrading of the quality of evidence ratings; the process of moving from evidence to recommendations is clear and structured; and the interpretation of the recommendations as strong or weak are clear and unambiguous to the user of the guidelines [14].

The universality of interpretation and use of guidelines that follow this GRADE system of evaluation is acknowledged by the policy of the publisher of The British Medical Journal Group to require that authors submitting clinical guidelines articles use this GRADE system for grading evidence [15]. To date, the GRADE system is used by more than 106 organizations world-wide, amongst them the World Health Organization (WHO), American Association of Chest Physicians (AACP), Society of Critical Care Medicine (SCCM), American Thoracic Society (ATS), "Up to Date" and The Cochrane Collection [15].

Two major components of the GRADE system of grading are the evaluation of the quality of evidence and the strength of the recommendation.

Quality of Evidence

The GRADE system classifies the Quality of Evidence into: high, moderate, low and very low quality [14]:

High quality – Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality – Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality – Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality – Any estimate of effect is very uncertain."

Randomized controlled trials (RCT) are the pinnacle of evidence based studies and are rated "high" in quality. Observational studies lack the stringent data and organization of a RCT that they are rated "low" in quality. "Expert" reports, case reports and other uncontrolled clinical studies and observations are valued as "very low" in quality of evidence [14]. Ratings must remain fluid because they sail in a sea where weather and sea conditions change and can cause changes in the outcome of the voyage. Our confidence in the study may be decreased by flaws noted in the study, such as reporting bias, inconsistency of results, imprecision of estimates (manifested by wide confidence intervals), and study design limitations. In that case, our classification of the quality of evidence may be downgraded [16]. The

quality of evidence may be upgraded if there is "a very large magnitude of effect, (the evidence becomes stronger), if there is a dose-response gradient or if all plausible biases would reduce an apparent treatment effect" [16].

Why Separate the Evidence from the Recommendation?

A high quality of evidence does not necessarily translate into a strong strength of recommendation and vice versa. To give separate evaluations allows the clinicians to better understand the treatment recommended for a particular disease or condition. While the evidence from a robust RCT study shows clear benefits, there may be side effects that may lead to a weak recommendations. The therapy must match the patient both in compatibility and desires. The choice of the patient must be taken into consideration when weighing the pros/cons of the therapy. Most importantly, the overall benefit of the therapy for the individual patient should outweigh the possible adverse effects.

Strength of Recommendation

Simply put, the strength of recommendation is a reflection of our confidence that the purported desirable effects of the therapy are greater than the undesirable effects [17].

The recommendation can be "strong," "weak," or "conditional". It is dependent not only on the quality of evidence but on the balance between desirable/undesirable side effects, preferences of the patient (patient autonomy) and even best use of resources (global health).

Desirable effects may be an improved survival, reduced morbidity, improvement of quality of life, or any measure that is an indication of the success of the intervention. Undesirable effects are adverse side effects that may detract from the goal of therapy.

With a strong recommendation the author or patient or clinician are confident of the superiority of the desired over the undesired effects. With a weak recommendation, the confidence level is brought down to that of "probably outweighs". This simplifies possible decisions made by the patient. A strong recommendation is one that has overwhelming positive strengths and will most likely be acceptable to the patient and treating physician. A weak recommendation introduces enough doubt that the patient or clinician will weigh carefully the effects and may need additional discussions and possibly structured decision aids to help in tailoring the intervention to the patient [17].

The strength of recommendation also can be applied to diagnostic tests and treatment strategies. Here one deals with not only the accuracy of the test (true/false positives, true/false negatives) but more importantly, how does the diagnostic test

result impact the outcomes important to the patient. A true positive result in a diagnostic test may lead to the use of a therapy of benefit to patients while knowing a test is a true negative may spare the patients an unnecessary test/therapy. In the case of a false positive test, it may lead a patient to have unnecessary therapy and may even put him at risk unnecessarily. A false negative test may prevent a patient from receiving therapy that is necessary or even lifesaving [18]. Knowing the accuracy of tests help to guide the patient in the selection of tests needed. Despite the accuracy of tests, it is only if patients sustain an improved outcome do they have value [18].

Should costs of therapy be a factor in the GRADE evaluation? This is a challenge to most clinicians involved with guideline development. Costs could be considered as another outcome, relevant when comparing various ways of managing the patient. Many clinicians may feel that costs should not influence daily decisions for therapeutic intervention in patients. But healthcare costs do affect society and a particular treatment plan may increase or decrease these costs [19].

Policy makers charged with distribution of global health care resources need to incorporate costs into the availability and distribution of health care resources, especially if such resources are limited. The parable of "the tragedy of the commons" underscores the need to take a communal responsibility for providing effective healthcare and bearing responsibility for its costs [20].

Summary

This book is unlike any other in the field of surgical critical care because it incorporates the criteria of evidence based medicine in the text. We are well into the twenty-first century and live in an era where we have to question our behavior on a daily basis – where is the data that what I am offering my patient has merit and what is my confidence level in this data?

Medical information has exploded and complete mastery is impossible. We must rely on working groups to research the most focused and highest quality literature and provide information in the form of guidelines to steer us in the right direction in the care of our patients. Gone are the days when we were guided only by our personal experience. Gone are the days when our mentors can back up their teachings by saying "That's the way I've done it for years and it's always worked out well." We have to be observant, as our clinical experience is very important. We have to know how to read the literature, how to question "dogma," and know that our endpoint is to achieve the best outcome for our patients.

The GRADE system of evaluation is a transparent and accurate method of evaluating medical studies. A thumbnail sketch is provided above but the reader is encouraged to delve deeper into this system of grading by going to the web site of the GRADE Working Group, where the most up to date information is available [15].

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Part I
Quality, Care and Ethics

Chapter 2
Quality and Value in the Cardiothoracic Intensive Care Unit

Kevin Lobdell, Joe Mishkin, Rakesh C. Arora, and Rohan Mukund Sanjanwala

Introduction

High-value health care provides both high performance and high reliability [1, 2]. The domains of quality (Q), safety (S), value (V), as well as the applied resources (R), are fundamental to high-value cardiothoracic critical care (CCC)-where V α (Q + S)/R. Cardiac surgery and associated CCC efforts are common, costly, and contribute greatly to a hospital's income and profit margin [3, 4]. Cardiac surgical risk correlates with cost, additive costs of major complications associated with cardiac surgery are substantial, and a strong correlation between poor quality and increased cost has been demonstrated [5–10].

Various models for death and complications have been developed and lend insight into risk-adjusted performance, (but the statistician George E. P. Box would remind the reader that "all models are wrong, some are useful" [11]). Risk scoring systems can be static-calculated only prior to operative intervention, dynamic-evolve with patient's clinical course, general, organ specific, associated with a specific phase of care [12] (e.g. before anesthesia or in the intensive care unit), and may be specialty specific-such as the Society of Thoracic Surgeons Adult Cardiac Surgery Risk Calculator and EuroSCORE II [13, 14]. Risk model characteristics

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include, calibration-observed and expected rate of agreement, discrimination-ability to separate high & low risk or those that have event/disease from those that do not, accuracy, precision, etc. [15–17]

Search Strategy

The PICO question asked for this review was, "In the post cardio-thoracic surgery patients admitted to the intensive care unit, what is the impact of high-value critical care compared to standard care on outcomes such as ICU length of stay, postoperative complications, quality of life and survival?" Using the PICO framework (Table 2.1) an electronic search was performed using combination of MeSH terms and their synonyms that include "Open & Closed Intensive Care", "Intensive Care Staff Model", "Activity Based Staffing", "Acuity Based Staffing" "SBAR", "Goal Sheets", "Checklist", "Multidisciplinary Rounds", "Tele-ICU", "Teamwork", and "Goal Directed Therapy". The databases searched were PubMed, Cochrane Evidenced Based Medicine, Embase, Science Citation Index/Social Sciences Citation Index, and Google Scholar. Studies, including publication type such as systematic reviews, literature review, randomized control trials (RCT), prospective cohort studies (PCT), case reviews and editorial correspondence from 2000 till 2017 were included. The studies were graded according to the GRADE system.

Results

Cardiothoracic Critical Care (CCC) Structure

Organizational staffing of critical care units with "closed" management by dedicated critical care trained providers, as opposed to the "open" model of non-critical care trained providers, has been shown to correlate with lower mortality, morbidity, and shorter LOS [18]. Intensity of staffing and nighttime intensivist staffing requires further investigation [19–21]. Activity based staffing has been studied for decades and the concept of optimizing staffing for complexity is essential in high-value CCC [22, 23]. Refer Table 2.2 for quality of evidence.

Table 2.1 PICO terms for quality, value and risk assessment in the CCC

P-population studied	Adults (age ≥18 years), post cardiac-thoracic surgery patients, post cardiac surgical ICU, intensive care cardiac surgical unit, medical/surgical ICU
I-intervention	Critical care decision making, critical care models, patient-centered critical care, critical care processes
C-comparison	Standard care
O-outcome	ICU and In-hospital LOS, Postoperative survival, mortality and complications such as respiratory insufficiency, acute kidney injury, delirium Quality of life and survival

Table 2.2 Structures of the CCC

Study[a]	Type of study	N	Intervention	Control	Staffing model	Outcomes	LOE[a]
Pronovost et al. (2002) [18]	Systematic review: RCT and observational controlled trials	NA	High intensity staffing with critical care trained provider	Low-intensity staffing	Intensity of staffing, "Closed" Vs "Open"	ICU mortality (RR) 0.61%, In-hospital mortality (RR) 0.71%	High
Kerlin et al. (2017) [19]	Systematic review: RCT and PCT	NA	In-hospital night time intensivist staffing	Other night time staffing model	Intensity of staffing	No difference in the ICU and in-hospital mortality; no difference in the ICU and in-hospital LOS	High
Kerlin et. al. (2013) [20]	RCT	1598	Night-time in-hospital intensivist	Night-time telephone coverage by daytime intensivists	Intensity of staffing	ICU LOS (RaR) 0.98, ICU mortality (RR)1.07 ICU-readmission (RR) 1.56	High
Gupta et al. (2016) [21]	RCT	9072	24/7 mandatory attending-level intensivist coverage	On-demand attending level intensivist	Intensity of staffing	ICU LOS 6.4 days for intervention and 6.9 days for control Mortality 2.8% for the intervention and 4.0% for the control	High
Kumar et al. (2014) [24]	PCT	449	24/7 in- house intensivist coverage	Residents with intensivist backup	Intensity of staffing	Median in-hospital LOS was significantly shorter in the intervention group (12.3 days vs. 11 days) No difference in the ICU mortality, ICU LOS and 30 day mortality	Moderate
Guccione et al. (2004) [22]	Review article	NA	Nursing work load models	NA	Activity based staffing	Cost effectiveness	Very low

PCT Prospective cohort study, *RCT* Randomized controlled trials, *LOE* Level of Evidence, *NA* Not Applicable, *ICU* intensive care unit, *LOS* Length of stay, *RR* relative risk, *RaR* Rate ratio

[a]Study population included medical and/or surgical intensive care unit patients

Cardiothoracic Critical Care (CCC) Process

Reliable group interactions in high-risk environments, such as CCC, are fostered through disciplined communication and should include efforts such as Situation-Background-Assessment-Recommendation (SBAR) and read backs [25]. Goal sheet utilization positively correlates with improved communication of goals and shorter ICU LOS [26] (Table 2.3). Similarly, checklists and hand-off tools correlate with improved efficiency-LOS & readmissions-and efficacy-reduced mortality and morbidity [27, 28] (Table 2.3). Multidisciplinary teams are standard in contemporary cardiac efforts [29]. High performing CCC teams are proactive, interactive, precise, expert, and provide continuity [24, 30]. "Teaming" is increasingly utilized in other complex industries and vital to the delivery of high-value CCC [35]. Regularly scheduled multidisciplinary rounds capitalize on the expertise of the healthcare team and may mitigate mortality risk for critically ill patients [31, 32, 36]. Our patient-centered transformational redesign (PCTR) in CCC, utilizing tele-rounding and tele-ICU technology, mirrors that of others who have lowered mortality, morbidity, and reduced LOS [32, 36]. Comprehensive, integrated innovation such as PCTR, where talent is leveraged with technology, creates value by matching demand and resources, eliminating unnecessary variation, bottlenecks and waste, and affords the CCC team the opportunity to learn faster through an increased volume of patient encounters and learning through pattern recognition [33, 37]. CCC teams must share goals, mental models, learn together, and focus on "learning how" as opposed to "learning what" [38]. Disciplined programs to improve the quality, safety, and value of cardiac surgical care are well documented and should aim to avoid complications, arrest the cascade of complications, and improve failure-to-rescue rates [34, 39, 40]. Considerable variation in cost to rescue has been described without obvious outcome benefits from high-cost institutions [41].

Goal-Directed Therapy (GDT)

GDT-popularized by Shoemaker-sets physiologic goals and employs various therapeutic strategies with the aim of mitigating the risk of untoward outcomes [42–44]. Quantified goals include blood pressure, cardiac index, systemic venous oxygen saturation, & urine output. Additionally, oxygen consumption, oxygen debt, lactate levels, and other biomarkers may augment diagnostic modalities and therapeutic tactics. Intraoperative GDT has been studied and risk of acidosis, AKI, and respiratory insufficiency may be mitigated through these efforts [45–47].

GDT in CCC patients consistently demonstrates reduced complication rates and length of stay [48–51]. For example, Osawa et al. reported on 126 patients randomized to cardiac output driven algorithm and the primary outcome was a composite endpoint of 30-day mortality and major complications [52]. The study demonstrated that the cardiac output driven algorithm was associated with a significant reduction

Table 2.3 Various process and methods in the CCC

Study	Study type	Methods	Target processes	Outcomes (odds ration/mean/median/percentage)	Comments	LOE
Pronovost (2003) [26]	PCT	Daily goals form	Communication	After implementing daily goal forms 95% of the health care staff understood the goals for the day, ICU LOS decreased from mean 2.2–1.1 days	Improved understanding of daily goals 50% reduction in the ICU LOS	Moderate
Casale (2007) [27]	Before-after cohort study	Using re-engineered "ProvenCare" system	Checklist and handoffs	ICU readmission 2.8% for controls and 1% for the intervention In-hospital LOS decreased by 16%	Reengineered health-care delivery system such as electronic health record can reduce resource utilization and can improve patient care	Low
Toccafondi (2012) [28]	PCT	Use of hand over probe for transfer from high-acuity to low-acuity units	Communication and handoffs	From the senders perspective warning signs were mentioned in 50% and were relevant in 67%. In contrast, from the recipients perspective warning signs were mentioned in 10% and were relevant in 33%	Use of shared set of handover content items may assist in creating common ground to enable clinical teams to communicate effectively to help increase the reliability and safety of cross-unit hand overs	Moderate
Holmes (2013) [29]	Review article	MD Team concept	MDT	NR	Advocacy for MDT collaboration of cardiac surgeon, cardiologist, radiologist, anesthetist, nurse to reduce overlapping efforts, conflicting aims and patients' confusion	Very low
Shake (2013) [30]	Review article	Implement guidelines, protocols, patients' checklists, goal sheets initiatives	MDT, communication, performance measures	NR	Patient safety can be improved by eliminating "preventable" harm	Very low

(continued)

Table 2.3 (continued)

Study	Study type	Methods	Target processes	Outcomes (odds ration/mean/median/percentage)	Comments	LOE
Lobdell (2009) [31]	Correspondence	Regular multidisciplinary rounds (MDR)	MDR	NR	Reduced mortality risk, improved patient care	Very low
Lilly (2014) [32]	Literature review	Tele-medicine program: tele-rounding and tele-ICU	Communications, PCTR, MDT	Tele medicine programs are associated with lower ICU mortality (0.79) and in hospital mortality (0.83) and shorter ICU (−0.62 day) and in-hospital (−1.26 day) LOS	Increase adherence to ICU best practice using tele medicine programs results in low mortality, morbidity and ICU and in-hospital LOS	Very low
Rechel (2010) [33]	Review article	Hospital capacity planning	PCTR	NR	To sufficiently meet the health-care demands at effective cost, patient centered and "lean" transformational capacity planning is essential	Very low
Edwards (2016) [34]	PCT	NR	Failure to rescue (FTR)[a]	The centers with lower mortality have 11.4% complication and 6.8% FTR rates and the centers with higher mortality have 15.7% complication and 13.9% (double) FTR rates	CABG mortality if directly associated with rates of failure to rescue. Disciplined program targeted to reduce FTR improves care quality and patient safety	Moderate

PCT Prospective Cohort trial, *NA* not applicable, *NR* Not Reported, *ICU* intensive care unit, *LOS* Length of stay, *LOE* Level of Evidence, *MDT* multidisciplinary team, *PCTR* Patient-centered transformational redesign

[a](FTR) Mortality related to stroke, renal failure, reoperation and prolonged ventilation

in the composite endpoint along with reduced ICU and hospital length-of-stay (LOS), reduced infection rate, and reduced occurrence of the low cardiac output syndrome. Although the isolated 30-day mortality rate remained unchanged, the data suggest that GDT may significantly reduce complications and LOS for cardiac surgery [52]. Additionally, Kapoor et al. correlate GDT efforts with reduced LOS, duration of inotrope use, a more rapid decline in lactate levels after surgery, and lower levels of biomarkers-BNP and NGAL-that are associated with complications [53, 54].

Optimal goals, their means and rate of achievement (e.g. oxygen debt repayment schedule), their interactions, and potential to mitigate specific complications, such as AKI [55, 56], requires further investigation. Cost-effectiveness and value of GDT have been studied in surgical patients, but not in cardiac surgery [49, 57]. Refer to Table 2.4 for GDT in the CCC.

Recommendations

Use of "closed" staffing model such as greater use of intensivist may improve survival and reduce ICU and in-hospital LOS. Such approach is not associated with increased resource utilization. This recommendation is not consistent for prolonged ICU stay patients, nor for night-time intensivist staffing.

- ***Greater use of critical care trained staff may improve survival and reduce LOS (Level of evidence: Low, Limited Data; Strength of Recommendation: high (Ib), Benefits > risk)***

An experienced, multidisciplinary team evaluating patients in critical care may reduce efforts, conflicting aims, and patients' confusion resulting in improved patient safety by reducing preventable harm. The multidisciplinary collaboration can be enhanced by improved communication and information transfer tools such as goal forms, hand-offs, tele-ICU and checklists is associated with increase survival and reduced LOS (ICU and in-hospital).

- ***Multidisciplinary team and standardized use of communication tools improves patient safety, reduces LOS and improves survival (Level of evidence: Low, Limited data; Strength of Recommendation: moderate (IIb), benefits > risk)***

Goal Directed Therapy targeting physiological parameters such as Cardiac Index (CI), oxygen delivery (DO_2), maximum oxygen consumption (VO_2), pulmonary capillary wedge pressure (PCWP), systemic vascular resistance (SVR), systemic blood pressure, and urine output, with a goal to optimize perfusion may result in reduced incidences of acute renal failure; shorten ICU and hospital LOS and improved survival.

- ***GDT targeting perfusion parameters such as CI, DO_2, VO_2, PCWP, SVR, systemic blood pressure, and urine output results in reduced AKI, LOS and improved survival (Level of evidence: moderate; Strength of Recommendation: strong (Ib), benefits > risk)***

Table 2.4 Goal directed therapy (GDT) in the CCC

Study	Study design	GDT	Indicators	Outcome (odds ratio/ mean/median/ percentage)	Comments	LOE
Bland (1985) [42]	PCT	Physiological goals	Myocardial performance, pulmonary function, pulmonary vasoconstriction, oxygen delivery	NR	Variation in the key physiological patterns can dictate postoperative survival	Moderate
Shoemaker (1988) [43]	PCT	Physiological goals using invasive hemodynamic monitoring; swan-Ganz catheter	PCWP, SVR, CI, peripheral oxygen delivery	NR	For high risk postoperative patients the cardiorespiratory pattern of survivors' of critical illness i.e. higher CI and oxygen delivery is more appropriate	Moderate
De Somer (2011) [45]	Retrospective study	Oxygen delivery and carbon dioxide production	$(DO_2)/(VCO_2)$ ratio during cardiopulmonary bypass	Patients with low $(DO_2)/(VCO_2)$ are 3.1 times more likely to develop AKI	The GDT of maintaining DO_2 level intraoperatively may reduce AKI rates	Low
Rubino (2015) [46]	Retrospective study	Intraoperative parameters scoring system	Cardiopulmonary bypass parameters to calculated QualyP score	QualyP ≥2 is associated with 1.268 odds of developing AKI QualyP≥5 is associated with 1.49 odds of mortality	QualyP score adequately predicts quality of perfusion and postoperative rates of AKI, respiratory insufficiency and mortality	Low
Magruder (2017) [47]	PCT	Goal directed perfusion initiative	Maintenance oxygen delivery and reduction in vasopressor use	90% of GDT patients and 76.1 of Controls did not develop AKI; 5.7% of GDT and 19.3% of controls develop AKI	GDT perfusion initiative reduced rates of AKI	Moderate

Polonen (2000) [48]	RCT	Increasing oxygen delivery during immediate postoperative period	Svo_2 >70% and lactate Conc. <2 from admission to 8 h in ICU	Mortality in GDT patients was 2% and in the control group was 6% The median hospital LOS was 6 days for GDT and 7 days for control patients	GDT of maintaining adequate oxygen levels during early postoperative period reduces mortality and ICU and in-hospital LOS	High
Mckendry (2004) [49]	RCT	Nurse led circulatory status optimization	Increase stroke volume using colloid challenges with nitrates and inotropes	Duration of hospital LOS in the protocol group was reduced from a mean 13.9 to 11.4 days Duration of ICU LOS in the protocol group was reduced from a mean 3.2 to 2.5 days	GDT of maintaining circulatory status with nurse led protocol may shorten ICU and in-hospital LOS	High

GDT Goal dirated therapy, *PCT* Prospective Cohort Trial, *RCT* Randomized Controlled trial, *GDT* Goal direct therapy, *AKI* Acute Kidney Injury, *ICU* Intensive care unit, *LOS* Length of stay, *PCWP* Pulmonary capillary wedge pressure, *SVR* systemic vascular resistance, *CI* Cardiac Index, *QualyP* an additive score design to estimate perfusion adequacy

Personal View

It is said that "the future is here, it's is just not evenly distributed" [58]. This statement alludes to the considerable variation in care quality, safety, and cost. The future of quality, risk assessment and mitigation, safety, and value in CCC will be built on a foundation of real-time data management, analytic capability, computer decision support, and the widespread access and utilization by clinicians. The natural history of this technological innovation-diminished costs and increased accuracy and reliability-will also accelerate universal adoption. For example, biomarkers, wearable biosensors and the 'Internet of Things' [59] will facilitate the development of personalized, proactive strategies and early warning systems to assure quality and mitigate risk. Simultaneously, continuous, rapid learning by clinical teams will occur and compliance with protocols and pathways will be ascertained. Finally, workflow must be evaluated and comprehensively re-engineered to mitigate the risk of complications and clinician burnout [60–62].

Summary

The staggering costs and inefficiencies of cardiothoracic surgery and CCC coupled with an exponential improvement in data management, analytics, and decision support create an epic opportunity to revolutionize care. Systematic and meticulous risk assessment and mitigation of modifiable risks must be incorporated into all aspects of cardiac surgical care. Continued innovation in technology and teamwork communication will accelerate the transformation of high-value, networked, and decentralized CCC. Proteomic and genomic investigation and innovation will add additional insight.

Appendices

Appendix 1

Examples of the surgeon, anesthesia and intensivist handover checklist from the St. Boniface Hospital, Winnipeg, Canada

Cardiac Surgeons Checklist

- ☐ Patient Demographics (age, gender, etc)
- ☐ Indication of surgery
- ☐ Pertinent past medical history
- ☐ Surgical Plan/Surgery Completed
  (i.e. fully revascularized, adequacy of repair)
- ☐ Deviations for surgical plan/intraoperative complication
- ☐ Issues with separation from bypass
- ☐ CPB and X-clamp times
- ☐ Bleeding/coagulation Issues
- ☐ Need for protamine
- ☐ Systolic/MAP blood pressure limit
- ☐ Chest tube placement
- ☐ Pacer wires
- ☐ Chest tube placement
- ☐ Restart Plavix (y/n)
- ☐ Family discussion (y/n)
- ☐ Other issues relevant to ICU care
- ☐ Patient is enrolled in a study?
  Which Study _____

Cardiac Anesthesia Time-out Checklist

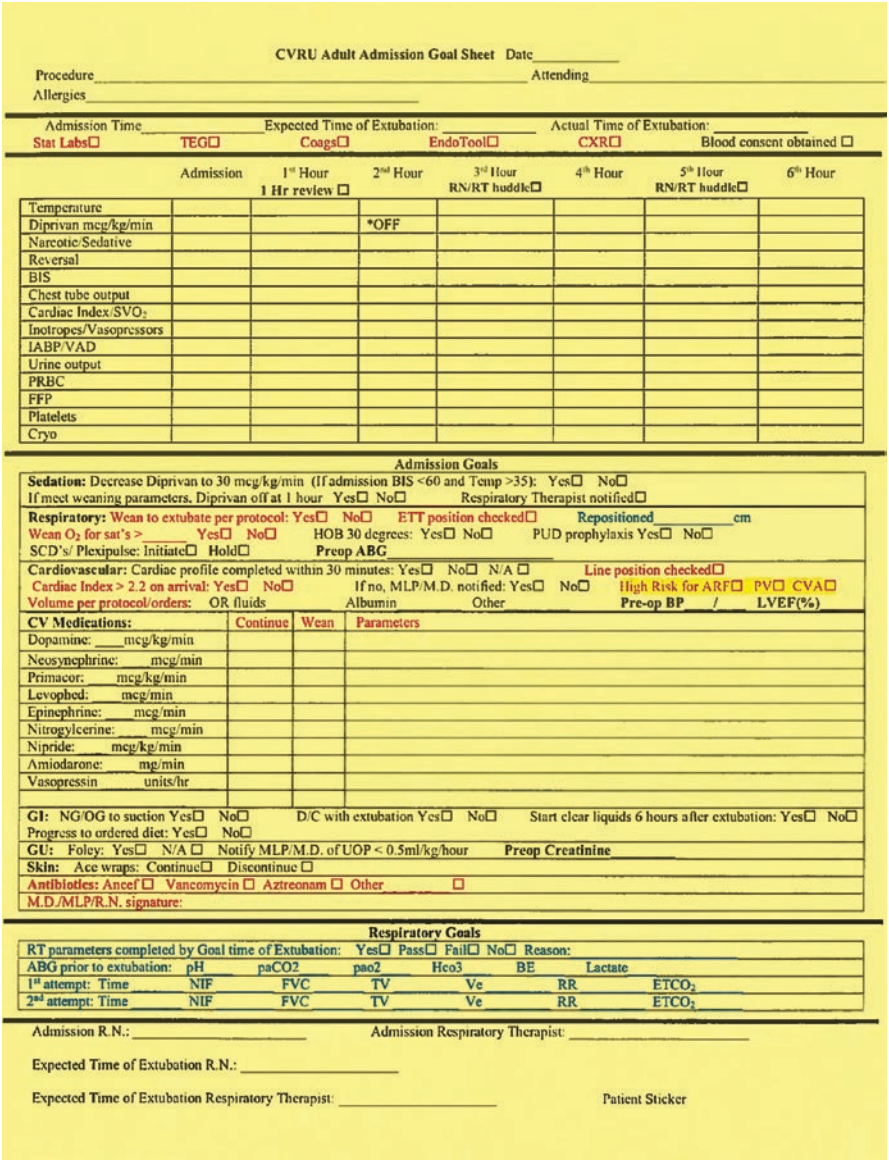
- ☐ Pertinent past medical history, physical exam and co-morbidities, medications
- ☐ Baseline HB, Cr, BP and HR
- ☐ Airway Issues
- ☐ Issues with Induction
- ☐ Oxygenation/ventilation issues
- ☐ IV and arterial-line placement
- ☐ Pre-CPB TEE findings
- ☐ Technical Considerations/Issues with separation from bypass
- ☐ Post-CPB TEE findings
- ☐ Drugs: allergies, inotropes/vasopressors, last antibiotic, analgesics, last paralytic
- ☐ Fluids/blood products administered
- ☐ Desired hemodynamic goals/filling pressures
- ☐ Desired period of sedation (if required)
- ☐ Other issues relevant to ICU care

ICCS/Anesthesia Attending
Time-out Checklist

- ☐ Sedation goals and planned titration
  (default: RASS 0- -2 unless indicated)
- ☐ Desired period of sedation (if required)
- ☐ Analesgia (amount and frequency)
- ☐ Oxygenation/Ventilation plan
  (default: non-physician protocol driven extubation)
- ☐ Desired hemodynamic goals/filling pressures
- ☐ IV fluids (maintenance)
- ☐ IV fluids boluses (amount and frequency)
- ☐ Inotrope/vasopressor wean (if applicable)
- ☐ Pacer settings
- ☐ Protamine (y/n)
- ☐ Delirium Risk
- ☐ Other issues relevant to ICU care

Appendix 2

Examples of goal sheets from the Carolinas Medical Center, Charlotte, NC



CVRU Adult Admission Goal Sheet Date_____

Procedure_____ Attending_____

Allergies_____

Admission Time_____ Expected Time of Extubation: _____ Actual Time of Extubation: _____

Stat Labs☐ TEG☐ Coags☐ EndoTool☐ CXR☐ Blood consent obtained ☐

	Admission	1st Hour 1 Hr review ☐	2nd Hour	3rd Hour RN/RT huddle☐	4th Hour	5th Hour RN/RT huddle☐	6th Hour
Temperature							
Diprivan mcg/kg/min			*OFF				
Narcotic/Sedative							
Reversal							
BIS							
Chest tube output							
Cardiac Index/SVO_2							
Inotropes/Vasopressors							
IABP/VAD							
Urine output							
PRBC							
FFP							
Platelets							
Cryo							

Admission Goals

Sedation: Decrease Diprivan to 30 mcg/kg/min (If admission BIS <60 and Temp >35): Yes☐ No☐
If meet weaning parameters, Diprivan off at 1 hour Yes☐ No☐ Respiratory Therapist notified☐

Respiratory: Wean to extubate per protocol: Yes☐ No☐ ETT position checked☐ Repositioned_____cm
Wean O_2 for sat's >_____ Yes☐ No☐ HOB 30 degrees: Yes☐ No☐ PUD prophylaxis Yes☐ No☐
SCD's/ Plexipulse: Initiate☐ Hold☐ **Preop ABG**_____

Cardiovascular: Cardiac profile completed within 30 minutes: Yes☐ No☐ N/A ☐ Line position checked☐
Cardiac Index > 2.2 on arrival: Yes☐ No☐ If no, MLP/M.D. notified: Yes☐ No☐ High Risk for ARF☐ PVC☐ CVA☐
Volume per protocol/orders: OR fluids Albumin Other **Pre-op BP** / **LVEF(%)**

CV Medications:	Continue	Wean	Parameters
Dopamine: ____mcg/kg/min			
Neosynephrine: ____mcg/min			
Primacor: ____mcg/kg/min			
Levophed: ____mcg/min			
Epinephrine: ____mcg/min			
Nitroglycerine: ____mcg/min			
Nipride: ____mcg/kg/min			
Amiodarone: ____mg/min			
Vasopressin ____units/hr			

GI: NG/OG to suction Yes☐ No☐ D/C with extubation Yes☐ No☐ Start clear liquids 6 hours after extubation: Yes☐ No☐
Progress to ordered diet: Yes☐ No☐

GU: Foley: Yes☐ N/A ☐ Notify MLP/M.D. of UOP < 0.5ml/kg/hour **Preop Creatinine**_____

Skin: Ace wraps: Continue☐ Discontinue ☐

Antibiotics: Ancef ☐ Vancomycin ☐ Aztreonam ☐ Other_____ ☐

M.D./MLP/R.N. signature:

Respiratory Goals

RT parameters completed by Goal time of Extubation: Yes☐ Pass☐ Fail☐ No☐ Reason:

ABG prior to extubation: pH paCO2 pao2 Hco3 BE Lactate

1st attempt: Time NIF FVC TV Ve RR $ETCO_2$

2nd attempt: Time NIF FVC TV Ve RR $ETCO_2$

Admission R.N.: _____ Admission Respiratory Therapist: _____

Expected Time of Extubation R.N.: _____

Expected Time of Extubation Respiratory Therapist: _____ Patient Sticker

CVRU ADULT CARDIOTHORACIC SURGERY REPORT/GOAL SHEET AM/PM DATE _____ POD _____ PO HOUR _____
SURGERY _____ ATTENDING _____ RESIDENT _____

PHYSICAL ASSESSMENT

PREOP WEIGHT _____ KG TODAY _____ KG 7 HRSHIFT I&O _____
T CURRENT _____ T MAX _____ 24 HR CUMULATIVE I&O _____
NEURO: ALERT□ ORIENTED X____ CONFUSED □ PERRL YES/NO
BIS _____ PAIN ___/10
RECENT ANALGESIA _____
IMAGING RESULTS _____

PULM: RR _____ O2SAT % _____ ETCO2 _____
NC ____ L/MIN FM ___L/MIN EZPAP/IPPB Q ____H
VENT SETTINGS:
MODE _____ RATE _____ VT _____ PIP _____ PS _____
PEEP _____ FIO2 _____ BIPAP/CPAP□ ORDERS OBTAINED □
RIGHT LUNG: CLEAR□ DIMINISHED□
RHONCHI□ RALES□ WHEEZE □ COARSE□
LEFT LUNG: CLEAR□ DIMINISHED□
RHONCHI□ RALES□ WHEEZE □ COARSE □

CV: HR _____ RHYTHM _____ BP _____/_____
CVP _____ PA _____/_____ PCWP _____
CO _____ CI _____ SVR _____
VAD FLOW _____ PI _____ POWER _____ SPEED _____
PA CATH: VIP □ CCO □
PULSES: RUE ____ LUE ____ RLE ____ LLE ____
CAP REFILL: RUE ____ LUE ____ RLE ____ LLE ____
ADDITIONAL CARDIAC ISSUES:

LIST CARDIAC HOME MEDS _____

GI/HEPATIC: BS _____ SOFT □ FIRM □ RIGID □ FLAT □
DISTENDED□ LAST BM _____ NG□ OG □ DHT □
PLACEMENT VERIFIED □ DIET ORDER ENTERED □

GU: FOLEY □ VOID □ ANURIC □ DIALYSIS □
URINE: CLEAR□ CLOUDY □ SEDIMENT □ HEMATURIA □
> 0.5 ML/KG/HR □ < 0.5 ML/KG/HR □ MD NOTIFIED □
UOP GOAL _____ UOP/7HR SHIFT _____ UOP /24HRS _____

SKIN: PINK □ PALE □ CYANOTIC □ WARM □ COOL □ DRY □
DIAPHORETIC □ STERNOTOMY □ THORACOTOMY □ (RIGHT/LEFT)
LEG INCISIONS (RIGHT/LEFT) WOUNDS/PRESSURE ULCERS _____

LINES/WIRES: PW: ATRIAL MA ____ VENTRICULAR MA ____ PACING (YES/NO) RATE _____
A-LINE _____ CENTRAL LINE _____
PERIPHERALS _____
OTHER

CHEST TUBES: RIGHT _____ LEFT _____ MEDIASTINAL ____
SUCTION □ WATER SEAL □ AIR LEAK □

NURSING:
BATH □ CHG BATH □ DRESSING CHANGE □
□ OUT OF BED 1X 2X 3X /PER DAY
PROCEDURES PLANNED _____
TRAVEL OUT OF DEPT PLANNED _____
OTHER ISSUES: _____

AM SHIFT RN SIGNATURE _____ DATE/TIME _____
PM SHIFT RN SIGNATURE _____ DATE/TIME _____
MD/MLP SIGNATURES _____ DATE/TIME _____

Carolinas HealthCare System
10/14 CVRU Adult Cardiothoracic Goal Sheet

GOALS FOR CURRENT SHIFT

LABS □ IMAGING□ LABS DUE _____ TIME _____
CULTURES REVIEWED BLOOD□ URINE□ SPUTUM□ OTHER□
SEDATION: D/C □ WEAN □ CONTINUE □ VACATION □
COMMENTS _____
DRIPS: DIPRIVAN ____ MCG/KG/MIN MORPHINE ____ MG/HR
NIMBEX ____ MCG/KG/MIN VERSED ____ MG/HR
PRECEDEX ____ MCG/KG/HR FENTANYL ____ MCG/KG
RESTRAINTS: D/C□ CONTINUE□ N/A□ ORDER RENEWED□

MECHANICAL VENTILATION/PULMONARY BEST PRACTICE
EXTUBATE □ WEAN □ CONTINUE □ SBT □
COMMENTS _____

CLRT	YES □	NO □
HOB 30 DEGREES	YES □	NO □
PUD PROPHYLAXIS	ORAL□	IV □ PATIENT HX? □YES □NO
SCDS	YES □	NO □
HEPARIN/LOVENOX SQ	YES □	NO □
ORAL CARE	BASIC□	CHLORHEXIDINE □

CV MEDICATIONS VS GOAL HR _____ BP _____ MAP _____

				WEAN ORDER
DOPAMINE	MCG/KG/MIN	WEAN □	CONTINUE □	
EPINEPHRINE	MCG/MIN	WEAN □	CONTINUE □	
NOREPINENPHRINE	MCG/MIN	WEAN □	CONTINUE □	
MILRINONE	MCG/KG/MIN	WEAN □	CONTINUE □	
DOBUTAMINE	MCG/KG/MIN	WEAN □	CONTINUE □	
NEOSYNEPHRINE	MCG/MIN	WEAN □	CONTINUE □	
VASOPRESSIN	UNITS/MIN	WEAN □	CONTINUE □	
NITROGLYCERINE	MCG/MIN	WEAN □	CONTINUE □	
NITROPRUSSIDE	MCG/KG/MIN	WEAN □	CONTINUE □	
AMIODARONE	MG/MIN	WEAN □	CONTINUE □	
OTHER		WEAN □	CONTINUE □	

NUTRITION: DIET _____ KCAL/KG ADDITIVES _____
ENTERAL INITIATE □ CONTINUE □ HOLD □ (START D5W) RATE ____
PARENTERAL INITIATE □ CONTINUE □ HOLD □ (START D5W) RATE ____
INSULIN IV□ SLIDING SCALE□ ACCUCHECKS ACHS□ Q 6 HRS□
FOLEY CATHETER DISCONTINUE□ CONTINUE □
FLUIDS/DIURETICS: NAME AND DOSAGE _____
INITIATE □ CONTINUE □ HOLD □ LAST FLUID BOLUS _____
MAINTENANCE IV FLUID _____ ML/HR

SKIN:
ACE WRAPS DISCONTINUE □ CONTINUE □
DRAINS DISCONTINUE □ CONTINUE □

LINES/WIRES
PACING WIRES DISCONTINUE □ CONTINUE □
PA CATH DISCONTINUE □ CONTINUE □
A-LINE DISCONTINUE □ CONTINUE □
CENTRAL LINE DISCONTINUE □ CONTINUE □

CHEST TUBES DISCONTINUE □ CONTINUE □
DRAINAGE/7 HR SHIFT _____ DRAINAGE/24 HOURS _____

ANTICOAGULATION
ASA ____ MG INITIATE □ CONTINUE □ HOLD □
HEPARIN IV ____ UNITS INITIATE □ CONTINUE □ HOLD □
COUMADIN INITIATE □ CONTINUE □ HOLD □
PLAVIX ____ MG INITIATE □ CONTINUE □ HOLD □
HEPARIN SQ/LOVENOX INITIATE□ CONTINUE□ HOLD□

BETA BLOCKER INITIATE □ CONTINUE □ HOLD □ _____
NAME AND DOSAGE _____
MEDICATION RECONCILIATION INITIATE HOME MEDICATIONS□ HOLD□
ANTIBIOTICS _____ DISCONTINUE□ CONTINUE□ DOSE ADJUSTMENT□
CAN ANY IV MEDS BE CHANGED TO PO? YES/NO ORDER WRITTEN□
PHARMACIST □ RT□ PT □ NUTRITION□ SPEECH□ PT/FAMILY□
CONSULTS: ENDOCRINE□ PULMONARY □ CARDIOLOGY □ EP□ HF□
NEPHROLOGY □ NEUROLOGY□ ID□ WOCN□

PATIENT IDENTIFIER

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Chapter 3
OR to ICU Patient Handoff: A Matter of Communication

Subhasis Chatterjee

Introduction

Since the landmark Institute of Medicine's report "To Err is Human" was published in 1999, the estimate of 44,000–98,000 preventable hospital deaths annually in the United States has justifiably focused attention on patient safety [1]. In 2007, The Joint Commission's (TJC) Annual Report on Quality and Safety Mandate listed the implementation of a standardized approach to "handoff" communications, including an opportunity to ask and respond to questions, as a requirement for hospitals [2]. Other medical specialties have shown similar encouraging benefits of handoffs in surgery [3] and procedural checklists for central line placement promoting patient safety [4]. Handoff communications involves the transfer of information, responsibility and authority to ensure patient care continuity and safety. In this chapter we will review some of the important questions regarding handoff checklists:

1. Why should we have handoff checklists?
2. Is there data that shows that handoffs make a difference?
3. How do I implement checklists in my intensive care unit?

Editor's Note This chapter is an introductory "white paper" into the need for handoff checklists in the CT surgical intensive care unit. It was presented at the 2018 Annual Meeting of The Society of Thoracic Surgeons (STS). The STS Workforce on Critical Care took up the task of performing a systematic review of this topic and is in the process of preparing a Practice Guideline on Handoffs from the OR to Cardiothoracic Surgical ICU that will be published in The Annals of Thoracic Surgery in 2019. The reader is encouraged to download this document (https://doi.org/10.1016/j.athoracsur.2018.11.010) for a full evidence based medicine review, critique and recommendations of this important ICU communications tool.

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Why Have Handoff Checklists?

Handoffs are more important now due to the recognition that breakdown in communication during transitions of care may result in adverse events. With resident duty hour restrictions, there is an increasing recognition of the "discontinuity of care" as postoperative care is divided amongst more caregivers. One investigation found that 85% of sentinel events were a result of communication breakdowns while 77% of communication errors occurred during the late shift in surgical intensive care units [5]. Additional challenges in a cardiothoracic surgical ICU include a decrease in mandated cardiac surgery rotations by the American Board of Surgery. As a result, surgical residents are increasingly replaced by advanced care practitioners (e.g. Physician Assistants, Nurse Practitioners) as primary first-line caregivers in the intensive care unit (ICU). Such a development represents a significant change in the landscape of the surgical ICU landscape over the last 10–15 years.

Increased documentation requirements for billing impacts intensivists by requiring significant increases of an intensivist's time for this purpose. Intensivists must ensure that rounds and handoffs are efficient without sacrificing important information. Nursing shortages may result in less experienced nurses working at night, a vulnerable time in an ICU. In academic medical centers cross coverage demands routinely require a single resident to cover 20–40 ICU patients a shift. Moreover, it has been demonstrated that preventable adverse events have doubled under cross-coverage. Since a typical patient may experience 15 "handoffs" in a week, this requires that a proper handoff is performed to prevent untoward complications [6].

The Society of Thoracic Surgeons has recognized the critical role of communication: "Operating room to intensive care unit handoffs are a particularly vulnerable area for communication breakdown, with a clear risk for direct patient harm" [7]. It is vital to communicate surgical and anesthetic concerns from the operating room to the multidisciplinary intensive care unit teams. When evaluated it has been shown that postoperative information is lost after 52% of handoffs with only 30% of essential surgical information transferred [8]. Root cause analysis frequently implicates inadequate ICU handoffs in near miss scenarios. At its worst, handoffs have been described as "remarkably haphazard" [9]. Rushing the handoff can lead to small but critical errors that may lead to patient harm. Patient safety recognizes that individual clinicians interact with each other (team) and with their environment (system). On the other hand, handoffs are also an opportunity to be able to improve care. During a handoff, the person accepting the responsibility has a fresh perspective while having the opportunity of detecting fixation errors [10]. The team immediately taking care of a patient in the OR or ICU may be highly focused on one particular approach of patient care. A "fresh set of eye" may provide an alternative approach to the patient.

Communication failures are a prime cause of sentinel events. Indeed, it has been recognized that a focus on improved communication is a key aspect of reducing medical error. An analysis of 444 closed surgical malpractice claims found that 60 (13.5%) cases demonstrated communication breakdowns [11]. This was distributed across all surgical phases with 38% identified in the preoperative phase, 30% intra-

operative, and 32% postoperatively. Furthermore, status asymmetry between specialists and experience levels was identified as an important component of the communication breakdown. Further analysis showed that 43% of communication breakdowns occured during handoffs [11]. This responsibility often falls on the shoulder of the attending intensivist who must create a culture where less experienced members of the care team do not feel intimidated to voice a concern. The critical care teams must view these as "teachable moments" and an opportunity for education. Successful reduction in the breakdowns of communication can improve patient safety and reduce errors.

The ability to look at other industries and learn lessons that are applicable is important. Prof. Marc de Leval of the Great Ormond Street Hospital sought to analyze Formula 1 pit stop crews to better understand the handoffs in congenital cardiac operating rooms to the ICU [12]. The journey from the operating room to the intensive care unit was identified as a high-risk environment. It was discovered that current handoffs were unstructured with distractions, parallel conversations, and that key personnel were not always present and available simultaneously. A structured organization of the handoff process was found to lead to a reduction in errors [12]. Hierarchy and the perception of feeling incompetent is often a reason why information transfer may not occur. Promoting the concept that sharing information is not a sign of weakness but a sign of competent strength is important to establish a culture of safety.

Is There Data That Handoffs Make a Difference?

What kind of complications can be reduced? In a large review, the big difference observed was a reduction in preventable complications (prolonged hypotension, line complications, anaphylaxis/allergic reactions, iatrogenic pneumothorax) as opposed to serious complications (cardiac arrest, death, myocardial infarction, sustained metabolic acidosis, neurologic injury/stroke, acute renal failure) [13]. A systematic review of important characteristics of handoff checklists identified specific items: a standardized process (checklists and handoffs), completing urgent clinical tasks before the handoffs, allowing only patient-specific discussions during the handoff, requiring all relevant team members to be present, and providing training in team skills and communication [14]. Each of these suggests that communication between the ICU and the surgical team is important. An extension of that is the concept of "trigger events" which are serious events, staff concerns, or changes in patient location that prompt communication with a surgical attending directly. This may have prevented 26–44% of the communication breakdowns in one analysis [11].

What can we learn from other industries? In airline safety culture, the Tenerife airport disaster of 1977 is a case in point. Two Boeing 747s' collided on the runway in the Canary Islands killing almost 600 people. Investigation into that crash revealed that garbled transmission from the air traffic controllers to the cockpit along with culture of adherence to strict hierarchy prevented questioning the captain,

even in the face of imminent catastrophe, with disastrous consequences [15]. As a result, this led to the development and implementation of a standardized handoff communication practice. [16]. NASA psychologist John Lauber developed the concept of "crew resource management," which were a set of training procedures to use when human error could result in serious adverse consequences [17]. After studying airline cockpits for several years, Lauber realized that while it was necessary to retain a command hierarchy, the concept was intended to foster a less authoritarian cockpit culture. Co-pilots were encouraged to question captains if they observed them making mistakes. Gordon, Mendenhall, and O'Connor's book "Beyond the Checklist" is instructive and emphasizes the need for buy-in at the highest levels [18]. Moreover, the concepts of standardized information transfer, up-to-date information, limited interruptions, and structured face-to-face handoffs are integral for safety. As clinicians we need to engage thusly as an active part of the environment where we practice.

How to Implement Checklists

In 2013, the American Heart Association issued a Class I recommendation that formal handoff protocols be implemented during the transfer of cardiac surgical patients [19]. The process of handoffs should begin in the operating room with a phone call to the intensive care unit staff to provide notification of when a patient is expected to arrive from the OR to the ICU [20]. This allows for preparation of personnel and equipment for a smooth transition. Breaks and personnel allocation can be planned with this in mind and simultaneous expected arrivals can be anticipated. Close coordination between nursing, critical care, respiratory therapy, radiology technicians can be facilitated for the arrival of the patient in the ICU. The handoff structure requires that the room is quiet and there are no interruptions. A protocol determines who speaks and in what order i.e. surgery then anesthesia. Checklists provide a structured format of the expected contents for a verbal handoff (usually consisting of a separate surgeon and anesthesiologist checklist). An integral element of structured handoffs is avoiding a noisy environment with multiple simultaneous conversations so that an orderly multidisciplinary exchange of information can occur. After allowing for the transfer of equipment and monitoring lines, the verbal report begins when the receiving nurse is ready. This is done to reduce parallel conversations and improves caregiver and provider satisfaction. Moreover, it has been demonstrated to improve teamwork and unit cohesion [21]. A key component includes discussing the expected and anticipated adverse events during the postoperative course in the handoff [22]. What the surgical and anesthesia teams are most concerned about a patient can be illuminating and help focus attention to particular problems (bleeding, low cardiac output, blood pressure management, arrhythmias, and hypoxemia). It may lead to proactive steps and resource allocation to mitigate adverse events. Most experienced critical care practitioners are highly attuned to pattern recognition in the postoperative period. Intraoperative events or surgical

concerns may impact the postoperative course and provides useful information. In addition, it facilitates better surgeon-ICU communication by highlighting priorities. A brief question and answer period from the receiving team follows and then a critical care summary care plan is provided. To engage in a culture of safety, all team members should feel empowered to speak up for clarification or concern. We are all our patients' advocates.

The keys include designing the checklist based on caregiver's needs and workflow. The most important items need to be addressed first. The handoff checklist should not be made too long and it is critical to pay close attention to usability since any negative effects on workflow will reduce compliance. Rigorous pilot testing and validation before full-scale implementation is recommended. Finally, continual reevaluation and periodically updating the most recent version as local practice warrants is necessary [23]. A physician champion is vital to encourage compliance. Finally, buy-in from the primary personnel (surgery, anesthesia, and nursing) and accountability is required.

The expected resistance to checklists includes senior staff citing tradition, "We've never done it this way before." Next, inadequacy of the checklist that it is time-consuming or contains inappropriate information. Dixon and colleagues in a before and after implementation of handoffs found that after 30 handoffs the duration of handoffs only increased from 6 to 8 min [24]. Finally, the data also supports a consistent increase in nursing and provider satisfaction [20].

Keys to implementation are to summarize evidence into checklists, identify and mitigate local barriers to implementation, measure performance, and ensure that all patients reliably receive intervention. Sometimes, one-on-one attention to individuals who appear to be unsatisfied with the handoff process and seeking their advice on improving the process is advisable. The Joint Commission Center for Transforming Healthcare demonstrated that the major contributing factors for defective handoffs included interruptions, needless repetition of information, inaccurate or incomplete information, or a lack of standardized procedures.

There are also additional handoffs critical in an intensive care unit. This includes resident/midlevel to resident/midlevel ICU or intershift handoffs. Implementation of the I-PASS Study Group showed that implementation of a handoff program leads to decreases in medical errors [25]. I-PASS (Table 3.1) stands for the important pieces of information to convey: I-Illness severity, P-Patient summary, A- Action list for next team, S- Situation awareness and contingency, S- Synthesis and "read back." They demonstrated a 23% reduction in medical errors (NNT = 16) and a 30% reduction in adverse events [25]. However, not all of the nine sites showed similar improvement. After the intervention of the I-PASS system, the most significant area of improvement was in illness severity assessment which went from less than 15% pre-implementation to almost 90% post-implementation. In addition, it is beneficial to have contingency planning that allows discussion to think through what could go wrong and what to do about it. Discussion points could include: what has or hasn't worked before; difficult family or psychosocial situations; the code status. Another technique that is widely used is the SBAR technique (Table 3.1): Situation, Background, Assessment, and Recommendation [26].

Table 3.1 Handoff examples in the surgical ICU

I-PASS (Data from [25])
I-Illness severity
Is the patient stable, potentially unstable, or unstable?
P-Patient summary
Brief summary. Operation, postoperative day. OR events. Hospital course. Plan for the day and plan for the night
A- Action list for next team
To do list and what to follow-up on
S- Situation awareness and contingency planning
Knowing what's relevant, problems during the day, possible issues overnight, expected interventions, specific items that the surgeon/surgical team may want to know
S- Synthesis
Summary by the receiver, questions, acknowledges what needs follow-up
SBAR (Data from [26])
S-Situation
Identify the patient, reason for admission, procedure, postoperative day
B-Background
History, significant postoperative events
A-Assessment
Assessment of postoperative course, patient condition
R- Recommendation
Recommendations for course of care

Finally, an interesting analysis looked at attending intensivist handoff procedures in mixed medical, surgical, and cardiothoracic ICUs of 30 intensivists [27]. When interviewed regarding the components of the "perfect" handoff the critical components included succinct written and verbal communication and person to person interaction. About 60% of the time, it was done by phone, 17% in person and 17% of the time by email. The end observation was that attendings were not particularly exemplary with respect to handoffs [27].

Handoffs and checklists are vital components of patient care and safety and reduce the risk that critical information is shared. Given the current healthcare organizational models, the ability to organize the transfer of information and responsibility as efficiently as possible is necessary.

Recommendations

1. Handoff checklists have demonstrated improved provider satisfaction and leads to less information lost in transfer.
2. Handoff checklist implementation has demonstrated a reduction in adverse events.
3. Successful development and implementation of handoff checklists require the participation and buy-in of relevant stakeholders – nursing, critical care, surgery, and anesthesiology.
4. Handoff checklists are designed to promote and enhance an institution's commitment to patient safety.

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Chapter 4
Palliative Care in the Intensive Care Unit: A Universal Need

Allen N. Gustin

Introduction

In 1997, the Institute of Medicine evaluated "end of life" care in the USA and found significant suffering at the end of life and emphasized the need for further improvements [1]. Ten years after that report and as a result of the findings, hospice care utilization doubled and the field of palliative care further expanded and matured with practice guidelines and quality measures for patients with severe illness [2]. One in five deaths in the USA occurs during or shortly after admission to the ICU, with more deaths occurring in the ICU than any other setting in the hospital [3]. Palliative care is an inter-professional specialty composed of many trained care providers who focus on the symptom management of patients with serious and complex illness [4, 5]. As more patients with severe critical illness survive the ICU in higher numbers every year, investigators have identified that significant symptom burdens persist in both patient and family beyond the ICU. This spectrum of symptoms has been termed as "the survivorship syndrome" [4]. As these symptoms are recognized and studied, early management of symptoms has become a focus within the ICU and the subsequent care outside the ICU. Specialized palliative care consultation is uniquely positioned to support these patients and families as the work demands of the ICU may not afford ICU clinicians the time to manage both patient and family needs. The key focus of palliative care is from the patient, family, and caregiver perspective rather than from the ICU physician/surgeon perspective. Integrative palliative care approaches include a specialized palliative care clinician

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in the daily rounding and care planning for the intensive care unit. This is in contrast to consultative specialized palliative care approaches where the palliative care clinician would only be engaged when the perceived palliative care need would arise. Palliative care has been slow to be integrated into the surgical intensive care units. Many barriers to the integration of palliative care exist which include specific surgeon barriers regarding the use of either the integrative or the consultative palliative care approaches within surgical oriented ICUs.

Search Strategy

A literature search of English language publications from 2007 to 2017 was used to identify published data on palliative care/palliative medicine/end of life care within the cardiac surgical intensive care unit using the PICO outline (Table 4.1). Databases searched were PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Science Citation Index/Social Sciences Citation Index, and Cochrane Evidence Based Medicine. Terms used in the search were "palliative care/palliative medicine/end of life care/cardiac surgery/quality of life/adult/resource utilization," "palliative care/palliative medicine/cardiac surgery/quality of life/adult/resource utilization," "end of life care/cardiac surgery/quality of life/adult/resource utilization", AND "palliative care/palliative medicine/end of life care/cardiac surgical ICU/cardiac surgery critical care/critical care medicine/adult/quality of life." I excluded case series, editorials, and review articles. After hand searching all the articles, **no articles exist regarding the use of palliative care interventions within a cardiac surgical intensive care unit**. Next, I changed the terms for the search by removing "cardiac" and used "surgery" as the primary means of search. I excluded case series, editorials, and review articles. After hand searching though the results, only two articles were identified where integrative palliative care interventions were initiated in surgical/trauma intensive care units. Unfortunately, no cardiac surgical patients were admitted nor involved in either of the two studies. Of the 35 total articles identified where palliative interventions were introduced into an ICU, 33 were focused in medical intensive care units without any surgical patients. The Quality of data (in the papers evaluated) were classified according to the GRADE system.

Table 4.1 PICO table of palliative care intervention for cardiothoracic surgical intensive care unit patients

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Patients within a cardiac surgical intensive care unit	Patients with consultation with a palliative care specialist	Patients without consultation with a palliative care specialist	Timing of death, relief of symptom burden, symptom relief, timing of do not resuscitate orders

Results

Of all those articles, most showed a reduction in ICU and hospital length of stay. No evidence of harm has been observed in any study to date with the use of a palliative care intervention in a critical care setting. Given the differences between medical and surgical intensive care units (and more importantly the differences between cardiac surgical ICU patients and all other ICU patients), this author has chosen to avoid the addition of any medical ICU interventions into the discussion. Of the two remaining articles, one article focused on an ICU which was primarily a trauma based ICU within an academic institution and all subjects were trauma patients admitted from the emergency room or from the operating room [6]. The other ICU was a surgical intensive care unit within an academic institution but specifically only involved the liver transplantation patients [7]. Both articles were a single center, before and after study testing a multifaceted, interdisciplinary intervention to integrate palliative care into standard of care in a both ICUs [6, 7]. Both interventions focused on usual care versus the integrated model of integrated palliative care with attention to the enhancement of communication between physicians, nurses, and families around prognosis, pain and symptom assessment, and goals of care, as well as early psychosocial support for families [6, 7]. Both studies used a Part I and a Part II criteria for involvement. Part I occurred within 24 h of admission and included psychosocial support to families and an interdisciplinary meeting palliative care assessment (prognosis, advanced directive, pain and symptom management, and family needs) [6, 7]. Part II occurred within 72 h of admission and included an interdisciplinary family meeting with physicians and nurses focused on communication of likely outcomes, goals of care discussion, and assess family understanding [6, 7]. Both of these studies are discussed in the following two paragraphs (Table 4.2).

Mosenthal et al. evaluated a before (control group) and after intervention of an integrative palliative care model (intervention group) within a trauma surgical intensive care unit [6]. No significant differences existed in age, gender, head injury, or probability of survival between groups. At the conclusion of the study, ICU mortality did not vary between the control group and the intervention group (15% and 14% respectively). The rate of DNR orders was unchanged between groups (43% and 43% respectively). However, the timing of DNR orders was significantly early in the intervention group (7 days) versus the control group (20 days). Shorter times were also noted in the time to withdrawal of care (comfort care) in the control group versus the intervention group. No change in frequency of the family meetings nor the timing of family meetings was seen. The intervention resulted in more discussions among the ICU teams regarding symptom management (pain) and goals of care than in the control group. The intervention was associated with shorter ICU and hospital stays only for the patients who died [6].

Lamba et al. evaluated before and after intervention of an integrative palliative care model within a surgical intensive care unit focused solely on liver transplant or liver failure patients [7]. At the conclusion of the study, mortality rates did not differ

Table 4.2 Research results

Article title	Study results	Type of study and quality of evidence
Mosenthal AC, et al. Changing the culture around end of life care in the trauma intensive care unit. *J Trauma*. 2008;64(6):1587–1593 [6]	No difference in ICU mortality in either group. Rates of DNR orders did not differ. Timing of the DNR orders occurred significantly sooner in the Palliative Care Intervention. Shorter ICU stays only in those patients who died. More discussion in the intervention group	Prospective, observational, pre/post study of consecutive trauma patients admitted to an ICU after a structured palliative care integration. Quality of evidence: VERY LOW
Lamba S, et al. Changing end of life care practice for liver transplant service patients: structured palliative care intervention in the surgical intensive care unit. *J Pain Symptom Manage*. 2012;44(4):508–519 [7]	Mortality rates did not differ between groups. DNR orders significantly increased in those patients who died. Mean time to DNR orders decreased. Discussions of goals of care increased. Length of ICU stay decreased only in those patients who were transitioned to comfort care	Prospective, observational, pre/post study of consecutive liver transplant/ICU patients before and after a palliative care intervention. Quality of evidence: VERY LOW

between groups. Active DNR orders significantly increased in those who died from 53% in the control group to 81% in the intervention group. The mean time from admission to active DNR orders decreased from 38 days in the control group to 19 days in the intervention group. Discussions of goals of care on daily rounds with the ICU team increased from 2% in the control group to 39% in the intervention group. Length of ICU stay only decreased in the intervention group only in patients who were transitioned to withdrawal of care (comfort care) [7].

Although there are no studies specifically about integrative palliative care in the Cardiac Surgical ICU, support for such a team can be extrapolated from such teams in the medical ICUs.

Data highlights that survivors of the intensive care unit (ICU) are increasing in number and are now being studied beyond their ICU stay. As a result of this research, a new syndrome has emerged and has been termed "the survivorship syndrome" or "post intensive care syndrome." [4, 8, 9] A broad array of physical and psychological symptoms (including impairments in function and cognition) appear to impair the quality of a patient's life during and after the ICU [4, 10]. Patients can develop functional and neurocognitive deficits after surviving an ICU admission [4, 11–17]. Not only does the ICU patient experience symptoms of survivorship, but the family members of those patients exhibit psychological problems which can include signs of anxiety, depression, complicated grief, and posttraumatic stress disorder [11, 12].

ICU patients may be unable to participate in shared decision-making within the ICU team given their clinical condition. Given this lack of direct patient communication, decisions regarding the patient's ICU course require the patient's surrogates [18, 19]. Surrogate discussions can be difficult because surrogates have been shown

Table 4.3a Survivorship syndrome experienced by ICU patients who survive past ICU discharge

Neurocognitive deficits [16]
Pain [10]
Periodic confusion [10]
Anxiety [13]
Depression [10, 13]
Physical limitations (dyspnea with exercise) [13–15]

Table 4.3b Survivorship syndrome experienced by the family members of a critically Ill patient

Anxiety [11]
Depression [11]
Complicated grief [12]
Posttraumatic stress disorder [12]

to react to communications with ICU staff by focusing on details rather than the larger picture, relying on their own personal instincts or beliefs (not necessarily the patient's beliefs), and sometimes rejecting prognostic information [4, 19]. This furthers the argument for the need for specialist palliative care consultation within the ICU. The ICU team should always be providing basic palliative care (basic control of symptoms and communication with patient/surrogate/family) at all times to all patients within the ICU. Unfortunately, ICU personnel do not tend to follow patients outside of the ICU whereas 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, acute care facilities, nursing homes, home, etc.) [4] (Tables 4.3a and 4.3b).

Unique barriers exist for implementation of a formal specialized palliative care program in any ICU [4]. These barriers 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 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, 5]. Despite these barriers, specialized palliative care is increasingly accepted as an essential necessary component of comprehensive ICU care for critically ill patients, regardless of the diagnosis or the prognosis [4, 10] (Tables 4.4a and 4.4b).

Table 4.4a Barriers to palliative care implementation in any intensive care unit [4, 5, 10]

Unrealistic expectations from the family and the care team
Misperception that palliative care and critical care are not complementary
Confusion between the concepts of palliative care and hospice
Concern that palliative care involvement will hasten death
No rewards for evidence of palliative care excellence
Inability to apply effective approaches for system culture change in order to improve palliative care

Table 4.4b Unique barriers to palliative care implementation in a surgical intensive care unit [4, 5, 17, 20]

Surgical sense of accountability for all patient outcomes
Surgeons having a "covental" relationship with patients and the family
Disagreement with the ICU team over goals of care
Surgeons management of poor outcomes with patient, family and ICU team

Implementation of any specialized palliative care service in a surgical ICU can be especially challenging [4]. Evidence suggests that surgeons have an exaggerated sense of accountability for patient outcomes, thus doing everything possible to avoid patient death [4, 20]. Surgeons may believe that they enter into a "covenantal" relationship with the patient (and by extension, the family or surrogate) [4, 20]. As a result of this covenant, patients and their families may consciously or unconsciously cede any sort of decision-making to that surgeon, particularly related to what the patient's goals of care should be after any surgical procedure [4, 20]. In a national survey, many surgeons described conflict with both the ICU physicians and the ICU nurses with respect the appropriate goals of postoperative care [4, 20]. Surgeons have 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, 20]. Given the strong sense of responsibility for patient outcomes, surgeons can be resistant to any integrated specialized palliative care program in the ICU and further surgeon involvement/approval may require additional encouragement from other specialties to consider possible specialized palliative care options for patient care [4, 5, 17] (Table 4.4b).

International/National Organizations Guidelines and Recommendations/Palliative Care

One international organization has recognized the global need for maintaining access to palliative care. The World Health Organization (WHO) has declared that access to Palliative Care to be a human right [21]. Multiple national societies within the USA representing critical care and cardiac professionals have published practice recommendations or guidelines intended to highlight the importance of palliative care integration within the ICU. The American College of Critical Care Medicine has published consensus recommendations for end-of-life care in the intensive care unit as well as practice guidelines for the family and the patient centered care within the ICU [5, 22]. Within these guidelines, strong recommendations exist that support proactive palliative care consultation being provided to all patients with a prolonged ICU stay [22]. Though the evidence is considered low quality, a number of studies have shown that palliative care consultation has decreased ICU length of stay [22]. Though more research is needed to further determine these trends, the results were of sufficient weight and with relativity low risk of palliative

Table 4.5 Consensus statements of various organizations associated with ICU patients

Organization	Consensus statement
American College of Chest Physicians	(2005) Strongly supports the position that palliative and end of life care of the patient with an acute devastating or chronically progressive pulmonary or cardiac disease and his her family should be an integral part of the cardiopulmonary medicine [5]
American College of Critical Care Medicine	(2007) Recommends proactive palliative care consultation being provided to all patients with a prolonged ICU stay [5]
American Thoracic Society	(2008) Advocates for using palliative care for the care of patients with respiratory disease and critical illness [5]
American College of Cardiology Foundation	(2016) Advocates for the use of palliative care in the management plans for severe congestive heart failure [5]
American Heart Association	(2016) Advocates for the use of palliative care in the management plans for severe congestive heart failure [5]
Critical Care Societies Collaborative	(2014) Recommends that clinicians not continue life support for patients at high risk for death or with severely impaired functional recovery without offering patients and their families the alternative of care focused entirely on comfort [5]

care consultation that the guidelines included this recommendation. Also, the American Thoracic Society published a clinical policy statement on palliative care for patients with respiratory disease and critical illnesses [5]. Chest (formally the American College of Chest Physicians) published a position statement on palliative and end of life care for patients with cardiopulmonary disease [5]. Within this position statement, Chest strongly supports the position that palliative and end of life care of the patient with an acute devastating or chronically progressive pulmonary or cardiac disease and his her family should be an integral part of the cardiopulmonary medicine [5, 23]. Both the American Thoracic Society and Chest have specifically addressed the management of dyspnea [5]. The American Heart Association and American College of Cardiology Foundation included palliative care in the management plans for patients with severe congestive heart failure [5]. Finally, included among the five recommendations of the "Choosing Wisely" campaign, the Critical Care Societies Collaborative recommended that clinicians not continue life support for patients at high risk for death or with severely impaired functional recovery without offering patients and their families the alternative of care focused entirely on comfort [5, 24] (Table 4.5).

Clinical Relevance of Integrative Palliative Care Consultation Within Non-cardiac Surgical Intensive Care Units

Time to earlier establishment of an active DNR status is seen in both studies. Given the issues associated with ICU resources, integrative palliative care did shorten both the ICU stay and hospital stay in those patients who died.

Risk Factors

No perceived nor documented risk currently exist for the use specialized palliative care involvement in ICU care.

Recommendations Based on the Data

A consistent international and national theme exists regarding the need to provide access to palliative care for all patients. The WHO has declared that access to Palliative Case should be a human right. USA based national organization best practice guidelines propose that palliative care should be integrated into the care of any patient with chronic disease or critical illness. From the information provided by both international/national organizations, the following concepts should be clarified with regard to palliative care for any intensive care unit patient:

1. Access to Palliative Care is a human right [21]. (Quality of Evidence: VERY LOW; Level of Recommendation: WEAK)
2. Early institution of Palliative Care within the ICU should be available for any patient with chronic disease or critical illness [4]. (Quality of Evidence: VERY LOW; Level of Recommendation: WEAK)
3. Palliative Care does not equal end of life care. Palliative Care can be provided alongside all aggressive acute care measures for the patient while focusing on both the patient and family experience within the ICU [4]. (Quality of Evidence: MODERATE; Level of Recommendation: STRONG)
4. Palliative care gives continuity of care beyond the ICU after transfer to the floor (even when the patient transitions to home) [4]. (Quality of Evidence: MODERATE; Level of Recommendation: STRONG)
5. Palliative care should be provided to all patients with chronic heart failure [4, 5]. (Quality of Evidence: VERY LOW; Level of Recommendation: WEAK)

A Personal View of the Data and of the Practice of Perioperative Palliative Care

In this author's opinion, the surgical model of palliative care tends to focus on the situation where a patient first receives life-prolonging/life-sustaining therapy until it absolutely fails, and only then is palliative care offered and provided [4, 25]. Many specialized palliative care physicians feel that surgeons are slow to consider palliative medicine until all efforts to restore the patients' health have failed. To some degree, many surgeons are confused about the definitions of palliative care, end of life care, and hospice. Though these concepts are complementary to one

another, differences do exist [4, 25]. Palliative care can be offered to every patient with a serious illness regardless of the curative/intensive care being provided within the ICU. Most palliative care clinicians prefer the palliative care model where palliative care is delivered at the beginning of an illness and is provided concurrently with life-prolonging therapy. The amount of palliative care can increase or decrease depending on the preferences and needs of both the patient and the family [2, 25]. Surgeons should also realize that usual "life-prolonging" medical or surgical care in any care environment ends with the patient's death, whereas palliative care engagement and application peaks at the patient's death and continues after death to address the bereavement needs of the patient's family. While in the ICU, international organizations, national societies, and multiple expert statements recommend coordinating palliative care with life-prolonging care. Life sustaining medical/surgical care and palliative care can be aligned as long as the patient's medical/surgical condition and the patient's goals of care are in parallel and complementary [4]. The American Academy of Hospice and Palliative Medicine (AAHPM) "Choosing Wisely" Initiative in 2013 listed the top five initiatives that should be considered in patient care [26]. One of those top five items encouraged the concept that palliative care should be provided to all patients with a serious illness and should not be delayed while that serious illness exists or while the patient is being actively treated. Palliative care is appropriate at any age (pediatric to geriatric), at any stage of serious illness, and can be provided concurrently with curative/all life-prolonging therapies [4].

Final Comment No current research exists regarding the implementation of palliative care in a cardiac surgical ICU. Despite this lack of data, multiple organizations and expert opinions exist regarding the need and importance of Palliative Care engagement in in any ICU for any ICU patient. More specifically, national organizations with a focus on cardiac patients, recommend the use of Palliative Care for patients with chronic disease, patients with critical illness, and patients with cardiopulmonary disease.

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Chapter 5
Ethics: When to Turn Off the VAD

Scott B. Grant and Peter Angelos

Introduction

Difficult decisions are part of the daily life of physicians caring for patients in the intensive care unit who have received a ventricular assist device (VAD). There is no longer a question of whether VADs improve the quality of life (QOL) of patients compared to optimal medical management. Furthermore, VAD as destination therapy (DT) has been covered by Medicare since 2002, so there is little controversy about whether it is acceptable to place DT-VAD in patients with severe heart failure. Recent data suggests that DT-VAD patients have a 2-year post-implantation survival of approximately 70% [1]. However, numerous ethical issues remain in this group of patients. Unlike turning off a defibrillator which does not have an immediate effect, turning off a VAD causes virtually immediate death in the vast majority of cases. This very fact has led to significant differences in opinion regarding the deactivation of VADs. In a recent study, 60% of cardiologists believed that a patient should be imminently dying before deactivating a VAD, whereas only 2% of palliative medicine clinicians felt similarly [2]. This disparity of views regarding how to manage patients with VADs near the end of life has prompted significant discussion.

Over the past several years, there have been a number of calls for increased involvement of palliative care (PC) specialists in the management of severe heart failure patients. In 2013, the International Society for Heart and Lung Transplantation

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stated that PC consultation should occur during the evaluation phase before DT-VAD implantation and early discussions should explore patient goals and preferences for care approaching the end-of-life (EOL) [3]. In 2014, the Centers for Medicare and Medicaid Services (CMS) stated that a PC consultant should be a member of the mechanical circulatory support interdisciplinary team [4]. As of the same year, The Joint Commission has required evaluation by a PC specialist before consideration of VAD placement for Advanced Certification in Ventricular Assist Device for Destination Therapy [5]. Despite these multiple calls for PC specialist involvement in the pre-implantation care of VAD patients, the value of involvement of PC specialists in post-implantation outcomes has not been clear. There has only recently been data to examine how to increase such PC involvement and whether it has an impact on VAD patient outcomes. In the following pages we explored these topics by examining the impact of PC consultations on VAD patient outcomes at EOL.

Search Strategy

We sought to explore the literature on this topic by searching the terms, "ventricular assist device" and "palliative care." On a PubMed search of these terms, 98 articles were identified for all years searched with no limits placed. Out of this group, 24 were found to be relevant to the questions at hand. This number was supplemented by reviewing the references of each article for additional relevant papers. The PICO model used is outlined in Table 5.1 below. The quality of the data in the papers evaluated were classified according to the GRADE system.

Results

Little data was found to actually assess the overall number of VAD patients that have had PC consultants involved in their care. The numbers of PC consultations for pre-implantation VAD patients has been reported to vary between 35% and 89% [6, 7]. However, on a national level, there is no good data to assess the rates of PC specialist involvement in VAD patients.

Table 5.1 PICO model for clinical questions

P	Patient population	Adult VAD patients (postop cardiothoracic ICU or chronic patient) at end of life
I	Intervention	Palliative care consultation as part of critical decision making
C	Comparison	Standard care without palliative care consultation
O	Outcomes measured	End-of-life process, quality of life

Data Showing Increasing Palliative Care Consultations

Several studies have examined strategies for increasing PC consultations in preimplantation VAD patients. Sinha et al. developed a protocol based on the electronic medical record and the generation of an automatic PC consult once a heart failure patient with potential need for VAD was admitted to the hospital [8]. These authors showed that PC consultations for potential VAD patients increased from 17.2% prior to the implementation of the protocol to 96.6% after the protocol. Utilizing a different approach, Solomon et al. found that mandating a PC consultation within 24 hours of admission of potential VAD patients was not as successful as desired; however, success improved if an "LVAD champion" was designated from among the PC attendings who attended weekly interdisciplinary rounds with the VAD team [9]. This group found that in the three quarters of 2015 prior to designation of an "LVAD champion," 35% of patients receiving a VAD had PC consultation whereas in the quarter after implementing this change, the rate of PC consultation rose to 71% [9].

Potential Value of Palliative Care Specialist Involvement

The value of increasing PC involvement is only evident if there are aspects of the involvement of palliative care specialists that provide benefits to VAD patients. Several groups have suggested that there are multiple important benefits of having PC specialists involved in the care of VAD patients. Certainly, the PC consultant may have particular expertise in managing the symptoms of complications that might arise. The PC specialist may also be particularly helpful as an "outsider" who may have a different perspective than the heart failure team, especially when VAD patients may not want to decline treatment and potentially disappoint the heart failure team [10]. Meyers et al. suggested that PC specialists could help VAD patients in five ways: (1) increasing shared decision making between physicians and patient, (2) facilitating naming of a surrogate decision maker, (3) helping to articulate a patient's values ("What is most important to you at present and in the future?"), (4) identification of conditions in which the patient would want to discontinue potentially life-prolonging devices or treatment, and (5) in helping a patient to decide under what circumstances to decline attempts at resuscitation [11]. In addition to the potential benefits noted above, Sagin et al. suggest that PC providers can give extra support to the members of the mechanical circulatory support team members and they can also potentially improve the experiences of VAD patients and family caregivers with the decisions at the EOL [12]. Although there is little data to empirically support these claims of benefit, there are multiple examples of how PC specialist involvement would potentially be of value.

Theoretical Constructs from the Literature

In 2011, Petrucci et al. described a "3 phase model" of the ethical considerations for VAD patients prior to implantation [13]. These authors based their recommendations on a study of 175 VAD patients treated over a 20-year period. They identified three helpful ethical phases: the Initial Information stage, which focused on initial diagnosis and informed consent; the Preimplant Preparation phase, in which advance directives should be discussed and cultural/religious preferences identified; and the VAD-Specific End-of-Life stage, in which palliative care planning should be undertaken and decisions made regarding acceptable device withdrawal processes [13]. All of the items that the authors suggest would certainly be valuable to address in a systematic fashion with prospective VAD patients. However, sometimes the clinical situation precludes the time to progress through all these stages prior to VAD placement.

In an attempt to offset some of the ethical issues such as how to proceed when a VAD patient might request deactiviation of the VAD or when the medical team believes that continuing with the device may be futile [14], the helpful concept of "preparedness planning" was discussed by Swetz et al. in 2011 [15]. These authors suggested the value of a PC consultant in the multidisciplinary assessment of VAD patients to provide psychosocial support to not only the patient and the family, but also to the caregiver team. Swetz et al. suggest that preparedness planning includes not only the careful discussion of the patient's goals, but also his or her views regarding end-of-life planning [15]. In an effort to improve outcomes, Verdoorn et al. suggest that prior to implantation, prospective VAD patients should have a PC consultation with the focus on planning for the following issues: device failure, post-VAD quality of life, catastrophic device-associated complications, and progressive co-morbid conditions [16].

One of the central ethical issues for VAD patients revolves around how to manage the device when the patient is nearing the EOL. Although it is widely accepted that patients can exercise autonomy in deciding whether to continue with such life-sustaining treatments as dialysis or artificial fluids and nutrition [17], a number of authors have suggested that there are unique challenges to deactivating a VAD. VAD treatment is in many ways different from dialysis in that it is continuous and constitutive (meaning death almost inevitably follows withdrawal) [18]. However, as Swetz et al. have argued, a VAD is not a replacement therapy like getting a heart transplant, but rather a supportive treatment which is ethically and legally permissible to withdraw [19]. Furthermore, although great precautions are taken in screening prospective heart transplant candidates regarding potential compliance with therapy, post-transplant the patient still retains the right based on respect for autonomy to decide to stop taking the immunosuppression medications necessary to sustain the heart transplant [20].

One of the more helpful outcomes of PC specialist involvement in the care of VAD patients undoubtedly comes from management of the decisions regarding device deactivation. This scenario is a challenging one not only for the patient and

family, but also for the many caregivers who may have come to know the VAD patient very well over significant periods of time. Schaefer et al. have suggested a potentially valuable "deactivation checklist" that may help to alleviate some of the concerns with VAD withdrawal (See Table 5.2 below) [21]. These authors suggest

Table 5.2 The ventricular assist device deactivation checklist (Modified from Shaefer et al. [21])

1. The following individuals must be informed before proceeding with deactivation:
Physician of record
Advanced heard disease cardiologist (and fellow, if applicable)
Surgeon who implanted the VAD
VAD coordinator
Bedside nurse and nursing manager
Palliative care consultant
Social work
Chaplain, as indicated
Ethics consult, as indicated
2. Family meeting
Outline the process for deactivation, including the unpredictable timing of death after deactivation (minutes to days)
Decide which family members will be present at the time of deactivation, and note planned religious rites, as applicable
Review the goal for comfort, and specify the timing of discontinuation of other life-prolonging interventions
When appropriate, discuss decisions that will be faced after death: tissue, organ, or body donation; autopsy; and funeral arrangements
Document in the medical record the health care proxy, and any advance directives, and content of family meeting
3. Clinical team meeting
Review all orders and discontinue those that are inconsistent with goal of VAD deactivation and/or have the potential of causing the patient discomfort
Continue all orders addressing patient's comfort
Review planned steps and sequence for deactivation of VAD and other life support modalities, including mechanical ventilation, if applicable
Plan deactivation of ICD (both defibrillator and pacing functions), if applicable
Set the date and time for deactivation of VAD and review each team member's role during the procedure (some staff may prefer not to have a role)
4. Interdisciplinary preparations at the bedside
Identify person in charge of deactivation of the device, i.e., VAD coordinator, MD or RN
Assure social work, chaplaincy, and interpreter services at bedside, as indicated
Assess family's perception of patient's level of comfort and address concerns
Review anticipated symptoms/signs of distress (agitation, air hunger, anxiety, pain, noisy secretions) and enter orders for anticipatory management[a]
Ensure adequate sedation and premedication prior to deactivation (e.g., consider bolus and/or continuous infusion with fast-acting opioid and/or bendzodiazepine),[a] and reassess frequently
Turn off monitors

[a]Refer to institution-specific medication guidelines, as applicable

attention to who should be informed before proceeding with deactivation, suggestions for the family meeting, a checklist for the clinical team in its deliberations, and interdisciplinary preparations at the bedside [21]. Whether all of these items can be shown to be beneficial or not, such a checklist has clear value in providing a comprehensive consideration of the practical steps in device deactivation [22].

Despite the widespread suggestion in many papers that having PC involvement in VAD patients is beneficial, there is also the clear realization that there are not enough PC specialists, especially those with experience in treating VAD patients, to meet this growing patient population [23]. As an alternative, "primary palliative care" has been suggested as a solution whereby the physicians providing the primary medical care to the patient would also provide the palliative care needs [24]. Although having the cardiac specialists managing a VAD patient also provide the palliative care needs seems like it would be another possible solution, at the present time, we believe there is inadequate training to allow for such a solution, and there is a potential conflict of interest. The potential conflict of interest stems from the close scrutiny that cardiac surgeons and VAD programs are under regarding their outcomes, survival, and perioperative mortality. One can envision a scenario in which a patient desires to deactivate a VAD due to post-operative complications, but where the surgeon pushes the patient to continue ongoing, possibly burdensome, life-sustaining treatment to ensure no mortalities during the first 30 days or 1st year after surgery.

Outcomes of Empirical Studies of Palliative Care Involvement in VAD Patient Care

Despite the numerous calls for PC involvement in VAD patient care, and even the requirements for such involvement from some regulatory agencies, there has been little empirical data to assess the impact of PC consultation on VAD patient outcomes. Based on our extensive literature review, we were able to identify only six such studies (Table 5.3). In the paragraphs that follow, we will review each of these studies.

MacIver and Ross reported on 22 patients who had a VAD placed at Toronto General Hospital between 2001 and 2004 [25]. Seven patients died following withdrawal of the VAD with the average time from implantation to withdrawal being only 7 days. In four out of the seven cases, the patient's family initiated the withdrawal discussion. Although the authors concluded, "Establishing a process for device withdrawal has been a key factor in the success of our VAD program," [25] it is difficult to weigh these outcomes since there was no control group.

Brush et al. reported on the outcomes of 69 patients who received 92 VADs at the Intermountain Medical Center in Salt Lake City between 1999 and 2009 [10]. In their specific assessment of patients who participated in EOL decision making, they found that only 20 patients actively participated in decisions at the EOL and of these,

Table 5.3 Empirical data of palliative care specialist involvement in VAD patients

Reference and reference Number	Years of study	Number of patients	Outcomes	Type of study and quality of evidence
Brush et al. [10]	1999–2009	69	20/69 patients actively participated in EOL decisions 11/20 died at home 17/20 decided to deactivate Only 3/49 who did not participate in end of life decisions died at home	Retrospective observational study; low quality evidence
McIver et al. [25]	2001–2004	22	Average time from implantation to withdrawal was 7 days 4/7 cases family initiated withdrawal discussion	Retrospective observational study; low quality evidence
McGonigal [26]	Unknown but prior to 2013	11	4 patients with PC involvement – with PC called 2 days prior to death, 4 days prior to death ×2, and 28 days prior to death	Retrospective observational study; low quality evidence
Kitko et al. [27]	Unknown but prior to 2016	15	Longitudinal interviews showed QOL assessment discrepancy between 3 distinct phases: (1) life saving procedure accepted, (2) postimplant QOL not what expected, (3) final phase of what next	Observational study; low quality evidence
Dunlay et al. [28]	2007–2014	89	46% patients saw PC within 1 month of death Of patients enrolled in hospice, 12/13 died at home	Retrospective observational study; low quality evidence
Nakagawa et al. [29]	2014–2016	112	Family awareness of unacceptable health states increased VAD deactivations 70.5% VAD patients identified what was an unacceptable health state 58% of family members could identify what was an unacceptable health state 42% participated in EOL deactivation Of the 42% of family who could not identify what was an unacceptable health state, none participated in EOL deactivation	Retrospective observational study; low quality evidence

17 elected to deactivate the device. Patient participation in EOL care had a significant impact on where the patients died. Eleven of the 20 who participated in EOL decisions died at home, whereas only 3 of the 49 VADs patients not participating in EOL care died at home [10]. Certainly, these groups are quite different in that the sickest patients

were least likely to be able to participate in EOL decisions, yet the value of such participation in allowing patients the opportunity to die at home may be of significant value. In this study, all patients had PC involvement in their management.

In a small retrospective study, McGonigal reviewed the medical records of all inpatient VAD deaths at a single institution over a 12 month period prior to 2013 and identified 11 VAD patients [26]. Only four patients had PC involvement in their management at any time during their hospital stay – two as bridge to transplant and two as destination therapy. The overall length of stay was 53.6 days for VAD patients and among the four who had PC involvement, one had PC consultation 2 days prior to death, two patients had PC consultation 4 days prior to death and one patient had PC consultation 28 days prior to death [26]. The article does not specify the reason for PC consultation. However, in 8 of 11 cases, a DNR order was written on the day the patient died, and "comfort care" orders were used in 50%. There was no comparison of the outcomes of this group of patients with the remaining seven patients who did not have PC consultation, but given the late involvement of PC, it is unlikely that a measurable difference would have been detected. Despite the very small numbers, the author concluded that more consistent PC involvement earlier in the care of VAD patients might have improved EOL decision making.

Kitko et al. reported on a longitudinal study of 15 VAD patients before and after implantation who were followed from the pre-implantation visit for 2 years or until death [27]. These investigators found three central themes in the VAD patients. First, in the pre-implantation phase, patients felt that they had "no choice" but to accept the device since they were not ready to die. Second, after receiving a VAD, the central theme was, "I thought I would be doing better" suggesting that the QOL was not what they had anticipated. Third, VAD patients reported, "I feel good, but now what?" suggesting a concern for the future and long term outcomes [27]. It should be noted with respect to the third theme above, that 10 of the 15 subjects had received a VAD as a bridge to transplant and this may have added to their concern for whether they would receive a heart transplant. Although this study did not specifically explore the role of PC consultation in VAD patients, the authors nevertheless suggested that unrealistic expectations of outcomes was an argument in favor of PC specialist involvement in patient care preimplantation [27].

Dunlay et al. explored the deaths of all patients receiving a VAD as DT at the Mayo Clinic in Rochester from 2007 to 2014 [28]. A total of 89 patients' deaths were examined in a retrospective chart review. The median time to death was 14 months. 46% of patients saw had a PC consultation within 1 month of death. Only 15% of patients were actually enrolled in hospice at the time of death and these patients did so a median of 11 days before death. A total of 49 patients had the VAD deactivated before death with most of these patients dying within 1 h of deactivation and all dying within 26 h [28]. Of the 13 patients enrolled in hospice, 12 died in an outpatient setting. The authors concluded that the high rate of death in an outpatient setting was a strong argument in favor of greater involvement of PC specialists in VAD patient care [28]. Prior studies have shown that patients dying in the hospital and their caregivers have a lower quality of life and suffer greater emotional distress at EOL than patients who die at home with hospice involvement [30].

Nakagawa et al. explored the impact of PC consultations before VAD implantation at Columbia University Medical Center between 2014 and 2016 [29]. This study assessed 112 patients all of whom had PC consultation prior to VAD placement. The authors focused on whether VAD patients could identify an unacceptable health state (70.5% answered "yes") and whether their loved ones were aware of the unacceptable health state (58% aware). There was a striking difference between those VAD patients whose families were aware of their unacceptable health states having 42% VAD deactivations at EOL compared to no VAD deactivations in the family-not-aware group [29]. The authors concluded that PC consultations prior to VAD implantation were feasible and that increasing the family members' awareness of the patients' unacceptable health conditions could result in greater VAD patient involvement in EOL decision making as evidenced by greater numbers of device deactivations [29].

Recommendations Based on the Data

As seen above, there are few studies that actually explore PC consultation in VAD patient care. All of the studies provide low quality evidence primarily due to the small numbers, retrospective, single institution design, and lack of a control group. Furthermore, the involvement of PC specialists is assumed to be a positive thing so there is little data to actually explore whether this is the case. The strongest evidence of the value of PC involvement are the two studies (Brush et al. and Dunlay et al.) which showed that enrollment in hospice shifted more patients to die in outpatient settings [10, 28]. If one accepts the evidence from the oncology literature that there is a benefit to patients and their caregivers for patients to die outside of the hospital compared to in the hospital [30], then one must conclude that PC involvement and the potential for greater hospice enrollment prior to death would be a good thing. The opportunity to study the involvement of PC consultants in VAD patient outcomes has likely passed as there are now Joint Commission requirements for PC involvement in such patients' care.

Personal View of the Data

Although there is no high quality evidence to prove the value of PC consultations in VAD patient outcomes, one can hardly imagine a negative effect of such involvement. Without a doubt, VAD patients and their families are faced with challenging questions about goals of care and wishes with respect to EOL, and as such, it seems obvious that involving caregivers whose specialty requires focusing on such items would be beneficial. Certainly, encouraging all members of the mechanical circulatory support teams to engage in frank discussions with patients about their goals of care and unacceptable health states is valuable, but it may be asking too much for

the experience and expertise in such conversations to be immediately achieved by all caregivers. For this reason, specific involvement of palliative care specialists in heart care teams seems to be an important step. It remains to be seen how many institutions have the palliative care capacity and expertise to provide such consultations to all pre-VAD patients. Yet, it seems clear that the development of institutional expertise in managing VAD patients should be viewed in a comprehensive fashion that includes not only cardiology, cardiac surgery, and critical care expertise, but also the expertise of palliative care consultants to participate in the care of such complex patients.

Recommendations

1. Recommend that a Palliative Care consultant be part of the VAD multidisciplinary team (Quality of evidence: low; Recommendation: strong)
2. Recommend that the Palliative Care specialist participate in preimplant preparation, quality of life evaluation after implant, and end of life decisions (Quality of evidence: low; Recommendation: moderate)

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Chapter 6
Communication Surrounding Prognostication in the ICU: More Than Mere Talk?

Darren S. Bryan and Selwyn O. Rogers Jr

Introduction

Quality end of life care requires a thoughtful analysis of patient and family values, with subsequent incorporation into the medical decision making process. This can represent a unique and significant challenge. Since the patients' rights movement of the 1960s, there has been a progressive shift away from medical paternalism, with emphasis placed instead on the concept of patient autonomy [1]. Furthermore, there has been acknowledgment of the potential pitfalls and lack of guidance that accompany an "independent choice" model of medical decision making, in which the patient is provided with unbiased information by the clinician in order to make a decision [2]. Instead, Western medical culture has placed value on a more involved, participatory patient-physician relationships that respects patient agency and autonomy, the individual's right to make informed decisions regarding their care, as well as embracing a broader definition of "health" [3, 4]. The necessity of shared decision-making is magnified at the end of life. However, physiologic disturbances often prevent direct physician-patient communication so this important information cannot be directly gleaned through conversation. In such cases, surrogates acting on the patient's behalf are faced with extraordinarily difficult decisions. Often times, this requires the suspension of their own personally held value and belief system, and instead necessitates an individual to act on the principle of substituted judgment, making choices on the patient's behalf [5]. While keeping this in mind, the appointed decision maker must act based largely upon information provided by the medical care team.

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To make care decisions at the end of life that are commensurate with values, patients and surrogate decision makers look to providers for information on *what will happen*. While some scenarios encountered in care are now quite medically predictable, emotionally substantive questions frequently asked in the ICU—*Will he make it out of the hospital? If she lives, will she be able to enjoy life? What is she experiencing?*—cut to the core of care and doctoring, and are often met with great uncertainty and poorly communicated [6].

The physician's duty is to know their patient. It is important to be able to provide prognostic information in an ICU setting, often times without directly communicating with the patient, framed in a manner that facilitates decision-making. Furthermore, the provider must walk alongside the recipient(s) of information while arriving at a decision. Here, we review data surrounding the provision of prognostic information to patients or their surrogate decision makers in the ICU and attempt to make evidence-based recommendations on the various methods that may be employed in such communications.

Search Strategy

We utilized the PubMed database to conduct a literature review. We searched for publications indexed with MeSH terms and subheadings falling under: "prognosis" and "intensive care". Results were limited to English language human clinical trials published in the last 10 years. The search resulted in the identification of 573 articles, which were hand screened for relevancy. Studies focusing on communication of prognostic information with measurable outcomes were included. Study references were examined and cross-checked for relevant articles not identified using the initial search criteria. We critically reviewed nine studies related to the delivery, perception, and interpretation of prognostic information by caregivers and surrogates. Focusing on measurable outcomes, we narrowed our results to seven publications. Within the existing literature, there exists a significant heterogeneity of outcome measures. Therefore, we broadly considered literature concerning patient-reported perceptions and metrics of quality relating to physician prognoses. The GRADE system was used to evaluate strength of evidence and quality of data (Table 6.1).

Table 6.1 PICO table of prognostication in the intensive care unit

Patient	Intervention	Comparison	Outcome
Adult patients and surrogate decision makers in intensive care settings	Data driven delivery of prognostic information	Current standard of care	Patient and surrogate perception of prognostic information

Results

When considering end-of-life care and the accompanying decision making, the failure of modern medicine to accurately predict patient outcomes is well recognized. In a multi-institutional study that conducted structured interviews with surrogate decision makers for patients who were critically ill, investigators found that 64% of surrogates doubted the accuracy of physicians' diagnoses surrounding medical futility [7]. Perhaps more stirring was the finding that even with a survival estimate of less than 1%, 32% of surrogates elected to continue life support, and 18% elected continuity of treatment even when physicians stated that no possibility for life existed [7]. While the complexities surrounding the diagnosis and determination of "medical futility" are outside the scope of this chapter, Zier and colleagues demonstrated that a measurable portion of the population espouses a baseline belief in biologic existence above all else. Conversely, some individuals elect for stringently minimalistic courses of care, forgoing all but the most basic and non-invasive of treatments. The majority of patients, however, lie somewhere in between, and rely on effectively communicated prognostication to make decisions. Several themes emerge in the literature; provider-patient or provider-surrogate expectation discordance, and the framing of prognostic information. These offer points for improvement and emphasis, and are explored in depth below.

Discordance in Expectations

When amassing relevant medical information, studies have shown patients and their surrogate decision makers naturally construct their own prognoses, rarely based solely on information provided by providers [8]. Ideally, these self-prognoses are adjusted upwards or downwards based on physician-provided information to help complete a full picture and guide decision-making. However, difficulty often arises when decision-maker and physician prognoses differ significantly. The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments *(SUPPORT)* trial observed ICU patients and their surrogate decision makers' interactions with physicians during hospitalization for life-threatening illnesses. The authors demonstrated a substantial communication deficiency between physicians and their patients, with less than 50% of providers being aware of a patient's preference to avoid cardiopulmonary resuscitation [9]. In a separate multi-institutional survey-based cohort study of surrogates and physicians, Chiarchiaro found a 63.5% prevalence of discordance (defined as greater than 20% difference) in survival estimation between involved parties [10]. Surrogates were further asked to rate the quality of prognostic information. The authors found no significant relationship between the perceived quality of provider-supplied prognostic information and the

presence of discordance, indicating that simple provision of information may not be sufficient for true internalization and understanding. In another study, White and colleagues conducted semi-structured interviews with surrogate decision makers and providers [11]. They demonstrated a 53% prevalence of prognostic discordance; 80% of which were surrogates with overly optimistic views. Common themes backing surrogate optimism included religious beliefs, a belief in patient's strengths unknown to the physician, and a belief that remaining consciously optimistic would improve outcomes (termed performative optimism).

These studies suggest that discordance is a real and frequently occurring phenomenon. Secondly, it is important that the provider understand the source of the discordance. Chiarchiaro et al. advocate for a "teach-back" method following prognostic conversations, in which the provider asks the surrogate to repeat the recently discussed information. Other groups have also examined the teach-back method [12, 13]. While it risks causing emotional stress, it has been recognized as a useful tool. Drawing on the conclusions of White, a useful follow-up to the teach-back method would be to elicit the basis of the surrogate expectation [12]. If discordance exists, knowledge of the cause (i.e. heavily weighted on religious beliefs or a performative optimism versus a simple misunderstanding of medical information) can help to drive further conversation.

Framing Prognostic Information

Aside from the nature of the prognostic information being delivered, the manner in which it is communicated has been hypothesized to significantly influence the patient's and surrogate's perceptions and subsequent development of the "self-prognosis". The search criteria identified two randomized trials that examine framing and communication of risk between providers and surrogate decision makers [14, 15]. Chapman randomized surrogate decision makers to one of two questionnaires with associated fictional clinical scenarios, differing in the method in which risk was communicated: frequencies (one in five chance of dying) or percentages (20% risk of death). Questionnaires asked surrogates to associate the level of communicated risk on a qualitative 4 point Likert scale, as well as a numeric 1–10 scale. The authors found that surrogates associated frequency-based risk communication with a higher risk. Qualitative statements such as "high chance of death" led to a wide degree of variability in interpreted risk, leading to the recommendation that such statements, when possible, should be avoided [15]. A similar study performed by Lee Char and colleagues randomized surrogates to viewing one of two fictional video scenarios, in which information was communicated in qualitative or quantitative terms ("very unlikely to survive" vs. "10% chance of survival"). They found no significant difference ($p = 0.21$) in risk interpretation between subjects receiving qualitative information (mean estimate of survival 26%) and quantitative information (mean estimate of survival 22%) [14].

A study published in 2005 surveyed surrogate decision makers for patients in the ICU, focusing on the timing of communication of prognostic information.

They found that early communication in a hospitalization was associated with increased satisfaction [16]. Perhaps unsurprisingly, longer hospitalizations were associated with decreased frequency of communication between providers and surrogates. Surrogates reported an associated decrease in satisfaction as communication frequency fell, leading to the conclusion that providers should continue, throughout a hospitalization, to actively evaluate the necessity of ongoing discussions regarding patient prognosis and goals of care. Additionally, when possible, providers should strive for early prognostic conversations.

Patients, surrogate decision makers, and providers may have different views as to the best way in which prognostic information is communicated. In one qualitative study that conducted semi-structured interviews, physicians were found to prefer communication utilizing non-numerical information [17]. Patients and surrogates, however, valued numerical estimations of risk, finding it helpful in decision-making. While differences in beliefs existed, all parties surveyed agreed on the importance of iterative and evolving discussions throughout the course of care.

While these studies indicate there may be advantages associated with particular methods of communication, the wide array of variables involved in end of life care makes blanket recommendations difficult. Rather, these studies underscore the importance of phrasing and should be taken collectively as an avocation for clinicians who employ a variety of communication tools when discussing risk (Table 6.2).

Recommendations

The body of literature surrounding prognostic communication is small and has been conducted using a variety of modalities. Such data heterogeneity makes simple, clean, evidence-based recommendations difficult. However, on review of the available data, prognostic discordance and prognostic framing emerge as consistent themes. Based on the available data, we make a weak recommendation for utilization of a modified "teach-back" method when discussing prognoses with patients and surrogates, ideally minimizing discordance in expectations. We are unable to make an evidence-based recommendation as to the ideal framing of prognostic information (quantitative or qualitative, frequencies or percentages). While two randomized, controlled trials exist and have interesting findings that should guide future research, they were performed with hypothetical scenarios and were limited in size.

Summary of Recommendations

- Providers should strive to provide prognostic information early in a hospital course, evaluating patient and surrogate perceptions, and revisiting frequently if necessary (evidence quality low, moderate recommendation).
- We recommend that providers consider the use of a modified "teach back" method when discussing prognosis with patients and their surrogate decision makers (evidence quality low, moderate recommendation).

Table 6.2 Published studies meeting inclusion criteria

Author (year)	Methods	N	Outcome variable measured	Findings	Study design (quality of evidence)
LeClaire (2005) [16]	Surveys	70 surrogates	Frequency of communication with physicians Time to receiving prognosis Satisfaction with physician communication Shared decision making	Shorter time to prognostic interval associated with increased satisfaction with communication ($p = 0.06$) Inverse relationship between ICU length of stay and communication frequency Decreased overall satisfaction with communication as LOS increased	Prospective, multi-institution observational study (medium)
Boyd (2010) [8]	Semi-structured interviews	179 surrogates	Not applicable	Few surrogates based self prognosis solely on physician-provided information	Single-institution qualitative study (high)
Lee Char (2010) [14]	Randomized to method of prognostic presentation in hypothetical, recorded scenario	169 surrogates 83 received numeric prognosis 86 received qualitative prognosis	Personal estimation of prognosis Surrogate understanding of physician prognosis	Many surrogates do not view physician prognoses as accurate No difference between qualitative and quantitative communication of prognosis	Single institution, prospective, randomized trial (high)
Anderson (2015) [17]	Semi-structured interviews	118 stakeholders 47 surrogates 45 clinicians 26 health communication experts	Not applicable	Support for ICU guidelines Helping families to "see" prognosis Physician dislike of numeric prognostic information Non-physician stakeholders found value in numeric prognostic information Prognostic process should be iterative and evolving	Multi-institutional, qualitative study (high)

Chapman (2015) [15]	Randomized to method of prognostic presentation in hypothetical, written questionnaires	140 surrogates 70 prognoses in frequencies 70 prognoses in percentages	Perception of risk	Framing and word choice has impact on perception of risk Quantitative framing with frequencies as opposed to percentages (i.e. 1 in 5 vs. 20%) leads to higher perception of risk Qualitative communication of risk (i.e. "high risk of death") associated with highly variable surrogate interpretation	Single-institution, prospective, randomized trial (high)
Chiarchiaro (2015) [10]	Surveys	546 surrogates 150 physicians	Quality of prognostic communication Surrogate and physician prognoses	Discordance in survival predictions is common (64%) Surrogate perception of quality of communication does not predict accurate expectations	Multi-institutional, cross sectional cohort (medium)
White (2016) [11]	Surveys and qualitative interviews	229 surrogates 99 physicians	Discordance about prognosis Misunderstandings by surrogates Differences in belief (surrogate actual estimate versus belief of physician estimate)	53% physician-surrogate prognosis discordance Surrogate prognosis more optimistic than physician prognosis due to: "need for optimism", "belief in unique strength of patient, unknown to physician", and religious beliefs	Multi-institutional, quantitative and qualitative (high)

A Personal View

While limited, the body of literature surrounding prognostic communication has grown over recent years. Additional research and inquiry into the way physicians, patients, and surrogates communicate is of vital importance and requires a variety of methodologies, including sound qualitative approaches. In the care of the critically ill patient, given the importance of individual values which guide goals of care at the end of life, providers must establish a relationship with those for whom they provide care. When unable to do so, physicians must get to know their patients' surrogate decision makers. As Sur advocates, we recommend early, honest, open, and frequent communication in the ICU between all involved parties as a means to bridge the communication chasm [18]. Further research on improving communications in the critical care setting is vital to ensure the best care for the diverse patients that we serve.

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Part II
Resuscitation

Chapter 7
Defibrillation/Pacing First for Witnessed Cardiac Arrest in Post-cardiac Surgery Patients

Lu Wang and Joel Dunning

Introduction

Every year, over 699,000 patients in USA and 250,000 in Europe undergo cardiac surgery. Among them, 0.7–2.9% would experience cardiac arrest post-operatively [1]. How to appropriately resuscitate these patients according to the best evidence available is critical, as they have relatively favourable outcome with 54–79% of them surviving to hospital discharge [2]. One of the questions which was often debated in the last few decades is whether defibrillation/pacing should be given first prior to external cardiac massage for cardiac arrest in patients who arrest after cardiac surgery. According to the advanced cardiovascular life support (ACLS) protocol, immediate external cardiac massage should be given first [3]. However, post-cardiac surgery cardiac arrest has many unique features which distinguishes it from other cardiac arrests. For example, it happens in a highly monitored environment with readily available personnel and resources, thus it is usually identified immediately. Moreover, its common causes, such as tamponade, tension pneumothorax, and hypovolaemia, can all be treated with emergency resternotomy. These unique features warrant an evidence based recommendation of deviations from ACLS protocol.

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Search Strategy

A literature search of papers published in English language from 2000 to 2017 was performed to identify the published best evidence on defibrillation/pacing first for witnessed cardiac arrest in post-cardiac surgery using the PICO outlined (Table 7.1). The databases searched were PubMed, Embase, and Cochrane Evidence Based Medicine. Terms used in the search included "defibrillation OR pacing", "cardiac surgery OR cardiac procedure OR heart surgery OR heart procedure", "resuscitation OR CPR", "external cardiac massage", "chest compression", and "cardiac arrest". In total, 1785 papers were found, among which 9 research study papers and 4 systematic review and meta-analysis papers are most pertinent to this question. These papers were classified using the GRADE system (Tables 7.2 and 7.3).

Results

There are no studies in the literature designed to directly compare immediate defibrillation and external cardiac massage prior to defibrillation in the patients who had witnessed cardiac arrest post-cardiac surgery. Therefore, we have extrapolated our finding on the outcomes of patients who arrest in general to the cardiac surgical population. We considered two issues, (1) the success of either methodology and, (2) harm that could be caused by a period of external cardiac massage.

The Effect of Defibrillation/Pacing and External Cardiac Massage

The recommendation of deferring external cardiac massage for immediate defibrillation in a cardiac arrest post-cardiac surgery was first made in the paper 'Guideline for Resuscitation in Cardiac Arrest after Cardiac Surgery' [1] published in 2009 and then incorporated into the European Resuscitation Council guideline for Resuscitation 2010 [17]. This recommendation was based on the systematic review by Lockowandt et al. [4], which examined 22 key papers. It is also supported by the 13 best evidence papers identified in the literature search.

Table 7.1 PICO table for defibrillation/pacing following cardiac arrest

P	I	C	O
Patients	Intervention	Comparator	Outcomes
Adult post-cardiac surgery patients who developed witnessed cardiac arrest in ICU	Defibrillation or pacing first, prior to external cardiac massage	External cardiac massage first	Survival to hospital discharge, return of spontaneous circulation

Table 7.2 Outcomes of in-hospital VF or VT cardiac arrest

Author (year)	Patient group	Outcomes	Key results	Comments	Study type	Quality of evidence
Lockowandt et al. (2008) [4]	22 papers reviewed	Recommendation	No evidence to support or refute external cardiac massage prior to defibrillation in-hospital if the response time is less than 4–5 min No in-hospital data to support very short periods of external massage prior to defibrillation and there have been examples of damage to the myocardium due to external massage		Systematic review	
Davis et al. (2016) [5]	2005–2013 106 pts 2005–2008 Group 1 – 31 pts Rx: 3 stacked defibrillation first 2008–2011 Group 2 – 33 pts Rx: 2 min of chest compression prior to and in between defibrillations 2011–2013 Group 3 – 42 pts Rx: 3 stacked defibrillation first	Survival to hospital discharge Return of spontaneous circulation	Group 1 58% (18/31) Group 2 18% (6/33) Group 3 71% (30/42) $P < 0.01$ Group 1 76% Group 2 56% Group 3 90% $P < 0.05$	Patients who had monitored VF or VT should undergo expeditious stacked defibrillation prior to chest compression	Retrospective observational study University of California San Diego Healthcare System, USA	Moderate

(continued)

Table 7.2 (continued)

Author (year)	Patient group	Outcomes	Key results	Comments	Study type	Quality of evidence
Mhyre et al. (2010) [6]	Jan 2000-Feb 2008 865 pts	Survival to hospital discharge	Periprocedural cardiac arrest Defib <2 min 62.1% Defib >2 min 31.6% P = 0.018 AOR 0.49 Intraoperative cardiac arrest Defib <2 min 39.6% Defib >2 min 46.8% P = 0.47 For patients with myocardial infarction during the current admission Defib <2 min 79.1% Defib >2 min 36.8% P = 0.001 AOR 0.16	Delayed defibrillation was associated with lower rates of survival for patients with periprocedural, but not intraoperative, cardiac arrest Among patients with myocardial infarction during the current admission, delayed defibrillation was independently associated with lower rates of survival	Prospective multicentre registry data 259 hospitals participating in the National Registry of Cardiopulmonary Resuscitation in USA	Moderate
Chan et al. (2008) [7]	Jan 2000-Jul 2005 6789 pts	Survival to hospital discharge according to time to defibrillation	≤1 min 39% (1577/3994) 2 min 38% (286/750) 3 min 34% (160/472) 4 min 23% (67/291) 5 min 25% (98/394) 6 min 19% (27/145) >6 min 14% (103/743)	Delayed defibrillation (defib >2 min) was associated with a significantly lower probability of surviving to hospital discharge (22.2% vs. 39.3% P < 0.001) There was a graded association between increasing time to defibrillation and lower rates of survival to hospital discharge for each minute of delay	Prospective multicentre registry data 369 hospitals participating in the National Registry of Cardiopulmonary Resuscitation in USA	High

Spearpoint et al. (2000) [8]	Apr 1997–Mar 1999 102 pts 81 pts Rx: defibrillation <2 min (15 pts defibrillation only) 21 pts Rx: defibrillation >2 min	Survival to hospital discharge Return of spontaneous circulation	Defib <2 min 48% (39/81) Defib >2 min 14% (3/21) P < 0.05 Defib only 80% (12/15) Defib <2 min 84% (68/81) Defib >2 min 52% (11/21) P < 0.05	Rapid defibrillation (defib <2 min) prior to any other resuscitation intervention enhanced a favourable outcome	Prospective cohort study Hammersmith Hospital, UK,	Moderate

Table 7.3 Outcomes of out of hospital cardiac arrest

Author (year)	Patient group	Outcomes	Key results	Comments	Study type	Quality of evidence
Jost et al. (2010) [9]	Sep 2005-Mar 2008 845 pts Rx: randomisation to 3 stacked defibrillation first or 1 min of external cardiac massage (ECM) first	Survival to hospital discharge Survival to hospital admission	Defib first 10.6% (45/424) ECM first (56/421) 13.3% P = 0.20 Defib first 42.7% (181/424) ECM first 43.2% (182/421) P = 0.87	No improvement in survival rates was seen with ECM first protocol compared to stacked defibrillation first protocol	Single-blinded randomised controlled trial Paris	Moderate
Baker et al. (2008) [10]	Jul 2005-Jul 2007 202 pts Rx: randomisation to defibrillation first or 3 min of ECM first	Survival to hospital discharge	Defib first 17.1% (18/105) ECM first 10.3% (10/97) P = 0.16 Subgroup analysis showed no difference in survival to hospital discharge from CPR before defibrillation to immediate defibrillation for cases with response time ≤5 min and >5 min	A tendency for reduced survival to hospital discharge in the 3 min ECM first group, irrespective of the response times, but this was not statistically significant	Randomised controlled trial South Australia	Moderate
Jacobs et al. (2005) [11]	Jun 2000-Jun 2002 Survival to hospital discharge Return of spontaneous circulation 256 pts Rx: randomisation to defibrillation first or 90 s of ECM first		Defib first 5.1% (7/137) ECM first group 4.2% (5/119) CI 0.25–2.64 Defib first 8.0% (11/137) ECM first 9.2% (11/119) CI 0.49–2.80	No improvement in outcome was detected in those patients who received 90 s of ECM prior to defibrillation compared to those who received defibrillation first	Randomised controlled trial Perth, Western Australia	Moderate

Wik et al. (2003) [12]	Jun 1998–May 2001 200 pts Rx: randomisation to defibrillation first or 3 min ECM first	Survival to hospital discharge Return of spontaneous circulation 1-year survival	Defib first 15% (14/96) ECM first 22% (23/104) P = 0.17 Defib first 46% (44/96) ECM first 56% (58/104) P = 0.16 Defib first 15% (14/96) ECM first 20% (21/104) P = 0.30 Subgroup analysis showed that ECM first improved outcomes for cases with response time > 5 min P < 0.05 for all three outcomes	Compared with immediate defibrillation, ECM first prior to defibrillation offered no advantage in improving outcomes for patients who had out-of-hospital VF cardiac arrest However, ECM first did improve outcome for patients with ambulance response time >5 min	Randomised controlled trial Oslo, Norway	Moderate
Freese et al. (2013) [13]	May 2006-Jun 2009 987 pts Rx: randomisation to defibrillation first or selective treatment with 2 min ECM first	Survival to hospital discharge Return of spontaneous circulation	Defib first 17.2 (86/500) Selective treatment 15.6% (76/487) P = 0.55 Defib first 41.2% (206/500) Selective treatment 42.3% (206/487) P = 0.70	Although this RCT did not compare the outcomes of ECM and immediate defibrillation directly, 53.8% (262/487) of the patients in the selective treatment group received 2 min ECM before defibrillation Waveform analysis to guide the initial treatment of out-of-hospital VF cardiac arrest did not improve overall survival outcome	Multicentre, double-blind, randomised controlled trial London, UK, and New York City, USA	Moderate

(continued)

Table 7.3 (continued)

Author (year)	Patient group	Outcomes	Key results	Comments	Study type	Quality of evidence
Huang et al. (2014) [14]	4 RCTs reviewed 3090 pts	Survival to hospital discharge Return of spontaneous circulation, neurological outcomes at hospital discharge, and survival at 1 year	Defib first 11.54% ECM first 11.88% CI 0.54–2.20 No significant difference was found between treatment groups	No adverse effects were associated with either treatment It was inconclusive that external cardiac massage should be the initial therapy for patients with out-of-hospital cardiac arrest	Systematic review and meta-analysis of randomised controlled trials	Moderate
Meier et al. (2010) [15]	4 RCTs reviewed 1503 pts	Survival to hospital discharge Return of spontaneous circulation	Defib first 11.4% (7.1–16.6%) ECM first 12% (6.4–19.2%) P = 0.686 Defib first 37.3% (17–60.2%) ECM first 39.2% (19.8–60.5%) P = 0.979	ECM first does not improve the outcome of patients in out-of-hospital cardiac arrest	Meta-analysis of randomised controlled trials	Moderate
Simpson et al. (2010) [16]	3 RCTs reviewed 658 pts	Survival to hospital discharge	Defib first 11.5% ECM first 11.9% CI 0.46–1.94 Subgroup analysis showed no difference in survival to hospital discharge from ECM first to defibrillation first for cases with response time ≤5 min and >5 min	Delaying initial defibrillation to allow ECM in out-of-hospital cardiac arrest due to VF demonstrated no benefit over immediate defibrillation for survival to hospital discharge irrespective of response time	Systematic review and meta-analysis of randomised controlled trials	Moderate

In-Hospital Cardiac Arrest

All of the four studies, that recruited patients who suffered from in-hospital ventricular fibrillation (VF)/ventricular tachycardia (VT) cardiac arrest, demonstrated the superiority of immediate defibrillation over external cardiac massage on the survival outcome (Table 7.2).

Davis et al. [5] reported the significant different outcome of three groups of patients received different resuscitation protocols over three periods of time in one Healthcare System. From 2005 to 2008, the first group of patients who had VF or VT cardiac arrest were resuscitated with three expedited stacked defibrillations first. Then from 2008 to 2011, the protocol was changed to 2 min of external cardiac massage first prior to defibrillation. However, the survival to hospital discharge of the second group of patients were only 18% compared to 58% of the first group. From 2011 to 2013, the resuscitation protocol was changed back to three expedited stacked defibrillation first with some other modifications. Consequently, the survival of the third group of patients were 71% ($P < 0.01$). The return of spontaneous circulation of these three groups of patients, 76%, 56%, and 90% respectively, demonstrated a similar trend ($P < 0.05$).

Mhyre et al. [6] found from the prospective multicentre registry data that, for in-hospital VF or VT cardiac arrest occurred in the periprocedural areas, delayed defibrillation (>2 min) was associated with lower rates of survival, 31.6%, compared to that of defibrillation <2 min, 62.1%, ($P = 0.018$, adjusted odds ratio (AOR) = 0.49). An even more significant difference in survival to hospital discharge was seen in the patients with pre-existing myocardial infarction during the current admission (36.9% vs. 79.1%, $P = 0.001$, AOR = 0.16). Interestingly, such a difference did not exist in the patients who had intraoperative cardiac arrest (46.8% vs. 39.6%, $P = 0.47$).

In another study based on the prospective multicentre registry data, Chan et al. [7] did not only demonstrate that delayed defibrillation (>2 min) was associated with a worse survival to hospital discharge for patients who had in-hospital VF or VT cardiac arrest (22.2% vs. 39.3%, $P < 0.001$), but also reported a graded inverse association between time to defibrillation and rate of survival to hospital discharge. The power of this study stemmed from the enrolment of 6789 patients across 369 hospitals over a 5-year period of time.

Similarly, Spearpoint et al. [8] analysed the data from 124 in-hospital VF cardiac arrest occurred in the Hammersmith hospital across a 2-year period and demonstrated the survival to hospital discharge, 14%, was significantly lower if defibrillation was delayed (>2 min), compared to that of early defibrillation (<2 min), 48% ($P < 0.05$). In this study, 15 patients received defibrillation only without any external cardiac massage and 80% of them survived to hospital discharge.

Out-of-Hospital Cardiac Arrest

While the in-hospital cardiac arrest data emphasised the importance of immediate defibrillation on survival outcome, the out-of-hospital cardiac arrest data, including five randomised controlled studies directly comparing immediate defibrillation

against external cardiac massage first prior to defibrillation and three meta-analysis papers pooling the data from these five studies, consistently proved that external cardiac massage does not improve survival outcome (Table 7.3).

Jost et al. [9] randomised 845 patients who had out-of-hospital cardiac arrest requiring defibrillation to receive either 1 min of external cardiac massage prior to defibrillation or three stacked defibrillation first. The survival to hospital discharge was 13.3% for external cardiac massage first group and 10.6% for defibrillation first group (P = 0.20).

Baker et al. [10] performed a randomised controlled trial where 202 patients who had out-of-hospital VF cardiac arrest were assigned to either 3 min of external cardiac massage prior to defibrillation or immediate defibrillation. 10.3% of the patients who received external cardiac massage first survived to hospital discharge, while that of the patients who received immediate defibrillation was 17.1%. However, this difference in survival was statistically insignificant (P = 0.16) as well. The subgroup analysis showed that, regardless of the response time being ≤5 min or >5 min, there was no difference in survival to discharge between these two groups of patients either.

Another trial performed by Jacobs et al. [11] randomly allocated 256 patients who had unwitnessed out-of-hospital VF or VT cardiac arrest to receive either 90 s of external cardiac massage prior to defibrillation or immediate defibrillation. Again, although the group of patients who received external cardiac massage first performed slightly worse, the difference in survival was not significant (4.2% vs. 5.1%, confidence interval (CI) 0.25–2.64).

Wik et al. [12] also compared the effect of 3 min of external cardiac massage and immediate defibrillation on the outcome of out-of-hospital VF cardiac arrest by randomising 200 patients into two groups. In this trial, external cardiac massage did not improve survival to hospital discharge either (22% vs. 15%, P = 0.17). However, the subgroup analysis showed that for patients with response time >5 min, the group received external cardiac massage first had better survival outcome.

In contrast to the four studies mentioned above, the randomised controlled trial conducted by Freese et al. [13] assigned 987 patients who had out-of-hospital VF cardiac arrest to receive either waveform analysis-guided treatment or immediate defibrillation. Among the 487 patients in the waveform analysis-guided treatment group, 262 patients had initial rhythms deemed to be unlikely to respond to immediate defibrillation and thus received 2 min of external cardiac massage prior to defibrillation. Despite of this modification in the study design, this trial did not show difference in survival outcome of the two treatment methods.

The three meta-analysis papers, written by Huang et al. [14], Meier et al. [15], and Simpson et al. [16] respectively, which pooled the data from 3 or 4 of the above-mentioned randomised controlled trials, arrived at the same result that, there was no evidence to support or refute the superiority of external cardiac massage over immediate defibrillation in resuscitating out-of-hospital cardiac arrest.

In a systematic review analysing data from 15 papers, Richardson et al. demonstrated that, for VF or VT cardiac arrest, the success rate of the first attempt of defibrillation was around 78%, that of the second attempt was around 35%, and that of the third attempt was 14% [18]. Hence, three consecutive defibrillation was

recommended for VF or VT cardiac arrest in patients post-cardiac surgery, if external cardiac massage would not be deferred for more than 1 min [1].

For cardiac arrest post-cardiac surgery, about 30–50% cases are due to VF or VT. The reminder cases have bradycardia, asystole or pulseless electrical activity, which are not amenable to defibrillation. Although there was no study in the literature comparing pacing and external cardiac massage, pacing is still a possible intervention if cardiac arrest is thought to be due to extreme bradyarrhythmia and functioning pacing wires are present. However, for cardiac arrest which are not amenable to defibrillation/pacing or pacing wires are not readily available, external cardiac massage should be commenced immediately to provide basic life support to patients arrested post-cardiac surgery [1].

The Harm of External Cardiac Massage

Although no cohort study or randomised controlled trial was found to investigate the complications caused by external cardiac massage in patients resuscitated post-cardiac surgery, it is well documented that external cardiac massage frequently causes cardiovascular, thoracic and even intra-abdominal injuries. For example, in the systematic review performed by Miller et al., data pooled from 27 relevant studies showed the incidence of rib fractures in cardiopulmonary resuscitation (CPR) treated patients was 31.2%, sternum fractures 15.1%, pericardial injury 8.9%, and haemopericardium 7.5% [19]. The incidence of complications was reported to be higher in the prospective forensic autopsy cohort study published by Rudinska et al. [20]. Patients post-cardiac surgery with newly closed sternotomy wound, recently anastomosed grafts and coronary arteries, and/or other potential bleeding points are only more susceptible to complications caused by external cardiac massage.

Recommendations

Witnessed cardiac arrest post-cardiac surgery is very different from out-of-hospital cardiac arrest and most in-hospital cardiac arrests that happen in unmonitored environments. Firstly, as post-cardiac patients' cardiac rhythm, blood pressure, central venous pressure (CVP), CO_2 trace, and O_2 saturation are constantly monitored, cardiac arrest is usually identified immediately once it starts, either by the healthcare professionals looking after them or because of the monitoring alarms. Secondly, in the highly monitored environment where post-cardiac surgery patients are placed, skilled and experienced healthcare professionals could be summoned and appropriate equipment could be gathered within a very short period of time for resuscitation. Moreover, as the cardiac rhythm is readily available on the monitor, the appropriate arm of the cardiac arrest protocol could be initiated without delay. Hence, if post-cardiac arrest is due to VF or VT, patients should be able to receive defibrillation within 1 min, which is associated with a better outcome as the in-hospital cardiac arrest data

suggest. If post cardiac arrest is due to asystole or severe bradycardia and patients still have pacing wire attached, pacing should be attempted first prior to provide external cardiac massage [1]. In addition, many cardiac arrests post-cardiac surgery are due to tamponade, tension pneumothorax or severe hypovolaemia, all of which could be treated with emergency resternotomy [21]. All the other causes of cardiac arrest should either be addressed during resuscitation or be identified and treated after emergency resternotomy [1]. Therefore, if defibrillation/pacing is inadequate to restore circulation, emergency resternotomy should be performed within 5 min [22].

Given the improved survival rate associated with immediate defibrillation suggested by the in-hospital cardiac arrest data, similar outcome of immediate defibrillation and external cardiac massage first protocol in the out-of-hospital cardiac arrest data, the potential complications of external cardiac massage, and the special conditions of post-cardiac surgery patients, we make a strong recommendation of providing defibrillation/pacing first for witnessed cardiac arrest in patients post-cardiac surgery.

A Personal View of the Data

There has not been a single study directly comparing defibrillation/pacing and external cardiac massage in the population of post-cardiac surgery patients. Hence, the impact of them on the survival outcome of in-hospital and out-of-hospital cardiac arrest were scrutinised instead. In summary, most evidence showed no difference in survival outcome between defibrillation and external cardiac massage for VF or pulseless VT out-of-hospital cardiac arrest, and all evidence support immediate defibrillation for in-hospital cardiac arrest. After cardiac surgery, external cardiac massage carries an even higher risk of potentially devastating complications and delays defibrillation/pacing which may immediately reverse the cardiac arrest. Therefore, I strongly recommend that three sequential shocks should be given without intervening external cardiac massage. This recommendation had been part of the European Association for Cardio-Thoracic Surgery (EACTS) guideline for resuscitation in cardiac arrest after cardiac surgery [1]. Subsequently, it was endorsed by the European Resuscitation Council in 2010 [17] and the Society of Thoracic Surgeons (STS) in 2017 [21].

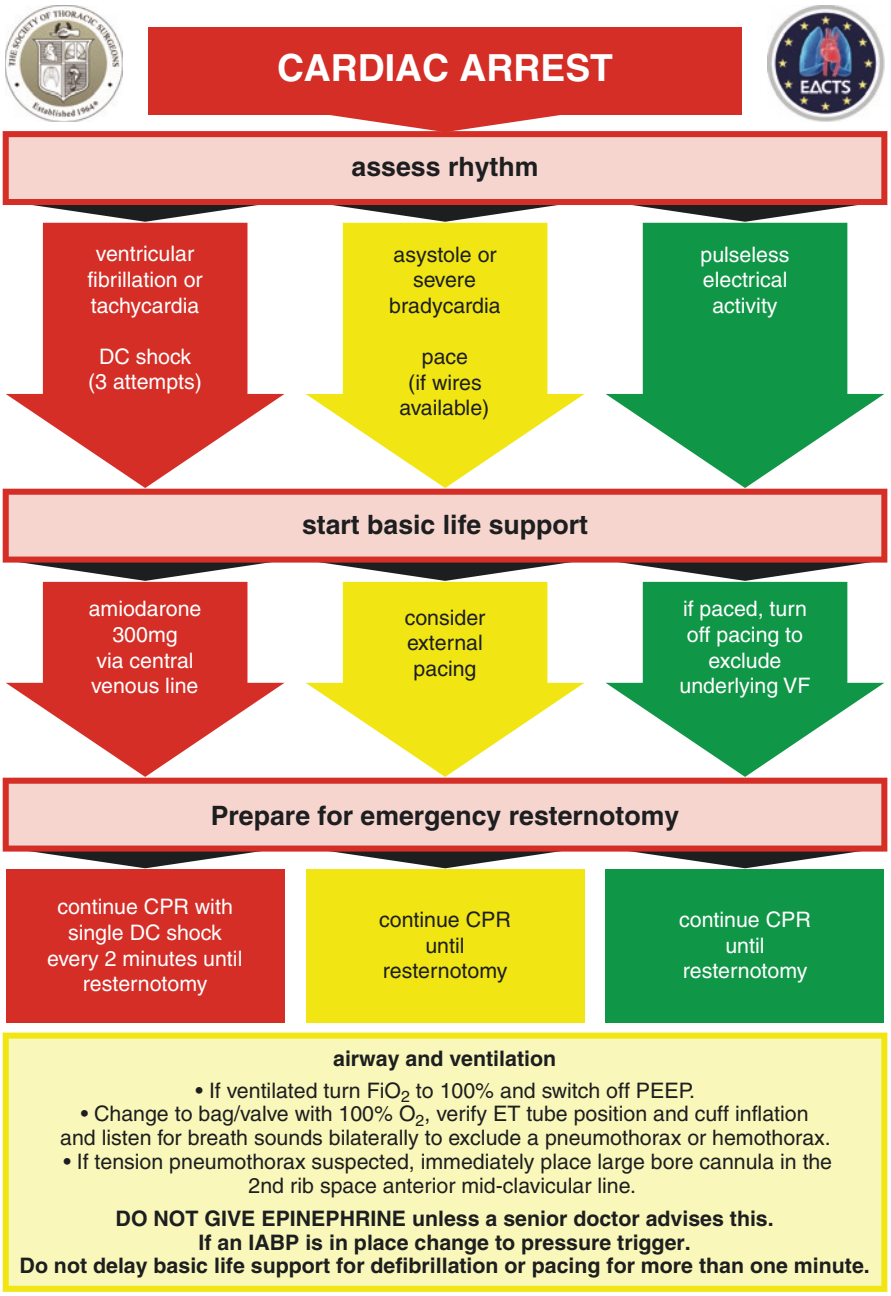
Recommendation

For post-cardiac surgery patients who developed VF or pulseless VT, immediate three sequential shock should be attempted without intervening external cardiac massage. (Moderate evidence quality, strong recommendation)

For post-cardiac surgery patients who developed cardiac arrest due to asystole or severe bradycardia and who have temporary pacing wire attached, pacing should be attempted immediately before external cardiac massage. (No evidence, strong recommendation)

Appendix

STS/EACTS Guidelines for the management of patients who arrest after cardiac surgery



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Chapter 8
Emergency Resternotomy in Post-operative Cardiac Surgery Patients Who Suffer Cardiac Arrest

Lu Wang and Joel Dunning

Introduction

Emergency resternotomy is an integral part of resuscitation after cardiac surgery, after all other reversible causes have been excluded. Once adequate airway and ventilation have been established, and if three attempts at cardioversion have failed in ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT), pacing failed in asystole and severe bradycardia, and external cardiac massage (ECM) failed in pulseless electrical activity (PEA), both the Society of Thoracic Surgeons (STS) and European Association for Cardiothoracic Surgery (EACTS) guidelines recommend that emergency resternotomy should be performed within 5 min from the onset of the cardiac arrest [1, 2]. The Hs (Hypovolaemia, Hypoxia, Hydrogen ion, Hyper-/hypokalaemia, and Hypothermia) and Ts (Tamponade, Tension pneumothorax, Thrombosis, and Toxins) have already been assessed, as they are incorporated into the resuscitation algorithm at the onset.

Resuscitation teams should be well rehearsed in the technique of emergency resternotomy, so that it can safely be performed within 5 min of the commencement of the arrest. Six key roles for resuscitation and two additional members for resternotomy have been identified as the essential components of a resuscitation team in the cardiac arrest situation after cardiac surgery [1] (Appendix 1). Resternotomy equipment should be prepared as soon as an arrest is identified. Simplification of the

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resternotomy tray (Appendix 2) and regular manikin rehearsals are key measures to ensure a prompt resternotomy [3]. All medical members of the patient care team should be trained to perform resternotomy, in case a surgeon is not available within the 5-min time frame.

In this chapter, we first performed a literature review to examine the scientific basis for the above-mentioned recommendations, and then went on to explore other alternative treatment strategies that could have been recommended in the available guidelines.

Search Strategy

A literature search of papers published in English language was performed to identify the published best evidence on emergency resternotomy for cardiac arrest in post-cardiac surgery patients using the PICO outlined (Table 8.1).

Medline was searched from January 1998 to January 2018 using the OVID SP interface: [exp Cardiopulmonary Resuscitation/OR heart arrest.mp. or exp. Heart Arrest/] AND [exp Thoracic surgery/OR cardiac surgery.mp]. Embase was searched from January 1998 to January 2018 using the OVID SP interface: [exp cardiopulmonary resuscitation/OR exp. resuscitation] AND [cardiac surgery.mp. or exp Heart Surgery/]. AHA EndNote Master library, Cochrane database for systematic reviews, Central Register of Controlled Trials, Review of references from articles were also hand searched.

All papers reviewed in this chapter report outcomes and/or interventions relating to patients who arrest after cardiac surgery, which include paediatric cardiac surgery, cardiac and lung transplant surgery by sternotomy, and cardiac surgery via incisions other than sternotomy. Patients must have undergone surgery on the same admission as the cardiac arrest. Studies pertaining to patients undergoing lung or oesophageal surgery, patients with left ventricular assist devices, and patients undergoing cardiac arrest in the operating room were not included. The relevant papers found were classified using the GRADE system (Table 8.2).

Table 8.1 PICO table for emergency resternotomy following cardiac arrest

P	I	C	O
Patients	Intervention	Comparator	Outcomes
Adult and paediatric patients undergoing cardiac surgery and suffering a cardiac arrest post-operatively	Emergency resternotomy	Alternative treatments, such as conservative treatment, and advanced life support resuscitation	Death, morbidity, or failure to resuscitate

Table 8.2 Key on emergency resternotomy for cardiac arrest in post-cardiac surgery patients

Author (year)	Patient group	Outcomes	Key results	Comments	Study type and quality of evidence
Pottle et al. (2002) [4]	4-year retrospective audit of 72 patients Dates: April 1995 – March 1999 Patient group: Patients undergoing open chest cardiac compression via resternotomy 38 adults and 34 children 66% within 48 h of surgery Two London centres: Brompton and Harefield	Causes of arrest	19 (26%) VF 15 (21%) asystole 26 (36%) EMD 12 (17%) bradycardia	They recommend resternotomy after 5 min of CPR	Retrospective cohort study Moderate
		Interventions during arrest, or causes of arrest	Relief of tamponade 13 Bleeding 10 Further surgery 3 Investigation of clot 4 Not stated or other 42		
		Arrest survival	33/72 (46%)		
		Out of hospital survival	12/72 (17%)		
		Resuscitation not in ICU	13/72 (18%) on ward No survivors		
		Incidence requiring CPR	72/2500: 2.9% resternotomy		
Lees et al. (2012) [5]	6-year prospective audit of 97 patients Dates: April 2005 – March 2011 Patient group: Post-operative adult patients who had cardiac arrest in the ward and were subsequently transferred to the operating rooms or ICU for resternotomySingle centre: Royal Papworth	Causes of arrest	26 (26.8%) VF/VT 71 (73.2%) non-VF/VT	The key factor of a favourable "scoop and run" outcome was whether the arrest occurred during daytime ($p < 0.05$) The "scoop and run" allows early institution of CPB, compared to the resternotomy at the scene of cardiac arrest	Prospective cohort study Moderate
		Interventions during arrest, or causes of arrest	21 (21.6%) resternotomy in ICU or operating room ("scoop and run") 15/21 (71.4%) "scoop and run" pts had institution of CPB 64 (66%) recovery of spontaneous circulation after initial resuscitation 12 (12.4%) death at the scene		
		Out of hospital survival	52 (53.6%) overall 5/21 (23.8%) pts requiring "scoop and run" (all 5 survivors had cardiac arrest during day time) 47/64 (73.4%) pts who survived initial resuscitation without requiring "scoop and run"		
		Longest time to resternotomy resulting in survival to discharge	14 days post-surgery		

(continued)

Table 8.2 (continued)

Author (year)	Patient group	Outcomes	Key results	Comments	Study type and quality of evidence
Mackay et al. (2002) [6]	6-year prospective audit of 79 patients Dates: April 1995 – March 2001 Patients group: Post-operative patients who required resternotomy after a cardiac arrest call from switchboard All adults, including transplant patients Single centre: Royal Papworth	Causes of arrest	22/79 (27%) VF 36/79 (46%) EMD 12/79 (15%) Asystole 9/79 (11%) other	39% survival if resternotomy within 24 h of operation 48% survival to discharge if resternotomy within 10 min of arrest There were no survivors of resternotomy on the ward	Prospective cohort study High
		Interventions during arrest, or causes of arrest	22/79 (28%) required bypass 16 bleeding 14 graft occlusion/avulsion 9 arrhythmias 29 poor cardiac output 2 dissection		
		Arrest survival	Not reported		
		Out of hospital survival	20/79 (25%)		
		Resuscitation not in ICU	21 on ward, one survivor and patient recovered output, went to ICU and arrested having the resternotomy there		
		Incidence requiring CPR	503/9600 (5.2%) arrest calls 79/9600 (0.8%) resternotomy		
		Longest time to resternotomy resulting in survival to discharge	23 patients had resternotomy >72 h from surgery, 1 survivor		

Birdi et al. (2000) [7]	4-year retrospective audit of 55 patients Dates: April 1995 – October 1998 Patient group: Adult patients requiring emergency reinstitution of cardiopulmonary bypass after sternal closure and return to ICU (crash-BOB) Not necessarily after cardiac arrest Single centre: Royal Papworth	Causes of crash-BOB	23 cardiac arrest 20 bleeding 7 hypotension 1 ischaemia 4 others	Calculated that crash-BOB cost £7170 per life saved Predictors of poor outcome were higher Parsonnet score of patient, identification of a surgical cause to arrest	Retrospective cohort study Moderate
		Crash-BOB survival	35/55 survived emergency bypass		
		Out of hospital survival	23/55 survived (42%)		
		Resuscitation not in ICU	14 pts were not in ICU 6 survived to discharge (42%)		
		Incidence requiring crash-BOB	55/6882 patients (0.8%)		
		Longest time to resternotomy resulting in survival to discharge	20 days was longest time that crash-BOB required		
Ngaage et al. (2009) [8]	A cohort of 108 patients Dates: April 1999 – June 2008 Patient group: Consecutive patients who arrested after CABG or AVR Single centre: Castle Hill	Causes of arrest	70% VF 17% asystole 13% PEA 53% MI 24% tamponade 5% CHB 6% Hypokalaemia 12% cause unknown	Factors associated with an adverse outcome were: MI, poor ejection fraction, age, and long CPB time	Cohort study Moderate
		Interventions during arrest, or causes of arrest	52% Resternotomy 16% CPB 6% re-grafting 45% IABP 2% VAD		
		Arrest survival	Only out of hospital quoted		
		Out of hospital survival	43 (50%) survival		
		Incidence requiring CPR	100%		

(continued)

Table 8.2 (continued)

Author (year)	Patient group	Outcomes	Key results	Comments	Study type and quality of evidence
Anthi et al. (1998) [9]	30-month audit of 29 patients who suffered an unexpected cardiac arrest Dates: Dec 1993 – Mar 1996 Patient group: Patients in the ICU suffering a cardiac arrest within 24 h of surgery Protocol CPR and if no restoration of output after 3–5 min then proceed to resternotomy Single Centre: Onassis Cardiac Surgery Centre, Athens	Causes of arrest	13/29 (45%) VF/VT 11/29 (38%) Brady arrhythmia 5/29 (17%) EMD	50% of arrests in the first 3 h after surgery	Prospective cohort study Moderate
		Interventions during arrest, or causes of arrest	14/29 (48%) MI 5/29 (17%) tamponade 3/29 (10%) graft malfunction 7/29 (24%) unknown		
		Arrest survival	13/13 (100%) with closed-chest CPR 14/16 (87.5%) with open-chest CPR		
		Out of hospital survival	23/29 (79%) survived to discharge		
		Resuscitation not in ICU	Excluded in this study		
		Incidence requiring CPR	29/3982 (0.7%) required CPR in the first 24 h		
		Longest time to resternotomy resulting in survival to discharge	Over 24 h excluded in this study		

Dimopoulou et al. (2001) [10]	3-year prospective audit of 29 patients Dates: December 1993 – March 1996 Patient group: Followed up the group also reported by Anthi et al. of patients who suffered an unexpected cardiac arrest within 24 h of their operation Follow up 4 years after discharge by interview Single Centre: Onassis Cardiac surgery centre Athens	Arrest survival	13/13 (100%) with closed-chest CPR 14/16 (87.5%) with open-chest CPR	Excluded patients returned to ICU unstable or bleeding	Prospective cohort study Moderate
		Survival to hospital discharge	23/29 (79%) survived to discharge from hospital		
		4 year survival	16/29 (55%) 4 year survival		
		Causes of death after hospital discharge in 7 patients	2 heart failure 1 lung cancer 1 arterial embolism 1 ruptured AAA 2 unknown		
		NYHA class at 4 years	12 (75%) class I 3 class II 1 class III		
		Living independently at home	16/16 (100%) living independently		
		Quality of life measures	10% had a job 90% could do housework 90% had social life 60% had a sex life 80% had hobbies 70% went on holidays		

(continued)

Table 8.2 (continued)

Author (year)	Patient group	Outcomes	Key results	Comments	Study type and quality of evidence
El-Banayosy et al. (1998) [11]	2-year retrospective audit of 113 patients Dates: Jan 1993–Dec1994 Patients group: All patients with circulatory collapse requiring CPR within 7 days of surgery Adults but transplants and paediatric patients excluded Single Centre: North Rhine heart Centre, Bad Oeynhausen, Germany. Protocol: After 20–30 min of CPR IABP performed. If unsuccessful and operation <48 h – resternotomy Unsuccessful and operation >48 h – Fem Fem Bypass	Causes of arrest	58/113 (51%) VF 22/113 (19.5%) EMD 6/113 (5.3%) asystole	Duration of CPR 2–230 min (mean 30 min) Significant predictors of adverse survival: CPR time, CK-MB rise, time from surgery	Retrospective cohort study Moderate
		Interventions during arrest, or causes of arrest	47 MI 9 bleeding 4 heart failure 5pts had Fem Fem bypass – all died 49/113 had IABP (24–49% survived) 24/113 had resternotomy (13 or 54% survived) 6 patients had a VAD (7 or 47% survived)		
		Out of hospital survival	79/113 (70%) survived to discharge		
		Resuscitation not in ICU	15 arrests outside ICU but 7 survived (47%)		
		Incidence requiring CPR	113/4988 (2.3%) required CPR		
		Longest time to resternotomy resulting in survival to discharge	18 arrests more than 48 h post-surgery (10 survived)		

Parra et al. (2000) [12]	2-year retrospective audit of 32 children Dates: June 1995 – June 1997 Patient group: All children who had cardiopulmonary arrest in the paediatric CICU 25 arrests post-surgery, 38 episodes of arrest (Age range 1 day to 21 years) Single Centre: Miami, USA	Causes of arrest	29% arrhythmia 31% hypotension 11% respiratory failure 8% metabolic 21% other	Success of resuscitation not related to use of adrenaline	Retrospective cohort study Moderate
		Interventions during arrest, or cause of arrest	4 required CPB		
		Arrest survival	24/38 episodes of arrest successful (63%)		
		Out of hospital survival	14/32 (43%)		
		Incidence requiring CPR	32/786 (4%) of admissions		
Kim et al. (2016) [13]	10-year retrospective study of 101 patients July 2003 – July 2013 Patient group: Patients underwent first time resternotomy post cardiac surgery Patients who arrested were included 61 patients had resternotomy in the theatre, and 40 in the ICU Single centre: Seoul National University Bundang Hospital	Causes of resternotomy	37/101 (36.6%) non-cardiac bleeding 34/101 (33.7%) cardiac bleeding 30/101 (29.7%) undetermined	3 patients with cardiac arrest died during the wait or transportation to the theatre for resternotomy	Retrospective cohort study Moderate
		Resternotomy survival (ICU vs. OR)	77.5% vs. 86.9% (p = 0.218)		
		Complications	Blood loss 1.9 vs. 1.7 (p = 0.668) Superficial wound dehiscence 12.5% vs. 4.9% (p = 0.168) Mediastinitis 2.5% vs. 4.9% (p = 0.542)		
		Incidence requiring resternotomy	101/2719 (3.7%)		

(continued)

Table 8.2 (continued)

Author (year)	Patient group	Outcomes	Key results	Comments	Study type and quality of evidence
Charalambos et al. (2006) [14]	9-year retrospective study of 240 patients Dates:1991–2000 Patient group: Patients who had chest resternotomy for bleeding or tamponade on the ICU Patients who arrested were excluded Majority reopened in the ICU rather than theatres Single centre: Manchester Royal Infirmary	Causes of resternotomy	20/240 (86%) bleeding 22/240 (9%) tamponade 11/240 (5%) both	95% within 24 h	Retrospective cohort study Moderate
		Causes of resternotomy	125/240 (55%) focal bleeding 74/240 (33%) diffuse bleeding 11/240 (5%) both 25/240 (12%) packed and not closed. 13/240 (10%) further resternotomy		
		Resternotomy survival	224/240 (84%) survival		
		Complications	7 sternal wound infections (2.9%)		
		Incidence requiring resternotomy	240/6890 patients (3.4%)		

Adam et al. (2009) [15]	A survey performed on CTSNET on a wide range of issues on the subject of cardiac arrests after cardiac surgery, not adequately answered by the current literature There were 349 respondents from surgeons from 53 countries	Incidence of cardiac arrest	Cardiac arrest 1.8% Emergency resternotomy 0.5% Emergency reinstitution of bypass 0.2% Survival to discharge 50%	It is unknown exactly who the respondents were, due to the anonymous nature of the survey Countries of origin were derived from the IP address of the computer that submitted the survey to CTSNET	Survey Very low
		Precordial thump	32% have witnessed success with this 21% have heard of success 14%would have a go 11% think this is potentially harmful		
		ECM or defibrillation first in VF arrest	66% advocate ECM 43% advocated immediate defibrillation		
		Adrenaline administration	9% would reserve this for after resternotomy or not at all 26% would give this after 3 failed shocks 13% would give this after 2 min or one shock 29% would give this after 1 failed shock or 1 min		
		Person performing resternotomy	34% say a surgeon only should do this 58% say a trained non surgeon could do this 8% said any non-surgeon could do this		
		Current guidelines	31% of respondents had not read current guidelines for resuscitation by the AHA/ERC 28% do not agree with these guidelines		
		No. of shocks prior to resternotomy	3 shocks was the median value		
		Time to resternotomy for non VF	5 min was the median time for resternotomy		

Modified from Table 1 in Dunning et al. [2]

Results

Emergency Resternotomy

Improved survival and better quality of life with rapid resternotomy in patients who suffer cardiac arrest following cardiac surgery is well documented in the literature in the recent two decades. For example, 72 patients who arrested at the Brompton and Harefield were analysed for predictive factors for poor outcome [4]. They found that there was a poorer outcome if the emergency resternotomy was performed in over 5 min.

In three papers published by the group from the Royal Papworth [5–7] they found that after a 6-year audit of practice, the survival was 48% if the emergency resternotomy was performed within 10 min but only 12% if it took longer than this. They also found a very poor outcome for patients who had emergency resternotomy on the ward and during night time, as well as in patients who arrest more than 24 h after their surgery.

Ngaage et al. [8] demonstrated that the main causes of cardiac arrest are tamponade, bleeding and post-operative myocardial infarction, supporting prompt resternotomy which allows internal cardiac massage (ICM). Their overall survival to hospital discharge in this group of patients is 50%, similar to that reported by the Royal Papworth team.

Anthi et al. [9] presented a protocol for emergency resternotomy within 3–5 min of the arrest after cardiac surgery. Seventy-nine percent patients survived to discharge. Forty-five percent of those having ECM survived, compared to 87.5% (14 of 16) of those who had ICM. They attributed this relatively high survival rate partially to the use of internal cardia massage following prompt resternotomy. The long term outcome and quality of life of this group of patients were reasonably good as well [10].

El-Banayosy et al. [11] found that in an audit of 113 patients who arrested within 7 days of surgery, length of CPR was an adverse predictor of survival. In addition, 50% of those who had a resternotomy survived compared to no patient who went straight to femoral bypass.

Parra et al. [12] reported an audit of 32 children arresting after cardiac surgery with a 63% survival. The causes of arrests were similar to that of adults.

Kim et al. [13] and Charalambos et al. [14] looked into the safety issue of resternotomy in the ICU environment. They found that the incidence of mediastinitis was only 2.5–5% after resternotomy in the ICU and other complications were not significantly higher compared to resternotomy in the operating theatre.

Adam et al. [15] performed a survey of 349 surgeons from 53 countries in 2009 to investigate their opinions and experiences on the issues around resuscitation prior to the EACTS guidelines publication [2]. There was broad support for early resternotomy and for skilled staff to be performing the emergency resternotomy.

Alternative Treatment Strategies

Subxiphoid Incision

At the STS Workforce for evidence based surgery consensus meeting in 2016, this alternative was discussed at considerable length to the extent that it appeared as a recommendation in some of the early drafts. However, the more it was considered, the more it was felt to be a potentially very dangerous manoeuvre with little, if any, benefit (Joel Dunning, personal communication on January 25, 2016).

Arguments in favour of a subxiphoid incision were as follows: it might potentially be possible to perform this before the five-piece set was available or in the situation where key equipment such as wire cutters were not available. This might avoid the need for a full sternotomy on the ICU or ward and if the heart is restarted it may allow transfer of the patient to an operating room to complete the sternotomy in a cleaner environment.

However, the arguments against this manoeuvre greatly outweighed any potential benefit stated above.

First of all, if the STS expert consensus is followed there should be a team gowned and gloved and ready with a five-piece resternotomy set to perform an emergency resternotomy [1] and thus a subxiphoid incision should not be necessary as a time saving procedure.

Moreover, a subxiphoid incision would still require gowning and gloving and a scalpel, sucker and potentially forceps and a sterile drape, so in fact it is only the wire cutter that is the additional piece of equipment required to perform the full sternotomy.

There are not many papers in the literature documenting this procedure, although many surgeons verbally state that they have tried it. I am aware of only one article submitted as a single case report and that patient required a subsequent sternotomy and also was not in arrest when the subxiphoid incision was performed [16].

The incidence of mediastinitis is only 5% after emergency resternotomy [13, 14, 17, 18] and thus the concerns over subsequent sepsis are far lower than the chance of survival from the arrest which is currently only around 50% [19].

Training was the most important issue against this manoeuvre, as it was not possible to come up with a guidance as to when a subxiphoid incision should be performed in preference to a sternotomy. In addition, there was a significant concern over being able to safely train inexperienced practitioners to blindly place a finger or sucker under the sternum without damage to a right sided vein graft or a distended right ventricle.

Also if catastrophic bleeding was the cause of the arrest rather than tamponade, it would not be possible to compress or occlude the area of bleeding with this manoeuvre, and removal of the blood would not restore a spontaneous circulation.

Finally, in simulation, it was found not to be a quicker manoeuvre but in fact was slower as the practitioner slowed down considerably due to their apprehension over the technique.

Nonetheless, in rare circumstances when it is not favourable to perform a resternotomy for any reason, for example, lack of experienced personnel or wire cutters, a subxiphoid incision should still be considered as a minimum to relieve a cardiac tamponade.

ECMO

Emergency resternotomy is strongly recommended in the STS expert consensus statement after initial resuscitative measures fail. There are, however, some situations in which extracorporeal membrane oxygenation (ECMO) is recommended [1]: a patient who has undergone a previous cardiac surgical operation by sternotomy and has then returned to have minimally invasive cardiac surgery. Examples would most commonly be redo mitral valve repair by port access or a right sided thoracotomy or mini-sternotomy for redo aortic valve replacement. As a sternotomy is not rapidly possible due to adhesions, the protocol would recommend resuscitative ECMO, i.e. extracorporeal cardiopulmonary resuscitation (eCPR), or peripheral cardiopulmonary bypass in this situation.

Furthermore, the slightly more controversial situation in which ECMO is allowed as an alternative to emergency resternotomy is in the situation when a hospital has an active programme for rapid initiation of ECMO. There was little support for this in the literature review in preference to emergency resternotomy. Thus, in the STS expert consensus statement, a recommendation was made that a team would still gown and glove in readiness for an emergency resternotomy [1]. However, if a skilled unit with access to emergency ECMO was available and could place a patient on ECMO within 10 min, then this would be acceptable [5]. However, it should be acknowledged that a severe tamponade could still potentially impede circulation, even of an ECMO circuit.

Conduct of the Emergency Resternotomy

The Consensus statement recommends the following protocol be adhered to [1]:

Two or three providers don a gown and gloves in a sterile fashion using the closed glove technique. ECM must continue until you are ready to apply the all-in-one sterile thoracic drape.

When ready, ask the person performing ECM to stand aside after removing the sternal dressing.

Apply preferably an all-in-one sterile drape (single, full-bed, sterile drape with an operative plastic window), or skin preparation followed by appropriate thoracic draping, ensuring the whole bed is covered by drapes.

Recommence ECM (changeover from non-sterile ECM to sterile ECM should take no more than 10 s).

When the equipment is ready, cease ECM and use the scalpel or scissors to cut the sternotomy incision, including all sutures deeply down to the sternal wires.

Cut all sternal wires with the wire cutters and pull them out with the heavy needle holder. The sternal edges will separate and a tamponade may be relieved at this point if present. This is significantly faster if one person cuts the wires with the wire cutter and a second assistant removes the wires with the heavy needle holder. Use sterile suction to clear excessive blood or clot. Place the retractor between the sternal edges and open the sternum. If cardiac output is restored, you have successfully treated the cardiac arrest and should wait for expert assistance.

If there is no cardiac output, carefully identify the position of any grafts and then perform two handed ICM and internal defibrillation as appropriate.

If the pericardium or mediastinal fat has been closed over the heart, the sutures used for this should be carefully and slowly cut to allow visualisation of the heart.

Recommendations

The main causes of cardiac arrest post-cardiac surgery include tamponade and uncontrolled bleeding. Both of them, as well as other causes such as graft failure and severe hypovolaemia, would not respond well to prolonged closed-chest resuscitation. Hence, delays to resternotomy should be minimised. Our literature review demonstrated the superior outcomes that can be obtained with emergency resternotomy and the safety of performing it even in the ICU environment.

Two alternative strategies to emergency resternotomy were also considered. Although subxiphoid incision can help relieve a cardiac tamponade, it does not provide access for exploration in cases when the cardiac arrest is caused by other reasons. In addition, it requires almost the same amount of the instrument as that of emergency sternotomy, apart from a wire cutter, and is not an easy procedure for a non-surgical team member to learn. Hence, it is not incorporated into the guideline. eCPR with ECMO, on the other hand, is a promising alternative [20]. However, as time is crucial for the success of cardia arrest resuscitation, eCPR should only be considered in a well-equipped unit with a skilled team that can put a patient on ECMO within 5 min. Therefore, for most of the cardiac arrest in post-cardiac surgery patients, emergency resternotomy is the only treatment option once initial resuscitation has been unsuccessful and all the easily reversible causes have been excluded.

In summary, although the resuscitation pathways differ slightly for different types of cardiac arrest, i.e. VF/VT should be treated with three attempts of defibrillation and amiodarone, asystole or severe bradycardia with pacing and atropine, and PEA with ECM, if patients fail to respond to these initial resuscitation strategies, emergency resternotomy should be carried out within 5 min. Both the STS expert consensus statement [1] and the EACTS guidelines [2] have endorsed this recommendation.

A Personal View of the Data

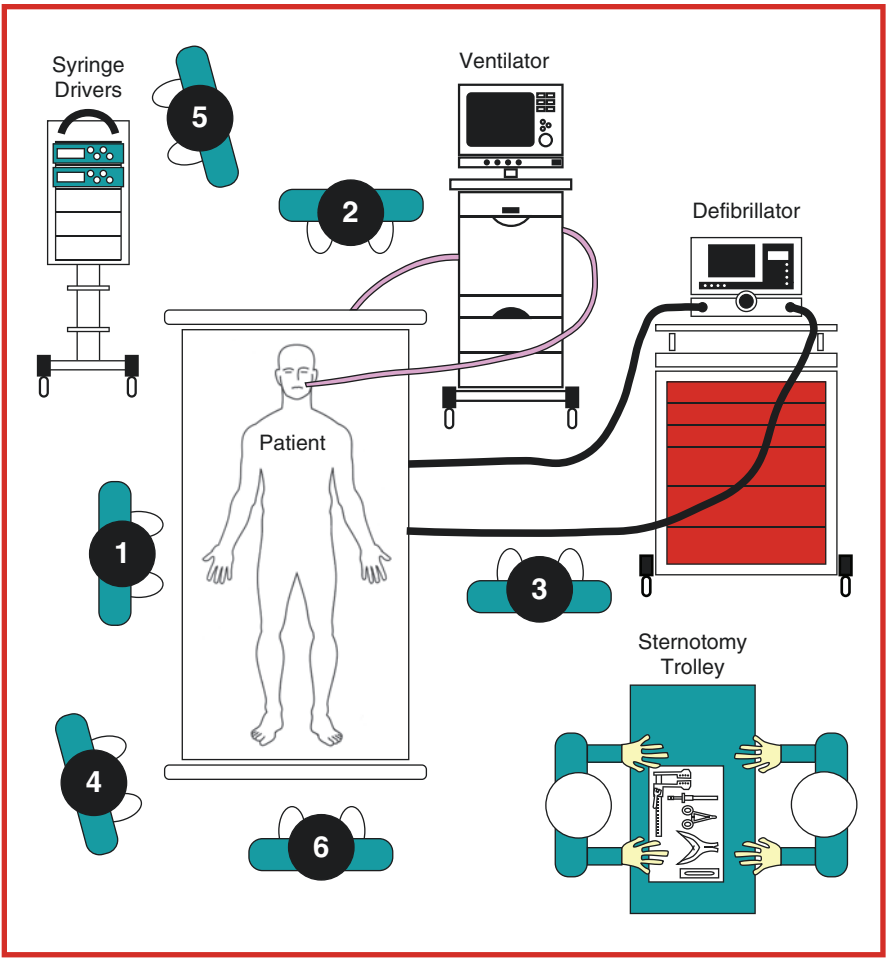
Emergency resternotomy is an integral part of an established protocol for resuscitation of patients who arrest after cardiac surgery. This protocol had been part of the European Association for Cardio-Thoracic Surgery (EACTS) guideline since 2009 [2]. Subsequently, it was endorsed by the European Resuscitation Council in 2010 [21] and the Society of Thoracic Surgeons (STS) in 2017 [1]. I believe that the majority of post-cardiac surgery patients who did not survive after cardiac arrest were due to causes rectifiable by prompt resternotomy. In order to perform an organised resuscitation including the preparation as well as the conduct of emergency resternotomy, it is essential to have a skilled team that is very familiar with the protocol and has rehearsed the process. There are now structured training programmes, the Cardiac Surgical Advanced Life Support Course, in place worldwide in order to implement this well accepted strategy [3]. (www.csu-als.com) Gratifyingly, there are cardiac surgery units that have reduced the post-operative mortality by more than half since they started to practice for cardiac arrest.

Recommendation
For post-cardiac surgery patients who suffered cardiac arrest, emergency resternotomy should be performed within 5 min, after initial resuscitation and exclusion of readily reversible causes. (Moderate evidence quality, strong recommendation)

Appendix 1

The Society of Thoracic Surgeons protocol for the organisation of the six key roles for resuscitation and two additional members for resternotomy in the cardiac arrest situation after cardiac surgery [2]

Six key roles in the cardiac arrest

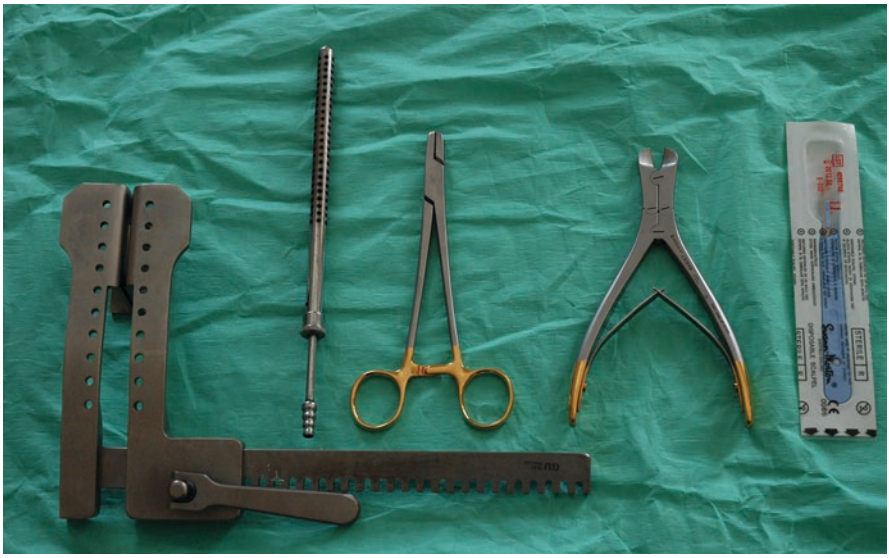


Six key roles in the cardiac arrest:

1. External cardiac massage
2. Airway and breathing
3. Defibrillation
4. Team leader
5. Drugs and syringe drivers
6. ICU co-ordinator

Appendix 2

A small resternotomy set packed with a scalpel on top (above) and opened (below) [2]



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Chapter 9
Epinephrine and Vasopressin Use Following Cardiac Arrest After Cardiac Surgery

Aymen Benkreira and Yoan Lamarche

Abbreviations

ACLS	Adult advanced cardiovascular life support
AHA	American Heart Association
AVR	Aortic valve replacement surgery
CA	Cardiac arrest
CABG	Coronary Aortic Bypass graft surgery
CACS	Cardiac arrest following cardiac surgery
CPP	Coronary perfusion pressure
ERC	European Resuscitation Council
IHCA	In hospital cardiac arrest
OHCA	Out of hospital cardiac arrest
PEA	Pulseless electrical activity
ROSC	Return of spontaneous circulation
VF	Ventricular fibrillation
VT	Ventricular tachycardia

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Introduction

For over a century [1], epinephrine has been used for resuscitation of cardiac arrest (CA). However, the vasoactive and inotropic pharmacologic components of resuscitative treatment are increasingly controversial for patients in general, and more specifically, after cardiac surgery. Initially, most studies supporting epinephrine administration were performed on animal models and benefits were expected to extend to humans. Beneficial effects were defined in both animal and human studies as the return of spontaneous circulation (ROSC) after CA. The American Heart Association (AHA) has taken a stance towards recommending standard cardiovascular life support (ACLS) resuscitation in their 2015 guidelines. However, they acknowledge that the supporting evidence for epinephrine use is conflictual in regards to the risk benefit ratio of epinephrine β effects which increase myocardial work and reduce subendocardial perfusion [2].

Nevertheless, they recommend that a standard 1 mg dose every 3–5 min may be reasonable for patients in CA. Administration is intended for either patient suffering from CA with shockable rhythm after two unsuccessful shock deliveries or patients presenting with asystole or pulseless electrical activity (PEA) [2].

At the start of the 1990s, it was suggested that vasopressin could have beneficial effects for patients having undergone CPR. This came to light after higher endogenous levels of vasopressin were found in the patients who survived CPR [1]. According to the 2015 AHA guidelines update, whether vasopressin was administered as a standalone drug or in combination with epinephrine, neither method offered a significant advantage over epinephrine alone in the adult ACLS and its use is thus not recommended [2]. Although this does not specifically refer to vasopressin use in post cardiac surgery settings, it is applied in the same manner.

In the 2010 and 2015 updated AHA guidelines, only minimal pharmacologic recommendations are made for settings other than OHCA, notably, for perioperative cardiac arrest after cardiac surgery (CACS) [3]. Despite concerns already existing on the safety and pertinence of epinephrine administration in OHCA, the AHA 2010 guidelines have insufficient evidence on epinephrine dose to recommend deviating from standard resuscitation guidelines [2]. The evidence used to establish a conclusion of relative benefit of this intervention for patients having undergone cardiac surgery was based on one study. Cipolotti et al. reported two cases in which CA was unresponsive to routine therapies and patients received 5–10 mg doses of epinephrine [4]. These patients were successfully resuscitated with sinus rhythms and neurologically intact hospital discharge. While the AHA guidelines do acknowledge elevated bleeding risks in CACS patients from the resulting hypertension, it does not distinguish the use of epinephrine in OHCA from intra-hospital cardiac arrest such as postoperative cardiac surgery. The European Resuscitation Council (ERC) guidelines do provide recommendations for cautious usage of epinephrine with titration to obtain effects in post cardiac surgery care [5].

Cardiac arrest is an infrequent complication in a cardiac postoperative unit where the incidence is reported to be 0.7–8% [2, 5–8]. Furthermore, a 2013 survey of 81 German cardiac surgery sites revealed a 30% usage of epinephrine in low cardiac output settings compared to a 32% usage of dobutamine [9]. This variability in clinical practice amongst professionals further emphasizes the magnitude of this controversial subject.

In a study reporting patients having undergone coronary aortic bypass grafting or aortic valve replacementss (CABG or AVR) [7], cardiac arrests were reported to be principally caused by postoperative myocardial infarction which led to ventricular fibrillation (VF) and ventricular tachycardia (VT) as dominant mechanisms of CA. The second most frequent cause of arrest (24%) was tamponnade. Shockable arrhythmias are a dominant cause in most post cardiac surgery setting CA. According to the AHA guidelines, administration of two electric shocks initially should be prioritized before proceeding to the administration of epinephrine in CA after cardiac surgery. However, there has been growing concern from experts about the potential side effects of epinephrine in postoperative cardiac surgery CA (proarrythmia and severe hypertension) especially considering its administration timing.

Epinephrine can be considered a secondary line of treatment (after cardioversion, drainage of tamponade, or pacing) in the AHA algorithm and is recommended to be used cautiously by the European guidelines of cardiac arrest in various settings. Questions have been raised about the importance of epinephrine in the treatment for a postoperative cardiac surgical CA patient. More specifically, while epinephrine is still currently used for patients, it's timing, dosage and overall physiologic benefit are increasingly the subject of controversy and compared throughout time to evaluate potential disadvantages to the repetitive administration of this otherwise naturally occurring hormone.

Search Strategy

As presented in the PICO table (Table 9.1), topics of interest in publications which were considered pertinent varied from ROSC, survival of event, survival at discharge from hospital or neurologically intact after CA [10]. The evidence review began by focusing on current 2015 AHA and ERC guidelines as well as the Society

Table 9.1 PICO search strategy

Population studied	**Cardiac surgery postoperative adults (age ≥18 years) in the ICU, suffering cardiac arrest**
Intervention	Usage of epinephrine or vasopressin during cardiac arrest
Comparison	High dose vs lower doses of vasoactive pharmacotherapy components
Outcome	ROSC, neurologic state, hospital LOS, ICU LOS, QOL, Postoperative survival

of Thoracic Surgeons recommendations. Articles released between 2008 and 2017 were also considered in the literature review. Research was done with keywords [adrenaline.mp OR epinephrine.mp OR exp Epinephrine/] AND [exp Resuscitation/ OR resuscitation.mp OR exp Cardiopulmonary resuscitation/] AND [exp survival/ OR survival.mp OR exp. Patient discharge/OR discharge]. Keywords were searched on PUBMED and SCOPUS databases. Additional research was done to target vasopressin physiology, coronary response to vasopressors and vasopressor physiology receptor effects. Pediatric and non-English and non-French studies were excluded. Studies and references pertaining to vasodilatory shock after cardiotomy were reviewed but not used.

Evidence Review

Of all the papers reviewed, 38 were retained and deemed pertinent for the elaboration of this chapter. Most of the repeated search attempts resulted in 265 articles and only 8 relating to cardiac surgery on both databases. Three meta-analyses were found pertinent and brought forth more studies from which the data was derived, many of which were animal studies. Bibliographies of these documents were also studied. The quality of this data was classified according to the GRADE system. Table 9.2 offers an overview of some key articles in OHCA and IHCA epinephrine use.

Results

Epinephrine

Cardiac effects of epinephrine include increments in chronotropic and inotropic functions as well as optimized heart conduction and increase coronary perfusion pressure (CPP).

Throughout the years, epinephrine side effects have been studied and various complications have been linked to: higher doses, high sensitivity or exaggerated physiologic responses. Studies in CA settings were motivated by the appearance of an association between poor survival odds in patients treated with epinephrine compared to those without pharmacologic treatment. Most of the physiologic studies were performed on animals and many have proposed different mechanisms to elucidate the poor neurological or survival prognosis accompanied by epinephrine administration.

Table 9.2 OHCA and IHCA studies

	Study	Type of study	Study population	N	Outcomes	Findings/dosage	Quality of evidence and recommendations
1	Wenzel V. 2004 Au [1]	Randomized control trial (RCT)	OHCA	1186	ROSC Survival to admission (SHA) Survival to discharge (SHD)	Randomization to either vasopressin or epinephrine for OHCA patients. Two doses of **40 UI** of vasopressin were used in comparison to 2 doses of **1 mg** epinephrine. 732 patients initially received 2 doses of vasopressin were also treated with additional epinephrine doses. The effects of vasopressin were similar to those of epinephrine in managing CA with **VF or PEA**. Vasopressin was superior than epinephrine for patients with **asystole**. This median dose was **5 mg** of epinephrine ROSC for asystole: vasopressin (16%) vs epi (16.5%) ($p = 0.87$) SHA for asystole: v (29%) vs epi (20.3%) ($p = 0.02$) SHD for asystole: v (4.7%) vs epi (1.5%) ($p = 0.04$) All results for other rhythms were statistically **non-significant**	Moderate for ROSC and SHD High for SHA Authors provided no recommendations
2	Jacobs I. 2011 At [28]	RCT	OHCA	534		Randomization to either 1:1000 epinephrine or placebo for OHCA for 2 similar groups ROSC: epinephrine (23.5%) and placebo (8.4%) OR: 3.4 (CI: 2.0–5.6) SHD: 4% and 1.9% OR: 2.2 (CI: 0.7–6.3) All results were statistically **non-significant**	High Authors provided no recommendations
3	Olasveengen T. 2009 N [29]	RCT	OHCA	851	SHD ROSC SHA	**Doses** administered were **unknown** as this study centered interests on comparison between IV access vs no IV access patients in OHCA. Short term survival, ROSC were improved in the IV access group SHD: IV (10.5%) vs no IV (9.2%) ($p = 0.61$) ROSC: 32% vs 12% ($p < 0.001$) SHA without neurological sequel: 9.8% vs 8.1% ($p = 0.45$)	High Authors provided no recommendations
4	Warren S. 2014 US [24]	Retrospective review	IHCA	20,909	SHD	Less frequent average dosing was associated with improved hospital discharge rates after IHCA ROSC was obtained in 36.2% of patients SHD obtained in 7.0% When 9–10 min intervals were compared to 4–5 min for SHD, OR: 2.17 (CI: 1.62–2.92) $p < 0.001$	Moderate Authors provided no recommendations

Vasopressin

Despite current evidence not supporting widespread vasopressin [2] usage in cardiac arrest situations, the physiologic mechanism by which the drug could potentially augment coronary perfusion is interesting as it has different mechanisms of action than epinephrine. Vasopressin acts on three different localized receptors. Vasoconstriction is obtained through direct stimulation of smooth muscle V1 receptors and leads to higher levels of arterial systemic pressure.

Coronary Perfusion and Vital Organ Blood Flow

Vasopressin and epinephrine both potentiate diastolic and systolic pressures. On the one hand, diastolic optimization provides more blood flow towards the myocardium whereas systolic support will maintain perfusion in the more distal vital organs such as the brain and kidneys. CPP is maximal during the diastolic phase and is defined as the aortic diastolic pressure minus the right atrial diastolic pressure [11]. Diastolic pressure correlates more with arterial pressure than it does with myocardial contractility and is less affected by cardiac massage than are systolic arterial pressures. Cardiac massage will however decrease LV transmural pressure thus increasing diastolic flow to myocytes.

Rationale

One of the primary clinical objectives in CA settings has been obtaining ROSC rapidly, before end-organ damage. Coronary perfusion pressure elevation of above 15 or 20–30 mmHg during CPR is known to be one of the best predictors of ROSC [1, 11]. Hence, the rationale behind the use of drugs is to optimize CPP and maintain blood flow to vital organs to recover from the hypotensive shock of CA and prevent complications from cellular hypoxia [12]. This logic originated from the idea that diastolic pressure support was the key to resuscitation [11]. In the experimental setting, administration of epinephrine and vasopressin led to increased systemic arterial pressure. However, there was no improvement in survival after CA. Indeed, many studies struggled to reproduce laboratory findings from animal models to humans. From different vasopressor combinations, to different timing of administration and doses, researchers were unable to determine the limiting factor in the similar methods employed. Hypotheses were made ranging from different species, underlying diseases or OHCA CPR and laboratory CPR with regards to the timing, start or method of CPR instauration and methods [1].

Despite obvious limitations in evaluating for patient outcomes in CA settings and although arguments were made against its use, clinicians and guidelines main-

tained the opinion that epinephrine was likely useful to increase the CPP and would help patients achieve ROSC. Unfortunately, data is lacking to support the coronary perfusion hypothesis in IHCA patients. Most data obtained for IHCA is centered on short-term benefits (ROSC) without mention of long-term outcomes for patients (survival or neurological state). This led authors to question ROSC altogether as the primary outcome justifying epinephrine use in OHCA patients [12–14].

As summarized in Table 9.2, two independent randomized control trials were conducted in OHCA patient population by the Jacobs et al. and Olasveeengen et al. research teams since 2008. Both studies compared ROSC, SHA and SHD for patients exposed to epinephrine and those not. Jacobs et al. reconfirmed knowledge that epinephrine was better than placebo to obtain ROSC but found no statistical difference or advantage for SHA or SHD in the epinephrine group [15].

Olasveeengen et al. reported patients with unknown doses of epinephrine administration (patients with IV access) compared to patients without IV access. Patients were randomized to either and were administered drugs if they had IV access. When comparing sub-groups of patients with VF or VT in both groups, no difference was observed for either short or long term outcomes between IV and no IV access groups. There was however a higher chance of obtaining ROSC within the subgroup of patients with non-shockable rhythms. Ultimately, because patients had higher survival in the no IV access group, there was no difference in longterm outcomes. This study emphasizes the potential toxicity from the drugs administered which can result in increased post resuscitation myocardial dysfunction which in turn can lead to more neurological complications [16].

Epinephrine use in CPR is controversially considered beneficial for all patients in CA. However, in post cardiac surgery treatment units, patients with CA are currently the center of a growing interest regarding epinephrine administration. Issues relating to negative effects of epinephrine and overall negative survival impact has emerged. Indeed, several experts have come forth and shared their concern towards epinephrine's potential disadvantages particularly in CS patients [11, 17–20].

With concerns towards epinephrine use on the rise, clinicians turned towards vasopressin, a drug that seemed more effective in certain studies than epinephrine at obtaining CPP. Laboratory findings established that vasopressin use was associated with better cerebral oxygen delivery, higher chances of survival and positive neurological outcome than epinephrine [1]. Clinical observations in OHCA reported improved coronary perfusion, higher likelihood of ROSC, better 24 h survival rates and superior results in asystole for OHCA patients [1]. However, despite these favorable outcomes, for the patient suffering from post-cardiac surgery CA, the use of vasopressin setting would present the same potential drawbacks as the use of epinephrine.

Larabee et al. reviewed in 2012 the use of vasopressors in CA. They concluded that epinephrine was associated with short term but no long-term survival benefits. This was also true when high dose epinephrine was compared to low dose [10].

Nolan et al. reviewed in 2013 data on the influence of epinephrine use in CPR [21]. The authors underline two prospective controlled trials for OHCA patients that associated better rates of ROSC and epinephrine use without data on long-term

outcome results. The authors also relate data from several observational studies that mention the same result but associate these patients to worse long-term outcomes. Some of these outcomes are the neurological symptoms patients retain after CA linked with the cerebral microvascular injury as seen in pig models [21, 22].

Patanwala et al. and Lin et al. are, to our knowledge, the most recent (2014) metanalyses on epinephrine efficiency in survival after CA. While ROSC remains a critical objective of CA treatment, long-term negative outcomes have been the center of epinephrine critique. Despite results based on OHCA patients, the authors' conclusions concurred with current expert reticence to the use of epinephrine. In these metaanalyses, the evidence does not support the use of epinephrine to increase survival at hospital discharge nor does it support favorable neurological prognosis [23–25].

Warren et al. conducted a study aimed at the effects of cumulative doses of epinephrine on survival to hospital discharge in IHCA patients. In this retrospective review of prospectively acquired data, most doses were under 1 mg although accumulation would undoubtedly result in a cumulative amount of more than 1 mg. This study found that by comparing to a reference standard of 4–5 min between each dose, patients receiving less frequent doses were more likely to survive to hospital discharge. The survival favorable dosing frequency was lower than those of the currently recognized guidelines. This further emphasizes the importance of proper titration of epinephrine use as it is associated with more negative outcomes when more frequently used in a hospitalized population [26] independently of rhythms being shockable or not.

Potential Disadvantages

While many studies have found associations between poor clinical outcomes and epinephrine use in OHCA others have focused their attention on physiological effect studies. Thus, whether it be a higher risk of neurological deficits at discharge or a lower likelihood of survival for patients receiving epinephrine, these studies were principally held on OHCA patients or animals. To support these studies, physiologic explanations in animal-based models were gathered and have identified various receptor specific hypotheses.

Throughout different animal experiments and clinical studies, epinephrine has been associated with various side effects [27]. Whether it be ventricular arrhythmias, increased myocardial oxygen consumption or severe post resuscitation myocardial dysfunction [12, 14, 28], patients in CA are prone to developing life threatening complications which have been associated to epinephrine use [14]. Some studies have supported that high-dose epinephrine had better rates of resuscitation effects in CPR settings but this led some animal subjects to hyperadrenergic states associated to higher mortality [1]. Epinephrine at high dose (7 mg) has also been compared to standard doses (1 mg) by Stiell et al. The authors concluded there was no improved survival or neurological outcome despite better ROSC. This study

Table 9.3 Deleterious effects of drugs used in resuscitation

	Organ specific adverse effects		
Drugs	Heart	Systemic	Target organ blood flow
Epinephrine	Dysrhythmias Coronary vasospasms	Hypertensive episode	Lowered brain microcirculation identified in pig models Decreased kidney blood flow
Vasopressin combined with norepinephrine	Decreased cardiac output	Sustained hypertension	–

reported worse outcomes for the high-dose patient group and for patients receiving epinephrine more than 10 min after CA [14]. Not only were these overloaded subjects more likely to die but they also suffered negative cumulative effects with reperfusion and lowered cerebral microcirculation [22].

According to a cardiac surgery CA treatment expert consensus and ERC guidelines, epinephrine is cautioned because of its high responsiveness in an already vasoactive drug loaded patient [5, 6]. Indeed, the principal reluctance to using epinephrine comes from the resulting systemic hypertension which may cause aortic grafts and sutures to bleed and worsen the prognosis for the patients [6, 18] as well as other effects summarized in Table 9.3. The proarrythmic effect of high dose epinephrine on potentially irritable or ischemic myocardium is also concerning [29].

Recommendations

In CA post-cardiac surgery, epinephrine and vasopressin current doses can result in extreme hypertension and dysrhythmias. Despite having less cardiac pro-arrhythmic and negative effects on oxygen transportation, knowing that vasopressin has a longer lasting hypertensive effect than epinephrine makes its use even more problematic than a more easily controlled short acting hypertensive.

Since most of the evidence supporting epinephrine use in cardiac surgery is extrapolated from good OHCA studies and guidelines, it seemed logical to extract most data relating to the studies supporting its cautioned usage. Data specific to cardiac surgical patients was collected from a thorough review of perioperative publications. Furthermore, while vasopressin may be viewed as an interesting alternative in perioperative CA, cardiac surgery predisposes patients to an increased risk of adverse events and is not recommended by the AHA or ERC guidelines.

As seen in Table 9.4, ERC guidelines mention that postoperative CA is usually attributable to a specific reversible cause such as tamponade or hemorrhage. In such conditions, early recognition of the potential for emergency resternotomy is considered essential [5]. Should patients develop asystole or VF, it is recommended to administer external defibrillation or temporary pacing. External chest compressions seem to be considered reasonable but resternotomy within 5 min of CA debut is preferred as to avoid lacerating the right ventricle during CPR maneuvers after three

Table 9.4 Guidelines

	Study	Type of study	Study population	Findings/dosage	Level of evidence
1	AHA 2010–2015	Review and guidelines	General population	Standard dose epinephrine of 1 mg every 3–5 min **may** be reasonable for patients in CA High dose epinephrine is not recommended for routine use in CA Vasopressin offers no advantage as a substitute for epinephrine in CA. Vasopressin also offers no advantage in combination with epinephrine	Class IIb Level B-R Class III Level B-R (no benefit) Class IIb Level B-R
			Cardiac arrest post cardiac surgery	**Rebound hypertension** has the ability of inducing significant **bleeding** in this population. There is **insufficient data to recommend** deviating from standard resuscitation guidelines	–
2	ERC 2015 [5]		General population	Standard dose epinephrine of 1 mg every 3–5 min **may** be reasonable for patients in CA Use adrenaline very cautiously and titrate to effect. IV doses up to 100 mcg	–
			Cardiac arrest post cardiac surgery	Use adrenaline very cautiously and titrate to effect. IV doses up to 100 mcg	–
3	STS 2017 [6]			Patients undergoing cardiac arrest should **not receive epinephrine or vasopressin** after cardiac surgery unless directed by a clinician experienced in their use	Class III Level C (Harm)

Summary

Both guidelines specify that standard doses and not high doses of epinephrine may be reasonable to treat cardiac arrest in a general population

This review and two major guidelines all caution about epinephrine usage to treat cardiac arrest after cardiac surgery

defibrillation attempts. When considering epinephrine, ERC recommends IV doses of 100 μg in adults to be titrated (as opposed to 1 mg every 3–5 min in the AHA general guidelines). Amiodarone is the preferred drug proposed for patients with refractory shockable rhythms such as VF or polymorph VT. Diastolic pressure of >25 mmHg should be targeted during massage to favor ROSC [24].

The Society of Thoracic Surgeons (STS) recently released an expert consensus and addressed wide pharmacologic intervention in CA occurring after cardiac surgery [6]. The current chapter includes the eight studies reported by the STS, is based on the Dunning and al guidelines [20] and draws similar conclusions. Usage is recommended based on ROSC and favorable neurologically intact discharge at the

cost of lower survival. The STS review mentions 2 RCTs from 2009 to 2011' with 851 and 534 patients respectively as well as metanalyses from 2014 regrouping all published trials of vasopressors [15, 16]. These RCTs are of moderate to high quality based on OHCA patients and led to a recommendation by STS [6] of administrating epinephrine boluses of 50–300 μg for impending CA situations. Once CA has begun, neither vasopressin nor epinephrine should be routinely given as a first line treatment. It should be administered, only as small quantities at a time, to increase blood pressure during CPR. Patients who do receive such drugs should have them prescribed by experienced clinicians who understand the distinctive risks for cardiac postoperative patients (Class III level C Potentially harmful).

The challenge with epinephrine and concomitant risk in vasopressor overloading is the resulting hypertensive and proarrythmic events. Despite this complication, recent studies have exposed dismal prognosis associated with epinephrine use. In OHCA, patients having received epinephrine are less likely to survive their hospital stay and more at risk of neurological complications.

Although all the potential drawbacks associated with epinephrine usage are concerning, experts employ it to obtain a vasoconstrictive effect as well as an inotropic effect. Indeed, specialists agree that the most crucial part of CSCA CPR is recuperating cardiac activity [19] and whilst the ß receptors may be the ones mediating part of the negative side effects, they offer myocardial maximal stimulation when faced with high afterload induced by vasoconstriction.

- LOE C, III
  - CS patients are a fragile population prone to developing unanticipated proarrythmias and in which tailored pharmacotherapy can be considered.
  - Patients with CACS are more likely to develop problematic hypertensive states and malignant arrhythmias with usage of routine dose epinephrine.
  - Usage of routine doses of epinephrine in CACS can cause harm to patients by increasing stress on fresh suture lines and induce bleeding in the thoracic cavity.
- No LOE stated by AHA and ERC guidelines.
  - Rebound hypertension has the ability of inducing significant bleeding in this population. There is insufficient data to recommend deviating from standard resuscitation guidelines.
  - Use epinephrine very cautiously and titrate to effect. IV doses up to 100 mcg [5].

Personal View of the Data

Considering the quality and different studies, it seems that the drug itself is not problematic as much as it's dosage and timing are important in fragile settings. While epinephrine remains a second-line treatment for cardiac surgery patients, it seems that the effects are optimal in the early minutes of CA. When one considers

dosage, it is difficult to extrapolate that the 1 mg doses recommended by the AHA for general CA (LOE IIb) would be universally beneficial and non-harmful in a cardiac surgical patient. Hence, we conclude that this population deserves a more tailored approach to resuscitation. Epinephrine use is controversial and the recommendations for the general population are at best a supposition and with the current a gap in knowledge for epinephrine use even for IHCA it is unwise to generalize the safety to CACS, an even more fragile population. Therefore, we find that cardiac surgery patients are at risk of developing significant adverse effects from the administration of routine doses, deemed safe for a general OHCA patient. We support the current expert opinion that despite lower quality of evidence it is reasonable to use epinephrine in low doses such as 100 μg for an adult who is already in the ICU following cardiac surgery is reasonable if prescribed by a clinician with sufficient experience in the field. We do not recommend the use of vasopressin as it can lead to prolonged hypertension that predisposes the patient to critical complications. Further studies on cardiac surgery patients are required to elucidate the needs of such a delicate population.

Recommendation

- Once CA has begun, neither vasopressin nor epinephrine should be routinely given as a first line treatment.

  1. QOE: moderate, Recommendation: strong

- It should be administered, only as small quantities at a time, to increase blood pressure during CPR.

  2. QOE: moderate, Recommendation: strong

- Patients who do receive such drugs should have them prescribed by experienced clinicians who understand the distinctive risks for cardiac postoperative patients (Class III level C Potentially harmful).

  3. QOE: moderate, Recommendation: strong

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Chapter 10
Cardiac Arrest in the Minimally Invasive Cardiac Surgery Patient: Is Conservatism an Aggressive Approach?

Brody Wehman and Husam H. Balkhy

Introduction

Over the last several decades a range of techniques have evolved to allow for less invasive cardiac surgery, including the ability to avoid a sternotomy and the morbidity associated with it. Sternal-sparing approaches to commonly performed cardiac operations have been well described and are now practiced routinely in many centers. However, such advances inevitably present new and distinct challenges. One clinical dilemma that remains as it relates to sternal-sparing cardiac surgery is how to safely and quickly resuscitate a non-sternotomy patient in refractory cardiac arrest. By contrast, cardiac surgery patients who have undergone a sternotomy have the option of undergoing immediate re-sternotomy at the bedside to alleviate tamponade, control hemorrhage or perform manual cardiac massage. As such, the consensus guidelines from both the European Association of Cardiothoracic Surgery and the Society of Thoracic Surgeons (STS) recommend immediate sternal re-entry as a central tenet to resuscitation of the post-operative cardiac surgery patient in cardiac arrest [1, 2]. The optimal approach to the non-sternotomy patient is, however, less straight-forward and without a clear consensus.

The purpose of this chapter was therefore to summarize the existing literature and to provide a recommendation for the resuscitation of the patient who is in refractory arrest after sternal-sparing cardiac surgery.

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Search Strategy

A literature search of English language publications was performed to identify reported cases of post-operative arrest in cardiac surgery patients following minimally invasive cardiac surgery using the PICO table outlined below (Table 10.1). The following databases were searched: Pubmed, Embase and Cochrane Evidence Based Medicine. The search terms used were the following: [“cardiac arrest” OR “resuscitation”] AND [“minimally invasive cardiac surgery” OR “robotic cardiac surgery” OR “minimally invasive aortic valve replacement” OR “minimally invasive mitral valve” OR “minimally invasive coronary artery bypass” OR “robotic coronary artery bypass” OR “robotic mitral” OR “nonsternotomy” OR “sternal sparing”].

A second search was performed to examine large series of sternal-sparing cardiac surgery for reports of post-operative cardiac arrest within the manuscript. Representative large series publications from the following forms of sternal-sparing cardiac surgical procedures were reviewed:

- Minimally invasive mitral valve repair (both robotic and thoracotomy approaches)
- Minimally invasive aortic valve replacement
- Robotic totally endoscopic coronary artery bypass
- Minimally invasive coronary artery bypass (robotic and thoracotomy)

Results

Cardiac Arrest After Sternal Sparing, Minimally Invasive Cardiac Surgery

The incidence of post-operative cardiac arrest in patients specifically undergoing minimally invasive, sternal-sparing cardiac surgery is unclear. Larger series of robotic, thoracoscopic, totally endoscopic or mini-thoracotomy approaches to cardiac surgery do not specifically report whether a post-operative arrest has occurred (Table 10.2) [3–10]. Other post-operative outcomes were provided, including mortality, however cardiac arrest was not a reported outcome measure in any of the large

Table 10.1 PICO table for cardiac arrest in the minimally invasive cardiac surgery patient

P	I	C	O
Patients	Intervention	Comparator	Outcome
Patients suffering cardiac arrest after “minimally invasive” cardiac surgery (i.e. robotic, mini-thoracotomy, thoracoscopic)	Emergent sternotomy	Alternative treatment such as peripheral venoarterial extracorporeal membrane oxygenation	Failure to resuscitate, death or morbidity

The quality of data in the papers evaluated was classified according to the GRADE system

Table 10.2 Reported incidence of post-operative cardiac arrest and interventions after sternal-sparing cardiac surgery.

Author (year)	Patient group	# Patients	In hospital mortality (%)	Incidence of post-operative arrest	Comment	Type of study	Quality of evidence
Murphy DA (2015) [3]	Robotic MVr	1257	0.9	N/A		Retrospective	Very low
Gillinov AM (2018) [4]	Robotic MVr	1000	0.1	N/A		Retrospective	Very low
Vollroth M (2002) [5]	Right thoracotomy MVR/r	714	4.2	N/A		Retrospective	Very low
Lamelas J (2018) [6]	Minimally invasive AVR	1018	1.3	N/A		Retrospective	Very low
Glauber M (2015) [7]	Minimally invasive AVR	593	1.5	N/A	5.1% reopened for bleeding or tamponade	Retrospective	Very low
Bonatti J (2013) [8]	Robotic TECAB	500	1	N/A		Retrospective	Very low
Halkos ME (2014) [9]	Robotic MIDCAB	307	1.3			Retrospective	Very low
McGinn JT (2009) [10]	MICS CABG	450	1.3	N/A	2.7% return to operating room for graft revision or bleeding	Retrospective	Very low

MVr mitral valve repair, *MVR/r* mitral valve replacement/repair, *AVR* aortic valve replacement, *TECAB* totally endoscopic coronary artery bypass, *MIDCAB* minimally invasive direct coronary artery bypass, *MICS CABG* minimally invasive cardiac surgery coronary artery bypass grafting

series we reviewed. Additionally, our review of the literature indicates that series reporting on the incidence and outcomes of post-operative cardiac arrest in the cardiac surgical patient do not address patients undergoing sternal sparing approaches [11–13].

In general, approximately 5% of all patients undergoing cardiac surgery will have a post-operative cardiac arrest according to a recent review of 80,000 patients (range 2.6–5.5%) [11]. The inciting event may be cardiac tamponade, air embolus, uncontrolled hemorrhage or technical issues related to the primary operation which may progress to hypotension, hypoxemia, ischemia and ultimately pulseless electrical activity, asystole or ventricular tachyarrhythmias. Failure to rescue these patients has been shown to vary among hospitals, and in one series an average failure rate of 60% that ranged from 50% to 83% was found across 17 hospitals [11]. This series did include patients who had undergone sternal-sparing cardiac surgery, however we were not able to extract this specific subset of patients from the database reviewed to determine the incidence of arrest and resuscitation strategy.

ECMO/ECPR After Cardiac Surgery

The majority of the published experience with Extracorporeal Cardio-Pulmonary Resuscitation (ECPR) or extracorporeal membrane oxygenation (ECMO) after cardiac surgery is related to pediatric cardiac surgery [14]. There are a limited number of series reporting the use of ECPR for post-operative adult cardiac surgery patients in refractory cardiac arrest. Mazzaffi et al. reported 23 patients who underwent either peripheral or central venoarterial (VA) ECMO after cardiac surgery [13]. Thirty day mortality and in-hospital mortality were 65.2% and 69.6%, respectively. Six of the 23 patients (26.1%) were discharged with a favorable neurologic outcome. This institution reported their experience with both resternotomy and central VA ECMO as well as femoral cannulation for peripheral VA ECMO. Because of a large institutional experience with ECPR and ECMO in general, peripheral VA ECMO has now become this center's strategy of choice for post-operative cardiac surgery patients in refractory cardiac arrest [13]. Similar results were found by Zhou et al. who reported a 33% survival to discharge in 24 patients, although 50% had a major neurologic injury [12].

Current Guidelines for Resuscitation

With regards to non-sternotomy patients the STS Guidelines emphasize the use of an agreed upon protocol for fresh sternotomy in the ICU or in the OR as outlined by the operating surgeon [2]. As an alternative to sternotomy, the Guidelines state that "experienced surgeons" may use ECMO as an alternative to fresh sternotomy.

Given the paucity of data for ECPR in adult cardiac surgery patients, the STS Guidelines provide little discussion of the use of ECMO in arresting patients [2]. Similar to the recommendations in non-sternotomy patients, the guidelines recommend the use of ECPR as an alternative to re-sternotomy in "expert institutions" that are capable of rapid deployment of ECMO [2].

Recommendations

Published reports of non-sternotomy cardiac surgery patients suffering cardiac arrest are sparse. Therefore the following recommendations are comprised from the authors' combined experience and in some cases a modification of existing guidelines for sternotomy patients [2].

For non-sternotomy patients in cardiac arrest we recommend the following:

1. Hospitals that perform sternal-sparing approaches to cardiac surgery should produce and rehearse an ICU-specific protocol for cardiac arrest in this patient population. This protocol should be based on the level of training and experience of

the providers in the ICU at night (surgical residents, ICU intensivists, nurses only, etc.) and also account for the institutional experience with ECMO or ECPR. Quality of Evidence: low, Level of Recommendation: Strong

2. For the non-sternotomy cardiac surgery patient in refractory cardiac arrest, peripheral VA ECMO is the optimal intervention to restore perfusion to the brain, coronary arteries and visceral organs. Quality of Evidence: Low, Level of Recommendation: Strong
   (a) Note: In the setting of cardiac tamponade peripheral VA ECMO can result in undrained upper extremity and cerebral venous blood flow, placing the patient at risk for cerebral edema. Therefore, peripheral VA ECMO may act as a temporizing measure for immediate resuscitation yet the patient should undergo sternotomy and relief of tamponade in an operating room as soon as possible.
3. If available, set-up for VA ECMO and preparation of the groin should begin as soon as a code is called in a non-sternotomy patient, in parallel to conservative efforts at resuscitation. This is equivalent to the immediate preparation for resternotomy described at the onset of a code in the STS resuscitation guidelines [2]. Quality of Evidence: Low, Level of Recommendation: Strong
4. If an ECPR or ECMO program is not already in place, its development should be considered in hospital centers regularly performing sternal sparing cardiac surgery procedures. Quality of Evidence: Very low, Level of Recommendation: Strong
5. Closed chest CPR is more effective in a patient with an intact sternum than a post-sternotomy patient and perhaps should be continued longer than the 5 min recommended for patients with previous sternotomy [2]. Quality of Evidence: Very low, Level of Recommendation: Strong
6. *Alternative:* If ECPR/ECMO is not an option, a protocol to perform a fresh sternotomy in the ICU or in the OR should be developed with the operating surgeon and the ICU per the STS guidelines [2]. Sternal saw and saw blades should be available on the unit and tested regularly. ICU personnel who may be performing the sternotomy should be familiar with its assembly and use. A fresh sternotomy in the ICU should be performed by a surgeon or provider who has been adequately trained. Quality of Evidence: Very low, Level of Recommendation: Weak

A Personal View of the Data

The optimal approach to the non-sternotomy patient in refractory cardiac arrest differs from that of the conventional cardiac surgery patient. Fortunately, these events are infrequent yet when they do occur it is often at night when an attending surgeon may not be immediately available. In such a scenario, our view is that the safest mode of resuscitation is via initiation of peripheral VA ECMO. The use of ECMO

in these patients should be viewed as a temporizing measure prior to further evaluation either in the catheterization lab or operating room as necessary.

We believe the use of peripheral ECMO over a fresh sternotomy in these patients has the following advantages:

1. Avoids the need to interrupt chest compressions for a sternotomy
2. Avoids the need for the immediate presence of a qualified cardiac surgeon
3. Avoids reliance on an inexperienced surrogate to perform an emergent sternotomy
4. Femoral access can be obtained by ICU providers as the code is initiated who may then either continue with cannulation if sufficiently trained or have the patient prepared for immediate cannulation upon arrival of the on call surgeon
5. Prevents the risk of a technical complication occurring during a fresh sternotomy in an arresting patient (i.e. – avoids a "bad to worse" situation):

    - Saw or finger sweep injury to a grossly distended RV
    - Ongoing and difficult to control blood loss from bone marrow and engorged bridging veins
    - Injury to bypass grafts
    - Injury to RV during manual cardiac massage
    - In the event central VA ECMO is required, central cannulation after emergent sternotomy in the ICU can be challenging due to:

        – Poor visualization of structures (hemorrhage, poor lighting)
        – Lack of necessary supplies, instruments, help
        – Frequent interruption of cardiac massage

When executed properly, the use of peripheral VA ECMO in this population can rescue the patient in refractory arrest and result in a favorable neurologic outcome if instituted early and with adequate concurrent CPR.

Finally, given the paucity of data on this topic, these recommendations were arrived at after reviewing our own experience as well as discussing with other practitioners of this approach their experience. We recommend that future prospective studies on sternal sparing cardiac surgery include management of cardiac arrest as one of the endpoints, and that future retrospective studies include this information in their results.

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Part III
Hemodynamics

Chapter 11
Intravascular Devices in the ICU

Danisa Daubenspeck and Aalok Kacha

Introduction

Although there has been much debate over how best to measure hemodynamic variables it is likely that optimizing tissue perfusion is important in managing both the postoperative surgical patient and critically ill patients in general. For many decades the most common diagnostic tool used was the pulmonary artery catheter (PAC) which yielded a variety of information including thermodilution cardiac output, mixed venous oxygen saturation, central venous pressure, pulmonary artery pressures, and an estimate of left atrial pressure. In more recent years there has been move towards the use of minimally invasive hemodynamic monitoring such as pulse contour analysis devices, which include lithium dilution cardiac output (LiDCO) and Pulse Index Continuous Cardiac Output (PiCCO) monitors.

All of these devices involve obtaining intravascular access, which comes with a risk of complications, the most common being infection. It is estimated that up to 80,000 catheter-related infections occur each year, incurring costs up to 2.3 billion US dollars [1]. The pulmonary artery catheter has been under scrutiny ever since it was first introduced over three decades ago [2] and studies have showed inconsistent results. The introduction of newer minimally invasive

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monitors such as the PiCCO and LiDCO devices may avoid some of the risks associated with usage and placement of the PAC but come with their own limitations, and there is little evidence to guide practice in terms of the utility of traditional cardiac output and CVP monitoring or the value of these newer methods. One of these studies conducted by Hadian et al. showed that although pulse contour analysis devices and the PAC show similar cardiac output values the data trends are different in response to therapy [3], which makes it difficult to say one is superior to the other.

This chapter discusses the most commonly used types of intravascular devices used as well as the data that they provide. It will also address how the information used can guide patient management and the effect on various outcomes including mortality, morbidity, length of ICU stay, and cost.

Search Strategy

A literature search of English language publications ranging from 1989 to 2016 were used to identify data regarding the use of intravascular monitoring devices such as the pulmonary artery catheter and the LiDCO and PiCCO systems for cardiac output measurement and the central venous catheter for central venous pressure monitoring. This search was conducted using a PICO outline (Table 11.1) and data was classified using the GRADE system (Table 11.2). Databases included MEDLINE, PubMed, ScienceDirect and Cochrane Library. Search terms used were "central venous pressure, monitoring", "pulmonary artery catheterization, intensive care", "cardiac output, monitoring, pulmonary artery catheter", "cardiac output, monitoring, lithium dilution", "invasive hemodynamic monitoring" AND ("postoperative") "cardiothoracic", "cardiac surgery", "coronary artery bypass graft", "heart failure". Given that there were few trials that specifically included invasive hemodynamic monitoring and cardiac or thoracic surgery we also expanded our search to include "critically ill patients". Articles were excluded if the studies did not specifically involve adult critically ill or perioperative patients. Five randomized control trials, four observational studies, eight cohort studies, one case-control study, and three review articles were included.

Table 11.1 PICO table for usage of hemodynamic monitoring devices

P	I	C	O
Patients	Intervention	Comparator	Outcome
Adults, Intensive care unit, postoperative, congestive heart failure	Invasive and minimally invasive hemodynamic monitoring devices	No hemodynamic monitoring devices	Morbidity, mortality, ICU length of stay, quality of life

Table 11.2 Included studies and classification using the GRADE system

Author (year)	N	Device	Population	Outcome	Findings	Study type (quality of evidence)
Pronovost et al. (2006) [1]	103 ICUs, 1981 ICU-months, 375,757 catheter-days	CVC	ICU patients	Catheter related bloodstream infections	Median rate of CVC-BSI per 1000 catheter-days decreased from 2.7 to 0 at 3 months ($P \leq 0.002$) and decreased from 7.7 to 1.4 at 16–18 months ($P < 0.002$)	Cohort study (High)
Sandham et al. (2003) [2]	1994 (997 with PAC, 999 without PAC)	PAC	High risk patients scheduled for surgery followed by ICU stay	Mortality, length of hospital stay	No significant change in mortality (7.7% vs. 7.8%) or length of hospital stay (median LOS was 10 days in each group). Use of PAC resulted in higher rate of pulmonary embolism (8 events versus 0 events, $P = 0.004$)	Randomized controlled trial (High)
Parienti et al. (2015) [4]	3333 (1284 jugular, 1171 femoral, 1016 subclavian	CVC	ICU patients	Catheter related bloodstream infections, symptomatic DVT	The number of primary outcome events (composite of CVC-BSI and symptomatic DVT) was 8, 20, and 22 for subclavian, internal jugular, and femoral sites respectively (1.5, 3.6, and 4.6 per 1000 catheter days, $P = 0.02$)	Randomized controlled trial (High)
Pronovost et al. (2010) [5]	90 ICUs, 1532 ICU-months, 300,310 catheter-days	CVC	ICU patients	Catheter related bloodstream infections	Mean rate of CVC-BSI decreased from 7.7 to 1.1 from 16–18 to 34–36 months post-implementation	Cohort Study (High)
Bion et al. (2013) [6]	215	CVC	ICU patients	Catheter related bloodstream infections	The mean CVC-BSI rate decreased over 20 months from 3.7 to 1.48 per 1000 CVC-patient days ($p < 0.0001$)	Prospective, Non-randomized study (High)

(continued)

Table 11.2 (continued)

Author (year)	N	Device	Population	Outcome	Findings	Study type (quality of evidence)
Connors et al. (1996) [7]	5735 (2184 with PAC, 3551 without PAC)	PAC	ICU patients	Mortality, cost of hospital stay, ICU length of stay	PAC patients had increased 30 day mortality (odds ratio 1.24, 95% CI 1.03–1.49). The mean cost per hospital stay was $49,300 with PAC and $35,700 without PAC. Mean LOS in the ICU was 14.8 days with PAC versus 13.0 without PAC	Prospective Cohort Study (High)
Gattinoni et al. (1995) [8]	762 (252 in control group, 253 in cardiac index group, 257 in mixed venous oxygen saturation group)	PAC	ICU patients	Mortality	Despite achieving hemodynamic targets in control, cardiac index, and mixed venous oxygen saturation mortality was 48.4%, 48.6,% and 52.1% at 6 months in each group, respectively (P = 0.638)	Randomized Controlled Trial (High)
Rhodes et al. (2002) [9]	201 (95 in PAC group, 106 in control group)	PAC	ICU patients	Mortality, hospital length of stay	Mortality was 47.9% for the PAC group versus 47.6% for non-PAC group (95% CI, p > 0.99). Median hospital LOS was 13 days in PAC group vs. 14 days in non PAC group	Randomized controlled trial (High)
Harvey et al. (2005) [10]	1041 (519 with PAC, 522 without PAC)	PAC	ICU patients	In-hospital mortality	68% versus 66% in hospital mortality in PAC versus non-PAC (p = 0.39, 95% CI 0.94–1.27)	Randomized controlled trial (High)
Binanay et al. (2005) [11]	433 (215 in PAC plus clinical assessment, 218 in clinical assessment alone)	PAC	CHF patients	Mortality, hospital length of stay	No significant difference in days alive and out of hospital at 6 months (133 days vs. 135 days, 95% CI 0.82–1.21; P = 0.99), mortality (43 vs. 38 pts, 95% CI 0.78–2.03; P = 0.35), or LOS (8.7 vs. 8.3 days, 95% CI 0.86–1.27; P = 0.67)	Randomized controlled trial (High)

NHLBI-ARDSnet Study (2006) [12]	1000 (513 PAC group, 488 CVC group)	PAC, CVC	ICU patients with acute lung injury	Mortality, catheter related complications	Rates of death during first 60 days before discharge similar between PAC and CVC groups (27.4% vs 26.3%). PAC group had approximately twice as many complications (100 in PAC vs 41 in CVC)	Randomized controlled trial (High)
Brovman et al. (2016) [13]	116,333 (40,036 with PAC, 76,297 in control group)	PAC	Cardiac surgery patients	PAC use, mortality, blood transfusion	Use of PAC increased from approximately 25% to 38% of cases. No statistically significant difference in mortality (0.23% vs. 0.12%, 95% CI: 0.25–1.1, P = 0.086). Transfusion was less likely in the PAC group versus no PAC (1.26% vs. 0.29%, 95% CI: 0.084–0.64, P = 0.0048)	Retrospective cohort (Low)

CVC central venous catheter, *PAC* pulmonary artery catheter, *CVP* central venous pressure, *NICO* non-invasive cardiac output monitor, *LOS* length of stay, *BSI* bloodstream infection, *DVT* deep venous thrombosis, *CI* confidence interval

Results

Central Venous Catheter

Central venous catheters (CVC) can provide secure intravenous access, a means to deliver therapies such as vasoactive medication, ScvO2 monitoring, and information regarding intravascular volume status and cardiac function. Due to these useful benefits, CVC are commonly used in postsurgical or critically ill patients including those suffering from cardiogenic, septic, or other shock. The sites used include the subclavian, internal jugular, and femoral veins. Determination of where to place the catheter is guided by patient specific factors including comorbidities, anatomic and physiologic factors as well as the risk of infectious, thrombotic, or mechanical complications [1, 4].

In the 3SITES study, a multi-center, randomized controlled trial conducted by Parienti et al., venous site choice was studied in ICU patients requiring non-tunneled CVCs. Patients were randomly assigned in a 1:1:1 ratio to receive subclavian, internal jugular, or femoral central venous catheters [4]. The primary outcome was a composite of catheter-related bloodstream infection and symptomatic deep-vein thrombosis. This important study revealed a lower rate of infectious and thrombotic complications with the subclavian site whem compared to the femoral or jugular sites. The rate of pneumothorax was higher with subclavian insertion compared to jugular insertion. An additional consideration is the potential for future venous access needs in patients with chronic kidney disease. The American Society of Diagnostic and Interventional Nephrology recommends that the subclavian vein not be used for central venous access in patients with stage 3–5 chronic kidney disease and recommend the internal jugular site [14]. This is due to an increased rate of venous thrombus and stenosis with subclavian catheterization which may preclude future hemodialysis access including surgical arteriovenous fistula or graft placement.

Infection remains one of the more costly and potentially deadly complications related to central venous catheters. Pronovost and colleagues conducted a prospective cohort study at multiple ICUs in Michigan to determine if the implementation of five evidenced based procedures would reduce the incidence of catheter related infection [1]. These procedures included hand washing, using full barrier precautions during insertion, cleaning the insertion site with chlorhexidine, avoiding the femoral site if possible, and removing unnecessary catheters. Their study showed that there was a significant reduction in infection rates from 2.7 infections per 1000-catheter days at baseline to 0 at 0–3 months of implementation of the interventions, and was sustained at 0 at 18 months of follow-up. Due to the design of this study, it is not known what contribution the individual elements of this bundle make to the observed decrease in infection rate. This study was a part of the Keystone ICU project and the intervention included multiple elements including the implementation of a daily goals sheet, designation of team leaders to implement training, development of CVC supply carts, daily discussions on rounds to determine ongoing

necessity of a CVC, and ongoing feedback regarding infection rates. A follow-up study noted a reduced rate of catheter related bloodstream infection for an additional 18 months following the initial 18 month study [5]. Larger scale implementation of interventions to decrease CVC-blood stream infections has been investigated in the UK. The authors found a decrease in the infection rate following the implementation of their intervention, but noted that this was superimposed on a secular trend towards fewer infections, making it difficult to attribute the improvement solely to the intervention [6].

Central venous pressure has typically been used to assess cardiac preload [15]. The use of the CVP as a sole predictor for volume responsiveness is questionable. A review of studies evaluating predictive factors for fluid responsiveness determined that central venous pressure, or right atrial pressure, as a single value is a poor predictor of changes in cardiac output with volume administration [16]. Thus, it is important to have knowledge of a patient's cardiac function in addition to the CVP in order to decide if volume administration will result in clinical improvement. Magder and colleagues argued that interpretation of a CVP needs to be done in conjunction with an assessment of cardiac function, specifically cardiac output. They conducted a prospective observational study in ICU patients, the majority of whom were post cardiac surgery, in which they examined volume responsiveness over a range of CVP values in order to determine a CVP value above which it is unlikely that volume administration would increase cardiac output [17]. Patients who were deemed "responders" to fluid administration were those who had an increase in CVP $\geq$2 mmHg as well as an increase in cardiac index >300 mL/min/m^2. They determined that a CVP >10 mmHg would be considered high and that above that value there is a low probability that volume administration would result in an increase in cardiac output. They did, however, also determine that no single value of CVP is a good predictor of volume responsiveness. More importantly, they concluded that CVP should not be used to indicate if a patient needs volume, but if they would respond to fluid administration.

As a measure of right atrial pressures, the CVP may have the most utility in monitoring right ventricular function. A rising CVP may reflect right ventricular failure in the correct clinical context such as a patient after heart transplantation or left ventricular assist device placement.

Pulmonary Artery Catheter

The pulmonary artery catheter (PAC) is a flow-directed balloon-tipped catheter which facilitates transit through the right side of the heart into the pulmonary artery. The PAC can provide information regarding cardiac output, pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP), right atrial pressure, and mixed venous oxygen saturation. Cardiac output is measured using the thermodilution principle with thermistor equipped catheters, either manually by injecting small boluses of cold fluid or automatically by catheters that contain a heating element.

Pulmonary capillary wedge pressure is measured when the balloon is inflated and partially occludes a branch of the pulmonary artery. This pressure measured reflects the pressure in the pulmonary veins, which should reflect left atrial pressure, in the absence of mitral regurgitation or high pulmonary vascular resistance. Finally, mixed venous oxygen saturation is obtained by oximetry analysis of pulmonary arterial blood. This sampling location reflects total body oxygen extraction with mixed blood from the SVC, IVC, and coronary sinus. The utility of the PAC has been a topic of much debate and has prompted numerous studies over the years since its inception to determine its effect on morbidity, mortality, as well as its cost effectiveness. Results of these studies have ranged from negative effects, to positive effects, to none at all.

A prospective cohort study conducted by Connors and colleagues examined the association between PAC use and survival, length of ICU stay, and cost and intensity of care in 5735 patients in five U.S teaching hospitals between 1989 and 1994 [7]. They determined that patients with a PAC had an increased 30 day mortality, increased mean cost per hospital stay (US$49,300 with PAC versus US$35,700 without PAC). An earlier study by Gattinoni et al. found that supranormal oxygen delivery or normalization of the mixed venous oxygen saturation did not improve morbidity or mortality [8].

Similarly, a retrospective cohort study published in 2000 by Ramsey and colleagues examined PAC use in patients undergoing non-emergent coronary artery bypass grafting [18]. They found that PAC was associated with an increased risk of in-hospital mortality, greater length of stay, and higher total costs. Of note, mortality risk was greater in smaller hospitals that inserted fewer numbers of PACs per year, indicating that experience with PAC use could have an effect on patient outcomes. These findings were counter to many of the results of subsequent studies including a randomized controlled trial conducted by Rhodes and colleagues which examined 200 intensive care unit patients who were managed with a PAC or without a PAC and determined that although the PAC group received significantly more fluids in the first 24 h there was no increased risk of mortality from PAC use [9].

A randomized controlled trial conducted by Sandham et al. compared goal directed therapy guided by a PAC compared to standard of care without the use of the PAC [2]. Their patient population included high risk patients 60 years of age or older who were American Society of Anesthesiologists (ASA) class III or IV and were scheduled for major surgery with planned ICU admission post-operatively. They studied a total of 1994 patients and observed that the PAC was not associated with an increase in mortality or length of hospital stay, and determined that there was no benefit to therapy directed by the PAC in that particular population, although the PAC group had a higher rate of pulmonary embolism. The PAC group included specific oxygen delivery index, cardiac index, mean arterial pressure, PCWP, heart rate, and hematocrit goals. Due to the study design, it remains possible that the use of the PAC to guide a different clinical algorithm would result in a different outcome. The PAC-MAN trial by Harvey et al. was a randomized controlled trial in 1041 ICU patients that determined no difference in hospital mortality and length of ICU stay in patients managed with and without PAC [10]. The most common PAC

related complications included hematoma at insertion site (n = 17, 4%), arterial punctures (n = 16, 3%), and arrhythmias needing treatment within 1 h of insertion (n = 16, 3%). Interestingly, the most frequently reported management changes related to the PAC were infusion of 200 mL or more of fluid above maintenance levels in 1 h (n = 205, 42%), changes in dose of vasoactive drugs of greater than 25%, (n = 211, 43%) and introduction of vasoactive drugs (n = 156, 32%).

Unlike many of the studies performed evaluating PAC use in surgical patients, the ESCAPE trial attempted to determine if therapy guided by PAC measurements in congestive heart failure (CHF) patients would improve survival time in the first 6 months following hospital discharge as well as improve quality of life [11]. PAC specific targets included a pulmonary capillary wedge pressure of 8 mmHg and a right atrial pressure of 12 mmHg. The study showed that, independent of PAC use, therapies to reduce volume overload improved outcomes in CHF patients The PAC did not affect duration of hospitalization or overall mortality. The study did show that there was a trend to improved quality of life in the PAC group, which they attributed to decreased symptoms of heart failure in patients who had lower cardiac filling pressures. Similarly, Mimoz et al. conducted a prospective cohort study in intensive care unit patients who receive PAC to determine if assessment of PAC measured variables which prompted changes in therapy improved outcomes [19]. Interestingly, they noted improved outcomes, specifically lower mortality rate, in patients who received PAC directed changes in therapy. In this study, patients with circulatory shock unresponsive to standard therapies benefited most from the PAC. In intensive care unit patients with acute lung injury, the NHLBI compared 60 day mortality in a population of patient's managed with a PAC versus CVP alone and determined that PAC use did not improve mortality and was actually associated with more catheter related complications, predominantly arrhythmias [12].

In a specific population of patients undergoing cardiac surgery Tuman et al. noted that managing post coronary artery bypass graft patients with PAC did not affect outcomes, specifically length of stay, occurrence of post-operative myocardial infarction, in-hospital death, major hemodynamic issues, and other non-cardiac complications [20]. They also noted that there were no changes in outcome in 39 patients who were managed with CVP monitoring alone, although many of those patients ended up receiving PAC during their hospitalization due to issues maintaining stable hemodynamics.

PAC use is unlikely to be relevant to all ICU patient populations, although there is little data to guide the selection of patients who may benefit from PAC placement. Many centers routinely place PAC in all cardiac surgery patients, which may be an unnecessary use of resources. One of the few studies to look at patient selection for PAC was a retrospective cohort study by Schwann and colleagues. They evaluated the criteria used to place PACs in cardiac surgery patients to investigate whether routine placement versus selective placement of PACs impacted specific outcomes: length of stay, operative mortality, perioperative MI, re-operative bleeding, and respiratory failure [21]. The selection criteria they used for PAC placement included emergency surgery, re-operation, unstable angina, severe coronary artery disease, recent myocardial infarction, severe left ventricular failure, or other organ dysfunc-

tion such as renal failure or severe COPD. They concluded that using selective criteria for PAC placement in cardiac surgery patients was safe, and extrapolated that this would result in less catheter associated complications, less resource utilization, and did not negatively affect surgical outcomes.

Despite the wide range of studies that determine that use of PAC is equivocal and possibly even harmful, a retrospective study of patient's undergoing cardiac surgery between 2010 and 2014 from the National Anesthesia Clinical Outcomes Registry from the Anesthesia Quality Institute showed that PACs were placed in 34% of these patients, indicating the PAC placement is common practice among cardiac surgery patients [13].

Minimally Invasive Cardiac Output Monitoring

Cardiac output monitoring is commonly used and many practitioners consider it a valuable tool in postsurgical and critically ill patients for assessment and to guide therapy. Concerns about invasive monitoring with the PAC may have prompted the development of less invasive methods to assess cardiac output such as the Pulse Index Continuous Cardiac Output (PiCCO) and the Lithium Dilution Cardiac Output (LiDCO) monitors. Both of these devices measure cardiac output based on pulse contour analysis. This methodology is used to estimate stroke volume by analyzing the arterial pressure waveform on an arterial line.

The PiCCO monitor requires placement of a central line and a specific thermistor-tipped arterial line, which should be placed in the femoral artery for the greatest accuracy, but alternate catheters are available for other sites including the brachial or radial arteries. The system is calibrated by transpulmonary thermodilution: a bolus of cold saline is injected into the central line and read out at the arterial line. This can also provide an estimate of cardiac output. Once the device is calibrated it can analyze the arterial pressure waveform to estimate stroke volume. The LiDCO system is logistically similar to the PiCCO system in that both venous and arterial access are required. Instead of cold saline, a lithium chloride solution is injected and cardiac output is estimated based on change in concentration instead of change in temperature. An advantage is that this device does not require a large artery for the arterial line, nor does the lithium have to be injected into a central vein [22].

There are limited studies available to evaluate the use of these devices. Hadian et al. compared cardiac output trending by LiDCO, PiCCO, and PAC in postoperative cardiac surgery patients [3]. In this study they found that all the monitors displayed similar mean cardiac outputs, however the trends differed in response to therapy. Additionally the LiDCO monitor was more closely correlated with the PAC then the PiCCO monitor was. They concluded that each device would need to be validated independently as opposed to in comparison to the PAC. Cecconi et al. performed such a study with the LiDCO monitor [22]. Although they used a

small number of patients (n = 35), they concluded that in order for the measurement of cardiac output to be most accurate, three measurements should be made and averaged. A study by Gueret and colleagues compared cardiac output measurement by pulse contour analysis against bolus thermodilution with a PAC in patients undergoing off pump coronary artery bypass grafting [22, 23]. They concluded that pulse contour analysis is not interchangeable with bolus thermodilution in this group of patients and may actually over-estimate cardiac output. Several studies have validated the use of LiDCO in comparison to traditional thermodilution using a PAC. A study by Rodig et al. compared the PiCCO monitor with both continuous cardiac output monitors and bolus thermodilution technique used intraoperatively during coronary artery bypass surgery and found that these devices produced similar cardiac output measurements. A limitation was that large changes in systemic vascular resistance affected the calibration of the PiCCO monitor [24]. There are few data available to support or argue against the use of these devices.

Recommendations

A common clinical dilemma that arises in the care of postoperative and critically ill patients is how one should assess and manage intravascular volume status and the use of vasoactive agents to achieve adequate tissue perfusion. There are several hemodynamic monitoring devices that have been used to help guide treatment to achieve those goals.

All of the monitors we reviewed require central venous access. There is high quality evidence that subclavian or internal jugular placement is superior to femoral placement of central venous catheters. Procedures such as the use of sterile technique with maximal barriers and active evaluation and removal of unnecessary catheters decreases the rate of catheter related infections. Thus, we make a strong recommendation to place central venous catheters in the subclavian or internal jugular veins using evidence-based sterile technique and catheter management. There is a lack of high quality evidence regarding the use of a specific hemodynamic monitoring modality in improving morbidity and mortality. We make a weak recommendation of using CVP monitoring routinely to guide volume responsiveness. We also make a weak recommendation that the PAC may be of most use in patients with severe heart failure. There are not enough studies regarding minimally invasive monitors and how they compare to PAC and CVP monitoring. We make no recommendation regarding pulse-contour analysis devices such as the LiDCO and PiCCO monitors.

The value of a device and the information provided is only as valuable as the knowledge and comfort level of the physician interpreting the information, the data the clinician has about the patient they are managing, and the treatment algorithms in place.

A Personal View of the Data

The care of postoperative and critically ill patients requires an assessment of the circulation to allow for decision-making that can affect end-organ perfusion. Despite the lack of evidence supporting CVP monitoring and the measurement of cardiac output or stroke volume, the clinical use of these devices persists. This raises the possibility that the information obtained from invasive monitors may be useful in current practice. It may complement echocardiography and arterial waveform analysis such as pulse pressure variation. Invasive monitors are likely to be useful when there is concern about right-sided cardiac function such as patients with right ventricular failure or severe pulmonary hypertension. These states are present in some of the highest acuity patients found in the CT-ICU such as those with heart transplant, left-ventricular assist device implant, or lung transplant. The need for invasive monitoring must be balanced with the risk of infectious complications, vascular injury, and line-associated thrombosis.

Recommendations

- In order to minimize the risk of infection when placing a central venous catheter, one should utilize the subclavian site first if possible, followed by the internal jugular site, before placement into the femoral vein (Evidence quality: High, Strong recommendation)
- During placement and management of a central venous catheter procedures such as hand washing, sterile barrier technique, swabbing the site with chlorhexidine, and removal of unnecessary catheters will decrease the change of catheter associated infection (Evidence quality: High, strong recommendation)
- Use of the pulmonary artery catheter to guide management of congestive heart failure patients improves outcomes and quality of life (Evidence quality: high, weak recommendation)

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Chapter 12
Role of Ultrasound Guidance for Central Venous Access, Chest Tube Insertion, and Interventional Management of Cholecystitis in ICU Patients

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Introduction

The applications for ultrasound imaging has extended beyond the realm of diagnostic radiology to provide new treatment potential. Many specialties have embraced image guidance to develop innovative techniques with practical solutions for both complex and simple treatment challenges. Ultrasound guided procedures are particularly apposite for critically ill patients by virtue of potentially achieving comparable outcomes via a less invasive approach relative to conventional surgical approaches. Understanding the comparative outcomes for percutaneous ultrasound guided versus non-image guided methods can aid in the advocation and pursuit of the most appropriate treatment option. Common clinical necessities for which ultrasound guided procedures may be considered for patients in the CT ICU include central venous access, chest tube insertion, and interventional management of cholecystitis. In this chapter, we review the literature for comparisons of success rates and complications for both ultrasound guided and traditional surgical approaches.

Search Strategy

A literature search of English language publications from 2003 to 2018 was used to identify published literature to compare procedural outcomes, complications, and recommendations using the PICO outline (Table 12.1) between the ultrasound and non-image guided approaches for central venous access, chest tube

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Table 12.1 PICO table for ultrasound guided interventions of central venous access, chest tube insertion, and interventional management of cholecystitis in the ICU patient

P (Patients)	I (Intervention)	C (Comparator)	O (Outcome)
ICU Patients requiring central venous access	Ultrasound guided placement	Non-image guided placement by anatomic landmarks	Technical success, complications
ICU Patients with pneumothorax or pleural effusion requiring intervention	Ultrasound guided placement small bore chest tube (<18F) via Seldinger Technique	Blunt dissection for placement of large bore chest tube (>18)	Technical success, complications
ICU Patients with cholecystitis requiring intervention	Ultrasound guided gallbladder aspiration or cholecystostomy placement	Laparoscopic cholecystectomy	Technical success, complications

insertion, and interventional management of cholecystitis. Databases searched were PubMed, Science Citation Index/Social sciences Citation Index and Cochrane Evidence Based Medicine. The following terms were used: "ICU" or "high risk", AND "ultrasound" or "anatomic landmark", AND "central venous access", "chest tube", "thoracostomy", "small bore", "gallbladder aspiration", "cholecystostomy", or "laparoscopic cholecystectomy". Studies were excluded if procedures were not performed for ICU or high-risk patients. The data was classified using the GRADE system.

Results

Central Venous Access

Central venous assess is a common ICU requirement with principal risks that include failure to access and puncture damage of adjacent structures. Traditionally, needle trajectory is guided by anatomical landmarks and palpation of adjacent arteries. Familiarity with ultrasound may allow visual localization of the target vein and evaluation of surrounding anatomy by realtime two dimensional grey scale and color Doppler images. Upon confirmation of puncture suitability, the central vein may then be accessed by direct ultrasound guidance throughout needle insertion. Alternatively, sonographic evaluation may guide the operator by identification of the most suitable skin location for skin entry, so that the skin may be marked for a subsequent blind approach. Four systematic reviews and six guidelines were included in this comparative analysis of central venous access by ultrasound versus anatomic landmark guidance (Table 12.2). Given the robust literature coverage from these studies, details of individual single-center studies are here within not reported.

For the use of ultrasound guidance in access to the internal jugular vein, a Cochrane review of the literature from 1966 to 2013 reported a modestly improved

Table 12.2 Central venous access outcomes comparing ultrasound and anatomic landmark techniques

					Total complication rate			Procedural success rate			Arterial puncture		
Author (year)	Study type (quality of evidence)	Venous access	Total studies included	Total N	Anatomical landmark	Ultrasound guidance	Relative effect (95% CI)	Anatomical landmark	Ultrasound guidance	Relative effect (95% CI)	Anatomical landmark	Ultrasound guidance	Relative effect (95% CI)
Brass (2015) [1]	Systematic review (low)	Internal Jugular	35	5108	135 per 1000	39 per 1000	RR 0.29	876 per 1000	982 per 1000	RR 1.12	94 per 1000	26 per 1000	RR 0.28
Brass (2015) [2]	Systematic review (3-low)	Subclavian	9	2341	111 per 1000	58 per 1000	RR 0.52	877 per 1000	921 per 1000	RR 1.05	59 per 1000	12 per 1000	RR 0.21
Lalu (2015) [3]	Systematic review (low)	Subclavian	10	2168	168 per 1000	98 per 1000	OR 0.531	860 per 1000[a]	886 per 1000[a]	N/A	62 per 1000	20 per 1000	
Brass (2015) [2]	Systematic review (low)	Femoral	4	2030	N/A	N/A	N/A	789 per 1000	876 per 1000	RR 1.11	168 per 1000	67 per 1000	RR 0.4
Rabindranath (2011) [4]	Systematic review (low) specifically hemodialysis	Internal Jugular, Femoral, Subclavian	7	830	N/A	N/A	N/A	918 per 1000[a]	998 per 1000[a]	N/A	92 per 1000	16 per 1000	RR 0.22

[a]Calculated from reported total failure data

success rate (23 trials, 4340 participants, RR1.12, 95% CI 1.08–1.17; $p < 0.00001$, $I^2 = 85\%$) and a decreased number of required attempts for successful access (16 trials, 3302 participants, mean difference −1.19 attempts, 95% CI −1.45 to −0.92; $p = <0.00001$, $I^2 = 96\%$) when compared to the use of anatomical landmarks [1]. The same review reported significantly decreased complication rates with ultrasound guidance, an overall reduced rate of total complications by 71% (14 trials, 2406 participants, RR 0.29, 95% CI 0.17–0.52; $p < 0001$), a reduction of inadvertent arterial puncture by 72% (22 trials, 4388 participants, RR 0.28, 95 CI 0.18–0.44; $p < 0.00001$), and an overall reduced chance of hematoma formation by 73%. A special note was made that the data support the use of direct realtime ultrasound guidance throughout needle insertion into the internal jugular vein, and not merely for skin marking.

The correlative Cochrane review for access to the subclavian and femoral veins was less supportive [2]. For subclavian vein access, no difference was found in the number of attempts for successful cannulation, although fewer complications were summated for arterial puncture (3 trials, 498 participants, RR 0.21, 95% CI 0.06–0.82; $p = 0.02$, $I^2 = 0\%$) and hematoma formation (3 trials, 498 participants, RR 0.26, 95% CI 0.09–0.76; $p = 0.01$, $I^2 = 0\%$). For femoral vein access, no difference was found in complication rates, although overall success was mildly increased (RR 1.11, 95% CI 1.00–1.23; $p = 0.06$, $I^2 = 50\%$). In 2015, Lalu and colleagues performed a systematic review of ultrasound guided subclavian vein catheterization for the Canadian Perioperative Anesthesia Clinical Trials Group that included 10 studies with a total of 2168 participants [3]. Although failure rates were unchanged the use of ultrasound resulted in reduced complications from arterial puncture, pneumothorax, and hemothorax formation as well as a reduced overall complication rate (OR: 0.531, 95% CI 0.41–0.69; $I^2 = 69.0\%$). Additional study findings support the use of real-time dynamic 2D ultrasound during catheterization to significantly reduce overall complications (OR; 0.298; 95% CI 0.20–0.44; $I^2 = 52.2\%$).

Another Cochrane review in 2011 specifically evaluated ultrasound guidance for dialysis access [4]. Recommendations are made for ultrasound guidance in both tunneled and non-tunneled access into the internal jugular vein. There is no recommendation for ultrasound guidance in femoral or subclavian vein hemodialysis access, as only one included study covered access into all three major central veins. This systematic review found real-time two-dimensional Doppler ultrasound guidance significantly reduced the first attempt failure (5 studies, 595 catheters, RR 0.40, 95% CI 0.30–0.52), the risk of arterial puncture (6 studies, 535 catheters: RR 0.13, 95% CI 0.04–0.37), and the complication of hematoma (4 studies, 323 catheters; RR 0.22, 95% CI 0.06–0.81). Ultrasound guidance was also noted to decrease time for successful cannulation, as described in one study within this review.

Several US and international societies have published recommendations and guidelines with some small variations in categorical level of evidence, degree of consensus, and strength of recommendations. Selected recommended guidelines are listed in Table 12.3 to include the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists in 2012 [5], the American Society of Anesthesiologist task force in 2012 [6], a decentralized international conglomerate

Table 12.3 National and International Consensus recommendations for the use of ultrasound guidance for central venous access

Author (year)	Overall recommendation (category-evidence level)			Specific recommendations
	Internal jugular	Subclavian	Femoral	
Trioanos (2012) [5]	Strongly recommended (A-1)	Equivocal (A-3)	Equivocal (C-2)	Internal jugular vein: recommended use of real-time ultrasound whenever possible to improve success and reduce complications
				Subclavian vein: current literature does not support routine use of ultrasound for uncomplicated patients. High-risks patients may benefit from ultrasound screening to identify location and patency
				Femoral vein: equivocal with insufficient evidence to support recommendations. Recommendation of committee that real-time ultrasound used to identify vessel overlap and patency when feasible
Rupp (2012) [6]	Equivocal (A1–2)	Equivocal (A2–3)	Equivocal (A2–3)	Consultants and members agree that status ultrasound imaging should be used in elective situations for internal jugular vein access, equivocal for subclavian and femoral vein. Consultants agree and members equivocal that real time ultrasound should be used for intraanal jugular or femoral veins, and are both equivocal for subclavian vein
Lamperti (2012) [7]	Not specified by vein	Not specified by vein	Not specified by vein	Ultrasound guidance should be routinely used for short term and long term central venous access in adults (level A evidence, very good degree of consensus, strong level of recommendation)
Frankel (2015) [8]	Strong (A-1)	Conditional (C-2)	Strong (A-1)	Internal jugular vein: recommend dynamic ultrasound guidance to improve success, shorten procedure time, reduce complications
				Subclavian vein: suggest ultrasound guidance is of limited value
				Femoral vein: recommend dynamic ultrasound guidance to improve success rate and reduce complications, although this benefit is mostly realized by novice operators
Jenssen (2016) [9]	Not specified by vein	Not specified by vein	Not specified by vein	Ultrasound vessel screening and imaging of target vessels should be performed to determine most appropriate anatomical site and optimal patient positioning for central vascular access (D-5, strong consensus)
				Real-time ultrasound guidance rather than assistance should be routinely used for both short-term and long-term central venous access (A-1, strong consensus)
Bodenham (2016) [10]	Recommended (category/level not specified)	Recommended (category/level not specified)	Recommended (category/level not specified)	Ultrasound should be used routinely for internal jugular venous catheter insertion, recommends use for other central venous access sites, but recognizes evidence is limited

that published their recommendations in Intensive Care Medicine in 2012 [7], the American College of Critical Care Medicine in 2015 [8], the European Federation of Societies for Ultrasound in Medicine and Biology in 2016 [9], and the Association of Anaesthetics of Great Britain and Ireland in 2016 [10].

Chest Tube Placement

Tube thoracostomy is a common procedure performed within the CT ICU. The placement of small bore drains (<18F) via an ultrasound guided Seldinger technique is gaining prevalence as a minimally invasive alternative to traditional blunt dissection placement of large bore drains (>18F). Procedural risks for either approach include damage to the subcostal artery resulting in hemothorax, perforation of intrathoracic or intraabdominal organs, and diaphragmatic laceration. This comparative review specifically focuses on overall outcomes comparison for ICU patients with pneumothorax or pleural effusion. In-depth subgroup comparison based on etiology of pneumothorax or effusion, exact drain sizes, and the concomitant use of fibrinolytic or other agents for empyema are beyond the scope of this concise review. Only three cohort articles were included in this analysis with specific criteria for ICU or high risk patients (Table 12.4).

Pneumothorax management by the placement of small bore chest tubes using an ultrasound guided Seldinger technique is described in multiple small cohort retrospective reviews in non-ICU patients with high technical success and low complication rates. No prospective randomized study, systematic review, or evidence-based recommendation guidelines could be found specifically for ICU patients. In Lin and colleagues' 2009 retrospective single-center review of 62 ICU patients with pneumothoraces that underwent 70 episodes of pigtail drain placement (12-16F), complication rate was 5.7% and overall success rate was 68.6% (48/70) with higher rates of success for iatrogenic pneumothorax compared to barotraumatic (87.5% vs 43.3%, $P < .0001$) [11]. In their 2012 retrospective single-center review, Contou and colleagues retrospectively assessed outcomes in 212 intermediate ICU patients with pneumothorax treated by a single-lumen 5F catheter placed via Seldinger technique compared to conventional dissection placement of a 14-20F drain [12]. Similar failure rates were reported for both techniques (18% vs 21%, $P = 0.6$), although patients treated with small bore technique had significantly decreased duration of drainage (3.3 vs 4.6, $P < 0.1$) and an observed decreased hospitalization (4.5 vs 5.2, $p = 0.20$). It is uncertain the degree to which selection bias affected this finding. Both of these retrospective studies note that in the event that small bore drainage failed, large bore drainage was often performed with some improvement in outcomes. For Lin and colleagues, 16 of the 20 small bore drain failures were subsequently treated by large bore blunt dissection with additional surgery avoided in 14 of these patients. Similarly, 7 of 20 patients with small bore technique failures for Contou and colleagues underwent blunt dissection for large bore drain placement, with additional surgery avoided in 4. The small cohort size

Table 12.4 Treatment of ICU or high risk patients with ultrasound guided placement of a small bore chest tube versus blunt dissection placement of a large bore chest tube

Author (year)	Disease managed	Study purpose	Study design	Total N	Overall complications		Clinical success rate	
					Small bore	Large bore	Small bore	Large bore
Lin (2009) [11]	Pneumothorax	Efficacy and safety of small bore chest tube in mechanically ventilated patients (12–16 Fr)	Retrospective cohort	62	5.7% (4/70 – no major, 3 pleural infections, 1 clogged tube)	N/A	68.6% (48/70)	N/A
Contou (2012) [12]	Pneumothorax	Compare effectiveness of treatment with 5 Fr vs 14–20 Fr drains	Retrospective cohort	212	Not reported	Not reported	82.1% (92/112)	79% (79/100)
Liang (2009) [13]	Pleural effusion or empyema	Effectiveness of ultrasound-guided pigtail catheter drainage (10–14 Fr)	Retrospective cohort	133	12% (16/133)	N/A	57.9%[a]	N/A

[a]See discussion in text for success rate subgrouped by type of effusion

and likelihood for selection bias based on severity of underlying disease and comorbidities render these studies low impact.

In the management of pleural effusion and empyema, there are again small retrospective reviews that describe high technical success rates and low complication rates for ultrasound guided placement of small bore chest tubes using Seldinger technique in the non-ICU patient. These low impact studies suggest the technique as an efficacious alternative to blunt dissection placement of a large bore tube. Again, no prospective randomized study, systematic review, or evidence-based recommendation compares clinical outcomes specifically for ICU patients. In 2009, Liang and colleagues retrospectively reported on their single-center outcomes for ultrasound placement of 10-14F pigtail drains for 133 ICU patients with pleural effusion or empyema [13]. Small bore drain placement success rate was reported at 57.9% (77/133), highest when treating traumatic hemothoraces (3/3) and postoperative pleural effusions (17/20) and most likely to fail for empyema (25/59) although the application of tissue plasminogen factor or DNAse were not mentioned.

Cholecystitis Requiring Intervention

Calculous and acalculous cholecystitis not responding to antibiotics can present a critical clinical dilemma in the ICU patient. While cholecystectomy may be the ultimate curative intervention, comorbidities in this patient population may preclude safe execution. Furthermore, a propensity for delayed diagnosis of acalculous cholecystitis until advanced stages can increase risk for gallbladder perforation, abscess, or sepsis. For these reasons, the ultrasound guided techniques of percutaneous gallbladder aspiration and cholecystostomy tube placement have been used as alternative therapies, with the option to perform cholecystectomy at a future date when overall patient conditions improve. The application of these techniques is largely at the discretion of the provider or treatment teams, without large prospective outcomes comparisons. No widely accepted guidelines exist for procedure indications, techniques, or timing of subsequent cholecystectomy. One randomized control trial, four systematic reviews, and four cohort studies were included in the analysis. Table 12.5 summarizes studies with reported complication and clinical outcomes.

Ultrasound guided gallbladder aspiration may be approached for reduction of gallbladder pressure, infection, or inflammation. Multiple small cohort single center studies report technical success and complication rates with a high degree of variability in technique and reporting detail. Technical variability includes differences in needle gauge, reporting of single versus repetitive aspiration, and the use of concomitant antibiotic instillation. In addition, reporting appears incomplete for appropriate subcategorization of patients between those with acalculous versus calculous cholecystitis. Lastly, reporting is inconsistent for recurrence rates of cholecystitis in patients not treated with subsequent cholecystectomy. In a literature review spanning 2000–2015, Rassameehiran and colleagues identified 3 studies with a total of

Table 12.5 Treatment of ICU or high risk patients with cholecystitis with percutaneous gallbladder aspiration or cholecystostomy tube placement versus cholecystectomy

Author (year)	Intervention	Study purpose	Study design	Percutaneous treatment			Cholecystectomy (combined open and laparoscopic)		
				Total N	Overall complications	Clinical success	Total N	Overall complications	Clinical success
Rassameehiran (2015) [14]	Aspiration	Evaluate benefits and risks of percutaneous gallbladder aspiration for acute cholecystitis (high risk group identified)	Systematic Review (3 studies)	131	2.3% (3/131)	80.9% (106/131)	N/A	N/A	N/A
Komatsu (2016) [15]	Aspiration	Evaluate management outcomes of acute cholecystitis with percutaneous aspiration (high risk subgroup included)	Retrospective cohort	160	Not reported	95.6% (153/160)	N/A	N/A	N/A
Winbladh (2009) [17]	Tube placement	Evaluate efficacy and safety of cholecystostomy tube treatment for acute cholecystitis in the elderly population	Systematic review (50 studies)	1751	6.2% (104/1687)	85.6% (1498/1751)	N/A	N/A	N/A
Friedrich (2016) [18]	Tube placement	Evaluate safety of percutaneous cholecystostomy tube treatment in critically ill patients	Retrospective cohort	96	68.8% (66/96)	82.3% (79/96)	N/A	N/A	N/A
Hall (2017) [21]	Tube placement	Comparison of percutaneous cholecystomy tube placement to laparoscopic and open cholecystectomy in critically ill	Systematic review (Vizient database)	1682	13.26%	N/A	6456	4.86%	N/A
Melloul (2011) [22]	Tube placement	Compare percutaneous gallbladder drainage to emergency cholecystectomy in septic patients	Retrospective cohort	23	8.7% (2/23)	91.3% (21/23)	19	47.4% (9/19)	100% (23/23)

131 high-risk surgical patients with combined overall technical and clinical outcome success rate of 80.9% (106), with 18 of the technical failures requiring salvage cholecystostomy tube, and overall no procedural complications [14]. In 2016, Komatsu and colleagues report their single center retrospective experience with a 95.6% success rate (153/160 patients) in high risk patients, with 7 patients required semi-urgent cholecystectomy and 48 undergoing elective surgery [15]. Although several retrospective studies compare gallbladder aspiration to cholecystostomy tube placement, no randomized controlled trial specifically compares the treatments in high-risk ICU patients or directly compares gallbladder aspiration to laparoscopic cholecystectomy.

Percutaneous image guided placement of cholecystostomy tube has been adopted in many institutions as a more definitive ultrasound guided intervention than aspiration in the high risk patient, as reflected in the literature. For example, Ito and colleagues' prospective randomized controlled trial in non-ICU patients concluded that the clinical effectiveness outcome within 72 h was significantly superior for tube placement over aspiration (27/30 vs 14/28, $p < 0.05$); although the 18% aspiration failure rate may be critiqued as a small-bore 21 gauge needle was standardly employed despite viscous gallbladder fluid [16]. In their 2007 literature review for ultrasound guided percutaneous cholecystomy tube placement in the elderly or critically ill, Winbladh and colleagues described an overall high technical success rate of 98.9% (1693/1712; 50 papers), with complete resolution of clinical symptoms within 48–72 h in 85.6% of patients (1498/1751; 48 papers) [17]. Complication rate was 6.24% (104/1687; 44 papers) of which pneumonia was the most common, while catheter slippage or dislodgement occurred in 8.57% of patients (98/1144; 35 papers). Overall mortality was reported at 15.4% (288/1870; 50 papers) with only 0.36% associated with the procedure itself (7/1861; 51 papers). The most common cause of death was persistent biliary infection. The authors point out that in patients with an accurate diagnosis of acute cholecystitis, percutaneous cholecystostomy tube placement has a high success rate to convert septic cholecystitis into a non-septic condition; however, subsequent laparoscopic cholecystectomy is prudent for definitive treatment. While several small cohort papers do describe low complication rates, Friedrich and colleagues found a remarkably high overall complication rate in ICU patients of 69% and concluded that complication rates may be underreported in the medical literature [18]. These findings prompt further assessment for proper indications and follow up. For example, there are is high variability in the literature regarding any potential maximal time threshold for cholecystostomy placement after diagnosis of acute cholecystitis. In addition, there is a lack of consensus on the best timing for laparoscopic cholecystectomy after tube placement. In their 2015 retrospective review of 46 patients, Yamada and colleagues concluded that the most important predictor for successful laparoscopic cholecystectomy following percutaneous drain placement was placement of cholecystostomy tube within 73.5 h of acute cholecystitis onset [19].

Direct comparison of cholecystotomy to ultrasound gallbladder aspiration or cholecystostomy placement is challenging given the aforementioned variance in reported variables and lack of prospective randomized comparative studies.

Another concerning reality that permeates through all reviews is the acknowledged possibility for possible selection bias as patients treated percutaneously by aspiration or cholecystostomy tube placement may present with worsened clinical comorbidity. For the aforementioned reasons, two comparative reviews were unable to draw conclusive results [17, 20]. A 2009 review for elderly patients >65 years suggested that although percutaneous cholecystostomy technical success and procedure mortality rates were favorable, the sum of 30-day mortality rates plus in hospital mortality were increased for percutaneous drainage relative to a comparable elderly population found on literature review treated with cholecystectomy (15.4% vs 4.5% respectively, $P < 0.0001$) [17]. Furthermore, the etiology of acute cholecystitis in the high risk patient may present different clinical outcomes. Some reports suggest ultrasound guided percutaneous intervention may be favored for acalculous cholecystitis and alternatively surgical intervention may be favored for calculous cholecystitis. In their retrospective review of the Vinzient Clinical Database in 2017, Hall and colleagues compared percutaneous cholecystectomy to open and laparoscopic cholecystectomy specifically for calculous cholecystitis, and concluded cholecystostomy tube placement had higher complication rates, increased length of stay, and greater mortality; however, selection bias and incomplete clinical data are inherent as this database was created for financial and administrative purposes [21]. Conversely, Melloul and colleagues found overall lower morbidity after percutaneous cholecystostomy placement compared to emergency cholecystectomy performed with either open or laparoscopic technique in their single center retrospective review of 42 patients (8.7% and 47% respectively, $p = 0.011$), and concluded that percutaneous drainage represents a valuable alternative treatment but that subsequent cholecystectomy is mandatory in cases of acute calculous cholecystitis [22]. Direct comparison of 30 and 90 day mortality rates in the studies described is limited by the inconsistent documentation of clinical acuity, duration of acute cholecystitis before intervention, conversion rates from tube placement to cholecystectomy, and variable comorbidities. Future guiding evidence may be provided by Kortram and colleagues upon completion of their randomized CHOCOLATE trial [23].

Recommendations Based on the Data

Central venous access with ultrasound access has received high grade recommendations from national and international groups based on low level evidence. The use of ultrasound has been shown to reduce procedural complications, with the use of real-time 2-D and Doppler ultrasound throughout cannulation is favorable over merely using the ultrasound to mark the skin for needle access. Impact is more apparent for access to the internal jugular vein than the subclavian or femoral veins. We make a strong recommendation for the use of ultrasound guided access of internal jugular veins, a weak recommendation for femoral veins, and no recommendation for subclavian veins.

In the treatment of pneumothorax and pleural fluid collection, small bore drains <18 Fr appear to have at least similar outcomes to conventional insertion of large bore drains placed via blunt dissection by the available very low level evidence. Adequate comparison of outcomes or complication rates is not possible due to lack of prospective studies and high variability in reported techniques. We make a very weak recommendation for the use of ultrasound guided placement of small bore drains for the treatment of pneumothorax, pleural effusion, or empyema.

Gallbladder aspiration or drainage under ultrasound guidance provides a potential treatment alternative to cholecystectomy in the high risk patient, with low level evidence to suggest a high technical success rate and low immediate procedural complication rate. Cholecystostomy tube placement has low level evidence suggesting superiority to percutaneous gallbladder aspiration. These ultrasound techniques may be more appropriate for acalculous cholecystitis as a temporizing treatment to bridge for cholecystectomy at a later date. Subsequent cholecystectomy should be performed as soon as possible to minimize tube related complications and provide definitive treatment. We make no recommendation for the treatment of cholecystitis by ultrasound guided percutaneous techniques due to the very low level of evidence.

A Personal View of the Data

The use of ultrasound guidance provides minimally invasive alternatives to conventional surgical approaches that may minimize complications in the high risk ICU patient population, with minimal cost and time investment. Techniques are easily learned and may be suitable for appropriate clinical situations.

All central venous access could benefit from ultrasound guidance, regardless of the selected vein. The use of real-time ultrasound throughout needle puncture, or at the very least a cursory evaluation of the anticipated puncture site for suitability, course, and patency can provide a quick and useful adjunct to anatomical landmarks in order to decrease complication rates.

The placement of small bore chest drains (<18 Fr) using ultrasound guidance presents a minimally invasive treatment option with high technical success and low complication rates. Optimal tube size is uncertain, and has been reported from 5 to 16 Fr. An 8–12 Fr initial access allows the option for tube upsize and repositioning should the small caliber drainage fail.

Ultrasound guided gallbladder aspiration or cholecystostomy placement offer minimally invasive treatment options with overall high technical success, demonstrated clinical outcome within 72 h, and low early complication rates. Patient selection criteria are still uncertain, however, the decision to perform percutaneous treatment could be considered to bridge the high risk patient to subsequent cholecystectomy in the near future. Cholecystectomy remains the gold standard.

Recommendations

- For high risk ICU patients requiring central venous access, we recommend the use of real-time ultrasound guidance for internal jugular vein access (evidence quality low; strong recommendation) and femoral vein access (evidence quality low; weak recommendation). An equivocal recommendation for ultrasound guidance during subclavian vein access is based on low quality evidence.
- For high risk ICU patients with pneumothorax, pleural effusion, or empyema requiring intervention, the placement of a small bore <18 Fr chest drain using ultrasound guidance may be considered in lieu of large bore >18 Fr chest drain using blunt dissection (evidence quality very low; very weak recommendation).
- For high risk ICU patients with cholecystitis requiring intervention, the minimally invasive treatments of percutaneous gallbladder aspiration and cholecystostomy tube may be considered as a temporizing measure until the clinical acuity stabilizes for definitive cholecystectomy (evidence level low; weak recommendation).

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Chapter 13
Focused Cardiac Ultrasound in the CT ICU: Helpful or Just Another Toy?

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Introduction

Cardiac imaging in the CTICU (cardiothoracic intensive care unit) is an essential tool in the pre- and postoperative management of patients. The critical nature and complex instrumentation of these patients makes the ability to perform cardiac imaging at the bedside paramount. While plain radiography is commonly used to assess endotracheal tube and line position as well as the lung fields, it is of little help in assessing cardiovascular structure and hemodynamics. Echocardiography is the mainstay for cardiac imaging in the CTICU as the equipment is readily brought to the bedside and results are available in real time with no need for advanced image processing or image display on a dedicated workstation.

While echocardiography is an indispensible tool in the evaluation of critically ill CTICU patients, comprehensive examinations performed by a sonographer and interpreted by a cardiologist are not typically available 24/7. In addition, at times patients may need urgent or frequent serial evaluation, which are difficult for echocardiography labs to address quickly and/or frequently enough. Miniaturized ultrasound platforms, which are easier to operate and substantially smaller in size and lower in cost, have become available in the last decade. This has lead to the concept of focused cardiac ultrasound (FCU) examination. **FCU is an examination of the cardiovascular system using ultrasound by a non-cardiologist to identify a defined list of diagnoses in specific clinical settings.** These FCU findings when used in conjunction with other bedside measures, such as physical exam and

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monitoring devices, allow formulation of a diagnostic impression and guide appropriate triage and management. This chapter will address the use of FCU in critically ill patients, with a focus on the CTICU where data is available.

Search Strategy

A literature search of English language publications in Medline from 2007 to 2017 was used to identify published data on FCU use in the ICU/CTICU setting (Table 13.1). A 10-year span was selected (rather than longer) because this technology has been rapidly evolving. Terms used for FCU were: "ultraportable echocardiography", "focused cardiovascular ultrasound", "focused transthoracic echocardiography", "focused echocardiography", "focused cardiac ultrasound", "point of care transthoracic echocardiography", "point of care echocardiography", "point of care cardiac ultrasound", "hand-held echocardiography", "hand-held cardiac ultrasound", "hand-held ultrasound", "pocket echocardiography", "pocket-sized transthoracic echocardiography", "pocket-sized echocardiography", "pocket-size echocardiography", "pocket-size cardiac ultrasound", "pocket ultrasound", "hand-carried echocardiography", "hand-carried cardiac ultrasound", "hand-carried ultrasound", "hand-carried ultrasonography", "point of care ultrasound", "cardiovascular limited ultrasound examination", "bedside ultrasonography", "bedside ultrasound", "bedside echocardiography", "goal-directed transthoracic echocardiography", "bedside cardiac ultrasound". FCU search terms were combined with terms for CTICU: "cardiac surgery", "thoracic surgery", "cardiothoracic surgery", "critical care", "critically ill patients", "surgical icu", "surgical intensive care", "intensive care unit", "intensivist".

Papers that focused primarily on the following topics were excluded for further review in this chapter: pre-operative assessment (n = 3), trauma (n = 1), pediatric critical care (n = 5), case reports (n = 2), or imaging by medical students or nurses (n = 5). Several papers were not pertinent including non-cardiac applications (n = 6), non-ICU setting (n = 2) or multi-organ point of care ultrasound in which the cardiac results are not reported separately (n = 4). Of the remaining 69, a remarkable number were review articles or opinion/editorials (n = 30), which unfortunately speaks to the plethora of opinion on this topic rather than critical evaluation. This chapter is not intended to review the use of bedside ultrasound in non-cardiac thoracic applications (lung) or ultrasound procedural guidance.

Table 13.1 PICO table of focused cardiac ultrasound in the ICU setting

Patients	Intervention	Comparator	Outcomes
Patients being treated in an ICU setting	Focused cardiac ultrasound	Usual care and/or comprehensive echocardiography	Diagnostic accuracy Management change Patient outcome

Results

Confounding Factors in the Literature: Setting/Personnel/Equipment

Only two studies have specifically studied use of FCU in the CTICU setting and in neither of these was the imaging done by a cardiovascular surgeon or resident [1, 2]. The remainder of the papers reviewed were performed in a variety of ICU settings (surgical, medical, and unspecified ICU). It is important to restrict this review to studies where FCU was performed in the ICU setting, as ICU patients are the most difficult patients to image. They frequently are ventilated, have bandages restricting access to the chest wall and are difficult to position in an optimal left lateral decubitus position. Providers with limited experience in cardiac ultrasound will have the most difficultly obtaining useable images in these patients. Accuracy and feasibility where FCU is performed on non-ICU inpatients, outpatients or in the emergency room setting simple don't apply to the ICU.

Assessing the cardiac status at the bedside of critically ill patients after hours or after a change in clinical status is certainly a common scenario for physicians who practice in an ICU setting. While one could argue that cardiac surgical trainees would pickup FCU rapidly given their familiarity with echocardiography and cardiovascular anatomy/pathology, there is simply no significant literature to demonstrate proven clinical value of this strategy. The majority of FCU ICU use published involves imaging by an intensivist, emergency medicine physician or anesthesiologist. A critical look at the value of FCU in the ICU requires understanding the training level of the physician performing and interpreting the images. The results from studies in which the images are acquired or interpreted by providers who have completed level II training in echocardiography or a yearlong ultrasound fellowship simply can't be applied to physicians who have received FCU training. For this reason several studies that were identified in the original search were omitted from further discussion [1–9]. The concept behind FCU is getting trainees or practicing physicians enough training to become proficient in a limited number of high yield cardiac ultrasound views that require limited training and can be performed quickly (Table 13.2).

The final confounder when looking at the FCU CTICU use literature is the equipment used. Ultrasound platforms for cardiac imaging can be broadly characterized into four groups: (1) full functionality platforms, (2) small ultrasound platforms, (3) hand-carried platforms, (4) pocket devices. The size, expense, functionality and

Table 13.2 Key features of an FCU examination in the CTICU

Performed at point of care/bedside
Adjunct (not replacement) to physical examination
Problem/symptom directed
Simplified, targeted imaging protocol
Real time interpretation of imaging
Qualitative over quantitative interpretation
Actionable results for clinical decision making

image quality of these instruments vary substantially. FCU users typically prefer smaller devices, as their portability and ease of use make them well suited for the ICU environment. The larger devices can be used, but increase expense and add functionalities that a provider who had limited FCU training can't take advantage of or may attempt to use without the appropriate training risking erroneous assessments. Unfortunately there is no standardization of terminology in the field. A study that advocates the value of "bedside ultrasound in the ICU" could have been performed by a level II trained echocardiographer on a full platform device or by an FCU user with 6 hours of training on a pocket sized platform. While both have valid data, their applicability is markedly different.

Protocols

For cardiac imaging in the CTICU, a limited number of views requires less training to master and should be adequate to assess the typical focused questions that arise [10, 11]. Because some views may be limited in a specific patient due to surgical wounds and bandages, familiarity with the subcostal, parasternal and apical windows is reasonable. Providers should not perform any view without being competent in acquisition and interpretation of that view. The parasternal short and long axis views are easier to master than apical or subcostal views [12–14]. Parasternal landmarks are more reliable, and these views consistently provide more interpretable images than apical views. [14, 15] Importantly in the ICU, parasternal views and subcostal views are less dependent on patient positioning and can be performed in a supine, ventilated patient.

FCU Diagnosis

There are a multitude of cardiac diagnoses that can be made using cardiac ultrasound in hands of providers without formal echocardiographic or dedicated ultrasound fellowship training. The FCU user in the CTICU should seek to become proficient in identifying abnormalities that: (1) Are pertinent to their scope of practice in the CTICU. (2) Are within their image acquisition and image interpretation expertise. (3) Have high value when used in combination with other bedside data to direct patient management. (4) Can be acquired quickly at the bedside. (5) Can be obtained in critically ill, supine, ventilated, bandaged and instrumented patients. (6) Have evidence-based data supporting accurate diagnosis by physicians with limited training in cardiac ultrasound.

An international, multispecialty group developed a consensus document for appropriate specific diagnostic targets for an FCU examination (Table 13.3) [11]. These included: LV dimensions and systolic function, RV size and systolic function, volume status, pericardial effusion/basic signs of tamponade and gross valvular abnormalities. The use of Doppler techniques in FCU, was not felt to be in scope by

Table 13.3 Evidence-based targets for an FCU examination

Target	Assessment	Level of evidence
LV systolic function	Normal/reduced/severely reduced	++++
LV size	Normal/enlarged	++
LVH	Normal/mild/marked	++
RV size	Normal/enlarged	+++
LA size	Normal/enlarged	++
Pericardial effusion	Absent/present/large	++++
IVC size/collapse	Small/collapsible Large/non collapsible	+++
Gross structural valve abnormalities	Abnormal	++
Large intracardiac masses	Abnormal	++
Aortic dissection	Not appropriate for users with FCU experience	
Vegetation		
Wall motion		
Intracardiac thrombus		
Congenital heart disease		

this consensus panel [11]. Although the ability to detect abnormalities at the bedside with FCU is lower than a comprehensive echocardiogram, FCU allows detection of cardiac pathology more accurately than traditional bedside physical examination assessment [16]. This is particularly true in the typical CTICU patient who is ventilated, immobile and instrumented in whom cardiac physical examination is often very limited.

Clinical Use

FCU is not just to detect disease, but should impact clinical decision-making. However, most studies have focused on evaluating FCU accuracy to detect specific abnormalities and have not addressed the added clinical value of FCU. There are limited data on the use of FCU in the ICU to affect medical decision-making, and even fewer studies addressing FCU use on patient outcome. Unfortunately, some of the studies used to justify the value of FCU in critically ill patients have not simulated real-life FCU use as the images were acquired or interpreted by providers with at least level II echocardiographic training [3, 5] or evaluated the value of comprehensive echocardiography in the ICU [17–20].

Manasia and colleagues did test the value of FCU guided management in the SICU in a 2005 paper [21]. They showed that intensivists with limited ultrasound training (10 h total didactic and hands-on) who performed a goal-directed ultrasound examination provided new information and changed management in over one-third patients and useful information (without immediate management change) in nearly one-half of patients. Killu reported on their experience with a point of care ultrasound

program in three surgical ICU fellows whose training included 30 h of didactic and 25–50 examinations in several areas of diagnostic focus including lung and pleura, abdominal, procedural guidance and FCU/hemodynamics. The authors reported new diagnoses were frequently made (65%) as were changes in patient management (37%), although the contribution from FCU is not individually delineated [22].

In the absence of more studies addressing impact on patient care, the diagnostic ability of FCU in the ICU can be reviewed (Table 13.4). Providers without ultra-

Table 13.4 Useof FCU in the ICU for diagnosis and patient management

Author	Setting	Patients	Ultrasound targets	Comparison	Results	Quality evidence
Carr (2007) [29]	SICU	70	LVF/LVS IVC	Expert clinical	65–75% Concordance in assessment of hypovolemia	Low
Vignon (2007) [23]	MICU	61	LVF/LVE RVE/PE	TTE	Good agreement (kappa) LVF 0.76; LVE 0.66; RVE 0.71; PE 0.68	Low
Gunst (2008) [26]	SICU	22	LVF/LVE RVF/RVE PE/IVC	PA Catheter	"Significant correlation" with CI and CVP	Low
Mark (2009) [28]	SICU	80	Visual LVF	TTE	Mean bias −3.4 for LV EF	Low
Melamed (2009) [27]	MICU	44	LVF	TTE	82% correct classification	Low
Stawicki (2009) [35]	SICU	124	IVC	RAP	Correlation with invasive pressure at high and low RAP	Low
Vignon (2011) [30]	MICU/ SICU	201	LVF; LVE; RVE; PE; IVC;	TTE	Agreement (kappa) for LVF (0.84); LVE (0.90); RVE (0.76); IVC (0.79)	Moderate
Prekker (2013) [36]	MICU	65	IVC	Predict RAP >10	85% sensitivity	Low
Hulett (2014) [24]	MICU	*	LVF; RVF; PE; IVC	Assessment tool	Knowledge 58–86%; Acquisition skill 0–79%	Moderate
See (2014) [25]	MICU	343	LVF; LVE; RVE; PE; IVC;	Expert review FCU images	Progressive improvement from 10–20 to 30–>30 scans for LVF; RVF; PE; IVC	Moderate
Townsend (2016) [13]	SICU	390	LVF/RVE; PE; IVC	Expert review of FCU images	85% competency; LVF; RVE; IVC	Moderate

Abbreviations: SICU Surgical intensive care unit, *MICU* medical intensive care unit, *LVF* left ventricular function, *LVE* left ventricular enlargement, *RVF* right ventricular function, *RVE* RV enlargement, *IVC* inferior vena cava, *PE* pericardial effusion

sound experience can learn to identify the presence or absence of **pericardial effusion** in ICU patients after brief training [7, 23–25]. As pericardial effusion is one of the simpler pathologies to detect, diagnostic accuracy has even been shown with pocket-sized devices in the ICU [7]. FCU has been shown to improve bedside assessment of LV systolic function [7, 13, 23–30]. Physicians who have had proctored hands-on FCU training can readily distinguish CHF patients with normal versus reduced LV systolic function [31, 32]. It is clear that FCU is superior to physical examination, ECG, chest radiograph, and blood chemistries for detection of **LV systolic dysfunction** in patients with ADHF [31]. FCU may also be used to identify findings suggestive of **pulmonary embolism** (right ventricular enlargement) in ICU patients [13, 23–25, 30].

Identification of **volume depletion** in a hypotensive patient or **volume excess** in a dyspneic patient can facilitate diagnosis and treatment. For patients in the CTICU, the JVP is difficult to assess as patients are supine and often have neck instrumentation. In non-ICU patients, FCU assessment of the inferior vena cava (IVC) is both more feasible and accurate than physical exam to detect elevated central venous pressure [33]. ICU FCU of the IVC correlates with central venous pressure and can assist in management [4, 13, 24, 25, 29, 30, 34–36]. However there are many confounding issues in CTICU patients that lower the value of ultrasound appraisal of the IVC as a measure of volume status including mechanical ventilation, significant tricuspid regurgitation and right heart failure [2].

Training

Several studies have demonstrated acceptable accuracy of FCU in the MICU and SICU setting [13, 23–25, 27–30, 35–38]. However, few of these studies have used surgical providers performing FCU [13, 21, 22, 34]. Training protocols differ with respect to ultrasound device, hours of didactic, duration of training, imaging protocol, number of proctored studies, use of simulation and clinical setting (Table 13.5). A structured training program is the best approach to equip providers with the necessary knowledge and technical skills to perform FCU [39, 40].

Although there is general agreement that proficiency in FCU be determined by competency-based assessment before it is used by a clinician for clinical decision-making, no validated tools exist to determine competency in FCU [11]. There is general agreement that a number of supervised and unsupervised studies be logged before a competency assessment is performed [11, 39, 40]. Focused cardiac ultrasound training should include three core components: didactic education, hands-on imaging practice, and image interpretation/review experience [39, 40]. Simulation and imaging normal subjects can be used to teach basics [13, 37, 41, 42]. However, bedside imaging in the ICU is invaluable experience and acquisition skill seems to increase with number of supervised studies performed [25, 40, 43]. Review of additional cases and images are essential because the variety of pathology experienced during hands-on training does not demonstrate all pathologies and normal variants seen in clinical practice.

Table 13.5 Training protocols for ICU FCU

	Specialty	Hours didactic	Proctored imaging	Studies required	Simulation	Views
Carr [29]	CC/ER	3	Y	25	N	SC; PLAX; PSAX; AP4C
Vignon [23]	CC	3	Y	5 h	N	PLAX; PSAX; SC; AP4C
Gunst [26]	CC/ Surgery	"2-day course"	*	*	N	PLAX; PSAX; SC; AP4C
Mark [28]	ER/CC	3	Y	25	N	SC; PLAX; PSAX; AP4C
Melamed [27]	CC	2	Y	4 h	N	PLAX; PSAX; SC; AP4C
Stawicki [35]	ER/CC	3	Y	25	N	IVC
Vignon [30]	CC	6	Y	6 h	N	PLAX; PSAX; SC; AP4C
Prekker [36]	CC/ER	2	Y	5	N	SC
Beraud [37]	CC	8	Y	25 ± 7	Y	PLAX; PSAX; SC; AP4C
Hulett [24]	CC	2	Y	2 h	N	PLAX; PSAX; SC; AP4C
See [25]	CC	10 (self-directed)	Y	5 (proctored); 40 total median;	N	PLAX; PSAX; SC; AP4C
Townsend [13]	Surgery	3	N	20	Y	SC; PLAX; PSAX; AP4C

Abbreviations: CC critical care, *ER* emergency medicine, *PLAX* parasternal long-axis, *PSAX* parasternal short-axis, *AP4C* apical four-chamber, *IVC* inferior vena cava

A systematic review of critical care ultrasound training studies concluded that initial focus should be on a basic qualitative approach for the assessment of global function and assessment of IVC collapsibility. The mode of education seemed most efficient when a hybrid method was used incorporating both web-based and didactic learning sessions and learning on both simulated and real patients was suggested with a minimum of 30 independent studies [40].

Recommendations Based on Data

The value of comprehensive echocardiography or cardiac ultrasound performed by providers with level II echocardiographic training or completion of an ultrasound fellowship is clear, but not pertinent to a CTICU provider who has completed only FCU training. Providers with limited training in cardiac ultrasound can reliable

identify several cardiac abnormalities in ICU patients including LV systolic dysfunction, pericardial fluid, RV enlargement and IVC size and collapsibility using FCU, although published experience specifically in the CTICU is severely limited. While the ability to recognize a narrow list of cardiac diagnoses with FCU is established, there is very limited data demonstrating how FCU users can alter patient diagnosis and management plan in the CTICU. Training of CTICU providers should be formalized and include didactic, hands-on imaging and case review. Limiting the protocols to specific views both reduces the duration of training and shortens the duration of the bedside FCU examination. The highest yield views appear to be the parasternal long and short-axis views and the subcostal window. These are the views most reliably performed by novice examiners. There is good evidence that adequate clinical accuracy can be achieved with supervised imaging of 25–40 examinations.

Recommendation Summary

- Providers with limited training in cardiac ultrasound can reliable identify several cardiac abnormalities in ICU patients including LV systolic dysfunction, pericardial fluid, RV enlargement and IVC size and collapsibility using FCU (quality of evidence low, strength of recommendation weak).
- Training of CTICU providers should be formalized and include didactic, hands-on imaging and case review (quality of evidence moderate, strength of recommendation strong).

Personal Recommendations

FCU is a valuable tool at the bedside for the evaluation of patients on the intensive care unit. The key issues for successful implementation from my experience training hundreds or residents/students are:

– Formalized training needs to include didactic, but this can be performed independently.
– Formalized training needs to include proctored imaging. Performing only independent studies, while valuable to build volume is not sufficient. The value of having an experienced imager provide “tips” cannot be underestimated.
– Training that involves only simulation or performing studies on normal volunteers at a course are not adequate. While useful to learn basic views and techniques, these do not prepare providers to image in the ICU.
– Training must include case reviews. Proctored and independent imaging may not provide the breadth of clinical diagnoses the provider should be able to recognize. These can be tailored to specific subspecialties.

– Providers must stick to their skill set and scope of practice. Making diagnoses that are subtle or require more experience than the provider has can lead to clinical errors.
– Significant abnormalities should have formal echocardiographic studies ordered.
– FCU images used for clinical decision-making (rather than training only) should be stored and available for clinical review and quality assurance.

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Chapter 14
Inotropes and Vasopressors in the CT ICU: Getting the Mixture Right

Allison Dalton

Introduction

Inotropic and vasoconstrictive medications are commonly used in the cardiothoracic intensive care unit following cardiac surgery to treat cardiogenic and vasoplegic shock respectively. Although clinically proven to improve hemodynamics and optimize cardiac performance, both inotropes and vasopressors have adverse effects. Therefore, it is best practice to optimize inotropic and vasoconstrictor therapy to augment hemodynamic performance while minimizing side effects. Given lack of significant highly graded data there is also great variance in the use of specific inotropes and vasopressors in intensive care units [1–3].

Search Strategy

A literature search of English language publications from 2005 to 2017 was performed to identify the management of inotropic and vasopressor support in adults after cardiac surgery using the PICO outline (Table 14.1). Databases searched include PubMed and Cochrane Library. Search terms included "cardiac surgery," "heart surgery," "postoperative," "ICU," "intensive care unit," "inotrope," "inotropic," "vasopressor," "pressor," "dobutamine," "epinephrine," "dopamine," "levosimendan," "norepinephrine," "vasopressin," "phenylephrine," "methylene blue," "vasoplegia," "vasoplegic shock," "treatment," "mortality," and "arrhythmia." Articles were excluded if they did not pertain to postoperative management or

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Table 14.1 PICO tab

P	I	C	O
Patients	Intervention	Comparator	Outcomes
Adults in shock in the intensive care unit following cardiac surgery	Escalating pharmacologic support by adding drugs	Escalating pharmacologic support by increasing single drug dosage	Hemodynamic stability, cardiovascular stability, arrhythmias, mortality

discuss specific inotropes/vasopressors. Those article's references were also evaluated for relevant sources for inclusion. One meta-analysis, ten randomized trials, four prospective studies, five reviews, one guideline, three retrospective studies and two surveys were identified (Table 14.2). The quality of data in the evaluated papers was classified according to the GRADE system.

Results

Inotropic Drugs

The ideal inotropic medication would be a rapidly titratable drug that improves cardiac output and oxygen delivery without increasing myocardial oxygen demand, while improving diastolic dysfunction and minimizing side effects like arrhythmias. At the same time the ideal inotrope would exhibit long-term survival benefits [4]. Not surprisingly, no ideal inotropic agent has yet been developed. Patients with low cardiac output syndrome (LCOS), defined as cardiac index [CI] <2.4 l/min/m^2 and evidence of organ dysfunction, are at higher risk for longer hospital and ICU stays as well as significant morbidity and mortality [5, 6]. Although no specific agent has been proven to be superior, inotropic agents are utilized in postoperative LCOS to increase cardiac index [5]. Three types of inotropes have been developed for use in LCOS following cardiac surgery.

Catecholamines

Catecholamines increase the production of cAMP by activating adenylate cyclase via beta adrenergic stimulation. The most commonly utilized beta agonists postoperatively, dobutamine and epinephrine, are associated with increases in inotropy and chronotropy with resultant increases in myocardial oxygen demand [4, 5, 7]. Patients may develop tachyphylaxis to catecholamine based inotropes when used for extended periods of time.

Epinephrine has both beta and alpha agonist properties. At low doses epinephrine has predominantly inotropic effects via beta receptor agonist effects but has comparatively more peripheral vasoconstriction than dobutamine secondary to alpha activity.

Table 14.2 Studies analyzed with study type and quality of evidence

Author/published date/citation	Inotropes evaluated	Vasopressors evaluated	Results	Study type/quality of evidence
Argenziano (1998) [20]	N/A	Vasopressin	Vasopressin increases MAP and SVR decreases norepinephrine doses	Retrospective, low
Belletti (2015) [6]	Yes	Yes	Inotropes/vasopressors are associated with decreased mortality in vasoplegia, sepsis and cardiac surgery. Levosimendan is associated with improved survival	Meta-analysis of RCTs, high
Butterworth (1992) [9]	Dobutamine Epinephrine	N/A	Epinephrine and dobutamine significantly increase cardiac index, stroke volume index, heart rate. When compared to dobutamine, epinephrine increases cardiac index significantly less and has less elevations in heart rate	Prospective, low
De Backer (2010) [23]	N/A	Dopamine Norepinephrine	Compared to norepinephrine, dopamine is associated with higher 28 day mortality among patients with cardiogenic shock. Dopamine was associated with more arrhythmia events than norepinephrine	RCT, high
Erb (2014) [16]	Levosimendan	N/A	Compared to placebo, levosimendan is associated with lower requirements of epinephrine and nitroglycerine after 24 h	RCT, low
Follath (2002) [13]	Dobutamine Levosimendan	N/A	Compared to dobutamine, levosimendan improves 180 day mortality, cardiac output and pulmonary capillary wedge pressure	RCT, moderate
Hajjar (2017) [21]	N/A	Norepinephrine Vasopressin	When compared to norepinephrine, vasopressin is associated with a lower composite rate of mortality and severe complications (CVA, mechanical ventilation >48 h, deep sternal wound infection, reoperation, or acute renal failure) within 30 days. Vasopressin is also associated with decreased rates of atrial fibrillation	RCT, high
Landoni (2017) [14]	Levosimendan	N/A	When comparing levosimendan to placebo, there was no significant difference in 30 day mortality, duration of mechanical ventilation, ICU or hospital stay, rates of hypotension, and cardiac arrhythmias	RCT, moderate
Levin (2004) [26]	N/A	Methylene blue	In patients with postoperative vasoplegia, methylene blue is associated with lower morbidity and mortality than placebo. The duration of vasoplegia was shorter in patients receiving methylene blue versus placebo	RCT, low
Levy (2011) [8]	Dobutamine Epinephrine Norepinephrine	N/A	When compared to a regimen of norepinephrine plus dobutamine, treatment with epinephrine is associated with increased heart rate, new arrhythmias, and increased lactate	RCT, low

(continued)

Table 14.2 (continued)

Author/published date/citation	Inotropes evaluated	Vasopressors evaluated	Results	Study type/quality of evidence
Leyh (2003) [25]	N/A	Methylene blue	In catecholamine resistant vasoplegic shock, methylene blue use is associated with significant increases in MAP and SVR. The administration of methylene blue is associated with decreasing norepinephrine dosing	Prospective, low
Mazzeffi (2017) [27]	N/A	Methylene blue	In patients with post-CPB vasoplegic shock, methylene blue is associated with significant increases in MAP	Retrospective, cohort, low
Mehaffey (2017) [28]	N/A	Methylene blue	In patients with post-CPB vasoplegic syndrome, early (in the OR) vs late (in the ICU) administration of methylene blue was associated significantly reduced mortality and rates of renal failure, reoperation, prolonged ventilation, operative mortality, and major adverse event composite	Retrospective, low
Mehta (2017) [15]	Levosimendan	N/A	As compared to placebo, prophylactic levosimendan is not associated lower rates of composite end point of death, RRT, periop MI or use of mechanical cardiac assist device	RCT, high
Mishra (2016) [18]	Levosimendan Milrinone	N/A	When compared to milrinone, levosimendan is associated with higher heart rate, increased cardiac index, decreased systemic vascular resistance index and increased requirement of norepinephrine in patients with pulmonary hypertension undergoing cardiac valve surgery	RCT, moderate
Özal (2005) [29]	N/A	Methylene blue	In patients high risk for vasoplegia and undergoing CABG, in comparison to placebo, methylene blue is associated with significantly shorter ICU and hospital length of stay. In the OR, the use of methylene blue is associated with increased SVR and lower norepinephrine, inotropic or fluid requirements	Prospective, moderate
Salgado Filho (2015) [17]	Epinephrine Levosimendan	N/A	When compared to levosimendan, epinephrine is associated with significantly improved LV myocardial performance index and cardiac index. Epinephrine is also associated with lower SVR and higher HR. Epinephrine is also associated with increased likelihood of CPB weaning on the first attempt versus levosimendan. Levosimendan is associated with a significantly higher norepinephrine requirement	RCT, moderate
Tarvasmäki (2016) [1]	Yes	Yes	Epinephrine is associated with increased 90-day mortality as compared to norepinephrine, dopamine and vasopressin	Prospective, low

Dobutamine is a beta1- and beta2- agonist. It causes peripheral vasodilation by way of beta2 receptor activity. When compared to epinephrine, dobutamine has been found to be more effective at increasing cardiac index and is associated with less myocardial oxygen consumption, less arrhythmias and lower renal biomarker levels [1, 8, 9].

Isoproterenol has both beta1- and beta2 agonist effects. Isoproterenol leads to increase inotropy while producing systemic and pulmonary vasodilation [10]. Given its effects on inotropy, chronotropy, and the pulmonary vasculature, isoproterenol may be a preferred agent following heart transplantation in patients with elevated pulmonary vascular resistance [10]. The International Society of Heart and Lung Transplantation recommends the use of isoproterenol for increasing heart rate when indicated following cardiac transplantation [11].

At inotropic doses **dopamine** has less significant increases in cardiac index as compared to dobutamine and can result in increasing pulmonary artery pressures without further increases in cardiac output [5]. Levy et al. recommends that dopamine should never be used to treat LCOS in cardiogenic shock likely related to its' elevated risk of adverse effects compared to other inotropes [7]. Patients may develop tachyphylaxis to catecholamine based inotropes when used for extended periods of time.

Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors (PDE-I) are inodilators that increase cAMP by inhibiting the enzyme, phosphodiesterase, which catalyzes the breakdown of cAMP. In addition to inotropy, PDE-I cause systemic and pulmonary vasodilation and have a specific indication in treatment of pulmonary hypertension and right ventricular failure. In comparison to the beta agonists, **milrinone**, the most used PDE-I, is associated with a lower cardiac index, less tachycardia, and a more significant decrease in mean arterial pressure (MAP) [4, 5]. The significant decrease in MAP leads to an increase requirement for concomitant vasopressor use [5]. Levy and colleagues note that PDE-I use in cardiogenic shock should be limited to patients with right ventricular failure, pulmonary hypertension, catecholamine-resistant shock, or those patients requiring chronic beta blockade [7].

Calcium Sensitizers

Levosimendan is an inodilator that causes increased calcium sensitization of the cardiac myocyte and prolongs the actin-myosin cross-bridge association rate [12]. Given that there is no increase in cAMP or intracellular calcium, levosimendan is not associated with increased myocardial oxygen consumption. In addition to improving cardiac index, levosimendan also leads to pulmonary, systemic and peripheral vasodilation, which can be advantageous in pulmonary hypertension but may result in systemic hypotension [12]. Follath et al. found improved survival in

patients receiving levosimendan [13] but subsequent studies have been unable to replicate those results [14–16]. When compared to epinephrine, intraoperative use of levosimendan resulted in a lower cardiac index and lower incidence of weaning from cardiopulmonary bypass on the first attempt [17]. When compared to milrinone, levosimendan produces comparable cardiac indices and a similar degree of pulmonary vasodilation but may require higher doses of vasopressors to maintain MAP [18]. Levy et al. recommends levosimendan use as a second line agent in patients with LCOS who are resistant to catecholamines treatments or in those on chronic beta blocker therapy [7].

Vasopressors

Vasoplegic shock can confound cardiac surgery and is associated with prolonged cardiopulmonary bypass, endothelial injury and the subsequent release of cytokines and other inflammatory mediators [19]. Patients with a history of low ejection fraction (<35%) or are on preoperative angiotensin-converting enzyme inhibitors (ACE-I) or diuretics are at greater risk for postoperative vasodilatory shock [20]. There are three major classes of vasopressors useful in postoperative vasoplegic shock.

Catecholamines

Catecholamines stimulate the alpha receptors in vascular smooth muscle leading to increases in vascular tone and mean arterial pressure (MAP). Tachyphylaxis may result following prolonged infusion of catecholamine agents in the treatment of severe vasoplegic shock.

Norepinephrine has been considered the standard treatment for postoperative vasoplegia [21]. Norepinephrine increases MAP, provides moderate inotropy via mild beta agonist activity with minimal effect on heart rate [7, 22]. When compared to alpha range doses of epinephrine, norepinephrine is associated with lower cardiac index, lower lactate levels, lower base excess values, and less tachycardia and arrhythmias [7, 22]. Norepinephrine is associated with mild increases in pulmonary vascular resistance and may worsen pulmonary hypertension and right ventricular failure [10].

Phenylephrine is an alpha-1 selective catecholamine associated with significant increases in MAP with minimal effects on heart rate, pulmonary artery occlusion pressure, central venous pressure or cardiac index [22]. Phenylephrine may have detrimental effects on internal mammary artery graft flow [22].

At high doses, **dopamine** acts via alpha-1 receptors to increase MAP. Dopamine has been associated with increases in heart rate and arrhythmias following cardiac surgery [22]. De Backer and colleagues note that in patients with cardiogenic shock there is significantly decreased 28 day mortality with the use of norepinephrine as compared to dopamine [23].

Vasopressin Agonists

Following cardiopulmonary bypass, there is a physiologic deficiency of endogenous arginine vasopressin (AVP) [24]. As a vasoconstrictor, **vasopressin** principally acts on the vasopressin-1 receptor in vascular smooth muscle leading to increased intracellular calcium levels and, subsequently, increased MAP. Postoperative use of vasopressin has been associated with shorter intubation time, shorter ICU length of stay, increased urine output and increased recovery of renal function [22]. When compared with norepinephrine, vasopressin may decrease rates of renal failure, renal replacement therapy, and atrial fibrillation without any significant difference in mortality [21]. Vasopressin is also associated with shorter duration of inotrope and vasopressor support and shorter ICU and hospital stays [21]. When added to norepinephrine, vasopressin can decrease norepinephrine doses by 25–60%, decrease the duration of catecholamine use, and decrease the number of hypotensive episodes while maintaining similar MAP and cardiac index [22]. In a retrospective analysis, Argenziano and colleagues showed that the addition of vasopressin to norepinephrine following heart transplant and LVAD insertion significantly increases MAP and systemic vascular resistance (SVR) as well as decreases norepinephrine doses without changes in cardiac index [20].

Methylene Blue

In refractory vasoplegic shock, one may consider the use of **methylene blue**, an inhibitor of nitric oxide and the enzyme guanylate cyclase. Methylene blue is associated with increased MAP, decreased use of vasopressor medications, and even complete resolution of vasoplegic shock following its administration [25–27]. Multiple studies have shown survival benefit in patients with severe vasoplegic shock after cardiopulmonary bypass [22, 26, 28], but other cohorts of patients have revealed no mortality benefit [27]. Mazzeffi and colleagues note delay in administration of methylene blue may account for loss of mortality benefit [27]. Ozal and colleagues have shown effectiveness in prophylactic administration for prevention of post-CPB vasoplegic shock [29]. Methylene blue is associated with dose dependent adverse effects including cardiac arrhythmias, coronary and pulmonary vasoconstriction, decreased cardiac output, and decreased renal and mesenteric blood flow [29].

Recommendations Based on the Data

Postoperative shock is associated with significant morbidity and mortality. The inotropic and vasoconstrictive medications each have different properties and effects on a patient's hemodynamics and vascular tone (Table 14.3).

Table 14.3 Effects of inotropic and vasopressor medications

	Receptors	Dose	SVR (LV afterload)	PVR (RV afterload)	Contractility	Heart rate
Phenylephrine	α_1	20–200 μg/min	↑↑	↑	–	↓
Vasopressin	V1 (smooth muscle)	0.01–0.04 units/min	↑↑	–	–	–
Norepinephrine	α_1, β_1	2–30 μg/min	↑↑	↑	↑	–/↑
Epinephrine	β_1, β_2	1–5 μg/min	↑	–/↑	↑↑	↑
	α_1	5–10 μg/min	↑↑	↑	↑	↑↑
Dopamine	DA	1–5 μg/kg/min	↓	–	↑	–
	β	5–10 μg/kg/min	–	–	↑↑	↑
	α_1	>10 μg/kg/min	↑	↑	↑	↑↑
Dobutamine	β_1, β_2	1–5 μg/kg/min	↓	↓	↑↑	↑
		5–10 μg/kg/min	↓↓	↑	↑↑	↑↑
Isoproterenol	β_1, β_2	0.5–5 μg/min	↓	↓	↑	↑↑
Levosimendan	Calcium sensitizer	0.05–0.2 μg/kg/min	↓↓	↓↓	↑	↑
Milrinone	PDE-I	0.25–0.75 μg/kg/min	↓	↓↓	↑	↑

Cardiogenic Shock

For patients in cardiogenic shock following cardiac surgery, we recommend strongly for the use of an inotropic medication. There is no significant data that would suggest a specific inotrope over another. Given the combination of its effect on cardiac contractility and favorable side effect profile, I would make a weak recommendation for the use of catecholamines over PDE-I and calcium sensitizers as the first line treatment for cardiogenic shock. For patients with isolated right ventricular shock or pulmonary hypertension, milrinone may be considered for its pulmonary vasodilatory effects. For patients with catecholamine-refractory shock or for those on preoperative beta blockers, PDE-I and levosimendan may be considered. No recommendations can be made whether the addition of inotropic medications or the increase in dosage is most effective to increase inotropic support.

Vasoplegic Shock

Cardiopulmonary bypass places patients at risk for vasoplegia postoperatively. Patients most at risk include those with a preoperative left ventricular dysfunction and those on beta blocker medications. For patients with postoperative vasoplegic shock, we strongly recommend for the use of vasoconstrictive medications. Catecholamines are the standard treatment for vasoplegic shock following cardiac surgery. Due to its vasopressor effects as well as its mild beta effects and comparatively favorable side effect profile, I would give a weak recommendation for the use of norepinephrine as the first line agent for postoperative vasoplegic shock. Clinicians

should consider vasopressin either in addition to or instead of norepinephrine in catecholamine resistant vasoplegic shock (weak recommendation). Finally, in life-threatening, catecholamine-resistant vasoplegic shock, methylene blue may be considered to improve mortality and morbidity (weak recommendation).

A Personal View of the Data

Postoperative shock, whether cardiogenic or vasoplegic, following cardiac surgery is associated with increased morbidity and mortality. Treatment of cardiogenic shock with inotropes and vasoplegic shock with vasoconstrictive medications can improve morbidity and mortality. Catecholamines should be considered first line treatment for both conditions. There is some data to support the addition of other classes of medication (namely vasopressin and methylene blue) in vasoplegic shock. To date, there have been no studies in cardiogenic shock evaluating the effectiveness of supplementing initial treatment with additional medications as compared to increasing the dose of a single inotropic drug. This may be a consideration for future study.

Recommendations

1. For patients with postoperative cardiogenic shock, we recommend the use of inotropic support to improve cardiac index (evidence quality high; strong recommendation)
2. For patients requiring inotropic support, we recommend the use of catecholamines as a first line agent (evidence quality low; weak recommendation)
3. For patients requiring vasopressor support following cardiac surgery, we recommend for the use of norepinephrine as the first line treatment (evidence quality low; weak recommendation)
4. For patients with isolated right ventricular shock and/or pulmonary hypertension, we recommend consideration of PDE-I for treatment of shock (evidence quality low; weak recommendation)
5. For patients with catecholamine-resistant cardiogenic shock, we recommend the use of levosimendan or PDE-I (evidence quality low; weak recommendation)
6. For patients with postoperative vasoplegic shock after cardiac surgery, we recommend the use of catecholamines to increase MAP (evidence quality moderate; strong recommendation)
7. For patients with catecholamine-resistant vasoplegic shock, we recommend the addition of vasopressin (evidence quality moderate; weak recommendation)
8. For patients with life-threatening catecholamine-resistant shock, we recommend for the consideration of administration of methylene blue (evidence quality low; weak recommendation)

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Chapter 15
Prevention of Postoperative Atrial Fibrillation After Adult Cardiac Surgery

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Introduction

The incidence of postoperative atrial fibrillation (POAF) after cardiac surgery is 10–65% [1, 2]. Patient risk factors such as advanced age, male gender, a history of atrial fibrillation, increased left atrial size, hypertension, congestive heart failure, and chronic obstructive pulmonary disease have been linked to its development [1–3]. Given the association of POAF after cardiac surgery with increased morbidity, mortality, length of hospital stay, and healthcare costs [1–4], there has been a great deal of research into measures to prevent its occurrence. As multiple mechanisms are presumed to lead to the development of POAF, a variety of agents have been studied with the intent to decrease systemic inflammation, alter the neurohormonal axis, prevent electrolyte imbalance, reduce ischemia, and thwart electromechanical aberrancies. This chapter reviews the effectiveness of pharmacologic prevention of POAF after cardiac surgery in adults.

Literature Search Strategy

Based on the PICO table (Table 15.1), Pubmed and CENTRAL searches incorporating the terms "prophylaxis" and "atrial fibrillation" and ["cardiac surgery" or "open heart surgery"] were used to review the literature. The bibliography of applicable

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articles was also reviewed. The search was narrowed to focus on clinical pharmacologic intervention, although studies that included a non pharmacologic treatment arm (biatrial overdrive pacing, posterior pericardiotomy, etc.) were included if they also had a pharmacologic arm. Articles specifically about the treatment of postoperative atrial fibrillation, Cox-MAZE procedures, or the effectiveness of left atrial appendage excision were excluded. Studies were included if they were published in the last 20 years. We gave preference to well powered randomized controlled trials and meta analyses, although some consensus statements and review articles are also cited for completeness.

We chose to focus on beta blockers, sotalol, amiodarone, and magnesium, as they have been most widely studied in the literature in the prevention of POAF (Table 15.2). Many other agents have been trialed regarding prophylaxis of POAF, including statins, steroids, fish oil, digoxin, calcium channel blockers, ranolazine, N-acetyl cysteine, and procainamide. In an effort to be concise, we have limited our discussion to the aforementioned four agents. The quality of the data were classified according to the GRADE system, as explained in Chap. 1.

Table 15.1 PICO table of prevention of atrial fibrillation after adult cardiac surgery

Population	Intervention	Comparison	Outcomes
Adults after cardiac surgery	Medical prophylaxis against atrial fibrillation	No medical prophylaxis against atrial fibrillation	Incidence of postoperative atrial fibrillation Length of hospital stay/ ICU length of stay Mortality Stroke incidence Adverse events

Table 15.2 Agents considered in the prevention of POAF

	Beta blockers	Sotalol	Amiodarone	Magnesium
Effective?	Yes	Yes	Yes	Maybe
Benefits	Favorable side effect profile	May be more effective than beta blockers and amiodarone	May reduce stroke risk and length of hospital stay	Not proarrhythmic
Drawbacks	Cannot be used in heart block, cardiogenic shock, bronchospasm, or sinus bradycardia	May induce ventricular arrhythmias	Pulmonary and hepatic toxicity	Optimal dose and timing unknown Use with caution in renal impairment

Results

Pharmacologic Agents

Beta Blockers

The 2011 focused update of the ACC/AHA 2006 Guidelines recommend beta blocker therapy for all cardiac surgery patients who do not have a contraindication to its use [5]. Postoperative beta blocker withdrawal has been shown to increase the risk of developing POAF [2, 3]. Thus, it is recommended that patients on a beta blocker preoperatively should continue it postoperatively. Dose changes may be necessary and the presence of heart block, cardiogenic shock, bronchospasm, or sinus bradycardia may be a contraindication to maintaining beta blockade. In a recent Cochrane review of 118 randomized controlled trials (RCTs), 33 of which evaluated beta blockers (n = 4698), beta blockers were effective in reducing the incidence of postoperative atrial fibrillation from 31.7% in the control group to 16.3% in the treatment group (OR 0.33; 95% CI 0.26–0.43) (Table 15.3) [4]. Dosing regimens, route of delivery, and type of beta blocker administered varied among the studies, and in some studies beta blockers were

Table 15.3 Beta blockers and sotalol in the prevention of POAF

	Intervention	n	OR or RR	95% CI	P value	Type of study	Quality of evidence
Arsenault[4]	Beta blocker vs control	4698	OR = 0.33	0.26–0.43	<0.00001	Meta analysis	High
	Sotalol vs control	1609	OR = 0.34	0.26–0.43	<0.00001		
Burgess [6]	Beta blocker vs control	4452	OR = 0.36	0.28–0.47	=0.001	Meta analysis	Moderate
	Sotalol vs control	2622	OR = 0.37	0.29–0.48	<0.001		
Ji [7]	Beta blocker vs control	2157	RR = 0.53	0.37–0.75	<0.00001	Meta analysis	Moderate
Kerin [8]	Sotalol vs placebo	988	RR = 0.55	0.45–0.67	<0.001	Meta analysis	High
	Sotalol vs no treatment	615	RR = 0.33	0.24–0.46	<0.001		
	Sotalol vs beta blocker	1043	RR = 0.64	0.50–0.84	<0.001		
Auer [10]	Sotalol vs placebo	128	OR = 0.32	0.14–0.71	<0.01	RCT[a]	Moderate

[a]*RCT* randomized controlled trial

withdrawn in the control group [4]. The vast majority of patients began beta blockade postoperatively (81.8%) [4]. Another meta-analysis of several pharmacologic and non pharmacologic interventions in the prevention of POAF found similar favorable results for beta blockade in the prevention of POAF (OR 0.36; 95% CI 0.28–0.47; $p < 0.001$) [6]. However, when studies confounded by postoperative non study beta blocker withdrawal were excluded, the effect was less significant (OR 0.69; 95% CI 0.54–0.87; $p = 0.002$) [6]. There was no significant reduction in length of stay with the use of beta blockers [6].

In the most recent meta-analysis looking specifically at beta blockers in prevention of POAF, examination of six RCTs revealed a POAF incidence of 22.37% in the beta-blocker arm versus 34.45% in the placebo arm (RR 0.53; 95% CI 0.37–0.75; $p < 0.00001$) [7]. However, beta blockers were discontinued in the placebo group in all studies, so it is difficult to determine how much of this effect was the result of beta blocker withdrawal [7]. Beta blocker prophylaxis is most effective when given both preoperatively and postoperatively, as compared to only pre- or postoperatively [4, 6]. Several studies have compared the effectiveness of different types of beta blockers, dosing, and route of delivery, but these debates are beyond the scope of this short chapter.

Sotalol

While sotalol is a beta blocker, it is also a potassium channel blocker, and so is addressed separately in this text and in most studies regarding its effectiveness. Sotalol has side effects similar to conventional beta blockers, but can also induce ventricular arrhythmias, in particular torsades de pointes. For this reason, sotalol should not be used in patients who have a prolonged QT interval, and should be used with extreme caution in patients with electrolyte disturbances.

Two meta-analyses of multiple agents found similar results for sotalol in the prevention of POAF. The first analysis was a series of 11 studies on 1609 patients, all comparing the use of sotalol with placebo (Table 15.3) [4]. There was a significant reduction in the incidence of POAF in the sotalol group versus the placebo group (OR 0.34; 95% CI 0.26–0.43) [4]. In the second analysis, 14 trials were selected, 5 that used a beta blocker in the control arm, 7 that used placebo, and 2 that had both placebo and beta blocker control arms [6]. When all the trials were pooled, there was a significant reduction in the incidence of POAF in the treatment groups compared to the control groups (OR 0.34; 95% CI 0.26–0.45; $p < 0.001$) [6]. In the five trials that used a beta blocker in the control arm, the incidence of POAF was reduced from 26% in the beta blocker groups to 14% in the sotalol groups (OR 0.42; 95% CI 0.26–0.65; $p < 0.001$) [6]. However, more patients withdrew from treatment in the sotalol groups than in the placebo groups due to undesirable side effects (6% vs 1.9%; $p = 0.004$) [6]. The withdrawal rate was not significantly different between the sotalol and beta blocker groups (7.2% vs. 4.8%; $p = 0.25$) [6].

Another recent meta-analysis looking specifically at sotalol in the prevention of POAF showed it to be superior to placebo (RR 0.55; 95% CI 0.45–0.67;

p < 0.001), no treatment (RR 0.33; 95% CI 0.24–0.46; p < 0.001), and beta blocker therapy (RR 0.60; 95% CI 0.50–0.84; p < 0.001) [8]. There was no advantage for preoperative versus postoperative sotalol administration, and preoperative administration was associated with more side effects and a higher rate of discontinuation [8].

The REDUCE trial randomized 160 cardiac surgery patients to receive amiodarone or sotalol postoperatively. POAF occurred in 17% of patients in the amiodarone group versus 25% of patients in the sotalol group [9]. Stroke volume was significantly lower in patients in the sotalol group versus the amiodarone group at 24 h, and the sotalol group required more inotropic and vasopressor support [9].

The SPPAF trial randomized 253 patients to receive either oral amiodarone and metoprolol, metoprolol alone, sotalol, or a placebo [10]. Patients receiving sotalol had a significantly lower frequency of POAF than patients receiving placebo (OR 0.40; 95% CI 0.19–0.82; p = 0.01) [10]. However, patients in the sotalol group experienced a high rate of side effects, with 29% of patients having gastrointestinal discomfort/nausea, 13% having symptomatic bradycardia, and 13% requiring sustained pacing [10]. The study was not powered to make comparisons among the treatment groups.

Amiodarone

Amiodarone is a class III antiarrhythmic that is frequently used to treat atrial fibrillation. Four early double blinded randomized controlled studies were conducted that randomized cardiac surgery patients to receive oral amiodarone or placebo perioperatively as prophylaxis against POAF (Table 15.4) [11–14]. Two studies were positive, one was negative, and one was positive only for a subgroup [11–14]. The AFIST trial randomized patients greater than 60 years of age undergoing cardiac surgery to receive oral amiodarone or placebo beginning preoperatively, in addition to a beta blocker [11]. The amiodarone treated patients had a lower incidence of POAF (22.5% vs. 38%; p = 0.01), symptomatic atrial fibrillation (4.2% vs. 18%; p = 0.001), stroke (1.7% vs. 7.0%; p = 0.04), and ventricular tachycardia (1.7% vs. 7.0%; p = 0.04) compared to the placebo treated patients [11]. Somewhat surprisingly, there was no significant difference in the rates of symptomatic bradycardia and hypotension between the groups [11]. A study by Daoud et al., found that patients treated with perioperative amiodarone had a statistically significant lower frequency of POAF (25% vs. 32%; p = 0.003), and that these patients were hospitalized for significantly fewer days (6.5 ± 2.6 vs. 7.9 ± 4.3 days; p = 0.04) [12]. There was also a cost differential in favor of amiodarone [12].

The negative study randomized just 143 patients undergoing coronary artery bypass grafting (CABG) and found that, while there was a trend toward decreased risk of POAF in the amiodarone group, the difference was not statistically significant (24.7% in the amiodarone group vs. 32.8% in the placebo group; p = 0.30) [13]. In a larger study of 315 patients undergoing CABG, the incidence of POAF was

Table 15.4 Amiodarone in the prevention of POAF

	Intervention	n	Results for primary endpoint	P value	Type of study	Quality of evidence
Mooss [9]	Amiodarone vs sotalol	160	17% developed POAF in amiodarone group v 25% in sotalol group	=0.21	RCT[a]	Moderate
Kluger [11]	Amiodarone vs placebo	220	22.5% developed POAF in amiodarone group v 38% in placebo group	=0.01	RCT[a]	High
Daoud [12]	Amiodarone vs placebo	124	25% developed POAF in amiodarone group v 32% in placebo group	=0.003	RCT[a]	High
Redle [13]	Amiodarone vs placebo	143	24.7% developed POAF in amiodarone group v 32.8% in placebo group	=0.30	RCT[a]	Low
Maras [14]	Amiodarone vs placebo	315	19.5% developed POAF in amiodarone group v 21.2% in placebo group	=0.78	RCT[a]	Moderate
	Amiodarone vs placebo age >59	140	26.7% developed POAF in amiodarone group v 43.1% in placebo group	=0.05		
Mitchell [15]	Amiodarone vs placebo	601	16.1% developed POAF in amiodarone group v 29.5% in placebo group (HR = 0.52)	<0.001	RCT[a]	High
Burgess [6]	Amiodarone vs control	3295	19.8% developed POAF in amiodarone group v 33.25% in control group (OR 0.48)	<0.001	Meta analysis	Moderate
Crystal [16]	Amiodarone vs control	1384	22.5% developed POAF in amiodarone group v 37% in control group (OR 0.48)	<0.00001	Meta analysis	High
Arsenault [4]	Amiodarone vs control	5402	19.4% developed POAF in amiodarone group v 33.3% in control group (OR 0.43)	<0.00001	Meta analysis	High

[a]*RCT* randomized controlled trial

similar between the amiodarone and placebo groups (19.5% vs. 21.2%, respectively; p = 0.78) [14]. However, there was a significant difference in patients over the age of 59 (26.7% in the amiodarone group vs. 43.1% in the placebo group; p = 0.05) [14]. Both studies only included CABG patients, who have the lowest risk of developing POAF compared to valve or combined surgery patients, and thus may have been underpowered to detect a significant difference.

After the publication of these four trials, the PAPABEAR trial sought to enroll enough patients such that a statistically significant difference could be detected among subgroups of patients. The authors randomized over 600 patients undergoing CABG and/or valve surgery to oral amiodarone versus placebo, and found that atrial

tachyarrhythmia occurred in significantly fewer amiodarone patients (16.1% vs. 29.5%; HR 0.52; 95% CI 0.34–0.69; $p < 0.001$) [15]. The advantage remained even in the subgroups of patients younger than 65 years and patients who had CABG only [15]. There was an increased need for dose reduction or discontinuation of the administered drug in the amiodarone group (11.4% vs. 5.3%; $p = 0.008$) [15].

Multiple meta-analyses have also been conducted demonstrating the effectiveness of amiodarone in the prevention of POAF. In a meta-analysis of 18 trials (3295 patients), the incidence of POAF was reduced from 33.2% in the control group to 19.8% in the amiodarone group (OR 0.48; 95% CI 0.40–0.57) [6]. Dosing and route of delivery differed among the trials. While more patients experienced bradycardia in the amiodarone group than in the control group (6.8% vs. 3.4%; OR 1.66; 95% CI 1.73–2.47), significantly fewer patients in the amiodarone groups had ventricular tachycardia or ventricular fibrillation (2.2% in the amiodarone group versus 5.2% in the control group; OR 0.45; 95% CI 0.29–0.69) [6]. The stroke rate was lower and the hospital length of stay was shorter in the amiodarone group [6]. Another meta-analysis of nine trials (1384 patients) found similar results, with reduction of POAF from 37% in the control group to 22.5% in the amiodarone group (OR 0.48, 95% CI 0.37–0.61) [16]. A recent Cochrane review of 33 studies (5402 patients) again found favorable results for amiodarone, with the amiodarone group experiencing a significantly reduced rate of POAF (19.4%) compared to the control group (33.3%) (OR 0.43, 95% CI 0.34–0.54; $I^2 = 63\%$) [4]. About half of the studies began amiodarone administration preoperatively [4].

Regarding the safety of amiodarone, a meta-analysis of 18 randomized controlled trials (3408 patients) showed that the amiodarone group had an increased incidence of bradycardia (OR 1.70; 95% CI 1.05–2.74) and hypotension (OR 1.62; 95% CI 1.04–2.54) [17]. How clinically significant these events were, and whether or not they required discontinuation of the drug, is unknown. The greatest risk occurred in patients who were given intravenous amiodarone as opposed to oral amiodarone, and in patients who started amiodarone postoperatively rather than preoperatively [17]. Patients who received greater than 1 g daily on average were more likely to experience bradycardia [17]. There was no significant difference in the incidence of heart block, nausea, stroke, myocardial infarction, and death, but not all studies reported on these indices [17]. A preoperative slow loading oral amiodarone regimen (3.8 g over 6 days) was compared to a preoperative fast loading oral regimen (2.6 g over 2 days) in a randomized controlled trial [18]. Both regimens were effective in reducing the incidence of POAF lasting more than 24 h and symptomatic POAF compared to placebo, but the slow oral load was more effective in decreasing the incidence of any POAF than the fast oral load [18].

Magnesium

Administration of magnesium is considered very safe in patients without renal impairment, and it is an attractive drug for prophylaxis of POAF as it is not proarrhythmic. It is often effective therapy for patients in atrial fibrillation with concomitant hypomagnesemia. However, many trials regarding its use as prophylaxis against

Table 15.5 Magnesium in the prevention of POAF

	Intervention	n	Results for primary endpoint	P value	Type of study	Quality of evidence
Miller [19]	Mg[a] vs placebo	2490	18% developed POAF in Mg[a] group v 28% in control group (OR 0.54), significant heterogeneity	=0.0003	Meta analysis	Low
Burgess [6]	Mg[a] vs control	2896	19% developed POAF in Mg[a] group v 29% in control group (OR 0.57, significant heterogeneity)	=0.007	Meta analysis	Low
Lancaster [20]	Mg[a] vs no supplement	2041	47% developed POAF in Mg[a] group v 36% in no supplement group	=0.005	Retrospective cohort	Low
Gu [21]	Mg[a] vs placebo	1028	15% developed POAF in Mg[a] group v 22% in control group (RR 0.64)	=0.001	Meta analysis	Low

[a]*Mg* magnesium

POAF are fraught with heterogeneity. A meta-analysis of 20 RCTs (2490 patients) showed that magnesium administration decreased the incidence of POAF in cardiac surgery patients from 28% in the control group to 18% in the treatment group (OR 0.54; 95% CI 0.38–0.75), with significant heterogeneity between trials ($p < 0.001$) (Table 15.5) [19]. There was no difference in length of hospital stay or mortality [19]. The authors performed subgroup analyses to identify the sources of heterogeneity and found that it was attributable to several factors: dosage, timing, continuous cardiac monitoring techniques, definition of atrial fibrillation, exclusionary criteria, and type of procedure performed [19]. Low dose magnesium (<35 mmol) and preoperative magnesium administration appeared to be most effective [19].

Two other meta-analyses showed that magnesium was effective in reducing incidence of POAF but less so than beta-blockers and amiodarone [4, 6]. In fact, in the meta-analysis by Burgess et al., magnesium supplementation had a favorable effect on the reduction of POAF (OR 0.57: 95% CI 0.40–0.57; $p < 0.001$), but with significant heterogeneity between trials ($p = 0.001$) due to dose and timing of delivery, as well as variation in concomitant use of beta blockers [6]. When combined with beta blocker supplementation, the effect of magnesium was diminished (OR 0.83; 95% CI 0.60–1.16) [6]. The largest effect of magnesium was in the two trials that did not use a beta blocker (OR 0.05; 95% CI 0.02–0.16) [6].

Indeed, a recent retrospective study of 2041 adult patients undergoing cardiac surgery showed that patients who developed POAF actually had higher potassium (4.30 versus 4.21 mmol/L; $p < 0.001$) and magnesium (2.33 versus 2.16 mg/dL; $p < 0.001$) levels than controls [20]. On multivariate logistic regressions analysis, age, Caucasian race, preoperative beta blocker use, valve operation, postoperative pneumonia, and magnesium level (OR 4.26; $p < 0.001$) were independent predic-

tors of developing POAF [20]. Rates of POAF were equal in patients who received prophylactic potassium supplementation compared to those who did not, whereas those who received magnesium supplementation had higher rates of POAF (47% versus 36%; p = 0.005) [20]. The authors conclude that while hypokalemia and hypomagnesemia have been shown to predispose to ventricular arrhythmia, the association with atrial arrhythmias is much cloudier. The study is of course limited by its retrospective nature, in that clinicians may have been more aggressive about electrolyte supplementation in patients perceived to be at higher risk for the development of POAF.

Nevertheless, some studies do suggest that magnesium supplementation may be effective. A recent meta-analysis including seven RCTs with 511 total patients found that intravenous magnesium supplementation reduced the incidence of POAF by 36% (RR 0.64; 95% CI 0.50–0.83; p = 0.001) with no heterogeneity (p = 0.8; I^2 = 0%) [21]. One of the studies only followed patients for 1 day postoperatively and when this study was excluded from analysis, the results were similar (RR 0.66: 95% CI 0.51–0.85; p = 0.002; I^2 = 0%; heterogeneity p = 0.8) [21]. While the results of this meta-analysis are encouraging and lack heterogeneity, the overall sample size was relatively small compared to other meta analyses. In addition, the amount of magnesium administered varied from 8 to 100 mmol between trials [21], so it is unclear how there was no heterogeneity detected.

Recommendations Based on the Data

Despite a preponderance of high quality evidence supporting the use of beta blockers, sotalol, and amiodarone in the prevention of POAF in cardiac surgical patients, the only ACC/AHA Class I guideline that encourages prophylactic use of these drugs exists for beta blockers. In our literature search, we identified multiple randomized controlled trials and meta analyses which found a significant reduction in the incidence of POAF with the use of any three of these agents. While there were many studies supporting the use of magnesium, the evidence was weaker. This is somewhat unfortunate, because aforementioned, magnesium is not proarrythmic, is inexpensive, and is generally effective in the treatment of atrial fibrillation associated with hypomagnesemia. Given that the dose, timing, duration, and route of delivery of magnesium were highly variable between studies, it is highly possible that further controlled trials in this area would better elucidate a stronger benefit of magnesium prophylaxis.

As POAF after cardiac surgery is such a prevalent complication and a major cause of morbidity, it is imperative that adult cardiac surgeons should make efforts to prophylax against it in their practice. Based on the data given here, a beta blocker, amiodarone, or both agents combined offer significant protection against the prevention of POAF. Sotalol is another option, and while we found it to be highly effective in the studies that we looked at, it is associated with significant side effects such as torsades de pointes. While it makes sense to treat hypomagnesemia to

prevent arrhythmias, it is unclear based on the current literature whether loading patients with magnesium prevents POAF.

- **In the absence of contraindications, preoperative beta blocker use should be continued postoperatively in patients undergoing cardiac surgery (quality of evidence high; recommendation grade 1A).**
- **In the absence of contraindications, perioperative beta blocker use is recommended to reduce the incidence of postoperative atrial fibrillation in patients undergoing cardiac surgery (quality of evidence high; recommendation grade 1A).**
- **Sotalol is effective in reducing the incidence of POAF in cardiac surgery patients, and may be more effective than conventional beta blockers, but has a more disagreeable side effect profile. It is recommended for use with caution in high risk patients and is contraindicated in patients with a prolonged QT interval or an electrolyte disturbance (quality of evidence moderate; recommendation grade 1B).**
- **Amiodarone is effective in reducing the incidence of POAF in cardiac surgery patients and is recommended in the absence of contraindications, especially in high risk patients (those undergoing valve or combined CABG/valve surgery, elderly patients) (quality of evidence high; recommendation grade 1A).**
- **When possible, a slow oral load of amiodarone not to exceed 1 g/day is preferable to a fast intravenous load of amiodarone (quality of evidence moderate; recommendation grade 2A).**
- **Perioperative magnesium loading may be effective in reducing the incidence of POAF after cardiac surgery, but is not recommended for use in place of beta blockers or amiodarone (quality of evidence low; recommendation grade 2B).**

A Personal View of the Data

As per ACC/AHA guidelines, all of our patients who are on a beta blocker preoperatively are continued on one perioperatively, as long as they have no important contraindications (cardiogenic shock, decompensated heart failure, bradycardia, etc.). Often this requires a decreased dose postoperatively. Patients who are not on a beta blocker preoperatively are started on metoprolol postoperatively, and this is occasionally changed to a less beta-1 selective agent in patients with hypertension. We also use amiodarone postoperatively for patients who are not hypotensive, bradycardic, or have decreased cardiac output. The drug is begun intravenously several hours postoperatively in a dose not to exceed 800 mg/day, and is switched to an oral regimen as soon as possible. Patients with a history of tachyarrhythmia are loaded with amiodarone in the operating room once they are off pump and demonstrate acceptable ventricular function and heart rate.

Amiodarone is arbitrarily continued for 1 month. Only rarely do patients continue it long term, due to concern for toxicities, in particular pulmonary complications. As hypomagnesemia is associated with the development of atrial fibrillation, electrolytes are monitored and repleted as necessary. However, we do not load patients with magnesium in an effort to decrease the incidence of POAF, as the evidence behind this practice is less convincing than the evidence for beta blockers and amiodarone. We do not routinely use sotalol due to its unfavorable side effect profile.

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Chapter 16
Atrial Fibrillation: Aggressive Treatment in the Postoperative Cardiothoracic Surgery Patient

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Introduction

Postoperative atrial fibrillation (POAF) is a common complication following cardiothoracic surgery. POAF occurs in approximately 35% of cardiac surgery patients and between 10% and 30% of thoracic surgery patients [1–5]. The precise pathogenesis of POAF is poorly understood but likely involves interplay between structural heart changes associated with aging and disease and acute postoperative inflammation and oxidative stress [2, 4, 6, 7]. POAF occurs both in patients with a history of AF and those with no history of arrhythmias. Patients with preexisting AF are at increased risk for developing POAF, likely because some underlying pathology necessary for the development and maintenance of arrhythmias already exists in those patients [1, 2, 8]. While advanced age is the most consistently reported and widely accepted risk factor for POAF, other risk factors include cardiovascular conditions, such as congestive heart failure and coronary artery disease, and non-cardiovascular conditions, including obesity, diabetes, and chronic obstructive pulmonary disease (COPD) [1, 2, 8–10].

POAF is sometimes well tolerated, but can cause acute hemodynamic instability or heart failure [2, 4, 6, 10]. The development of POAF has been linked to numerous detrimental sequelae, including a two- to fourfold increased risk of stroke, cardiac arrest, renal and respiratory failure, and a twofold increase in all-cause 30-day and 6-month mortality [1, 2, 4, 6, 8]. Patients who develop POAF incur an average of additional $10,000–$20,000 in hospital treatment costs, including the cost of 12–24 h prolonged ICU stay and an additional 2–5 days in the hospital [1, 5, 7–9].

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Clinically, perioperative management of POAF includes prophylaxis for patients at risk for developing POAF and treatment of the arrhythmia when it presents. Due to the high incidence of POAF and the associated major health burden, it is imperative that clinicians understand best practice guidelines for the prevention and treatment of POAF in cardiothoracic surgery patients.

Search Strategy

A literature search of English language publications from 2009 to 2017 was used to identify published data and clinical guidelines on POAF in cardiothoracic surgery patients using the PICO outline (Table 16.1). Reviewed articles were limited to professional society guidelines, meta-analyses, and high-quality randomized control trials and case-controlled studies. Databases searched included PubMed and Cochrane Evidence Based Medicine. Search terms included: "atrial fibrillation," "postoperative atrial fibrillation" AND "cardiothoracic surgery," "prevention of atrial fibrillation" AND "cardiothoracic surgery", "treatment of atrial fibrillation" AND "cardiothoracic surgery," "management of postoperative atrial fibrillation," "management of atrial fibrillation" AND "cardiothoracic surgery," and "complications of postoperative atrial fibrillation." Relevant studies were classified using the GRADE system.

Results

POAF Prophylaxis

POAF prophylaxis for cardiothoracic surgery patients has included the use of beta blockers, amiodarone and other antiarrhythmic drugs (AADs), nondihydropyridine calcium channel blockers, steroids, statins, colchicine, electrolyte repletion and supplementation, polyunsaturated fatty acids (PUFAs), and biatrial pacing.

Table 16.1 PICO table for aggressive treatment of atrial fibrillation in the postoperative cardiothoracic surgery patient

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Cardiothoracic surgery patients with a predisposition for AF and/or who develop POAF	Prophylaxis and treatment of POAF in cardiothoracic surgery patients	No prophylaxis for or treatment of POAF following cardiothoracic surgery	Incidence of AF in the postoperative period, morbidity and mortality, length of stay, and cost

There is very strong evidence supporting the practice of beta blocker continuation prior to cardiothoracic surgery in patients who take them chronically in order to prevent withdrawal symptoms. This practice is endorsed by nearly all professional society guidelines and is supported by numerous trials and large-scale meta-analyses [1, 2, 7, 9–12]. Many guidelines also list as a Class I, Level of Evidence (LOE) A or B recommendation the preoperative or perioperative administration of traditional beta blockers to patients without contraindications who have not been taking beta blockers preoperatively [4, 5, 7, 9–12]. While a recent randomized trial by Onk and colleagues showed that prophylactic metoprolol was effective in reducing POAF, a large-scale retrospective cohort study of over 500,000 patients undergoing coronary artery bypass (CABG) at 1107 hospitals called this practice into question by reporting that preoperative administration of traditional beta blockers actually was associated with a small but significant increase in POAF (Table 16.2) [5, 13]. Other recent smaller trials have shown that ultrashort-acting beta blockers like landiolol may provide a greater prophylactic benefit than traditional beta blockers (Table 16.2) [14].

Amiodarone and sotalol (Class III AADs) have also been used for POAF prophylaxis. Preoperative amiodarone is currently listed as a Class IIa, LOE A or B recommendation by most clinical guidelines [1, 4, 5, 7, 9, 10, 12, 15]. Preoperative sotalol is listed as a Class IIb, LOE B recommendation by several guidelines and may be a reasonable choice to administer to patients in whom amiodarone is contraindicated [4, 9, 10, 15]. Prophylactic administration of nondihydropyridine calcium channel blockers such as diltiazem is also deemed reasonable by some guidelines for high-risk patients who are not taking beta blockers [1, 4]. While calcium channel blockers are typically well tolerated, their prophylactic benefit remains unclear.

Hypomagnesemia and hypokalemia have long been considered to be central to the pathogenesis of POAF, and thus electrolyte supplementation and repletion has become common practice. However, recent analysis has called this conclusion into question (Table 16.2) [16]. Electrolyte supplementation and repletion currently is not highly recommended or is only conditionally recommended by most clinical guidelines [1, 7, 11]. Prophylactic treatment with biatrial pacing, steroids, statins (Table 16.2), PUFAs, or colchicine is not supported by high-quality evidence and is not endorsed by most guidelines [1, 7, 11, 17]. However, the 2016 Canadian Cardiovascular Society guidelines conditionally recommended that patients with contraindications to beta blockers and amiodarone undergo preoperative or postoperative prophylactic treatment with colchicine or postoperative biatrial pacing [11].

Treatment of POAF

Episodes of POAF may resolve spontaneously within minutes to hours without intervention, but persistent POAF and episodes occurring in hemodynamically unstable patients warrant clinical intervention [3, 4, 11]. POAF treatment most often involves beta blockers, amiodarone, and/or nondihydropyridine calcium channel blockers. Treatment-refractory POAF and POAF episodes occurring in

Table 16.2 Selected recent high-quality studies that confirm or call into question current clinical treatment guidelines

Author (year)	Topic/intervention	Findings	N	Study type	Level of evidence
Onk (2015) [5]	Preoperative and postoperative metoprolol or amiodarone prophylaxis in CABG patients	There was no statistically significant difference in POAF reduction between patients receiving prophylactic amiodarone or metoprolol ($p = 0.612$)	251 patients	Randomized control trial	Level 1
		Prophylactic metoprolol or amiodarone was associated with reduced POAF (19.3% vs. 18.1% at 4 weeks postoperatively, respectively), and reduced length of stay and hospital costs			
		There were no statistical differences between the two groups in terms of postoperative complications or mortality			
Brinkman (2014) [13]	Preoperative beta blocker prophylaxis in nonemergent CABG patients	New-onset POAF was higher in intervention group (21.5% vs. 20.1%, $p < 0.001$)	506,110 patients at 1107 hospitals	Retrospective cohort study using STS database	Level 3
		There were no statistic differences between experimental and control group in terms of operative mortality, stroke, prolonged ventilation, reoperation, renal failure, or deep sternal wound infection			
Zheng (2016) [17]	Perioperative statin prophylaxis	POAF rates were comparable in patients receiving statin or placebo ($p = 0.72$)	1922 patients	Randomized control trial	Level 1
		Statin prophylaxis was associated with increased postoperative acute kidney injury ($p = 0.005$)			
		Statin prophylaxis was not associated with decreased myocardial injury ($p = 0.80$), length of stay, or left ventricular function			

Sezai (2015) [14]	Postoperative ultrashort-acting beta blocker prophylaxis with LVEF ≤35%	Patients receiving ultrashort-acting landiolol hydrochloride experienced less POAF (10% vs 40%, p = 0.002) and shorter hospital length of stay (p = 0.019) than controls	60 patients	Randomized control trial	Level 1
		There were no significant differences in complication rates or mortality between experimental and control groups			
Gillinov (2016) [3]	Rate control vs. rhythm control for POAF treatment	There were no significant differences between patients treated with rate control or rhythm control in terms of:	523 patients	Randomized control trial	Level 1
		Freedom from AF at 60 days from discharge (p = 0.41)			
		Hospital length of stay (p = 0.76)			
		Serious adverse events (p = 0.61)			
		Death (p = 0.64)			
Lancaster (2016) [16]	Potassium and magnesium supplementation	Patients with POAF had higher potassium and magnesium levels than controls (p < 0.001)	2041 patients	Retrospective cohort study	Level 3
		Prophylactic potassium supplementation did not reduce POAF (p = 0.813)			
		Magnesium supplementation was associated with increased POAF (p = 0.005)			
Kowey (2009) [20]	POAF treatment with vernakalant	47% of cardiac patients with POAF converted to sinus rhythm after administration of vernakalant (mean conversion time = 12 min) versus 14% of patients who received placebo (p < 0.001)	150 patients	Randomized control trial	Level 1
		Vernakalant was associated with bradycardia in some patients but was well tolerated overall			

hemodynamically unstable patients may require direct current (DC) cardioversion to restore sinus rhythm. Due to the risk of stroke associated with AF, care must also be taken to avoid thromboembolism by ruling out thrombus in the left atrial appendage using transesophageal echocardiography (TEE) [1, 7]. If patients have been fully anticoagulated for over 48 h, this has generally been considered sufficient and DC cardioversion can be performed safely.

POAF treatment can be divided into two general strategies: heart rate control (aimed at slowing the heart rate by using beta blockers and/or calcium channel blockers) and rhythm control (conversion to sinus rhythm using Class Ic or III AADs or DC cardioversion) [3, 4, 11, 18]. A recent high-quality randomized control trial found that neither heart rate control nor rhythm control offered a significant advantage over the other in terms of persistence of AF at 60 days, complication rates, days of hospitalization, or all-cause postoperative mortality (Table 16.2) [3]. The choice of treatment strategy should therefore be made based upon individual patient characteristics. Treatment guidelines are similar for new-onset POAF and POAF occurring in patients with chronic AF; patients with a history of AF should be monitored for postoperative arrhythmias closely since a higher percentage of these patients will develop POAF and may require both cardioversion and antiarrhythmic therapy in the postoperative period [1, 10].

Treatment with beta blockers is listed as a Class I, LOE A or B recommendation by most clinical guidelines but should be avoided in patients with hypotension, left ventricular dysfunction, or heart failure due to their negative inotropic effects and heart rate depression [1, 3, 4, 15, 19]. When traditional and ultrashort-acting beta blockers are contraindicated or ineffective, nondihydropyridine calcium channel blockers may be used for heart rate control. Treatment using calcium channel blockers is listed as a Class I or Class IIa recommendation by various clinical guidelines [1, 4, 12, 15]. Similar to beta blockers, calcium channel blockers also should be avoided in patients with hypotension, left ventricular dysfunction, or heart failure [1].

The Class III AADs amiodarone, sotalol, ibutilide, and dofetilide are used clinically and are listed as Class IIa, LOE A or B recommendations for POAF treatment [1, 4, 7, 9, 15]. Vernakalant, a new Class III AAD with potassium channel-blocking action, is listed as a Class IIb, LOE B recommendation by the 2016 European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) guidelines for treatment of POAF in hemodynamically stable patients and patients without structural heart disease, but its efficacy has not been confirmed by large-scale randomized controlled trials and it is not widely used in the US (Table 16.2) [7, 20].

Class Ic AADs such as flecainide and propafenone are listed as a Class IIa, LOE B recommendation for POAF treatment and may be used for rhythm control when Class III AADs are ineffective or contraindicated [1, 9]. Class Ic AADs are contraindicated in patients with prior myocardial infarction, coronary artery disease, and/or severe structural heart disease [1]. Digoxin is also listed as a Class II recommendation for treatment in new-onset POAF [1, 9, 12].

DC cardioversion for refractory POAF in hemodynamically stable patients is listed as a Class I or Class II recommendation, depending on the guideline [1, 4, 9, 15].

After initial unsuccessful cardioversion attempts, pretreatment with amiodarone, sotalol, digoxin, diltiazem, propafenone, or flecainide before reattempting cardioversion may be effective and is listed as a Class IIa recommendation [1, 9]. In order to prevent thromboembolism and stroke in patients undergoing DC cardioversion for POAF episodes lasting >48 h, current clinical guidelines indicate a Class I recommendation for anticoagulation with warfarin, new oral anticoagulants (dabigatran, rivaroxaban, apixaban), or low molecular weight heparin (LMWH) 3 weeks prior to cardioversion and continuation for at least 4 weeks thereafter [1, 7, 9, 15]. Stable patients undergoing cardioversion for POAF episodes <48 h should be anticoagulated based upon their risk of stroke and bleeding. In these patients, TEE should be performed prior to cardioversion in order to exclude intracardiac thrombi if anticoagulation has not been complete for at least 48 h [1, 7]. Anticoagulation is warranted in patients with a CHA_2DS_2-VASc score >0 [1, 2].

Emergent DC cardioversion may be required for POAF in patients with severe hemodynamic instability, myocardial ischemia, or acute myocardial infarction. For episodes of POAF lasting <48 h, it is appropriate to initiate cardioversion without prior anticoagulation [1, 9, 19]. Emergent cardioversion in unstable patients with episodes of POAF >48 h should be preceded by a bolus of heparin if the patient is not already at an increased risk for bleeding [7, 9].

Prolonged POAF is closely linked with thromboembolism and stroke. In order to avoid thrombus formation in patients with POAF >48 h and a CHA_2DS_2-VASc score >0, anticoagulants or antithrombotics should be given. Administration of anticoagulants is listed as a Class I recommendation and administration of antithrombotics is listed as a Class II recommendation [1, 4, 15, 19]. New oral anticoagulants may be used in patients with contraindications to traditional anticoagulants [1, 2, 4].

Recommendations Based on the Data

POAF Prophylaxis

Because of the potential for beta blocker withdrawal and subsequent POAF, we strongly recommend that patients using chronic beta blockers before surgery resume taking them as soon as possible after surgery. The effectiveness of preoperative or postoperative beta blocker prophylaxis is less clear, however, as recent studies have called into question the methodology of the trials used to form clinical guidelines regarding their use for prophylaxis. The literature surrounding beta blocker prophylaxis is of “moderate quality” and we offer a weak recommendation in favor of their use in patients without contraindications. Due to the risk of bradycardia, hypotension, and bronchospasm, beta blockers should be avoided in patients with heart failure, poorly controlled asthma, or other conditions that may become exacerbated by their use.

Onk and colleagues reaffirmed in a recent randomized trial that preoperative amiodarone prophylaxis is reasonable for patients with contraindications to beta

blocker prophylaxis. This study reported similar rates of POAF reduction following amiodarone or metoprolol prophylaxis (Table 16.2). At 4 weeks postoperatively, only 19.3% of patients given prophylactic amiodarone and 18.1% of patients given prophylactic metoprolol developed POAF ($p = 0.612$ between groups), compared to approximately 35% who do not receive prophylaxis, as reported in the literature [1, 4, 5]. Nevertheless, the side effects and contraindications associated with amiodarone and other Class III AADs may outweigh their benefit. The literature surrounding amiodarone prophylaxis is of "moderate quality" and we only conditionally recommend its use for prophylaxis.

The effectiveness of nondihydropyridine calcium channel blockers for POAF prophylaxis remains unclear. Based upon the "moderate quality" of evidence surrounding their prophylactic benefits and the conclusions formed by several clinical guidelines, we offer a weak recommendation in favor of their use for prophylaxis in high-risk patients who are not taking beta blockers and for whom amiodarone is contraindicated. The quality of evidence is low regarding biatrial pacing, steroids, statins, PUFAs, colchicine, and electrolyte supplementation, and we do not recommend that these measures be utilized for POAF prophylaxis.

Treatment of POAF

Due to the vast sequelae of complications associated with POAF, we strongly recommend in favor of treating prolonged and recurrent episodes of POAF. Per Gillinov and colleagues' recent findings (Table 16.2), we suggest that POAF be treated with either heart rate control or rhythm control [3]. Primary treatment should center around one of the three mainstay medications: beta blockers, nondihydropyridine calcium channel blockers, and amiodarone. There is high quality evidence surrounding each medication's ability to convert patients in POAF to sinus rhythm, and the choice of medication should therefore be based on individual patient characteristics. Treatment should begin with a single agent and a second medication may be added as required, but all three agents should not be used concurrently due to the high risk of bradycardia and hypotension. The evidence surrounding the effectiveness of flecainide, propafenone, and digoxin is moderate- to low-quality, and we conditionally recommend their use only when other treatment options fail. Due to the novelty of vernakalant, this drug has not been widely utilized in clinical practice. We have not utilized this drug and therefore cannot offer a recommendation regarding its use to treat POAF.

Patients with POAF refractory to other treatments and hemodynamically unstable patients with POAF should undergo conversion to sinus rhythm with DC cardioversion. Per clinical guidelines, we strongly recommend that patients undergo anticoagulation and TEE in order to exclude intracardiac thrombi prior to cardioversion. Anticoagulation and administration of antithrombotics should also be considered in patients with prolonged POAF not requiring cardioversion in order to avoid

thromboembolism. Patients with POAF should be monitored regularly for thromboembolism, and anticoagulation must be weighed against bleeding risk.

A Personal View of the Literature

The efficacy of beta blocker prophylaxis for POAF has recently been called into question. In a large-scale retrospective review of over 500,000 patients, Brinkman and colleagues reported that preoperative beta blocker prophylaxis was associated with increased POAF in patients undergoing CABG (Table 16.2) [13]. However, we believe that these results may have been confounded by inadequately low prophylactic doses and beta blocker withdrawal symptoms. A randomized trial of 251 patients by Onk and colleagues confirmed the results of previous studies, which showed that beta blocker prophylaxis was associated with decreased POAF incidence and no increase in postoperative complications (Table 16.2). Follow up studies are warranted to determine the effectiveness of prophylactic beta blockers more precisely.

Although several clinical trials have shown that postoperative prophylactic biatrial pacing may be effective in reducing POAF, an examination of the methodology used in these studies calls this conclusion into question. It is possible that the results from studies showing that biatrial pacing is beneficial were confounded by a tight level of control in study design that is not practical in clinical practice. Pacing is, however, generally well tolerated and is not likely to cause harm [19].

The efficacy of electrolyte supplementation and repletion for POAF prophylaxis has gained much attention recently. Few randomized trials have examined the benefits or harms associated with electrolyte supplementation and repletion, but our group recently published a retrospective study showing that high serum magnesium levels were associated with POAF in a dose-dependent manner and that serum potassium levels were not correlated with POAF (Table 16.2) [16]. More research is warranted on this topic, but based on our findings we do not endorse prophylactic supplementation or repletion of magnesium or potassium for mild hypokalemia.

It also should be noted that most current clinical guidelines have formed their recommendations based upon the results of randomized trials performed several decades ago. It may become necessary to repeat and update these randomized trials as new data become available. Recent pertinent additions to the literature have been tabulated in Table 16.2.

Finally, much of the literature surrounding POAF prophylaxis and treatment comes from the cardiac surgery literature, with much less data focused on thoracic surgery [1, 7]. While patients undergoing thoracic surgery share many comorbidities and characteristics with those undergoing cardiac surgery, not all interventions and treatments may be equally efficacious between the two groups. Future studies should seek to develop efficacious POAF prophylaxis and treatment options specifically for patients undergoing thoracic surgery.

Summary of Recommendations

POAF Prophylaxis:

- Beta blockers – weak recommendation *in favor* of their use pre- or postoperatively in patients without contraindications (moderate quality evidence)
- Amiodarone – weak recommendation *in favor* of its use (moderate quality evidence)
- Nondihydropyridine calcium channel blockers – weak recommendation *in favor* of their use in patients who do not use beta blockers (moderate quality evidence)
- Biatrial pacing; steroids; statins; PUFAs; colchicine, electrolyte supplementation – weak recommendation *against* their use (low quality evidence)

Treatment of POAF:

- Beta blockers – strong recommendation *in favor* of their use* (high quality evidence)
- Amiodarone – strong recommendation *in favor* of its use* (high quality evidence)
- Nondihydropyridine calcium channel blockers – strong recommendation *in favor* of their use* (high quality evidence)
- DC cardioversion – strong recommendation *in favor* of its use in patients with hemodynamic instability or treatment-refractory POAF (with TEE and anticoagulation as necessary) (high quality evidence)
- Flecainide, propafenone – weak recommendation *in favor* of their use as second-line treatment (low quality evidence)
- Digoxin – weak recommendation *in favor* of its use as second-line treatment (low quality evidence)

*First-line treatment for POAF should include either beta blockers, calcium channel blockers, or amiodarone, depending on patient characteristics. A second agent may be added as required, but all three agents should NOT be used concurrently.

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Part IV
Pulmonary Support in the CT Patient

Chapter 17
What is the Role of the ABCDEF Bundle in Patients on Extracorporeal Membrane Oxygenation?

Mina F. Nordness and Mayur B. Patel

Introduction

Ventilator weaning, early extubation, and spontaneous breathing and awakening trials have become vibrant topics in critical care medicine. In the early days of ICU care, it was common to maintain patients at high levels of sedation while mechanically ventilated with the intent to decrease agitation and discomfort. Over the last three decades, this goal-amnestic approach to sedation in the ICU was noted to be associated with several complications such as polyneuropathy of critical illness [1], delirium [2, 3], PTSD [4] and even higher mortality [5, 6]. During this time, a plethora of evidence has arisen in support of early-protocolized sedation weaning and/or minimization, as well as ventilator liberation.

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A	Assess, prevent, manage pain
B	Spontaneous awakening trials (SAT) and spontaneous breathing trials (SBT)
C	Choice of analgesia and sedation
D	Delirium: assess, prevent and manage
E	Early mobility and exercise
F	Family engagement and empowerment

Fig. 17.1 The ABCDEF bundle

This overall movement gave rise to the ABCDEF bundle (Fig. 17.1: **A**ssess, Prevent and Manage Pain; **B**oth Spontaneous Awakening/Breathing Trials; **C**hoice of analgesia and sedation; **D**elirium: Assess, Prevent, Manage; **E**arly Mobility; **F**amily engagement), described in the following section. This bundle is primarily derived from the 2013 new clinical practice management guidelines titled "Management of Pain, Agitation and Delirium in Adult Patients in the Intensive Care Unit (ICU PAD) [7]." It has been pioneered and developed by both the ICU Delirium group at Vanderbilt University Medical Center and the Society of Critical Care Medicine (SCCM) [8, 9]. Currently, one of the most contested patient populations for implementation of the ABCDEF bundle are those with precarious cardiovascular and/or cardiopulmonary support devices in place, specifically, Extra-Corporeal Membrane Oxygenation (ECMO). Some recent literature has shown potential of implementing parts of the bundle in patients on ECMO, which is the topic of interest for this chapter. Before diving into this complex relationship, we will first provide some background on the ABCDEF bundle in general critical care.

Background on the ABCDEF Bundle

Assess, Prevent and Manage Pain

Commonly, clinical pain assessments fall on a subjective one to ten scale that requires patients to be interactive and able to vocalize, which is often not possible in critically ill settings. The ICU PAD Guidelines recommend usage of evidence based scoring systems to assess pain in patients that cannot communicate verbally (e.g., decreased mental status, on mechanical ventilation) such as the Clinical Pain Observation Tool (CPOT) [10] and the Behavioral Pain Scale (BPS) [11] demonstrated in Tables 17.1 and 17.2. Both the CPOT and BPS scales are evidence based and reliable methods of assessing pain in patients that are unable to communicate verbally [10, 12]. According to the ICU PAD Guidelines, pain should be treated

Table 17.1 Critical care pain observation tool (CPOT)

Indicator	Description	Score	
Facial expression	No muscular tension observed	Relaxed, neutral	0
	Presence of frowning, brow lowering, orbit tightening and levator contraction	Tense	1
	All of the above facial movements plus eyelid tightly closed	Grimacing	2
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movements	0
	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection	1
	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness	2
Muscle tension	No resistance to passive movements	Relaxed	0
	Resistance to passive movements	Tense, rigid	1
	Strong resistance, inability to complete passive movements	Very tense or rigid	2
Compliance with the ventilator (intubated patients)	Alarms not activated, easy ventilation	Tolerating ventilator or movement	0
	Alarms stop spontaneously	Coughing but tolerating	1
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator	2
OR			
Vocalization (extubated patients)	Talking in a normal tone or no sound	Talking in normal tone or no sound	0
	Sighing, moaning	Sighing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2

A CPOT score greater than 2 may indicate an unacceptable level of pain requiring sedation and/or analgesia. A reasonable CPOT score is typically <3

with either opiates or opiates in combination with multimodal therapy with a CPOT score ≥3, a BPS score >5 or a standard pain scale score >4 [7].

Both Spontaneous Awakening/Breathing Trials (SATs/SBTs)

SATs were first initially discussed in the literature in the early 2000s [13]. Currently, they are described as planned daily pausing of continuous sedation and analgesia to allow for the patient to fully awake so long as their clinical physiology safely permits, and are typically paired with spontaneous breathing trials (SBTs). Some institutions have developed a screening platform for performing SAT/SBTs with inclusion and exclusion criteria. For example, at our institution, inclusion criteria

Table 17.2 Behavioral pain scale (BPS)

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (brow lowering)	2
	Fully tightened (eyelid closing)	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

The range of BPS score is from 3 to 12, reflecting no pain to highest pain, respectfully. A reasonable CPOT score is typically <6

include: No agitation, oxygen saturations >88%, no myocardial ischemia, no vasopressor use and the patient must make inspiratory efforts. Exclusion criteria include: respiratory rate >35 or <8, Oxygen saturation <88%, increased work of breathing/respiratory distress, mental status changes or acute cardiac arrhythmia [8, 14].

SATs are only one aspect of a larger movement aimed at preventing ICU delirium and minimizing prolonged intubation. The combination of interventions including getting patients up, mobilized, and moving to extubation earlier with support by family members and minimizing sedation is known as the ABCDEF Bundle [15]. These interventions are all evidence based and have been implemented across the country and internationally [2, 16]. Proper implementation of the bundle, which has awakening and breathing trials as a major component, has demonstrated improved rates of delirium and survival [16]. Daily SATs/SBTs have been associated with decreased ventilator days and decreased ICU stay [13]. Prolonged deep sedation has been associated with increased ventilator days, delirium, and mortality [17].

Choice of Analgesia and Sedation

Historically continuous or intermittent benzodiazepines were used for sedation for mechanically ventilated patients. However, research like the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction Study (MENDS), which compared benzodiazepines to dexmedetomidine infusion demonstrated that patients who received benzodiazepines were at significantly higher risk of delirium that even increased per dose of benzodiazepine [3]. Not only choice, but also depth of sedation are important factors to consider. In other work, patients with Richmond Agitation-Sedation Scale (RASS) scores (Table 17.3) in the deep sedation range (−4 to −5) were at higher risk of delayed extubation and even at higher risk of death

Table 17.3 Richmond agitation-sedation scale score

Richmond Agitation-Sedation Scale Score		
+4	Combative	Violent, immediate danger to staff
+3	Very agitated	Pulls or removes tubes or catheters; aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained awakening to *voice* (eye opening and contact ≥10 s)
−2	Light sedation	Briefly awakens to *voice* (eye opening and contact <10 s)
−3	Moderate sedation	Movement or eye-opening to *voice* (but no eye contact)
−4	Deep sedation	No response to voice, but movement or eye opening to *physical* stimulation
−5	Unarousable	No response to *voice or physical* stimulation

both during hospitalization and at 6 months. Every score within the deep sedation range in the first 48 h of ICU admission was associated with a 12.3 h delay in extubation [5].

Delirium: Assess, Prevent, Manage

Delirium is defined as acute brain dysfunction, typically with an underlying contributing factor most commonly: sepsis, polypharmacy, hypovolemia, multisystem organ dysfunction – many of which are present in critically ill patients. There are two types of delirium: hyperactive which is characterized by agitation or aggressive behavior, and is inherently much more easily identified and treated. The second type is termed hypoactive delirium and is characterized by withdrawal, and decreased consciousness, typically with decreased sedation scores. Hypoactive delirium can be more harmful as it typically goes unrecognized. Delirium is considered a significant complication of hospitalization. It is independently associated with higher mortality, prolonged intubation, increased length of stay and even long term cognitive impairment [18–20]. There are a handful of bedside tools for detecting delirium, but the one we primarily utilize is the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) (Fig. 17.2) [21]. The CAM-ICU tool can easily be used at the bedside by nursing staff and is an objective tool with the goal of early identification and subsequent treatment of delirium.

Early Mobility

Mobilizing patients who are critically ill in prior eras was considered dangerous. However, we know that early initiation (<3 days) of physical and occupational therapy has been shown to independently decrease ventilator and delirium days as well

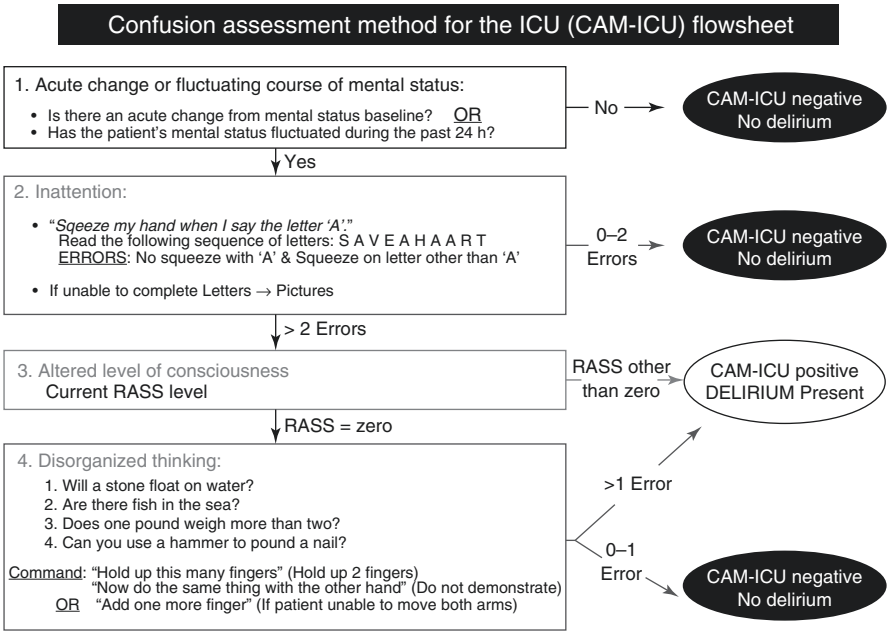

Fig. 17.2 Confusion Assessment Method for the Intensive Care unit (CAM-ICU)

as result in better physical independence at hospital discharge [22, 23]. A cohort study of patients readmitted after being treated for acute respiratory failure demonstrated that lack of early ICU mobility was even an independent risk factor for hospital readmission [24].

Family Engagement

The newest and in many ways one of the most important aspects of the ABCDEF bundle is family engagement. Traditionally, when a patient was critically ill, family members were asked to wait in the waiting room while procedures, rounds or other interventions occurred. Now, many ICUs are including the patient's family on multidisciplinary rounds and allow their presence for some procedures and even during the performance of CPR [25]. The better the family understands the overall care plan and trajectory, not only will they be better able to support their loved one, but they have also been shown to experience better feelings of inclusion and respect. Unfortunately for some patients there are difficult decisions to be made and the deluge of interventions are unlikely to change their outcome. Engaging the family consistently and early on with effective communication, with or without the use of palliative care or ethics specialists, has been shown to reduce ICU length of stays when the patient's expected outcome is poor [26, 27].

Search Strategy

A literature search of English language publications from the year 2000 to 2017 was used to identify any available literature on the use of the ABCDEF bundle elements in patients on ECMO using the Population, Intervention, Comparator, and Outcome (PICO) model (Table 17.4). Databases searched include Cochrane Library, PubMed, and EMBASE. Search words included "extracorporeal membrane oxygenation" OR "ECMO" AND "sedation" OR "mobilization" OR "delirium" OR "extubation". Articles not specifically addressing the elements of the ABCDEF bundle in ECMO patients were excluded. The quality of evidence was classified using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system.

Results

After review of the resultant articles, there were no interventional studies on implementing the ABCDEF bundle in ECMO patients, but four articles were identified and included in our analysis after our literature search. Two of these articles were surveys, one a case report and one a retrospective cohort analysis (Table 17.5).

Results: Sedation Practices Among ECMO Providers

Two surveys both by Marhong et al. [28] and Buscher et al. [29] demonstrated wide variability in sedation practices among ECMO providers (Table 17.5). There were a wide range of sedation practices, some targeting very deep levels of sedation, while others targeting awake unsedated patients. There were variable uses of paralytic agents across practitioners. Based on this survey data, there did not appear to be a unified or protocolized approach to sedation in ECMO patients, as many of these choices were up to the individual provider. This practice was very different than that

Table 17.4 PICO table for ABCDEF bundle elements in patients on ECMO

P	I	C	O
Adult patients on either VV or VA ECMO	ABCDEF bundle	No implementation of ABCDEF bundle	Ventilated days ICU LOS Delirium incidence Reintubation Mortality

Abbreviations: ABCDEF bundle Assess, Prevent and Manage Pain, Both Spontaneous Awakening/Breathing Trials, Choice of analgesia and sedation, Delirium: Assess, Prevent, Manage; Early Mobility, Family engagement, *ECMO* extracorporeal membrane oxygenation, *ICU* intensive care unit, *LOS* length of stay, *VA* venoarterial, *VV* venovenous

Table 17.5 Comparison of studies assessing ABCDEF bundle elements in patients on ECMO

Author, year	Design	Demographics	Intervention	Sedation and target	Sedation, analgesic, and/or paralytic agents	Mobilization	Delirium assessment treatment	Quality of evidence
Marhong (2017) [28]	Survey	Of survey sent to 394 ECMO centers, 209 responders VV ECMO only 63% teaching hospitals 46% had <10 VV ECMO patients/year	None, descriptive survey	97% used sedative/analgesic infusions **Targets:** "sedated" or "very sedated" (59%) "calm and cooperative" (29%) "unarousable" (16%)	**Sedatives:** Midazolam (48%) Propofol (19%) **Opiates:** Fentanyl (44%) Morphine (20%) **Paralytics:** 85% use 26% with protocol	**PT:** Participation: 84% Initiation of PT <72 h: 41% Passive ROM: 100% Ambulation 22% **Barriers to PT:** Hemodynamic instability (72%) Level of dependence on VV ECMO (49%) Hypoxemia (48%) Delirium (20%)	**Nonpharmacologic interventions:** Family presence (54%) Verbal reorientation (41%) Environmental modification (39%) **Pharmacologic interventions:** Haloperidol (27%) Quetiapine (23%) **Physical restraints:** 83% **Use of delirium protocol: 23%** **Use of delirium scale: 55%**	**Very low**

Buscher (2013) [29]	Survey	Of web-based survey sent to 194 ELSO centers, 102 responders VV ECMO only, Majority 10–20 ECMO runs per year 18 "experts" identified	None, descriptive survey	**Targets (overall, expert):** **Sedation status:** Cooperative and Tranquil (33%, 39%); Response to commands only (18%, 17%); Brisk response to light glabellar tap or loud auditory stimulus (8%, 6%); Sluggish response to glabellar tap or loud auditory stimulus (26%, 22%); No response (15%, 17%) **Sedation score use:** yes (49%,50%); no (33%, 50%); sometimes (18%, 0%) **Daily awakening:** yes (43%, 44%); no (22%, 22%); sometimes (35%, 33%)	**Most common agents used (overall, expert):** **Benzodiazepines:** Midazolam (79%, 100%) **Opioid** Fentanyl (45%, 28%); Morphine (43%, 50%) **Propofol:** yes (35%, 44%); no (64%, 56%) **Other sedatives:** Ketamine (28%, 33%); Clonidine (25%, 56%); Dexmedetomidine (41%, 28%); Barbiturate (6%, 6%); None (29%, 22%) **Paralytic agents:** Atracurium (11%, 22%); Cisatracurium (21%, 28%); Rocuronium (10%, 11%); Vecuronium (40%, 6%); none (11%, 22%)			**Very low**

(continued)

Table 17.5 (continued)

Author, year	Design	Demographics	Intervention	Sedation and target	Sedation, analgesic, and/or paralytic agents	Mobilization	Delirium assessment treatment	Quality of evidence
Abrams (2014) [48]	Retrospective cohort study	100 patients on ECMO either respiratory or cardiac failure Majority of pts on VV ECMO; eight patients on VA ECMO; BTT or BTR status 35 (35%) of patients participated in active physical therapy (PT) Medical ICU patients; exclusion of immediate post-operative patients (i.e. cardiovascular ICU)	Early mobility (i.e., PT)			**Max PT score:** 8 for BTT, 2 for BTR **Number of PT sessions/patient median:** 5 **Median sessions/ patient/week**: 2.8 **Ambulatory patients:** 18 **Maximum distance:** 175 ft **Survival at discharge:** 23 (66%) **Disposition**: home (13,57%), rehab (8,35%), subacute rehab (2,9%)		**Very low**

Rahimi (2013) [49]	Case report	Three patients requiring VV ECMO for respiratory failure	Early mobility (i.e., PT)			**Two of three cases able to participate in PT;** the limiting factor in the one case was significant hypoxi a, instability and critical illness eventually requiring lung transplantation; found to have severe cognitive deficits and neuromuscular weakness on evaluation post-transplant		**Very low**

Abbreviations: BTR bridge to recovery, *BTT* bridge to transplant, *ECMO* extracorporeal membrane oxygenation, *ICU* intensive care unit, *PT* physical therapy *PT Scores, Range 1–8* 1 being no mobilization, 8 being ambulation; *Rehab* rehabilitation, *ROM* range of motion, *VA* venoarterial; *VV* venovenous

of cardiac surgery care, which has developed a very protocolized approach to sedation for example, fast track cardiac anesthesia (FTCA).

FTCA emerged in the late 1990s, early 2000s and is defined as lower doses of opioid only anesthetic and directed earlier tracheal extubation times [30]. This technique has become popular as a cost-saving method for hospitals as it has been shown to decrease ICU length of stay, which significantly decreases hospital costs without significant differences in mortality or high morbidity complications [30, 31]. Prominent in more recent literature is the use of dexmedetomidine in post-cardiac surgery patients. Dexmedetomidine is a central alpha-2 agonist that decreases overall central sympathetic outflow [32]. There have been several retrospective studies that compare dexmedetomidine to more standard sedations such as propofol [33–37]. Dexmedetomidine when compared to propofol has been shown to decrease time to extubation, hospital length of stay and decrease hospital costs [33]. Dexmedetomidine in cardiac surgery patients has also been shown to decrease rates of atrial fibrillation [38] and the incidence of post-operative delirium when compared to other sedatives [34, 39]. Major drawbacks of dexmedetomidine in the literature include bradycardia and hypotension related to its overall dampening of sympathetic tone [35]. As mentioned earlier, in a general critical care population, the MENDS trial compared dexmedetomidine to standard benzodiazepine infusion and demonstrated that patients sedated with dexmedetomidine infusion as compared to lorazepam had significantly more delirium- and coma-free days [3].

In one of the surveys of ECMO providers (Table 17.5), dexmedetomidine was only used 28% of the time by experts, and only 41% of the time overall. Benzodiazepines, which have been shown in large randomized control trials to be deliriogenic [3], are still the mainstay of sedation in ECMO patients based on survey data. Nearly half (48% of providers) used midazolam in one very recent survey [28], and 100% of experts with 79% of overall providers used midazolam in another survey [29]. The unique entity in ECMO patients with the choice of sedation is the altered pharmacokinetics seen in ECMO patients with an increased volume of distribution, destruction of certain pharmacologic materials within the ECMO circuit, and wide variability in sedation uses and dosages [40, 41].

In a recent review, there have been a handful of reports published on “awake ECMO,” patients who have been extubated but remain on the ECMO circuit [42]. This allows for better respiratory mechanics and limits the negative impact of sedation, prolonged intubation, and relative immobilization. However, this is very new and requires a very complex multidisciplinary approach to the patient’s care, as the inability to control ventilation with an awake patient can be clinically challenging [42].

To date, there is no standardized protocol for approaching sedation on ECMO, no standardized agents or combination of agents to be used in the setting of altered pharmacokinetics of the ECMO circuit. Another significant difference between uncomplicated cardiac surgery patients and ECMO patients is their hemodynamic instability and critical illness. There are no clear guidelines or scoring systems specific to ECMO that have been devised to assess the degree of critical illness in order

to direct sedation practices. More prospective work needs to be done to risk-stratify patients that truly require deep sedation.

Results: Delirium Assessment and Management in ECMO Patients

Only one of the two available surveys (Table 17.5) addressed delirium assessment and management in ECMO patients [28]. This survey demonstrated a wide variability in the assessment and management of delirium, with only 23% of providers utilizing a delirium protocol and only 55% of providers utilizing a delirium scale. Interventions ranged from family presence, verbal reorientation and environmental modification, as well as pharmacologic interventions with typical and atypical antipsychotics in only 27% and 23%, respectively. Of providers in this survey, 83% utilized physical restraints in these patients.

Although delirium has not been well studied in ECMO patients, it has been investigated in cardiac patients overall. Delirium in post-cardiac surgery patients has been well-described and is associated with poorer outcomes including a significantly increased mortality risk from 2% to 13.5% based on prospectively collected data [43]. Reported rates of delirium vary significantly in the literature and are influenced by multiple factors [44]. A review article by Hollinger et al. in 2015 identified a total of 123 risk factors mentioned in a comprehensive literature review of 196 publications [44]. Some of the many reported factors for delirium in cardiac patients include: age, pre-operative Mini Mental Status Exam (MMSE) score, length of bypass time, whether or not the patient had "open" or "closed" surgery and preoperative albumin levels [44, 45]. Other risk factors specific to coronary artery bypass graft patients only include the presence of preoperative atrial fibrillation, high European system for cardiac operative risk evaluation scores, pre-existing cognitive impairment, prolonged surgery duration, and electrolyte disturbances [46].

There have been prospective scoring systems to assess the risk for delirium preoperatively in patients undergoing cardiac surgery. Rudolph et al. in 2009 [47] performed a prospective derivation and validation study of a tool to evaluate delirium risk in cardiac patients >60 years of age. The derived four independently predictive risk factors including MMSE ≤23, abnormal albumin (defined as <3.5 or >4.5), Geriatric Depression Scale >4, or history of Stroke/Transient Ischemic Attack (TIA). They assigned 2 points to an MMSE ≤ 23, 1 point to MMSE 24-27, 1 point to stroke/TIA history and 1 point to abnormal albumin. Delirium rates with the prediction model demonstrated that at ≥3 points, the rate of delirium was 86% in the derivation group and 87% in the validation group [47].

Currently, there are no guidelines specific to ECMO patients on how to approach delirium. Many ECMO patients are kept deeply sedated without even daily awakening trials given their instability. There have been no prospective studies to assess the long-term cognitive outcomes of these patients, however, presence of untreated

delirium in these patients is likely just as detrimental as it has been in other critical care populations with potentially increased risk of mortality.

Results: Early Mobilization and Physical Therapy in ECMO Patients

Mobility in ECMO patients is incredibly variable given the wide variety of cannulation practices as well as hemodynamic and oxygenation stability. Patients with femoral cannulation tend to have more limited mobility based on survey and retrospective data (Table 17.5) [48, 49]. Also, hemodynamic instability as well as issues with oxygenation play a large role in patients' ability to mobilize. This is also further confounded by the more common concurrent use of higher sedative techniques in these more unstable patients, which limits their ability to follow commands and participate in physical therapy [49].

Recommendations

Implementation of the ABCDEF bundle in ECMO patients has been piecemeal, at best, based on only survey data across ECMO providers. There are currently no dedicated guidelines to approaching the ABCDEF bundle in ECMO patients, although some recommendations can be extrapolated from the critical care literature. Reportedly, ECMO patients require much higher levels of analgesia and sedation and overall doses due to their critical illness and instability, cannula position/need for adequate flows for the ECMO circuit, as well as pharmacokinetic changes that occur when a patient is on ECMO, but all of this is being challenged [41]. There need to be prospective studies to assess and predict which patients truly require such high levels of analgesia and/or sedation, whether or not sedation pauses are safe even in more seemingly unstable patients, and what the long-term cognitive and physical consequences are for patients on ECMO. The best data the literature has available on ECMO patients is in regards to mobility, and this is based on retrospective cohort and/or survey data. Also, these mobility practices vary significantly by institution. There needs to be more prospective assessment of mobility and outcomes of early mobility practices and ECMO, as well as the role of family engagement.

A Personal View of the Data

Despite decades of evidence in support of the elements of the ABCDEF bundle internationally in critical care and somewhat in cardiac surgery, ECMO patients have not been distinctly studied in major clinical trials or cohorts. Often, ECMO

patients are kept heavily sedated, without daily interruption of sedation, assessment of delirium, and frequently do not participate in mobility and physical therapy. These patients do have many special considerations including adequate flows on the ECMO circuit, pharmacokinetic changes, etc., as previously discussed. However, none of these elements have ever been studied prospectively, and there are no guidelines to assess ECMO patients for their need of level of sedation based on their illness and/or cardiopulmonary support requirements. Many of the current guidelines within the ABCDEF bundle would not apply to ECMO patients, and some of these, such as the restrictions on when to perform SAT/SBTs would likely need to be liberalized and are already being challenged by cutting-edge cardiovascular centers of excellence. For example, many would view vasopressor use only as a relative contraindication, and if hemodynamic stability is proven on $\leq$2 inotropes at low-doses, this would still be acceptable for ventilator weaning and SATs/SBTs. Much more work needs to be done on the ECMO population to evaluate truly what their pain, agitation, sedation, delirium, mobility, and family engagement needs are based on evidence, and not just individual provider/center assessment and management.

Recommendations

- Similar to other critical care populations, ECMO providers should strive to attempt daily awakening and breathing trials to assess neurologic status using standardized sedation scales (evidence quality is very low, weak recommendation)
- ECMO providers should consider alternative sedative choices in avoidance of benzodiazepines, which are known to be deliriogenic (evidence quality is very low, weak recommendation)
- Extrapolating from the critical care literature, ECMO patients should have daily assessment of delirium by standardized delirium scoring systems and use non-pharmacologic and/or pharmacologic treatment accordingly (evidence quality is very low, weak recommendation)
- Despite the barriers of hemodynamic instability, hypoxia, level of ECMO dependence, and/or cannulation sites, ECMO providers should strive for early mobility, if anatomically and physiologically manageable under a standardized protocol (evidence quality is very low, weak recommendation)

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Chapter 18
ECMO as a Bridge to Lung Transplantation

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Introduction

Lung transplantation has become an established therapeutic option for patients with end-stage pulmonary disease. Its universal practice, however, remains limited by organ availability and logistical constraints, which result in considerable waitlist mortality [1]. As such, recent efforts have focused toward restructuring allocation strategies to help optimize organ utilization—but, to date, the growing demand for transplantable lungs remains unmet. Extracorporeal membrane oxygenation (ECMO) has evolved as an excellent alternative to support patients with end-stage lung disease until a viable donor becomes available. Over the last decade, key innovations have enhanced the attractiveness of contemporary ECMO as a suitable bridging platform to lung transplant, thereby expanding the possibilities available to select patients [1].

Historically, there was reluctance to endorse ECMO as a reasonable and safe strategy to transition patients toward transplantation because of hemolysis, infection, bleeding, hemodynamic instability and overall poor outcomes in early experiences [1]. However, this trend has changed as patients are presenting at more advanced disease stages and more transplant recipients are being hospitalized in the intensive care unit (ICU) at transplant, signaling a broader need to incorporate ECMO as bridge until a suitable donor is identified [2–4]. For example, in 2014,

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1949 lung transplants were performed, the most ever in a single year, and patients who underwent lung transplant in 2014 had higher lung allocation scores (LAS) than previous years indicating that they were sicker than ever before [5]. When the LAS system was implemented in 2005, the median LAS at transplant was 36.7; median LAS at transplant increased to its highest value (44.4) in 2014. Also, more transplant recipients were hospitalized in the ICU at transplant—15.5% of recipients in 2014 as compared with 9.8% in 2009. In 2014, 5.3% of transplant recipients were supported by ECMO at transplant. There appears to be a shift from use of a ventilator alone to ECMO—alone or with a ventilator—to provide support for respiratory failure before transplant [5].

Search Strategy

A literature search of English language publications from 2000 to 2018 was used to identity published data on ECMO support prior to lung transplant using the PICO outline (Table 18.1). PubMed and the Cochrane Library were searched. Search terms used were ("preoperative extracorporeal membrane oxygenation" OR "preoperative ECMO") AND "lung transplantation"; ("extracorporeal membrane oxygenation" OR "ECMO") AND "bridge to lung transplantation". A recent systematic review was identified, and the 14 articles included in that analysis were given particular attention. Single-patient case reports were excluded as well as studies that examined ECMO in pediatric patients, exclusively examined ECMO prior to heart-lung transplant, or examined economic endpoints. Publications focusing on technical details without reporting outcomes were also excluded. One systematic review, 22 case control studies, and 14 case series were included in our analysis. The data were classified using the GRADE system.

Table 18.1 PICO literature review strategy

Patient population	Intervention	Comparator	Outcome studied
Patients with respiratory failure who are candidates for lung transplantation	ECMO	No ECMO support, support with mechanical ventilation or NO;	Survival to lung transplant; days to transplant complications during ECMO support
Lung transplant recipients	ECMO	No ECMO support; support with mechanical ventilation or NO	Survival after lung transplant; allograft function; length of ICU and hospital stay after transplant; complications after transplant including the need for posttransplant ECMO support

Results

Cannulation Strategies

The basic ECMO configuration includes a closed system comprised of a venous drainage cannula, a pump, a control console, an oxygenator, a blender/cooler, and a return cannula. The condition being treated dictates the specific ECMO cannulation strategy employed, which in turn confers certain advantages, limitations, and considerations [6–9]. ECMO cannulation strategies can be adjusted according to the needs of the patient, and typically when bridging patients with a single insult of pulmonary etiology to lung transplantation, veno-venous (VV) ECMO is employed.

During VV ECMO, the ECMO circuit is in series with the lungs and does not provide cardiac support. The most common cannulation strategy for this approach utilizes percutaneous insertion of two cannulas: one inserted into the right internal jugular vein (IJV) and the other into either femoral vein (Fig. 18.1) [9]. Femoral-femoral VV ECMO is possible but is less often used, because it is associated with a greater incidence of recirculation [6]. Other more sophisticated cannulation strategies exist—i.e. axillary cannulation via the subclavian vein, the innominate vein or the incorporation of other mechanical circulatory support devices; however, these are used less often than the standard configuration [6–9]. Veno-arterial (VA) ECMO, where the ECMO circuit functions in parallel to the native heart and lungs, is less frequently employed when bridging to lung transplantation and is reserved for patients with acute hemodynamic collapse, severe pulmonary hypertension, or right ventricular dysfunction.

Beyond the traditional platform setup, there are other veno-venous cannulation strategies that utilize a single, dual-lumen ECMO cannula placed into the right IJV. The Avalon Elite® (Maquet, Germany) [10] is a dual-lumen catheter with inflow to the distal and proximal ends of the catheter (positioned in the inferior and superior vena cava) and outflow from the mid-portion into the right atrium (Fig. 18.1c). Of note, a novel dual-lumen VV ECMO cannula, the Protek Duo (Cardiac Assist, Pittsburgh, PA, USA) received Food and Drug Administration approval in 2014. The Protek Duo is also inserted into the right IJV, but in contrast to the Avalon Elite®, the distal tip of the cannula is placed into the main pulmonary artery [6]. (Fig. 18.2) This cannula can provide both respiratory support and right ventricular assistance [10].

Under optimal conditions, VV ECMO support will provide sufficient oxygenation to meet the patient's metabolic needs. ECMO complications are associated with cannulation (pneumothorax, vascular disruptions, bleeding, infection, emboli), systemic anticoagulation (gastrointestinal bleeding, intracranial bleeding etc.), or circuit disruptions, which can result in exsanguination. Recirculation is a limitation of VV ECMO related to cannula position and the requisite return and drainage of venous blood [6]. These potential complications require that a trained ECMO specialist must be present at the bedside or immediately available in addition to the patient's usual nursing staff [9].

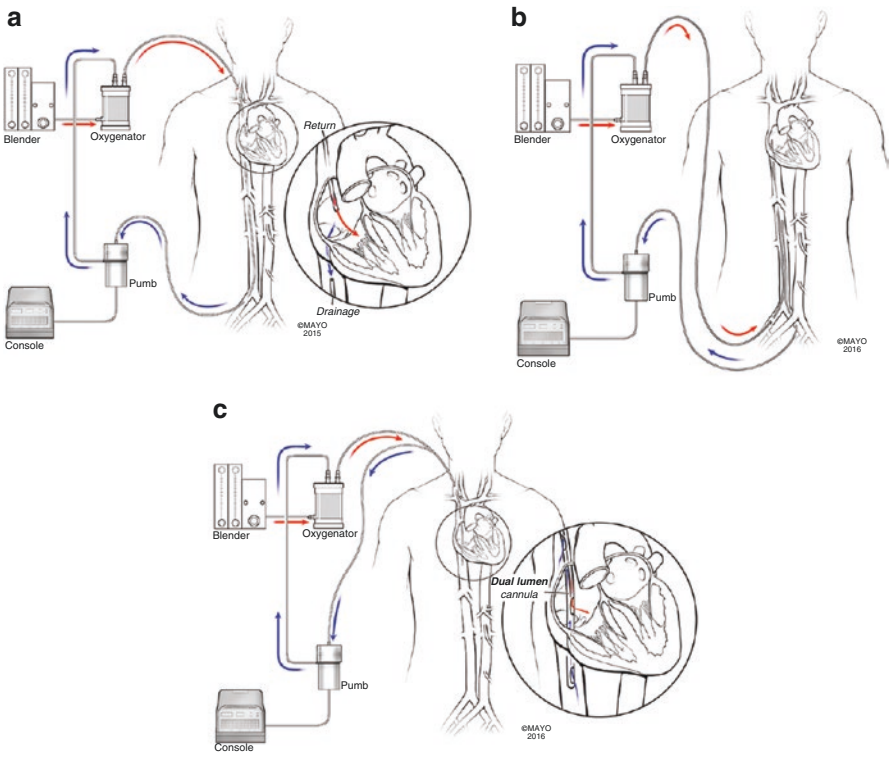

Fig. 18.1 Common VV ECMO configurations. Common veno-venous extracorporeal membrane oxygenation configurations. (**a**) Conventional veno-venous extracorporeal membrane oxygenation, where the tip of the drainage cannula lies at the inferior vena cava-right atria junction and the tip of the return cannula is in the right atrium. (**b**) Femoral-femoral veno-venous extracorporeal membrane oxygenation, where the tip of the drainage cannula is in the infrahepatic inferior vena cava and the tip of the outflow cannula is in the right atrium. (**c**) The Avalon Elite® veno-venous extracorporeal membrane oxygenation cannula, with bicaval drainage ports and a return port that directs oxygenated blood toward the tricuspid valve. (Reprinted from: Jayaraman et al. [6]; ©Wolters Kluwer Medknow Publications, used with permission)

Outcomes of ECMO as a Bridge to Lung Transplantation

It is difficult to compare ECMO with conventional means of support including mechanical ventilation (MV). Ideally, a therapy like ECMO should be studied with a prospective, randomized clinical trial where patients who meet inclusion criteria are randomized to receive either ECMO or conventional therapy. Increasing evidence from cohort studies has shown that ECMO is a viable option to bridge patients to transplant, and it would be difficult to consider a strict trial without allowing transition to "rescue ECMO" for patients who are determined to have failed conventional therapy. ECMO use has increased dramatically over the last 10 years, and

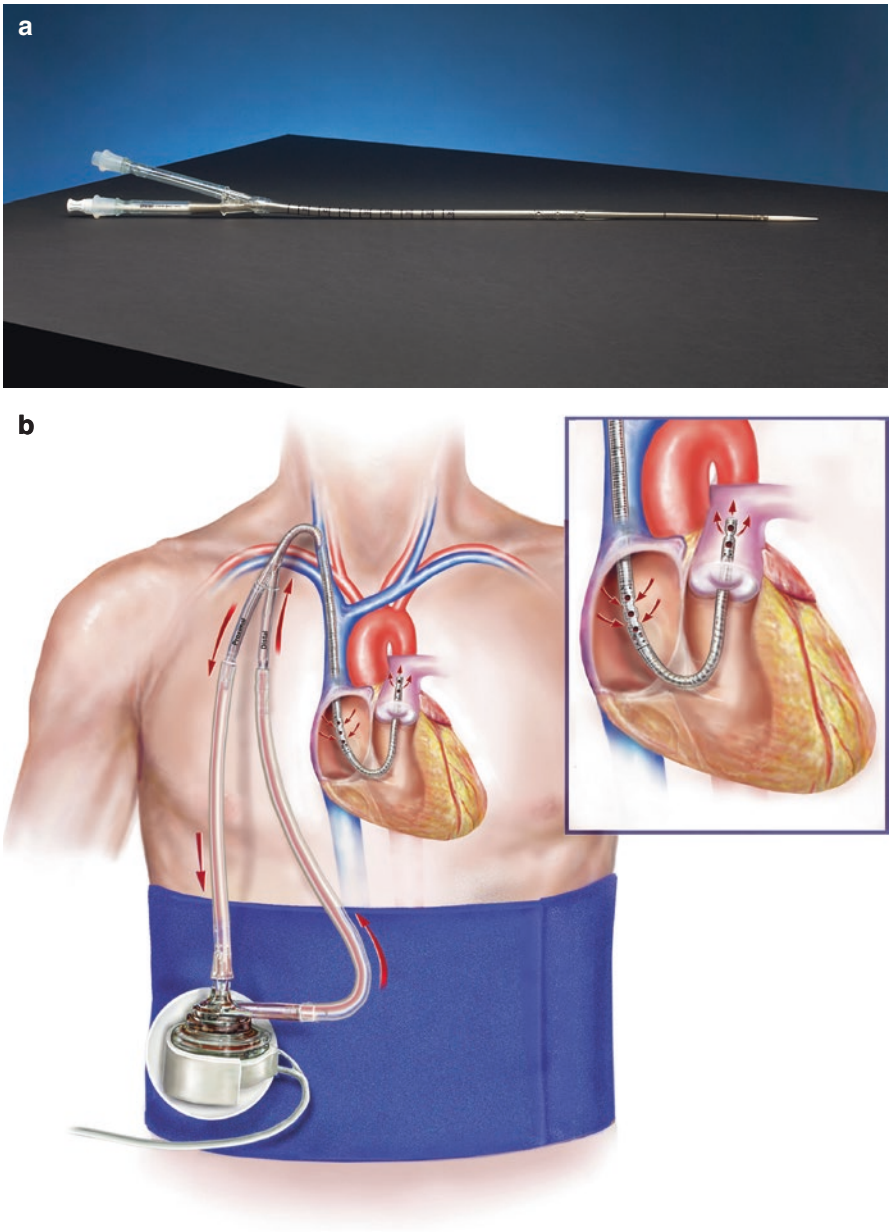

Fig. 18.2 The Protek Dua cannula. (**a**) Protek Duo dual-lumen cannula. (**b**) Adequate positioning from the right atrium to the pulmonary artery. (©TandemLife, Cardiac Assist, Inc. used with permission)

ECMO is now used post-cardiotomy, for cardiogenic shock, for acute respiratory failure, for cardiopulmonary failure, and as a bridge to lung or heart transplantation. Among these indications for ECMO support, in-hospital mortality seems to be lowest as a bridge-to-transplant [11].

ECMO as a bridge to lung transplantation has been studied retrospectively in case series and in case control studies examining single-institution experiences, multi-institution experiences, and the UNOS database (Table 18.2) [2, 3, 12–21]. Regardless of the study type, when interpreting survival outcomes after ECMO support, it is important to remember that conventional medical therapies have failed in the vast majority of patients studied, and that initially ECMO was rarely used before MV was initiated. ECMO support has only recently become an alternative, before MV is initiated, to avoid the respiratory complications associated with MV.

Outcomes of ECMO in respiratory failure were elusive for decades, but with better ECMO technology outcomes have improved significantly. The best survival-to-hospital-discharge rate (75%) is for newborns supported with ECMO for neonatal respiratory failure [22]. Survival- to-hospital-discharge for adults with severe respiratory failure is 52%. The randomized Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) Trial assessed whether ECMO improved survival [23]. Furthermore, survival outcomes following the use of ECMO in patients with acute respiratory failure during the H1N1 influenza pandemic of 2009 validated the role of ECMO as an important management strategy in adults with severe respiratory failure. Most recently, the EOLIA trial has confirmed the effectiveness of ECMO in patients suffering from acute respiratory distress syndrome (ARDS) [24].

Since improvements in outcomes in patients with ARDS following ECMO support were first observed, transplant specialists have focused in the use of ECMO technology in lung transplantation. Mason and colleagues analyzed United Network for Organ Sharing (UNOS) data from 1987 to 2008 in one of the first large, case control studies on ECMO as a bridge to lung transplant. During the 21 years included in their analysis, only 51 lung transplant recipients (0.3%) in the United States were supported by ECMO preoperatively [19]. In this early study, the 1-year survival was 50%, and 2-year survival was 45% for patients with pre-transplant ECMO as compared with 1-year survival of 79% and 2-year survival of 70% for unsupported patients. Therefore, ECMO was considered a contraindication for lung transplantation in many centers because of the poor outcomes.

These initial poor outcomes of lung transplantation after pretransplant ECMO support were in part due to the system used to prioritize transplant recipients. Before the introduction of the current lung allocation score (LAS) system in the United States in May 2005, donor lung allocation was primarily based on the time the patient spent waiting for a transplant. This waiting-time–based lung allocation favored patients who were well enough to wait and did not favor critically ill patients. Therefore, patients on ECMO would have to wait a long time for donated lungs, and the outcomes of lung transplantation were suboptimal because complications, such as muscular deconditioning, infection, thromboembolism, bleeding, and poor nutrition, occurred while on ECMO. However, with the LAS system, critically

Table 18.2 Retrospective, case control studies of ECMO as a bridge to transplant

Author (year)	Transplant dates	N (bridged with ECMO)	N (survived on ECMO to LTx or recovery)	N (LTx without ECMO)	Bridge time, days (range)	30-day survival (ECMO)	30-day survival (control)	1-year survival (ECMO)	1-year survival (control)	Other findings	Notes	Quality of evidence/study type
Bermudez (2011) [2]	1991–2010	17	N/A	1288	3.2 (0–49)	81%	93%	74%	78%	Allograft function 1 year after transplant did not differ significantly from controls; 3-year survival 62% ECMO, 65% controls		Low Retrospective, case control
Bittner (2012) [12]	2002–2009	9	N/A	81	3.6 (0.5–15)	63%	97%	33%	83%		Survival analysis included patients with ECMO before [9], during [12] or after [11] transplant	Low Retrospective, case control

(continued)

Table 18.2 (continued)

Author (year)	Transplant dates	N (bridged with ECMO)	N (survived on ECMO to LTx or recovery)	N (LTx without ECMO)	Bridge time, days (range)	30-day survival (ECMO)	30-day survival (control)	1-year survival (ECMO)	1-year survival (control)	Other findings	Notes	Quality of evidence/study type
George (2012) [13]	2005–2011	122	N/A	1874	NR	76%	95%	58%	81%	Among patients who survived to 6 months, there were no differences in survival at 2-years ($p = 0.2$)	UNOS database study; comparison group was LTx recipients with highest quartile LAS (median 65.4) but without ECMO	Low Retrospective, case control

Hayanga (2015) [3]	2000–2011	119	N/A	12,339	NR			74% [a]	86%[a]	Pretransplant ECMO increased the risk of dialysis-dependent renal failure (OR 3.1–13.6, depending on interval studied); survival after pretransplant ECMO improved over time from 25% in earliest interval to 74% in most recent interval	UNOS database study	Low Retrospective, case control
Hayes (2016) [14]	2005–2010	39	N/A	1521	NR			53%	68%	Pretransplant ECMO only increased the post-transplant mortality hazard in low-volume transplant centers	UNOS database study	Low Retrospective, case control

(continued)

Table 18.2 (continued)

Author (year)	Transplant dates	N (bridged with ECMO)	N (survived on ECMO to LTx or recovery)	N (LTx without ECMO)	Bridge time, days (range)	30-day survival (ECMO)	30-day survival (control)	1-year survival (ECMO)	1-year survival (control)	Other findings	Notes	Quality of evidence/study type
Inci (2015) [15]	2007–2013	30	28	160	21 (1–81)	89%	96%	68%	85%	Patients with CF had better survival after ECMO bridging than patients with IPF Patients bridged with ECMO had a higher incidence of post-transplant renal failure (42% vs. 15.6%) and critical illness (53.8% vs. 2.5%)	VV ECMO was used in 10 patients, VA ECMO in 4, iLA in 5, and a stepwise combination in 7	Low Retrospective, case control
Lang (2012) [16]	1998–2011	38	34	NR	4.5 (1–63)			60	90	When 1-, 3- and 5-year survival were examined conditional on 3-month survival, survival was not significantly different in patients without pretransplant ECMO		Low Retrospective, case control

Lee (2015) [17]	2006–2014	12	N/A	15	12 (NR)	100%	100%	61%	87%			Low Retrospective, case control
Lehmann (2015) [18]	2002–2011	13	N/A	130	NR	85%	95%	68%	71%		Study included ECMO and iLA	Low Retrospective, case control
Mason (2010) [19]	1987–2008	51	N/A	15,297	NR	72%	93%	50%	79%		UNOS database study	Low Retrospective, case control
Schechter (2016) [20]	2005–2013	65	N/A	11,607	NR			70%	84%	3-year survival was not significantly different for patients supported by pretransplant ECMO (64.5% vs. 67.0%).	UNOS database study. Examined iMV, ECMO, and iMV+ECMO	Low
										A significantly higher percentage of patients with ECMO bridging, with or without iMV, received blood transfusions before transplantation		Retrospective, case control

(continued)

Table 18.2 (continued)

Toyoda (2013) [21]	2005–2011	31	24	691	3.8 (NR)	96%	97%	83%	83%	Incidence of primary graft dysfunction requiring post-transplant ECMO was higher in patients receiving pretransplant ECMO (54% vs. 6%)		Low Retrospective, case control

Abbreviations: CF cystic fibrosis, *ECMO* extracorporeal membrane oxygenation, *iLA* interventional lung-assist support, *iMV* invasive mechanical ventilation, *IPF* idiopathic pulmonary fibrosis, *LTx* lung transplant, *N/A* not applicable due to study design, *NR* not reported, *UNOS* United Network for Organ Sharing, *VA* venoarterial, *VV* venovenous

[a]1-year survival for patients transplanted 2009–2011; 67 ECMO, 4596 control

ill patients who are in imminent danger of death; and therefore, in direst need of lung transplantation, receive a high score and have priority in lung allocation. Patients on ECMO have a high LAS, which may result in finding suitable donor lungs in a timely fashion, potentially leading to better outcomes [19].

Bermudez and colleagues provided insight on mid-term survival in a study that analyzed outcomes after lung transplantation over a 19-year period in patients who received ECMO support [2]. In this retrospective, single-center review, 1305 lung transplants were performed from March 1991 to October 2010. Seventeen patients (1.3%) were supported with ECMO before lung transplant. Diagnoses included re-transplantation (n = 6), pulmonary fibrosis (n = 6), cystic fibrosis (n = 4) and chronic obstructive pulmonary disease (n = 1). Fifteen patients underwent double lung transplant, one had single lung transplant and one had a heart-lung transplant. Mean duration of support was 3.2 days (range 1–49 days) and mean patient follow-up was 2.3 years. Survival and allograft function was compared between the patient who were supported by ECMO and those who were not. Their findings ultimately revealed 30-day, 1-year, and 3-year survival of 81%, 74% and 65%, respectively, for ECMO-supported patients and 93%, 78% and 62% in the control group. At 1-year follow-up, allograft function for the ECMO-supported patients did not differ from the control group, demonstrating that ECMO as a bridge to lung transplant is associated with high perioperative mortality but acceptable midterm survival in select patients. Late allograft function also did not differ in patients who received ECMO support before lung transplantation from as compared with those who did not receive ECMO—perhaps signaling the safety of ECMO therapy prior to transplantation [2].

In another study, Hayanga and colleagues used the United Network for Organ Sharing data base to analyze 12,458 adults who underwent lung transplantation between 2000 and 2011 [3]. In their study, patients were categorized into 2 cohorts: 119 patients who were bridged to transplantation using ECMO and 12,339 who were not. The study period was divided into four 3-year intervals: 2000–2002, 2003–2005, 2006–2008 and 2009–2011. One-year survival was compared for the two cohorts of patients in each of the time periods and risk of 1-year mortality was estimated. One-year survival for patients bridged with ECMO was significantly lower than 1-year survival of patients without pretransplant ECMO. However, this survival progressively increased with each period as the number of patients bridged using ECMO increased from four patients from 2000 to 2002 with 25% survival to 67 patients from 2009 to 2011 with 75% survival [3].

Javidfar and colleagues reported similarly encouraging results from their single-center experience of placing patients on ECMO with the intention of bridging them to lung transplantation. End points included successful bridging, duration of ECMO support, extubation, weaning from ECMO, overall survival and ECMO-related complications [4]. Thirteen patients (72%) were successfully bridged: ten to transplant and three to baseline respiratory function. Eleven patients (61%) survived longer than 3 months, including ten (56%) who underwent transplantation and are still alive. The median duration of ECMO support for patients who underwent transplantation was 6 days (range 3.5–31 days) versus 13.5 days (11–19 days) for those who did not undergo transplantation. Six patients (33%) were extubated on ECMO, four of them underwent transplantation. Four (22%) were too unstable for conventional inter-hos-

pital transfer and were transported on ECMO to the tertiary care center. In this subgroup, 75% were bridged to transplant or recovery, and all of the transplanted patients survived (100%). With these promising results, Javidfar and colleagues concluded that ECMO is a safe and effective means of bridging select patients with refractory respiratory failure to lung transplantation or return to their baseline condition [4].

Gordon and colleagues reported similar findings in their single-center, retrospective review of 28 consecutive patients from 2012 to 2016 who underwent ECMO as a bridge to lung transplantation [25]. Patients were divided into two groups: those who survived to lung transplant and those who died. Survival to transplant, discharge and 1-year survival was analyzed. Of their cohort of 28 patients, the most common diagnosis was idiopathic pulmonary fibrosis (n = 20). Fifteen patients were emergently evaluated and listed for transplantation during hospitalization. The mean lung allocation score at death or transplant was 89 ± 5. Twenty-four patients received VV ECMO, four patients required VA ECMO. The median duration of ECMO was 15 days (range 1–91 days). Eighteen patients initially used bi-caval, dual lumen catheters for VV ECMO. Ten patients on VV ECMO required ECMO changes, three patients required configuration changes to increase flows, and two patients required central cannulation to preserve oxygenation. The most common ECMO complications were thrombocytopenia, bleeding and sepsis. There was a trend toward increased transfusion requirement for patients who did not survive to transplant. Of the 28 patients included in the study, 16 underwent transplantation (15 double lung, 1 heart/lung), and 1 patient recovered without transplantation. There was a trend towards higher pre-formed reactive antibodies and rare blood types in those who died on ECMO. Thirty-one percent of patients required ECMO post-transplantation (range 1–6 days). Median duration of mechanical ventilation was 30 days. From these outcomes, the group concluded that ECMO was, indeed, a viable option for bridging select patients to transplantation, with ECMO complications and not duration of ECMO therapy designated as the most significant factor limiting successful transplantation [25].

Similarly, Dellgren and colleagues investigated early and late outcomes in 16 patients with end-stage pulmonary disease bridged with ECMO to transplantation between 2005 and 2012 [26]. Most of the patients in the cohort were late referrals for lung transplantation, and all failed to stabilize on mechanical ventilation. Twelve patients underwent lung transplantation after mean ECMO support of 16 days. Most patients were not on the waiting list while receiving ECMO, but after being assessed were on the waiting list for a median of 6 days before lung transplantation or death. Four patients died on ECMO waiting for a donor, and the success for bridging, as intention-to-treat, was 80% with 1-year survival of 63%. Of those who underwent lung transplantation, 2 patients died in-hospital after transplant; 11 are still alive, and 1-year survival for the transplanted patients was 75%. Median ICU stay before transplant was 9 days and median ICU stay after transplant 20 days. At follow-up, lung function was evaluated, and mean forced expiratory volume in 1 s was 62% ± 20% of predicted, and forced vital capacity was 74 ± 24% of predicted. From these findings, the group's conclusion mirrored the experience of others, that ECMO as a bridge to lung transplantation resulted in acceptable early and late survival in selected patients with end-stage pulmonary disease [26].

Chiumello and colleagues performed a systematic review of published studies of ECMO as a bridge to lung transplantation [27]. They initially identified 82 studies published from 2000 to 2014. Their final analysis included 441 patients from 14 publications with a high degree of heterogeneity between the studies. Post-transplant ICU stay duration ranged from 15 to 47 days, and post-transplant hospital stays ranged from 22 to 47 days. The most frequent post-transplant complications were need for tracheostomy, PGD requiring ECMO, pneumonia, and kidney failure requiring dialysis, and critical illness polyneuropathy/myopathy. One-year survival was acceptable, ranging from 50% to 93% in the reviewed studies. The systematic review indicated that pretransplant ECMO results is associated with increased perioperative morbidity and mortality, but can result in 1-year survival very similar to that seen in patients supported with MV without ECMO [27].

"Awake" ECMO

As we have enhanced our understanding of the physiologic changes of patients supported on ECMO and because of the recently acquired ability to support patients with a single, dual-lumen catheter, we have seen increasing interest in extubating and mobilizing patients on ECMO, especially those waiting for a lung transplant. This ability to rehabilitate patients on ECMO and avoid complications associated with MV has expanded the use of ECMO to patients who are awake and spontaneously breathing, as a novel bridging strategy (Table 18.3) [20, 28–32]. Fuehner and colleagues explored this strategy in their review of outcomes of patients treated with "awake ECMO" as a bridge to transplantation [33]. In this retrospective, single-center, intention-to-treat analysis of consecutive lung transplant candidates with terminal respiratory or cardiopulmonary failure who were supported by awake ECMO, they found that survival after transplantation was 80% in patients supported with awake ECMO group versus 50% in patients supported with mechanical ventilation. Additionally, patients supported with awake ECMO required shorter postoperative mechanical ventilation and showed a trend toward shorter postoperative hospital stay; thereby, underscoring the notion that ECMO support in patients who are awake and non-intubated is a promising bridging strategy [33]. Biscotti and colleagues reached similar conclusions in their analysis of awake ECMO support as a bridge to lung transplantation. Of 72 patients supported by awake ECMO who ultimately underwent transplantation, 37 survived to discharge, and 21 survived for 2 years. Daily participation in physical therapy was achieved in 50 patients (69.4%) [34]. Inotropic or vasopressor support (70% vs 93.8%; $p = 0.011$), Simplified Acute Physiology Score (26.8 vs 30.5; $p = 0.048$), and ambulation (80% vs 56.2%; $p = 0.030$) were significantly better in the patients who underwent lung transplantation than in those who did not. Patients with cystic fibrosis were more likely to have a bridge to transplantation than patients with other lung diseases (47.5% vs 25%; $p = 0.050$). This study demonstrated favorable survival and that high rates of physical therapy could be achieved and mechanical ventilation could be avoided during ECMO support in patients awaiting lung transplantation [34].

Table 18.3 Retrospective, case control studies examining the impact of awake ECMO and invasive MV during ECMO

Author (year)	Transplant dates	Study comparisons	N (bridged with ECMO)	N (LTx without ECMO)	N (survived to transplant)	Bridge time, days	Post-transplant survival outcomes	Other findings	Quality of evidence
Crotti (2013) [28]	2007–2011	Outcomes by ECMO bridging duration and used of iMV	25 ECMO≤14 days n = 11 ECMO>14 days n = 14	N/A	17	5.8 ± 4.5 For ECMO ≤14 days 29.8 ± 11.5 For ECMO>14 days	Mortality increased with longer bridging duration; 1-year survival: ECMO≤14 days 100%, ECMO >14 days 50%; HR = 1.06 per day	iMV during ECMO was associated with increased mortality and complications after LTx	Low Retrospective, case control
Fuehner (2012) [33]	2008–2011	Awake ECMO vs. MV as first-line support	26	34[a]	20 awake ECMO; 24 MV	Awake ECMO 9 (range 1–45); MV 15 (range 1–71)	6-month survival, Awake ECMO 80%; MV 50%	Patients supported with awake ECMO required shorter postoperative mechanical ventilation and showed a trend toward shorter postoperative hospital stay	Low Retrospective, case control

Lang (2014) [29]	2008–2012	Awake ECMO vs. mechanical ventilation vs. no support in patients requiring retransplantation for BOS	5	23	5 Awake ECMO; 20 no ECMO	NR		Awake ECMO did not increase the need for postoperative MV or post-transplant hospital ICU or hospital stay duration; iMV increased the need for post-transplant MV and ICU and hospital stay duration	Low Retrospective, case control
Mohite (2015) [30]	2007–2013	Awake ECMO vs. all other LTx recipients;	7	249	N/A		1-year survival 86% in both groups	No significant differences observed	Low Retrospective, case control
Nosotti (2013) [31]	2008–2011	Awake ECMO vs. ECMO with iMV	7 Awake ECMO	4 ECMO with iMV	N/A	12.1	1-year survival 86% awake ECMO, 50% ECMO with iMV, not significant	No significant differences observed	Low Retrospective, case control

(continued)

Table 18.3 (continued)

Rehder (2013) [32]	2007–2012	Ambulation and rehabilitation while on ECMO vs. ECMO with no rehabilitation	5 ECMO with ambulation and rehabilitation[b]	4 ECMO w/o rehabilitation	N/A	5 (range 0.5–14)	100% in both groups	Post-transplant duration of ventilation, post-transplant ICU stay, post-transplant hospital stay, total ICU stay, and total hospital stay were all shorter for subjects receiving rehabilitation	Low Retrospective, case control

Table 18.3 (continued)

Schechter [20]	2005–2013	UNOS database study of ECMO vs. iMV vs. ECMO + iMV vs. no support	65 ECMO; 119 iMV+ECMO	612 iMV; 11,607 no support	N/A	NR	One-year survival was worse for all supported groups (ECMO 70.4%, iMV 72%, iMV+ECMO 61%, no support 84.2%); 3-year survival was similar between patients supported with ECMO alone (64.5%) and those not supported (67%), but significantly worse in patients requiring iMV only (57%)or ECMO + iMV (45%)	Among patients with invasive respiratory support at transplant listing, significantly fewer supported by iMV (53%) or iMV+ECMO (61%) received a transplant as compared with patients supported with ECMO (69%)	Low Retrospective, case control

Abbreviations: BOS bronchiolitis obliterans syndrome, *ECMO* extracorporeal membrane oxygenation, *ICU* intensive care unit, *iMV* invasive mechanical ventilation, *LTx* lung transplant, *N/A* not applicable due to study design, *NR* not reported, *UNOS* United Network for Organ Sharing

[a]Of 34 patients supported with MV initially, 14 received ECMO or other extracorporeal lung assistance before transplant

[b]Dual-lumen cannula was used in rehabilitation group

Recommendations Based on the Data

It was once controversial whether patients receiving ECMO should be listed for transplant, because they are hospitalized and almost always on MV, and these patients were frequently denied for listing or removed from the waitlist, resulting in pretransplant mortality [35]. However, the findings of retrospective series over the last 8 years have made it clear that less than ideal outcomes after ECMO support should not be a deterrent to pretransplant ECMO support in patients who require a bridge to lung transplantation (Evidence quality moderate; Strong recommendation). Practice guidelines have evolved to assist in guiding the selection of suitable candidates for initiation of ECMO as a bridge to transplantation.

True indications for establishing ECMO are not well established; however, it is broadly accepted that patients with severe ventilation or oxygenation problems benefit the most from ECMO therapy. In general, and until recently, only patients who were not responsive to MV were considered for ECMO support. Patients with an arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2; PF) ratio <70 on 90–100% FiO2 or with persistent symptomatic hypercardia or acidosis despite adequate MV are considered for ECMO support. Patients must be listed for transplant with acute decompensation and suffer from an acute decompensation or progressive respiratory deterioration with CO2 retention or hypoxemia with the potential to avoid intubation as a sequela of single-system pulmonary disease. There can be no evidence of uncontrolled infection, the patient must be younger than 65 years of age, and they should not otherwise meet frailty criteria (Fig. 18.3) (Evidence quality low; Conditional recommendation). More recently, as outcomes and our understanding of ECMO physiology have improved, we also have considered ECMO support before intubation in patients with hypoxemia or CO2 retention. Most of these patients have cystic fibrosis with symptomatic CO2 retention and good potential for rehabilitation. Single cannulation strategies should be considered in these patients.

ECMO is contraindicated in the presence of other organ dysfunction, particularly of the kidney or liver, or neurologic dysfunction. Most centers will place patients on ECMO support if the lung is the only failing organ. Although longer durations of ECMO support are associated with worse outcomes, most active centers will support patients on ECMO until transplant unless the patient presents with renal failure, persistent infection, or ECMO-related complications that preclude them from transplantation.

As ECMO technology improves, ECMO support without invasive MV and sedation has been applied an increasing number of patients. Awake ECMO allows the possibility for the patient to ambulate and undergo rehabilitation, and early evidence suggests this approach improves posttransplant outcomes. Awake ECMO and ambulation should be attempted in patients presenting with progressive respiratory deterioration with CO2 retention or hypoxemia. (Evidence quality low; Conditional recommendation).

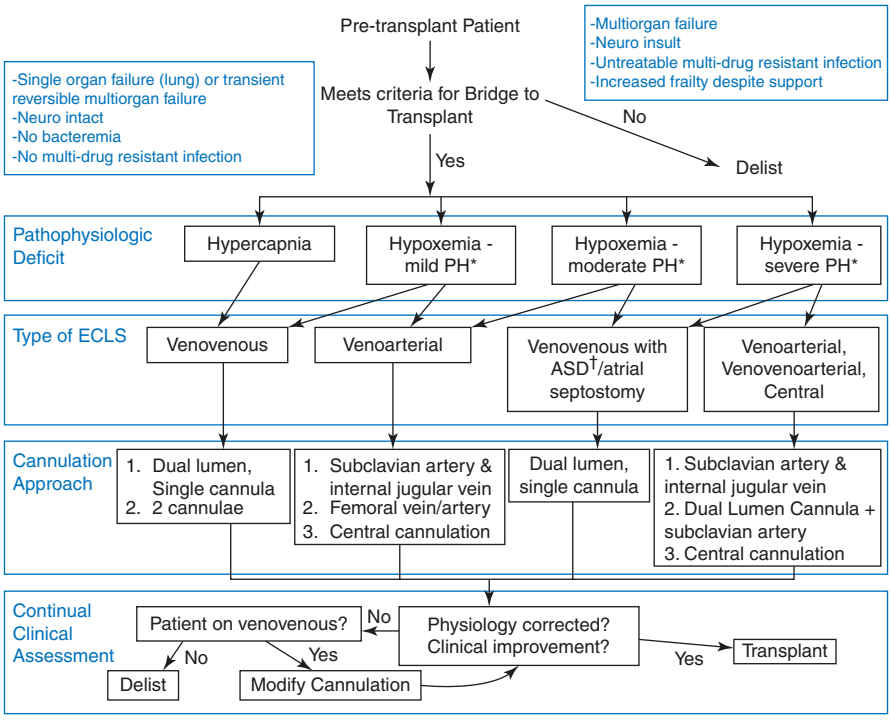

Fig. 18.3 ECMO as bridge to transplantation. (Adapted from: Biscotti et al. [34] Copyright (2017), with permission from Elsevier)

A Personal View of the Data

As ECMO technology continues to improve, so does our ability to manage and bridge patients safely to lung transplantation. ECMO has become an established technique to support patients as a bridge to transplant in active transplant centers where 5–10% of the patients who eventually receive a lung transplant are bridged on ECMO. The ability to rehabilitate and mobilize these patients, avoiding or decreasing the time on MV, has been associated with improvement in outcomes and has become an important consideration when selecting patients who are deteriorating while on the waiting list.

Despite this improvement, controversy exists as to the ability to uniformly implement ECMO support in all transplant centers, and inferior outcomes as compared with non-supported patients have been reported in patients when a prolonged time on the waitlist is expected with higher rate of complications. This reflects the limitations of the technology and the centers' ability to provide a safe environment for prolonged ECMO support. In our experience, the average time on support may vary between 10 and 15 days before a patient can be transplanted and could be considerably longer in patients with smaller chest sizes or who are sensitized to human leu-

kocyte antigen (HLA). Recently, an association was observed of lower transplant volume with higher mortality of ECMO as a bridge to lung transplant [14, 36]. For this reason, although ECMO seems to be an excellent alternative to support patients with respiratory failure and to be used as a bridge to lung transplant, ECMO should be considered cautiously depending on the local expertise to manage this complex patient population and the ability to transplant ECMO-supported patients with a reasonable time on the waitlist. Further studies are needed to define the appropriate timing of ECMO implantation, the type of support needed to minimize complications, and the local infrastructure and organ availability needed to make ECMO a realistic alternative.

Future Directions

Innovations, such as the hollow-fiber oxygenator and the Mendler-designed centrifugal pumps, and advances in cannula technology have revolutionized modern ECMO therapy [20]. Additionally, improvements in circuitry have reduced heparin and blood product requirements, leading to fewer complications. Because of positive outcomes in contemporary trials, ECMO has evolved into an attractive option to successfully support adults for months at a time, as a bridge to either recovery or transplantation. Further advances are needed to simplify the initiation of ECMO therapy and minimize any associated complications. These advances would expand the options available to patients awaiting lung transplantation. As the current technologies evolve, there are also ongoing research efforts to design devices with improved biocompatibility and gas exchange, which may allow prolonged support (months to years), that could revolutionize this field in the next decade.

Recommendations

- Less than ideal outcomes after ECMO support should not be a deterrent to pretransplant ECMO support in patients who require a bridge to lung transplantation. (Evidence quality moderate; Strong recommendation)
- ECMO support as a bridge to transplant is indicated in patients on the transplant waiting list who are younger than 65 years of age with advanced chronic respiratory failure, who are suffering an acute decompensation unresponsive to MV or NO, and who are not contraindicated for lung transplant based on well-established listing criteria. (Evidence quality low; Conditional recommendation)
- ECMO strategies that allow the patient to be awake and non-intubated are very promising. Awake ECMO and ambulation should be attempted in patients presenting with progressive respiratory deterioration with CO2 retention or hypoxemia. (Evidence quality low; Conditional recommendation)

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Chapter 19
When on ECMO: Awaken, Extubate and Mobilize

Rakesh C. Arora, Dave Nagpal, Yoan Lamarche, Rohan Sanjanwala, and Andrea Szwajcer

Abbreviations

ARDS	Acute respiratory distress syndrome
ECMO	Extracorporeal membrane oxygenation
E-CPR	Extracorporeal membrane oxygenation (ECMO) assisted cardiopulmonary resuscitation
ICU	Intensive care unit
PICS	Post-intensive care syndrome
prICULOS	Prolonged ICU length of stay
PTSD	Post-traumatic stress disorder
SCCM	Society of Critical Care Medicine
VA-ECMO	Veno-arterial extracorporeal membrane oxygenation
VV-ECMO	Veno-venous extracorporeal membrane oxygenation

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Introduction

The extracorporeal membrane oxygenation (ECMO) can be utilized to support end organ perfusion in patients suffering from severe but potentially reversible respiratory or cardiac failure. ECMO provides isolated respiratory support using veno-venous ECMO (VV-ECMO) by oxygenating blood and removing CO_2 in the venous circulation. Veno-arterial-ECMO (VA-ECMO) provides both respiratory and hemodynamic support by bypassing both the heart and the lungs. Once deemed a therapy of last (and often too late) resort, following the H1N1 influenza pandemic [1–3] in 2009, ECMO has seen an incredible resurgence over the past decade. The use of ECMO in adults has increased by 433% across the United States between 2006 and 2013 [4].

This explosion of ECMO use has revealed new issues for the healthcare team involved with these complex patients. Recent editorials examining intensive care unit (ICU) "survivorship" in patient with prolonged ICU length of stay (prICULOS) has challenged us to consider if we *"are creating survivors…or victims"* with the use of cardiac support devices particularly when implemented in urgent or emergent situations [1, 2]. Examination of survivorship data from patients recovering non-cardiac critical illness reveals 40% mortality in the 1st year following "successful" hospital discharge [3]. Further, long-term outcomes have shown long term depression, anxiety, and post-traumatic stress disorder (PTSD) symptoms, cognitive impairments, as well as functional disability, often referred to as Post Intensive Care Syndrome (PICS) [3, 5–9]. As such, there is an urgent need to identify strategies to reduce negative outcomes in critically ill patients requiring ECMO support.

In a now seminal randomized controlled trial, Schweickert and colleagues demonstrated that an intervention, combining daily sedation interruption and physical and occupational therapy, improved functional outcomes and independent walking among mechanically ventilated critically ill patients [10]. In this trial of 104 patients, their proposed "whole-body" rehabilitation was demonstrated to be safe and well tolerated, and importantly resulted in more ventilator-free days, a shorter duration of ICU care, reduced complications such as delirium. In addition, the intervention group experienced a better functional outcome (defined as an improvement in six domains of activities of daily living (ADLs: consisting of: bathing, dressing, eating, grooming, transferring from bed to chair, using the toilet)) at hospital discharge compared with standard care.

Targeting minimal sedation in any critically ill patients is increasingly recognized as a best practice to promote patient interaction and engagement up to cooperation with early mobilization protocols (please also see www.iculiberation.org). In addition, previous reports have shown that minimal sedation facilitates early extubation and a reduction in ventilator-induced lung injury (VILI) and has short term mortality benefits [11–14]. Langer and colleagues recently provided a review of the advantages and disadvantages of "awake" ECMO management [15]. The Cohort study by Gay et al. reported extubation after minimal sedation of patients treated with ECMO after cardiac arrest or cardiogenic shock [16]. This study of 99 patients reported a 17.7% mortality for extubated patients (3 out of 17) and 66.7% mortality among sedated and mechanically ventilated patients (8 out of 12).

Gap in Knowledge

In 2013, the Society of Critical Care Medicine (SCCM) provided detailed guidelines on the management of pain, agitation and delirium for the critically ill patients [17], in which they have provided strong recommendations for the use of early mobilization daily sedation interruption or a light target level of sedation be routinely used in mechanically ventilated adult ICU patients (Level of evidence: moderate; Recommendation: Strong). This expert consensus, however, did not have any specific recommendation for the patient requiring ECMO. This is an important distinction as these patients are often are more tenuous from a respiratory and hemodynamic standpoint as compared to other non-ECMO supported patients.

There remains, however, a lack of consensus on the feasibility, safety, and appropriateness of early mobilization in these complex patients. In general, there is a dearth of literature pertaining to the patient requiring ECMO support, particularly in appropriate sedation target and extubation in the patient on ECMO support. As such the aim of this chapter is to undertake a focused literature search to review current evidence evaluating the effects of early mobilization as a whole on critically ill cardiothoracic surgery patients receiving ECMO.

Methods

Search Strategy

The PICO question for this review was "In adult cardiothoracic surgery patients receiving extracorporeal membrane oxygenation (ECMO), what is the effect of sedation interruption, extubation and early mobilization on outcomes such as length of dependency on ECMO, length of hospital stay, length of ICU stay, and postoperative survival compared with standard care?"

In collaboration with a medical librarian (A.S.), a base search strategy was developed to capture all relevant studies from MEDLINE: Ovid; subsequently, the search strategy was adjusted to retrieve studies from Embase, SCOPUS, and CHINAL databases. Searches were conducted with no restrictions in terms of language or date of publication and type of study. The key areas searched were sedation interruption (awaken), spontaneous breathing (extuabtion), early mobilization and extracorporeal membrane oxygenation along with their respective synonyms and derivations. Boolean operator 'OR' was used to combine results within each area and operator 'AND' was used to combining results between the two areas. Cross-referencing of selected articles was done to identify and retrieve additional relevant studies. In addition, the title of each selected study was used to search PubMed for "related articles," and the first 20 articles of the "related articles" search results were screened. Studies including patients <18 years of age, or only considering chest

Table 19.1 PICO for early mobilization for critically-ill patients

Population studied	Adults (age ≥18 years) critically ill patients receiving ECMO (VV/VA)
Intervention	Sedation interruption, spontaneous breathing, early mobilization program or description of physiotherapeutic intervention
Comparison	Standard care: lack of early mobilization program or usual ICU care
Outcome	Length of dependency on ECMO, hospital LOS, ICU LOS, QOL, postoperative survival

physiotherapy and breathing exercises were excluded. The title and abstract of the retrieved studies were evaluated to determine fit to the inclusion criteria. The potential studies were then fully analyzed in terms of eligibility based on PICO as defined in Table 19.1. The studies evaluating post cardiac surgical adults patients during intensive care stay and receiving ECMO are included. The studies describing the effect of early mobilization or other physiotherapeutic intervention to standard care or lack of early mobilization program were included.

Results

As expected, there are limited high-quality published data on this topic. There is a larger pool of evidence evaluating critically ill patients in general [18–24], but limited evidence specifically evaluating cardiothoracic surgery patients receiving ECMO support. The majority of evidence found are case studies, case series or retrospective case series. Given the paucity of available data in cardiothoracic surgical patients, study inclusion criteria was expanded to include all critically ill adult patients receiving VV/VA ECMO, with sedation interruption, extubation and early mobilization as research interventions. The quality of selected studies was assessed using GRADE system.

The clinical course of the critically ill patient is frequently complicated with ICU acquired weakness (loss of physical function) as well as complications such as delirium, long-term function disability, PTSD, and PICS. The ABCDEF bundle is an evidence-based approach focused on liberating critically ill patients of the consequence of an ICU stay. Within the ABDCEF bundle, early mobilization in the ICU can decrease the duration of mechanical ventilation, reduce the length of ICU and hospital stay [10, 20, 21, 25–28]. Extracorporeal membrane oxygenation is increasingly utilized as an adjuvant treatment for critically ill patients with respiratory failure [6, 8, 29–31]. ECMO receiving patients share common clinical course with other critically ill patients not receiving ECMO. We, therefore, base the rationale for efficacy on general critical care mobilization and rely on the published (and personal) experience to confirm the safety of mobilizing ECMO patients.

Early Sedation Interruption (Awaken) and Spontaneous Breathing (Extubate)

The life-sustaining ICU practice to achieve physiological restoration and mortality prevention includes respiratory and hemodynamic support. The collateral damage stemming from extended immobility and bed rest, achieved through deep sedation, results in negative sequel of severe muscle weakness, functional impairment and loss of quality of life. The studies included here (Table 19.2) evaluate the impact of reducing sedation dosage or of practicing sedation interruption (awake trials) along with spontaneous breathing trials on patients' recovery [32–39]. The intensive care unit patients receiving such intervention had shorter duration of mechanical ventilation, lower hospital mortality and shorter duration of ICU and hospital stay. The multicenter prospective trials by Shehabi et al. demonstrated that patients receiving early deep sedation (RASS −3 to −5) had delayed time to extubation (Hazard ratio (HR): 0.90), higher hospital (HR:1.11) and 180- day (HR:1.08) mortality [32, 33]. The study by Girard et al. randomized intensive care unit patients to either intervention group receiving sedation interruption and spontaneous breathing trials or to the control group receiving sedation per usual care plus spontaneous breathing trials [37]. The study reports that the 'awaken and spontaneous breathing trials' group was associated with favorable outcomes including more days spent without mechanical ventilation and shorter length of ICU and hospital stay. Please refer to Table 19.2.

Feasibility and Safety of Early Mobilization Intervention for Critically Ill Patients' Receiving ECMO Support

All 11 included papers reported intensive care-critically ill patients treated with ECMO (VV/VA/mixed) and presented data concerning feasibility and safety of early mobilization. Five studies reported [5, 7, 8, 40, 41] specific indications, physiological and cognitive, for early mobilization in patients' receiving ECMO. Table 19.3 summarizes these indications for mobilization.

All studies reported physiotherapy interventions for all patients receiving VV/VA ECMO support. Together, 118 patients received early mobilization therapy, and only 8 patients received passive physiotherapy, illustrating feasibility of mobilization in this complex patient cohort.

Table 19.4 summarizes all adverse events that occurred at the time of mobilization. Two studies [31, 42] reported cannula dislocation and bleeding from the cannulation site. The study by Lee et al. [5] retrospectively reviewed 99 patients; including 4 patients requiring (type: not reported) ECMO support. A total 520 early mobilization sessions were performed. There were 17 adverse events reported including respiratory distress, desaturation, tachypnea, bradycardia, patients' request to stop mobilization, and tracheostomy dislodgement. None of the safety

Table 19.2 Sedation interruption (awaken) and spontaneous breathing trials (extubate)

Study	Study design	Population	Setting	Intervention	Outcome (OR/HR/MD/mean/median/percentage)	Comments	LOE
Shehabi (2012) [32]	PCT	Medical/surgical ICU patients, ventilated and sedated ≥24 h	Multicenter (25 centers-Australia, New Zealand)	Early sedation RAAS −3 to −5	Early deep sedation is independent predicator of **time to extubation** (HR: 0.90), **hospital mortality** (HR: 1.11) and **180-day mortality** (HR: 1.08)	Early deep sedation is associated with delayed extubation, increased hospital and 180-day mortality	Moderate
Shehabi (2013) [33]	PCT	Medical/surgical ICU patients, ventilated and sedated ≥24 h	Multicenter (11 centers -Malaysia)	Deep sedation RASS ≤−3	Early deep sedation is independent predicator of **time to extubation** (HR: 0.93), **hospital mortality** (HR: 1.11) and **180-day mortality** (HR: 1.09)	Early deep sedation, irrespective of type of sedative, is associated with delayed extuabtion, increased hospital and 180-day mortality	Moderate
Tanaka (2014) [34]	PCT	Medical/surgical ICU patients, ventilated ≥48 h	Multicenter (45 centers-Brazil)	Early (<48 h) deep sedation	Compared to light sedation, early deep sedation is associated with **longer duration of mechanical ventilation** (7 vs. 5 days), **no. of tracheostomies** (38.9% vs. 22%, **hospital mortality** (OR: 2.36)	Early deep sedation is associated with delayed extubation as well as higher risk of hospital mortality	Moderate
Kress (2000) [36]	RCT	Medical ICU patients, ventilated	Single center	Sedation interruption vs. continuous sedative infusion	Compared to the continuous sedative infusion group, the sedation interruption group had shorter **duration of ventilation** (4.9 vs. 7.3 days), and **length of ICU stay** (6.4 vs. 9.9 days)	Daily sedation interruption decreases the duration of mechanical ventilation and ICU length of stay	High

Girard (2008) [37]	RCT	Intensive care unit patients, ventilated ≥12 h	Multicenter (4 centers-USA)	Sedation interruption and spontaneous breathing trial vs. usual care	The sedation interruption group spent more **days without mechanical ventilation** (MD 3.1 days), **shorter length of ICU** (median time: 9.1 vs 12.9 days) and **hospital** (median time; 14.9 vs. 19.2 days) stay	Wake up and spontaneous breathing protocol is associated with better clinical outcomes	High
Strom (2010) [38]	RCT	Critically ill adult patients expected to need ventilation for more than 24 h	Single center, Denmark	No sedation vs. sedation	The group receiving no sedation has more **days without ventilation** (MD: 4.2 days), Shorter **length of ICU** (13.1 vs. 22.8 days) and **hospital** (34 vs. 58 days) stay	No sedation protocol for the critically ill patients is associated with shorter duration of mechanical ventilation, ICU and hospital stay	High
Balas (2014) [39]	PCT, before and after study	Medical/surgical critically ill patients	Single center, USA	Awakening and breathing coordination, Delirium monitoring/ management and, exercise and mobility bundle	The cohort managed with bundle at decreased **risk of delirium** (OR: 0.55) and increased risk of **out-of-bed mobilization during ICU stay** (OD:2.11) compared to the before-cohort	The Critically ill patients managed with the bundle have shorted length of mechanical ventilation and are more likely to be mobilized during ICU stay	Moderate

Abbreviations: LOE level of evidence, *PCT* prospective cohort trial, *RCT* randomized controlled trial, *ICU* intensive care unit, *OD* odds ratio, *HR* hazard ratio, *MD* mean difference

Table 19.3 Summary of indications for early mobilization of patients receiving ECMO [5, 7, 8, 40, 41]

Clinical parameter	Indications	Contraindications
Heart rate	No arrthymia, 60–120 bpm	Arrthymia
Blood pressure	Stable blood pressure	Hemodynamic instability
	MAP: >60 mmHg	MAP: <55 or >120 mmHg
	SBP: 90–180 mmHg	SBP: <90 or >180 mmHg
Vasopressor medication	<2 vasoactive agents	>2 vasoactive agents, escalating dose
Respiratory rate	Stable, 10–30 bpm	Respiratory distress
Oxygen saturation	SpO_2 >90%; FiO_2 <0.6	Hypoxemia resistant to oxygen therapy
	PEEP<10 cmH_2O	
Cognition/alertness	Alert, cooperative	Positive CAM-ICU
	RASS −2 to +2	RASS >+3 or <−3
Cannulation site	Stable cannulation site	Bleeding, thrombosis at the cannulation site

events required additional therapy or lengthened hospital stay. In this study, the patients on ECMO support received 69 sessions of early mobilization; 9 adverse events were reported. The remaining studies reported no adverse events related to early mobilization. The most frequent adverse events reported are bleeding from the cannulation site, patients' request to stop mobilization, tachycardia, and tachypnea.

Effect of Early Mobilization on Duration of ECMO

The retrospective cohort study by Munshi et al. [6] evaluated 61 ARDS patients receiving ECMO and early mobilization therapy (VV ECMO: 93% and mixed: 7%). Depending on the patients' tolerance and physical capacity, the patients received ICU physiotherapy consisting of sitting at the edge of the bed, standing or tilt table, stepping, transfer to chair and ambulation. Among the survivors, the median duration of ECMO therapy for patients receiving early mobilization was 13 days (IQR: 10–19), compared with 8 days (IQR: 7–10) for those who were not mobilized. However, stratified outcome data controlling for clinical baseline and severity-of-illness characteristics was not reported. In addition, 39% of the patients receiving ICU physiotherapy could perform low intensity physiotherapy (active in-bed exercise) and 17% patients could perform high intensity exercise (including sitting at the edge of bed or higher). Furthermore, the feasibility of high intensity physiotherapy was not associated with baseline clinical characteristic and severity of illness characteristics. Alternatively, the sedation agitation scale score was found significantly associated with higher intensity physiotherapy while on ECMO; emphasizing sedation titration with a goal to awaken the patients and subsequently assess mobilization feasibility.

Table 19.4 Early mobilization for intensive care unit patients receiving ECMO

	Study	Type of study	Study population	N	Diagnosis	Type of ECMO	Early mobilization	Multidisciplinary mobilization team	Outcomes	Adverse event reported	LOE[a]
1	Polastri et al. (2016) [42]	Systematic review: case reports, case series, retrospective cohort	Studies describing physiotherapeutic activities of intensive care unit subjects >18 years, awake and receiving VV ECMO	52	CF = 18 ILD = 7 COPD = 3 IPF = 3 PF = 1 PAH = 1 ARDS = 11 COPD = 4 PAH = 4	VV ECMO	Physiotherapy commenced within 2–5 days included passive and active movements, in-bed positioning and ambulation	Yes; Anesthesiologist, Surgeon, Perfusionist Physiotherapist, nurse, respiratory therapist and ICU physician,	**Feasibility and Safety;** Included nine studies reported on physiotherapeutic intervention for all the patients	Cannula dislocation	Low
2	Garciaet al. (2011) [31]	Retrospective case series	Patients with severe respiratory failure	10	Pneumonia/ ARDS = 4 COPD = 1 IPF = 4 PAH/RVF = 1	VV ECMO	Ambulation (N = 4/10); Physiotherapy (N = 6/10)	Not reported	**Feasibility** 4/10 ambulation **Mean ICU LOS Post ECMO among survivors**[b] (Ambulated): 32 (days) Not Ambulated: 55 (days) **Mean Hospital LOS Post ECMO among survivors**[b] (Ambulated: 37.25 (days) Not Ambulated: 57 (days)	Bleeding reported among the 4 patients receiving ECMO	Very low
3	Ko et al. (2015) [40]	Retrospective case series	Patients receiving physiotherapy while on ECMO	8	ILD = 2 IPF = 4 Dilated cardiomyopathy = 1 Necrotizing pneumonia = 1	VV ECMO = 7 VA ECMO = 1	Mobilization = 7 Passive physiotherapy = 1	Yes; Physiotherapist, Incharge nurses, respiratory specialist, perfusionist, intensivist	**Feasibility** (7/8)	Tachycardia = 3 sessions Tachypnea = 2 sessions	Very low

(continued)

Table 19.4 (continued)

	Study	Type of study	Study population	N	Diagnosis	Type of ECMO	Early mobilization	Multidisciplinary mobilization team	Outcomes	Adverse event reported	LOE[a]
4	Lee et al. (2015) [5]	Prospective cohort	Medical ICU patients with RASS −2 to +2, stable respiratory function, hemodynamic stability	99 patients; 4 ECMO patients (69 sessions)	Respiratory = 55 Sepsis = 24 Cardiovascular = 6 CNS = 5 Others = 9	Not reported	4 ECMO patients receiving 69 mobility sessions	Yes	**Feasibility** Out of 520 mobilization sessions 69 sessions were performed on patients receiving ECMO	Out of 69 session 9 safety events reported for patient receiving ECMO (Including: tachypnea = 2, desaturation = 2, tachycardia = 1, patients' intolerance = 4)	Low
5	Munshi et al. (2017) [6]	Retrospective cohort	Adult patients with ARDS supported with ECMO	61 ARDS patients receiving ECMO	ARDS	VV ECMO	Physiotherapy = 50 No physiotherapy = 11	Yes	**Feasibility:** 50/61 **Duration of ECMO:** No physiotherapy: 8 days (7–10) Physiotherapy: 13 days (10–19) **ICU mortality**: No physiotherapy = 7 physiotherapy = 1 (P-value = 0.006) **In hospital mortality:** No physiotherapy = 7 physiotherapy = 1 (P-value = 0.006)	No adverse events noted that were directly related to physiotherapy in this population	Low
6	Chavez et al. [7]	Case report	Case 1: chronic non ischemic cardiomyopathy (no ECMO) Case 2: ARDS with ECMO support	1 patient	ARDS	VV ECMO	Physiotherapy	Yes	**Feasibility** 2/2	No adverse event reported	Very Low

7	Abrams et al. (2014) [8]	Retrospective cohort study	Adult patients receiving ECMO medical intensive care unit:	100 patients; physiotherapy = 35	CF = 10 ARDS = 9 ILD = 6 COPD = 6 PAH = 4	VV ECMO = 23 VA ECMO = 4 Fem-Fem = 8	35 patient received physiotherapy; ambulation as maximum level of physical therapy	Yes	**Feasibility** 35/100	No physiotherapy related adverse events reported	Low
8	Rahimi et al. (2013) [9]	Case series	Adults patients with respiratory failure requiring ECMO	3 patients	Case 1: ARDS Case 2: IPF Case 3: CF	VV ECMO	Early physiotherapy	Yes	**Feasibility** 3/3	No adverse events reported	Very low
9	Rehder (2013) [29]	Retrospective case series	Adults patients receiving ECMO as a bridge to lung transplantation	9 patients	IPF: 2 IP: 2 CF: 5	VV ECMO	5/9 received mobilization	Yes	**Feasibility** 5/9 **Total hospital stay** Mobilization: 49 No mobilization: 98 (P-value = 0.05) **Total ICU length of stay** Mobilization: 27 No mobilization: 49 (P-value = 0.01)	No adverse event reported	Low
10	Boling et al. (2016) [41]	Retrospective cohort study	Patients canulated at right Internal jugular vein and ambulated while on ECMO	18 patients	CF: 3 IPF: 6 CWP: 2 MCTD: 1 ARDS: 1 Others: 5	VV ECMO	9/9 received early ambulation	Yes	**Feasibility** 5/9 **Survival to hospital discharge** Ambulation: 67% No ambulation: 45%	No adverse events related to ambulation were reported	Low

Abbreviations: CF cystic fibrosis, *IPF* interstitial pulmonary fibrosis, *IP* interstitial pneumonia, *ARDS* acute respiratory distress syndrome, *MCTD* mixed connective tissue disease, *COPD* chronic obstructive pulmonary disease, *RF* respiratory failure, *ECMO* extra corporeal membrane oxygenation, *VV* veno venous, *VA* veno-arterial

[a]Level of evidence as per the GRADE approach

[b]Computed from the data presented in the study

ICU and Hospital Length of Stay for Patients Receiving ECMO

The retrospective case series by Rehder et al. [29] evaluated nine patients awaiting lung transplantation with respiratory failure receiving VV ECMO. All patients in the rehabilitation group (N = 5) received physical therapy within 5 days of ECMO cannulation. The rehabilitation cohort had shorter ICU length of stay (27 vs 49 days) and hospital length of stay (49 vs 98 days). These findings are in agreement with the results of another retrospective case series by Garcia et al. [31]. This study consisting of ten respiratory failure patients received VV ECMO with a goal of minimal mechanical ventilation and aggressive rehabilitation. Six out of ten patients survived to hospital discharge. An attempt was made to extract data on survivors to hospital discharge (N = 6) and the post ECMO mean ICU and mean hospital length of stay were computed. The patients receiving mobilization (N = 4) experienced shorter post ECMO mean ICU length of stay (32 vs 55 days) and decreased post ECMO mean hospital length of stay (37 vs 57 days).

ICU and In-Hospital Mortality

The study by Munshi et al. [6] reported higher in-hospital and ICU mortality in the patients that did not receive early mobilization intervention. Seven patients (64%) died in ICU in the cohort not receiving physiotherapy compared to one (22%) death in ICU in the cohort receiving physiotherapy (p-value = 0.006); similar findings are reported for in-hospital mortality in this study [seven patients (64%) died in the no physiotherapy cohort; one died (22%) in the physiotherapy cohort (P-value = 0.006)]. Another retrospective cohort study by Boling et al. [41] of 18 patients with respiratory pathology and receiving VV-ECMO, demonstrated a survival of 67% among the ambulated cohort and a survival of 45% in the cohort not receiving ambulation as an intervention.

Patient Management

Each of the selected studies endorsed multidisciplinary team involvement for early mobilization of ECMO patients. The early mobilization team consisted of a registered nurse, physiotherapist, perfusionist, and intensivist. Patients were evaluated for safety before mobilization by the multidisciplinary team, and each team member monitored key areas to assure patients safety during mobilization.

Recommendations Based on the Data

The cardiothoracic surgery patients with a complicated post-operative clinical trajectory are exposed to similar intensive care unit stressors including systematic inflammatory response, prolonged bed rest as well as disorientation [43, 44]. Deep sedation during intensive care unit stay is associated with poor outcome including longer hospital stay, longer duration of mechanical ventilation, higher in hospital and long term mortality [32–34, 45]. Critically ill patients in the intensive care unit are recommended to receive early sedation interruption as well as spontaneous breathing trials [35]. Sedation interruption and spontaneous breathing trials decreases mechanical ventilation days, hospital length of stay and reduces delirium occurrence [35–39].

- ***Early sedation interruption and extubation for all critically ill patients results in reduced duration of mechanical ventilation, duration of ICU and hospital stay as well as hospital mortality. (Level of evidence: high (Ib), Strenght of recommendation: strong (A)***

Several weakness syndromes are encompassed in the overarching syndrome of ICU acquired weakness. An experienced, multidisciplinary team should assess the physiological status and hemodynamic stability of intensive care unit patients including those receiving ECMO for safety and appropriateness for attempting early mobilization. However, early mobilization has consistently shown benefits in a wide variety of patients, including post cardiac surgery patient receiving ECMO. Early mobilization can enhance recovery to baseline functioning as well as shorten the duration of ECMO, reduce length of ICU and hospital stay, and ICU and hospital mortality.

- ***Multidisciplinary teams and early mobilization of intensive care unit patients, including those receiving ECMO, reduces the risk of preventable harm, enhances patients' safety, and reduces the duration of ECMO, length of ICU and hospital stay as well as reduced ICU and hospital mortality. (Level of evidence: low (C), limited data; Strength of recommendation: moderate (II a), Benefit > Risk).***

Most of the reported studies are quasi-experimental (retrospective cohort studies), case series and case reports. Table 19.3 summarizes indications reported in the studies for mobilizing such patients. The table is based on five studies reporting indication/contraindication for early mobilization of patients receiving ECMO [5, 7, 8, 40, 41]. The patients that are hemodynamically unstable, having cognitive deficits or otherwise moribund were deemed unfit for early mobilization and were excluded. The healthier patients selectively received early mobilization intervention and as a result have reported lower mortality. No adverse events data is available if sicker patients have to undergo mobilization along with ECMO support.

- ***A priori safety profile and clinical parameters assessment decreases the risk of possible safety adverse events such as death, cardiac or respiratory arrest, falls, removal of medical devices and abnormal physiological responses in intensive care unit patients on ECMO receiving early mobilization (Level of evidence: low (C), limited data; Strength of recommendation: moderate (IIa), Benefit>Risk).***

Personal View of the Data

There is a growing body of evidence documenting the benefit of early sedation interruption, extubation, and mobilization of critically ill patients. This ethos is progressing in most intensive care units worldwide, and teams are becoming experts at mobilizing more and more complex patients. Concurrently, the number of patients receiving ECMO has grown exponentially in the last decade, with indications for support in constant evolution. These critically ill patients represent a challenge for mobilization, one that has been overcome safely by many teams.

Early mobilization in the critically ill patients and more so in the patients on ECMO support is a "team sport". The interdisciplinary ICU team needs to move together with consideration of their local clinical context and infrastructure to ensure patients' and teams' safety. By way of example, it may be appropriate for the interdisciplinary critical care teams to invest in becoming experts at early interruption of sedation, extubation, and mobilization of non-ECMO patients before attempting it on ECMO patients. The patients receiving ECMO, mechanical ventilation or prone ventilation represents additional challenges and are generally more complex to mobilize and ambulate. The potential risks of adverse events, associated with early mobilization, are much higher in such patients (i.e. inadvertent decannulation, hemodynamic instability). In general, veno-venous ECMO with single neck cannula are typically the "easiest" to ambulate with less risk of acute decompensation. On the other end of the spectrum is the open-chest post-cardiotomy on VA-ECMO with central cannulation. In those patients, most centers would generally avoid mobilization until a more stable configuration of support can be provided, or at very least sternal closure. In summary, before attempting early mobilization in ICU patients receiving ECMO, individual patients' evaluation by a competent multidisciplinary team with a goal to evaluate the spectrum of patients' morbidity, therapeutics and patients' functional status is necessary to ensure favorable outcomes as well as patients' safety.

Not unlike other complex ICU patients, care bundles including checklists before mobilization have been used in many centers prior to verticalization or mobilization of patients on ECMO support (unpublished data from CANCARE Society participating sites (see www.cancaresociety.com). The factors such as hemodynamic or respiratory instability despite ECMO support, a high risk cannula displacement due to positioning and/or anatomical factors, and lack of patient's collaboration are crucial and should be included in the safety checklist. The safety checklist could help avoid complications as steps to ensure safety are multiple, including the presence of

specialized staff members. The lack of randomized trials and the overall modest quality of the available literature on the subject limit the generalizability of the recommendations. Selection bias is likely in all reported studies with comparisons of groups with and without mobilization. Nonetheless, it is our impression that if no contraindications to mobilization are identified, an expert, interdisciplinary ICU team should attempt progressive physiotherapy and mobilization.

The presence of retrospective reports only in this area illustrates the novelty of the subject and the rapid development of ECMO in the last decade. While this therapy becomes more widespread and the indications expands (ARDS, bridge to lung transplant, cardiogenic shock, post-cardiotomy, ECMO assisted cardiopulmonary resuscitation (E-CPR), etc.), there will be a need for higher quality data including formal evaluation of safety of the mobilization bundles in critically ill ECMO patients. Randomized trials on the topic are currently not feasible, but a refined understanding of contraindications and incidence of adverse events should develop as more centers publish their experience. Collaborative efforts with interdisciplinary involvement as well as multi-institutional data could help in accelerating the generation of an improved understanding of this rapidly evolving topic.

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Part V
Mechanical Assist Devices

Chapter 20
Percutaneous Assist Devices as Salvage from Cardiogenic Shock

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Introduction

Cardiogenic shock (CS) is defined as end-organ hypo-perfusion resulting from inadequate cardiac output despite adequate intravascular volume [1]. There are multiple etiologies of CS, the most common of which is acute myocardial infarction (MI), accounting for up to 80% of cases [1]. According to the SHOCK trial registry, the majority of cases of CS (78%) were due to left ventricular failure while other causes such as acute severe mitral regurgitation (6.9%), ventricular septal rupture (3.9%), isolated right ventricular failure (2.8%), and free wall rupture (2%) were less commonly observed [2]. In addition, post-cardiotomy syndrome, myocarditis, stress-induced cardiomyopathy, and cardiac tamponade are important causes of CS.

Despite advances in revascularization and mechanical support strategies, mortality from CS can be as high as 50% [1, 3–5]. Initial treatment of CS involves the use of pharmacologic circulatory support in the form of sympathomimetic inotropic and vasopressor agents. Furthermore, in patients who develop CS in the setting of acute coronary syndrome, urgent revascularization is vital in improving patient outcomes [6, 7]. In the SHOCK trial, all-cause mortality was significantly lower at 6 months in patients with ST-segment elevation MI and CS who underwent early revascularization compared with those who had medical stabilization alone [6]. Current ACC/AHA guidelines recommend early revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in patients with CS due to acute coronary syndromes [8]. As a result, the use of revascularization for treatment of CS has increased. Despite these treatment modalities, some patients

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develop refractory CS and in these patients, mechanical circulatory support (MCS) may be necessary.

MCS devices help maintain organ perfusion while also reducing cardiac filling pressures, left ventricular volume and wall stress, resulting in decreased myocardial oxygen demand. They include counterpulsating intra-aortic balloon pump (IABP), continuous flow Impella devices, as well as TandemHeart and total cardiac support with extracorporeal membrane oxygenation (ECMO). This chapter will focus on these percutaneous cardiac support devices, which are currently approved by the Food and Drug Administration (FDA), and their use in CS. Of note, there are a number of novel devices undergoing clinical study, such as the HeartMate PHP (Abbott Vascular, Santa Clara CA), which will not be discussed in this chapter.

Search Strategy

A literature search of English language publications from 1999 to 2017 was used to identify published data on the use of percutaneous assist devices for CS using the PICO outline (Table 20.1). Databases searched were PubMed, CrossRef, Cochrane Evidence Based Medicine, EMBASE, and Google Scholar. Terms used in the search were "cardiogenic shock" AND "percutaneous assist device", "Impella", "Intra-aortic balloon pump", "TandemHeart", and "extracorporeal membrane oxygenation". Articles were excluded if they only addressed medical therapy or revascularization without use of percutaneous assist devices as treatment for CS. Quality of the data, within each article reviewed, were classified according to the GRADE system.

Results

Intra-aortic Balloon Pump

The first clinically used MCS device was the IABP which was developed in the late 1960s [1]. IABP provides counterpulsation with a helium filled balloon inflating in diastole, resulting in diastolic pressure augmentation, increasing coronary

Table 20.1 PICO table of percutaneous assist devices used to treat cardiogenic shock

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Adult patients in cardiogenic shock	Percutaneous assist devices including IABP, Impella, TandemHeart, ECMO	Medical therapy	Overall mortality, procedural complications, reversal of cardiogenic shock

artery perfusion and myocardial oxygen supply. The balloon deflates in systole, which results in reduced systemic resistance and therefore reduced left ventricular afterload. Optimal hemodynamic benefits of IABP depends upon its position within the aorta, the blood displacement volume, the balloon diameter in relation to the aorta, the timing of the inflation and deflation of the balloon, the intrinsic heart rate and rhythm, a competent aortic valve, the systemic vascular resistance and the arterial blood pressure [9, 10]. Importantly, IABP augments the cardiac output by 30–40%, and up to 1 L/min, but is unable to provide support without adequate intrinsic cardiac output. This is unlike the MCS devices discussed later in the chapter which provides continuous support regardless of the intrinsic cardiac output. Due to the ease of use, IABP is by far the most widely used MCS device [11].

In 2000, the SHOCK trial studied patients who had acute MI complicated by CS and was designed to evaluate the outcomes of patients treated with IABP. In this trial 85% of patients were treated with IABP. It was discovered that those who were treated with IABP, with or without medical therapy, had a mortality rate of 46.5% and 52.6% respectively, while those who did not have an IABP implanted had a higher mortality rate of 76.5% [2]. This suggested that use of the IABP decreased mortality in patients with CS. However, a more recent study has provided less encouraging results. The IABP-SHOCK II Trial published in 2012 randomized 600 patients with acute MI complicated by CS to IABP placement or to medical therapy alone. The investigators found no mortality difference at 30 days between patients who were treated with IABP, with a rate of 39.7%, versus medical therapy, with a rate of 41.3% [12]. These recent equivocal results have resulted in downgrading the use of IABP from Class I in both the ESC and ACC/AHA guidelines to Class III and Class IIb recommendations respectively [9, 13].

The main complications associated with the IABP are bleeding, stroke, thrombocytopenia, infection and peripheral limb ischemia. In the IABP-SHOCK II trial they discovered no difference between the groups in regards to the rates of stroke (0.7% in IABP group versus 1.7% in the medical therapy group), sepsis (15.7% in IABP group versus 20%% in the medical therapy group), re-infarction (3% in the IABP group versus 1.3% in the medical therapy group), stent thrombosis (1.3% in the IABP group versus 1% in the medical therapy group), or peripheral ischemic complications (4.3% in the IABP group versus 3.4% in the medical therapy group) [12]. It is worth noting that IABP devices are placed through the femoral artery and require patient immobilization when placed in this position. However, in more recent years the IABP is more commonly being placed via the subclavian or axillary artery which allows the patient to remain mobile. The placement of subclavian IABP in heart failure patients as a bridging device provided adequate hemodynamic support in 84–93% of patients so that they did not require escalation of their inotropic support and 90% of these patients were successfully bridged to their next therapy [14, 15]. Of these patients 95–100% of them were able to extensively ambulate and receive physical therapy [14, 15] (Fig. 20.1).

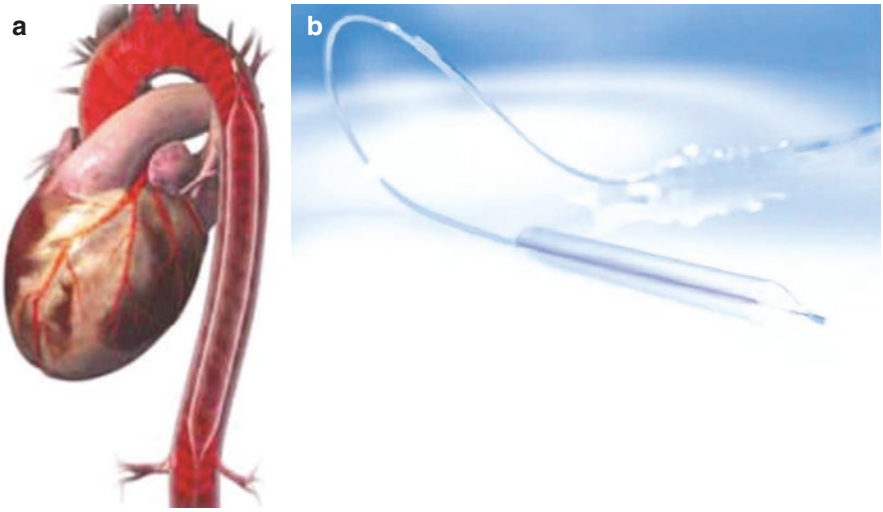

Fig. 20.1 Intra-aortic balloon pump within the descending aorta. (Courtesy of Maquet, Wayne NJ)

Impella

The Impella system (Abiomed, Danvers, MA) is a short-term percutaneous left ventricular assist device (LVAD) that provides continuous axial flow from the left ventricle to the ascending aorta. There are currently three Impella systems available to unload the left ventricle, the Impella 2.5, the Impella CP and the Impella 5.0, providing flows from 2.5 to 5.0 L/min. Of these, the Impella 2.5 and CP are inserted percutaneously into the femoral artery (via a 12–14 Fr access), while Impella 5.0 requires a femoral cutdown due to its larger motor size. As with durable LVADs, these Impella devices only unload the left ventricle and therefore a competent right ventricle is required to provide left ventricular preload [9]. Additionally, it is contraindicated in patients with severe aortic valve disease, mechanical aortic valve and LV thrombus due to its design requiring its placement across the aortic valve into the left ventricle [16]. For cases of CS due to isolated right ventricular failure, a temporary percutaneous right ventricular assist device (RVAD), Impella RP, has been recently approved by the FDA [9]. The Impella RP system can be used for up to 14 days in patients with refractory RV shock [1]. The Impella RP system is inserted via the femoral vein into the right atrium and through to the pulmonary artery where it can provide 2.5–5.0 L/min of flow.

There are cohort studies which suggest that initiation of Impella prior to revascularization in patients who failed to be stabilized with the use of vasopressor support and/or IABP support were associated with a survival rate of 65% when compared to initiation of Impella after revascularization at 30 days with a survival rate of 40% [17, 18]. Placement of Impella was also associated with improvement of left

ventricular function from an average of 10% pre-implantation to 30% after Impella removal [17, 19]. This was also supported by analysis of real-world data from the global catheter-based ventricular assist device (cVAD) registry which showed that survival to hospital discharge was significantly improved with implantation of the Impella device prior to PCI [20]. In these cases, Impella may provide more stable hemodynamics prior to and during revascularization allowing more complete revascularization. Impella can be placed on average in 22 min with the IABP taking on average 14 min [21]. The overall dose of the vasopressors was similar in both IABP and Impella groups, 4.2 mg/kg and 7.1 mg/kg of epinephrine respectively, and the medium vasopressor support time for both groups was 46 h [21].

In the ISAR-SHOCK trial, comparing the use of Impella to IABP implanted after revascularization, it was noted that hemodynamic variables were significantly improved with Impella support as compared to IABP support within 30 min of implantation, but after this time point there was no significant difference between the two groups [21]. The IMPRESS trial then investigated Impella versus IABP implantation after revascularization and showed no significant difference in regards to all-cause mortality at 30-days and at 6-month follow up [17, 22, 23]. At 30 days the all-cause mortality rate for the IABP group was 50% while the mortality rate for the Impella group was 46%, and at 6 months the mortality rate for both groups was 50% [23]. Also in the IMPRESS trial the investigators reviewed follow up echocardiography which showed that left ventricular ejection fraction was similar between the two groups with an ejection fraction of 46% on average in the Impella group and an ejection fraction of 49% on average in the IABP group. The PROTECT II trial, which studied Impella versus IABP in high risk patients undergoing PCI, did not show a benefit to Impella in the primary endpoint of 30-day major adverse cardiovascular events [24, 25]. Of note, the PROTECT II trial had to be stopped early because those in the Impella arm were treated more often with rotational atherectomy as opposed to the IABP arm which introduced a new confounding variable into the study. However, the secondary endpoint of major adverse events at 90 days did show a benefit towards the patients who were treated with Impella [24, 25].

Bleeding and/or arterial complication rates with Impella are similar to IABP [16, 21]. Hemolysis is a common complication associated with Impella devices, occurring at a rate of 5–10% [16], usually within the first 24 h after implantation [22]. If hemodynamically tolerated, decreasing the device speed may help reduce the degree of hemolysis [16]. In some cases, severe hemolysis may require discontinuation of Impella support. A rare complication of Impella devices is LV perforation [16]. Since migration of Impella devices can occur, close monitoring of the Impella console waveforms is vital to ensuring proper placement. If adjustments are necessary, they must be performed under echocardiographic guidance. Suction alarms may indicate migration to the LV apex, acute hypovolemia from bleeding, dehydration or right ventricular failure. Purge alarms can signal complications along the system including leakage, air, blood in the motor or tube kinking [16] (Fig. 20.2).

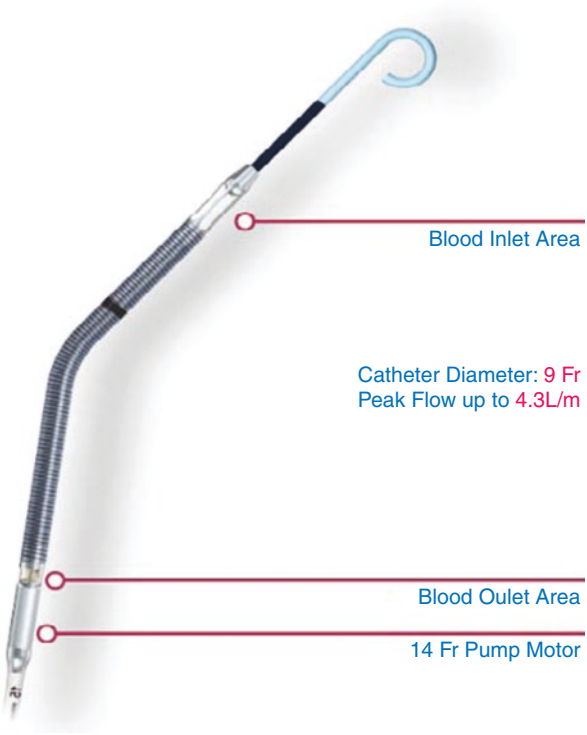

Fig. 20.2 Impella. (Courtesy of Abiomed, Danvers MA)

TandemHeart

The TandemHeart system is a temporary continuous flow centrifugal extracorporeal assist device. A trans-septal puncture is used to insert a venous inflow cannula into the left atrium. Oxygenated blood is drawn from the left atrium and returned extracorporeally via a cannula in the ileofemoral arterial system. This system is capable of delivering flow up to 5.0 L/min depending on the size of the femoral artery cannula [1]. Contraindications for placement of this device include intracardiac thrombus and ventricular septal defect [16]. For cases in which CS is secondary to right ventricular failure, there is the TandemHeart right ventricular support device that has been associated with acute reduction in right heart filling pressures and improved cardiac index over a 48-h period [26]. Of note, the TandemHeart right ventricular support device is currently not FDA approved as an RVAD [9].

There have been several small trials comparing left ventricular TandemHeart to IABP which show favorable hemodynamic variables with the use of TandemHeart [27]. Compared to patients treated with IABP, whose cardiac indices increased by 0.6 after IABP placement, those treated with TandemHeart had an increase in their cardiac index by 1.2–2.1 [27]. However, there was no significant difference in 30-day survival when comparing those treated with a IABP and those treated with

the TandemHeart with mortality rates of 36–46% and 46–47% respectively [21, 22, 27]. Since these studies were small they were underpowered to evaluate mortality.

Patients who were treated with the TandemHeart were noted to have severe bleeding and a trend toward limb ischemia [22, 27, 28]. Due to large cannula size both TandemHeart and ECMO are most often associated with limb ischemia, bleeding and vascular injury. Unique to this device is the possibility of residual atrial septal defect due to the need for a trans-septal approach [16]. Dislodgement of the device into the right atrium can cause shunting with deoxygenated blood being delivered to the arterial system [16] (Fig. 20.3).

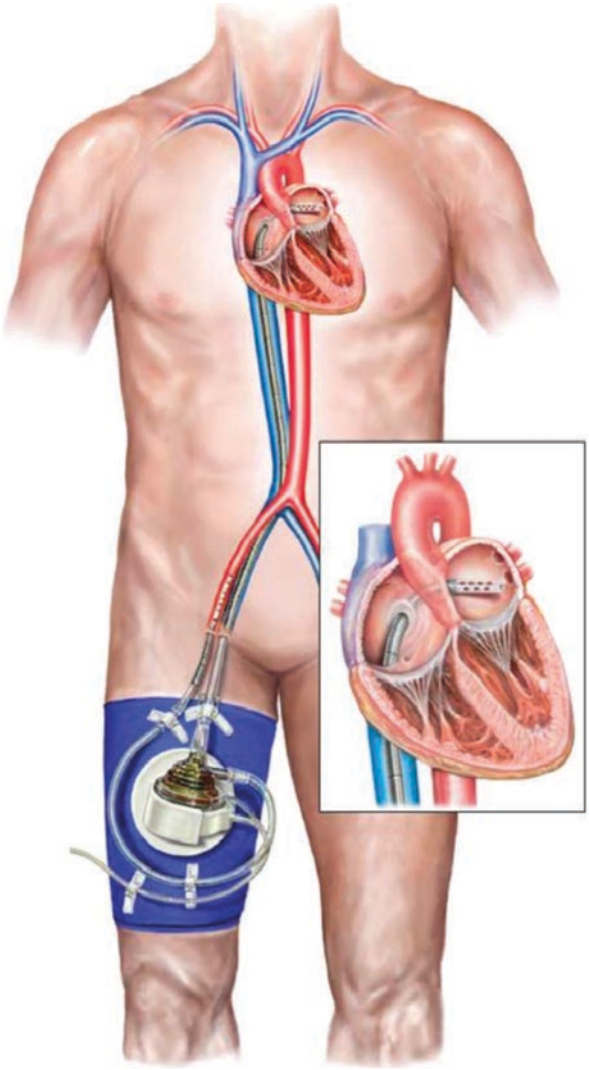

Fig. 20.3 TandemHeart. (Courtesy of TandemHeart, Pittsburgh PA)

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation provides full biventricular support at flows higher than any other MCS device, up to 6.0 L/min depending on cannula size. ECMO may be configured to be veno-arterial (V-A) or veno-venous (V-V), however, for CS, V-A therapy is required to provide support. ECMO can be inserted peripherally via the femoral vein and femoral artery or centrally with cannulation of the right atrium and the ascending aorta. Peripheral ECMO has the benefit of being placed percutaneously at the bedside or in the cath lab, allowing for quick support in patients who are critically ill.

In retrospective studies comparing ECMO to placement of other percutaneous ventricular assist devices, such as TandemHeart or Impella, there was no significant differences in rates of long term support, complications or in hospital mortality [29]. When comparing ECMO to IABP in a recent meta-analysis, ECMO does appear to have a higher 30-day survival rate than IABP with an absolute risk difference of 13% but not when compared to other percutaneous assist devices, which was consistent with the findings of the retrospective studies [16, 29].

The most common complications reported with ECMO were major bleeding with rates of 40%, limb ischemia with rates of 16%, stroke with rates of 6% and infection with rates of 30% [16]. Among all current percutaneous assist devices, ECMO has the highest rates of limb ischemia, bleeding, and vascular injury because of the large cannula size that it requires. Hemorrhage from ECMO is not only from cannula sites but also include neurologic and pulmonary hemorrhage [16]. Renal complications are also common in ECMO with estimates of acute kidney injury being as high as 80% with many patients progressing to renal failure [30]. The mechanism behind this is still unclear.

It is important to understand that unlike other percutaneous assist devices, ECMO increases left ventricular afterload due to retrograde blood flow into the aorta. The markedly elevated left ventricular afterload leads to increased ventricular wall stress and high myocardial oxygen demand. The left ventricle, therefore, must be unloaded either by venting the left ventricle or placing another assist device such as a IABP or Impella. In patients with ECMO who received IABP the mean pulmonary artery pressure was reduced from 22 to 18 mmHg [31]. In ECMO patients who underwent Impella placement for left ventricular unloading their systolic pulmonary artery pressure decreased from 48 to 21 mmHg [32]. There was improvement in end organ perfusion as evidence by improvement in creatinine from 1.39 to 1.06, AST from 710 to 150 and lactate from 3 to 1.3 [32]. The ECMO and Impella group also showed lower in-hospital mortality with a mortality rate of 47% as compared to 80% in the ECMO only group as well as a higher rate of successful bridging to the next therapy or recovery with a rate of 68% as compared to 28% in the ECMO only group [33].

In the setting of poor native cardiac function, the ECMO device is responsible for perfusing both coronary and cerebral circulation because it is providing retrograde flow of blood back towards the heart. However, when cardiac function recovers a mixing point can develop against the flow of the ECMO causing what is called “North-South” or “Harlequin” syndrome in which the upper half of the body becomes hypoxemic [16]. It is for this reason that a pulse oximeter is recommended to be used in the upper extremity when possible in order to detect upper body hypoxemia. This development of a mixing point could also cause left ventricular over distention and worsening pulmonary edema if device speeds are not reduced (Tables 20.2 and 20.3).

Table 20.2 Clinical outcomes of percutaneous assist devices

Trial author year	Device being evaluated	Control group	Number of patients (N)	Device group mortality	Control group mortality	P-value	Type of study (quality of evidence)
SHOCK Hochman et al. (2000) [2]	IABP	Medical therapy	232	47–53%	77%	<0.005	RCT (moderate)
IABP-SHOCK Thiele et al. (2012) [12]	IABP	Medical therapy	600	40%	41%	0.69	RCT (high)
ISAR-SHOCK Seyfarth et al. (2008) [21]	Impella 2.5	IABP	26	46%	46%	0.97	RCT (moderate)
IMPRESS Ouweneel et al. (2017) [23]	Impella CP	IABP	48	46%	50%	0.92	RCT (moderate)
PROTECT II O'Neill et al. (2012) [24]	Impella 2.5	IABP	452	35% and 40%, 30-day and 90-day MAE, respectively	40% and 49%, 30-day and 90-day MAE, respectively	0.27 for 30 day MAE and 0.066 for 90 day MAE	RCT (high)
Burkhoff et al. (2006) [27]	TandemHeart	IABP	42	46%	36%	Not signficant	RCT (moderate)

Abbreviations: *MAE* major adverse events

Table 20.3 Review of percutaneous assist devices [34]

	IABP	TandemHeart™	Impella™ 2.5/CP	Impella™ 5.0	ECMO
Mechanism	Pulsatile	Centrifugal (continuous)	Axial (continuous)	Axial (continuous)	Centrifugal (continuous)
CO or Flow	↑ CO 0–0.5 L/min	Flow ~4.0 L/min	Flow 2.5–4.0 L/min	Flow up to 5.0 L/min	Flow >4.0 L/min
Size	7-8 Fr	Arterial: 15–19 Fr Venous: 21 Fr	12–14 Fr	21 Fr	Arterial: 14–19 Fr Venous: 17–24 Fr
Advantage(s)	Readily available Familiarity Rapid insertion Easy to adjust No extracorporeal blood	Independent of rhythm Robust CO support	Independent of rhythm Easy insertion No extracorporeal blood	Robust support No extracorporeal blood	Independent of rhythm Robust CO support Pulmonary support
Disadvantage(s)	Minimal ↑CO Requires stable rhythm No effect on mean BP or lactate	Difficult insertion Requires transseptal puncture Vascular complications	Vascular complications Hemolysis	Vascular complications Hemolysis Requires surgical insertion	Vascular complications May not unload heart (may need venting) Regional hypoxemia

Abbreviations: CO cardiac output, *ECMO* extra-corporeal membrane oxygenation, *Fr* French, *IABP* intra-aortic balloon pump

Recommendations

Early identification of CS is critical as there is high morbidity and mortality associated with it, no matter the etiology. In those patients in CS, who fail to respond to medical therapy, the use of percutaneous assist devices may be indicated for cardiovascular support. IABP is the most commonly used percutaneous device in CS due to its ease of use and relatively low risk profile. However, recent data regarding the use of IABP has been disappointing. After the IABP-SHOCK trial failed to show improvement in outcomes with IABP, the European Society and ACC/AHA guidelines have downgraded routine use of IABP in CS to Class III and Class IIb recommendations respectively [9, 13]. The most recent scientific statement for management of HF has significantly softened the recommendation for IABP as well, to patients with CS with acute mitral regurgitation or a ventricular septal defect, or in select patients when other MCS devices are not available or contraindicated [34]. We agree with these most recent recommendations from the ESC and AHA given the disappointing data. There is weak evidence to support the use of IABP as the first line MCS in most patients with CS who fail medical therapy. Rather, IABP should be reserved for patients with acute ischemia, acute mechanical complications of MI (acute mitral regurgitation, ventricular septal defect), and in select patients with CS who have anatomy unfavorable for other MCS devices.

Impella is used in patients with minimal response to IABP or as first line therapy in patients who require higher level of support due to its ability to provide 2.5–5 L/min of flow. Similarly, TandemHeart is able to provide up to 5 L/min of continuous cardiac output and has been has been shown to improve hemodynamics more than IABP in the short term. ECMO provides complete cardiopulmonary support but increases left ventricular afterload. Therefore, left ventricular un-loading with the concurrent use of another percutaneous assist device such as Impella or IABP or by venting the left ventricle directly is recommended. Based on the published data, we make a moderate recommendation for the use of Impella, TandemHeart, or ECMO in patients in cardiogenic shock who fail to respond to medical therapy.

Importantly, the selection of patients who may benefit from these MCS devices as well as which MCS to choose in a patient should be highly individualized, taking into account specific patient characteristics (level of support needed, vascular anatomy, availability of devices) as well as operator experience and familiarity with each device.

A Personal View of the Data

Cardiogenic shock is associated with significant morbidity and mortality. The goal of management of these acutely ill patients is to provide support to allow recovery from the acute insult, or to provide a bridge to definitive surgical treatment with durable ventricular assist devices or cardiac transplant. The currently available

devices all support the failing ventricle through slightly different mechanisms and have different risk profiles. Even with treatment using percutaneous assist devices, mortality remains high. Therefore, given current evidence, early identification of the patient in CS is critical so as to provide the greatest degree of ventricular support as early as possible. IABP is still beneficial in patients with acute ischemia or mechanical complications from ischemia due to its ability to reduce LV afterload reduction. Because IABP only augments cardiac output by 20–40% of native output, in many patients with cardiogenic shock, higher level of cardiac support is necessary. In these patients, Impella, TandemHeart, and ECMO are all options that provide continuous hemodynamic support (ranging from 2.5 to 5 L/min) to allow for cardiac recovery or as bridge to decision regarding transplant or durable mechanical left-ventricular assist device.

Recommendations

1. For patients with cardiogenic shock, the intra-aortic balloon pump, due to its wide availability, ease of use and low risk profile, remains first line therapy in patients who fail medical treatment. However, recent data have called into question the routine use of IABP. (Evidence quality moderate; weak recommendation).
2. In patients who require a higher level of support, the micro-axial Impella or TandemHeart are the preferred temporary percutaneous MCS options. While the data for the use of these devices are limited, early use favors improved outcomes. (Evidence quality weak-moderate; moderate recommendation).
3. Early identification of patients in profound cardiogenic shock who may benefit from biventricular support (or are hypoxic) is critical as extracorporeal membrane oxygenation is the treatment of choice in these patients. (Evidence quality low; moderate recommendation).
4. The choice of percutaneous assist device is based on the provider's evaluation of each patient, taking into account patient anatomy, level of support necessary, and the operator familiarity with the device. (Evidence quality low; strong recommendation).
5. No matter which MCS device is utilized for treatment of cardiogenic shock, multi-disciplinary discussions regarding a patient's candidacy for transplant or durable mechanical assist device are imperative. (Evidence quality low; strong recommendation).

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Chapter 21
The LVAD Patient with Dark Urine and Elevated LDH: Diagnosis and Treatment of Pump Thrombosis

Erin M. Schumer and Mark S. Slaughter

Introduction

Over the last decade, ventricular assist device (VAD) therapy has evolved as a durable treatment for patients with end-stage heart failure (HF), resulting in continued growth in the number of devices implanted annually [1]. Currently, continuous flow VADs account for a large proportion of device implantations, as they are smaller and more resilient than the first generation pulsatile flow devices. The majority of devices implanted are the HeartMate II (St. Jude Medical, Inc. [Thoratec Corporation], Pleasanton, CA) and HVAD (HeartWare Inc., Framingham, MA), with the newer introduction of the HeartMate III (St. Jude Medical, Inc. [Thoratec Corporation], Pleasanton, CA) in 2016 in the United States gaining popularity. Despite survival and quality of life advantages offered to patients with HF, VAD therapy is limited by complications including bleeding and thrombotic events of which the pathophysiology continues to be poorly understood.

Hemolysis occurs to some degree in all VAD patients, and differentiating clinically significant from non-significant hemolysis may be challenging. Thus, multiple definitions of hemolysis are used clinically. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) [1] divides hemolysis into major and minor categories. Minor hemolysis is classified by a serum-free hemoglobin (sfHg) >20 mg/dL or a serum lactate dehydrogenase (LDH) >2.5 times the upper limit of normal range of the implanting center occurring 72 h after

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implantation and without clinical symptoms of hemolysis or abnormal pump function. Major hemolysis is defined by the same laboratory values as minor hemolysis with clinical symptoms of hemolysis or abnormal pump function with either hemoglobinuria, disproportionate or unexplained anemia, hyperbilirubinemia, or pump malfunction/abnormal pump parameters. The INTERMACS criteria may be considered too stringent thus hemolysis may be defined simply by a serum LDH > 600 IU/L. An elevated LDH is associated with decreased 1-year event-free survival; however, 37% of all VAD patients will develop elevated LDH, again making the diagnosis of hemolysis difficult based on LDH criteria alone. Finally, dual hemolysis is defined when serum LDH >600 IU/L and sfHg >40 mg/dL. Simultaneous elevation of these markers is associated with increased risk of adverse events compared to LDH criteria alone but occurs in only 18% of LVAD patients [2]. Unfortunately, sfHg has fallen out of favor due to low sensitivity and high variability.

Ultimately, hemolysis may lead to pump thrombosis which is labeled either suspected or confirmed pump thrombus by INTERMACS [1] based upon clinical parameters versus visualized device inspection, radiologic studies, or absence of Doppler flow signals on echocardiography, respectively. Suspected pump thrombus must include two of the three following criteria of hemolysis, heart failure not explained by structural heart disease, or abnormal pump parameters [1]. This chapter aims to describe the incidence of hemolysis and thrombotic events in LVAD patients and discuss the treatment and possible prevention of these issues.

Search Strategy

A literature search of English language publications from 2007 to 2017 was used to identity published data on hemolysis and thrombosis in the adult LVAD population using the PICO outline (Table 21.1). Databases searched were PubMed and Google Scholar. Terms used in the search were “ventricular assist device”, “HeartMate II,” “HeartMate III,” “HVAD,” AND (“rate” OR “incidence” OR “complications”) AND (“hemolysis” OR “thrombosis”). Articles were excluded if they did not include one of the three continuous flow LVADs relevant to this chapter. The data was classified using the GRADE system.

Table 21.1 PICO Table of the thrombotic complications of LVAD’s

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Adult LVAD patients with symptoms and signs of device thrombosis	Medical management with anti-coagulation vs. thrombolytics	Surgical intervention with pump exchange or pump removal or heart transplantation	Incidence of pump thrombosis, stroke, death

Results

Clinical Relevance

While rates of hemolysis and thrombosis have decreased since the first generation pulsatile pumps, the annual rate of device thrombosis and hemolysis remains clinically significant at 8–11% and 0.48–0.55 events/100 patient months [1], respectively. Once thrombosis occurs, the patient is at high risk of the need for further surgical intervention with pump exchange, pump modification or heart transplant, or thromboembolic events such as stroke, or death [3–5]. While pump thrombosis has been one of the main drawbacks of VAD therapy since its inception, this issue gained increased attention in 2013 with the multi-center publication identifying an increase in the incidence of pump thrombosis in the HeartMate II LVAD [6] and was later substantiated by an analysis of the INTERMACS database [7]. The HeartWare HVAD was also fraught with an increase in pump thrombosis during the same era, suggesting the breadth and complexity of this issue as it pertains to all commercially available VADs [4]. The incidence of thrombosis and thromboembolic events for the landmark trials for continuous flow LVADs is shown in Table 21.2 [8–12].

Risk Factors

Risk factors for thrombosis are both complex and inter-related while not currently fully understood. They may be thought of as belonging to three categories: patient-related, clinical management-related, and pump design factors. Patient-related factors shown to be associated with increased rate of pump thrombosis include age, body mass index, and sex, but there are contradicting studies for each risk factor [13, 14]. Clinical management issues include factors related to the implantation itself, manipulation of pump speed, antithrombotic management, and management of blood pressure [15]. Finally, the pump design including metal surfaces, small gaps, and bearings lead to a low level of hemolysis. Coupled with heat generation and changes in flow conditions as a result of natural variance in the cardiac cycle, the coagulation cascade may be activated disproportionately as to lead to the formation of thrombus [16].

Clinical results from the early era of VAD implantation may at least partially explain the increase in thrombotic events observed in the 2013 study. It is hypothesized that the relatively high incidence of gastrointestinal bleeding led to laxity in antithrombotic therapy [17]. Additionally, no surgical consensus existed on surgical principles including inflow positioning and the avoidance of outflow graft kinking. Finally, it was believed that aortic valve opening was an important objective, thus causing some institutions to adopt a principle of lowering pump speeds in order to facilitate aortic valve opening [18]. These factors combined, although they may not fully explain the phenomenon, are likely responsible for the increase in pump thrombosis observed in 2013.

Table 21.2 Incidence of adverse clinical outcomes in landmark VAD studies

Study	N	Treatment	Incidence of pump thrombosis N (%)	Incidence of hemolysis N (%)	Stroke rate N (%)	Device Replacement N (%)	Mortality N (%)	Study type and quality of evidence
Miller et al. (2007) [8][a]	133 (HMII)	BTT	2 (2)	4 (3)	11 (8)	3 (2)	25 (19)	Prospective, non-randomized (High)
Slaughter et al. (2009) [9][b]	134 (HMII) 66 (HM XVE)	DT	5 (4) 3 (5)	Not reported	24 (18) 8 (14)	12 (9) 20 (34)	44 (33) 27 (41)	Prospective, randomized (High)
ADVANCE [a] (Slaughter et al. 2013 [10])	332 (HVAD)	BTT	14 (4.2)	4 (1.2)	51 (15.3)	29 (8.7)	26 (8.7)	Prospective, non-randomized (High)
ENDURANCE[b] (Rogers et al. 2017 [11])	297 (HVAD) 148 (HMII)	DT	26 (8.8)[c] 24 (16.2)	24 (8.1) 13 (8.7)	88 (29.7) 18 (12.1)	23 (7.7) 20 (13.5)	103 (34.7) 39 (26.4)	Prospective, randomized (High)
MOMENTUM 3[a] (Mehra et al. 2017 [12])	152 (HMIII) 142 (HMII)	BTT and DT	0 14 (10.1)	1 (0.7) 2 (1.4)	12 (7.9) 15 (10.9)	1 (0.7) 11 (7.7)	13 (8.6) 14 (9.9)	Prospective, randomized (High)

Abbreviations: *BTT* Bridge to transplant, *DT* Destination therapy

[a]Study outcomes reported at 180 days

[b]Study outcomes reported at 2 years

[c]This number represents the rate of device malfunction or failure as pump thrombosis incidence is not reported in the ENDURANCE trial

Diagnosis

The diagnosis of pump thrombosis may be a clinical challenge and often requires the use of multiple investigation modalities. Patients may present clinically with hemolysis (elevated LDH or sfHg), device alarms or increased power consumption, new onset heart failure, or fulminant shock. As discussed above, clinically significant hemolysis includes signs such as fatigue and hemoglobinuria and is most often attributed to pump thrombosis but also may occur due to low volume, valve stenosis/prosthesis, transfusion reactions, or immune-mediated reactions. Laboratory values should be obtained at a minimum for LDH ± sfHg, hemoglobin/hematocrit, total bilirubin, creatinine, and prothrombin time/international normalized ratio. Imaging begins with a chest X-ray to evaluate pump position and pulmonary edema. An echocardiogram should be performed for suspected pump thrombosis and should be compared to the post-implant baseline echocardiogram. An echocardiogram will provide data on pump position, flow velocities, and characterization of the aortic valve for both insufficiency and valve opening with an increase in VAD speed. If the ventricle is able to empty with increases in VAD speed, the likelihood of VAD thrombosis is low. Computed tomography angiography (CTA) is unable to diagnose pump thrombosis but does provide additional information on pump position and outflow graft kinking and patency and should be considered in patients with abnormal velocities on echocardiogram with a low suspicion for pump thrombosis [19]. Cardiac catheterization provides similar information to CTA and is considered again for patients with abnormal velocities and low suspicion of pump thrombosis [20].

Treatment

Our institution has adopted a treatment protocol once hemolysis is identified. The patient is admitted for initiation of continuous intravenous heparin and eptifibatide while and coumadin and aspirin are discontinued. The target range for partial thromboplastin time is 50–65. The patient is given approximately 72 h to see if they respond to therapy. If the LDH is declining, then treatment is continued until the LDH reaches a nadir for 48–72 h, and the patient is then converted back to Coumadin and aspirin with the addition of clopidogrel. In the special instance of heparin-induced thrombocytopenia and negative platelet serotonin-release assay, Argatroban is used instead of heparin. Daily and as needed labs are drawn with particular attention paid to serum creatinine.

When the serum LDH does not decrease with medical treatment, intravenous tissue plasminogen activator (TPA) may be considered for patients with an HVAD pump [21]. For patients with a HeartMate II pump, treatment is continued unless there is any evidence of worsening renal dysfunction. At this point or with failure or contraindication to TPA, the pump is exchanged or the patient is considered for

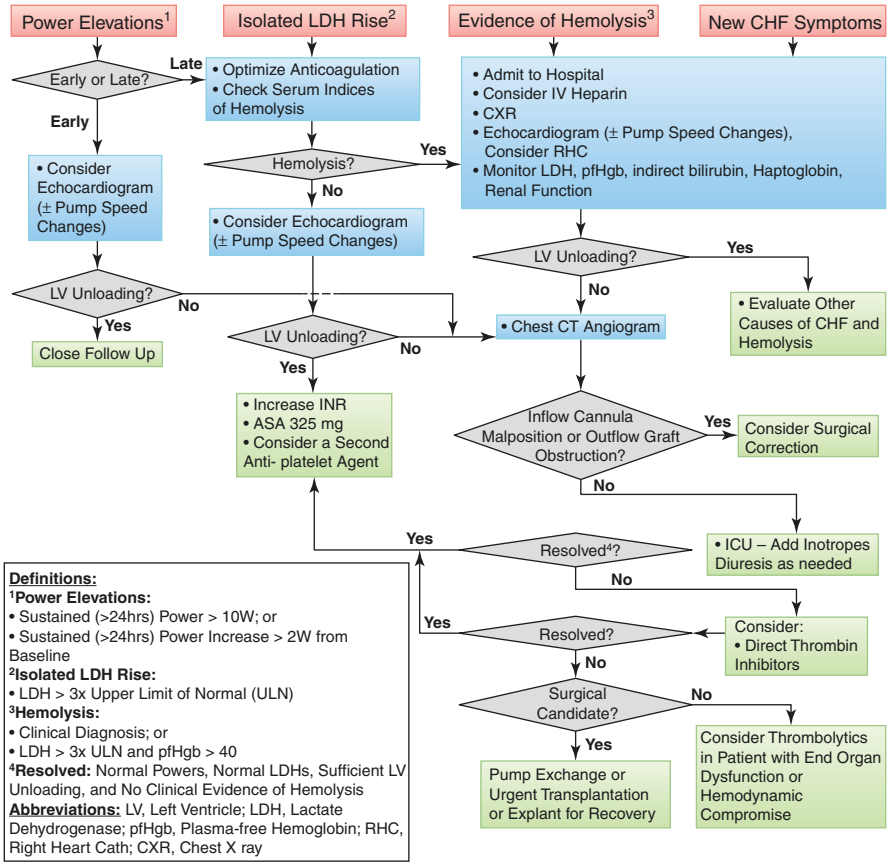

Fig. 21.1 ISHLT Working Group Algorithm for the diagnosis and management of pump thrombosis. (Reprinted with permission from Goldstein et al. [23])

urgent heart transplantation. Additional therapeutic approaches can be used for patients with an HVAD including the use of a washout maneuver by stopping and restarting the pump, pump body exchange for thrombosis limited to the pump body alone, and stenting for outflow graft obstruction [22]. The washout procedure involves stopping and restarting the pump. Because of the potential for emboli, filters may be placed in the carotid arteries for brain protection [22]. A full algorithm by Goldstein et al. for the diagnosis and treatment of continuous flow pump hemolysis and thrombosis is shown in Fig. 21.1 [23].

Success of medical therapy is mixed but generally approximates 50% [4]. However, morbidity and mortality is high for patients treated medically [6]. Hemorrhagic stroke, in particular, is a devastating complication with TPA therapy and approaches 21% [21]. Some data support early surgical intervention with pump exchange or urgent transplantation with low mortality of 5% [6]. The new introduction of a minimally invasive approach to pump exchange may also help to decrease morbidity and mortality associated with a redo sternotomy, but future studies are needed to verify early results [24, 25].

Prevention Strategies

In response to the increase in pump thrombosis, investigators sought to understand why this occurred and how to prevent its occurrence. Thus, the PREVENT trial was initiated and eventually published in 2017 [15]. This prospective, multi-institutional study included 300 patients non-randomized to a single treatment arm. They demonstrated that adherence to all surgical, anticoagulation and antiplatelet, pump speed, and blood pressure management recommendations reduced the incidence of pump thrombosis to 1.9% and hemolysis to 5.7% [15]. The initial ramp test post-implantation is crucial to optimizing pump speed. Under echocardiography, ventricular function and decompression along with valvular function can be monitored at different speeds in order to identify the ideal speed for VAD functionality [19]. The full summary of the PREVENT trial recommendations and definition of pump thrombosis is shown in the appendix.

The presence of hemolysis is now recognized is a precursor event to pump thrombosis and adverse events and occurs in 18% and 37% of patients using the INTERMACS and LDH criteria, respectively [2]. Cowger et al. [2] found that a rise in serum LDH 2.5 times the upper limit of normal was an independent risk factor for pump exchange, urgent transplantation, thromboembolic events, or death. The authors suggest the universal adoption of their definition of hemolysis with the goal to identify hemolysis before additional adverse events occur such as worsening pump dysfunction, renal injury or thromboembolic event.

Recommendations

Pump thrombosis remains a difficult problem for ventricular assist device technology and results in significant morbidity and mortality. Meanwhile, hemolysis occurs in nearly 40% of adult patients with LVADs and is a strong predictor of pump thrombosis and additional adverse events [2, 26]. We strongly recommend to identify patients with hemolysis early through frequent monitoring of serum LDH and to treat accordingly, either medically or surgically. Additionally, surgical and perioperative management principles as outlined in the PREVENT study [15] should be followed in order to reduce the risk of pump thrombosis.

- Patients with ventricular assist devices should undergo frequent monitoring of serum LDH. LDH is considered elevated at 600 IU/L. sfHg may also be used as a biochemical marker of hemolysis but is less reliable than LDH. sfHg is considered elevated at 40 mg/dL (High quality of evidence, Strong recommendation)
- Once hemolysis is identified, patients should be admitted for medical therapy with intravenous heparin and eptifibatide or for surgical intervention if the clinical condition warrants (Low quality of evidence, Weak level of recommendation)
- Prevention through adoption of the PREVENT trial recommendations is crucial to reduce thrombosis (High quality of evidence, strong level of recommendation)

A Personal View of the Data

Ventricular assist device therapy is an effective for end-stage HF that both improves survival and quality of life, but it is limited but several complications including pump thrombosis. The PREVENT trial is an excellent start to reduce the incidence of pump thrombosis and also highlights the need to recognize early hemolysis. Universal adoption of surgical implant technique and strict adherence to post-operative anti-thrombotic and anti-hypertensive regimens are crucial to reduction of pump thrombosis but does not eliminate the issue. Early data demonstrating a low incidence of pump thrombosis with the HeartMate III device are encouraging and suggest that hemolysis and pump thrombosis can be eliminated through technological innovation. Collaboration between clinicians, scientists, and industry is key to advancing VAD technology and improving survival and quality of life for patients with heart failure.

Appendix (Tables 21.3 and 21.4)

Table 21.3 Overview of PREVENT surgical recommendations

Surgical recommendations
1. Create an adequately sized pump pocket, located inferiorly deep and lateral
2. Position the inflow cannula parallel to the septum, oriented to the central left ventricle
3. Position the outflow graft right of the sternal midline to avoid compression of the right ventricle
4. Position the pump below the diaphragm
5. Fixate the pump (e.g., to the diaphragm or the chest wall) to prevent migration
Anti-coagulation and anti-platelet management:
1. In patients without persistent bleeding, begin bridging with unfractionated heparin or LMWH within 48 h of device implantation with a goal PTT of 40–45 s in the first 48 h, followed by titration up to PTT of 50–60 s by 96 h. If heparin is contraindicated, consider other alternatives, including argatroban, intravenous warfarin, and bivalirudin
2. Initiate warfarin within 48 hours to obtain goal INR of 2.0–2.5 by post-operative days 5–7, at which time heparin therapy may be discontinued
3. When there is no evidence of bleeding, initiate aspirin therapy (81–325 mg daily) 2–5 days after HMII implantation
4. Maintain the patient throughout LVAD support on aspirin and warfarin with goal INR of 2.0–2.5
Pump speed management:
1. Run pump speeds >9000 RPM, and avoid speeds <8600 RPM
2. Adjust pump speed to permit intermittent aortic valve opening only after above goals are achieved
Blood pressure management:
1. Maintain a MAP <90 mm Hg

Abbreviations: HMII HeartMate II, *INR* international normalized ratio, *LMWH* low-molecular-weight heparin, *LVAD* left ventricular assist device, *MAP* mean arterial pressure, *PTT* partial thromboplastin time

Table 21.4 Definition of pump thrombosis

Pump thrombosis is an event in which the pump or its conduits contain a thrombus that results in or could potentially induce circulatory failure
Suspected pump thrombus is an event in which clinical or mechanical circulatory support device parameters suggest thrombus in the blood contacting components of the pump, cannulae, or grafts. Signs and symptoms should include at least 2 of the 3 following criteria:
1. Presence of hemolysis (clinical hemolysis and/or sustained LDH >3.0 upper laboratory normal limit)
2. Worsening heart failure (or lack of left ventricular unloading when a ramp test is performed)
3. Abnormal pump parameters (elevated pump powers >10 W or 2 W higher than baseline)
Suspected pump thrombus should be accompanied by ≥1 of the following events or interventions:
1. Treatment with intravenous anti-coagulation (e.g., heparin), intravenous thrombolytics (e.g., tPA), or intravenous anti-platelet therapy (e.g., eptifibatide, tirofiban)
2. Pump replacement
3. Pump explantation
4. Urgent transplantation (UNOS status 1A)
5. Stroke
6. Death
Confirmed pump thrombus: A suspected pump thrombosis event in which a thrombus is confirmed in the blood contacting surfaces of device inflow cannula or outflow conduit or grafts. This can be reported via direct visual inspection (documented by a photograph if available) on pump explantation or by sending the pump back to Thoratec/St. Jude Medical for evaluation. Any pump explanted for suspected device thrombosis should be sent back to Thoratec/St. Jude Medical for analysis. All pump thrombosis events will be adjudicated by an independent committee

Reprinted with permission from Maltais et al. [15]
Abbreviations: LDH lactate dehydrogenase, *tPA* tissue plasminogen activator, *UNOS* United Network for Organ Sharing

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Chapter 22
Liver Dysfunction in a Patient with Ventricular Assist Device

Helen S. Te

Introduction

Patients with severe or chronic heart failure (CHF) are at risk for hepatic ischemia due to poor global perfusion or for passive congestion of the liver, both of which can lead to significant liver dysfunction. Such patients are also commonly being considered for ventricular assist device (VAD) implantation, either as a bridge to heart transplantation or as destination therapy. Following VAD placement, most patients demonstrate overall improvement in their liver function with improvement in hemodynamic parameters, but a few develop further decline in liver function along with other end-organ functions, and are at considerable risk for death.

The ability to use preoperative liver function to predict postoperative mortality after VAD implantation is critical to identify the patients who would truly benefit from VAD. In addition, reversing liver dysfunction before and that persists after VAD implantation can improve overall patient outcome. This chapter will review the evidence behind the predictive value of liver function on patient survival after VAD implantation and alternative strategies beyond standard of care for prevention and management of liver dysfunction following VAD implantation.

Search Strategy

A literature search of English language publications from 2008 to 2017 was conducted to identify published data on the predictive value of liver function on patient survival following VAD placement, as well as data on alternative strategies to manage

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V. A. Lonchyna (ed.), *Difficult Decisions in Cardiothoracic Critical Care Surgery*, Difficult Decisions in Surgery: An Evidence-Based Approach,
https://doi.org/10.1007/978-3-030-04146-5_22

Table 22.1 PICO table for management of liver dysfunction before and following ventricular assist device (VAD) placement

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Adult patients with liver dysfunction who are undergoing or have had VAD placement	Extracorporeal life support (pre-VAD); Early right ventricular support	Standard of care: Inotropes, intraortic balloon pump (pre-VAD); inotropes, pacing, pulmonary vasodilators (post-VAD)	Recovery of liver function, patient survival

liver dysfunction before and after VAD placement, using the PICO outline (Table 22.1). Databases searched were PubMed, Medline and Cochrane Evidence Based Medicine. Terms used in the search were "ventricular assist device" or "VAD" and "liver" or "hepatic." Publications that did not address liver function specifically were excluded from analysis. In total, 13 cohort studies and one review article were included in our analysis. The data was classified using the GRADE system (Tables 22.2 and 22.3).

Results

Relevance of Liver Function on Outcomes After VAD

Implantation of VAD has significantly improved survival and quality of life in patients with advanced heart failure, but the presence of preoperative end-organ dysfunction, such as liver dysfunction, has been determined to impact postoperative outcome. In this light, the Model for End-Stage Liver Disease (MELD) score has been evaluated as a prognostic tool for outcomes following VAD placement. The MELD score is a weighted sum of the serum bilirubin, creatinine and international normalized ratio (INR) [1]:

$$\text{MELD score} = 9.57\left(\log_e \text{Creatinine}\right) + 3.78\left(\log_e \text{Bilirubin}\right) \_ 11.21\left(\log_e \text{INR}\right) + 6.43$$

It is a well-validated predictor of mortality in patients with liver failure [1, 2] and is the backbone of the liver donor allocation system in the United States and other parts of the world. It has also been used as a predictor of mortality in patients with congestive heart failure [3] and as an operative mortality risk assessment tool for major thoracic, abdominal, and orthopedic surgeries in patients with cirrhosis [4].

To evaluate the role of the MELD score in predicting post-VAD outcomes, a retrospective analysis was conducted on patients enrolled into two mechanical circulatory support databases (n = 211 and n = 324). In this study, every five-unit increase in preoperative MELD score increased the unadjusted odds of perioperative death by 50–60%. In addition, MELD scores also predicted the total perioperative blood product exposure, need for post-operative renal replacement therapy, the frequency of right ventricular (RV) failure requiring assist devices and LVAD infections, and the lengths of stay in the ICU and the hospital. The 6 month sur-

Table 22.2 Role of liver function in predicting clinical outcomes after ventricular assist device (VAD) implantation

Author, year	No. of patients	Liver Measure	Mortality	P value	Type of study (quality of evidence)
Matthews (2010) [5]	211 324	MELD <17 vs MELD ≥17	12% vs. 26% (6 months)	0.009	Retrospective cohorts from two databases (moderate)
			18% vs. 33% (6 months)	0.032	
Bonde (2012) [6]	286	Every 1 unit increase in MELD score	HR 1.07 (1.03–1.10) (6 months)	0.0001	Retrospective cohort (low)
Deo (2013) [7]	68	MELD ≥19	HR 8.39 (1.46–48.05) (6 months)	0.02	Retrospective cohort (low)
			HR 3.94 (1.03–15.99 (24 months)		
Tsiouris (2015) [8]	200	AST	HR 1.03 (1.01–1.05) (6 months)	0.01	Retrospective cohort (low)
		ALT	1.02 (1.01–1.04) (6 months)	0.02	
Yost (2017) [9]	256	MELD <9 vs. MELD ≥9	Mortality rate is NA; RV failure 17% vs. 39%	<0.001	Retrospective cohort (low)
Yang (2012) [11]	255	MELD <17 vs. MELD ≥17	26% vs. 37% (18 months)	0.005	Retrospective cohort (low)
		MELD-XI <17 vs. MELD-XI ≥17	23% vs. 40% (18 months)	0.02	
Imamura (2012) [20]	69	TBS* <11 vs. TBS* >11	94% vs. 59%	<0.001	Retrospective cohort (very low)
Maxhera (2014) [21]	24 (with prior ECLS)	MELD ≤25 vs. MELD >25	30% vs. 100% (1 year)	<0.0001	Retrospective cohort (very low)

Abbreviations: MELD model for endstage liver disease, *MELD-XI* model for endstage liver disease except INR, *AST* aspartate aminotransaminase, *ALT* alanine aminotransaminase, *TBS* total bilirubin score, *ECLS* extracorporeal life support

*Total bilirubin score = (0.15 × age) + (1.1 × preoperative total bilirubin)

vival for patients with MELD scores <17 was better at 88 ± 3% as compared to 74 ± 6% in those with MELD scores ≥17 ($p = 0.009$) in the first cohort, and 82 ± 3% vs 67 ± 5% ($p = 0.032$) in the second cohort [5]. The MELD score was similarly found to be predictive of post-VAD mortality in another retrospective study of 286 patients who received continuous flow LVAD (n = 57), pulsatile LVAD (n = 143) and biventricular assist device (BiVAD) (n = 86). After controlling for gender, type of device, diagnosis, intention to treat (bridge to heart transplantation vs. destination therapy), urgency of implantation, and inotropic use, the preoperative MELD

Table 22.3 Effect of bridge-to-bridge strategy with extracorporeal life support to ventricular assist device (VAD) implantation on liver function

Author, year	No. of patients	Liver tests at baseline vs. after VAD implantation	*p* value	Mortality	*p* value	Type of study (quality of evidence)
Scherer (2009) [27]	5	AST 206 ± 107 vs. 71 ± 33 U/L	NA	20%	NA	Case series (very low)
		ALT 334 ± 78 vs. 78 ± 40 U/L	NA			
Durinka (2014) [28]	17	AST 166 ± 239 vs. 61 ± 7 U/L	NA	In hospital overall: 24% (8% in ≤14 days transition to LVAD vs. 75% in >14 days)	<0.05	Retrospective cohort (low)
		ALT 140 ± 193 vs. 68 ± 65 U/L	NA			
		TB 5.6 ± .2 vs. 2.0 ± 1.7 mg/dl	NA			
Riebrandt (2014) [29]	22	AST 1426 ± 2176 vs. 277 ± 259 U/L	0.04	In hospital: 9% 1 year: 14%	NA	Retrospective cohort (low)
		ALT 982 ± 1466 vs. 357 ± 447 U/L	0.04			
		TB 2.03 ± 1.30 vs. 3.08 ± 2.13 mg/dl	0.05			
Marasco (2016) [30]	23	ALT 530 vs. 86 U/L	0.02[a]	Overall: 87%	NA	Retrospective cohort (low)
		TB 2.8 ± 1.7 vs. 1.67 ± 1.26 mg/dl	0.02[a]			
Shah (2017) [31]	22	AST 612 ± 190 vs. 142 ± 70 U/L	0.012	NA for ECLS subgroup	NA	Retrospective cohort (low)
		TB 1.8 ± 0.2 vs. 1.9 ± 0.2 mg/dl	0.541			
		Albumin 2.7 ± 0.2 vs. 2.5 ± 0.2 g/dl	0.182			
		INR 1.7 ± 0.1 vs. 1.3 ± 0.05	0.006			

Abbreviations: AST aspartate aminotransaminase, *ALT* alanine aminotransaminase, *TB* total bilirubin, *INR* international normalized ratio, *NA* not available

[a]p = 0.01 as statistically significant

score was predictive of respiratory dysfunction, renal dysfunction, and mortality at 6 months after VAD implantation with a hazard ratio (HR) of 1.07 (1.03–1.10, p = 0.0001) [6]. In a third retrospective analysis of consecutive patients who received continuous flow LVAD in a single center, the INR, MELD score and left ventricular end-systolic dimensions predicted early mortality in a univariate analysis of first surgery patients (n = 68), but the cohort was too small to allow for multivariate analysis. MELD >19 had a hazard ratio of 8.31 (1.46–48.05) for death within 6 months and 3.94 (1.03–15.99) for death up to 24 months after first time VAD implantations (p = 0.02) [7]. More recently, a larger retrospective single center study of patients implanted with continuous flow VAD (n = 200) again identified preoperative liver dysfunction (based on serum AST and ALT) as an independent predictor of post-VAD survival, as well as post-operative ventilator-dependent respiratory failure, tracheostomy and RV failure requiring RVAD support [8]. Finally, another retrospective single center study of 256 patients who received continuous flow LVAD as destination therapy or bridge to transplant identified the MELD score to be an independent predictor for post-operative RV failure with OR 1.125 (1.035–1.22, p = 0.005). A MELD score cut-off of 9 was identified as the most sensitive in predicting RV failure, which was seen in 16.8% of patients with MELD scores <9 as compared to 39.2% of patients with MELD scores ≥9 (p < 0.001) [9]. While the MELD score has been mapped out with its corresponding 3-month mortality rate in patients with cirrhosis, allowing for accurate prognostication (Fig. 22.1), such detailed correlation for patients with heart failure who undergo VAD placement is not available.

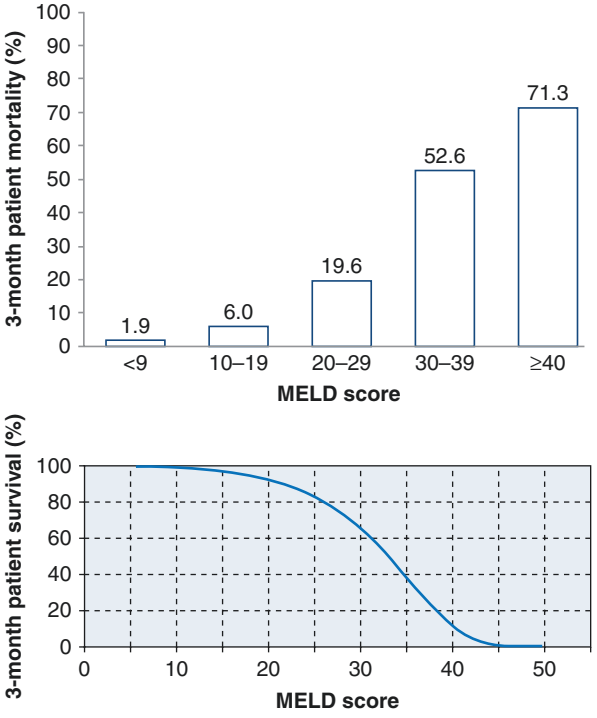

Fig. 22.1 MELD score and survival in patients with cirrhosis. (Adapted from Wiesner et al. [2] with permission)

The use of the MELD score in patients with advanced heart failure is often limited by the common practice of anticoagulation in this population, causing an artificial prolongation of the INR. MELD-excluding INR (MELD-XI) score has been proposed as a surrogate for MELD score in patients with medically-induced INR elevations [10]. MELD-XI was found to have a tight correlation with MELD scores even in patients not receiving anticoagulation who were being considered for VAD in a retrospective analysis of patients who received long term pulsatile (n = 147) or continuous flow LVAD (n = 108) at a single center. Following VAD placement, patients with MELD scores <17 had a higher 18-month survival (73.5% vs 63.2%, p = 0.005) and 2-year on-VAD survival (p = 0.0069). Similarly, MELD-XI scores <17 also had higher 18-month survival (77.2% vs 59.8%, p = 0.022) and 2-year on-VAD survival (p = 0.0437). MELD-XI scores improved following VAD support, and on-VAD and overall survival were significantly better for those who had MELD-XI <17 after 30 days of VAD support [11].

The Impact of VAD on Liver Function

In addition to the survival benefit of VAD in patients with advanced CHF, a positive effect on end-organ function, such as the liver and the kidney, has also been demonstrated. In the early days of VAD support, a post-hoc analysis of a multinational clinical trial utilizing Thoratec VAD in patients awaiting heart transplantation (n = 193) reported improvement in renal and hepatic function in most patients after 1–3 weeks of VAD support, with greater improvement seen in patients who were on VAD longer than those who were on it <7 days [12]. A prospective, multicenter clinical trial of 280 heart transplant candidates who received the pulsatile HeartMate Vented Electric Left Ventricular Assist System showed significant improvement of baseline liver chemistry tests from a median serum aspartate aminotransaminase (AST) of 42 U/ml (range, 9–5146 IU/ml) to 32 U/ml (6–1008 IU/ml) (p = 0.001), a median serum alanine aminotransaminase (ALT) of 47 U/ml (4–3612 IU/ml) to 26 U/ml (2–1910 IU/ml) (p = 0.001), and a median serum total bilirubin of 1.2 mg/dl (0.2–23.3 mg/dl) to 0.7 mg/dl (0.2–59.8 mg/dl) (p = 0.001) at the time support was stopped due to either heart transplantation or death [13]. Today, pulsatile VAD has been replaced with continuous flow VAD for its smaller size, lower complications rates and better long-term durability.

A single-center, small retrospective study (n = 58) compared the effects of the centrifugal (VentrAssist), pulsatile (HeartMate XVE), and continuous flow (HeartMate II) devices on hepatic function. Total bilirubin decreased significantly, and AST and ALT improved from baseline or remained within the normal range in all three groups after 1 month, with results sustained at 3 months of support [14]. The first large study on the effect of continuous flow LVAD on hepatic function was a post-hoc analysis of the HeartMate II bridge-to-transplantation trial (n = 309). In this trial, baseline mean AST and ALT of the cohort (excluding patients with severe hepatic dysfunction defined as INR >2.5, total bilirubin >5 mg/dl or transaminases >2000 U/L) were elevated at 80 ± 214 U/L and 95 ± 230 U/L, respectively, while baseline mean total bilirubin and INR were mildly elevated at 1.3 ± 0.9 mg/dl and 1.3 ± 0.3 mg/dl, respectively. Patients with elevated baseline

AST and ALT levels who received 180 days of VAD support normalized the AST (121 ± 206 U/L to 46 ± 27 U/L) and ALT (171 ± 348 U/L to 40 ± 26 U/L) at 1 month, which were sustained at 6 months. In contrast, mean total bilirubin increased by day 7 before returning to baseline, with the highest increase to >5 mg/dl noted in the subgroup with elevated baseline bilirubin. However, the mean total bilirubin normalized by 2 months and remained normal at 6 months. Patients who received heart transplantation with less than 180 days of support also showed improvements in AST, ALT and total bilirubin, but patients who died with <180 days of support showed an increase in total bilirubin despite no changes in serum aminotransaminase levels. The authors concluded that normalization of hepatic function occurs with minimally pulsatile, continuous-flow devices similar to previous results seen with pulsatile LVAD, and that the continuous blood flow does not appear to have any intermediate-term harm on hepatic function [15].

In the study evaluating MELD-XI as a predictor of mortality after VAD implantation (n = 255), liver chemistry tests (serum aminotransaminases, albumin and total protein) were also seen to improve following VAD placement, but cholestasis (serum alkaline phosphatase or bilirubin) worsened in the first 30 days following VAD support, suggesting that the increased hepatic perfusion from the VAD may at least temporarily worsen hepatic congestion in those with RV dysfunction, leading to worse cholestasis. The alkaline phosphatase decreased subsequently in patients with pulsatile devices, but not in patients with continuous flow devices, possibly due to hemolysis and differences in intrahepatic blood flow from the continuous flow device [11]. In a retrospective study of hepatic function in 61 patients who received continuous flow VAD, mean total bilirubin decreased from 1.0 mg/dl [IQR, 0.7–1.55; median 17.1 (range, 12–26.5)] to 0.9 mg/dl [IQR, 0.6–1.2; median 15.4 (range, 10.2–20.5] 1 month after VAD implantation (p = 0.0005), and continued to improve up to a year after VAD implantation (p = 0.06). Mean serum albumin increased from a pre-VAD level of 3.8 g/dl (IQR, 3.4–4.2) to 4.2 g/dl (IQR, 4–4.4) after 6 months of support (p < 0.0001), and continued to improve in the next 6 months (p = 0.002) [16]. Finally, a longer term retrospective study of 59 patients in a single center who were supported with an LVAD for a minimum of 3 years showed significant improvement in the total bilirubin, ALT, and albumin levels at 1 month after the procedure ($p < 0.05$), which remained within normal range for up to 3 years [17].

While most of the above studies included patient populations with normal and abnormal liver tests prior to VAD implantation, a few studies have focused on the effect of VAD on hepatic function in patients with significant preoperative hepatic dysfunction. In a retrospective review of prospectively collected data from 42 patients with preoperative "hepatic failure" (defined as elevations of total bilirubin or ALT above twice the upper limit of normal), the mean total bilirubin levels decreased from 3.02 ± 2.24 mg/dl (51.67 ± 38.32 mmol/L) to 1.48 ± 2.2 mg/dl (25.37 ± 37.65 mmol/L) (p < 0.001) and mean ALT levels decreased from 242.14 ± 268.60 U/L to 35.74 ± 49.47 U/L (p = 0.007) after 1 month of continuous flow VAD support. The preoperative mean MELD-XI score of 16.03 ± 5.57 also improved to 10.62 ± 5.66 (p < 0.001) at 7 days and to 5.83 ± 4.98 at 30 days, postoperatively. However, similar to Yang's study, there was a transient increase in total bilirubin before a declining trend, which may be due to a transient worsening of the RV function in the initial post-implant period [18]. Another study in 23

patients with "advanced hepatic dysfunction" (defined as AST or ALT ≥5 times normal, total bilirubin ≥3× normal, and/or requirement of a liver biopsy before or during device implantation) showed improvement in liver chemistry parameters starting at 1 month, with normalization at 3 months, and improvement of AST from 209 ± 199 U/L to 29 ± 8 U/L (p = 0.009), ALT from 238 ± 296 U/L to 27 ± 13 IU/L (p = 0.022), total bilirubin from 6.9 ± 6.0 mg/dl to 0.6 ± 0.1 mg/dl (p = 0.044), and serum albumin levels from 3.2 ± 0.6 g/dl to 4.3 ± 0.3 g/dl (p = 0.003) at 12 months amongst those who remained on the support (n = 13). The 1-year survival of patients with "advanced hepatic dysfunction" and that of patients without hepatic dysfunction (n = 277) were similar [19].

The ability to predict the reversibility of hepatic dysfunction with VAD implantation would be useful in determining which patients are likely to fully benefit from VAD. In a single center study of 69 patients who received either continuous flow VAD (n = 18) and pulsatile VAD (n = 51), a higher age (p = 0.004) and a higher preoperative total bilirubin (p = 0.007) were identified as independent predictors of persistent liver dysfunction. In addition, a total bilirubin score of >11 [calculated as 1.5 × (0.1 × age) + (1.1 × total bilirubin in mg/dl)] alone or in combination with a creatinine score >14.1 [calculated as 2 × (0.1 × age) + (3.6 × creatinine in mg/dl)] were predictive of 6-month mortality from multi-organ failure. There was no difference between pulsatile and continuous flow VAD in terms of recovery of hepatic function [20]. Furthermore, in 24 patients who had previous extracorporeal life support (ECLS) and later received VAD support, the pre-VAD MELD score was identified as the most important predictor of survival in this challenging population, whose survival remains limited as compared to that of patients with electively implanted VAD. The authors identified a MELD score >25 as a proposed cut-off to exclude ECLS patients from long-term VAD support [21].

Prevention and Management of Post-VAD Liver Dysfunction

Optimization of the patient's hepatic function prior to VAD implantation is crucial in altering the patient's clinical outcome for the better, and the key to improving hepatic function lies in optimizing the left and right heart function. A low cardiac output from a failing left heart can result in ischemic hepatitis, typically heralded by serum transaminase elevations from hepatocyte necrosis that can lead to liver failure. Right ventricular failure, on the other hand, causes passive congestion of the liver with eventual fibrosis or cirrhosis over time, typically presenting with cholestatic liver chemistry tests or with isolated hyperbilirubinemia.

Prior to VAD implantation, a full set of liver chemistry tests and prothrombin time should be obtained for risk assessment. A careful evaluation of the cardiac, hepatic and nutritional status will allow for a multidisciplinary approach to patient optimization. Correcting a low cardiac output with inotropic support, or with temporary mechanical circulatory support as needed, can improve hepatic perfusion. Amelioration of right-heart failure with aggressive diuresis to achieve the lowest central venous pressure (CVP) as possible, with or without the use of ultrafiltration or renal replacement therapy as indicated, can alleviate passive congestion in the liver, although cirrhosis will persist if present

and may render the liver vulnerable to other hepatic injuries such as drug toxicity. Correction of vitamin K deficiency to improve coagulation [22] and restoration of other nutritional deficiencies via nutritional supplementation, enteral tube feedings or parenteral nutrition will help mitigate the operative risks [23]. Management of both the cardiac output and right heart pressures should continue into surgery, with minimization of the cardiopulmonary bypass time and maintenance of adequate intravascular volume to limit ischemic injury to the liver. Careful monitoring and proactive correction of coagulopathy throughout surgery and in selected cases, judicious use of intraoperative temporary RV support to lower the right heart pressures, may allow for a better outcome [24]. The decision to implant an RVAD intraoperatively is important, as delayed RVAD implantation have worse outcomes than those who received LVAD and RVAD simultaneously [25, 26].

Pre-operative optimization of end-organ dysfunction in patients with refractory cardiogenic shock can improve outcomes after VAD implantation. Extracorporeal life support has been utilized as a bridge-to-bridge strategy to stabilize end-organ function before VAD implantation in patients who are not responding well to optimal inotropic and pressor therapy or intraaortic balloon pump support. Earlier reports of using ECLS as a bridge support before VAD implantation have had unfavorable results with high mortality rates, but later reports have had more encouraging results. In a case series of five patients in cardiogenic shock with hepatic and renal dysfunction, all five were successfully bridged to LVAD implantation after 8 ± 4 days on ECLS with an overall survival rate of 80%. During the ECLS support, the mean baseline AST decreased from 206 ± 107 U/L to 71 ± 33 U/L and ALT from 334 ± 207 U/L to 78 ± 40 U/L at the time of LVAD implantation. There was concomitant improvement in renal function as well, and there were no cases of right heart failure after removal of the ECLS 3 days after LVAD implantation [27]. In a larger United States (US) retrospective, single center study of 17 patients, ECLS was used for 12.1 ± 7.9 days prior to mechanical circulatory support (MCS) (LVAD or total artificial heart placement) with an overall at-discharge survival rate of 76%. However, the survival of patients transitioned from ECLS to MCS within 14 days was significantly better at 92% as compared to 25% for those who were on ECLS for >14 days ($p < 0.05$) [28]. In a European retrospective, single center study, 22 consecutive patients with refractory cardiogenic shock complicated by ischemic hepatitis and renal dysfunction [Interagency Registry for Mechanical Assisted Circulatory Support (INTERMACS) Level I] were bridged with ECLS for 8 ± 7 days prior to a permanent VAD placement. Renal, pulmonary and hepatic function all improved on ECLS, with mean AST decreasing from 1426 ± 2176 U/L to 277 ± 259 U/L ($p = 0.04$) and ALT from 982 ± 1466 U/L to 357 ± 447 U/L ($p = 0.04$). However, total bilirubin increased slightly on ECLS from 2.03 ± 1.30 mg/dl to 3.08 ± 2.13 mg/dl ($p = 0.05$). Catecholamine pressor support was reduced during ECLS as well, and the in-hospital mortality was 9.1% and 1-year survival was 86.4%, which are better than historical rates. There were no cases of acute liver failure after the VAD placement [29]. An Australian retrospective single center study included 23 INTERMACS Level I or II patients who received ECLS prior to LVAD implantation and showed improvement in end-organ dysfunction. The peak bilirubin from ECLS institution decreased from 2.8 ± 1.7 mg/dl (47.9 ± 29 mmol/L) to 1.67 ± 1.26 mg/dl (28.5 ± 21.5 mmol/L) prior to VAD implantation ($p = 0.02$) and the peak ALT decreased from 530 U/L (123–1372 U/L) to 86 U/L (31–242 U/L)

(p = 0.02), although these did not reach statistical significance which was set at p = 0.01. The overall survival was 87%, similar to that observed in patients who did not require ECLS prior to VAD implantation in the same study [30]. Finally, a US multicenter retrospective review of prospectively collected data included 68 patients who received temporary circulatory support (TCS), 22 of whom were on ECLS. Both renal and hepatic functions improved with TCS, with AST declining from 612 ± 190 U/L to 142 ± 70 U/L (p = 0.012) and international normalized ratio (INR) from 1.7 ± 0.1 to 1.3 ± 0.05 (p = 0.006), although serum albumin and bilirubin remained unchanged. One-year survival for patients on TCS was 70%, but survival in the ECLS subgroup itself was not reported [31]. Thus, improvement in liver dysfunction reflective of ischemic hepatitis can be expected from temporary ECLS.

Post-VAD hepatic dysfunction is more commonly due to RV dysfunction rather than from ischemic hepatitis. Right ventricular failure may occur in up to 44% of LVAD recipients [26, 32], and has been strongly linked to increased morbidity and mortality [24, 25, 32]. In a retrospective, single center study of 101 patients who developed early post-VAD liver dysfunction, defined as maximum total bilirubin level of >5 mg/dl within the first 2 weeks of VAD placement, the overall 90-day mortality rate was 36%. The central venous pressure on post-operative day 3 was identified to be an independent predictor for recovery of liver dysfunction and for 90-day survival, with the total bilirubin on day 3 approaching statistical significance as well. Interestingly, post-VAD cardiac output was not a factor in recovery from liver dysfunction or in survival, supporting the larger role of the right heart, rather than left, in causing post-VAD hepatic dysfunction [33]. A similar relationship between intraoperative CVP and the post-VAD right heart failure was demonstrated in an earlier, retrospective, single center study of 108 patients [34].

Only one review article addressed the management of liver dysfunction after LVAD implantation, which is primary geared towards optimization of RV function [24]. The management of post-VAD RV dysfunction, particularly if transient, typically includes the use of inotropic agents such as milrinone and pulmonary vasodilator therapy as with inhaled nitric oxide. Faster paced heart rates may also improve RV function by limiting RV distension [24, 26, 32]. However, early use of temporary mechanical support for the RV may have to be considered if hemodynamics are marginal despite escalating doses of inotropes, pressors and pulmonary vasodilators [24]. Indeed, RVAD implantation for RV failure after LVAD implantation have been shown to improve clinical outcome in some patients, most of whom were bridged to heart transplantation [25, 32, 35–39]; however, such studies have focused on patient survival, and direct data on the effect of RVAD on liver function itself have not been reported. Thus, stability or improvement of hepatic dysfunction will have to be extrapolated from the patient survival data.

Recommendations

Liver dysfunction is not uncommon in patients with advanced CHF, and the MELD and MELD-XI scores appear to be decent predictors of post-VAD outcomes. Most cases of hepatic dysfunction will improve with better hemodynamic parameters

resulting from the VAD support. In patients with severe cardiogenic shock refractory to medical and IABP support, however, the severity of hepatic dysfunction from poor perfusion can significantly decrease post-VAD survival, and optimization of hepatic function with ECLS before VAD placement can improve the prognosis, although the evidence supporting its use is of low grade. Post-VAD implantation, hepatic dysfunction results mostly from right heart failure, and optimization of the right heart function is key to its management. While there is indirect data that supports improved overall outcome from temporary mechanical support for persistent right heart failure in some patients, data on its impact on the liver function in post-VAD patients is not available.

A Personal View of the Data

Adequate vascular inflow and outflow are necessary to allow the liver to function. In most patients suffering from inadequate forward flow from left heart failure, LVAD implantation usually improves hepatic perfusion and consequently, hepatic function. However, left heart failure is sometimes complicated by right heart failure, which threatens the liver through passive congestion. Identification of significant liver dysfunction with the use of MELD or MELD-XI (for patients on anticoagulation) $\geq$17 is important in determining the need to delay VAD implantation for additional optimization of the liver function, so as to improve patient outcome after VAD placement. In patients with severe cardiogenic shock where hepatic dysfunction persists despite appropriate inotropic and hemodynamic support, the use of ECLS may be needed to improve forward flow to the liver before the VAD is placed. While the evidence to support this is of low grade, a randomized controlled trial is unlikely to be performed in this population who is at very high risk for mortality, as patient recruitment can prove to be difficult. In patients with pre-operative right heart failure, lowering the CVP to the lowest level possible before VAD implantation would be ideal. In cases of persistent or worsening liver dysfunction from right heart failure after LVAD implantation, early temporary right heart support can be considered, although data on its direct impact on liver function is not available and can only be extrapolated from survival data that is compared to historical controls.

Recommendations

- The MELD and MELD-XI scores (in patients on anticoagulation) can be used as predictors of patient outcomes following VAD placement (evidence quality low; strong recommendation).
- Most cases of hepatic dysfunction resolve with improvement in hemodynamics from the VAD support, but patients with severe cardiogenic shock refractory to inotropic and hemodynamic support are at high risk for mortality from end-organ dysfunction despite the VAD, and may benefit from ECLS to optimize end-organ function prior to VAD placement (evidence quality low; moderate recommendation).

- Persistent hepatic dysfunction after VAD placement is usually due to right heart failure, which is closely associated with poor patient outcome. In cases where hepatic dysfunction from RV failure persists despite escalating doses of inotropes and pulmonary vasodilators, early temporary RV support can provide survival benefit, but unfortunately, has no evidence to determine its impact on liver function.

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Part VI
Transplantation

Chapter 23
Vasoplegia in the Postoperative Period After Cardiac Transplantation

Joshua L. Chan and Fardad Esmailian

Introduction

Vasoplegia syndrome is a recognized complication related to the use of cardiopulmonary bypass. Initially described in 1994 by Gomes, the development of vasoplegia can present as a challenge for clinicians [1]. This condition is often described by its hemodynamic alterations, namely systemic vasodilation in the presence of normal cardiac function. Heart transplant recipients are particularly vulnerable as they present with several risk factors for developing vasoplegia and are especially susceptible to hemodynamic aberrations. Its clinical significance is highlighted by reports of up to 25% mortality associated with this condition [2–5]. The identification of optimal treatment options therefore remains an ongoing area of investigation. This chapter will examine the pathophysiology, implications, and risk factors for this condition, as well as detail the management techniques in patients who develop vasoplegia following heart transplantation.

Search Strategy

A literature search based on the PICO outline (Table 23.1) was conducted to identify all publications between 1994 and 2017 related to vasoplegia following adult cardiac transplantation. PubMed, Medline, Ovid, and Cochrane Library databases

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Table 23.1 PICO table for the management of vasoplegia following adult cardiac transplantation

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Adult, postoperative cardiac transplantation, in the intensive care unit	Use of vasopressin or methylene blue for the treatment of vasoplegia	Fluids and standard vasopressors for the treatment of vasoplegia	Recovery from vasoplegia, post-operative complication rates, and mortality

were utilized to access the search parameters. Search terms used were as follows: "cardiac transplantation vasoplegia," "heart transplantation vasoplegia," "cardiac surgery vasoplegia," "cardiopulmonary bypass vasoplegia," "vasopressin and vasoplegia," "methylene blue and vasoplegia", "vasoplegia management." Only articles published in English language were included. Publications were excluded if they did not specifically address vasoplegia within the field of cardiac surgery, involved multiple simultaneous organ transplantations, focused on pediatric populations, or primarily described secondary causes of global vasodilation such as sepsis or anaphylaxis. Ultimately, 44 articles were identified, and included 11 randomized control trials (RCT), 3 prospective observational studies, 12 retrospective analyses, 6 case reports, and 13 reviews. Data from these studies were classified based on the GRADE system.

Results

Pathophysiology

Prior studies attempting to elucidate the underlying pathophysiologic mechanisms have surmised that exposure of blood to the synthetic surfaces of the cardiopulmonary bypass circuit initiates a substantial inflammatory cascade, resulting in the presence and propagation of circulating inflammatory cytokines [6–10]. Further work on this topic has attributed many of the deleterious effects of cardiopulmonary bypass-induced vasodilatory shock to a complex array of mediators at the cellular and molecular level. The release of significant quantities of C5a, upregulation of E-selectin, inappropriate induction of nitric oxide synthase and ATP-sensitive K channels, and neutrophil-endothelium interactions have all been cited as participatory in the resultant profound and systemic collapse of vascular tone [3, 11–13].

Clinical Implications and Risk Factors

Vasoplegia is not an uncommon phenomenon. An incidence of 8–25% in the general cardiac surgery population developing vasoplegia has been described. Previous studies evaluating for clinical predictors have observed several patient subsets that are at greater risk for developing vasoplegia syndrome. These factors include an

elevated euroSCORE, left ventricular ejection fraction <35%, preoperative use of vasodilators, hemodynamic instability, anemia, thyroxine level, intraoperative acidosis, and procedures for the treatment of heart failure (e.g. ventricular assist device implantation, heart transplantation) [3, 14–17].

Following heart transplantation, the risk of developing vasoplegia has been observed to be substantially greater, with reports of it occurring in up to 54% of post-transplant recipients [5, 14, 18]. The etiology of this increased vasoplegia risk in heart transplant recipients has not been fully explained, and may ultimately be a combination of independent risk factors related to heart transplantation itself as well as other components specific to the heart failure patient population. End-stage heart failure is associated with a baseline elevation of several inflammatory cytokines and this systemic inflammatory response may be accentuated with exposure to allograft antigens [5, 19]. In the four contemporary studies retrospectively reviewing vasoplegia in heart transplant recipients, obesity, thyroid disease, prior cardiothoracic surgery, presence of a mechanical assist device, and longer ischemia and bypass times have been cited as independent predictors for vasoplegia [5, 14, 18, 20].

Although vasoplegia is typically a self-limiting process, heart transplant recipients who have limited physiologic reserve are especially susceptible to the morbidity related to a hemodynamically-compromised state [6]. Management of this unique population is further challenged as transplant recipients may not tolerate traditional measures such as aggressive administration of intravenous fluids and catecholamines [21, 22]. Heart transplant recipients with vasoplegia experience associated increases in multiple post-operative complications, including need for reoperation, prolonged mechanical ventilator support, renal failure, extended hospital length-of-stay, and increased 30-day mortality [5, 14, 18, 20].

Diagnosis

The development of vasoplegia syndrome is typically evident within 6 h of cardiopulmonary bypass. Patients with vasoplegia will be noted to have severe and persistent hypotension. Exclusion of other potential sources of hemodynamic compromise (hypovolemic, cardiogenic, septic, etc.) should be performed. A number of tools can be used for the diagnosis vasoplegia syndrome, many of which are routinely present in the intensive care unit setting during the immediate post-transplant period. Hemodynamic assessment using an indwelling pulmonary artery catheter is most frequently used, and will characteristically demonstrate normal or elevated cardiac index (cardiac index >2 L/min/m^2) in the presence of decreased systemic vascular resistance (SVR <800 dyn × s/cm^5). An arterial line catheter for continuous blood pressure monitoring would also likely demonstrate decreased mean arterial pressure (MAP <60–70 mmHg). A transthoracic or transesophageal echocardiogram may be additionally helpful in assessing for appropriate cardiac function (left ventricular ejection fraction >55%) while simultaneously eliminating the presence of valvular or other primary cardiogenic abnormalities that could cause a compromised hemodynamic state.

Management Strategies

Management of vasoplegia in the immediate post-cardiac transplantation period often initially relies on traditional critical care techniques in an attempt to restore hemodynamic stability, most commonly with intravenous volume expansion and norepinephrine administration. Significant degrees of distributive shock and vasopressor resistance may minimize the effectiveness of these conventional strategies [21, 22]. This may ultimately lead to aggressive fluid administration and/or high dose catecholamine infusions, both of which may have untoward and compromising physiologic effects in potentially critically unstable heart transplant recipients, including significant fluid overloading or mesenteric ischemia. Alternative strategies have therefore been evaluated to mitigate and ameliorate vasoplegia syndrome. Most of the available published literature on this topic is in regard to the general cardiac surgery population; in contrast, few reports have concentrated on transplant recipients specifically. While these two groups are not identical, many of these findings are applicable and serve as the basis of management at many transplant centers.

Vasopressin

Arginine vasopressin (AVP) has been found to be beneficial in the management of vasoplegia syndrome and may be related to a deficiency of endogenous AVP that has been observed in vasoplegia patients post-cardiotomy (Table 23.2) [23–25]. In addition to correcting low plasma levels, it has been hypothesized that AVP's effectiveness stems from the minimization of cGMP-induced nitric oxide and nitric oxide synthase as well as potentiating the vasoconstricting effects of norepinephrine [24, 26, 27]. Morales et al. assessed the safety and efficacy of an AVP infusion (0.09 ± 0.05 U/min) in a retrospective study of 50 patients receiving a left ventricular assist device (LVAD). Following AVP treatment, there was a noted increase in MAP (58 ± 13 to 75 ± 14 mmHg; $P < 0.001$) and reduction in norepinephrine requirements (11.7 ± 13 to 7.9 ± 6.0 mcg/min; $P = 0.023$) [28]. These findings were further confirmed by a prospective, randomized, controlled study of 48 patients, showing significant improvement in multiple objective hemodynamic parameters with the additional of an AVP infusion (4 units/h) including, MAP, cardiac index, norepinephrine requirements, incidence of tachyarrhythmias, and gastrointestinal perfusion [29]. More recently, the VANCS randomized, control trial was conducted to determine whether the use of AVP as a first-line vasopressor agent for the treatment of vasoplegia following cardiac surgery was superior to norepinephrine [30]. In this study, 330 patients were randomized to either AVP (0.01–0.06 units/min) or norepinephrine (10–60 μg/min). The study's primary endpoint, which the authors defined as a composite of mortality and morbidity (stroke, prolonged intubation, deep sternal wound infection, reoperation, acute renal failure) within 30 days, was noted in 32% of AVP-treated patients compared to 49% in the norepinephrine group (adjusted

Table 23.2 Use of arginine vasopressin for the treatment of vasoplegia syndrome

Author (year)	Sample size	Intervention	Effect on hemodynamics	Morbidity	Mortality		Study type (quality of evidence)
					Control	AVP	
Argenziano (1997) [23]	10	LVAD placement; postoperative AVP (0.1 U/min)	MAP increased (57 to 84 mmHg; *P* to 0.001) NE dosage decreased (26.7 to 10.7 mg/min)	–	–	10%	RCT (low)
Morales (2000) [28]	50	LVAD placement, postoperative AVP (0.09 U/min)	MAP increased (58 to 75 mmHg; $P < 0.001$) NE dosage decreased (11.7 to 7.9 μg/min; $P = 0.023$)	Bleeding: 38% Right heart failure: 32% Ventricular arrhythmia: 14% Distal limb ischemia: 6%	–	26%	Retrospective review (low)
Dünser (2003) [29]	48	Cardiovascular surgery; AVP (4 U/h) + NE vs. NE alone	MAP increased with AVP + NE vs. NE @ 48 h (81 vs. 75 mmHg; $P < 0.001$) NE dosage decreased with AVP + NE vs. NE @ 48 h (0.34 vs. 0.54 $\mu g \cdot kg^{-1} \cdot min^{-1}$; $P < 0.001$)	Tachyarrhythmias decreased with AVP + NE vs. NE (8.3% vs. 54.3%; $P < 0.001$) No differences in the incidence of MI or ischemic skin lesions	70.8%	70.8%	RCT (moderate)
Hajjar (2017) [30]	330	Cardiac surgery on CPB; AVP (0.01–0.06 U/min) vs. NE	MAP decreased with NE vs. AVP @ 15 min (63 vs. 65 mmHg; $P = 0.0280$), no difference @ 30 min No difference in additional NE requirement (11.4% vs. 19.2%; $P = 0.06$)	Composite of death or severe complications within 30 days decreased with AVP vs. NE (32.2% vs. 49.0%; $P = 0.0014$) AF (63.8% vs. 82.1%; $P = 0.0004$) and ICU LOS (5 vs. 6 days; $P = 0.0071$) decreased with AVP vs. NE No differences in digital/mesenteric ischemia, MI, ventricular arrhythmias	15.9%	15.4%	RCT (moderate)

(continued)

Table 23.2 (continued)

Author (year)	Sample size	Intervention	Effect on hemodynamics	Morbidity	Mortality		Study type (quality of evidence)
					Control	AVP	
Morales (2003) [31]	27	Cardiac surgery on CPB; prophylactic AVP (0.03 U/min)	MAP unchanged with AVP (80 to 78 mmHg; P = NS) Peak NE dosage decreased with AVP vs. control (4.6 vs. 7.3 μg/min; $P = 0.03$)	ICU LOS (1.2 vs. 2.1 days; $P = 0.03$) and intubation time (1.0 vs. 1.4 days; $P = 0.02$) decreased with AVP vs control No differences in MI, limb ischemia, or stroke	7.1%	0%	RCT (moderate)
Papadopoulos (2010) [32]	50	CABG, prophylactic AVP (0.03 U/min)	MAP increased with AVP vs. control (84 vs 78 mmHg; $P = 0.026$) NE dosage decreased with AVP vs. control (0.16 vs. 0.44 μg/kg/min; $P = 0.000$)	PRBC transfusions decreased with AVP vs. control (3.1 vs. 4.2 units; $P = 0.031$)	0%	12%	RCT (moderate)

Abbreviations: AF atrial fibrillation, *AVP* arginine vasopressin, *CABG* coronary artery bypass surgery, *CPB* cardiopulmonary bypass, *ICU* intensive care unit, *LOS* length-of-stay, *LVAD* left ventricular assist device, *MAP* mean arterial pressure, *MI* myocardial infarction, *NE* norepinephrine, *NS* not significant, *PRBC* packed red blood cells, *RCT* randomized control trial

hazard ratio: 0.52; 95% CI: 0.36–0.75; $P = 0.0005$). Additionally, a statistically significant improvement in the incidence of postoperative atrial fibrillation (63.8% vs. 82.1%; $P = 0.0004$) and decreased hospital length of stay (13 days vs. 10 days; $P = 0.0016$) was observed.

Based on these findings, AVP administration in the preoperative setting has also been evaluated. Morales and colleagues initially demonstrated this concept in a randomized trial of 27 patients receiving angiotensin converting enzyme (ACE) inhibitor, which has been cited as an independent predictor for vasoplegia [7, 23]. Compared to the saline cohort, patients receiving AVP infusion (0.03 units/min) 20 min prior to the initiation of cardiopulmonary bypass were noted to have decreased peak norepinephrine requirements (4.6 ± 2.5 vs. 7.3 ± 3.5 μg/min; $P = 0.03$) and fewer hypotensive episodes (1 ± 1 vs. 4 ± 2; $P < 0.01$) [31]. Later, Papadopoulos utilized this prophylactic protocol and observed that the incidence of vasoplegia was significantly less compared to saline controls (8% vs. 20%; $P = 0.042$) [32]. Furthermore, prophylactic AVP was associated with improvements in catecholamine requirements (mean norepinephrine dose 0.16 ± 0.04 vs. 0.44 μg/kg/min $\pm$ 0.07; $P < 0.001$) and packed red blood cell transfusion needs (3.1 ± 1.7 vs. 4.2 ± 1.8 units; $P = 0.031$).

Methylene Blue

A therapeutic option that has received a substantial consideration as an adjunctive agent in the setting of vasoplegia syndrome has been methylene blue (MB). A derivative of phenothiazine, this heterocyclic aromatic chemical compound ($C_{18}H_{18}ClN_3S$) was an early regimen against malaria and has long been used as a treatment for methemoglobinemia [33, 34]. In addition to being applied to vasoplegic states post-cardiotomy, MB has been found to be useful in global vasodilatory circumstances related to sepsis and protamine-induced hypotension [35]. MB's proposed mechanism of benefit likely stems as a direct inhibitor of nitric oxide synthase as well as an inhibitor of soluble guanylyl cyclase, thereby reducing cGMP-dependent vasodilation [12, 35, 36].

The investigational use of MB as a treatment modality for vasoplegia was initially characterized in a number of case reports of post-cardiotomy vasoplegia refractory to medical management (Table 23.3) [37, 38]. Used as a therapy of last resort, these publications describe a rapid decrease in norepinephrine requirements and stabilization of hemodynamics occurring immediately following the intravenous administration (2 mg/kg) of one or two doses of MB. An anecdotal report by Kofidis et al. also notes similar effective reversal of vasoplegia in a heart transplant recipient [19]. In a review of 54 patients undergoing various cardiac operative interventions, including seven heart transplantations, Leyh and associates observed a significant increase in SVR (876 ± 184 vs. 547 ± 108 dyn × s/cm^5; $P < 0.001$) and a decrease in norepinephrine dosage [39]. Levin subsequently carried out a prospective trial, which randomized 56 elective cardiac surgery patients to receive MB (1.5 mg/kg) or placebo [40]. In this study, MB reduced overall morbidity and

Table 23.3 Use of methylene Blue for the treatment of vasoplegia syndrome

Author (year)	Sample size	Intervention	Effect on hemodynamics	Morbidity	Mortality		Study type (quality of evidence)
					Control	MB	
Yiu (1999) [37]	1	CABG; postoperative MB (2 mg/kg)	–	Acute renal dysfunction, deep vein thrombosis	–	–	Case report (very low)
Pagni (2000) [38]	1	AVR; postoperative MB (2 mg/kg)	–	Transient nodal rhythm, ventricular ectopy	–	100%	Case report (very low)
Kofidis (2001) [19]	1	OHT; postoperative MB (2 mg/kg)	NE dosage decreased @ 1 h (1–0.22 $\mu g \cdot kg^{-1} \cdot min^{-1}$), discontinued @ 6 h	–	–	–	Case report (very low)
Leyh (2003) [39]	54	Cardiac surgery on CPB; postoperative MB (2 mg/kg)	MAP increased @ 12 h (68 vs. 73 mmHg; $P = 0.02$)	Coagulopathy: 11% Re-exploration for bleeding: 2% New renal failure: 2%	–	5.6%	Retrospective review (low)
Levin (2004) [40]	56	Cardiac surgery on CPB; postoperative MB (1.5 mg/kg)	No differences in MAP between groups (47.4 vs. 48.3 mmHg; P = NS) No differences in NE doses between groups (0.73 vs. 0.69 µg/kg/min; P = NS)	Decreased supraventricular arrhythmia with MB (7.1% vs. 28.6%; $P = 0.03$) Decreased renal failure with MB (0% vs. 14.3%; $P = 0.05$) Decreased respiratory failure with MB (0% vs. 14.3%; $P = 0.05$) No differences in CVA events, ventricular arrhythmia, liver failure	21.4%	0%	RCT (moderate)
Grubb (2012) [44]	1	OHT; postoperative MB (1 mg/kg bolus +0.5 mg/kg/h infusion)	–	Serotonin syndrome	–	–	Case report (very low)

Weiner (2013) [43]	226	Cardiac surgery on CPB; postoperative MB (2 mg/kg bolus +0.5 mg/kg/h infusion)	–	Use of MB an independent predictor of morbidity (OR 4.80, $P = 0.001$)	15.4%	45.6%	Retrospective review (low)
Manghelli (2015) [35]	1	AVR, TVr; postoperative MB (0.82 mg/kg)	MAP increased from 54 to 74 mmHg NE dosage decreased from 0.4 to 0.24 μg/kg/min	–	–	–	Case report (very low)
Özal (2005) [41]	100	CABG; prophylactic MB (2 mg/kg)	NE requirement decreased with MB vs. control (4% vs. 82%; $P = 0.001$)	ICU LOS decreased with MB vs. control (1.2 vs. 2.1 days; $P = 0.001$) No differences in stroke, PRBC transfusions, or multi-organ failure	4%	0%	RCT (moderate)
Maslow (2006) [42]	30	Cardiac surgery on CPB; prophylactic MB (3 mg/kg)	MAP increased with MB vs. control (63 vs. 55 mmHg; $P < 0.05$) NE requirement decreased with MB vs. control (40% vs. 73%; $P < 0.05$)	No differences in nausea/vomiting, dizziness, rhythm abnormalities, cardiac ischemia	21.4%	0%	RCT (moderate)

Abbreviations: AVR aortic valve replacement, *CABG* coronary artery bypass surgery, *CPB* cardiopulmonary bypass, *CVA* cerebrovascular, *ICU* intensive care unit, *LOS* length-of-stay, *MAP* mean arterial pressure, *MB* methylene blue, *NE* norepinephrine, *NS* not significant, *OHT* orthotopic heart transplantation, *PRBC* packed red blood cells, *RCT* randomized control trial, *TVr* tricuspid valve repair

mortality (0% vs. 21.4%; $P < 0.01$) and minimized the duration of vasoplegia (6 h in all treated patients vs. >48 h in eight control patients; $P = 0.0007$).

In addition to postoperative considerations, prophylaxis with MB has also been investigated. Özal prospectively randomized 100 patients undergoing elective coronary artery bypass surgery (CABG) who were noted to be at high risk for vasoplegia (preoperative use of ACE inhibitors, calcium channel blockers, and heparin) [41]. In this study, a 2 mg/kg dose of MB was administered 1 h prior to surgery. Preoperative treatment was shown to decrease the incidence of vasoplegia (0% vs. 26%; $P < 0.001$) and reduce ICU (1.2 ± 0.5 vs. 2.1 ± 1.2 days; $P < 0.001$) and total hospital length of stay (6.1 ± 1.7 vs. 8.4 ± 2.0 days; $P < 0.001$). These findings were confirmed by Maslow when MB was administered intraoperatively at the onset of cardiopulmonary bypass [42]. Patients randomized to the saline placebo demonstrated lower MAP and SVR throughout cardiopulmonary bypass, requiring greater phenylephrine and norepinephrine support. In comparison, the group receiving MB intraoperatively experienced improvement in hemodynamic parameters with lower serum lactate levels, potentially reflecting improved tissue perfusion.

Despite these encouraging results, some authors have expressed caution in the routine use of this agent. Encompassing a single institution experience over 2 years, Weiner found that the use of MB was an independent predictor for in-hospital mortality (odds ratio: 4:26; 95% CI: 1.49–12.12) and morbidity (odds ratio: 4.8; 85% CI: 1.85–12.43) [43]. In propensity score matching, MB's associated increase in morbidity was demonstrated again. However, this study was limited by the lack of uniform institution of pulmonary artery catheters and the availability of hemodynamic profiles following MB administration. Separately, Grubb noted in a case report of a potential adverse interaction of MB-induced serotonin syndrome in a patient on chronic selective serotonin reuptake inhibitor (SSRI) treatment who underwent cardiac transplantation and subsequently developed serotonin syndrome [44]. It was postulated that this was a result of MB's interaction with SSRIs in the inhibition of monoamine oxidase. The FDA has additionally published recommendations recommending against the use of MB in patients on SSRIs, and if necessary, discontinuing it at least 2 weeks prior to use and continued cessation for a minimum of 24 h after. Clinicians should also be aware of other rare events related to MB administration, such as cardiac arrhythmias, coronary vasoconstriction, and increased pulmonary vascular resistance. Contraindications to MB therapy include preexisting severe renal disease as this agent is renally excreted, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and known drug hypersensitivity.

Angiotensin II

An alternate potential vasoactive agent that is currently under investigation is angiotensin II, which primarily works via the renin-angiotensin system (RAS) and exerts its effect through g protein-coupled receptors on vascular smooth muscle [45]. RAS

hormones are naturally secreted during shock, therefore leading investigators to postulate that the supplemental administration of angiotensin II in the context of vasoplegia may be beneficial [45, 46].

Although consideration of angiotensin II for shock has been sporadically described, interest in this agent has been renewed following a recent phase II clinical trial [47–49]. LJPC-501, a synthetic form of human angiotensin II, demonstrated a reduction of norepinephrine requirements in 20 patients with vasodilatory shock [50]. This has since been followed up by a multi-center, prospective, randomized phase III clinical trial (ATHOS-3) of 321 patients with vasodilatory shock on high dose vasopressors (>0.2 μg/kg/min norepinephrine or equivalent) [46]. Multiple causes of shock were included, of which postoperative vasoplegia accounted for 5.9%. In this study, the primary endpoint was defined as an improvement in mean arterial pressure of at least 10 mmHg from baseline or an increase to >75 mmHg without increase in vasopressor requirements after 3 h of drug infusion. This primary endpoint was reached in 69.9% of patients vs. 23.4% of saline controls ($P < 0.001$). Cardiovascular Sequential Organ Failure Assessment (SOFA) scores were also improved in the treatment group (−1.75 vs. −1.28; $P = 0.01$). Adjusted mortality between groups (46.0% vs. 53.8%; hazard ratio 0.78; 95% CI: 0.57–1.07; $P = 0.12$) was not found to be different. It should be noted that this study was not powered to evaluate mortality as an endpoint, nor was a comparison between other therapeutic agents performed [51]. Despite these promising findings, angiotensin II therapy for vasoplegia remains investigational and experimental in nature, and no specific recommendations on its use can be provided as it currently awaits FDA-approval. Editor's Note: On December 21, 2017, the FDA approved angiotensin II injection "for intravenous infusion to increase blood pressure inadults with septic or other distributive shock." (FDA News Release, December 21, 2017).

Recommendations Based on the Data

Heart transplantation is a known risk factor for vasoplegia syndrome. While the exact etiology of this increased frequency has not been fully elucidated, it has been surmised that the frequent presence of numerous comorbidities and established risk factors for vasoplegia, in addition to an inflammatory state associated with heart failure and heart failure treatment modalities (i.e. mechanical circulatory device support), may establish an environment that is highly susceptible to abnormal and muted vasoactive responses. The use of AVP and MB have been investigated as alternative therapeutic modalities for this condition. Based on the assessment of the cumulative results, we recommend treatment with low dose AVP infusion (0.03 U/min) for additional hemodynamic support in heart transplant recipients who develop vasoplegia refractory to conventional critical care (evidence quality moderate; strong recommendation). Higher doses have not been demonstrated to provide any further benefit and may place the patient at higher risk for peripheral ischemia. In

cases of severe vasoplegia unresponsive to treatment, administration of MB (2 mg/kg bolus, administered over 20–30 min) can be useful in mitigating vasoplegic effects of hemodynamic instability in patients without contraindications to therapy (evidence quality moderate; strong recommendation). The use of MB should be with caution in patients currently taking SSRIs or in those who have baseline renal impairment, G6PD deficiency, or a history of MB hypersensitivity. Some studies have additionally evaluated AVP and MB in prophylaxis. These agents may be beneficial for high risk heart transplant patients when used in the preoperative environment, although there is limited evidence at the present time clarifying the number and specific risk factors in which prophylactic measures would be indicated (evidence of quality moderate; weak recommendation).

A Personal View of the Data

Vasoplegia syndrome is associated with considerable morbidity and mortality in patients following heart transplantation. Appropriate identification of individuals at high risk for vasoplegia remains of principal importance and may allow earlier therapeutic intervention. While there is limited data assessing the use of AVP and MB in the treatment of vasoplegia following heart transplantation, the available data assessing these adjunctive agents in the general cardiac surgery literature can be extrapolated and applied to this specific patient subset. Therefore, it is reasonable to consider the use of AVP or MB to achieve hemodynamic stability in heart transplant recipients with vasoplegia syndrome, which we hypothesize will reduce the morbidity and mortality associated with this condition. The specific indications and circumstances for prophylactic use is unclear and should be assessed on a case-by-case basis. Further research in the context of high-quality multi-institutional prospective studies evaluating the use of these agents in the heart transplant population will be critical in further improving outcomes.

Recommendation Summary

- For heart transplant recipients with medically refractory vasoplegia syndrome, low dose AVP infusion is recommended to restore hemodynamic stability (evidence quality moderate; strong recommendation).
- MB administered as a bolus dose may also be considered as an adjunctive agent in mitigating unremitting vasoplegia syndrome if no contraindications to therapy are present (evidence quality moderate; strong recommendation).
- AVP or MB may be beneficial as a prophylaxis against vasoplegia syndrome in heart transplant candidates with multiple preoperative risk factors (evidence of quality moderate; weak recommendation).

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Chapter 24
Severe Hypertension After Cardiac Transplantation

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Introduction

Cardiac transplantation is the definitive treatment for eligible patients with end stage heart failure. The development of hypertension after cardiac transplantation is considered one of its most common comorbidities; it occurs early after transplant and can be difficult to manage [1, 2]. In general, 30–50% of patients who undergo cardiac surgery will experience hypertensive urgencies or emergencies that require administration of parenteral antihypertensive therapy during the perioperative period [3, 4]. The 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the European Society of Hypertension/European Society of Cardiology 2013 Guidelines for the Management of Arterial Hypertension define hypertensive urgency as a severe elevation of blood pressure (BP) (>180/120 mmHg) without signs of progressive target organ dysfunction; a hypertensive emergency is defined as blood pressure >180/120 mmHg complicated by evidence of impending or progressive target organ damage such as stroke or life-threatening bleeding [5, 6]. The development of hypertensive urgency or emergency perioperatively warrants expeditious assessment and management in an effort to evade the sequelae of uncontrolled acute postoperative hypertension. Such sequelae may include hemorrhage, disruption of vascular or cardiac suture lines, failure of anastomoses, cardiac arrhythmia, hyperperfusion syndrome, cerebral edema or ischemia, bleeding at the surgical site, and end organ damage [7–13]. Cautious and precise titration of a rapid-acting antihypertensive with close monitoring of arterial pressure and end organ function is necessary to minimize the risk of adverse events. The risks of uncontrolled hypertension during general anesthesia and surgery must be weighed against the risk of end organ

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hypoperfusion caused by the need to decrease blood pressure acutely, particularly in patients who were hypertensive at baseline.

Despite the widespread and long-standing recognition of acute postoperative hypertension, there is no consensus in the literature on a more precise, quantitative definition [14]. It has an early onset, being observed within 2 h after surgery, and is typically of short duration, with most patients requiring treatment for 6 h or less; however, it may persist for 24–48 h [6, 7]. The underlying pathophysiologic mechanism is uncertain and varies with surgical technique, method of anesthesia, patient characteristics, and pain management strategies. Activation of the sympathetic nervous system, as evidenced by elevated plasma catecholamine concentrations in patients with acute postoperative hypertension, appears to be the common pathway [15–17].

Additionally, it is postulated that the greater incidence of hypertension among orthotopic cardiac transplant recipients may be due to the interruption of the sympathetic and parasympathetic activity to the sinoatrial node that normally regulates heart rate. This loss of cardiac input to blood pressure homeostasis is due to the native heart being replaced by a functionally denervated donor heart. This leads to marked reductions in beat-by-beat heart rate variability and baroreceptor sensitivity [12]. Cardiopulmonary baroreceptors are located within the myocardium and provide tonic inhibition of sympathetic outflow to the heart and peripheral circulation, and subsequently lower blood pressure when filling volumes are adequate; baroreflexes are impaired when this tonic inhibitory input is disrupted [18]. Thus, heart transplant recipients respond to central blood volume reduction with an attenuated increase in sympathetic activity [19]. In turn, it has been demonstrated that dynamic cerebral autoregulation compensates for reductions in cardiac baroreceptor sensitivity in heart transplant recipients [12]. Furthermore, blood pressure after cardiac transplantation is characterized by altered regulation of sodium and volume balance, possibly also a consequence of chronic cardiac differentiation and the lack of response to a hypervolemic stimulus from the renin-angiotensin-aldosterone system [20]. A disrupted circadian rhythm without the typical nocturnal blood pressure drop and a greater 24-h hypertensive burden can also be seen in this patient population [20–22].

The excess risk of hypertension that persists beyond the immediate postoperative period and occurs in 50–95% of heart recipients is also largely attributable to the use of calcineurin inhibitors (CIs) as a mainstay of immunosuppression [1, 20, 23]. CIs are implicated in hypertension via direct effects and renal insufficiency associated with their use [24, 25]; cyclosporine (CSA) in particular contributes to post-transplant hypertension through activation of the sympathetic nervous system [26], nephrotoxicity [27], and inhibition of endothelium-dependent vasodilation [28]. It has also been implicated in disturbances of renin-angiotensin system and increasing peripheral vascular resistance [29]. Tacrolimus has since become the CI of choice following cardiac transplantation and the incidence of hypertension is lower in patients treated with tacrolimus than with CSA, though it is still a recognized adverse effect [30].

This chapter addresses the immediate risks and benefits of blood pressure management surrounding cardiac surgery, outlines the risk factors and unique pathophysiology implicated in the development of hypertension post-cardiac transplant, and reviews the clinical targets as well as pharmacologic agents available for evidence-based management of severe hypertension following cardiac transplantation. Most of the data come from studies conducted 20–30 years ago, yet advances in anesthesia, surgical procedures, intraoperative fluid management, and pain control have likely reduced the rates of severe hypertension following cardiac transplantation, though there is limited direct evidence to support this.

Search Strategy

A literature search of English publications from 1970 to 2017 was used to identify published data on the management of severe hypertension after cardiac transplantation using the PICO outline (Table 24.1). Databases searched were PubMed, Embase, and Cochrane Evidence Based Medicine.

Terms used in the search were "hypertension, severe/prevention and control," "hypertension, postoperative/prevention and control," AND ("intraoperative complications" OR "perioperative complications" OR "postoperative complications"), "cardiac transplantation," OR "heart transplantation," OR "cardiac surgery." Twenty-eight randomized control trials, 20 cohort studies, 3 guidelines, 1 Cochrane Review, and 9 review articles were included in our analysis. The data were classified using the GRADE system.

Results

Clinical Relevance of Severe Hypertension After Cardiac Transplantation

Prospective studies showing clinical benefits of aggressive blood pressure control in the immediate post-cardiac transplant period are lacking; however, it has been well demonstrated in cardiac surgery that blood pressure elevations may be associated with significant postoperative complications and thus aggressive treatment with

Table 24.1 PICO table for management of severe hypertension following cardiac transplantation

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Adult, post-cardiac transplant, ICU	Aggressive control of post-transplant hypertension	Standard care: judicious lowering of blood pressure	Hemodynamic stability, neurologic complications, bleeding complications, survival, QOL

intravenous vasodilators is indicated [3]. The International Society for Heart and Lung Transplantation (ISHLT) Guidelines for the Care of the Heart Transplant Recipient do not address the management of severe hypertension in the immediate postoperative period; however, they recommend that hypertension after heart transplant should be treated to achieve the same goals recommended for the general population [31–35]. Precise management of arterial pressure in the perioperative period has the potential to improve clinical outcomes by minimizing the harmful sequelae of severe postoperative hypertension such as hyperperfusion syndrome, ensuring adequate end organ perfusion, decreasing the risk of adverse drug effects, avoiding hypotensive episodes, and serving as a bridge to definitive long-term therapy in this patient population.

Risk Factors

The identification of risk factors for postoperative hypertension is a critical step in weighing the risks and benefits of hypertension management in the operative and immediately postoperative setting. The single best indicator for the development for perioperative complications and postoperative hypertension is preoperative uncontrolled stage 3 hypertension (systolic blood pressure (SBP) ≥180 mmHg or diastolic blood pressure (DBP) ≥110 mmHg) due to the multiple physiologic alterations associated with the disease and changes in the autoregulation of end organ blood flow. In a small percentage of patients, hyperperfusion syndrome may occur due to the restoration of blood flow to a normal or elevated perfusion pressure within a previously hypoperfused hemisphere. This may potentially lead to further complications such as cerebral edema, hemorrhage, and seizure [8–12]. However, current studies indicate that complications are principally associated with relative hypotension rather than uncontrolled hypertensive events [5, 36–38].

Goals of Therapy

The most commonly accepted thresholds for the treatment of hypertension in the setting of cardiac surgery are a BP >140/90 mmHg or a mean arterial pressure (MAP) of ≥105 mmHg, but there is presently no consensus [13, 15, 39–42]. To decrease the risk of hypertensive or hypotensive episodes, blood pressure should be monitored continuously and short-acting intravenous antihypertensive agents should be administered to target a MAP generally within ±20% of the patient's baseline value [36–38, 43–46]. This general recommendation is derived from several clinical studies; however, the best clinical evidence supporting the need to maintain MAP at pressures close to a patient's autoregulatory range comes from a randomized, controlled trial involving 248 cardiac surgical patients [37]. Patients were randomized to have their MAP controlled at 50–60 mmHg (low-pressure

group) or 80–100 mmHg (high-pressure group) during coronary bypass surgery. At 6 months after surgery, the overall incidence of combined cardiac and neurologic complications was significantly lower in the high-pressure group (4.8%) than in the low-pressure group (12.9%; p = 0.026). The high-pressure group had a total mortality of 1.6%, with a stroke rate of 2.4% and a cardiac complication rate of 2.4%. Conversely, the low-pressure group had a total mortality of 4%, a stroke rate of 7.2%, and a cardiac complication rate of 4.8%. This underscores the importance of maintaining strict control of blood pressure, not only to correct hypertension, but also to prevent hypotension. As such, the choice of antihypertensive agent should also be influenced by an effort to optimize end organ perfusion and avoid recognized adverse effects.

Management Strategies

First and foremost, remedial causes for postoperative hypertension including hypoxia, hypercarbia, and pain should be identified and mitigated before proceeding to further management with antihypertensive therapy. Additionally, the ISHLT recommends continuous infusion of an inotropic agent such as isoproterenol with or without dopamine, dobutamine with or without dopamine, or milrinone to maintain hemodynamic stability in the first 3–5 days post-cardiac transplant [31]. The requirement of inotropic support during this time frame may be a contributor to postoperative hypertension and weaning of these agents may offer adequate resolution.

Tables 24.2 shows the results of major studies examining the efficacy of different pharmacologic strategies for the management of hypertension in the setting of cardiac surgery. The ideal agent should have a rapid onset of action and a short duration of action to allow careful titration of the dosage and easy termination of effect. In addition, the agent should be highly vascular selective and thus have minimal effects on heart rate, cardiac function, and myocardial oxygen demand as well as have an otherwise benign adverse effect profile. Choice of therapy should also always depend on the clinical presentation, patient characteristics, properties of the drug, and clinician's experience.

Sodium nitroprusside is the most widely studied agent for severe postoperative hypertension and is commonly recommended as the drug of choice for this indication. As such, it has long been the standard against which other intravenous antihypertensive agents are compared [40, 47–52]. It is a direct-acting, potent nitrovasodilator that affects both the venous and arterial vasculature thus decreasing cardiac afterload and preload [53]. At a dose of 0.25–10 μg/kg/min intravenously, nitroprusside is almost always immediately effective for lowering blood pressure with a rapid onset of action and duration of effect between 1 and 2 min [5, 53]. A prospective crossover study by Fremes and colleagues reported that, after cardiac bypass surgery, reductions in MAP to 90–100 mmHg resulted in favorable effects on hemodynamics [50]. Indeed, several uncontrolled studies have demonstrated that

Table 24.2 Efficacy of management strategies for hypertension after cardiac surgery (in order of reference within text)

Study author (year) (ref)	N	Surgery type	Indication for intervention	End-point	Response rate (intervention)	Response rate (comparator)	P-value	Time to goal	Adverse effects	Study type (quality of evidence)
Halpern (1992) [48]	139	Cardiac and non-cardiac	(Cardiac surgery)	>15% reduction from baseline	NIC: 86%	SNP: 88%	p = NS	NIC: 14 ± 1 min	NIC: 7% (hypotension, n = 1)	PRCT (high)
			SBP ≥140 mmHg or DBP ≥95 mmHg within first 24 h post-op					SNP: 30 ± 4 min	SNP: 18% (hypotension, n = 5, 2 discontinued)	
								(p = 0.0029)	(p = NS)	
Fremes (1985) [50]	33	CABG	MAP >95 mmHg within first 4 h post-cross clamp removal	MAP ≤85 mm Hg	NTG: 100%	SNP: 100%	p = NS	NR	NR	Prospective cohort with crossover (low)
					−25 ± 12 mmHg	−20 ± 10 mmHg				
Flaherty (1982) [51]	17	CABG	MAP increase of ≥20 mmHg to a MAP of 95–150 mm Hg >15 min within first 3 h off CPB	10–33% (10–40 mmHg) reduction from baseline	NTG: 100%	SNP: 100%	Both p < 0.001 vs. control	NR	Sinus tachycardia	PRCT with crossover (moderate)
					−25 ± 9 mmHg	−25 ± 8 mmHg			SNP: 24%	
									NTG: 24%	
									(p = NS)	
									No hypotension	
Kieler-Jensen (1993) [52]	12	CABG	NR	MAP 75–80 mmHg	Prostacyclin 100%	NTG: 100%	p = NS	NR	NR	PRCT with crossover (moderate)
					(MAP 76.1 ± 1.3 mmHg	(MAP 78.3 ± 1.3 mmHg	(Prosta-cyclin vs. SNP and prosta-cyclin vs. NTG and SNP vs. NTG)			
						SNP: 100%				
						(MAP 77.0 ± 1.4 mmHg				

IV Nicard-ipine Study Group (1991) [64]	122	Cardiac (CABG) and non-cardiac	SBP ≥140 mmHg or DBP ≥95 mmHg within first 24 h post-op	>15% reduction from baseline	NIC: 94%	Placebo: 12%	$p < 0.001$	NIC: 11.5 ± 0.8 min	NIC: 11.5% (hypotension 4.5%, 2 discontinued; tachycardia 2.7%)	PRCT (high)
									Placebo: 6% (hypotension 2%, 1 discontinued)	
David (1991) [66]	74	CABG	MAP ≥100 mmHg within 3 h post-op	MAP 85 ± 5 mmHg within 50 min	NIC: 92%	SNP: 81%	p = NS	NIC: 26 ± 24 min	Severe hypotension (MAP ≤70 mmHg)	PRCT (high)
					−28.6 ± 10.3 mmHg	−33 ± 15 mmHg		SNP: 35 ± 16 min	NIC: 20%	
								($p < 0.01$)	SNP: 85%, 1 discontinued	
Vecht (1989) [67]	20	CABG	SBP >110 mmHg	SBP <110 mmHg	NIC: 100%	NTG: 50%	p = NS	NR	NR	PRCT (high)
Powroznyk (2003) [78]	30	CABG	MAP >90 mmHg for at least 10 min post-op	MAP 70–80 mmHg for 3 h	CLV: 93%	SNP: 100%	p = NS	NR	MAP <65 mmHg	PRCT (high)
									CLV: 0	
									SNP: 1 discontinued	
Singla (2008) [79]	110	CABG/valve replace-ment or repair	SBP ≥140 mmHg within first 4 h post-op	SBP decrease by ≥15% from baseline within 30 min	CLV: 91.8%	Placebo: 20.4%	<0.0001	5.3 min	CLV: 2 discontinued for hypotension (SBP 140–100 mmHg), 1 for atrial fibrillation	PRCT (high)
								(95% CI, 4–7 min)		

(continued)

Table 24.2 (continued)

Study author (year) (ref)	N	Surgery type	Indication for intervention	End-point	Response rate (intervention)	Response rate (comparator)	P-value	Time to goal	Adverse effects	Study type (quality of evidence)
Aronson (2008) [80]	1512	CABG/valve replace-ment or repair	SBP >135 mmHg intra-op; SBP >145 pre- and post-op	Maintain SBP within 65–135 mmHg intra-op and 75–145 mmHg pre- and post-op	CLV:	All comparators (NTG, SNP, NIC):	p < 0.0004	NR	Atrial fibrillation	PRCT (high)
									CLV vs. NTG: 34% vs. 32%	
					3.8	7.8			CLV vs. SNP: 36% vs. 32%	
					(Median magnitude of excursion outside SBP range)	(Median magnitude of excursion outside SBP range)			CLV vs. NIC: 36% vs. 35%	
									p = NS	
Hill (1993) [88]	20	CABG	SBP >130 mmHg	SBP <130 mmHg (≥25 mmHg below pre-treatment value)	FEN: 100%	SNP: 100%	p = NS	FEN: 30 min	NR	PRCT (high)
								SNP: 36 min		
								p = NS		
Gombotz (1998) [89]	64	CABG	MAP >105 mmHg over 10 min	MAP 80–95 mmHg	FEN: 100%	NIF: 100%	p = NS	At goal:	FEN: 1 discontinued due to AV block	PRCT (high)
					−38 ± 7 mmHg	−37 ± 1 mmHg		FEN: 70% at 30 min	NIF: 1 discontinued for bleeding	
								NIF: 10% at 30 min		

Abbreviations: CABG coronary artery bypass graft, *CI* confidence interval, *CLV* clevidipine, *CPB* cardiopulmonary bypass, *DBP* diastolic blood pressure, *FEN* fenoldopam, *H* hour, *MAP* mean arterial pressure, *Mins* minutes, *NIC* nicardipine, *NIF* nifedipine, *NR* not reported, *NS* not significant, *NTG* nitroglycerin, *PRCT* prospective randomized controlled trial, *SBP* systolic blood pressure, *SNP* sodium nitroprusside

sodium nitroprusside is universally effective in achieving the desired reduction in MAP in patients with postoperative hypertension after cardiac surgery [13, 42]. A prospective randomized controlled trial by Halpern and colleagues demonstrated that 88% of cardiac and noncardiac surgery patients randomly assigned to sodium nitroprusside achieved the therapeutic goal of a ≥15% reduction in blood pressure from baseline [48].

Hypotension is a well-established consequence, however, with reported rates of 9–92% of treated patients [48, 54, 55]. Nitroprusside also produces tachyphylaxis, even after short-term administration, and acute discontinuation may result in a rebound increase in blood pressure [56]. Perhaps its most significant limitation, however, is cyanide toxicity; this risk particularly affects patients undergoing cardiac surgery due to the alteration of nitroprusside metabolism during cardiopulmonary bypass. As such, the dosage should not exceed 5 μg/kg/min for more than a few minutes. The lowest possible dosage should be utilized for the shortest possible time [57–59].

Alternatively, nitroglycerin has widespread clinical use in postoperative hypertension despite few formal studies supporting such use [60–62]. It has been examined in trials of small patient populations after cardiac surgery, though typically with a crossover design, thus raising the concern for a potential carryover effect from the prior treatment. Two trials comparing nitroglycerin with sodium nitroprusside found similar decreases in MAP and non-significant increases in heart rate [50, 51]. Hypotension was not reported in either trial, but it is worth noting that the intent of these studies was to compare the hemodynamic response between the two agents after cardiac surgery, not overall clinical efficacy in treating hypertension perioperatively. A prospective study randomized 12 cardiac surgery patients to nitroglycerin, sodium nitroprusside, or prostacyclin to achieve a MAP between 75 and 80 mmHg. There were no significant differences in heart rate or oxygen consumption among the three groups. Sodium nitroprusside increased cardiac output and stroke volume and decreased vascular resistance to a greater extent than nitroglycerin [52]. The primary disadvantage of nitroglycerin is the development of tolerance to the vasodilatory effects after 48–72 h of infusion; however, due to the short duration of postoperative hypertension, nitrate tolerance is not an important limitation to its use in these patients [63].

Intravenous nicardipine, a second-generation dihydropyridine calcium-channel antagonist, is the most widely studied calcium-channel blocker for the treatment of postoperative hypertension [48, 64–69]. It is an arterioselective vasodilator that, when administered to anesthetized cardiac surgery patients, selectively decreases arterial pressure in a dose-dependent fashion with a maximum response in 100 s and recovery to half the maximum response within 3–7 min, without changes in heart rate, central venous pressures, left ventricular preload, left ventricular systolic performance, or cardiac output [70]. The gradual accumulation of nicardipine over time prolongs its duration of action; however, hypotension occurred in only 6% of patients treated with nicardipine in this setting. In small, open-label trials of acute postoperative hypertension in cardiac and noncardiac surgery, nicardipine effectively decreased MAP and SBP [68, 69]. It has been demonstrated to be as effective

as sodium nitroprusside and nitroglycerin as well as superior to placebo in the treatment of postoperative hypertension with an overall response rate of 86–94% [48, 49, 64, 67]. In comparison to nitroprusside for the treatment of emergency hypertension after cardiac surgery, nicardipine provided precise control of blood pressure sooner and with fewer dose changes [48, 71]. This shorter time to a therapeutic response may have been due to protocol design rather than to true differences in pharmacodynamics, however. Adverse effects were reported in 7–17% of patients participating in the controlled trials of intravenous nicardipine, but they were less common than with sodium nitroprusside and rarely required discontinuation of the drug [48, 64].

Clevidipine is a third-generation dihydropyridine calcium-channel blocker that exhibits rapid onset and offset because of its metabolism by blood esterases [72–75]. Additionally, its half-life after intravenous administration is approximately 1 min [72–74, 76, 77]. Small, dose-response studies have suggested that clevidipine may be effective in treating postoperative hypertension in cardiac surgery patients [75–78]. Singla and colleagues performed a randomized, double-blind study – the ESCAPE-2 study – that demonstrated in 206 cardiac surgery patients that clevidipine-treated patients had a significantly lower incidence of treatment failure than placebo patients (8.2% vs. 79.6%, $p < 0.0001$) [79]. Treatment success, defined as a reduction in SBP ≥15% from baseline, was achieved in 91.8% of clevidipine-treated patients with a median time to target SBP with clevidipine of 5.3 min (95% CI 4–7 min). Adverse event rates were similar for both treatment groups [71]. The ECLIPSE (Evaluation of CLevidipine In the Perioperative Treatment of Hypertension Assessing Safety Events) study compared clevidipine with nitroglycerin, sodium nitroprusside, and nicardipine. Patients who received clevidipine had lower rates of mortality (2.8% vs 3.8%), fewer total adverse effects, and improved BP control compared to patients who received the other two agents [80].

Other calcium channel blockers have been studied for acute postoperative hypertension including intravenous isradipine, sublingual nifedipine, intranasal nifedipine, and intravenous diltiazem [81–85]. Although they were all effective in lowering MAP, intravenous isradipine and intranasal nifedipine are not currently available, sublingual nifedipine has been inadequately studied, and intravenous diltiazem's negative chronotropic effects would be undesirable post cardiac transplant, as evidenced by the sinus arrest seen in one of the study patients [84].

Fenoldopam is a short-acting systemic vasodilator that activates dopamine-1 receptors and is FDA approved for use in the short-term management of severe hypertension. Its action on vascular dopamine type 1 receptors results in relaxation of vascular smooth muscle via cyclic adenosine monophosphate-dependent pathway, resulting in vasodilation. These receptors are distributed throughout most arterial beds but have the highest densities on renal and splanchnic arteries. As such, blood pressure reduction with fenoldopam has been found to be accompanied by enhanced renal blood flow, natriuresis, diuresis, and an increase in glomerular filtration rate [86]. A dose of 0.1–0.3 μg/kg/min as an intravenous infusion provides

clinical effect within 5 min and a duration of action less than 30 min [87]. Clinical trials suggest that it is as effective as sodium nitroprusside for lowering blood pressure [45]. It has also been demonstrated to be equivalent to sodium nitroprusside and intravenous nifedipine after coronary artery bypass grafting [88, 89]. The mean time to therapeutic goal was 28 min in a placebo-controlled trial and 70% of cardiac surgery patients achieved goal blood pressure levels 30 min after the start of fenoldopam [89, 90]. Hypotensive events ranged from 5% to 50% [54, 55]; however, due to its short half-life (5–10 min), the drug's effect dissipates quickly after cessation of the infusion. Approximately 50% of the effect is lost in 15 min [91]. The effects of fenoldopam on renal blood flow and glomerular filtration suggest it may be particularly attractive in the treatment of severe hypertension, especially for patients with or at risk for renal dysfunction [54]. In fact, one study demonstrated increased renal protection in patients undergoing cardiopulmonary bypass [92]. Limitations to its use include that it has been reported to cause electrocardiographic changes, specifically in T-wave morphology, though these changes do not appear to represent myocardial ischemia [91].

Certain agents used for acute postoperative hypertension in the general cardiac surgery population should be avoided in the post-cardiac transplant population. Agents with β-adrenergic blocking effects like labetalol and esmolol should be avoided due to concerns with excessive reductions in blood pressure, bradycardia, and conduction delays in the newly transplanted heart. Additionally, the ISHLT recommends continuous infusion of an inotropic agent such as isoproterenol with or without dopamine, dobutamine with or without dopamine, or milrinone to maintain hemodynamic stability in the first 3–5 days post-transplant [31]. As such, the use of labetalol or esmolol would be directly antagonistic to these recommendations.

Hydralazine has been widely used for many years in the treatment of acute postoperative hypertension despite the lack of evidence for its use in this indication. Hydralazine has a direct effect on arteriolar smooth muscle, causing a reduction in arterial vascular resistance with no effect on venous smooth muscle or epicardial coronary arteries. The hemodynamic effects after rapid administration are a reduction in MAP, SBP, and DBP along with an increase in heart rate, cardiac output, and myocardial contractility. It is not considered a first-line agent for the treatment of postoperative hypertension as its overall efficacy and safety have not been adequately defined for this indication [27, 60].

Similarly, angiotensin-converting-enzyme (ACE) inhibitors have limited data available for acute postoperative hypertension. The relative decompensated hemodynamic state during the first 24 h after anesthesia along with the long duration of action of ACE inhibitors and the typically short duration of acute postoperative hypertension suggest that these agents may not be suitable for antihypertensive therapy in the immediate postoperative period.

Strict management of perioperative and postoperative blood pressure reduces the harmful sequelae of severe postoperative hypertension and serves as a bridge to

definitive long-term therapy in this patient population. No randomized trials in cardiac transplant recipients are large enough to evaluate the effect of antihypertensive therapy on morbidity, mortality, and graft survival. Additionally, no studies have been performed in the immediate postoperative period for this population. However, it is likely that antihypertensive therapy in this population has similar, if not greater, benefits than in the general population [32].

Recommendations Based on the Data

Severe, postoperative hypertension is associated with the potential for significant morbidity following cardiac surgery. Patients with preexisting hypertension, particularly stage 3, are at an increased risk of perioperative and postoperative complications. To decrease the risk of hypertensive or hypotensive episodes, blood pressure should be monitored continuously and short-acting intravenous antihypertensive agents should be administered to target a MAP generally within ±20% of the patient's baseline value once alternative causes for postoperative hypertension (hypoxia, hypercarbia, pain) are mitigated. There is currently inadequate evidence to select one particular agent. Sodium nitroprusside with or without nitroglycerin and/or an intravenous calcium channel blocker such as nicardipine or clevidipine can safely and effectively lower MAP to the desired range. The use of intravenous fenoldopam is a reasonable alternative in patients with or at risk for renal dysfunction. We make a strong recommendation for the use of these agents to treat severe hypertension after cardiac transplantation. The choice of antihypertensive agent should largely be influenced by an effort to optimize end organ perfusion and avoid recognized adverse effects, as these agents are all equally efficacious. Choice of therapy should also always depend on the clinical presentation, patient characteristics, properties of the drug, and clinician's experience.

A Personal View of the Data

Hypertension is a frequent complication following cardiac transplantation that occurs early post-transplant and can be difficult to manage. Severe postoperative hypertension is associated with sequelae that may include failure of anastomoses, hyperperfusion syndrome, cardiac arrhythmia, cerebral edema or ischemia, hemorrhage, and end organ damage, thus making strict management of postoperative blood pressure imperative. Few studies have compared these agents with one another, and all are tolerated reasonably well. Additionally, there are no formal guidelines or a clear consensus as to the choice of antihypertensive drug. Thus, the drug of choice is often dictated by the individual patient circumstance and the

hospital formulary. No one agent is preferred, but given the current evidence, we recommend the use of effective options such as an intravenous calcium channel blocker (clevidipine or nicardipine) and/or intravenous sodium nitroprusside with or without nitroglycerin. In practice, sodium nitroprusside has many limitations to its use including rapid tachyphylaxis and toxicity. The dosage should not exceed 5 μg/kg/min for more than a few minutes, if used. The lowest possible dosage should be utilized for the shortest possible time given the risk of cyanide toxicity. The use of intravenous fenoldopam may also be considered in patients with or at risk for renal dysfunction.

Recommendations

- Continuous infusions of inotropes, as recommended by the ISHLT Guidelines, should be taken into account when dealing with severe postoperative hypertension following cardiac transplantation; weaning of these agents may offer adequate resolution of hypertension (evidence quality high; strong recommendation).
- For patients with severe hypertension, we recommend first-line use of an intravenous calcium channel blocker such as clevidipine or nicardipine and/or intravenous sodium nitroprusside with or without nitroglycerin to target a MAP generally within ±20% of the patient's baseline value (evidence quality high; strong recommendation).
- The use of intravenous fenoldopam may also be considered in patients with or at risk for renal dysfunction (evidence quality high; strong recommendation).
- Agents with β-adrenergic blocking effects like labetalol and esmolol should be avoided due to concerns with excessive reductions in blood pressure, bradycardia, and conduction delays in the newly transplanted heart (evidence quality high; strong recommendation). ACE inhibitors may not be suitable for antihypertensive therapy in the immediate postoperative period due to the relative decompensated hemodynamic state during the first 24 h after anesthesia along with the long duration of action of the drug (evidence quality high; strong recommendation).

Appendix (Table 24.3)

Table 24.3 Pharmacotherapeutic options

Drug	Class	Dose range	Mechanism of action	Onset of action	Circulatory half-life	Duration of action	Adverse effects
Sodium nitroprusside (SNP)[a, b]	Nitro-vasodilator	0.25–10 μg/kg/min	Venous (primarily) and arterial vasodilator	Rapid	~2 min	1–2 min	Hypotension (9–92%)
		(Recommended maximum 2–5 μg/kg/min to avoid toxicity)		(<2 min)	(Thiocyanate ~3 days; may double or triple in renal failure)		Tachyphylaxis
							Cyanide toxicity
Nitroglycerin (NTG)[c]	Nitro-vasodilator	5–20 mcg/min using non-absorptive tubing	Venous (primarily) and arterial vasodilator	Rapid	~3 min	3–5 min	Hypotension (<4%)
		(Starting dose of 25 mcg/min has been used in clinical studies using polyvinylchloride tubing)		(<2 min)			Nitrate tolerance (within 24–48 continuous hours)
Nicardipine (NIC)[d]	2nd generation dihydropyridine calcium channel blocker	5–15 mg/h	Arterial vasodilator	Rapid	3–45 min	≤8 h;	Headache (15%)
				(<2 min)	(Non-linear kinetic profile)	50% decrease in effect in ~30 min upon discontinuation	Hypotension (6%)
							Nausea/vomiting (5%)
							Tachycardia (4%)
Clevidipine (CLV)[e]	3rd generation dihydropyridine calcium channel blocker	1–2 mg/h; double the dose in 90 s intervals thereafter	Potent arterial vasodilator	2–4 min	1–15 min (biphasic)	5–15 min	Headache (6%)
		(Maximum 16 mg/h)					Nausea (5%)
							Vomiting (3%)
Fenoldapam (FEN)[f]	Dopamine-1 receptor agonist	0.1–0.3 μg/kg/min	Systemic vasodilator	10 min	~5 min	<30 min–1 h	Hypotension (5–50%)
		(Maximum 1.6 mcg/kg/min)					Headache (24%)
							Nausea (12%)
							T wave inversion (6%)
							Tachycardia (≤5%)
							Hypokalemia (≤5%)

[a]Nipride RTU (sodium nitroprusside) (prescribing information). Lenoir, NC: Exela Pharma Sciences LLC; March 2017
[b]Nitropress (sodium nitroprusside) (prescribing information). Lake Forest, IL: Hospira Inc; January 2014
[c]Nitroglycerin in 5% Dextrose Injection (nitroglycerin) (prescribing information). Deerfield, IL: Baxter; August 2016
[d]Cardene IV (0.1 mg/mL) (nicardipine) (prescribing information). Bedminister, NJ: EKR Therapeutics; December 2016
[e]Cleviprex (clevidipine) (prescribing information). Cary, NC: Chiesi USA Inc; August 2017
[f]Corlopam (fenoldopam) (prescribing information). Lake Forest, IL: Hospira Inc; December 2015

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Chapter 25
Post-Transplant Right Ventricular Failure

Marshall T. Bell and David A. Fullerton

Introduction

The right ventricle (RV) was historically considered a passive conduit and hemodynamically inconsequential; it is now understood to be anatomically and physiologically distinct. When compared to the left ventricle, the right ventricle is thinner- walled and more complaint. Unlike the more muscular left ventricle, which contracts with spiraling mechanics as it ejects, right ventricular ejection is dependent on inward displacement of its anterior wall toward the interventricular septum. As such, the right ventricle is more prone than the left to become dysfunctional or fail from either volume or pressure overload.

The inherent circumstances of cardiac transplantation are such that right ventricular failure is a specific risk of the procedure. Such failure may derive from mechanical dysfunction of the right ventricular myocardium (leading to volume overload) or from excessively high right ventricular afterload (pressure overload) or a combination or both. Probably because it has less myocardial mass, the right ventricle is more susceptible than the left to the obligatory injuries of ischemia and reperfusion associated with the heart transplant operation. Hence, the contractility of the right ventricular myocardium may be dysfunctional post-transplant. Such dysfunction of the RV myocardium is exacerbated in the setting of an elevated RV

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afterload. Given that RV ejection fraction is inversely related to RV afterload, the management of post-transplant RV failure is focused on optimizing RV contractility and RV afterload.

The primary clinical determinant of right ventricular afterload is pulmonary vascular resistance (PVR). Because of long-standing left ventricular failure, the PVR of most heart transplant recipients is at least modestly elevated going into the transplant procedure. The PVR may be further increased by acute lung injury incurred during the procedure associated with cardiopulmonary bypass, transfusion, etc. The transplanted heart is invariably procured from a donor with normal PVR; the RV of the donor heart is therefore not conditioned to eject against an elevated afterload. Even if a normally functioning heart is implanted into a recipient with elevated PVR, the unconditioned right ventricle may fail.

Management of RV failure requires aggressive multimodal treatment. Initial therapies are targeted at preload optimization, ionotropic support, and afterload reduction. Should these measures be insufficient, treatment requires mechanical circulatory support. In the present chapter these strategies will be presented along with the available supporting evidence.

Search Strategy

A literature search was conducted to identify published data on post-transplantation right ventricular failure as outlined in the PICO format. PubMed, Cochrane Library and Google Scholar were queried using the search terms "right ventricular failure/dysfunction cardiac transplant," "pulmonary hypertension cardiac transplant," "hemodynamics right ventricle heart transplant," and "mechanical circulatory support right ventricle failure heart transplant." Study designs included case series, retrospective studies, prospective cohort studies, randomized controlled trials, and systematic reviews from years 1980 to 2018. The quality of data were evaluated and classified according to the GRADE system (Table 25.1).

Table 25.1 PICO table for post-transplant right ventricle failure

P	I	C	O
Patient population	Intervention	Comparator	Outcome studied
Adult, postop cardiac transplantation, in ICU	Early treatment with drugs or devices	Standard care: maximizing drug support	Recovery of right ventricular function, graft survival, patient survival, ICU LOS, QOL

Table 25.2 Clinical diagnosis of post-transplant right ventricular failure

Primary graft dysfunction-right ventricle	Diagnosis requires both I + II or III	I. Hemodynamics with right atrial pressure >15 mmH, PCWP <15 mm Hg, CI <2.0 L/min/m^2 II. TPG <15 mm Hg and/or pulmonary artery systemic pressure <50 mm Hg III. Need for mechanical assistance

Results

Clinical Relevance of Post-transplant RV Failure

Approximately 2500 heart transplants are performed annually in North America with survival rates of 85% at 1 year and 70% at 5 years [1]. Right ventricular failure complicates approximately 3–4% of heart transplants and remains a significant contributor to perioperative morbidity and mortality, accounting for nearly one half of the postoperative complications [2]. Consensus guidelines from the International Society of Heat and Lung Transplant (ISHLT) define RV failure as primary graft dysfunction of the right ventricle (PDG-RV) with parameters recommended for established for clinical diagnosis [3] (Table 25.2)

Risk Factors

Recipient Selection

Pulmonary hypertension (PH) is the most well-defined patient specific risk factor for post-transplantation RV failure. Some degree of pre-transplant PH should be suspected in all patients with chronic heart failure. Once identified by right heart catheterization, affected patients undergo vasodilator administration to determine reversibility. A PVR >3 Wood units despite vasodilators is considered a contraindication to transplantation [4]. Costard-Jackle and colleagues first demonstrated the significance of pulmonary hypertension on post-transplant mortality. In a retrospective review of 293 consecutive cardiac transplant recipients, PVR >2.5 Woods units was associated with a significant increase in 90-day mortality of 17.9%, compared to 6.9% ($p < 0.02$) for patients with PVR of <2.5 Woods units [5].

Donor Selection

Patients with pre-transplant PH have long been thought to have improved outcomes by use of oversized donors. A larger RV was thought to be better able to function against an elevated PVR [6]. Recently, however, Kwon and colleagues retrospectively examined 107 heart transplant recipients between 2003 and 2008. Thirty-seven patients with undersized donor heart (donor weight/recipient weight <0.90) were compared with 70 patient receiving oversized donor hearts (donor weight/recipient weight >1.2). Post-operative pulmonary hypertension was observed in 51% of patients in the undersized group and 56% of patients in the oversized group. Additionally, there was no statistical difference in systolic pulmonary artery pressures (PAP), incidence of RV dysfunction, or mortality at 1 week, 1 month, or 6 months [7]. Hence, the strategy of using an oversized donor remains controversial.

Management Strategies

Optimizing Preload

In the presence of post-transplant RV dysfunction, the first step in management is to optimize RV preload. All patient should have continuous invasive monitoring of central venous pressure (CVP), PAP and cardiac output. These provide dynamic information about the filling pressures and RV function. However, it is crucial to avoid overly aggressive volume administration which will result in RV volume overload. Therefore, the CVP should be maintained <15 mm Hg. Volume overload of the RV will increase RV wall tension thereby increasing myocardial oxygen demand. It will likewise displace the RV papillary muscles, leading to tricuspid regurgitation and further hemodynamic compromise.

Improving Contractility

Beta-adrenergic receptor agonists and phosphodiesterase inhibitors are the primary agents used to support myocardial contraction post-transplantation. While the use of these agents has been widely adapted, consensus guidelines and clinical trials are lacking. Thus, the choice of inotrope is variable from institution to institution. Epinephrine and dobutamine are the most commonly used beta-agonists in the post-transplant setting. Should use of the agents be arrhythmogenic, use of a phosphodiesterase inhibitor (milrinone) may be an effective alternative.

It is essential to maintain systemic arterial pressure in order to preserve coronary perfusion pressure. While milrinone is a nonspecific vasodilator, it is a more potent

systemic than pulmonary vasodilator. Its usage may produce systemic hypotension, necessitating the addition of a systemic vasoconstrictor such as vasopressin or norepinephrine to support systemic pressure.

Afterload Reduction

Reduction of RV afterload via selective pulmonary vasodilation is the mainstay of therapy. The two clinically accessible agents that may be administered via the inspiratory limb of a ventilator are inhaled nitric oxide (NO) and epoprostenol. As selective pulmonary vasodilators, they reduce PVR without lowering systemic blood pressure.

A small number of prospective studies have demonstrated NO is effective in reducing PVR post-transplantation. Ardehali and colleagues prospectively enrolled 16 patients with mean PAP >25 mm Hg to receive NO at 20 ppm prior to termination of cardiopulmonary bypass. These patients were compared to historic controls of patients matched for pulmonary hypertension. A significant reduction in RV dysfunction (6.3% vs. 37.5%; $p < 0.05$) was observed in patients receiving NO postoperatively. Thirty-day survival was also significantly improved in the NO-treated group (100% vs. 81%; $p < 0.05$) [8].

Optimal dosing of NO was investigated by Solina and colleges in 62 consecutive cardiac surgery patients who demonstrated an elevated PVR preoperatively. The patients received NO at 10 ppm, 20 ppm, 30 ppm, and 40 ppm. While all dosages demonstrated a decrease in PVR from preoperative values, there was no statistical difference in PVR at escalating dosages of NO [9].

The hemodynamic impact of the prostenoid, epoprostenol, following cardiac surgery was originally demonstrated by Haraldson and colleagues in nine postoperative cardiac surgery and transplant patients. A reduction of PVR and transpulmonary gradient (TPG) (29% and 26%, respectively) was achieved at a concentration of 10 ug/mL [10]. More specifically, in post-transplant patients similar results were observed with administration of 20 μg of nebulized iloprost. This dose was effective in significantly reducing TPG/mean PAP and significantly increasing cardiac index (CI) [11].

In one of the few studies comparing NO to prostenoids, Khan performed a randomized controlled trial of inhaled prostacyclin (20,000 ng/mL) vs NO (20 ppm) in heart and lung transplant recipients. Heart transplant patients enrolled had a mean PA pressure of 25 mmHg or a CVP of >12 mmHg and a CI <2.2 l/min/m^2. The hemodynamic effects of NO and prostenoids were very comparable. Neither group had a 30-day survival benefit or exhibited any systemic toxicity [12].

If selective pulmonary vasodilators are unavailable, non-selective agents should be used.

Intravenous pulmonary vasodilators such as prostaglandin E1 and prostacyclin, milrinone, diltiazem, nitroprusside or nitroglycerin work through different mechanisms and may lower PVR. However, because they are all non-selective vasodilators they all carry the risks of (a) increasing intrapulmonary shunting and thereby compromising oxygenation and (b) systemic vasodilation with a drop in systemic blood

Table 25.3 Clinical available pulmonary vasodilators

Medication	Route	Dosage	Mechanism	Potency	Side effects
Nitric oxide	Inhaled	1–20 ppm	Increased intracellular cGMP ->pulmonary smooth muscle relaxation	++++	+++
Prostaglandin	Inhaled	0.5–2.0 mcg/kg/min	Increase intracellular cAMP ->pulmonary smooth muscle relaxation	++++	++
Sildenafil	IV or PO	0.5–2.0 mg/kg/dose	Inhibition phosphodiesterase type V ->increase intracellular c GMP->pulmonary smooth muscle relaxation	+++	+++
Milronone	IV	0.3–0.8 mcg/kg/m	Inhibition phosphodiesterase type III->increase intracellular c GMP->pulmonary smooth muscle relaxation	++	++++

pressure. When used in the post-transplant setting, these undesired consequences are particularly problematic.

Sildenafil has gained recent attention for treatment of RV dysfunction following transplant. It may be administered intravenously or orally and the beneficial effects of sildenafil post-transplantation have been demonstrated by a few small case series. De Santo and colleagues published the first case series of 13 patients with RV dysfunction post-transplant successfully treated with sildenafil. Patients were started on oral sildenafil via nasogastric tube on post-transplant day one and continued for 30 days. Patients demonstrated significant improvement in CVP, mean PAP, TPG, and CI by 48 h [13]. In pediatric recipients similar results have been reported with use of sildenafil. Singh and colleagues performed a retrospective observational study of 24 patients with post-transplantation pulmonary hypertension. Oral sildenafil was associated with a reduction in PVR from 4.7 ± 2.9 WU to 2.7 ± 1.0 WU ($p < 0.0007$) [14]. But as a non-selective vasodilator, sildenafil carries the same potential risks as do other non-selective vasodilators. It is often associated with increased intrapulmonary shunting and systemic vasodilation. Further, its long half-life means that its biologic actions persist for hours after cessation of the drug (Table 25.3).

Mechanical Circulatory Support-Graft Salvage

When medical management fails to reverse RV failure, mechanical circulatory support (MCS) provides the only means for graft salvage. The evolution of MCS has provided a variety of options for RV support. Among these, right ventricular assist devices (RVAD), extracorporeal membrane oxygenation (ECMO), and intra-aortic balloon pumps (IABP) have all been employed with varying degrees of success. While the use of IABP counterpulsion is a common strategy for augmenting coronary flow to support left ventricle function, it can successfully be employed to

support right coronary flow in patients with RV dysfunction. Arafa and colleagues reported graft salvage in five patients with placement of IABP for isolated RV failure. Twelve hours after initiation of therapy patients demonstrated significant increases in CI and mixed venous oxygen saturation, and a significant decrease in mean PAP. All patients were successfully weaned from their IABP and four patients were alive at 1 year [15].

Graft salvage with early placement of an RVAD has been reported in a variety of isolated case reports [16]. There is a small but growing number of devices for use, including implantable devices, percutaneous devices, and intra-corporeal or extracorporeal circuits. Each device has slightly different physiologic considerations and side-effect profiles. Sugiki and colleagues described seven post-cardiac surgery patients who required RVAD assistance for recovery with placement Impella Recover RD® device. The most common indication for Impella placement was post-heart transplantation failure in four patients. While two of the four patients survived to have explantation of their device, no patient survived past 25 days [17].

Veno-arterial (VA) ECMO provides an alternative to RVAD. As VA-ECMO can be initiated percutaneously at the beside, it has gained popularity as a means for rapid stabilization of life-threatening hemodynamic instability. Schmidt and colleagues examined the outcomes of 3846 patients with refractory cardiogenic shock in the international Extracorporeal Life Support Organization registry. The authors identified 216 patients placed on VA-ECMO following heart or lung transplantation. Survival at discharge in this subset of patients was significantly better (51.8%) than for the group of patients with cardiogenic shock as a whole (41.6%) [18]. Patients in this study were unfortunately not further stratified into RV failure versus biventricular.

In a single center review Tchantchaleishvili and colleagues identified 19 patients who required mechanical circulatory support following transplant between 2001 and 2015. Nine patients (47%) required RVAD placement via CetriMag or ROTAFLOW devices. These device provided excellent graft survival with 100% 30 day survival and 88.9% survival at 1 year [19].

Tagahavi and colleagues compared ECMO to RVAD implantation in 28 patients with refractory right ventricular failure following transplantation. Fifteen patients received an RVAD and ECMO was initiated in 13 patients. Successful separation from mechanical support was accomplished in 10% of patients with an RVAD and 77% of patients on ECMO [20].

Recommendations Based on the Data

Careful recipient selection has reduced the incidence of post-transplant RV failure by identifying those recipients with prohibitively high PVR. While dogma has suggested an oversized heart is less susceptible to RV failure, this remains controversial as additional evidence has failed to support this idea. However, consensus dictates that it is best to avoid significantly under-sizing the donor. Currently, the ISHLT guidelines recommends a donor with at least 70% of the recipient weight [21].

Data for optimizing preload and contractility are virtually non-existent. No studies were identified that provided evidence for targeted hemodynamic parameters; instead, treatment must be empirically determined. It is best to target a CVP <15 mm Hg. This parameter, however, is empiric and is not evidence-based. Similarly, no evidence is available to speak to the superiority of a particular ionotropic agent in the setting of post-transplantation RV dysfunction. Based upon a large clinical experience, we recommend the empirical use of epinephrine and/or dobutamine. The transplanted heart is denervated. Hence, its pre-synaptic nerve terminals are devoid of the neurotransmitter, norepinephrine. Since the inotropic actions of dopamine are indirect, via the release of pre-synaptic norepinephrine to stimulate post-synaptic myocardial beta receptors, dopamine has very limited inotropic actions on the transplanted heart.

The use of selective pulmonary vasodilators is the mainstay of treatment of post-transplantation RV failure. Sufficient evidence has demonstrated inhaled prostenoids and NO both produce reductions in PVR and TPG. Additionally, studies have demonstrated improvement in RV function and even survival benefits. However, comparison of these agents in the post-transplant setting is extremely limited and fails to demonstrate superiority of either agent. Extrapolation of literature from non-transplant, cardiac surgery patients suggests the two are equivalent [22].

Either inhaled NO or inhaled prostenoids may be effective, and both may be safely used. In our lengthy experience using inhaled NO, it is never necessary to exceed a dosage of 20 ppm. At this dosage, we have found no risk of increased circulating methemoglobinemia. High-dose administration of prostenoids may reduce systemic blood pressure and may produce platelet inhibition. However, prostenoids costs as little as one fifth that of NO [23]. It is important to remember that one agent may be ineffective in a given patient, while the other agent work well, and therefore, choice of one agent over the other must be empirically determined. We recommend very cautious use of sildenafil, if at all, in the acute setting of post-transplant RV failure. Its unwanted systemic vasodilation and increased intrapulmonary shunting complicate the management of acute ill patients.

Evidence for the superiority of ECMO or RVAD for isolated right-sided failure is lacking. Our choice of RVAD vs ECMO is determined by whether the patient requires an oxygenator in the circuit. If not, we recommend use of an RVAD with a centrifugal pump device. The inflow cannulation is typically via the right atrium and the outflow limb is via the main pulmonary artery. If ECMO is required, we recommend central cannulation. But this typically does require delayed sternal closure and greater perioperative bleeding.

Personal View of Data

Fortunately, post-transplant RV failure is relatively uncommon (3–4%). It is, however, highly morbid and associated with a high mortality. The data regarding its management are truly scant and there are no prospective, randomized clinical trials. It is therefore necessary to extrapolate data from left ventricular failure and cardiogenic shock to guide the management of post-transplant RV

Table 25.4 Summary of evidence supporting the use of pulmonary vasodilators in post-transplant patients with RV dysfunction

Authors	Design	Patient	Intervention	Comparison	Outcomes	Grade of evidence
Ardehali et al. 2001 [8]	Prospective observational	16 adult heart transplant recipients with lowest mean pulmonary artery pressures >25 mmHg	NO 20 ppm at termination of CPB	Historical cohort of 16 patients matched for pulmonary HTN	Reduction in RV dysfunction (6.3% vs. 37.5%; $p < 0.05$) postoperatively with NO. 30 day survival in NO-treated group (100% vs. 81%; $p < 0.05$)	Moderate
Theodoraki et al. 2006 [11]	Case series	8 adult heart transplant recipients RV dysfunction following transplantation	20 μg of inhaled iloprost administered via nebulized aerosol for a 20-min period	Pre-intervention hemodynamic parameters	Inhaled iloprost decreased the TPG at the end of the inhalation period relative to baseline (8.2 ± 1.6 mmHg vs. 11.2 ± 0.9 mmHg, $P < 0.05$	Low
Khan et al. 2009 [12]	Prospective, randomized	6 adult heart transplant recipients with mean PA pressure >25 mm Hg or RV dysfunction defined as CVP >12 mm Hg with cardiac index <2.2 L/min/m^2 and visual evidence of RV dysfunction 19 Lung transplant with PA pressure >25 mm Hg or hypoxemia (Pao_2/Fio_2 <150)	20 ppm NO	Inhaled prostacyclin(IP) (20,000 ng/mL)	Following 30 min of initiation NO and prostacyclin similarly reduce mPAP (NO 32 ± 1–>26 ± 1 Vs IP 37 ± 3–>28 ± 3) and improve CI (NO 2.5 ± .2–>3.0 ± .3 Vs IP 2.6 ± .3–>3.1 ± .9) and MVO2 Neither group had a 30-day survival benefit or exhibited any systemic toxicity	Low

(continued)

Table 25.4 (continued)

Authors	Design	Patient	Intervention	Comparison	Outcomes	Grade of evidence
De Santo et al. 2008 [13]	Case series	13 adult transplant recipients with RV dysfunction and pulmonary hypertension as identified on transesophageal echo	3 mg/kg oral sildenafil via nasogastric tube on post-transplant day one and continued for 30 days. Down-titration of sildenafil therapy to 2 mg/kg and then to 1 mg/kg was achieved over the first two postoperative months	Baseline values	Sildenafil significantly decreased the TPG and PVR index relative to baseline values; 5.6 ± 1.82 versus 10.4 ± 4.6 WU, (P < .05), 13.5 ± 3.4 mm Hg versus 18.7 ± 5.4 mm Hg (P < .05)	Low
Singh et al. 2009 [14]	Retrospective observational	24 pediatric heart transplant recipients with hemodynamic and echocardiographic evidence of right heart failure	Sildenafil dosing started at 0.5 mg/kg/dose orally every 8 h after weaning off inhaled vasodilators Dose increased by 0.5 mg/kg/dose every 48–72 h to a maximum dose of 1.5 mg/kg/dose (or maximum of 30 mg/dose if >20 kg)	Historic control of 35 pediatric heart recipients patients with elevated PVRI (>3 WU) treated with inhaled-pulmonary vasodilators	PVRI on the first postoperative cardiac catheterization was equivalent between the control and sildenafil (control -4.7 ± 2.9 WU vs. Sildenafil 4.1 ± 1.7 WU; p = 0.52). PVRI on sildenafil at median time from transplant of 21 days was significantly lower (2.7 ± 1WU) than the PVRI in the control group at a similar time point of 23 days (3.9 ± .8 WU); p = 0.043	Low

failure. Such has provided the straight-forward strategy of optimizing preload, selectively reducing PVR, inotropic support and if necessary, mechanical circulatory support (Table 25.4).

Recommendation

- For patient with clinical evidence of RV dysfunction following transplantation inhaled pulmonary vasodilators should be employed (evidence quality low; strong recommendation)
- Patients with pre-transplant pulmonary hypertension benefit from implantation of oversized allograft (evidence quality low; weak recommendation)
- VA-ECMO is not superior to RVAD for graft survival for patients with isolated RV-failure following transplantation; the choice is determined by whether the patient requires an oxygenator in the circuit (evidence quality very low; recommendation none)

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Chapter 26
Lung Infiltrates in Post-Operative Lung Transplant Patients: Pneumonia, Rejection or Edema?

Siddhartha G. Kapnadak, Erika D. Lease, and Michael S. Mulligan

Introduction

Lung transplantation (LTx) is a potentially life-saving therapeutic option for many patients with end-stage pulmonary disease. Outcomes have improved, with the most recent International Society for Heart and Lung Transplant (ISHLT) Registry report showing a median survival of 6.0 years for all, and 7.4 years for double lung transplant recipients, respectively [1]. However, overall outcomes remain inferior to recipients of other solid organ transplants, with LTx patients facing a high risk of complications throughout their post-transplant course.

The immediate post-operative period presents a particularly high risk time for this extremely vulnerable population, with 30-day mortality reported as 6–7%, 3-month mortality 10–12%, and some early complications also associated with the long-term development of chronic lung allograft dysfunction (CLAD) [1, 2]. In post-operative LTx recipients with respiratory compromise, there is a need for clinicians to quickly recognize and manage the wide array of possible complications including infection, rejection, pulmonary edema, primary graft dysfunction (PGD), bleeding, wound and airway complications, and venous thromboembolism [3]. Although comprehensive guidelines have recently been published on PGD [2], there is limited literature to guide clinicians on other post-operative diagnostic considerations, with practice patterns having been demonstrated to differ considerably

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in the post-operative period [4]. This chapter reviews important diagnostic considerations for LTx recipients with respiratory compromise in the immediate post-operative period, specifically summarizing the literature pertaining to infections, rejection, and pulmonary edema.

Search Strategy

A literature search of English language publications from 1995 to 2018 was used to identity published data on post-operative pulmonary complications after lung transplantation using the PICO outline (Table 26.1). Databases searched were PubMed and Cochrane Evidence Based Medicine. Terms used in the search were "lung transplant," "postoperative," "intensive care unit," "infection," "rejection," "pulmonary edema", "bronchoscopy", and "diagnostic imaging". Articles were excluded if they specifically addressed complications primarily occurring more than 1 month following lung transplantation surgery. No randomized control trials were identified. Studies found included retrospective reviews, case reports/series, cohort studies, surveys, and one systematic review. The quality of data in the included manuscripts were classified according to the GRADE system.

Results

Infection

Infection remains a significant contributor to mortality of LTx recipients early post-operatively, comprising nearly 20% of all deaths in the first 30 days following lung transplantation [1]. As a subset of the immediate post-transplant infectious complications, post-operative pneumonia has been reported to have an incidence of 17 per 100 lung transplants [5]. Pulmonary infections can arise in LTx recipients due to several factors including donor-derived infection, recipient-derived infection (i.e. due to pre-transplant chronic colonization), and infections related to hospitalization and/or critical illness (Table 26.2). Additional risk factors for pulmonary infection after LTx include anatomic and physiologic issues such as necrotic tissue at the airway anastomoses, denervation of the lung allograft leading to decreased

Table 26.1 PICO table for post-lung transplant pulmonary infiltrates

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Lung transplant recipients with pulmonary infiltrates	Aggressive modalities of evaluation and treatment of pulmonary infiltrates including early bronchoscopy	Standard care: empiric therapy with antibiotics, antirejection drugs, or diuretics	Length of mechanical ventilation, lung transplant function, chronic lung allograft dysfunction, survival

Table 26.2 Studies evaluating post-lung transplant pulmonary infections

Author (year)	Study type	# of patients	# episodes of pneumonia	Predominant organisms	Results	Evidence quality
Bonde (2006) [6]	Observational	80	n = 31/41%	Donor: *Staphylococcus* species, *n = 35* *Streptococcus* species, *n = 33* Recipient with post-transplant pneumonia: *Pseudomonas* species, *n = 13*	89% of donors with organisms on culture; presence of donor organisms did not predict post-transplant pneumonia	Low
Avlonitis (2003) [9]	Observational	115	Donor BAL culture positive in 46%	*Staphylococcus aureus,* n = 21 (40%) *Haemophilus influenza*, n = 13 (25%)	Recipients of lungs with positive donor BAL bacterial culture with lower post-transplant PaO_2/FiO_2, longer ICU stay and mechanical ventilation, inferior survival; no difference in episodes of early acute rejection	Low
Weill (2002) [8]	Observational	90	n = 14/16%	Donor gram stain positive in 43/72%	Positive donor gram stain did not predict the development of earl post-operative pneumonia, did not affect post-transplant oxygentation or duration of mechanical ventilation	Low
Riera (2015) [13]	Observational	170	n = 20/12% with ventilator-associated pneumonia	*Pseudomonas* species, n = 12 Enterobacteriaceae, n = 5	Post-transplant ventilator-associated pneumonia was associated with longer duration of mechanical ventilation, length of hospital stay, and had higher hospital mortality; presence of gastroparesis was associated with pneumonia	Low

(continued)

Table 26.2 (continued)

Author (year)	Study type	# of patients	# episodes of pneumonia	Predominant organisms	Results	Evidence quality
Dudau (2014) [15]	Observational	79 lung and heart-lung transplant recipients	n = 35/44% with first nosocomial pneumonia; 14/40% with recurrent nosocomial pneumonia	Enterobacteriaceae, 30% *Pseudomonas aeruginosa, 25%* *Staphylococcus aureus*, 20%	ICU mortality did not differ between those with nosocomial pneumonia, recurrence of nosocomial pneumonia, or those without nosocomial pneumonia; patients with nosocomial pneumonia had longer duration of mechanical ventilation, duration of ICU stay, and need for tracheostomy as compared to those without nosocomial pneumonia	Low
Mattner (2007) [12]	Observational	137	n = 59	Not cultured, 34% *Pseudomonas aeruginosa,* 23%	Pre-operative colonization with gram-negative rods was a risk factor for post-transplant pneumonia	Low

BAL bronchoalveolar lavage

mucociliary clearance and cough reflex, and continuous exposure of the allograft to the environment and microorganisms in the upper respiratory tract. Finally, high levels of immunosuppression early after surgery increase the susceptibility for both common as well as uncommon infections. Regardless of the source, early post-transplant pneumonia in LTx recipients appears to be associated with worse overall survival with one retrospective study by Bonde et al. finding an odds ratio of post-transplant mortality to be 3.86 (95% CI: 1.2–12.46, p = 0.02) [6]. Early post-operative infection may also impact long-term graft function. Valentine et al. found a positive association with the subsequent development of CLAD, specifically bronchiolitis obliterams syndrome (BOS), in LTx recipients who developed gram-positive or fungal pneumonia in the first 100 days after lung transplantation (HR 3.8; 95% CI 1.5–9.4, p = 0.004 and HR 2.1; 95% CI 1.1–4.0, p = 0.03 respectively) [7].

The clinical presentation of pulmonary infection in the early post-operative period can vary widely. A classic presentation of pulmonary infection including worsening oxygenation, elevated white blood cell (WBC) count, fever, increased respiratory secretions, and/or focal infiltrate on chest radiograph may be seen. However, patients may also present with atypical findings due to an abnormal response to infection in the setting of high levels of immunosuppression, or findings due to a mixed picture such as overlying pulmonary edema and/or PGD. The WBC count may be elevated even in non-infected individuals due to the high-dose corticosteroids frequently administered as induction immunosuppression, a fever response may be blunted due to immunosuppression, patients may already have significant respiratory secretions in the setting of decreased mucociliary clearance and/or pulmonary edema, and oxygenation may worsen due to other causes such as PGD, pulmonary edema, or pulmonary embolism. As such, there is a general consensus that the utility of any one clinical finding is low and the clinical picture in its entirety must be considered in diagnosing pulmonary infection early following lung transplantation.

The scope of donor-derived infections is not well understood due to the difficulty in assessing the risk of disease transmission, as well as the under-recognition and under-reporting of donor-derived infections. Donor-derived infection transmissions can be frequently anticipated prior to surgery, for example transmission of cytomegalovirus (CMV) from the donor to recipient, and measures can be taken to minimize the impact of these transmissions such as through prophylaxis or preemptive monitoring. Some infections, such as bacterial or fungal infection of the donor lungs, may be anticipated due to the known presence of organisms on the donor bronchoalveolar (BAL) cultures (Fig. 26.1), however the impact and recommended management in the LTx recipient are unclear. Commonly lung donors are administered antimicrobial agents targeting organisms found on pre-donation BAL cultures and these medications will frequently be continued in the recipient following the transplant surgery. The data are conflicting, however, as to the impact of positive donor BAL cultures on post-lung transplant recipient outcomes with some reporting longer intensive care unit (ICU) length of stay, time of mechanical ventilation, and worse overall survival while others report no difference in the incidence of post-transplant pneumonia or mortality [6, 8–10]. Moreover, there are no data as to which organisms

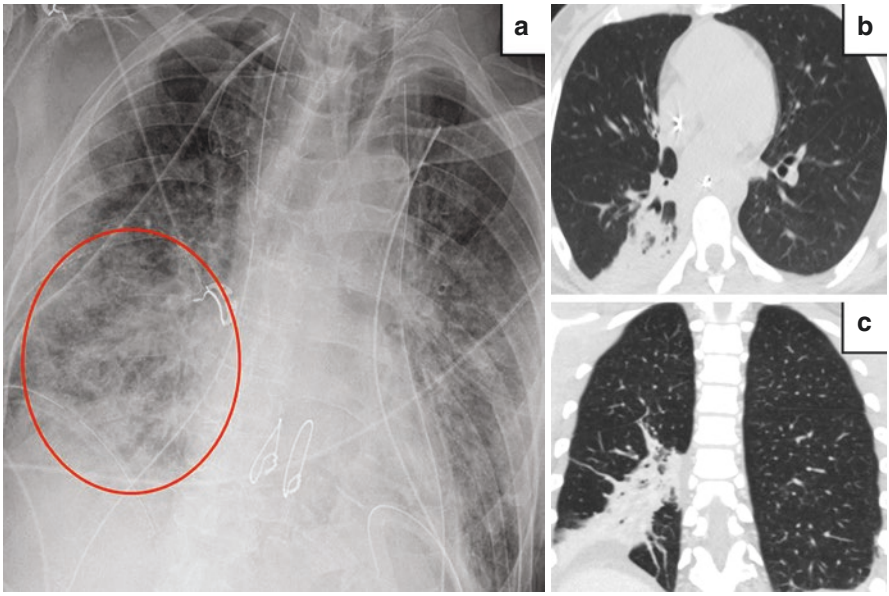

Fig. 26.1 68 year old man post-operative day 2 after double lung transplantation for interstitial lung disease, with persistently high oxygen requirement and copious respiratory secretions after extubation. (**a**) Anteriorposterior chest radiograph of the transplant recipient reveals a focal consolidation in the right lower lobe (circled). (**b**) Axial and (**c**) coronal images from the donor's chest computed tomography scan 1 day after declaration of brain death following a drug overdose (2 days prior to organ procurement), revealing a focal consolidation in the right lower lobe which corresponded to the recipient's post-operative radiograph. Directed bronchoalveolar lavage (BAL) from the recipient and pre-donation BAL from the donor both revealed *Escherichia coli*

should be treated as pathogens and the optimal duration of treatment in the recipient. Current guidelines recommend donor risk assessment, stratification, and mitigation with the decision of organ usability made on a case-by-case basis [11].

Pulmonary infections originating from the recipient are primarily the result of pre-transplant microbial colonization, particularly in patients with suppurative lung diseases such as cystic fibrosis (CF) and non-CF bronchiectasis. Recipients with known colonizing organisms are commonly administered targeted antimicrobials following surgery. There are limited data regarding the impact of pre-transplant colonization on the development of post-transplant pneumonia, although one retrospective study by Campos et al. found a positive association (RR = 4.76, 95% CI 1.02–22.10; p = 0.04) [10]. Mattner et al. also found a positive association specifically relating to pre-transplant colonization with gram-negative rods and the development of post-transplant pneumonia (OR 3.7; 95% CI 1.19–11.37, p = 0.004) [12]. To our knowledge, there are no studies evaluating the optimal treatment, timing, and duration for prevention of complications relating to pre-transplant colonizing organisms.

Similarly to other patients who are critically ill in the ICU, LTx recipients are susceptible to pulmonary infections early after lung transplant surgery in the setting

of mechanical ventilation and hospitalization. Several studies have found the incidence in post-operative lung transplant patients to be 3.5–12% for ventilator-associated pneumonia (VAP), 21% for ventilator-associated tracheobronchitis (VAT), 25% for health-care associated pneumonia (HCAP), and 12% for hospital-acquired pneumonia [13, 14]. Hospital-related infections appear to increase the duration of post-transplant mechanical ventilation, need for tracheostomy, duration of ICU length of stay, and duration of hospital length of stay; however there are conflicting data regarding the impact on mortality [13, 15]. Post-operative LTx recipients may also be at high risk for recurrence of pneumonia, with one study showing a recurrence rate of 40% at a median of 6 days (range 1–12) after completion of antibiotic therapy that is not explained by a difference in duration of antibiotic therapy or other clinical factors (duration of antibiotic therapy 10.7 days ± 3.5 days in those with no recurrence, 12.2 days ± 2.7 days in those with recurrence, $p = 0.06$) [15].

Rejection

LTx recipients face an elevated risk of rejection compared to other solid organs, with literature reporting prevalence of 30–50% during the first post-transplant year. In the immediate post-operative period, the intrinsically high risk is routinely addressed with high levels of immunosuppression, including induction agents used by 60% of LTx programs internationally [1]. Whether this practice reduces early rejection is unclear, with one meta-analysis showing no benefit of induction in reducing acute cellular rejection (ACR) or improving other LTx outcomes, although the six included trials were graded at high risk of methodological bias [16]. Furthermore, although there is limited literature defining risk specific to the post-operative period, shorter time from LTx has been consistently identified as an important risk factor for ACR [17]. In one cohort study of 481 recipients using a protocol including rabbit anti-thymocyte globulin (rATG) induction, Mangi et al. demonstrated the highest ACR risk in the first 2 months post-transplant, where at least minimal ACR (≥A1) was found on 54% of biopsies, after which risk decreased in a time-dependent manner [18]. Similarly, in another cohort study of 58 recipients receiving rATG induction, Krutsup, et al. found that 57% of biopsies at 2 weeks post-transplant had at least minimal ACR (≥A1), and 24% at least mild (≥A2), with ACR prevalence gradually decreasing over the first post-transplant year [19]. Moreover, in the first 30 post-operative days, registry data show that 3% of recipient deaths are due to acute rejection [1], along with an additional 24% during this period due to unspecified non-infectious graft failure, adding to the importance of rejection as a diagnostic consideration for early post-operative respiratory compromise.

Mechanistically, acute rejection is classified as cellular- (ACR) or antibody-mediated rejection (AMR), with the latter caused by antibodies classically against mismatched donor human leukocyte antigens (HLA), and criteria for definite AMR in LTx including: circulating donor specific antibodies (DSAs), allograft dysfunction,

histology with lung injury and capillary C4d deposition, and exclusion of alternate causes [20]. In the case of pre-transplant anti-HLA (or -ABO) antibodies, AMR can manifest as hyperacute rejection, marked by endothelial damage and fulminant lung injury presenting within hours of vascular anastomosis. Although an important consideration in the post-operative period, hyperacute rejection is extremely rare in LTx, particularly in the recent era because of advances in antibody detection and crossmatch techniques. To our knowledge only seven case reports of hyperacute rejection in LTx exist, all of which describe immediate post-operative graft dysfunction, positive cytotoxicity and/or flow cytometry crossmatch, and circulating DSAs [21–27]. Additionally, Scornick et al. in a cohort study in which 11 of 92 (12%) recipients had pre-transplant anti-HLA antibodies, six (6.5%) had a positive flow cytometry crossmatch at transplant. Three of these six (50%) [compared to only 4/86 (5%) with a negative crossmatch] developed severe, immediate graft dysfunction (radiographic infiltrates, P_aO_2/F_iO_2 <100, and rescue nitric oxide or extracorporeal membrane oxygenation) suspicious for hyperacute rejection, with one confirmed histologically [28].

Aside from hyperacute rejection, although several studies describe a worse prognosis associated with DSAs after LTx, there are limited data on the consequences of new (de novo) DSAs specifically in the post-operative period (Table 26.3). Le Pavec, et al. in a cohort study of 134 recipients evaluated DSAs as early as 7 days post-transplant, finding an association with CLAD, but immediate clinical outcomes were not assessed [29]. Snyder et al., in a cohort study of 441 recipients, found an association between de novo DSAs (detected as early as 19 days post-transplant) and both CLAD and death, but early outcomes were also not specifically evaluated [30]. To our knowledge only Ius et al. have examined the effect of DSAs in the immediate post-transplant period in a cohort study of 546 LTx recipients, where 100 (18%) developed de novo DSAs at a median of 14 days post-transplant. Those with de novo DSAs had a non-significant reduction in in-hospital survival (89% vs 93%, $p = 0.34$), along with significantly decreased 1-year survival (79% vs 88%, $p = 0.019$) [31].

With the exception of DSA testing supporting AMR, most literature on characteristic signs of acute rejection pertains to ACR (Table 26.4). However, the discriminatory performance of any individual sign is poor in general [17], and to our knowledge there are no studies defining the typical clinical (or radiographic) presentation of acute rejection specifically in the post-operative period, where many confounding issues are likely to make the appearance even less distinguishable (Fig. 26.2). In terms of radiographic findings more distant from transplant, authors have commented on the utility of ground glass opacities, interlobular septal thickening, consolidation, pleural effusions, and volume loss as possible ACR features, but there is general consensus that sensitivity and specificity of any individual finding is low. Park et al. evaluated high resolution computed tomography (HRCT) features of ACR in 26 patients undergoing 48 transbronchial lung biopsies (TBBx), and found significant associations between both interlobular septal thickening and ground glass opacities and rejection, with a combination of those findings 50% sensitive and 98% specific for ACR. However, mean time post-transplant to HRCT/TBBx in this study was 7.3 months, and it included only eight ACR events, with only one

Table 26.3 Studies evaluating the effects of post-lung transplant antibody associated episodes (positive crossmatch, development of new antibodies, rejection)

Author (year)	Study type	# of patients	Episode type (# of episodes)	Treatments	Results	Evidence quality
Campo-Canaveral de la Cruz (2012) [24]	Case report and review of literature	9	HAR (9)	Plasmapheresis Cyclophosphamide ATG Inhaled NO ECMO, Novolung Corticosteroids	6 of 9 patients died Deaths occurred 4 h to 13 days post-operatively.	Very low
Scornik (1999) [28]	Observational	92	+ Crossmatch (6) HAR (3)	NR	3 of 6 patients (50%) with + Crossmatch developed early graft failure suspicious for HAR. 1 of 3 patients with HAR (33%) died	Low
Le Pavec (2016) [29]	Observational	134	New DSAs by POD# 30 (82)	NR	DSAs at median fluorescence intensity scores ≥8 were associated with CLAD (HR 2.83, $p < 0.01$) and death (HR 2.71, $p < 0.01$).	Low
Snyder (2013) [30]	Observational	441	New anti-HLA antibodies (139) New DSAs (54)	NR	Median time to DSAs was POD# 52. Anti-HLA antibodies were associated with BOS (HR 1.54, $p = 0.04$) and death (HR 1.53, $p = 0.02$). DSAs were associated with death (HR 2.42, $p < 0.0001$).	Moderate
Ius (2014) [31]	Observational	546	New DSAs (100)	Plasmapheresis IVIG Rituximab	Median time to DSAs was POD# 14. 11% of patients with DSAs died before hospital discharge, versus 7% of those without DSAs ($p = 0.34$). 1- and 3-year survival in patients with DSAs was 79% and 57%, respectively (compared to 88% and 74%, $p = 0.019$).	Low

AMR Antibody mediate rejection, *ATG* Antithymoctye globulin, *BOS* Bronchiolitis obliterans syndrome, *CLAD* Chronic lung allograft dysfunction, *DSA* Donor specific antibody, *ECMO* Extracorporeal membrane oxygenation, *HAR* Hyperacute rejection, *HLA* Human leukocyte antigen, *LTx* Lung transplantation, *NO* Nitric oxide, *POD* Post-operative day

Table 26.4 Studies evaluating diagnostic modalities in the evaluation of pulmonary infiltrates in the immediate post-lung transplant period

Author (year)	Study type	# of patients	Diagnostic modality	Population and clinical event	Results	Evidence quality
Park (2014) [32]	Observational	26	HRCT	8 episodes of ACR HRCTs and TBBXs occurred at a mean 7.3 months post-transplant	Interlobular septal thickening and GGOs were associated with ACR ($p < 0.05$) HRCT (bilateral GGOs and interlobular septal thickening as the positive finding) was 50% sensitive and 97.5% specific for the diagnosis of ACR, with positive and negative predictive values of 80% and 90.1%, respectively	Very low
Gotway (2001) [33]	Observational	64	HRCT	64 HRCTs reviewed from patients within 6 months of transplant, 34 with ACR on TBBX, 30 without ACR	The combination of volume loss and septal thickening on HRCT was 100% specific for ACR HRCT was 35% sensitive and 73% specific for the diagnosis of ACR, with positive and negative predictive values of 60% and 50%, respectively No individual HRCT finding was significantly associated with ACR on TBBX	Very low
Burns (2003) [34]	Observational	41	Bronchoscopy with TBBX	Mechanically ventilated lung transplant recipients with acute respiratory failure undergoing TBBX and subsequent surgical lung biopsy	TBBX was 53.3% sensitive and 91.7% specific for the diagnosis of any ACR, with positive and negative predictive values of 94.1% and 44.0%, respectively A significantly higher histologic grade was seen on surgical lung biopsy compared with TBBX (mean 2.39 ± 1.02 vs 0.97 ± 0.11, $p < 0.0001$) Complications of biopsy: 2 tension pneumothoraces, 1 extrathoracic hemorrhage, 1 hemorrhagic pleural effusion	Low
Mohanka (2014) [35]	Observational	76	Bronchoscopy +/− Microbiologic sampling +/− TBBX	Patients admitted to the medical intensive care unit, median 7 months post-transplant 129 bronchoscopies with 20 TBBX were performed	Isolation of infectious pathogens led to modification in antimicrobial therapy in 35% of microbiological samples Acute lung injury was the most common histologic pattern on TBBX (70% of biopsies). ACR was found on 4/20 (20%) of TBBXs Complications of bronchoscopy: Hypoxia (3%) and hypotension (3%)	Low

ACR Acute cellular rejection, *GGO* Ground glass opacity, *HRCT* High resolution computed tomography scan, *TBBX* Transbronchial biopsy

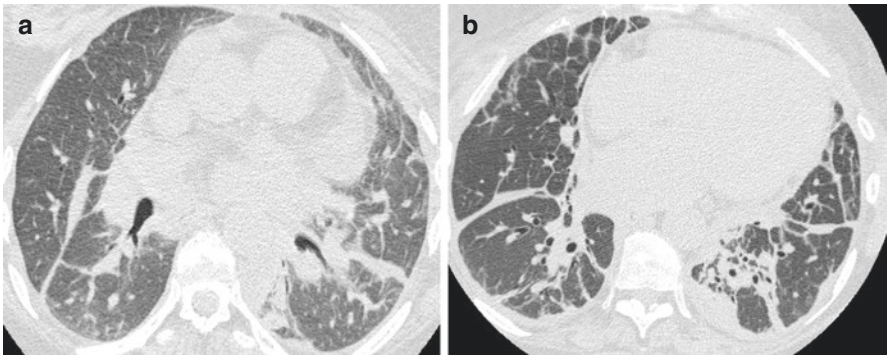

Fig. 26.2 60 year old woman post-operative day 9 after double lung transplantation for chronic obstructive pulmonary disease, with increasing oxygen requirement and dyspnea. (**a**, **b**) Axial computed tomography scan images show diffuse interlobular septal thickening and areas of ground glass opacity. B- and T-flow cytometry cross matches had been positive, and retesting of donor specific antibodies revealed newly positive IgG antibodies to class I human leukocyte antigens (highest median fluorescence intensity 11,200); Transthoracic echocardiogram revealed moderate diastolic dysfunction and mild mitral regurgitation, prompting treatment of both antibody mediated rejection and cardiogenic pulmonary edema with plasmapheresis, intravenous immunoglobulin, and diuretics, after which the patient improved and was weaned off oxygen on post-operative day 24

being in the 1st month after LTx [32]. Gotway et al. evaluated 64 recipients within 6 months of transplant, 34 of whom had ACR, and found that the overall sensitivity and specificity of HRCT was only 35% and 73%, respectively, with no individual HRCT finding associated with ACR [33].

Given the difficulties in diagnosing acute rejection with non-invasive means, by consensus bronchoscopy is the procedure of choice, with TBBx being the gold standard for diagnosis of ACR, and also providing ability to rule out airway complications and evaluate for infection. Despite the diagnostic benefits of bronchoscopy, there are limitations including sampling error and procedural complications, which may be more pronounced in critically ill LTx recipients [17]. Burns et al. evaluated the test characteristics of TBBx in 41 critically ill recipients receiving mechanical ventilation (time from transplant not reported), all of whom subsequently had surgical lung biopsy within 10 days which was used as the gold standard. Sensitivity and specificity for ACR were 53.3% and 91.7%, respectively, with TBBx also noted to underestimate the severity of more significant grades of ACR compared to surgical biopsy [34]. Mohanka et al. evaluated 129 bronchoscopies in LTx recipients admitted to the intensive care unit, 122 of 129 on mechanical ventilation, median time from transplant 7 months (12 days–154 months). Bronchoscopy was noted to be most helpful in this population for evaluating for airway complications and infections, changing management in 1/3 of patients, with complications including hypoxia (3%) and hypotension (3%). The yield of TBBx for ACR was 20%, with the most common histopathologic finding being acute lung injury [35]. How these data relate to critically ill patients in the immediate post-operative period are unclear, with no studies specifically evaluating the utility or safety of TBBx for rejection in this population.

Edema

With disruption of the pulmonary lymphatic drainage system during the lung transplant surgery, pulmonary edema is a common occurrence post-operatively. The distinction between cardiogenic pulmonary edema, PGD, and other early respiratory insults can be difficult to ascertain following LTx due to similar clinical presentations and frequently overlapping occurrences (Fig. 26.2). Post-transplant pulmonary edema can be precipitated by donor factors, recipient factors, and/or post-transplant clinical management practices. In donors, due to neuro-hormonal changes at the time of death as well as the frequent need for large-volume resuscitation in certain circumstances relating cause of death, lungs are susceptible to pulmonary edema at the time of organ donation, often despite optimal medical management. In addition, some donor factors such as smoking history have been found to increase the likelihood of pulmonary edema at the time of organ recovery. Ware et al. found that lungs from donors who were current smokers had more pulmonary edema as evidenced by significantly higher lung weights at the time of procurement than those lung recovered from non-smokers (median 408 g, IQR 364–500 vs. 385 g, IQR 340–460, p = 0.009) [36].

New or worsening pulmonary edema following allograft implantation can also be the result of various recipient factors including cardiogenic edema in the setting of myocardial infarction, post-operative atrial fibrillation, chronic diastolic dysfunction, valvular heart disease, or volume overload in the setting of significant acute kidney injury (Fig. 26.3). Although rare, pulmonary venous anastamotic complications

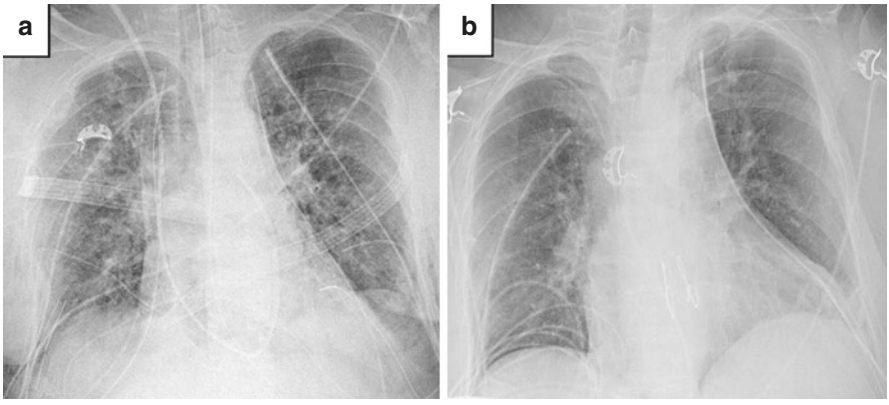

Fig. 26.3 64 year old woman status post-double lung transplantation for idiopathic pulmonary fibrosis, complicated by initial severe vasoplegia requiring fluid and blood product resuscitation. On post-operative day 5 she developed increasing oxygen requirementswhile on mechanical ventilation, also in the setting of new onset atrial fibrillation. (**a**) Post-operative day 5 chest radiograph reveals diffuse airspace opacities suggestive of pulmonary edema. After aggressive diuresis and antiarrhythmic management of atrial fibrillation the patient improved, allowing for extubation and weaning from supplemental oxygen, with (**b**) chest radiograph on post-operative day 10 demonstrating improved opacities

should also be considered [37]. In addition, lung transplant recipients may require large volume resuscitation with blood products and/or fluids intra-operatively or immediately post-operatively that can also contribute to pulmonary edema, even in the absence of overt structural heart disease. To our knowledge there are no data outlining the optimal diagnostic strategies pertaining to early pulmonary edema after LTx. From a management standpoint, keeping in mind normal post-transplant lymphatic disruption, general consensus favors a restrictive/conservative fluid management strategy in the early post-operative period in an attempt to mitigate pulmonary edema and the resulting respiratory compromise [3, 38].

Recommendations

In post-operative LTx recipients with respiratory compromise and pulmonary infiltrates, there is a need for clinicians to quickly recognize and manage the wide array of possible complications including infection, rejection, pulmonary edema, PGD, bleeding, and venous thromboembolism. There are limited data providing guidance in this period, with clinical signs of these entities lacking diagnostic specificity and often carrying a great deal of overlap. Consideration must be made for risk factors stemming from a variety of sources including those relating to the donor (predonation pulmonary edema or infection), perioperative issues (prolonged ischemic time, significant bleeding requiring resuscitation), contributing recipient factors (chronic pulmonary colonization, mismatch HLA), and post-operative consequences (nosocomial infection, postoperative atrial fibrillation, excessive fluid administration).Often multiple diagnostic possibilities will need to be considered and managed simultaneously. In a post-lung transplant recipient, a reasonable approach is to consider additional thoracic imaging such as CT, bronchoscopy for airway inspection and BAL sampling (+/− TBBx depending on time of infiltrate and concern for ACR), and measurement of circulating DSAs particularly in recipients with a positive post-transplant crossmatch or pre-transplant sensitization (Fig. 26.4). Overall management considerations include using a conservative fluid management strategy with diuresis if deemed clinically appropriate, lung-protective ventilation in patients requiring mechanical ventilator support, and broad-spectrum antimicrobial administration if there is significant concern for infection.

Personal View of the Data

Although outcomes have improved, lung transplantation remains an evolving field, with few existing randomized controlled trials addressing many important clinical questions. In regards to assessment and management of early post-lung transplant pulmonary infiltrates, the data are limited to primarily single-center retrospective reviews, case series, or case reports, and thus general consensus and clinical expertise

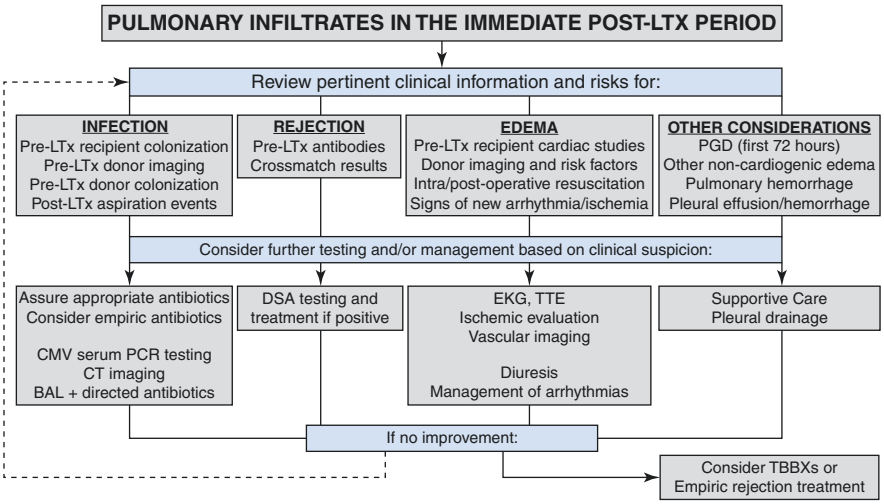

Fig. 26.4 Algorithmic approach to pulmonary infiltrates in the immediate post-lung transplant period. (BAL Bronchoalveolar lavage, CMV Cytomegalovirus, CT Computed tomography scan, DSA Donor specific antibody, EKG Electrocardiogram, LTx Lung transplantation, PGD Primary graft dysfunction, TBBX Transbronchial biopsy, TTE Transthoracic echocardiogram)

are needed in these situations. Larger, multicenter, prospective studies are greatly needed to delineate the optimal approach in this very important period after lung transplantation.

Recommendations (Graded)

1. For lung transplant recipients in the immediate post-operative period with respiratory compromise and pulmonary infiltrates, we recommend a review of clinical risk factors for infection, pulmonary edema, and rejection, which should include donor and recipient cultures, donor imaging, crossmatch results, and preceding post-transplant clinical events (evidence quality low; strong recommendation).
2. For lung transplant recipients in the immediate post-operative period with respiratory compromise and pulmonary infiltrates, we recommend a diagnostic strategy guided by clinical risk factors, to include serum cytomegalovirus testing, as well as consideration for computed tomography imaging, bronchoscopy with bronchoalveolar lavage, donor specific antibody testing, electrocardiogram, and echocardiography (evidence quality low; weak/conditional recommendation).
3. For lung transplant recipients in the immediate post-operative period with respiratory compromise and pulmonary infiltrates, we recommend ensuring adequate antimicrobial coverage based on culture data, induction immunosuppression to prevent rejection, and use of a conservative (low CVP) fluid management strategy as tolerated by hemodynamics, while monitoring for clinical improvement (evidence quality low; strong recommendation.

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Chapter 27
Clearance of Pulmonary Secretions After Lung Transplantation

Christopher H. Wigfield, Ankeeta Mehta, and Charles Alex

Introduction and Definition of Pulmonary Secretions

Bronchial and pulmonary secretions are expected after lung transplantation, a well established therapeutic option in end stage lung disease [1–3]. They may be defined as any substance or fluid present in the airway or alveolar space. This includes physiologic secretions of the resident mucosa and pathological accumulation from other sources or extrinsic matter. Additionally, a functional biofilm exists and maintains a delicate balance. Excessive production of bronchial secretions as well mucostasis in the airways may result in impaired patency at various levels of the respiratory tract or the alveoli. The current practice in critical care is not generally supported by evidence based principles. A paucity of specifically designed trials and application of only marginally relevant findings from other cohorts studied is responsible for this lack of evidence based medicine.

In order to provide a rational application of the possibly useful data available, we have to consider the physiological basis of secretions and the clinical imperative to manage these in the clinical setting.

Search Strategy

The search strategy included access to several online libraries with the initial search for relevant literature conducted via PubMed.gov with search terms *pulmonary clearance, bronchial secretions; lung transplantation; critical care;* this search

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Table 27.1 PICO table of clearance of pulmonary secretions after lung transplantation

PICO strategy
Patient population: adult, recipient, post-op lung transplantation, ICU
Intervention: bronchoscopy, pulmonary toilet
Comparisons: standard of care – suctioning, adjuncts and chest physiotherapy
Outcomes: lung transplant graft function, ventilation time, survival

provided 225 articles. The detailed review of these revealed a paucity of specific relevance to the topic. The available Cochrane Library reviews were assessed for applicability of trials conducted in this field and these are discussed in the text below where appropriate (Table 27.1).

A GRADE assessment could not be coherently applied. There is virtually no directly applicable trial based medical research data available for best "management of secretions" in the lung transplant population. As such, this review discusses the underlying clinical issues with the recognition that lung transplantation requires further research in this field for appropriate evidence based recommendations in the future. The quality of the data in the papers evaluated was assessed according to the GRADE principles as much as feasible and recommendations provided accordingly.

Results

Pathophysiology of Secretions in Lung Transplantation

Improving airway clearance from pulmonary secretions has a pathophysiological imperative. As summarized in Table 27.2, three clinical phases of airway optimization exist in this process: the ***first effort*** is directed at donor optimization, the ***second focus*** is the peri-operative management (i.e. the transplant procedure related practice) and the ***third period*** is related to extubation and maintenance of airway clearance thereafter. In order to appreciate the need for airway optimization in these patients, it is useful to review the multiple mechanisms that influence airway secretions and patency (see also Table 27.3).

Mucous Build-Up

Marked mucous build up occurs in donor airways. This is likely multifactorial in nature and requires careful clinical assessment. Airway clearance will be ineffective in donors after neurologic determination of death [4]. Several factors will increase the presence of secretion buildup of intubated and ventilated donors. The *donor*

Table 27.2 Key issues and clinical interventions for airway clearance during the three phases in lung transplantation

	Key issues	Clinical interventions
Donor airway optimization	Aspiration material	Bronchoscopy
	Ventilator related issues	Fluid balances
	Respiratory tract infection	Antibiotics
	Atelectasis	Ventilator modes
Peri-operative transplant related period	Ischemia reperfusion injury	Logistic optimization
	Bronchial anastomosis	Technical optimization
	Airway contamination	Bronchoscopy
Extubation and maintenance of airway clearance phase	Secretion build up	Preventative measures
	Mucosal edema	Pulmonary hygiene
	Epithelial sloughing	Daily physiotherapy
	Purulent accumulation	Bronchoscopy
	Micro aspiration	Early ambulation, positioning

Table 27.3 Factors influencing airway and airspace patency during and after lung transplantation

	Secretory substance	Patency changes
1. Airways	Mucous build-up	Inflammatory responses
	Biofilm changes	Airway edema
	Epithelial sloughing	Aspiration material
	Purulent material	Airway debris
	Reflux material	Anastomotic issues
		Bronchio-malacia
2. Airspaces	Innate immune responses	Loss of alveolar integrity
	Cytokine gradients	Neutrophilic sequestration
	Neurogenic edema fluid	Hemmorhagic alveolitis
	Transudative capillary filtrates	Atelectatic collapse
3. Other	Microbiome alterations	Tracheomalacia
	Volume status	Hypoventilation
	Upper respiratory tract contamination	Patient sedation
		West zones distribution

bronchoscopy may achieve variable degrees of temporary clearance from such pre-existing "secretions". The emphasis in the donor assessment is frequently on noting the amount and quality of the observed airway matter present. Differential diagnostic cultures to isolate potential pathogens are sent for subsequent planning of treatment strategies in the recipient [5, 6]. The donor bronchial clearance, however, is essential for adequate lung allograft preservation to take place. Lungs should be transported in a sufficiently aerated and expanded manner. Segmental atelectasis and lobar collapse due to obstructive material alters the tissue milieu and can be propagated into the post-transplant phase if not sufficiently addressed at the

procurement. Recipient pulmonary clearance therefore starts with best lung recovery and procurement practice.

Ischemia and Reperfusion

Pathophysiological events during the ischemia and reperfusion process include multiple factors that impact the bronchial epithelium, other airway tissues and the terminal air spaces. Cold preservation during ischemia reduces the metabolic rate, but inexorably the mucosal integrity is disrupted. Reperfusion of the airways does not occur *via vasa privata* of the bronchial circulation as these are not routinely re-anastomosed. This results in indirect re-perfusion with macroscopically notable airway inflammation present after transplantation. Within 48 hours after ischemia, significant superficial mucosal sloughing can be observed and circumferential epithelial erythema and edema of the airway may be present. Deliberate and comprehensive airway clearance is considered essential in this phase after lung transplantation to avoid luminal obstruction and secondary allograft consequences.

Innate Immune Responses

Transplanted lungs and airways are subject to a spectrum of immunogenic responses. This may result in primary graft impairment and can be evident in airway responses [7]. It is important in this context to recognize the absence of a fully functional lymphatic drainage system in the transplanted lung allografts.

Additionally, diffuse involvement of airspaces and lung parenchyma may develop. Innate immune responses produce neutrophilic cellular sequestration in alveolar spaces due to cytokine gradients. These likely aggravate the airway conduit related issues. Additionally, recent experimental data suggests that the integrity of airways may suffer due to immunosuppressive agents [8]. Resident alveolar cells secrete substances involved in the tissue repair mechanisms of the injured lung. Surfactant precursors have to be excreted for the re-generating lung to be functional. A protracted need for air-space reconstitution and maintaining patent conducting airways exists in this setting.

Airway Reactivity

The innervation of the airway is altered after transplantation. Parasympathetic vagal branches and visceral postsynaptic sympathetic branches to the pulmonary plexus are severed during the recipient pneumonectomy [9–13]. The loss of innervation does not allow for effective visceral autoregulation and this affects airway clearance. While loss of the cough reflex was once considered permanent, recent evidence indicates functional and structural restoration is a time-dependent process that occurs 6–12 months after lung transplantation. Cholinergic mucosal

hyperreactivity has been shown in this setting [14]. Pharmacologic stimulation of bronchial glands after postganglionic disruption has been reported. Additionally, even transient neuropraxia may impair phrenic and intercostal nerves with less than effective expectoration present after lung transplantation.

Smooth muscle fibers of sub-segmental respiratory alveoli as well as bronchioles without cartilaginous support may encounter airway spasm with occlusion secondary to noxious stimuli or due to mechanical causes [15]. The absent intrinsic cough reflex will confound the situation further. Precautionary and early supportive measures are mandatory to maintain adequate broncho-pulmonary clearance. This requires active support and daily clinical care plans adjusted to individual patient needs.

Microbiome Changes

The human microbiome is currently under much scientific scrutiny. The lung and airways harbor an individual microbiome with a selective continuity of bacterial populations, even in the healthy state [16]. Current clinical evaluation is restricted to isolating known pathogens responsible for significant respiratory tract infections in the immunosuppressed patient. Bronchial secretions are commonly increased in presence of bacterial and viral pathogens. Airway pathogens may cause excessive secretions ranging from thin bronchorrhea to frank purulence. As the properties of infective airway material can vary dramatically, the clearance methods are adjusted. Pseudomonas species are particularly adherent and difficult to eradicate, for example. The viscosity of the biofilm may be altered and antibiotic treatment may in turn alter the pathobiome. Frequent re-evaluation with cultures and sensitivities is required to allow for restoration of stable airway status. Lung allografts differ in this respect from other solid organs transplanted and the environmental exposure to acquired pathogens is particularly concerning in the hospital setting.

Clinical Approach to Minimize Secretion Accumulation and Optimize Clearance in the Post Lung Transplant Care Phase

Systemic Measures

The physiological need for balanced mucosal moisture and normal secretions of the respiratory tract should be recognized. The presence of a topical biofilm along the upper airways is well established and should be maintained [17]. Minimizing the dysregulation of this complex balance includes preventative measures to avoid airborne disease transmission. Tissue repair must be supported with nutritional essentials. Conversely, an abundance of pulmonary secretions requires consideration of

the patient's systemic factors. A euvolemic state, adequate osmolality and oncotic vascular pressure are important variables to consider.

General deconditioning, pre-transplant frailty and elevated body mass index are detrimental in the early recovery phase and must be addressed simultaneously to improve the chances of improved outcomes with airway measures. Similarly, the role of CNS function supports the notion of early withdrawal of sedative medications and providing non-narcotic analgesia wherever feasible.

Topical Factors

The mucociliary clearance of the donor airway is defective after lung transplantation. The loss of effective cephalad promotion of debris and redundant secretions can be detrimental. Airway irritation and injuries may occur after interventions, and may be focal—including bronchial anastomoses sites, or more diffuse, such as due to inhaled irritant substances or micro-aspiration. High flow oxygen can induce notable mucosal changes. Optimization of the recovery and avoiding caustic insults is a pre-requisite for recovery. The assessment of sputum samples obtained after topical changes (e.g. via broncho-alveolar lavage fluids) in turn allow for some extrapolation how to optimize the recipient's general fluid status, for example. High viscosity of secretions may require increasing the fluid balance.

Airway Clearance Principles

It is critical to recognize that clearance mainly provides reduction of obstructive effect from conducting airways i.e. the anatomic dead space. This is commonly achieved to only the first few orders of lobar bronchi. Some distal residual is inevitable due to suctioning resulting in sub-segmental occlusion pressure of the bronchioles. There may be little effective removal of contaminants or infective material beyond this and this is affecting large surface area. Resolution of such alveolar space processes and terminal airway involvement may require local macrophagocytosis or effective cephalad transport of secretions.

Best Airway Clinical Practice

Best practice principles for *pulmonary hygiene* have been debated in ventilated patients and assessed in post-operative patients. Airway clearance techniques (ACTs) are frequently advocated post lung transplantation and may facilitate expectoration of sputum. Most studies are in bronchiectatic disease processes. The short term utility and treatment effect on selected lung function parameters is less well documented in the

literature [18]. It achieves only low level for recommendation. A paucity of data exists specifically regarding lung transplantation. The available information, extrapolated from other patient populations may not be directly applicable. This therefore currently achieves only a very low level recommendation on basis of the available studies. Several key components of clinical practice have to be considered in this context.

A competent and protected upper airway is clearly essential and the absence of dysphagia must be ascertained [19]. Aspiration with subsequent pneumonitis or pneumonia represent a major source of morbidity in recipients after lung transplantation. Promoting best pulmonary hygiene and *preventative measures* must be the primary step. It is desirable to *avoid the clinical consequences of secretion build up in the first place.*

Adjuncts play an important role in the patient self-directed care. Some devices require learning and basic ability to utilize these on a regular basis. Supportive measures should complement patient efforts to achieve compliance and desired airway clearance. Respiratory mechanics are typically clinically supported. Diaphragmatic impairment, irrespective of etiology, is a key determinant of patient ability to achieve airway clearance after lung transplantation. Posture and positioning is often considered essential for facilitation of airway clearance and effective participation in respiratory care maneuvers (Table 27.4).

Adjuncts to Facilitate Improved Airway Patency

Extubation Protocols

Standardized extubation protocols should be followed in the critical care phase after lung transplantation. Evaluation of parameters to ensure a competent airway, sufficient cough and successful pressure support and spontaneous breathing trial will reasonably predict sufficient effort be maintained after extubation [20]. Cough augmentation techniques may be useful, but the limited evidence available is based on non-transplant cohorts [21]. The applicability and generalizability are frequently presumed but not actually confirmed by specific trials in lung transplantation. Commonly, clinical protocols are in place to promote good practice based on generic understanding of the known clinical challenges.

Applied Respiratory Therapy

Respiratory therapy procedures have long been advocated to improve mobilization of airway secretions in this phase [22]. Methods used by physiotherapy services include autogenic drainage, oscillating respiratory devices and positive expiratory pressure support which all appear to improve airway clearance in the short-term by increasing mucus transport [23].

Table 27.4 Studies of airway physiology after lung transplantation

Author	N in study	Disease studied	Problem discussed	Intervention assessed	Results	Type of study
Herve et al. [9]	13	Lung transplant recipients	Bronchial mucociliary clearance	Radioaerosol deposition technique versus normal controls	Significant impairment of mucociliary function	Small, controlled cohort study
Higabottam et al. [10]	7	Lung transplant recipients	Airway denervation	Nebulized distilled water bronchial response	Significant diminished cough response	Experimental case series
Duarte et al. [11]	7	Lung transplant recipients	Restoration of cough reflex	Longitudinal eval of cough frequency s/p lung transplantation	Absent cough reflex at 1.5 weeks distal to anastomosis; restored at 12 months	Non-randomized cross-sectional observational cohort study

Upright positioning and postural drainage have been a mainstay of chest therapy to improve airway clearance for decades [24]. Strategy implies that removal of excessive airway secretions is a benefit to respiratory mechanisms, gas exchange and recovery time from pulmonary processes. Both, the quantities of secretions extracted as well as the clinical evidence of airway clearance obtained were initially used as indicators of this approach being effective. The biological concept may be more complex as the inflammatory and innate immune response triggers may well be positively impacted and the dynamics of recovery from variable pathological states of the lungs may differ dramatically.

Adjunct devices play a role in the daily clinical management of airway clearance. Spirometry techniques employing handheld mechanical devices (an 'incentive' spirometer) are frequently used to reduce pulmonary complications during postoperative care after extubation [25]. Incentive Spirometer use evidence is limited, but this strategy is currently a prevalent 'preventative' clinical practice [26]. The relative risks or odds ratio without such clinical practice is not currently established. As cost effectiveness is not considered in clinical evidence based evaluation intervention, this adjunct is likely to persist despite methodological variations.

Flutter valve use to augment patients' independent airway clearance has been a long established adjunct [27]. The particular advantage with this kind of device is the elimination of the therapist's presence for application [28]. There is virtually no prospective lung transplant patient data to base recommendation levels on for these devices in widespread clinical use.

Inhaled Pharmaceutical Agents

A detailed overview of the clinical use of mucolytic agents that may promote airway clearance is available elsewhere [29]. Several agents have been included in protocolized approaches. Mostly applied from other pulmonary disease processes or from ventilator treatment trials, their effectiveness has not been conclusively assessed in the lung transplant population. Albuterol derivatives are included in many treatment regimens after lung transplantation. They are frequently used in isolation or as a combination therapy. Evidence for the broncho-dilator effect is reasonably well established in chronic obstructive airway dynamics, but the contingent impact on clearing secretions remains unproven.

Inhalation of hypertonic saline which has been shown to enhance mucociliary clearance in cystic fibrosis patients with some trials confirming improved lung function [30]. The optimal dosage and timing of administration in normal and transplanted lungs is less well established [31].

Therapeutic aerosols to improve innate resistance to microbial infection or achieve cytokine profile changes have been studied. These may potentially boost immune function and delivery of antibiotics, but are not often included in protocols after lung transplantation [32]. Inhaled antimicrobials may be underused, especially in patients with difficult-to-treat lung infections after lung transplantation. More

specific prospective evidence is required for such practice to be considered evidence based.

Mucostasis and an inflammatory milieu result in protracted secretion build up [33]. Other inhaled pharmaceuticals frequently used, include recombinant human deoxyribonuclease or DNase (rhDNase or Dornase). DNase has been shown to be an effective agent to reduce the viscosity of purulent secretions [34]. Mostly assessed in chronic bronchitic diseases and in cystic fibrosis, some indication for use may exist in the lung transplant patient population. Evidence if Dornase ALPHA is superior to hyperosmolar agents in improving overall lung function is lacking [35]. After transplantation for Cystic Fibrosis, the residual native respiratory tract promotes recurrence of muco-infective airway disease. Inhaled Amphotericin is frequently used in perioperative transplant protocols. It has caustic properties and is associated with poor patient tolerance but appears to be effective as preventative strategy. The evidence is inconsistent and generalizability to lung transplant population remains unclear (Table 27.5).

Interventions to Support Differential Diagnosis and Maintain Pulmonary Clearance for Airways and Lung Allografts

Non-invasive measures to support airway clearance are the first step in the treatment options for airway secretions [36]. Patients with atelectasis from mucous plugging or due to hyper-secretory states or secondary to pain from the thoracotomy may benefit from a variety of airway clearance methods. When implemented appropriately, basic techniques employ active cycle of breathing practices and use positive expiratory pressure and autogenic drainage, when positive pressure ventilation has not been effective [36].

Where recipient deconditioning is a concern or in the presence of neuromuscular impairment worsening sputum retention, Continuous Positive Airway Pressure (CPAP) may support with better air flow rates and cephalad clearance [37]. Manual percussion or use of vibratory or ultrasound based devices may be helpful for maintenance of clearance [27]. Evidence is reasonable, but contraindications may exist.

The complexity increases in patients with prolonged mechanical ventilation [38]. Management of sputum retention ideally would be a protocolized approach. Maintaining the residual mucociliary clearance function of the native airways, as well as established in line suction for secretion removal and humidification are the basic principles. Debris and secretions are often removed with inline suction devices [39] and established practice of care should be applied to the lung transplant patient population.

The risk to the healing bronchial anastomosis of blind passes of the tubing should be recognized and minimized. Research efforts are considering catheter coating materials to inhibit the biofilm formation of pathogens on surfaces to prevent nosocomial respiratory tract infections [40].

Table 27.5 Selected studies of interventions for of airway clearance

Author	Number of subjects/ studies	Disease studied	Problem discussed	Intervention assessed	Results	Type of study
Warnock et al. [23]	N/A subjects, (in 8 studies)	Cystic fibrosis	Chest physiotherapy	Multiple techniques and interventions to support expectoration and Pulmonary function tests	Conflicting results re: expectoration improvements weak evidence for FEV1 and FRC improvement	Systematic Cochrane review
Freitas et al. [26]	592 subjects	Postoperative coronary artery disease patients	Incentive spirometry utility after CABG surgery in addition to positive pressure breathing techniques	Inspiratory and expiratory pressures with incentive spirometry added to standard therapies	No additional benefit on respiratory muscle improvement	Cochrane database review
Sathe, N A et al. [29]	379 subjects (in 9 studies)	Variable lung diagnoses, (all non-cysticfibrosis)	Pharmacological agents to promote pulm. clearance	Acetylcysteine, variable administration and combination therapies	Conflicting data reported for heterogenous outcomes measures (sputum production; pulmonary function; atelectasis	Systematic review of RCTs
Wark et al. [30]	235 subjects (in 9 studies)	Cystic fibrosis	Inhaled hypertonic saline treatment twice daily	Bronchial clearance C/W deoxyribonuclease treatment	Improved FEV1 and clearance C/W placebo; inferior to DNAse	Systematic Cochrane review
Yang et al. [35]	2565 subjects (in 9 studies)	Cystic fibrosis	Dornase alpha use as mucolytic therapy versus placebo or hyperosmolar agents	Longitudinal effect on lung function improvement and clinical exacerbations	Decrease of pulmonary exacerbations; unclear if superior to hyperosmolar agents	Systematic Cochrane intervention review

Bronchoscopy Indications

Mucous may frequently exceed the normal amount and consistency in the airway after transplantation. Several factors dispose to inspissated forms that accumulate and obstruct segmental or lobar bronchi [41]. Such airway "plugging" requires early intervention to re-establish aeration of the affected zones. Secondary consequences of atelectasis and reactive effusion as well as post-obstructive pneumonia are significant morbidities in lung transplant recipients and best avoided. Bronchoscopy under either conscious sedation or general anesthesia provides assessment and removal of airway material as required in some cases where conservative methods to expectorate have failed. Clinicians may be able to perform this procedure with topical 4% lidocaine anesthetic. The pros and cons of this invasive measure must be considered carefully, but a proactive approach by an experienced bronchoscopists is often justified. Direct regional visualization and correlation with imaging studies facilitates clinical care decisions in this process. The evaluation of the epithelial integrity and the importance of biofilm alterations require lobar visualization and selective sampling [42].

Commonly, a scheduled bronchoscopy for surveillance of the anastomotic healing and detection of cellular rejection occurs within the 1st weeks after transplantation, if necessary in the ICU setting in prolonged critical care phases. A formal bronchio-alveolar lavage (BAL) should be obtained. The techniques to obtain adequate uncontaminated lower respiratory tract secretion samples for bacterial culture and viral assays has long been established [43]. Procedurally, it is important to overcome collapsing pressure with intermittent suction and use of bronchodilators.

Lower respiratory tract infections can occur *early* after lung transplantation and may result in purulent and adherent airway secretions. Their overall management requires specific mono- or poly-antimicrobial therapy. The evidence for treating upper and lower respiratory tract infections is well established within this patient population in the presence of immunosuppression. Selective cultures should be provided from bronchoscopy and alveolar lavages obtained for microbiocidal sensitivities of the isolated pathogens [44, 45]. Strong recommendations for this exist and are not the subject of this review.

Summary and Recommendations

Bronchial and pulmonary secretions after lung transplantation are multifactorial in etiology and a significant clinical challenge. There is a dearth of evidence to guide best management of lung transplantation recipients in this clinically complex issue. Strict application of the GRADE assessment for the available evidence for the lung transplant recipient is currently not feasible. In the absence of any randomized controlled trials or prospective study data in *this population*, applied information is of low and very low quality. Recommendations therefore have to recognize the potential for lack of transferable validity from other study populations. The clinical

decision making is therefore not currently sufficiently supported by evidence base derived from germane publications. Extrapolations from relevant other cohorts form the bulk of the evidence discussed.

Few of the current practices and protocols are therefore based on *specifically* supported recommendations in *this patient population*. It is important to recognize, however, that pulmonary secretions in lung transplant recipients require individual clinical assessment. To manage these patients proactively requires to some extent an *application of evidence from other cohorts*, despite methodological flaws and limited applicability for the lung transplant recipient population. Conclusive research may not currently exists even for the broader *non-transplant respiratory* disease patients for in this specific area of critical care medicine. Several Cochrane analyses and systematic reviews provide some useful assessment of clinical studies with rather variable consistency of outcomes. A notable lack of generalizability from other pulmonary disease patient populations remains.

As the available evidence in this setting is problematic, it requires prospective research with appropriate directness in lung transplant recipients to establish which interventions and adjuncts may have adequate effect size to influence outcomes.

Recommendations

- Because of decreased bronchial clearance and a reduced cough reflex following lung transplantation, deliberate and comprehensive airway clearance is essential. (Quality of Evidence high and Level of Recommendation weak).
- Chest physiotherapy (upright positioning, postural drainage, oscillating respiratory devices and positive expiratory pressure support) are advocated to improve mobilization of airway secretions. (Quality of Evidence low and Level of Recommendation weak).
- Adjunct devices such as incentive spirometry and flutter valves play a role in daily clinical management of airway secretions. (Quality of Evidence low and Level of Recommendation weak).
- Pharmacological agents such as mucolytics, inhaled hypertonic saline and rhDNase, can be used to promote airway clearance. (Quality of Evidence low and Level of Recommendation weak).

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Part VII
Electrolytes and Nutrition

Chapter 28
Perioperative Nutrition Support in Cardiothoracic Surgery

Krishnan Sriram

Introduction

Nutrition is often neglected in medical school curricula, as well as in residency and fellowship training. This chapter will explain the new definitions of malnutrition and the need to address it both during the preoperative period as well as the immediate postoperative period. Early attention to nutritional needs of the patient in the ICU has been shown to decrease complications. The focus of this chapter will be on enteral nutrition (EN) (by mouth or via tubes) rather than parenteral nutrition and limited to adult patients. Discussions will emphasize practical aspects to increase tolerance to enteral feeding in patients undergoing procedures on the heart, great vessels, lungs and esophagus.

Search Strategy

The format for research follows the PICO Model (Table 28.1). Searches were performed in PubMed and Google Scholar as well as in the nutrition journals of: JPEN (Journal of Parenteral and Enteral Nutrition), Nutrition in Clinical Practice, Nutrition, Clinical Nutrition and various critical care journals. The key words for the searches included: "nutrition AND postoperative care AND cardiac surgery" and "nutrition cardiothoracic ICU."

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Table 28.1 PICO table of nutritional therapy in the CT ICU

P	I	C	O
Patients	Intervention	Comparator	Outcomes
Adult, cardiothoracic patients in the ICU	Early post-operative enteral nutrition	Routine feeding (delayed)	Post-op early mobilization, ventilation time, ICU LOS, QOL

Results

Elusive Definitions of Malnutrition

The ill effects of malnutrition in surgical patients are numerous: poor wound healing, increased anastomotic leaks, infectious complications and pulmonary problems [1]. Vague definitions of malnutrition have been one of the reasons for why nutrition-related issues in hospitalized patients have been neglected in the past. Decades ago, reliance was placed on anthropometrics (such as mid arm muscle circumference, weight loss), skin testing for energy, and laboratory tests (lymphocyte count, visceral protein levels). These concepts have essentially been abandoned. Disease – related malnutrition based on inflammation has also been proposed but there are no easy diagnostic tools to quantify levels of inflammation or immunity. Recently, major societies and institutions joined forces to simplify the definition of malnutrition, based on etiology [2]. Two of the following six criteria are sufficient to make a diagnosis of malnutrition: Insufficient energy intake; Weight loss; Loss of muscle mass (sarcopenia); Loss of subcutaneous fat; Localized or generalized fluid accumulation that may sometimes mask weight loss; Diminished functional status as measured by handgrip strength (Table 28.2) [2].

There is no place for laboratory tests to identify malnutrition or to monitor the success of nutrition therapy. There is no such term as “nutritional lab tests”. Although low serum albumin levels are associated with postoperative complications, routine measurements have low sensitivity and specificity and will not modify nutrition-related management plans [3]. Although the diagnosis of malnutrition is still elusive [4], the recent recommendations have made it easier to diagnose and document malnutrition, both preoperatively and during hospitalization. The new International Classification of Diseases (ICD) – ten codes have several codes for malnutrition and related clinical conditions, as listed in Table 28.3 [5]. The need for preoperative nutrition risk stratification in adult cardiac surgery and a rational approach to nutritional support approach have been recognized by the surgical community, as evidenced by a recent consensus statement from an international expert group [6].

Table 28.2 Identification of malnutrition by clinical characteristics. Two of six criteria are needed for the diagnosis of malnutrition

Clinical Criteria for diagnosis of malnutrition:
Insufficient energy intake
Weight loss
Loss of muscle mass
Loss of subcutaneous fat
Localized or generalized fluid accumulation
Diminished functional status

Data from [2]

Table 28.3 Common International Classification of Diseases (ICD)-10 codes associated with malnutrition

ICD-10 code	Diagnosis
E43	Unspecified PCM
E44.0	Moderate PCM
E44.1	Mild PCM
E46	Unspecified PCM
E64	Sequelae of PCM
M62.5, 62.84	Sarcopenia

https://www.cdc.gov/nchs/icd/icd10cm.htm
Abbreviation: PCM protein calorie malnutrition

Preoperative Nutrition Assessment

All patients scheduled for elective surgery must have a formal nutrition assessment considered to be as important as cardiology or anesthesiology "clearance". Simple and easy to use screening tools are available such as the well-validated Malnutrition Screening Tool [7–10] (Table 28.4). Patients who screen positive undergo a further assessment based on history and a nutrition-focused physical examination without any reliance on laboratory tests or anthropometric measurements.

Malnourished patients should be provided oral supplements for at least 7–10 days prior to surgery. Early publications emphasized using immune-formulas, the exact definitions of which are not standardized. A more recent meta-analysis clearly showed that any standard polymeric formula will suffice. Preoperative use of oral nutritional supplements has been shown to decrease complications and length of stay [11].

Nutritional Aspects of ERAS®

Although the initial studies were on patients with upper gastrointestinal (GI) malignancies, these efforts have been extended to all patients. Even patients undergoing

Table 28.4 Malnutrition screening tool (MST)

Step 1	
1. Have you/the patient lost weight recently without trying?	
No	0
Unsure	2
If yes, how much (kg)?	
1–5	1
6–10	2
5–11	3
>15	4
Unsure	2
Weight loss score: _____	
2. Have you/the patient been eating poorly because of a decreased appetite?	
No	0
Yes	1
Appetite score: _____	
Weight loss and appetite scores =	
MST score _____	
Step 2	
Score to determine risk	
MST = 0 or 1: NOT at risk	
MST = 2 or more: AT RISK	
Step 3	
Action for score 2 or more:	
Implement nutrition interventions	
Perform nutrition consult within 24–72 h,	
Weigh patient's on admission and re-screen patients:	
(a) Weekly (acute)	
(b) Monthly (long-term care)	

Data from [7]

orthopedic surgery benefit from oral nutritional supplements. Cost-analysis studies have shown this intervention to be highly cost-effective [12]. An attempt to correct malnutrition, even partially, prior to procedures, is even more important in patients scheduled for esophageal surgery. Protein intake seems to be an important contributing factor to the benefits of oral nutritional supplements, in addition to micronutrients in appropriate dosages and bioavailable forms.

Enhanced Recovery After Surgery (ERAS®) protocols were first established for colorectal surgery [13], then rapidly advanced to all GI surgery and non-GI procedures. This has now been expanded to cardiac surgery too and referred to as ERACS® protocols [14]. Protocols to facilitate early ambulation, limiting narcotics for pain management, and early oral or enteral feeding are important components of both ERAS® and ERACS® protocols. These evidence-based protocols address surgical stress and ways to prepare the patient for surgery, decrease intraoperative stress, maintain postoperative homeostasis including minimizing insulin resistance [15].

Table 28.5 Potential elements for nutrition bundles

Nutrition bundle
Assess patients on admission to the ICU for nutrition risk and calculate both energy and protein requirements to determine goals of nutrition therapy
Initiate EN within 24–48 h following the onset of critical illness and admission to the ICU and increase to goals over the 1st week of ICU stay
Take steps as needed to reduce risk of aspiration or improve tolerance to gastric feeding (use prokinetic agent, continuous infusion, chlorhexidine mouthwash; elevate the head of bed; and divert level of feeding in the gastrointestinal tract)
Implement enteral feeding protocols with institution-specific strategies to promote delivery of EN
Do not use gastric residual volumes as part of routine care to monitor ICU patients receiving EN
Start parenteral nutrition early when EN is not feasible or sufficient in high-risk or poorly nourished patients

Data from [18]
Abbreviation: EN enteral nutrition

Fleming has shown that ERACS® is feasible and has the potential for improved postoperative morbidity after cardiac surgery, although large scale studies are lacking [14]. ERACS has been shown to significantly decrease the mean postoperative length of stay [4.05 (SD 1.43) days compared to 5.4 (SD 1.17)] days in the non-protocolized group [16]. ERAS® protocols have even been shown to decrease cardiovascular complications (including myocardial injury after non-cardiac surgery or "MINS") in non-cardiac surgery [17]. Several concepts emphasized in ERAS® protocols conflict with time-honored but unproven practice patterns. Surgeons are urged to spearhead interdisciplinary quality improvement initiatives to change institutional attitudes towards nutritional care [1]. Potential elements for nutrition bundles are listed in Table 28.5 [18, 19].

Intra-operative Considerations

Attention to maintain optimal and electrolyte levels continue during the operative procedure. The liberal use of epidural anesthesia is encouraged for its known benefits during the actual surgical procedure and for pain management during the postoperative period. Dependence on systemic narcotics is minimized, thereby decreasing postoperative nausea and vomiting, and increasing tolerance to early resumption or oral or enteral feeding. It is prudent to consider GI access during esophageal procedures to facilitate early resumption of EN. Although a GI anastomosis is no longer considered a contraindication to early enteral feeding even proximal to the actual anastomotic site [20], procedures on the esophagus are the exception. Depending on the clinical situation, pre-emptive access may include a soft bore nasoenteral tube with the tip positioned in the stomach or jejunum or a formal gastrostomy or jejunostomy. Most patients can be successfully managed with intragastric feeding, with postpyloric positioning only for patients deemed to

be at high risk for aspiration. Parenteral nutrition can be avoided by planning GI feeding access during the operative procedure itself, in case oral intake is not possible or enteral feeding access cannot be obtained or maintained.

Postoperative Patients on Ventilatory Support

The Society for Critical Care Medicine guidelines [20] based on high quality evidence, recommend that either trophic or full EN support should be administered for patients with acute lung injury expected to have a duration of mechanical ventilation ≥72 h. This should be initiated as soon as possible, ideally <24 h, but not later than 48 h after ICU admission [6]. Parenteral nutrition should be considered only after 7–10 days of serious attempts to optimize enteral feeding [20] unless it is clinically evident that this is not a realistic goal.

Postoperative Patients Breathing Spontaneously

Postoperative patients who are breathing spontaneously and with adequate mental status are offered a regular diet, with appropriate consistency, depending on ability to swallow. Recent guidelines based on expert consensus, clearly indicate that upon advancing the diet postoperatively, patients be allowed solid food as tolerated and that clear liquids are not required as the first meal [20]. There is no role for so-called special diets during the immediate postoperative period when patients need to be encouraged to increase oral intake. Current evidence indicates that it is irrational, obsolete and unscientific to prescribe generally unpalatable special diets during the immediate postoperative period [21]. There is no rationale to ordering a low cholesterol "cardiac diet" when the benefits of dietary intervention in atherosclerosis is more for epidemiological reasons rather than in the acute setting. Likewise, in ICU patients, there is no evidence that sodium intake is correlated with blood pressure or need for inotropes.

Routine provision of oral nutritional supplements has been shown to decrease hospital length of stay and significantly decrease unplanned readmission rates. When combined with early detection and documentation of malnutrition, these quality improvement initiatives resulted in a relative risk reduction of readmission of 19.5% with significant cost-savings [22].

Protein and Calorie Requirements; Selection of Enteral Formulas

Predictive formulas for calorie requirement have not proven to be effective. Generally, a simplistic weight-based equation of 25–30 kcal/kg/day is applicable for most patients. Protein intake has recently been emphasized and requirements are 2–2.5 g/

kg/day during the postoperative period [20]. For obese patients, the guidelines suggest using the weight-based equation of 11–14 kcal/kg actual body weight per day for patients with BMI in the range of 30–50, and 22–25 kcal/kg ideal body weight per day for patients with BMI >50. Regarding protein intake for obese patients, the guidelines emphasize that protein should be provided in a range from 2.0 g/kg ideal body weight per day for patients with BMI of 30–40 up to 2.5 g/kg ideal body weight per day for patients with BMI ≥40. These measures are important to minimize muscle wasting which is difficult to detect clinically or by standardized and cost-effective imaging or other tests. At least by postoperative day 3, 80% of the prescribed protein/energy requirements must be met, preferably with enteral feeding [6].

Polymeric enteral formulas with macronutrients in the right proportion and type, as well as micronutrients in bioavailable forms, can be used in most patients [20]. Most products usually providing 1 kcal/mL. Specialized disease-specific formulas include products designed for renal failure and glucose intolerance. Immune-modulating formulas (e.g., containing fish oil and additional selenium) may be considered for patients undergoing complex procedures to counteract the inflammatory response [6]. It is necessary to adjust fluid balance records depending on the free water content, which can range from 75 to 85 mL per 100 mL of the actual ready-to-use liquid formula.

Micronutrients

Micronutrients (vitamins and trace elements) have ubiquitous functions in the body and are critical for all enzyme functions [23]. Wound healing is affected by deficiencies of several micronutrients, notably zinc, copper, vitamin A, vitamin C, amongst several others. The micronutrients known to affect cardiac function include vitamin D, Vitamin B_1 (thiamine), selenium and copper. Preoperative measurement and correction is indicated only when a deficiency is suspected on clinical grounds. Polypharmacy, history of excessive alcohol intake, elderly patients and obesity are conditions where micronutrient deficiencies may go unsuspected [24]. Thiamine deficiency, common in patients with history of excessive alcohol intake, may result in unexplained lactic acidosis [25].

Drug-Nutrient Interactions

Clinicians should be aware of numerous drug-nutrient interactions, especially in elderly patients [26] and obese individuals [27]. Micronutrient deficiencies due to pharmaceuticals may go undetected if not suspected and treated appropriately prior to elective procedures. Various medications such as metformin and proton pump inhibitors produce deficiencies of zinc, vitamin C, vitamin B_{12} and folate, well summarized in a recent review [27]. Long term use of proton pump inhibitors has been shown to cause hypomagnesemia, a common cause of arrhythmias [28].

Nutrition Support in Chyle Leaks

The management of postoperative chyle leaks requires a thorough knowledge of the physiology of chyle and its composition. Loss of fluids, electrolytes, proteins, lymphocytes, and micronutrients may cause serious deleterious effects. Standard enteral feeding or oral diets is often not possible as long chain fatty acids are absorbed through intestinal lacteals and form a major component of chyle. Dietary modifications are tried first by limiting long chain fatty acids and using medium chain triglycerides. If unsuccessful, parenteral nutrition is required. A judicious combination of various nutritional support techniques (oral, enteral and parenteral nutrition) may be required to optimally manage these patients. A stepwise practical approach to this complex problem has been described [29].

Enteral Nutrition in Patients on Pressor Agents

The earlier reluctance to initiate enteral feeding in hemodynamically unstable patients stems from the fear that this may cause gut ischemia. However, this general approach is unfounded and surgeons are encouraged to approach this issue on a case-by-case basis. Patients on multiple pressors and enteral feeding actually had a pronounced survival advantage [30]. Enteral feeding has been shown to be feasible even in patients with extracorporeal life support systems using existing protocols [31]. The Society for Critical Care Medicine (SCCM) 2016 guidelines recommend that EN be withheld or not initiated with mean arterial pressures of <50 mm Hg or when escalating doses of pressor agents are needed to maintain hemodynamic stability [20]. In other instances, EN is feasible especially at lower infusion rate while closely observing patient for any signs of intolerance (abdominal distention, increasing nasogastric tube output, increasing and metabolic acidosis) which necessitates discontinuing EN [20].

Nutritional Support in Patients with "Open Abdomen"

The technique of "open abdomen" is sometimes needed for the management of abdominal compartment syndrome after trauma surgery and after resuscitation (in both surgical and non-surgical patients). Many surgeons are still reluctant to use EN in these patients although evidence clearly shows that this is feasible. Early EN in patients with open abdomens is beneficial in decreasing fistula formation and in facilitating early abdominal closure. Although jejunal access may be preferable, intragastric feeding is acceptable. The SCCM 2016 guidelines, based on expert consensus, recommends early EN in patients with open abdomen [20]. Patients need extra protein intakes of 30–50 g daily per liter of exudative losses from the peritoneal cavity.

Refeeding Syndrome

Refeeding syndrome (RFS) occurs if nutritional therapy, parenteral or enteral, is administered to severely malnourished patients and advanced too rapidly, sometimes leading to death. Clinical features include fluid balance abnormalities, disturbances in glucose metabolism, hypophosphatemia, hypomagnesemia, and hypokalemia and thiamine deficiency [32]. In addition, selenium deficiency may occur with its known effects on the myocardium, causing cardiomyopathy. Hypophosphatemia may contribute to failed weaning attempts, in addition to its effect on the oxygen dissociation curve. Surgeons should maintain a high index of suspicion to detect and intervene in patients suspected to have RFS. In patients at risk, nutritional support is initiated at very slow rates of 10 kcal/kg/day and advanced while electrolyte levels are being normalized [33], which may take 3–4 days to accomplish [20].

Team Approach

An interdisciplinary team approach is essential for successful implementation of current guidelines, as has been reported in other areas of medicine, surgery and critical care [34]. The process is slow and can be expected to take several months. Surgeons have an important role in quality improvement initiatives that deal with perioperative nutrition care. All members of a multidisciplinary team are encouraged to keep an open mind, although it is difficult to give up deeply embedded but unscientific practices. A multi-pronged approach to change the institutional culture and sensitivity to nutrition-related issues is urgently needed [1]. Anesthesiologists and surgical intensivists have a crucial role in implementing best practice guidelines for the optimal perioperative nutritional care of patients undergoing cardiac and thoracic surgical procedures.

Recommendations

1. Interdisciplinary teams with nutrition knowledge will facilitate optimal institutional care of surgical ICU patients.
2. Early EN (within 24–48 h) is recommended for surgical ICU patients.
3. PN should be limited to those unable to tolerate EN.
4. EN may be administered even if the patient is on moderate doses of vasopressor therapy.
5. ERACS® protocols should be utilized to decrease postoperative stress, decrease morbidity and LOS.

Conclusion

This chapter explains the newer diagnosis of malnutrition and the need to address patients at risk both during preoperative optimization and the immediate postoperative period. Evidence-based guidelines are used to make recommendations. Calorie and protein requirements are addressed as well as the importance of micronutrients. The importance of early enteral or oral feeding during the postoperative period is emphasized. The focus has been on information useful for the care of patients undergoing cardiothoracic surgical procedures. Sources for more detailed information are also provided for further reading.

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Chapter 29
Glycemic Control Does Matter in the Cardiac Surgery Patient

Stephanie Cha and Glenn J. Whitman

Introduction

Hyperglycemia is common in patients undergoing cardiac surgery, and likely represents a maladaptive response influenced by factors associated with the perioperative period, including co-existing diabetes and the stress response to surgery. Myocardial ischemia and infarction, fluid and vasopressor administration, and exposure to the cardiopulmonary bypass circuit also contribute. When one considers the increase in the incidence of diabetes and obesity in the population at risk, perioperative hyperglycemia may become an increasingly common condition [1].

Hyperglycemia in the perioperative or postoperative ICU period is associated with a host of detrimental effects, particularly with respect to the cardiovascular system. At a cellular level, these include an imbalance of myocardial oxygen supply and demand, maladaptive diversion of glucose from dependent organs, endothelial dysfunction, platelet aggregation, and impaired immune function [1, 2]. Hyperglycemia is associated with poorer clinical outcomes including increased short and long-term mortality, impaired wound healing, and most notably deep sternal wound infections, increased hospital and ICU length of stay, cognitive dysfunction, renal dysfunction, increased transfusions, and increased costs to the healthcare system [2, 3]. Perioperative glycemic control with insulin therapy has therefore been studied in an effort to determine if its control would improve clinical outcomes by tempering its detrimental effects.

The exact metric which best reflects glycemic control, target blood sugar concentrations and the method and protocol for insulin delivery continues to be controversial, as existing studies have widely varied methodologies. This chapter, therefore, attempts to address the following question- Is there a uniform postoperative

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glycemic control target and a preferred protocol known to improve outcomes in patients undergoing cardiac surgery?

Search Strategy

We performed a literature search of English language publications to identify published data on perioperative glycemic control in adult cardiothoracic surgical patients in accordance with the PICO outline (Table 29.1). PubMed, EMBASE, and Cochrane Library databases were searched. Terms searched include "cardiothoracic," "thoracic surgery," "cardiac surgery," "aortic valve replacement," "coronary artery bypass," "heart valve prosthesis implantation," "postoperative period," "postoperative care," "postoperative," "post-operative," and "glycemic control." Duplicates and articles with pediatric subjects were excluded. Regarding optimal glycemic target in postoperative cardiac surgical patients, nine studies resulted. Of these, there were five randomized controlled trials, two prospective cohort studies, and two retrospective case-control studies. Data was assessed using the GRADE system.

Results

Pathophysiology of Hyperglycemia in Cardiac Surgery Patients

Hyperglycemia has a variety of deleterious effects on the heart, all of which appear to mediate increases in morbidity and mortality during the care of the critically ill, and specifically, the postoperative cardiac surgery patient. Experimental evidence in animal models implicates hyperglycemia as a factor associated with increased infarct size after an ischemic insult [4]. In human cardiomyocytes, hyperglycemia abolishes the protective effect of ischemic [4, 5] and anesthetic preconditioning [6, 7] and furthermore, exacerbates the injury associated with reperfusion [8]. At a cellular level, hyperglycemia has been linked with greater degrees of hypophosphatemia [9] and lactemia [10]. Clinically, hyperglycemia may induce further myocardial damage in diabetics undergoing coronary artery bypass, evidenced by decreased troponin I release with tight glycemic control [11]. Diabetics may suffer more

Table 29.1 PICO table for glycemic control in the cardiac surgery patient

Patient	Intervention	Comparator	Outcome
Adult cardiothoracic surgical patients	Tight glycemic control	Moderate glycemic control, liberal glycemic control	Mortality, ICU length of stay, hospital length of stay, ventilator time, acute kidney injury, postoperative cognitive dysfunction, postoperative atrial fibrillation, recurrent ischemia, cost

myocardial hypertrophy due to longstanding effects of hyperglycemia, and similarly, diabetics undergoing surgical or trans-catheter aortic valve replacement for severe aortic stenosis exhibit poorer left ventricular mass regression following correction [12]. Hyperglycemia also potentiates vasospasm as it interferes with endothelin mediated relaxation [13, 14]. Additionally, fluctuations in blood sugar concentrations may increase oxidative stress, mediating an additional mechanism for endothelial cell dysfunction [15].

Adverse Effects of Preoperative Hyperglycemia

HbA1c

HbA1c is an important marker for long term glucose control in the diabetic population. In hyperglycemia, a vulnerable NH2 moiety of the hemoglobin molecule becomes irreversibly glycosylated, an event that lasts the duration of that red cell, 90–120 days. This glycosylation event occurs commonly in all of us, not just diabetic patients, but normally accounts for <6% of our Hemoglobin. Any value over 6.5% can be used for the diagnosis of diabetes; in the poorly controlled diabetic, the percent glycosylation can affect upwards of 10–12% of hemoglobin. Importantly, the HbA1c concentration represents, in effect, a window into the average glucose control of a patient over the previous 3–4 months, i.e. the lifespan of a red cell. The American Diabetes Association recommends that diabetics target a HbA1c level of <6.5% to mitigate the complications associated with their disease [16].

The relationship between an elevated HbA1c level and postoperative complications in cardiac surgery have addressed the issue almost solely in coronary artery bypass surgery (CABG) patients. Interestingly, the specific results are mixed, but in a recent systematic review, Tennyson et al. evaluated 11 publications which they felt represented the best evidence on the subject [17]. In that paper, only five studies were prospective, none were randomized, and there were no attempts to look at the data in a propensity matched way. Nonetheless, in all prospective studies there was a strong signal for increased complications for elevated HbA1c levels. The lack of significance seen in some of the studies was, in general, the result of small numbers of subjects. The fourfold increase in mortality seen by Halkos et al. [18] for HbA1c >8.5% was striking, as was the correlation those authors found between increased risk of morbidity and mortality for every percent increase in HbA1c above 6%. In the most recent paper addressing this topic, Narayan et al. [19] performed a retrospective look at close to 4700 patients, three quarters of whom had an off-pump approach. He found a 25% increase in respiratory complications and a more than twofold increase in deep sternal wound complications in that population with a preoperative HbA1c >6.5%. The observed 36% increase in mortality was at the $p = 0.08$ level.

There are no intervention trials addressing elevated HbA1c levels, nor have there been any attempts in the literature at propensity matching to isolate the HbA1c con-

centration as an independent risk factor for adverse outcomes after CABG. The most we can say at this moment is that there is a strong signal for an association. Justification for the postponement of surgery to lower the HbA1c concentration similarly has no evidentiary basis. Even were that to exist, 1 month of superb glucose control, yielding a concentration of 6% during that period would only have a partial effect on the overall HbA1c concentration, never lowering it more than 10–15% of the difference between the observed value and 6%. Thus, at least at present, there is only theoretical justification for postponing surgery for patients exhibiting recent, poorly controlled diabetes.

Admission Hyperglycemia and Coronary Artery Bypass Surgery

Given the experimental evidence alluded to in the introduction to this chapter, it is not surprising that the outcomes of any presentation of an acute coronary syndrome are much worse in the presence of hyperglycemia. Furthermore, the commonly prescribed oral hypoglycemic sulfonylureas, so frequently taken by diabetic patients, inhibit myocardial K_{ATP} channels, a structure intrinsically involved with the protective mechanisms of preconditioning, thereby worsening any ischemic insult. As a result, the ACC/AHA guidelines advise strict glucose control for all patients admitted with an acute coronary syndrome [20]. Similar reasoning provided the foundation for the Surgical Care Improvement Project emphasis on perioperative glucose control in postop coronary artery bypass patients [21].

To date, the focus of perioperative glucose control in the cardiac surgery patient has been on the intra- and postoperative phases of care. Few data exist regarding the effect of admission hyperglycemia on this group of patients. In 2001, Zindrou et al. [22] found in female patients who did not carry a diagnosis of diabetes, but had an admission glucose concentration >110 mg/dl, a fourfold increase in coronary artery surgery mortality. Surprisingly, this increase in mortality was not seen in men, at any given admission glucose level. In a more recent study, Thiele et al. [23] looked at 240 emergency coronary bypass patients, and found on multivariable analysis an independent effect of admission hyperglycemia on mortality, with a mortality increase of 16% for every 10 mg/dl increment in admission blood sugar for patients admitted with a blood sugar concentration >120 mg/dl.

Ascribing a causal effect to an elevated admission glucose may not be appropriate as the elevated blood glucose concentration may simply reflect the severity of illness of the patient. Nevertheless, we have referenced many important deleterious effects of acute hyperglycemia [7, 20, 22–28], and so it might be reasonable to implicate hyperglycemia as causal. However, this attribution of causation to admission hyperglycemia should be tentative, as, for example, the stress associated with an acute coronary syndrome may in and of itself cause a sympathetic mediated rise in serum glucose, and thereby account for an associative but not causal role of hyperglycemia and increased mortality and morbidity in this setting.

In summary, although admission hyperglycemia could be a marker for critical illness and thereby simply be associated with poor outcomes, the significant evi-

dence for toxic effects of hyperglycemia at the cellular and biochemical level argue for controlling admission glucose prior to surgery, if possible.

Intraoperative and Postoperative Hyperglycemia

Intraoperative or postoperative hyperglycemia is associated with increased mortality and morbidity. Doenst et al. found hyperglycemia (defined as glucose>360 mg/dl) occurring during cardiopulmonary bypass to be an independent risk factor for mortality. In addition, patients demonstrating hyperglycemia above this level during cardiopulmonary bypass carried an increased incidence of preoperative risk factors including reduced LVEF, CHF, cardiogenic shock, renal failure, previous cardiac surgery, or indication for emergency surgery [29]. Ghandi et al. similarly showed intraoperative hyperglycemia to be an independent risk factor for perioperative complications in a dose-dependent manner such that for every 20 mg/dl increase in blood glucose above 100 mg/dl patients suffered a 34% increase in perioperative complications [30]. Fish et al. determined a comparable relationship during the postoperative period finding that for every 30 mg/dl increase in serum glucose, hospital length of stay increased by 1 day. In addition, postoperative blood glucose exceeding 250 mg/dl was associated with a tenfold increase in complications, primarily cardiac or infectious [31]. Multiple subsequent studies corroborate postoperative hyperglycemia with adverse cardiovascular outcomes [32, 33].

Glycemic Control in the Perioperative Period

Glycemic Control in ICU Patients

Although the detrimental effects of hyperglycemia are well established, the optimal practice for perioperative glycemic control remains somewhat controversial. Results of large randomized controlled trials evaluating optimal glycemic target in critically ill patients is summarized in Table 29.2. In 2001, Van den Berghe et al. challenged the longstanding notion that hyperglycemia occurs as a tolerated component of the stress response. In that study, they demonstrated a 4% absolute mortality reduction in mechanically ventilated surgical ICU patients randomized to an intensive insulin regimen, targeting blood glucose level between 80 and 110 mg/dl, compared with "conventional" management, in which blood glucose was treated only when above 200 mg/dl [34]. This specific study formed the basis for the many major healthcare agency guidelines advising tight glucose control in the critically ill. However, the results of the Van den Berghe study have not been replicated, and, in fact, several large multicenter trials since have produced contradictory results [35–38]. In the NICE-SUGAR trial, mixed medical surgical ICU patients with an ICU length of stay anticipated to be >3 days were randomly assigned to intensive glucose control (BG 81–108 mg/dl) vs. conventional control (BG<180 mg/dL), The intensively

Table 29.2 Optimal glycemic target in critically ill patients (large randomized controlled trials)

Author (year)	Type of study (study population)	N (intervention/control)	Intervention target (mg/dl)	Control target (mg/dl)	Outcomes (intervention vs. control)	Quality of evidence
Leuven I	Randomized controlled trial (surgical ICU + mechanical ventilation)	765/783	80–110	180–200	Death during ICU: 4.6% vs. 8.0% ($p < 0.04$)	Moderate
Van den Berghe et al. (2001) [34]					In-hospital death: 7.2% vs. 10.9% ($p = 0.01$)	
Leuven II	Randomized controlled trial (medical ICU+ anticipated ICU LOS >3 days)	595/605	80–110	180–200	In-hospital death: 37.7% vs. 40.0%	High
Van den Berghe et al. (2006) [35]						
VISEP	Randomized controlled trial (severe sepsis)	247/289	80–110	180–200	Mean AM blood glucose: 112 vs. 151 ($p < 0.001$)	Moderate
Brunkhorst et al. (2008) [37]					28-day death: 24.7% vs. 26.0% ($p = 0.48$)	
					Hypoglycemia: 17.0% vs. 4.1% ($p < 0.001$)	
					Serious adverse events: 10.9% vs. 5.2% ($p = 0.01$)	
Glucontrol	Randomized controlled trial (medical-surgical ICU)	542/536	80–110	140–180	Hypoglycemia: 8.7% vs. 2.7% ($p < 0.0001$)	High
Preiser et al. (2009) [38]					ICU mortality: 15.3% vs. 17.2% (p. 410)	
NICE-SUGAR	Randomized controlled trial (mixed medical and surgical ICU +anticipated ICU LOS >3 days)	3154/3050	81–108	140–180	Death: 27.5% vs. 24.9% ($p = 0.02$)	High
Finfer et al. (2012) [36]					Hypoglycemia: 6.8% vs. 0.5% ($p < 0.001$)	
					ICU LOS: 6 vs. 6 ($p = 0.84$)	
					Hospital LOS: 17 vs 17 ($p = 0.86$)	
					Median number of days of mechanical ventilation 6.6 vs. 6.6 ($p = 0.56$)	

controlled cohort demonstrated an increase in mortality as well as severe hypoglycemic events, with no difference in ICU or hospital length of stay, days on mechanical ventilation, or initiation of renal replacement therapy [36]. The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study, similarly demonstrated an increased risk of adverse events related to hypoglycemia in critically ill septic patients treated with insulin targeting a blood sugar between 80 and 110 mg/dl vs. 180–200 mg/dl [37]. In the GluControl trial, mixed medical-surgical ICU patients treated with intensive insulin therapy (80–110 mg/dL) showed no clinical benefit but did demonstrate an increase in hypoglycemic events. Of note, this last study was stopped prematurely for study protocol violations, and was therefore underpowered [38]. Jacobi et al. recommends treatment of hyperglycemia >150 mg/dl with a maintenance target glucose <150 mg/dl and absolutely <180 mg/dl, with caution to avoid hypoglycemia, especially in certain vulnerable populations [39]. As it currently stands, the updated guidelines by the American Diabetic Association of Clinical Endocrinologists recommend targeting a blood glucose of 140–180 mg/dl in ICU patients [40].

Glycemic Control in Postoperative Cardiac Surgery Patients

Early glucose-insulin-potassium (GIK) solution trials in cardiac surgery patients showed a benefit of insulin therapy despite the occurrence of hyperglycemia in non-diabetics [41], suggesting a pleotropic and protective effect of insulin itself [42]. Lazar et al. went on to investigate the effect of glycemic control with GIK solutions by randomizing 141 diabetic patients undergoing CAB to either "tight" glycemic control with GIK (target glucose 125–200 mg/dl) vs. standard (<250 mg/dl) using intermittent SQ insulin before surgery to 12 h postop. GIK patients demonstrated lower blood glucose (mean 138 mg/dl) with an associated reduced incidence of postoperative atrial fibrillation, wound infections, hospital length of stay, 2-year survival, and recurrent ischemia [43].

The Portland Diabetic Project similarly established the benefit of glycemic control and insulin therapy by following 14,051 diabetic patients undergoing coronary bypass surgery treated either with SQ insulin (1987–1991 protocol) or continuous insulin infusion (1992–2001 protocol). In the continuous insulin infusion group, the glycemic target was periodically lowered according to protocol for goal 150–200 mg/dl during 1991–1998, 125–175 mg/dl during 1999–2001, and 100–150 mg/dl from 2001 on [44]. The group treated by continuous insulin infusion demonstrated improved glucose control as well as reduced mortality (2.5% vs. 5.3%), deep sternal wound infections, and hospital length of stay [45]. In 2007, D'Alessandro et al. further corroborated the benefit of glucose targeted insulin therapy by decreasing mortality in intensively treated diabetics. In this study, 300 diabetic patients undergoing CAB were risk-stratified by Euroscore. Patients exposed to glycemic control (initiation of intravenous insulin therapy for blood glucose >120 mg/dl) demonstrated reduced mortality compared with their Euroscore expected mortality, with the greatest reduction seen in moderate-high risk patients [46].

However, since the initial Van den Berghe trial, no study has shown improved mortality with insulin therapy that targets a blood glucose <110 mg/dl compared with moderate control (<180–200 mg/dl), although few studies suggest improved morbidity and cellular physiology [47, 48]. Even when "tight" control is relaxed to <140–160 mg/dl, few additional studies support an improvement in early mortality compared with targeting a blood glucose of simply less than 180 mg/dl [49, 50]. Improved morbidity has also been described with a glucose target <140–160 mg/dl vs. <180 mg/dl, though infrequently, and includes a diminution in postoperative cognitive dysfunction, postoperative atrial fibrillation, sternal wound infections, duration of mechanical ventilation, and degree of inotropic support [50–52].

Most evidence suggests equivalent outcomes among cardiac surgery patients treated with a moderate target (<180–200 mg/dl) vs a tighter one (<140–160 mg/dl) [53–60]. In 2007, Ghandi et al. established superiority of moderate glycemic control (defined as <200 mg/dl) vs. intensive control (80–100 mg/dl), as a result of an increase in mortality and stroke in patients treated with a lower blood glucose target [53]. Bhamidipati et al. investigated the effect of a target <140 mg/dl vs a target <180 mg/dl in patients undergoing isolated valve procedures, and showed equivalent mortality and rate of major complications [54]. That same year, those same investigators additionally examined patients undergoing isolated CAB, and demonstrated a superiority of <180 mg/dL over tighter as well as more liberal insulin regimens, with improvement in mortality as well as morbidity [55]. In 2015, Umpierrez et al. executed the GLUCOCABG trial, in which 303 patients undergoing coronary artery bypass were randomized to receive either intensive (100–140 mg/dl) or conservative (141–180 mg/dl) postoperative glycemic control. Although there was a statistically significant different in mean blood glucose among the two groups (132 vs. 154 mg/dl), there were no significant differences in any of the measured composite endpoints, including mortality, wound infection, pneumonia, bacteremia, respiratory failure, acute kidney injury, or major adverse cardiovascular events. Hypoglycemia did not occur at a statistically greater rate in the 100–140 mg/dl group [56]. Note that intensive therapy in the more recent studies no longer targets 80–110 mg/dl, but rather levels higher than that, so as not to expose patients to the morbid risk of hypoglycemia.

Interestingly, post-hoc analysis of the GLUCOCABG study showed that among nondiabetics, the 100–140 mg/dl insulin therapy group experienced improved clinical endpoints, suggesting the need for further investigation to support more intensive therapy aimed at the lower glucose targets in nondiabetics undergoing CAB [56]. Similarly, Greco et al. merged patient data from the Cardiothoracic Surgical Trials Network and University Health Consortium, and found that among patients undergoing cardiothoracic surgery (isolated valve, isolated CAB, or CAB/valve surgery), complications from hyperglycemic events were more common in nondiabetics, and furthermore, additional hospital costs associated with hyperglycemia were only seen in that patient group [61].

In cardiac surgery patients, glycemic control (and insulin therapy) consistently improves clinical outcomes and lessens morbidity, although the optimal target

remains controversial. Results of studies evaluating optimal glycemic target in post-operative cardiac surgery patients are summarized in Table 29.3. The exact target range has not been defined, nor has the issue of different targets for the diabetic vs the non-diabetic been resolved, although perhaps the non-diabetic population might benefit by tighter control. As it currently stands, the STS recommends a blood glucose targeted at <180 mg/dl in all patients, but stricter glycemic targets (<150 mg/dl) in high-risk patients, defined as those with a >3 day anticipated ICU length of stay, ventilator dependence, vasopressor use, and mechanical circulatory support [62].

Recommendations

Hyperglycemia in perioperative cardiac surgical patients is common, and has been linked to an increased rate of mortality and perioperative morbidity. Diabetics and patients with unrecognized impaired glucose metabolism suffer worse outcomes and should be identified preoperatively through screening by HbA1c levels as well as fasting blood glucose measurements.

- Perform preoperative screening utilizing HbA1c in all patients (evidence quality low; weak recommendation)
- Initiate a glycemic control protocol with continuous intravenous insulin therapy at the induction of anesthesia (evidence quality low; weak recommendation)
- Continue intravenous insulin therapy for all patients through the first night of surgery and transition to subcutaneous insulin on the first postoperative day, maintaining control for the first 3 days postoperatively (evidence quality moderate; weak recommendation)
- Target moderate- glycemic control (blood glucose 140–180 mg/dl) in most patients (evidence quality moderate; weak recommendation)
- Consider strict glycemic targets (blood glucose 100–140 mg/dl) in nondiabetics or high-risk patients (evidence quality low; weak recommendation)

Personal View of the Data

The ill effects of hyperglycemia on the cardiac surgery patient are well recognized at the biochemical, cellular, and patient based level. Although initial enthusiasm for control of blood glucose concentrations to levels between 80 and 110 mg/dl has waned, evidence supports the prevention of hyperglycemia above the range of 160–180 mg/dl. We believe all patients will benefit from preoperative screening and improved glucose control if indicated and time permits. Admission hyperglycemia should be treated prior to surgery, aiming for a level below 120 mg/dl. Intra- and postoperative blood sugar concentrations should initially be with intravenous

Table 29.3 Optimal glycemic target in postoperative cardiac surgical patients

Author (year)	Type of study (study population)	N (intervention/ control)	Intervention target (mg/dl)	Control target (mg/dl)	Outcomes (intervention vs. control)	Quality of evidence
Furnary et al. (2003) [44]	Prospective cohort study (diabetic patients undergoing any open-heart surgery)	2612 (1999–2001)/942 (1987–1991)	150–200 (1992–1994)	<200 (1987–1991) by subcutaneous insulin	Mean blood glucose: 177 mg/dl vs. 213 mg/dl ($p < 0.0001$)	Moderate
			125–175 (1999–2000) by continuous intravenous insulin		Death: 2.5% vs. 5.3% ($p < 0.0001$)	
Lazar et al. (2004) [43]	Randomized controlled trial (diabetic patients undergoing CAB)	72/69	125–200	<250	Mean blood glucose: 138 vs. 260 ($p < 0.0001$)	Moderate
					Atrial fibrillation: 16.6% vs. 42% ($p = 0.0017$)	
					LOS: 6.5 vs. 9.2 days ($p = 0.003$)	
					Recurrent ischemia: 5% vs. 19% ($p = 0.01$)	
					Wound infections: 1% vs. 10% ($p = 0.03$)	
Gandhi et al. (2007) [53]	Randomized controlled trial (on-pump cardiac surgery)	199/201	80–100	>200	Event (death, SWI, prolonged ventilation, cardiac arrhythmia, stroke, renal failure within 30 days of surgery): 44% vs. 46% (Risk Ratio = 1.0; CI = 0.8–1.2	Moderate
					Death: 4 vs. 0 ($p = 0.061$)	
					Stroke: 8 vs. 1 ($p = 0.020$)	
Leibowitz et al. (2010) [60]	Prospective cohort (diabetics or random blood glucose>150)	410/207	110–150	Standard of care	Mean blood glucose: 151 vs. 166 ($p < 0.0001$)	Low
					Infection: 11% vs. 5% ($p = 0.018$)	

Bhamidipati et al. (2011) [55]	Retrospective case-control (CAB)	134/2785	≤126	127–179	Mortality: 2.9% vs. 2.0% (p = 0.02) Major complications: 19.4% vs. 11.1% (p < 0.001)	Low
Song et al. (2012) [50]	Retrospective case-control (patients undergoing off-pump CAB)	453/251	110–150	>150	AKI: 3% vs. 8% (p = 0.004)	Low
Giakoumidakis et al. (2013) [49]	Randomized controlled trial	105/107	120–160	161–200	Mean blood glucose: 153.9 vs. 173.9 (p < 0.001) In-hospital mortality: 1 vs. 7 (p = 0.033)	Low
GLUCO-CAB Umpierrez et al. (2015) [56]	Randomized controlled trial (CAB)	151/151	100–140	141–180	Mean blood glucose: 132 vs. 154 (p < 0.001) Composite of complications: 42 vs. 52% (p = .87) Composite of complications (diabetics only): 24% vs. 55% (p = 0.008)	Moderate
Kurnaz et al. (2017) [51]	Randomized controlled trial (elective CAB)	20/20	80–120	80–180	POCD: 10 vs 11 (p = 0.047)	Very low

insulin and changed to subcutaneous insulin after the first postoperative day, when no longer critically ill, targeting blood sugars <160–180 mg/dl. Further research is necessary, however, to define glycemic targets in vulnerable populations, the optimal glucose metric for measurement, and glucose delivery protocol.

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Part VIII
Coagulopathy

Chapter 30
The Bleeding Post-op CT Patient: Coagulation Tests Versus Thromboelastography

Oksana Volod and Julie Wegner

Introduction

Coagulation is a highly complex and finely tuned process composed 80+ tightly coupled biochemical reactions involving both cellular elements and plasma proteins (procoagulant, anticoagulant, and fibrinolytic). Current models of coagulation focus on the interactions of the cellular elements (platelets) with plasma proteins as drivers of clot formation in the blood phase [1, 2]. Since coagulation is a dynamic process, functional and/or concentration changes of the blood components due to clinical interventions (antithrombotic drugs, cardiac surgery, etc.) can make the clotting capacity of the system difficult to predict [3–5].

Standard laboratory coagulation tests routinely used for the management of bleeding are plasma based, measure isolated components of the coagulation system, were developed to detect coagulation deficiencies versus provide precise information about a specific coagulation defect, and have limited ability to predict bleeding [6–8]. Historically, physicians have used clinical judgment with or without SCTs to treat patients with acute bleeding events associated with cardiac surgery. The treatment consists of consecutive administrations of a variety of therapeutic agents, namely allogeneic blood components or prothrombotic pharmacological agents such as fibrinogen concentrate or prothrombin complex concentrate. Although empirical treatment has been successful, its use is associated with the risk of

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excessive and unnecessary transfusions, with attendant morbidity, mortality, and increased costs [9–15].

The disruption of the hemostatic system caused by cardiac surgery and cardiopulmonary bypass has been well described; however, the extent of this disruption is variable between patients even in patients at low risk for bleeding [5, 16]. More importantly, the ability to predict excessive bleeding events in cardiac surgical patients has remained elusive [8, 17–19]. Transfusion practices vary widely between cardiac surgery programs in part due to lack of defined transfusion algorithms and partly due to inability to rapidly identify the coagulation defect and treat in a timely manner [20, 21]. VHA tests provide a means of rapidly identifying coagulation defects. Several studies have examined the utility of point-of-care viscoelastic coagulation assays in guiding blood transfusions during cardiac surgery [22–37]. Overall, these studies have found that the implementation of a VHA-based algorithm results in a reduction of blood transfusions. Updated knowledge of the structure and function of the coagulation system, point-of-care coagulation testing that provides a more complete picture of the status of the coagulation system, and availability of factor concentrates has allowed a more goal-directed approach to the management of bleeding in cardiac surgery.

Search Strategy

A literature search of English language publications from 1995 to June, 2017 was used to identity published studies on the effect of VHA-based transfusion algorithms on blood transfusions in adult cardiac surgery patients (Table 30.1). Databases searched were PubMed and Cochrane Evidence Based Medicine. Terms used in the search were: thromboelastography, thromboelastometry, cardiac surgery, adults, blood transfusions, bleeding, coagulation, randomized controlled trials, and observational studies. Articles were excluded if they specifically addressed non-cardiac surgery, cardiology applications, pediatric patients, were only in abstract form, or the manuscripts were unavailable. Seven randomized control trials (RCTs) and

Table 30.1 PICO table for VHA-based vs. SCT-based transfusion algorithms

Patients	Intervention	Comparator	Outcomes
Adult cardiac surgical patients (with CPB)	VHA-based transfusion algorithm	Clinical judgment guided with or without SCT; with or without defined transfusion algorithm	Primary outcome: blood component transfusion Secondary outcomes: Blood loss Ventilation time LOS Mortality

Abbreviations: CPB cardiopulmonary bypass, *VHA* visco-elastic assay, *SCT* standard coagulation test, *LOS* length of stay

seven cohort observational studies were included. Six meta-analysis/systemic reviews provided support for the conclusions of the studies. The data from the RCTs and observational studies was classified using the GRADE system.

Results

VHA measure clot kinetics using whole blood samples and a cup and pin mechanism. Citrated blood samples placed into a cup at 37 °C are subject to oscillation of either the cup (TEG) or the pin (ROTEM) depending on the device. As the clot forms, resistance to oscillation increases, resulting in an increase in the amplitude of the oscillation. Oscillation is detected either mechanically (TEG) or optically (ROTEM) and a characteristic tracing is generated, reflecting the changes in clot viscoelasticity across all stages of clot formation and resolution (fibrinolysis). The tracings for both TEG and ROTEM are similar (Fig. 30.1), however, the terminologies and reference ranges are device specific. In contrast, many other coagulation assays use time to initial fibrin formation as the primary end point. Both viscoelastic devices are able to monitor coagulation under systemic heparinization by using heparinase coated sample cups. Removal of the heparin effect also helps to identify the residual effects of heparin, as well as heparin rebound after protamine reversal. Finally, both devices provide monitoring of fibrinogen using tests such as the Functional Fibrinogen (TEG) and FIBTEM (ROTEM).

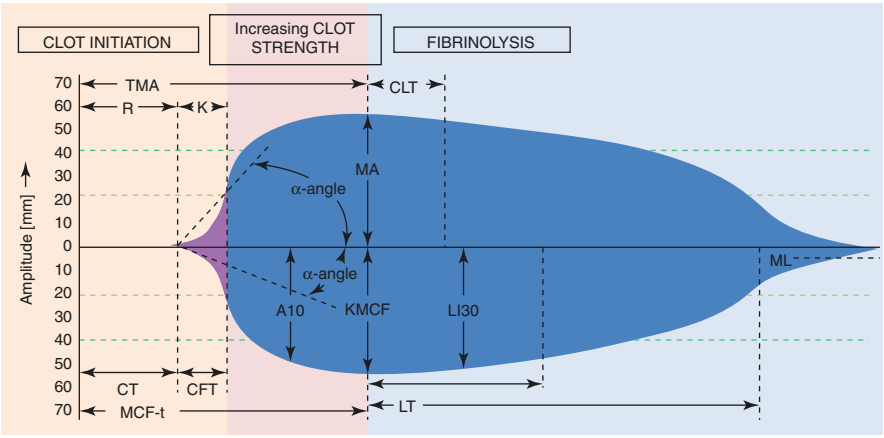

Fig. 30.1 TEG and ROTEM tracing TEG parameters: *R* reaction time, *K* kinetics, α-angle, *MA* maximum amplitude, *CLT* clot lysis time (time taken for amplitude to decrease by 2 mm from MA). **ROTEM parameters**: *CT* clotting time, *CFT* clot formation time, *α*-angle, *A10* amplitude at 10 min, *MCF-t* time to maximum clot firmness, *MCF* maximum clot firmness, *LOT* lysis onset time, *LT* lysis time (time taken from amplitude to drop by 10% of MCF), *LI30* lysis Index at 30 min (% drop in amplitude from MCF), *ML* maximum lysis (minimum amplitude achieved at the end of test run time)

The implementation of a VHA-based transfusion algorithm on the transfusion of blood products has been associated with a reduction in the use of blood products as demonstrated by six of the seven of RCTs (Table 30.2) and six of seven observational studies (Table 30.3). The decrease in allogeneic transfusions was attributed to earlier and more specific identification of the coagulation defect, allowing for timely and specific treatment of that defect, in other words goal-directed therapy [6, 22, 30, 33, 38]. Similar conclusions regarding the reduction of blood transfusions were arrived by six recent meta-analyses that have explored the question of the efficacy of VHA testing during cardiac surgery. Despite the finding of reductions in blood transfusions with the use of VHA testing, consistent improvements in other clinical outcomes such as blood loss, length of stay, and mortality have not been found [39–44]. The reason for the lack of improvement in other clinical outcomes has not been fully elucidated. Finally, the efficacy of using pre-operative VHA monitoring to predict the risk of excessive bleeding post-cardiac surgery has not been realized [17–19, 45].

Overall the quality evidence for the efficacy of VHA monitoring improving patient outcomes is low. This is due to the design of the studies, specifically small sample sizes, non-blinding of interventions, lack of standardization of testing, the nature of the comparator intervention, and the heterogeneity of algorithm triggers. The standardization and validation of VHA is currently being addressed. A recent study compared the results of VHA testing of plasma samples in nine laboratories around the globe. The initial results demonstrated significant inter-laboratory variance with CV (coefficient of variation) >10%. Whether or not the use of whole blood samples will provide lower CV still needs to be addressed [46]. The studies included in this analysis compared the implementation of a VHA-based transfusion algorithm with clinical judgment of physicians with or without a defined SCT-based algorithm. Studies have demonstrated that use of a transfusion algorithm for patient management is sufficient to reduce blood product utilization in cardiac surgical patients [24, 25, 30, 47]. The lack of consensus regarding transfusion triggers, the treatment parameters for specific defects of coagulation, and the available treatments (i.e. FFP, platelets, fibrinogen concentrate, PCC) have all contributed to the variability in the algorithms used and the management of bleeding events in cardiac surgery, which in turn influences patient outcomes. The efficacy of the different VHA-based transfusion algorithm has not been tested making it difficult to universalize a single algorithm [48].

Recommendations

Current evidence devalues the SCT (PT, aPTT, platelet count and fibrinogen) because they have long turnaround time (over 1 h from the time of blood collection) and capture only a small segment of the overall coagulation process. **Thus, SCTs are of limited use for the real time assessment and prediction of perioperative multifactorial coagulopathies and the monitoring of their management.** Several

Table 30.2 Summary of randomize clinical trial studies comparing VHA-based transfusion algorithms to SCT-based judgment or transfusion algorithm

Study	Patients	Intervention-control (C)	Intervention-VHA	Outcome	Quality of evidence
Weber (2012) [31]	Complex cardiac surgery with CPB with excessive post-CPB bleeding N = 100One center Randomized post-protamine	N = 50 Conventional (clinical judgment guided by SCT) SCT-based algorithm Hemostatic treatments included fibrinogen concentrate and PCC	N = 50 ROTEM- based algorithm Hemostatic treatments included fibrinogen concentrate and PCC	VHA group: Significant reduction in patients transfused with RBC (98% vs. VHA = 84% patient's transfused), FFP (C = 80% vs. VHA = 40% patient's transfused), platelet (C = 66% vs. 56% patient's transfused) Significant decrease in ventilation time (C = 700 vs VHA 315 min), LOS-ICU (C = 24 h vs. VHA = 21 h), 6 month mortality (C = 20% vs. VHA = 4%)	Low due to high risk of bias
Girdaukas (2010) [29]	High risk aortic surgery with HCA N = 56 One center	N = 29 Conventional (clinical judgment guided by SCT) SCT-based algorithm	N = 27 ROTEM-based algorithm	VHA group: significant reduction patient's transfused with FFP (C = 86% vs. VHA = 33%) No differences in patient's transfused with RBC (C = 93% vs. VHA = 89%), 24 h blood loss (C = 950 ml vs. VHA = 890 ml), LOS-ICU (C = 16.6 h vs. VHA = 17.0 h)	Low due to high risk of bias
Ak (2009) [27]	Primary CABG with excessive bleeding post-CPB N = 224 One center Randomized post-protamine 30 day follow-up	N = 110 Conventional (Clinical judgment guided by SCT) No transfusion algorithm indicated	N = 114 TEG-based algorithm	VHA-group: Significant reduction in risk of transfusion for FFP (C = 28% vs. VHA = 17%), platelets (C = 26% vs. VHA = 15%), No differences in risk of RBC transfusions (C = 54.5% vs. VHA = 45.6%), blood loss (12 h; C = 591 ml vs. VHA = 45.6 ml), 30-day mortality (C = 1.7% vs VHA = 2.7%)	Low due to high risk of bias

(continued)

Table 30.2 (continued)

Study	Patients	Intervention-control (C)	Intervention-VHA	Outcome	Quality of evidence
Westbrook (2009) Pilot study [28]	Low to high risk cardiac surgery with CPB N = 69 One center	N = 37 Conventional (clinical judgment guided by SCT) No defined transfusion algorithm	N = 32 TEG-based algorithm	VHA-group: No difference in transfusions of any blood products (RBCs: C = 33U vs.VHA = 14U; FFP: C = 22U vs. VHA = 18U; platelets: C = 15 U vs. VHA = 5 U); blood loss (12 h; C = 960 ml vs. VHA = 875 ml), LOS-ICU (C = 33 h vs. VHA = 29 h)	Low due to high or unclear risk of bias
Nuttall (2001) [24]	Elective cardiac surgery with abnormal bleeding post-CPB N = 92 One center	N = 51 Conventional (clinical judgment with or without guidance from SCT) No defined transfusion algorithm	N = 41 Partially TEG-based (platelet transfusion) + SCT-based algorithm Applied only intra-operatively	VHA-group: Significant reduction in median number of FFP (C = 3 U vs. VHA =0 U) and platelet (C = 6 U vs. VHA = 4 U) transfusions; significant decrease 24 h post-operative bleeding (C = 850 ml vs 590 ml)	Low due to high risk of bias
Royston (2001) [23]	Cardiac surgery with high risk of bleeding N = 60 One center	N = 30 Conventional (clinical judgment with guidance from SCT) No algorithm	N = 30 TEG-based algorithm Applied only intra-operatively	VHA group: Reduction in number of units of FFP (C = 16 U vs. VHA = 5 U) and platelets transfused (C = 9 U vs. VHA = 1 U) No difference in 12 h blood loss (C = 390 ml vs. 470 ml)	Low due to high risk of bias
Shore-Lesserson (1999) [22]	Moderate to high risk cardiac surgery N = 105 One center	N = 52 Conventional (clinical judgment with guidance from SCT) SCT-based algorithm	N = 53 TEG-based algorithm Applied only intra-operatively	VHA-group: Significant reduction in overall transfusion rate (C = 65% vs. VHA = 42%) and non-RBC transfusion rate (C = 33% vs. VHA = 13%) No significant difference in 24 h post-operative bleeding (C = 901 ml vs. VHA = 702 ml)	High due to low risk of bias

Abbreviations: CPB cardiopulmonary bypass, *VHA* visco-elastic assay, *SCT* standard coagulation test, *LOS* length of stay, *LOS-ICU* length of stay intensive care unit, *ROTEM* rotational thromboelastometry, *TEG* thromboelastography, *RBC* red blood cells, *FFP* fresh frozen plasma, *HCA* hypothermic circulatory arrest

Table 30.3 Summary of observational studies comparing VHA-based transfusion algorithms to SCT-based judgment or transfusion algorithm

Study	Patients	Study type	Intervention-VHA	Outcome	Quality of evidence
Ranucci (2017) [36]	Adult cardiac surgery with CPB/ patients with abnormal bleeding post-heparin reversal N = 6331 Single center	Retrospective N = 3165 historical controls (2005–2006)	Implementation of TEG-based transfusion algorithm N = 3166 (2006–2008)	VHA-algorithm group: Significant reduction of 12 h postoperative Bleeding (C = 500 ml vs. VHA = 425 ml) Significant increase of platelet transfusion rate (C = 7% vs. VHA = 12%)	Low
Spath (2017) [35]	Adult cardiac surgery with CPB N = 904 Single center	Observational Before and after comparison Before: using TEG guided blood product use without defined algorithm, N = 598	Implementation of TEG-based algorithm N = 306	VHA-algorithm group: Significant decrease in patients transfused with RBC (C = 37% vs. VHA = 30%); FFP (C = 27% vs. VHA = 18%); Platelets (C = 35% vs. VHA = 22%) No differences in blood loss, mortality, or LOS-ICU	Low Not peer reviewed (letter to editor)
Karkouti (2016) [37]	Adult cardiac surgery with CPB N = 7402 Multicenter study (12 hospitals)	Stepped-wedge cluster randomized control N = 3555 during control phase	Implementation of ROTEM-based transfusion algorithm N = 3847 during intervention phase	VHA-algorithm group: Significant reduction in rates of RBC (adjusted relative risk = 0.91); platelets (relative risk = 0.77); major bleeding events (relative risk = 0.83)	Low
Yildirim (2016) [34]	Adult CABG patients with CPB N = 246 Single center	Retrospective observational N = 82 historical controls	Implementation of ROTEM-based transfusion algorithm N = 164	VHA-algorithm group: Significant reduction patients transfused with RBCs (C = 39% vs. VHA = 20%) and Whole blood (C = 21% vs. VHA = 7%) and post-op bleeding (C- 586 ml vs. VHA = 381 ml) No differences in patients transfused with FFP (C = 32% vs. VHA = 24%)	Low

(continued)

Table 30.3 (continued)

Study	Patients	Study type	Intervention-VHA	Outcome	Quality of evidence
Fassl (2013) [32]	Adult aortic surgery with HCA and CPB N = 194 Single center	Retrospective case-control N = 41 (conventional transfusion management without defined algorithm)	Implementation of TEG-based transfusion algorithm N = 153	VHA-algorithm group: Significant reduction in patients receiving RBCs (C = 78% vs. VHA = 41%), FFP (C = 71% vs. VHA = 22%), and platelets (C = 32% vs. VHA = 16%); and 24 h blood loss (C = 540 ml vs. VHA = 450 ml)	Low
Gorlinger (2011) [30]	Adult complex cardiac surgery with CPB/patients with high risk of bleeding or excessive bleeding post-heparin reversal N = 3865 Single center	Retrospective observational cohort N = 1718 controls ROTEM-based algorithm	Implementation of updated ROTEM-based algorithm with fibrinogen concentrate and PCC as first line treatments N = 2147	Updated VHA-algorithm group: Significant reduction in patients receiving RBCs (C = 50% vs. VHA = 40%) and FFP (C = 19% vs. VHA = 1%) transfusions Significant increase in platelet transfusions (C = 10% vs. VHA = 13%) No change in mortality (C = 5.24% vs. VHA = 5.22%)	Low
Anderson (2006) [26]	Adult cardiac surgery/patients with abnormal post-op bleeding N = 990	Retrospective controls – 6 months prior to implementation of ROTEM-based algorithm N = 488	Implementation of ROTEM-based algorithm N = 502	VHA-algorithm group: Significant reduction in patients receiving RBCs (C = 60% vs. VHA = 53%), FFP (C = 17% vs. VHA = 12%), and platelet (C = 16% vs. VHA = 11%) transfusions	Low

Abbreviations: CPB cardiopulmonary bypass, *VHA* visco-elastic assay, *SCT* standard coagulation test, *LOS-ICU* length of stay intensive care unit, *ROTEM* rotational thromboelastometry, *TEG* thromboelastography, *RBC* red blood cells, *FFP* fresh frozen plasma, *PCC* prothrombin complex concentrate, *HCA* hypothermic circulatory arrest, *CABG* coronary artery bypass grafting, *RR* relative risk

bedside coagulation tests (point of care, POC) that are used in the cardiac surgery have been described. Activated clotting time (ACT) is a mainstay method for heparin monitoring in cardiac surgery. The ACT response to heparin varies among different analyzers. Additionally multiple factors not related to the heparin, including excess of protamine can prolong the ACT. Because of these drawbacks, heparin management systems (HMS) have been considered as better option of heparin monitoring in cardiac surgeries. However a recent study did not demonstrate their superiority [49]. Whole blood POC PT and aPTT are used for non-surgical patients and show reliable results. They have also been evaluated in the perioperative settings, but show poor correlation with the plasma based SCT [50, 51]. POC fibrinogen assays using a dry reagent method has been described and approved for clinical use in Japan. Similar to SCTs these POC tests measure only isolated components and do not provide information of the entire hemostasis. Viscoelastic hemostasis assays, on another hand, allow rapid and more comprehensive assessment of underlying coagulopathy. However, not even VHA provide information about the function of the entire hemostasis that is especially important perioperatively in cardiac surgeries. Von Willebrand factor (vWF) loss, factor XIII (fibrin stabilizing factor), and antiplatelet drugs effect can't be assessed with either TEG or ROTEM. VHA are performed at 37 °C, and may not adequately assess coagulopathy of the patients with hyper or hypothermia. Additionally, a belief that both TEG and ROTEM results are equivalent with interchangeable results and interpretations may be misleading. Despite the similarity between the TEG and ROTEM measured variables, results produced by these instruments cannot be directly compared. Numerous studies describe utility of viscoelastic assays, but only few directly compared TEG with ROTEM [52–55]. The clinical study in cardiac surgery by Venema et al. suggested that the maximal amplitude (MA) is the only parameter that can be used interchangeably. While both tests can be used to guide blood products transfusion, treatment recommendations vary according to specific parameters from each device [52, 56].

The strongest outcome data is for the VHA's ability to identify the presence of a coagulopathy and administration of goal-directed therapy (evidence quality low; weak recommendation). Evidence is low quality, but the consistency in the results and the fact that the TEG/ROTEM provides an integrated picture of coagulation are the reasons for adopting the VHA. Additionally, the expanded capabilities of the TEG/ROTEM for measuring fibrinogen levels and platelet function make the TEG/ROTEM better choices than conventional laboratory methods. **The data on mortality, blood loss, and length of stay at this time is inconsistent; primarily because most studies have been small or the information was not collected (no recommendation can be made**). The outcome for reversal of coagulopathy was not examined in studies, although it is mentioned that the TEG/ROTEM can monitor changes after hemostatic therapy **(no recommendation can be made).** Figure 30.1 merges the tracings obtained from both tests. **There is no evidence to indicate a difference in clinical effectiveness between the TEG and ROTEM devices.** The preference for which assay to use appears to depend on geographic location, with North American centers using TEG while European prefer ROTEM.

Recently TEG and ROTEM modifications TEG6s and ROTEM Sigma have been developed. Both instruments allow multiple types of tests with a single cartridge. As both devices principle is different from their precursors, studies are needed to determine whether the same normal values or algorithms can be used. Two additional VHAs, the Sonoclot (SCT, Sienco) and the Quantra (HemoSonics LLC) analyzers, have emerged as POC devices. Sonoclot measures changes in impedance to movement of a vibrating probe. The Sonoclot analyzer generates both a qualitative graph (known as the Sonoclot Signature), and quantitative results on the clot formation time (ACT) and the rate of fibrin polymerization (Clot RATE) [57]. The Quantra is a device based on Sonic Estimation of Elasticity via Resonance (SEER) sonorheometry, a proprietary ultrasound -based technology. The Quantra analyzer generates measured and calculated quantitative results on the clot stiffness. The device is designed to generate complete test results within 15 min of test initiation [58]. Although the TEG and ROTEM are currently being used clinically in many institutions, no VHA device has been designated as a gold standard. Thus, additional supporting evidence from well-designed scientific studies are warranted for all VHA devices.

Summary of Recommendations

- **SCTs are of limited use for the real time assessment and prediction of perioperative multifactorial coagulopathies. In contrast, VHA assays, allow for rapid and more comprehensive assessment of underlying coagulopathy (evidence quality low; strong recommendation).**
- **VHA's ability to identify the presence of a coagulopathy in real time allows for administration of goal-directed therapy (evidence quality low; weak recommendation).**
- **The outcome for reversal of coagulopathy was not examined in studies, although it is mentioned that the TEG/ROTEM can monitor changes after hemostatic therapy (no recommendation can be made).**
- **The data on mortality, blood loss, and length of stay at this time is inconsistent; primarily because most studies have been small or the information was not collected (no recommendation can be made).**
- **There is no evidence to indicate a difference in clinical effectiveness between the TEG and ROTEM devices (evidence quality low no recommendation can be made).**

Personal Experience

My personal experience and expertise is in utilizing TEG platelet mapping (TEGPM) for patients implanted with mechanical circulatory support devices (MCSD). TEGPM is a modification of the TEG assay that isolates the effect of platelet inhibitors on clot strength. Both hemorrhagic and thromboembolic complications

continue to be frequent adverse events and causes of death after MCSD implantation. Preoperatively many patients are either on antiplatelet/anticoagulant therapy or are placed on short term MCSD (ECMO or Impella) which further complicate their already complex perioperative period. The implantation of MCSD immediately creates a prothrombotic environment because of the activation of systemic inflammatory response. To regulate this prothrombotic state patients are placed on antithrombotic therapy shortly after the device implantation. Mechanical circulatory support devices are also associated with hemorrhagic complications due to acquired von Willebrand Syndrome [59–63]. The need to manage both ends of the hemostatic spectrum to keep a patient normocoaguable requires an assay that can provide a comprehensive assessment of the status of the coagulation system and assesses how anticoagulant and antiplatelet agents influences coagulation processes in the real time. A modification of TEG, the TEGPM, provides a way to assess the effects of heparin, warfarin and antiplatelet agents in one test and can be used to individually tailor patient's transfusion management and antithrombotic therapies. A large team of clinicians typically manage these patients. A standardized, yet individually tailored management protocol with defined target parameters that are easy to follow is essential for successful management and patient outcomes. Our current protocol was developed based on our pilot study results and includes a combination of VHA (TEGPM) and SCT (PT/INR) parameters. It also includes baseline preoperative coagulopathy assessment utilizing TEGPM, intraoperative rapid TEG (rTEG) and postoperative serial TEGPM along with more specialized coagulation assays such as heparin assay, VWF multimer analysis and AT3 level when necessary.

Despite data showing its clinical utility and availability of TEG, TEGPM and rTEG at our institution not everyone adheres to the proposed protocol or utilizes TEG results in their management decisions. Some patients are getting TEGPM after a thrombotic or bleeding event; as a result, the assay results for these patients may not accurately reflect the true nature of their coagulopathy at the time of the event, which complicates patient management. Lack of consensus regarding transfusion triggers, adherence to proposed protocols, and standardization of TEG/ROTEM, and complexity of performing VHA tests at point-of-care have all contributed to the variability in the management of bleeding events in cardiac surgery and ultimately patient outcomes. If the existing algorithms, recommendations and guidelines can be applicable to new more automated and less user-dependent VHA technologies (TEG6s, ROTEM sigma and Sonoclot) we may see their benefits not only in reducing blood products transfusion, but also in clinical outcome improvement and cost saving.

Appendix

This case demonstrates an accurate assessment of postoperative coagulopathy with VHA (TEG) compared to the SCT.

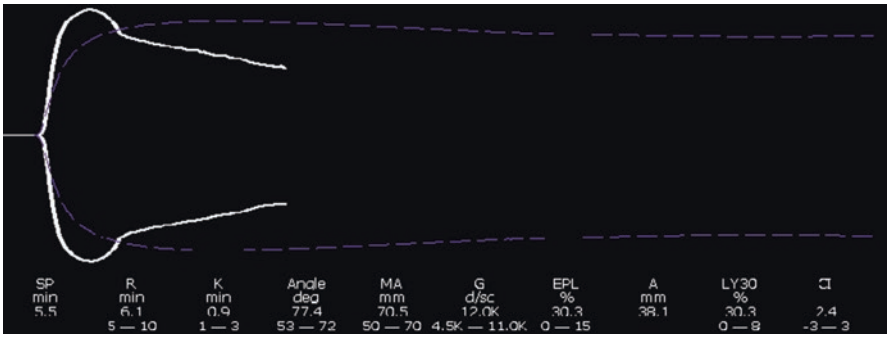

Fig. 30.2 TEG results of patient implanted with TAH post-operative day 12

Coagulation status of a 39-year-old female implanted with total artificial heart (TAH) implantation with anticoagulation being maintained with Coumadin and Aspirin. Routine laboratory study results were as follows: white blood cell (WBC) count, 25×10^9/L (elevated); platelet (PLT) count, 429×10^9/L; prothrombin time (PT), 22.5 s (normal, 11.9–14.4 s); partial thromboplastin time (PTT), 48 s (normal, 22–37 s) and fibrinogen 536 mg/dl (normal 200–400 mg/dl). Concurrent TEG showed normal clotting time (R), but clot lysis indices (LY30 = 30.2% and CI >1) suggesting secondary fibrinolysis, commonly seen in the first phase of sepsis or in disseminated intravascular coagulation (DIC). The excessive rate of clot breakdown clinically presents as bleeding which occurred in this patient few hours later. Her elevated WBC count was initially contributed to corticosteroid therapy. Later it was found that it was due to infection. TEG evaluation allowed a more accurate assessment of all phases of coagulation, which revealed incipient DIC. As a result, more appropriate therapy was instituted with a successful outcome (Fig. 30.2).

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Chapter 31
Bleeding in Cardiac Surgery: Should Massive Transfusion Be in a 1:1:1 Ratio?

James M. Bardes and Kenji Inaba

Introduction

Cardiac surgery accounts for up to 20% of worldwide blood product usage [1]. While the majority of these operations are straightforward, 9% of patients will require more than five units (U) of packed red blood cells (PRBC) postoperatively [2]. Postoperative hemorrhage can be devastating in these patients, and these massively transfused cardiac patients have an eightfold increase mortality [3]. The optimal transfusion strategy, in the post cardiac surgery patient requiring massive transfusion, is not well understood.

Trauma patients are another population at risk for severe hemorrhage requiring massive transfusions. Even in 2017, hemorrhagic death remains the number one preventable killer of trauma patients. While the primary goal of care is to obtain control of this bleeding, the coagulopathy of trauma has been recognized as a significant contributor to mortality. Given the rapid need for empiric transfusion, in these critically injured patients, the use of a fixed ratio transfusion strategy was developed and tested over the last decade. For these trauma patients requiring a massive transfusion, fresh frozen plasma (FFP) and platelet (PLT) replacement in a balanced transfusion ratio of 1:1:1 (plasma, platelets, red blood cells) has been shown to result in decreased hemorrhagic death. This practice has become widely accepted within the trauma community.

The impact of balanced transfusion ratios in cardiac surgery has not been well evaluated, with only a single retrospective study examining the outcomes. In that study, patients receiving a ratio of greater than 1:1 (PRBC:FFP) did demonstrate improved survival. This study however only included intraoperative data [4]. The

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aim of this chapter is to evaluate the literature available on the use of a 1:1:1 transfusion ratio in the massively hemorrhaging cardiac patient. Due to a lack of available cardiac surgery literature, data based on trauma patients will be presented as a surrogate. The effect this balanced transfusion ratio has on overall transfusion requirements, complications, intensive care unit (ICU) length of stay and survival will be evaluated.

Search Strategy

A systematic search for publications was performed from 2007 to 2017, to identify all English language publications on the use of a 1:1:1 massive transfusion ratio for hemorrhage after cardiothoracic surgery using the PICO outline (Table 31.1). Databases searched included PubMed MEDLINE, EMBASE, and Cochrane Evidence Based Medicine. Search terms included "massive transfusion," "transfusion ratio," "cardiac surgery," "cardiothoracic surgery," "postoperative hemorrhage," and "postoperative complications." References from selected articles were screened for additional sources. This strategy identified no publications that solely reviewed postoperative hemorrhage and transfusion. The majority of the patients studied were receiving a massive transfusion that started during their operation, or no clear delineation was made if the transfusion requirement was intraoperative or postoperative. Database searches from the trauma literature was then performed. The data was classified according to the GRADE System.

Results

Mortality and Control of Hemorrhage

The effect of a 1:1:1 transfusion ratio has been studied extensively in the trauma literature. (Table 31.2) Retrospective studies provided the first evidence for balanced transfusion ratios. As examples of this retrospective work, Borgman et al. performed early research on the use of FFP transfusion by the US military [5]. This retrospective study evaluated 246 patients at a US Army combat support hospital

Table 31.1 PICO table of massive transfusion practices

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Adult, postoperative cardiothoracic, in ICU	Transfusion with a balanced 1:1:1 ratio in massive transfusion	Standard care, standard transfusion practices	Transfusion requirements, complications, ICU LOS, survival

Table 31.2 Transfusion ratios in massively bleeding patients

Author (year)	N	Blood product comparison	Mortality in high ratio[a]	Mortality in low ratio[a]	OR in high ratio (CI)	Study type (quality of evidence)
Borgman (2007) [5]	246	FFP:PRBC	19%	65%	NR	Retrospective (low)
Holcomb (2008) [8]	467	FFP:PRBC	40.4%	59.6%	NR	Retrospective (low)
		Plt:PRBC	40.1%	59.9%	NR	
Stinger (2008) [7]	252	Cryo:PRBC	24%	52%	0.37 (0.17–0.81)	Retrospective (low)
Inaba (2010) [6]	657	Plt:PRBC	33.1%	72.1%	0.92 (0.89–0.95)	Retrospective (low)
Holcomb (2013) [11]	1245	FFP:PRBC	NR	NR	0.31 (0.16–0.58)	Prospective cohort (moderate)
		Plt:PRBC	NR	NR	0.55 (0.31–0.98)	
Shaz (2010) [10]	214	FFP:PRBC	41%	56%	NR	Prospective cohort (moderate)
		Plt:PRBC	37%	67%	NR	
		Cryo:PRBC	44%	49%	NR	
Holcomb (2015) [12]	680	FFP:Plt:PRBC	9.2%	14.6%	NR	RCT (high)
Mazzeffi (2017)[b] [4]	452	FFP:PRBC	19.4%	33.0%	0.34 (0.17–0.67)	Retrospective (low)

[a]High and low ratio vary by study, see text for ranges
[b]Cardiac patients receiving massive intraoperative transfusion
NR Not reported

that required a massive transfusion. Patients were grouped into low (1:8), medium (1:2.5), and high (1:1.4) FFP:PRBC ratio groups. Mortality decreased as the ratio of FFP:PRBC increased (65%, 34%, 19%, $P < 0.001$). Similarly the rate of hemorrhagic death decreased by 60% between the high and low ratio groups (92.5% vs. 37%, $P < 0.001$) The higher ratios of FFP:PRBC were independently associated with an improved survival, and a decrease in deaths within 4 h of admission.

Research by Inaba et al. evaluated the impact of platelet transfusion in the trauma patient receiving a massive transfusion [6]. This retrospective review collected 9 years of blood bank and registry data from an urban level 1 trauma center. The PLT:PRBC ratio was used to stratify patients, and regression analysis was performed to evaluate the effect on mortality. Over 650 patients were analyzed, and a stepwise decrease in mortality with increasing ratio of platelet transfusion was noted. The patients with a ratio of >1:6 had a 5.5-fold reduction in risk compared to patients in the lowest ratio group (<1:18). They concluded that a high PLT:PRBC ratio was independently associated with survival at 12 and 24 h ($P < 0.001$).

Stinger et al. provided evidence for the increased use of fibrinogen replacement [7]. This group evaluated the US military experience with the early use of cryoprecipitate (CRYO) transfusion. This retrospective study evaluated 252 patients who received a massive transfusion, defined as >10 PRBC over 24 h. The amount of fibrinogen transfused into each patient was calculated accounting for all of the blood products they received. This total was used to stratify patients into a low or high fibrinogen:PRBC group. Mortality was the primary outcome in this study and was significantly decreased in the high ratio group (52% vs. 24%, $P < 0.001$). Death from hemorrhage was specifically reduced as well (85% vs. 44%, $P < 0.001$). To account for the multiple confounders in a retrospective review, these authors also collected data on temperature, blood pressures, coagulopathy, and injury severity. After performing a logistic regression the higher fibrinogen:PRBC ratio was shown to be independently associated with a decreased mortality (OR 0.37, CI 0.171–0.812, $P = 0.013$).

These retrospective studies were limited by evaluating just a portion of the transfusion ratio. One of the earliest studies to evaluate the combined effect of platelet and FFP transfusion was performed by Holcomb et al. [8]. This large retrospective study evaluated 467 patients receiving a massive transfusion from 16 different trauma centers. Using multivariate analysis the authors showed a survival benefit for patients with the highest plasma (40.4% vs. 59.6%, $P < 0.01$) and highest platelet ratios (40.1% vs. 59.9%, $P < 0.01$). The authors noted the greatest affect on survival was seen in the hemorrhaging patient.

These retrospective studies are also limited by the potential for survival bias. Where those that survived may not have survived as a result of the higher volumes of plasma and platelets transfused, but happened to be those that survived long enough to receive the extra plasma and platelets [9]. As the next step in inquiry, several prospective observational studies were produced evaluating the impact a balanced transfusion ratio had on hemorrhaging trauma patients. Shaz et al. performed a study comparing retrospectively gathered massively transfused patients, to a prospective cohort. The prospective cohort was evaluated after the institution of a massive transfusion protocol (MTP) at their facility [10]. After initiating the MTP the blood bank would deliver coolers with the proper ratio of blood products to maintain a 1:1:1:1 transfusion of PRBC:FFP:PLT:CRYO. Analysis showed improved 24-h and 30-day survival for the patients transfused closer to 1:1:1:1. When each product was individually examined, again, a higher transfusion ratio lead to improved survival.

The first large scale prospective multicenter data came from Holcomb et al. in the Prospective, Observational, Multicenter, Major Trauma Transfusion *(PROMMTT)* study [11]. This study was performed at ten level 1-trauma centers and evaluated patients who required blood product transfusion. This study was unique in that each center provided dedicated research assistants to observe the resuscitation and record exact times for blood and fluid infusions. This allowed patient outcomes and transfusion ratios to be compared based on time intervals. This study identified a mortality benefit when patients received higher platelet and plasma ratios earlier in their

care, especially within the first 6 h. Patients that received a ratio of less than 1:2 were four times more likely to die. Interestingly, at 30 days there was no further survival benefit. The authors surmised that the late deaths occurred from traumatic brain injury and multisystem organ failure, and that the greatest impact of the early use of a 1:1:1 transfusion ratio is on early hemorrhagic deaths.

Based on this foundational data, a multicenter randomized control trial was performed. Holcomb et al. conducted the Pragmatic, Randomized, Optimal Platelet and Plasma Ratios (PROPPR) trial, a large, multicenter, randomized study comparing the effects of a balanced transfusion ratio of 1:1:1 compared to 1:1:2 [12]. This study was conducted at 12 large level 1-trauma centers across North America. Patients were severely injured (mean ISS of 26), and 75% would require either an operation or interventional radiology procedure within 2 h of admission. To maintain proper transfusion ratios, this study utilized coolers containing fixed ratios prepared by the blood bank at randomization. At both 24 h (12.7% vs. 17%, P = 0.12) and 30 days (22.4% vs. 26.1%, P = 0.26) there was no difference in overall mortality. However when hemorrhagic deaths were analyzed separately, there was a significant improvement in hemostasis rates (86% vs. 78%, P = 0.006), and there was a reduction in mortality at 24 h in the 1:1:1 group when compared to 1:1:2 (9.2% vs. 14.6%, P = 0.03) (Fig. 31.1).

While there has been significant research on transfusion ratios within the trauma literature, no studies were identified that had studied postoperative hemorrhage in cardiac surgery. A retrospective study did evaluate the impact of transfusion ratios on patients requiring massive intraoperative transfusion. Mazzeffi et al. examined over 7400 patients operated on in a single center. Of these, 452 (6%) patients received move than 8 units of PRBC during an operation [4]. These massively transfused patients were stratified by FFP:PRBC ratio into low (<1:2), medium (1:1 to 1:2) and high (>1:1) groups. Similar to existing trauma data, 30 day mortality decreased as transfusion ratios increased (33% vs. 25.3% vs. 19.4%, P = 0.05). Patients with the highest transfusion ratios also had decreased rates of renal failure, fewer reoperations and less multisystem organ dysfunction.

Complications and Outcomes

The effect a balanced transfusion ratio has on complication rates, acute respiratory distress syndrome (ARDS) multisystem organ failure (MSOF), and length of stay has also been evaluated. There is variation among the literature, and several studies have shown an increased length of stay in the ICU, and an increase in ARDS and subsequently ventilator days [8, 13]. Another demonstrated increased MSOF associated with FFP transfusion and cautioned against delivering blood products in fixed ratios [14]. PROPPR, the only randomized trial, also collected data on complications, showing no differences in infections, acute lung injury or ARDS, MSOF or VTE complications [12].

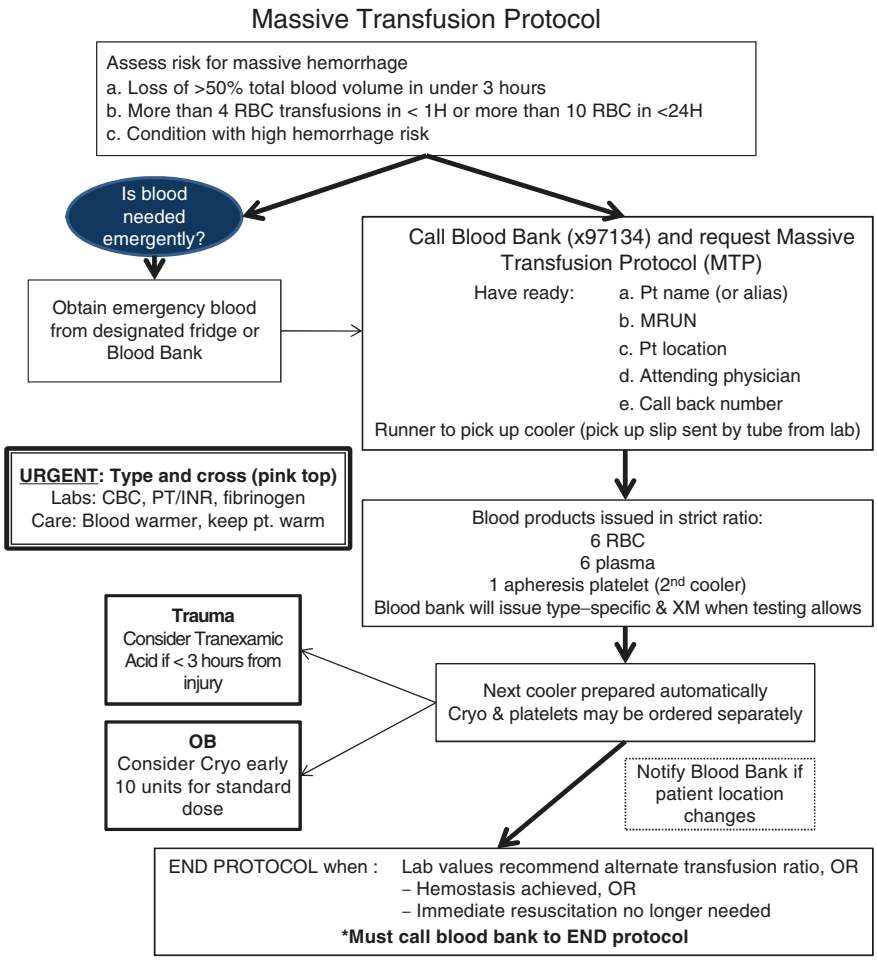

Fig. 31.1 An Example of a Balanced Massive Transfusion Protocol

Recommendations

The need for postoperative transfusion after cardiothoracic surgery occurs in 9% of patients and increases mortality eightfold. The cardiac literature has focused on the options for intraoperative treatment of coagulopathy. This has left the optimal treatment of postoperative hemorrhage uncertain in the literature. Data from the trauma literature may be applicable for the treatment of severe postoperative hemorrhage. A balanced transfusion ratio of 1:1:1 (plasma, platelets, red blood cells) has been shown to decrease overall mortality, and specifically hemorrhage related mortalities in trauma patients. Convincing evidence has been provided for increased ratios of plasma, platelets and cryoprecipitate. A randomized, multicenter trial confirmed these finding at multiple trauma centers. While this data is convincing, and the

overall evidence quality moderate, there is no direct evidence of its utility in the postoperative cardiothoracic patient with hemorrhage. Therefore, no recommendation can be made at this time for the use of a balanced 1:1:1 transfusion ratio after cardiac surgery.

A Personal View of the Data

Postoperative hemorrhage is a complication seen in all surgical specialties. In the setting of cardiothoracic surgery this can be particularly devastating due to several factors, including, the use of multiple anticoagulants, the coagulopathy due to time on pump, the hypothermia required for some cases, and the seriousness of a complications such as cardiac tamponade. Currently there is no data to directly support a recommendation on the correct ratio of transfusion for postop hemorrhage. This is not a unique deficiency, no other surgical specialty has studied this complication explicitly. The bleeding trauma patient, however, may be a suitable surrogate. Hemorrhaging trauma patients often arrive to trauma centers on anticoagulants and hypothermic. Their bleeding is also rapid and life threatening. The management of these patients has been studied extensively, and it has been recognized that the coagulopathy associated with this massive hemorrhage contributes to the mortality risk. Multiple retrospective studies were performed to evaluate the effect transfusion ratios have on mortality, and this data was followed by prospective observational work and finally by a multicenter randomized trial. This research has repeatedly shown a decrease in hemorrhage specific mortality when a balanced transfusion ratio was used.

Only recently have there been retrospective studies examining the effects of transfusion ratios in the bleeding non-trauma patient. One retrospective analysis evaluated blood bank utilization when massive transfusion protocols were used in non-trauma patients as well. This group showed minimal effect on hospital wide blood utilization, but did demonstrate the successful use of these protocols in the non-trauma setting [15]. Another recent study by Teixeira et al. retrospectively evaluated FFP:PRBC ratios for non-trauma patients requiring massive transfusion [16]. Similar to the trauma literature, patients receiving an increased FFP:PRBC ratio showed a decreased mortality. While no specific data exists to recommend this in the setting of hemorrhage after cardiothoracic surgery, all of the available data from the trauma literature would support its use.

The mortality benefit seen with balanced transfusion ratios has raised the question, would whole blood transfusion be beneficial? Balanced transfusions can be seen as an attempt to replicate, and replace, the whole blood lost in the hemorrhaging patient. Up until the end of the Second World War, whole blood was widely used for resuscitation. With the development of fractionation, we have slowly moved away from whole blood transfusion as a method to increase our blood product availability and storage. Currently whole blood is used at select centers and by the military. While early research has been positive, more studies will be needed before any final recommendation can be made.

Recommendations

- No recommendation can be made at this time, for the use of a balanced 1:1:1 (plasma, platelets, red blood cells) transfusion ratio, for the massively transfused postoperative cardiothoracic surgery patient.

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Chapter 32
If the Platelets Are Low, Is It HIT?

Theodore E. Warkentin

Introduction

Thrombocytopenia occurs universally following cardiac surgery [1]. Unfractionated heparin (UFH) is routinely given for intraoperative anticoagulation during cardiac surgery. Heparin administered during cardiac surgery has a high probability of inducing the formation of antibodies that recognize complexes of (anionic) heparin with (cationic) platelet factor 4 (PF4), a chemokine released from platelet α-granules. Sometimes, the antibodies are platelet-activating, potentially triggering immune heparin-induced thrombocytopenia (HIT), an adverse drug reaction with greatly increased risk of venous and/or arterial thrombosis (HIT-associated thrombosis). Clinicians need to be able to distinguish expected post-cardiac surgery thrombocytopenia from either HIT-related thrombocytopenia or non-HIT-related thrombocytopenia of diverse etiologies.

Expected Platelet Count Changes Post-cardiac Surgery

Early post-cardiac surgery thrombocytopenia, results from hemodilution (giving crystalloids, colloids, blood products), platelet consumption (onto the cardiopulmonary circuit and through wound hemostasis), and delayed marrow response

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(2–3-day lag for elevated thrombopoietin levels to increase postoperative platelet production). There is an approximate 50% (range, 30–70%) decline in platelet count from the preoperative to the nadir (lowest) value, usually seen on postoperative day (POD) 2 or 3; subsequently, platelet counts rise to peak levels (about twice the preoperative value) at approximately POD14, before declining (see shaded area in Fig. 32.1).

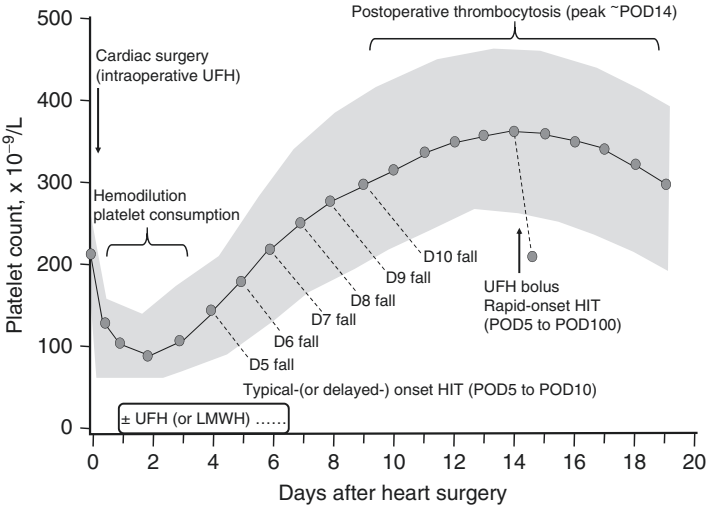

Fig. 32.1 HIT onset in relation to expected platelet counts post-cardiac surgery. The shaded area represents the range of expected platelet counts following cardiac surgery. Solid circles indicate typical median platelet count values. Post-cardiac surgery, there is an approximate 50% drop in platelet count (resulting from hemodilution and platelet consumption), with the nadir platelet count usually reached between postoperative day (POD) 1 and POD4 (median, POD2). Subsequently, thrombopoietin-induced increase in platelet production results in progressively rising platelet counts, reaching peak levels at approximately POD14 at levels that are 2–3× the preoperative value (thrombocytosis). These platelet count changes occur irrespective of whether postoperative anticoagulation is given with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). A second platelet count fall, indicated by the dashed lines (labeled "D5 fall" through "D10 fall"), indicates a high likelihood of either "typical-" or "delayed-onset" HIT; the former term indicates onset of HIT while receiving postoperative heparin and infers presence of HIT antibodies with predominantly heparin-dependent platelet-activating properties, whereas the latter term indicates onset of HIT that occurs in the absence of ongoing heparin exposure or that worsens after stopping postoperative heparin, and infers presence of HIT antibodies with both heparin-dependent as well as substantial heparin-independent platelet-activating properties. In contrast, "rapid-onset HIT" refers to any abrupt drop in platelet count that occurs after a bolus of heparin (or following an increase in heparin dose); since presence of HIT antibodies is required for rapid-onset HIT to occur, the risk period is usually between POD5 and POD100 (since it is uncommon for platelet-activating HIT antibodies to be present more than 100 days following cardiac surgery)

Table 32.1 PICO table for identifying HIT-related thrombocytopenia

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Post-cardiac surgery patients	Systematically applied definition of thrombocytopenia for identifying HIT	No systematic approach	Incidence of HIT (EIA+ and SRA+ [or HIPA+])

Abbreviations: HIT heparin-induced thrombocytopenia, *EIA+* positive PF4-dependent enzyme-immunoassay, *HIPA+* positive heparin-induced platelet activation assay (washed platelet asay), *SRA+* positive serotonin-release assay (washed platelet assay)

Search Strategy

Table 32.1 shows the PICO model framing the literature search. PubMed was searched (Jun 28, 2017) using key words "heparin-induced thrombocytopenia" and "cardiac surgery",[1] identifying 570 articles. I sought: (a) studies that systematically investigated specific post-cardiac surgery platelet count profiles as indicating possible HIT; and (b) observational studies describing different profiles of thrombocytopenia in patients with confirmed HIT post-cardiac surgery. Preference was given to reports using high-quality laboratory testing for HIT antibodies, especially the combination of a PF4-dependent enzyme-immunoassay and a washed platelet activation assay [2]. The quality of data in the papers evaluated was classified according to the GRADE system (see Chap. 1).

Presentations of HIT Postcardiac Surgery

Table 32.2 summarizes terminology used to describe various platelet count profiles of HIT post-cardiac surgery, including their relationship with heparin-dependent and heparin-independent (autoimmune) platelet-activating properties of the HIT antibodies. The various presentations of HIT post-cardiac surgery are illustrated using published cases with strong laboratory support for the diagnosis of HIT [3–7].

[1] Search details: Heparin-induced[All Fields] AND ("thrombocytopaenia"[All Fields] OR "thrombocytopenia"[MeSH Terms] OR "thrombocytopenia"[All Fields]) AND ("thoracic surgery"[MeSH Terms] OR ("thoracic"[All Fields] AND "surgery"[All Fields]) OR "thoracic surgery"[All Fields] OR ("cardiac"[All Fields] AND "surgery"[All Fields]) OR "cardiac surgery"[All Fields] OR "cardiac surgical procedures"[MeSH Terms] OR ("cardiac"[All Fields] AND "surgical"[All Fields] AND "procedures"[All Fields]) OR "cardiac surgical procedures"[All Fields] OR ("cardiac"[All Fields] AND "surgery"[All Fields])).

Table 32.2 Terminology used for describing different presentations of HIT

Terminology	Features (including timing of onset of thrombocytopenia)	Heparin-dependent antibodies	Heparin-independent antibodies (autoimmune)
Typical-onset HIT	Onset usually between POD5 and POD10 (inclusive)[a]	Always	Sometimes
Delayed-onset HIT	Onset usually between POD5 and POD10 (inclusive)[b]	Always	Always
Severe HIT with DIC	Platelet count nadir $<20\times10^9$/L; coagulation changes of DIC	Always	Usually
Early postoperative HIT	HIT that begins before POD5 due to immunizing preoperative course of heparin	Always	Sometimes
Early-onset and persisting thrombocytopenia	Thrombocytopenia that begins and persists following cardiac surgery; usually does *not* indicate HIT	Sometimes[c]	Sometimes[c]
Persisting HIT	Thrombocytopenia continues for >1 week after stopping heparin	Always	Always[d]
Rapid-onset HIT	Within 24 h after re-starting (or increasing dose) of heparin (risk period, up to ~POD100)	Always	Sometimes

Heparin-dependent anti-PF4/heparin antibodies are a universal feature of HIT; however, a subset of patients have a population of HIT antibodies that activate platelets in the absence of heparin (heparin-independent or "autoimmune" antibodies). Note that HIT-related disorders featuring HIT antibodies with heparin-independent platelet-activating properties, such as delayed-onset and persisting HIT, are sometimes referred to as "autoimmune HI"

Abbreviations: DIC disseminated intravascular coagulation, *HIT* heparin-induced thrombocytopenia, *POD* postoperative day

[a]Sometimes typical-onset HIT begins a few days later, i.e., up to POD14

[b]Although delayed-onset HIT usually begins during the characteristic "window" of HIT (POD5–10), some patients will present with thrombocytopenia and/or thrombosis after discharge from hospital, and thus present to medical attention after POD10

[c]Even when HIT antibodies are detectable, early-onset and persisting thrombocytopenia usually indicates an underlying non-HIT diagnosis; however, if there is a superimposed platelet count fall and/or thrombotic event that occur at a time consistent with formation of HIT antibodies, then HIT is a possible additional diagnosis

[d]Heparin-induced (autoimmune) antibodies explain persisting HIT unless the patient has another coinciding explanation for persisting thrombocytopenia

Typical-Onset HIT

HIT antibodies are formed in a narrow time period beginning approximately 5 days after an immunizing heparin exposure [8], which for cardiac surgery patients is usually UFH administered intraoperatively. Thus, HIT usually begins 5–10 days post-cardiac surgery irrespective of the patient's previous history of heparin exposure [1, 7, 9]. When HIT antibodies are predominantly heparin-dependent,

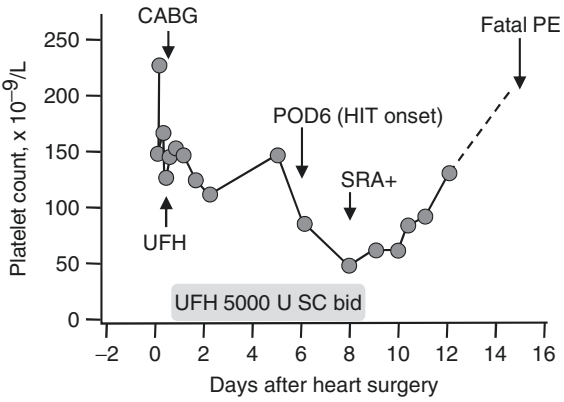

Fig. 32.2 Typical-onset HIT. This 68-year-old woman, who underwent coronary artery bypass grafting (CABG), and who received postoperative thromboprophylaxis with unfractionated heparin (UFH), 5000 units (U), subcutaneous twice-daily (SC bid), developed HIT beginning on postoperative day (POD) 6, confirmed by a positive serotonin-release assay (SRA+), with wholly heparin-dependent serum-induced platelet activation [3]. Although heparin was stopped and the platelet count quickly recovered, the patient died of pulmonary embolism (PE) on POD16. This patient case underscores the importance of treating acute HIT with an alternative non-heparin anticoagulant even in the setting of "isolated HIT", i.e., when HIT-associated thrombosis is not apparent. (Reprinted (with modifications), with permission, from [3])

stopping heparin results in platelet count recovery within a few days (Fig. 32.2). For 90% of patients with HIT, platelet counts return to normal within 1 week of stopping heparin (median, 4 days) [7]. Interestingly, some patients' platelet counts recover despite continued heparin administration; such patients have wholly heparin-dependent antibodies with levels that wane despite ongoing heparin ("seroreversion") [10].

Delayed-Onset HIT (Autoimmune HIT)

If the patient's HIT antibodies have "heparin-independent" platelet-activating properties, the thrombocytopenia can begin or worsen despite stopping heparin (Fig. 32.3) [4, 11]. Indeed, such patients can develop HIT between POD5 and POD10 even if no postoperative heparin whatsoever is given, a clinical picture called "delayed-onset HIT" [12–14]. However, this term is a misnomer, since timing of thrombocytopenia onset is identical to typical-onset HIT. Recently, the term "autoimmune HIT" [15] has been applied to these patients, as their clinical course is explained by heparin-*independent* platelet-activating antibodies. This subgroup of antibodies can fuse the positively-charged PF4 tetramers, overcoming their inherent repelling charge without the need for (negatively-charged) heparin [16].

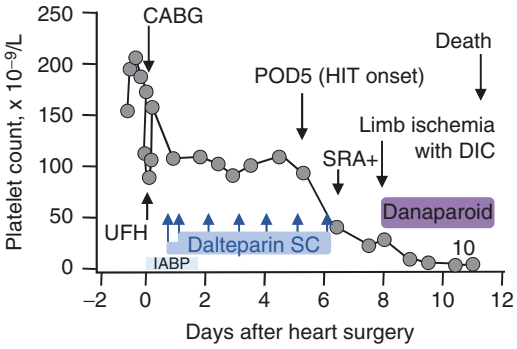

Fig. 32.3 Delayed-onset (autoimmune) HIT. This 72-year-old man, who underwent emergency coronary artery bypass grafting (CABG) with unfractionated heparin (UFH), requiring postoperative intraaortic balloon pump (IABP) support, and who received postoperative subcutaneous (SC) thromboprophylaxis with dalteparin, developed HIT beginning on POD5 [4]. The patient is classified as "autoimmune HIT", or "delayed-onset HIT", because the platelet count continued to fall despite stopping heparin (platelet count nadir, 10×10^9/L) and the positive serotonin-release assay (SRA+) showed strong platelet activation both in the presence and absence of heparin. The patient developed ischemic limb necrosis of three limbs (with palpable pulses) consistent with severe thrombocytopenia (platelet count nadir, 10×10^9/L), laboratory evidence of disseminated intravascular coagulation (DIC) and microvascular thrombosis. The patient died despite initiation of therapeutic-dose anticoagulation with danaparoid. (Reprinted (with modifications), with permission, from [4])

Autoimmune HIT accounts for a disproportionate number of life- and limb-threatening complications, as patients have a high frequency of HIT-associated disseminated intravascular coagulation (DIC) [4, 12, 15] (Fig. 32.3).

"Early" Presentations of HIT (Before POD5)

Rarely, HIT begins early in the postcardiac surgery period as a result of an immunizing course of heparin given shortly before surgery (Fig. 32.4) [5]. In essence, typical-onset or delayed-onset (autoimmune) HIT arising from the preoperative heparin course coincides with the early postcardiac surgery period. This clinical picture is uncommon (<10% of confirmed cases of postcardiac surgery HIT).

Another clinical picture, named "*early-onset and persisting thrombocytopenia*," indicates a cardiac surgery patient whose platelet count fails to recover promptly post-surgery. Most often, the persisting thrombocytopenia reflects critical illness, rather than the effects of HIT antibodies, even when such antibodies are detectable [7]. However, if a new (superimposed) platelet count fall and/or large-vessel thrombosis occurs that can be correlated with HIT antibody formation, then a contributing role for HIT is plausible. For example, Fig. 32.5 shows a critically ill patient

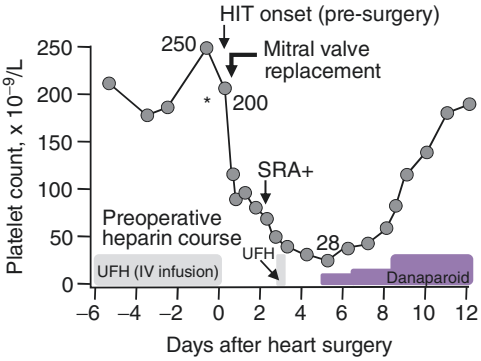

Fig. 32.4 Early postoperative HIT (due to preoperative UFH exposure). This 67-year-old female was admitted for acute flail mitral valve regurgitation, requiring mitral valve replacement [5]. Preoperatively, she received a 6-day course of unfractionated heparin (UFH) by intravenous (IV) infusion. She developed progressive thrombocytopenia during the postoperative period, with platelet count nadir of 28×10^9/L on POD5. The clinician suspected HIT on POD2, which was confirmed by a positive serotonin-release assay (SRA+) result. To explain the early occurrence of postoperative HIT, we tested earlier as-yet-undiscarded blood samples, and showed that the patient tested SRA+ prior to cardiac surgery. Indeed, it was apparent that the platelet count had fallen from 250 to 200×10^9/L immediately prior to surgery, suggesting that the patient was likely in the early phase of acute HIT at the time of cardiac surgery, which proceeded uneventfully. The patient was shown to have strong autoimmune HIT antibodies, thus explaining the progressive postoperative decline in platelet count with minimal further heparin exposure. Thrombosis surveillance showed only minimal catheter-associated thrombosis in the right internal jugular vein. The patient was treated with prophylactic- followed by therapeutic-dose danaparoid and made a full recovery. (Reprinted (with modifications), with permission, from [5])

with early-onset and persisting thrombocytopenia receiving fondaparinux thromboprophylaxis; when a symptomatic upper-limb DVT was documented on POD10, UFH was given, precipitating "rapid-onset HIT" [6]. In hindsight, autoimmune HIT was present from POD6 onwards.

In theory, acute intra- or early postoperative thrombosis, associated with intraoperative UFH exposure, could be a consequence of HIT, given that many patients have received heparin preoperatively and thus could harbor unrecognized HIT antibodies at time of surgery. However, to the author's knowledge, there is only 1 report plausibly describing this phenomenon [17]; other reports [18, 19] are not compelling [20]. Perhaps the high concentrations of heparin protect against adverse acute intraoperative complications of HIT antibodies, either because the amount of heparin is too high for optimal stoichiometric formation of the HIT antigens, or because high levels of heparin protect against HIT-associated hypercoagulability [20]. Indeed, one group performed emergency cardiac transplant and mechanical circulatory support device placement using heparin in patients with acute HIT, observing no adverse consequences [21].

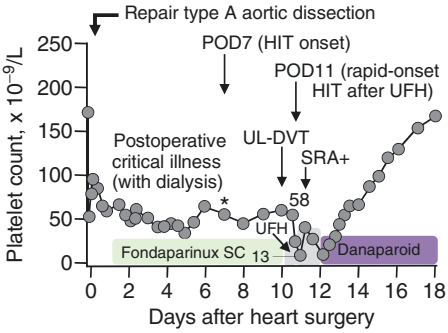

Fig. 32.5 Early-onset and persisting thrombocytopenia with superimposed HIT (including rapid-onset HIT). This 61-year-old man underwent emergency replacement of the ascending aorta for type A aortic dissection [6]. He had postoperative critical illness (hypotension, lactic acidosis, dialysis-dependent renal failure) with associated early-onset and persisting thrombocytopenia. He received postoperative thromboprophylaxis with fondaparinux in reduced doses given by subcutaneous (SC) injection (2.5 mg every 2nd day). He developed a minor platelet count fall beginning on POD7, which subsequently was shown to be associated with concomitant formation of autoimmune HIT antibodies that did not cross-react with fondaparinux (see asterisk [*] on POD7 indicating serotonin-release assay positive (SRA+) status shown in retrospect). He received therapeutic-dose unfractionated heparin (UFH) on POD9 (during hemodialysis) and also on POD10 for treatment of symptomatic catheter-associated upper-limb deep-vein thrombosis (UL-DVT). The abrupt platelet count fall from 58 to 13×10^9/L following use of therapeutic-dose UFH indicates "rapid-onset HIT" in the setting of "autoimmune HIT". (Reprinted (with modifications), with permission, from [6])

Late Presentations of HIT

Patients with autoimmune HIT can present with thrombocytopenia and thrombosis following discharge from hospital; although the onset of the platelet count fall likely occurred within the typical POD5 to POD10 window, the patient's intervening discharge from hospital prevented recognition of evolving thrombocytopenia. Usually, it is the occurrence of symptomatic venous or arterial thrombosis that leads to discovery of the thrombocytopenia, although sometimes otherwise unexplained postoperative thrombocytopenia is identified (Fig. 32.6 leftmost portion) [7, 22]. In such patients, thrombocytopenia sometimes lasts for several weeks or months ("persisting HIT"), with platelet count recovery inversely paralleling waning of heparin-independent platelet-activating properties [11, 22].

Another potentially late presentation of HIT is when a postoperative patient with a normal (or near-normal) platelet count is restarted on heparin, e.g., for treating thrombosis or acute atrial fibrillation, and an abrupt platelet count fall results ("rapid-onset HIT") (Fig. 32.6 rightmost portion) [7, 23]. This complication usually occurs within 1 month post-surgery, but sometimes occurs a few weeks later.

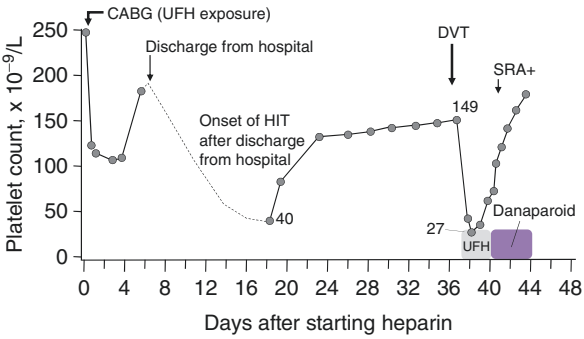

Fig. 32.6 Delayed-onset and persisting HIT (autoimmune HIT) with later rapid-onset HIT upon heparin re-exposure. This 68-year-old female underwent coronary artery bypass grafting (CABG) with unfractionated heparin (UFH) exposure but did not receive postoperative UFH [7]. However, she had unexplained thrombocytopenia noted on POD19 (platelet count, 40×10^9/L) that subsequently improved. However, on POD38 she developed symptomatic lower-limb deep-vein thrombosis (DVT), and developed rapid-onset HIT (to platelet count nadir of 27×10^9/L) when UFH was given (UFH re-exposure). In retrospect, the preceding period of thrombocytopenia was diagnosed as autoimmune (delayed-onset and persisting) HIT. The platelet count subsequently recovered during treatment with danaparoid. (Reprinted (with modifications), with permission, from [7])

The explanation for this risk period for rapid-onset HIT reflects the unusual transience of HIT antibodies; beyond 100 days, the probability of platelet-activating antibodies being detectable is low [9].

Results

Table 32.3a lists key studies [24–29] evaluating a biphasic platelet count pattern, i.e., the expected initial postoperative platelet count decline, followed by platelet count recovery (usually to $>100 \times 10^9$/L), with a second substantial (at least 40%) – and unexpected – platelet count fall beginning between PODs 5 and 10 [24–29]; Table 32.3b lists studies [26, 27, 29] examining a monophasic pattern of early-onset and persisting thrombocytopenia. One study [29] applicable to both patterns of thrombocytopenia focused on patients with a prolonged ICU stay beyond 7 days.

Typical- Versus Rapid-Onset HIT

HIT has historically been classified into "typical" and "rapid" onset thrombocytopenia [9]; the former indicates the typical interval (POD5–10) between starting an immunizing heparin exposure and the subsequent onset of thrombocytopenia, whereas

Table 32.3 Systematic studies of platelet count profile in HIT

Study	N	N_D	Definition of ?HIT	Key data	Type of study; quality of evidence
a. Biphasic thrombocytopenia: platelet count recovery with second platelet count fall (POD5–10)					
Post-cardiac surgery patients					
Pouplard (1999) [24]	328	6	>40% PC↓ POD5–10	SRA+ in 6/6 thrombocytopenic vs 2/322 non-thrombocytopenic controls (P < 0.0001)	Observational; high
Warkentin (2000) [25]	100	1	>50% PC↓ POD5–10	SRA+ in 1/1 thrombocytopenic vs 19/99 non-thrombocytopenic controls (P = 0.20)	Observational; moderate
Pouplard (2005) [26]	305	4	>40% PC↓ POD5–10	SRA+ in 4/4 thrombocytopenic vs 7/300 non-thrombocytopenic controls (P < 0.0001)	Observational; high
Selleng (2010) [27]	581	3	>50% PC↓ POD5–10	HIPA+ in 3/3 thrombocytopenic vs 68/578 non-thrombocytopenic controls (P = 0.0018)	Observational; high
Pooled data	1314	14	Large PC↓ POD5–10	Test+ in 14/14 thrombocytopenic vs 96/1299 non-thrombocytopenic controls (P < 0.0001)	Observational; high
Lillo-Le Louët (2004) [28]	84	39[a]	>40% PC↓ >POD4	SRA+ in 28/39 (72%) thrombocytopenic vs 7/45 non-thrombocytopenic controls (P < 0.0001)	Observational; moderate
Subgroup of post-cardiac surgery patients with prolonged ICU stay (>7 days)					
Selleng (2008) [29]	259	12[b]	>40% PC↓ POD5–10	HIPA+ in 2/12 thrombocytopenic patients (no serosurveillance controls)	Observational; moderate
b. Monophasic thrombocytopenia (early-onset and persisting thrombocytopenia)					
Post-cardiac surgery patients					
Pouplard (2005) [26]	305	1	<100 for >1 week	SRA+ in 0/1 thrombocytopenic vs 7/300 non-thrombocytopenic controls (P = 1.00)	Observational; high

Table 32.3 (continued)

Study	N	N_D	Definition of ?HIT	Key data	Type of study; quality of evidence
Selleng (2010) [27]	581	25	<100 for >1 week	HIPA+ in 5/25 thrombocytopenia vs 63/553 non-thrombocytopenic controls (P = 0.20)	Observational; high
Subgroup of post-cardiac surgery patients with prolonged ICU stay					
Selleng (2008) [29]	259	22[c]	<100 for >1 week	HIPA+ in 4/22 thrombocytopenic patients (no serosurveillance controls)[d]	Observational; moderate

All studies listed were observational; quality of evidence was ranked as "high" if studies were prospective (or involved consecutive patients), performed serological investigations irrespective of presence of thrombocytopenia ("serosurveillance"), and performed testing for HIT antibodies using a washed platelet activation assay (SRA or HIPA). Studies that did not meet all of these criteria were still regarded as having "moderate" quality data if a washed platelet activation assay was used

For Table 32.3a, "thrombocytopenic" refers to patients exhibiting biphasic thrombocytopenia.

For Table 32.3b, "thrombocytopenic" refers to patients exhibiting early-onset and persisting thrombocytopenia.

Abbreviations: HIPA heparin-induced platelet activation test, *N* number of patients studied, N_D number of patients who met the platelet count definition for possible HIT (?HIT), *PC↓POD5–10* platelet count decrease that begins between postoperative days 5 and 10 (inclusive), *SRA* serotonin-release assay

[a]This study is considered separately as a systematic serosurveillance study was not done; rather, thrombocytopenia patients post-cardiac surgery were studied, and separated into patients with biphasic (n = 39) versus monophasic (n = 45) thrombocytopenia. The data indicate an odds ratio (OR) of 13.8 (P < 0.0001) by univariate analysis, and remained highly significant after multivariate analysis

[b]Although 40 patients met the definition for thrombocytopenia shown (>40% PC↓ POD5–10), only the 12 patients who were investigated serologically for HIT are listed (the others were not believed to be HIT on clinical grounds)

[c]Although 30 patients met the definition for thrombocytopenia shown (platelet count <100 for ≥7 days), only the 22 patients who were investigated serologically for HIT are listed (the others were not believed to be HIT on clinical grounds)

[d]All four patients had "superimposed" >30% platelet count falls that occurred within the POD5–10 period (n = 3) or shortly thereafter (POD12, n = 1), and thus may have had HIT

the latter term refers to a rapid platelet count fall upon restarting heparin in a patient with circulating HIT antibodies that resulted from a recent heparin exposure. Figure 32.1 illustrates this pattern of biphasic thrombocytopenia characteristic of HIT.

Biphasic Thrombocytopenia with Onset POD5–10

Table 32.3a shows studies demonstrating that a biphasic platelet count fall, with the second drop beginning between POD5 and 10, and of considerable magnitude (at least 40% or 50% decline from the postoperative peak platelet count), is highly

specific for HIT. Data pooled from 4 studies [24–27] found that all 14 patients who met this definition tested positive for platelet-activating antibodies (and were thus diagnosed with HIT) versus 96/1299 (7.4%) patients who did not meet this definition ($P < 0.0001$). Another study [28] found an odds ratio of 13.8 for biphasic thrombocytopenia (versus monophasic thrombocytopenia) as indicating HIT.

Approach to Thrombocytopenia: Biphasic, Proportional

Thrombocytopenia is usually defined in *absolute* terms, e.g., platelet count less than 100×10^9/L. However, when evaluating biphasic platelet count falls in postoperative patients, it is more useful to analyze the second platelet count fall as a proportional (relative) drop in platelet count from the postoperative peak platelet count that immediately precedes the putative HIT-related platelet count fall. This approach takes into account the phenomenon of postoperative thrombocytosis (Fig. 32.1). For example, a >50% platelet count fall from 330 to 160×10^9/L that occurs from POD5 to POD10 strongly indicates a diagnosis of HIT, even if the nadir value of 160 is not traditionally viewed as indicating "thrombocytopenia." Thus, the highest postoperative platelet count that immediately precedes the putative HIT-related platelet count fall (rather than the preoperative platelet count) should be considered the "baseline" value for calculating the proportional platelet count fall [30].

Early-Onset and Persisting Thrombocytopenia (Monophasic Thrombocytopenia)

Table 32.3b shows a number of studies indicating that a monophasic platelet count decline described as "early-onset and persisting thrombocytopenia", i.e., a platelet count fall that persists below 100×10^9/L for more than 7 days, is not strongly associated with SRA or HIPA seroconversion [26, 27]. Indeed, a positive SRA or HIPA in such a patient is more likely to indicate subclinical seroconversion rather than true HIT [27]. However, there is a subgroup of patients with this platelet count profile who exhibit either a "superimposed" platelet count fall within the POD5–10 period, or who develop symptomatic large-vessel thrombosis, in whom a diagnosis of HIT is plausible [29].

HIT-Associated Thrombosis and HIT-Mimickers

HIT is strongly associated with thrombosis (relative risk, 12–15×; absolute risk, 50–70%) [31]. Although venous thrombosis predominates, arterial thrombosis also occurs, especially in arteriopathic patients who often undergo cardiac surgery [7, 32]. Table 32.4 describes thrombotic and other HIT-related sequelae in post-cardiac

Table 32.4 Thrombotic and non-thrombotic sequelae of HIT

Thrombosis
Venous
Deep-vein thrombosis (lower-limb)
Pulmonary embolism
Upper-limb (associated with central venous catheter)
Superficial vein thrombosis
Adrenal vein thrombosis (presents as adrenal hemorrhage, sometimes bilateral)
Cerebral venous (dural sinus) thrombosis
Mesenteric vein thrombosis
Arterial
Lower-limb artery thrombosis
Cerebral artery thrombosis
Coronary artery thrombosis
Saphenous vein grafts >> internal thoracic artery/radial artery grafts
Other arterial (brachial, radial, mesenteric, etc.)
Cardiac chamber
Intra-arterial thrombosis
Intra-ventricular thrombosis
Microvascular: acral limb ischemic necrosis
DVT-associated (venous limb gangrene[a])
Symmetrical peripheral gangrene (rare[b])
Anaphylactoid reactions (usually post-heparin bolus)
Symptoms and signs include: fever/chills, dyspnea, chest pain,
Flushing, diarrhea, cardiorespiratory arrest, transient global amnesia
Skin lesions
At heparin injection sites (necrotizing[c], non-necrotizing[d])
At sites distant from heparin injection sites

[a]Usually associated with warfarin
[b]Symmetrical peripheral gangrene usually has a non-HIT explanation
[c]Necrotizing skin lesions at heparin injection sites are strongly associated with platelet-activating HIT antibodies even if thrombocytopenia is not present
[d]Non-necrotizing skin lesions at heparin injection sites more often represent a delayed hypersensitivity reaction (T-lymphocyte-mediated) rather than immune HIT

surgery patients, occurrence of which can point to underlying HIT. Acute limb ischemia can result either from arterial thrombosis (platelet-rich "white clots") or microvascular thrombosis with deep-vein thrombosis ("venous limb gangrene") [33], or rarely from severe HIT-associated DIC alone [4].

One old study [34] found an association between post-cardiac surgery pulmonary embolism (PE) and HIT: 6/33 patients with PE had HIT versus only 4/1000 non-PE controls. The strong association between PE and HIT (OR ~55; $P < 0.0001$) mirrors that in a post-orthopedic surgery study (OR ~36; $P = 0.004$) [30].

Liu et al. [35] found saphenous vein graft (SVG) occlusion in 14/18 (78%) post-CABG patients who developed HIT and acute myocardial ischemia/infarction versus only 6/18 (33%) non-HIT patients who underwent angiography due to suspicion

of bypass graft failure; the individual SVG occlusion rate was 32/47 (68%) in the HIT patients versus 7/35 (20%) in the non-HIT controls ($P < 0.001$); in contrast, there was no difference in the occlusion rate of internal mammary grafts (1/14 vs 2/17, respectively). In a 100 patient study we found that high levels of IgG anti-PF4/heparin antibodies (without platelet count evidence of HIT) was associated with SVG (but not internal thoracic artery) occlusions [36]; none of the three SRA+ patients had SVG occlusion, however. In contrast, Gluckmann et al. [37] did not find any association between graft occlusions and presence of HIT antibodies. Similarly, in a study of over 1000 patients, anti-PF4/heparin seropositivity post-cardiac surgery (in the absence of thrombocytopenia indicating HIT) was not associated with increased risk of death or thrombosis [38].

Postoperative adrenal hemorrhage is a rare manifestation of HIT in post-cardiac surgery patients [39], and indicates adrenal vein thrombosis with secondary hemorrhagic necrosis. If both adrenal glands are affected, life-threatening adrenal crisis can result. Approximately 10% of patients with HIT develop upper-limb DVT, which invariably is associated with a central venous catheter, pointing to interaction between a systemic hypercoagulability state (HIT) with a local predisposing factor (catheter) [40]. Other unusual presentations of HIT post-cardiac surgery include transient global amnesia [41] and the occurrence of fever/chills, cardiorespiratory arrest, or other untoward symptoms/signs (including transient global amnesia) following a heparin bolus (HIT-associated anaphylactoid reaction) [23, 42].

Differential Diagnosis of Post-cardiac Surgery Thrombocytopenia

Many non-HIT thrombocytopenic disorders can occur in post-cardiac surgery patients (Table 32.5). These disorders can be grouped into those that present with early thrombocytopenia versus those that present with late thrombocytopenia (on/after POD5). Thrombocytopenia can also reflect in whole or in part the presence of a preexisting thrombocytopenic disorder.

Some thrombocytopenic disorders can closely mimic HIT, either because of thrombosis concurrence or timing of onset of thrombocytopenia. Five HIT-mimicking disorders are considered in more detail.

HIT Mimicker: Symmetrical Peripheral Gangrene

Sometimes, post-cardiac surgery shock (cardiogenic, septic/inflammatory) results in thrombocytopenia and coagulopathy; within a few days, limb ischemia develops, suggesting a potential diagnosis of HIT. However, acute DIC complicating cardiogenic or septic shock can lead to acral limb ischemic necrosis affecting both toes/feet, and sometimes also fingers/hands, for non-HIT reasons. Such “symmetrical

Table 32.5 Differential diagnosis of HIT-mimicking illnesses (partial list)

Early-onset thrombocytopenia
Hemodilution/platelet consumption
Occurs universally
Postoperative disseminated intravascular coagulation (DIC)
Cardiogenic shock, septic shock/systematic inflammatory response syndrome (SIRS), multi-organ system failure (MOSF)
Acute DIC/shock liver-associated symmetrical peripheral gangrene
Protamine (heparin)-induced thrombocytopenia (rare)
Thrombotic microangiopathy
Post-cardiac surgery thrombotic thrombocytopenic purpura (TTP) (rare)
Late-onset thrombocytopenia
Immune-mediated
Drug-induced immune thrombocytopenic purpura (D-ITP)
E.g., vancomycin, quinidine, cephalosporins
Posttransfusion purpura (PTP)
Preexisting thrombocytopenic disorders
Hypersplenism (e.g., subacute bacterial endocarditis, congestive heart failure, cirrhosis,)
Bone marrow neoplastic disorders, primary (e.g., myelodysplasia) or secondary (metastatic carcinoma)
Hereditary thrombocytopenia (e.g., MYH9 macrothrombocytopenia, β-tubulin)

Abbreviation: MYH9 myosin heavy chain 9

peripheral gangrene" develops despite palpable (or Doppler-identifiable) pulses. Recently, preceding "shock liver" (acute ischemic hepatitis, acute hepatic necrosis) has been implicated as a risk factor for DIC-induced microthrombosis (due to impaired hepatic synthesis of the natural anticoagulants, protein C and antithrombin) [4, 33]. In the author's experience, such patients are often misdiagnosed as having HIT. Indeed, one study of post-cardiac surgery thrombocytopenia noted that microvascular ischemia (defined as "acral hypoperfusion with temporary or permanent dark or black discoloration of fingers and/or toes") was more common when testing for HIT antibodies yielded *negative* results [43].

HIT-Mimicker: Protamine (Heparin)-Induced Thrombocytopenia (PIT)

Development of acute intra- or early postoperative thrombosis can be a consequence of protamine (heparin)-induced thrombocytopenia (PIT) [44]. This diagnosis is plausible if the patient develops intra- or early postoperative thrombocytopenia and thrombosis, in a clinical setting where protamine/heparin-dependent antibodies could be present. Risk factors include recent cardiac surgery (explaining immunization due to recent protamine neutralization of heparin) or recent preoperative administration of UFH or LMWH to a diabetic patient (who is receiving a

protamine-containing insulin preparation). PIT is caused by platelet-activating IgG that recognize multimolecular protamine/heparin complexes. Like HIT antibodies, anti-protamine/heparin antibodies are transient. Commercial assays for detecting PIT antibodies are not available, and so serum from suspected cases should be referred to laboratories performing research into this disorder.

HIT-Mimicker: Thrombotic Thrombocytopenic Purpura (TTP)

TTP is a rare immune-mediated disorder characterized by severe thrombocytopenia and microangiopathic hemolytic anemia (i.e., numerous red cell fragments found on the peripheral blood film). The pathogenesis involves autoantibodies that inhibit the von Willebrand factor (vWF)-cleaving metalloprotease, resulting in platelet-vWF microthrombi that form predominantly in arterioles. Sometimes, TTP is triggered by proinflammatory situations, including pregnancy, acute pancreatitis, and surgery, including cardiac surgery [45, 46]. Patients often exhibit neurological abnormalities and renal insufficiency, reflecting target organ arteriolar microthrombosis. Interestingly, post-surgery TTP usually occurs before POD5 (onset earlier than the typical timing of HIT). In the author's experience, the frequency of TTP in post-cardiac surgery patients is lower than in HIT by approximately two orders of magnitude. Treatment includes corticosteroids and plasma exchange.

HIT-Mimicker: Drug-Induced Immune Thrombocytopenia (DITP)

Table 32.6 lists two dozen drugs well established as causing severe thrombocytopenia due to immune mechanisms [47]; unlike HIT, which features platelet-activating antibodies, DITP is caused by antibodies that result in clearance of antibody-sensitized platelets by the macrophages of the reticuloendothelial system. Thus, platelet counts in DITP are usually $<20 \times 10^9$/L, with many patients evincing mucocutaneous hemorrhage (petechiae, ecchymoses, oral "blood blisters", gastrointestinal/genitourinary bleeding) [48]. If the responsible drug is started soon after cardiac surgery (e.g., vancomycin), then the onset of thrombocytopenia can resemble that of typical-onset HIT.

HIT-Mimicker: Post-transfusion Purpura (PTP)

PTP is a rare disorder in which severe thrombocytopenia begins about 5 days after receipt of a blood transfusion; the explanation is high titers of alloantibodies directed against a platelet-specific alloantigen which cross-react against autologous platelets,

Table 32.6 Established causes of drug-induced immune thrombocytopenia (D-ITP)

Abciximab
Acetaminophen
Amiodarone
Ampicillin
Carbamazepine
Eptifibatide
Ethambutol
Haloperidol
Ibuprofen
Irinotecan
Naproxen
Oxaliplatin
Phenytoin
Piperacillin
Quinidine
Quinine
Ranitidine
Rifampin
Simvastatin
Sulfisoxazole
Tirofiban
Trimethoprim-sulfamethoxazole
Valproic acid
Vancomycin

Although other drugs have been implicated in causing D-ITP, these 24 drugs have been identified using complementary strategies (clinical criteria; laboratory testing for drug-dependent antibodies) [47]

resulting in their immune clearance. More than 95% of PTP patients are elderly females who were exposed to the platelet alloantigen during remote pregnancy and where the blood transfusion triggers an anamnestic alloimmune response. Patients exhibit generalized mucutaneous bleeding and fatal hemorrhage can occur, particularly if the patient is coincidentally receiving warfarin anticoagulation (e.g., post-cardiac valve replacement surgery). Since blood products are often given at cardiac surgery, the timing of onset of thrombocytopenia can strongly resemble that of HIT triggered by intraoperative exposure to heparin [49].

Risk Factors

Risk of HIT in post-cardiac surgery patients primarily reflects the type, dose, and duration of postoperative heparin.

Frequency of HIT: Role of Heparin Type Used for Antithrombotic Prophylaxis

The risk of postcardiac surgery HIT depends strongly on whether postoperative heparin thromboprophylaxis is given or not, and if given, its dose, duration and whether the heparin is UFH or low-molecular-weight heparin (LMWH). If no postoperative heparin is given, then HIT will occur only if unusually potent HIT antibodies are formed that activate platelets in the absence of heparin (autoimmune HIT). This complication is uncommon (<1%). However, if postoperative UFH is given, and extended for at least 1 week, risk of HIT rises to ~1%; and if heparin use goes beyond POD10, and if given in therapeutic concentrations, the risk rises to approximately 2–3% [4]. The proportion of patients who develop HIT is a small minority among those who form anti-PF4/heparin antibodies [24–27, 29], suggesting that patient-specific factors (e.g., variable reactivity to HIT antibodies, etc.) are important.

Risk of HIT has been proven lower with LMWH (versus UFH) in various noncardiac surgery patient populations [50, 51]. However, despite universal intraoperative exposure to UFH (the major immunizing trigger), it seems likely (based on observational studies) that the risk of HIT with LMWH thromboprophylaxis given post-cardiac surgery (versus UFH) is also lower. For example, a review [4] of studies from the Tours (France) group found a frequency of serologically-confirmed HIT with UFH of 11/437 (2.5%) versus only 8/1703 (0.5%) with LMWH (dalteparin) ($P = 0.0004$). Similarly, another group [52] reported a frequency of HIT of 23/984 (2.3%) with UFH versus only 1/738 (0.1%) with LMWH ($P < 0.0001$). Another study also found a lower risk of HIT with LMWH (dalteparin) after heart valve surgery [53]. However, mitigating against a strong recommendation for LMWH thromboprophylaxis post-cardiac surgery is the lack of randomized trials proving antithrombotic efficacy of LMWH (versus UFH) in this clinical setting.

Frequency of HIT: Other Risk Factors

Other risk factors for HIT post-cardiac surgery are not well-established. One study found greater risk for females (OR = 1.92 [95% CI, 1.20–3.07]; $P = 0.005$) [54]. Another found an association between HIT and intraoperative platelet transfusions [32]. Although a relatively "short" cardiopulmonary bypass time of <2 h was identified in one study [28], this could reflect higher relative risk of non-HIT thrombocytopenia with prolonged pump times.

Recommendations Based on the Data

Overall Approach to Diagnosis of HIT

HIT is a clinical-pathological syndrome [2], i.e., the diagnosis should be based on both: (A) a compatible clinical picture, particularly, otherwise unexplained thrombocytopenia bearing a temporal relationship with proximate exposure to heparin, often accompanied by thrombosis, and (B) detectability of heparin-dependent, platelet-activating antibodies, either demonstrated directly (e.g., serotonin-release assay) or inferred through a strong-positive immunoassay. A scoring system can be used to help judge clinical probability of HIT.

4Ts Scoring System

A scoring system (4Ts) can help clinicians to determine clinical probability of HIT, based upon the 4Ts mnemonic: ***T***hrombocytopenia, ***T***iming (of onset of thrombocytopenia or thrombosis), ***T***hrombosis (or other sequelae of HIT); o***T***her explanation(s) for thrombocytopenia not likely [55]. Each of the 4Ts can be scored as 0, 1, or 2 points (maximum, 8 points). However, the maximum score for ***T***hrombocytopenia is only 1 point (rather than 2 points), if assessment is within 3 days of cardiac surgery [55]. The probability of HIT ranges from approximately 2% to 10% to 50%, respectively, for low ($\leq$3 points), intermediate (4 or 5 points), or high ($\geq$6 points) scores.

Platelet Count Monitoring for HIT

It is routine practice to measure the complete blood count (CBC) for the first few days post-cardiac surgery, to assess bleeding (hemoglobin), infection (white blood count), or dilutional/consumptive thrombocytopenia (platelet count). However, the strong predictive value of a biphasic platelet count fall for HIT infers that it is also reasonable to monitor the platelet count *at least* every other day from POD4 onwards [56, 57]. Since per Table 32.3 a biphasic platelet count fall occurring between POD5 to 10 is highly specific for HIT, regular platelet count monitoring during this period is appropriate, if the patient is still receiving heparin and if monitoring is practicable (i.e., in-patient status).

Laboratory Diagnosis

Laboratory testing for HIT antibodies is crucial for supporting or refuting a diagnosis of HIT. However, anti-PF4/heparin antibodies are frequently detectable after heart surgery, posing risk of HIT overdiagnosis. The probability of a true diagnosis of HIT increases greatly with greater strength of a positive test result (using a PF4-dependent enzyme-immunoassay) [58]. Detecting platelet-activating antibodies by platelet serotonin-release assay maximizes diagnostic specificity [2, 25, 59]. Recent availability of rapid assays (e.g., latex immunoturbidimetric assay, chemiluminescence immunoassays) with overall high sensitivity/specificity tradeoff offers opportunity for real-time diagnosis [60].

Personal View of the Findings

Platelet Count Monitoring for HIT

The more recent American College of Chest Physicians (ACCP) guidelines [57] recommend platelet count monitoring only for patients with expected risk of HIT >1%, which would probably include only those receiving postoperative UFH. However, this is controversial; the author's institution routinely performs daily post-cardiac surgery platelet count monitoring even though our standard is LMWH (dalteparin) thromboprophylaxis post-cardiac surgery, and even though our frequency of HIT is less than 1%. Our practice is more consistent with the earlier 2008 [56] versus the later 2012 ACCP guidelines [57]. In my opinion, a practical approach is simply to perform a daily CBC in postoperative patients until hospital discharge (or POD14, whichever is sooner); being alert to a biphasic platelet count fall that *begins* after POD4 is crucial for timely identification of HIT. Any such platelet count fall of at least 30% (i.e., the minimum platelet count threshold that yields 1 point in the 4Ts scoring system), in relation to the preceding postoperative peak platelet count, warrants a prompt repeat CBC, and if a falling platelet count is confirmed, investigations and possible treatment for HIT.

Treatment of HIT

Although a detailed description of HIT treatment is beyond this chapter's scope, some general comments are warranted. First, it is important to avoid warfarin (and other vitamin K antagonists) in patients with HIT and – if warfarin has already been

given – to provide vitamin K antidote [56, 57]. This is because vitamin K antagonism is a major risk factor for inducing microthrombosis, especially in a limb with a DVT (venous limb gangrene) [33].

Second, when HIT is strongly suspected or confirmed, it is important to begin anticoagulation with an alternative (nonheparin) anticoagulant [56, 57]. Although in my opinion the risk of continued heparin anticoagulation is not as great as commonly believed, for medical-legal reasons, it is important to stop heparin (if still being given), to avoid further heparin use (including through heparin flushes), and to anticoagulate with an alternative agent (usually in therapeutic doses). Although direct thrombin inhibitors (e.g., argatroban, bivalirudin) that require monitoring with the partial thromboplastin time (PTT) are frequently given (indeed, argatroban is approved by the U.S. Food and Drug Administration for treating HIT), this author prefers anticoagulants that do not mandate monitoring, such as danaparoid (not available in the U.S.), fondaparinux, or even a direct oral anticoagulant (e.g., rivaroxaban, apixaban) [22, 61]. This is because PTT values can be elevated due to severe HIT itself (or for other factors), in which case PTT monitoring can lead to erroneous dose adjustments ("PTT confounding") [62].

Sometimes a diagnosis of HIT is initially unclear, e.g., a patient presenting on POD14 with PE and a platelet count of 175×10^9/L. Pending test results, it is relatively straightforward to treat such a patient with a non-heparin anticoagulant such as fondaparinux [61, 63] or rivaroxaban [22].

Third, minimize prophylactic platelet transfusions (as HIT-related bleeding is uncommon) and avoid inserting an inferior vena cava filter (risk of severe limb-threatening lower-limb thrombosis) [56].

Heparin Rechallenge in a Patient with a Previous History of HIT

A special situation arises when a patient with a history of HIT requires heart surgery. Given risks of performing cardiac surgery with a non-heparin anticoagulant, the most common approach is to give UFH in such patients, provided that platelet-activating antibodies are unlikely to be present [64, 65], and to provide postoperative anticoagulation with a non-heparin anticoagulant, if required. In such patients, recurrent HIT will only occur on/after POD5, and only if autoimmune HIT antibodies are formed. In a series of 20 patients with previous HIT who underwent heparin reexposure (usually for cardiac surgery), only 1 patient (5%) developed recurrent HIT [64].

Recommendations
Below are recommendations aimed at improving diagnosis of HIT in post-cardiac surgery patients.

- Daily (or, at least, every-other-day) platelet counts (until POD14, hospital discharge, or discontinuation of heparin, whichever occurs first) are recommended to facilitate diagnosis of HIT (evidence quality moderate; strong recommendation.
- A biphasic platelet count fall (>40%) with the second platelet count fall *beginning* 5–10 days post-cardiac surgery indicates probable HIT unless proven otherwise (evidence quality high; strong recommendation).
- The "baseline" platelet count (for calculating per cent platelet count fall) is the highest postoperative platelet count that immediately precedes the putative HIT-related platelet count fall (evidence quality high; strong recommendation).
- Clinically-evident artery or deep-vein thrombosis/pulmonary embolism that begins 5–30 days after heart surgery should prompt consideration of a diagnosis of HIT (evidence quality moderate; strong recommendation).
- Laboratory testing for HIT antibodies is important for confirming a diagnosis of HIT; patients with HIT typically test (strongly) positive in both a sensitive immunoassay (e.g., PF4-dependent EIA) and a washed platelet activation assay (e.g., serotonin-release assay) (evidence quality strong; strong recommendation).

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Chapter 33
Newest Antithrombotic Agents: Uses, Challenges, and Reversal Strategies for Surgical Procedures

Eisha Wali and Sandeep Nathan

Introduction

An estimated 250,000 individuals on antithrombotic therapy require a procedural intervention each year, with an attendant risk for major bleeding [1]. In the perioperative setting, these patients present various challenges, due to significant risks of both bleeding and thrombosis. As the use of newer antithrombotics becomes more widespread, an updated understanding regarding optimal timing and duration of therapy, perioperative management, and reversal agents in the event of major bleeding complications is necessary. In this chapter we will review the pharmacokinetics and pharmacodynamics of commonly used oral antiplatelet and anticoagulant agents and detail their contemporary applications along with generally accepted strategies for discontinuation and reversal in the perioperative period.

Search Strategy

A PubMed search of English language literature published between 2002 and 2017 was performed to identify recently published data on management of anti-thrombotic agents in the peri-operative or intensive care settings, as outlined in PICO format in Table 33.1. The search terms "antithrombotic/anticoagulation/antiplatelet" along with "perioperative," "intensive care unit," "cardiothoracic surgery," or "reversal"

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Table 33.1 PICO table of reversal strategies of antithrombotic agents

Patients	Intervention	Comparator	Outcomes
Adults patients on antithrombotic therapy in the perioperative setting	Reversal of antithrombotic therapy	Standard care: judicious infusion of blood products	Transfusion requirements, bleeding complications, survival

were used. References of relevant articles were utilized to further expand the search. Current professional society practice guidelines and associated citations were also reviewed.

The quality of data in the papers evaluated was classified according to the GRADE system.

Results

Choosing an Antithrombotic Agent

Antiplatelet Therapy

Antiplatelet therapy is a mainstay of pharmacologic management of cardiovascular disease. Aspirin is the most commonly prescribed antiplatelet agent. In addition to its role as an antipyretic, analgesic, and anti-inflammatory agent, aspirin is also utilized for primary and secondary prevention of myocardial infarction (MI) as well as management of patients with acute coronary syndromes (ACS), cerebrovascular disease, and peripheral arterial disease (PAD) [2]. Aspirin irreversibly binds to cyclooxygenase-1 (COX-1), decreasing platelet-derived generation of thromboxane A2 (TXA2), thus limiting local availability of TXA2 for binding with the platelet thromboxane prostanoid receptor and inhibiting platelet activation [3, 4]. The adenosine $P2Y_{12}$ receptor is one of eight purinergic receptors found on the platelet surface and the one most closely linked with sustained platelet activation. Oral inhibitors of the ADP $P2Y_{12}$ receptor include the thienopyridines, clopidogrel and prasugrel, which irreversibly bind to the ADP-binding site of the $P2Y_{12}$ receptor as well as the cyclopentyltrazolopyrimidine, ticagrelor, which binds reversibly to an alternate site on the $P2Y_{12}$ receptor [3]. Clopidogrel is a prodrug that requires multi-step conversion to its active thiol metabolite via the cytochrome P450 pathway. Due to a variety of patient- and disease state-specific variables as well as genetic polymorphisms, approximately 30% of patients fail to respond appropriately to this compound [4, 5]. Clopidogrel is indicated for the acute and chronic management of patients with ischemic heart disease including acute coronary syndromes managed medically or with coronary revascularization as well as in patients with peripheral arterial disease [6]. Prasugrel is also a prodrug dependent on the CYP450 pathway; however, it is less susceptible to interindividual variability [5]. Prasugrel is indicated in the treatment of ACS or ST-segment elevation myocardial infarction (STEMI) managed with percutaneous coronary intervention (PCI); it is contraindicated in patients with history of transient ischemic attacks or ischemic stroke [7]. The non-thienopyridine $P2Y_{12}$ receptor antagonists include ticagrelor and cangrelor. Ticagrelor, as noted, binds reversibly to the $P2Y_{12}$

receptor and is indicated in patients with ACS or history of MI and has been shown to be superior to clopidogrel for reduction of major adverse cardiac events (MACE) inclusive of coronary stent thrombosis [8]. Ticagrelor has a more rapid onset and offset than clopidogrel, with greatest offset in platelet inhibition within the first 48–72 h after drug discontinuation [9]. Cangrelor is also a reversible P2Y-$_{12}$ receptor inhibitor; however, it is unique in that it is administered in a parenteral fashion and has an extremely short half-life (~3 to 6 min). Platelet function recovers within 60 min of discontinuing the IV infusion, making cangrelor an ideal bridge to surgery in patients for whom the thrombotic risk of discontinuing dual antiplatelet therapy (DAPT) and the bleeding risk of surgical intervention on antiplatelet therapy are both high [5].

Vorapaxar is a potent, reversible platelet protease activator receptor 1 (PAR-1) inhibitor which blocks thrombin-mediated platelet activation. In patients with recent MI or ischemic stroke or with significant PAD, vorapaxar in addition to standard DAPT therapy lead to a reduction in a composite primary end point of cardiovascular death, MI, and stroke; however, there is also a significantly increased risk of bleeding and use is contraindicated in patients with history of prior stroke [10]. Initiation of vorapaxar should be delayed by a minimum of 2 weeks after an MI [11].

A summary of pertinent pharmacokinetic and pharmacodynamics properties of the commonly used oral antiplatelet agents may be found in Table 33.2.

Table 33.2 Pharmacokinetics and pharmacodynamics of commonly used oral antiplatelet agents

Oral antiplatelet agents							
	MOA	Route	Onset	Half-life	Metabolism	Excretion	Specific reversal agents
Aspirin	Irreversible COX-1 inhibitor	PO	1–4 h	5–6 h	Metabolized in liver	Urine	None
Clopidogrel	Irreversible $P2Y_{12}$ receptor antagonist	PO	Dose-dependent	6 h (parent drug); 30 min (active metabolite)	Metabolized in liver	Urine, feces	None
Prasugrel	Irreversible $P2Y_{12}$ receptor antagonist	PO	<30 min (loading dose)	7 h	Prodrug; metabolized in intestine and liver	Urine, feces	None
Ticagrelor	Reversible $P2Y_{12}$ receptor antagonist	PO	30 min–2 h	7–9 h	Not a prodrug; metabolized in liver to active metabolite	Feces, urine, bile	None
Vorapaxar	Effectively irreversible thrombin receptor antagonist (PAR-1)	PO	1–2 h	4–8 d	Not a prodrug; metabolized in live	Feces, urine	None

Anticoagulation

There are four main classes of available medications for systemic anticoagulation: heparin-based anticoagulants, vitamin K antagonists, factor Xa inhibitors, and direct thrombin inhibitors. Heparin-based products potentiate antithrombin III-mediated inhibition of factor Xa. Unfractionated heparin (UFH) also inhibits thrombin to a variable degree. UFH is administered via continuous intravenous infusion and requires close laboratory monitoring to assess for adequate response to dosing. Low-molecular-weight heparins (LMHW) comprise a family of compounds varying in molecular size and ratio of anti-Xa:anti-IIa activity, are typically administered subcutaneously and do not typically require laboratory monitoring, although anti-factor Xa levels can be measured to assess response if indicated [12]. Heparin-based anticoagulants have a variety of clinical applications, including prevention and treatment of arterial and venous thrombosis and management of thromboembolic risks in atrial fibrillation [13]. Heparin-induced thrombocytopenia is a feared immune-mediated complication of heparin-based therapy that can lead to serious and sometimes fatal, thrombotic events [14].

Vitamin K antagonists (VKAs), such as warfarin, affect the coagulation cascade by preventing conversion of vitamin K to its 2,3 epoxide, thus preventing activation of the procoagulant vitamin K-dependent factors II, VII, IX, X and the anticoagulant proteins, C and S. Disadvantages include the need for frequent monitoring, a narrow therapeutic index, and several drug-drug interactions [15]. VKAs are indicated in patients with venous thrombosis, pulmonary embolism, and atrial fibrillation with increased thromboembolic risk [16]. While there are historical data to suggest incremental ischemic benefit of VKAs when combined with antiplatelet therapy in patients who have sustained MI, this drug class is rarely used in this capacity [17].

Fondaparinux is an indirect factor Xa inhibitor that is subcutaneously administered. It is approved for prophylaxis of deep vein thrombosis (DVT) in specific populations including orthopedic indications, treatment of venous thromboembolism (VTE) in conjunction with warfarin, and has also been validated as an effective anticoagulation strategy in patients with ACS [18, 19].

Direct oral anticoagulants (DOACs) target specific components of the coagulation cascade. The direct oral factor Xa inhibitors, rivaroxaban, apixaban, edoxaban and betrixaban bind reversibly to the active sites of both free and clot-bound factor Xa. These compounds do not require laboratory monitoring, have fewer drug-drug interactions than the VKAs and pose no interaction with dietary vitamin K intake however, are more difficult to assess with respect to the degree of anticoagulation. Rivaroxaban is non-inferior to warfarin for prevention of stroke or systemic embolism in patients with atrial fibrillation (AF) and for treatment of patients with VTE [20, 21]. Apixaban was found to be superior to warfarin in preventing stroke or systemic embolism in patients with nonvalvular AF with less rates of major bleeding and lower mortality [22]. Edoxaban is a newer direct factor Xa inhibitor approved for VTE and AF. Betrixaban is approved for the prophylaxis of venous thromboembolism (VTE) in adult patients [23].

Direct thrombin inhibitors (DTI), such as dabigatran, are DOACs that competitively inhibit the active site of thrombin, interfering with formation of fibrin polymers. In nonvalvular AF, high-dose dabigatran (150 mg BID) was found to be superior to warfarin at preventing stroke and was equally likely to cause major bleeding [24]. Dabigatran can also be used to prevent recurrence of DVT or PE.

The parenteral DTIs argatroban, lepirudin and bivalirudin are utilized in cases where heparin is contraindicated, such as in heparin-induced thrombocytopenia [3].

A summary of pertinent pharmacokinetic and pharmacodynamics properties of the commonly used oral and selected parenteral anticoagulant agents may be found in Table 33.3.

Perioperative Guidelines

In the perioperative setting, relative risks of bleeding and thromboembolism must be carefully assessed. Bleeding risk is dependent on both procedural characteristics as well as patient characteristics. Factors such as female sex, age greater than 75, renal disease, and body weight less than 60 kg have been associated with an increased risk of bleeding [5]. Various scoring systems, such has the HAS-BLED score which takes into account age, certain comorbidities, and concomitant use of drugs/alcohol, have been proposed to help estimate bleeding risk [1].

Per the ACC/AHA 2016 guidelines, elective surgeries should be delayed for 30 days after placement of a bare metal stent and 6 months after placement of a drug-eluting stent (class I recommendation) [25]. Patients requiring non-elective surgery less than 4–6 weeks after stent placement should continue DAPT unless the risk of bleeding is greater than the risk of stent thrombosis; if the $P2Y_{12}$ inhibitor must be stopped due to bleeding risk, it should be restarted as soon as possible after surgery and aspirin should be continued peri-operatively [25]. Patients undergoing coronary artery bypass grafting (CABG) should continue aspirin through the perioperative period and stop $P2Y_{12}$ inhibition five to seven days prior to surgery, contingent on the potency of the agent being used and the preference of the surgical operator [26]. While these recommendations may also be applied to many other open surgical procedures as well, duration of preoperative interruption of one or both antiplatelet agents may need to be modified depending on the type of surgery being performed and the potential consequences of perioperative bleeding. In patients with ACS or coronary stent implantation who require CABG, bridging with low-dose cangrelor (0.75 μg/kg/min) up until one to six hours prior to surgery has been shown to effectively maintain low levels of platelet reactivity during the treatment period without an increase in CABG-related bleeding [27]. Timing of oral DAPT reinitiation following surgery along with optimal duration of DAPT, should be addressed prior to discharge.

For patients on anticoagulation, the CHEST guidelines suggest risk stratifying patients to determine potential for perioperative thromboembolism [26]. This includes calculating a classic $CHADS_2$ score (incorporating presence of congestive

Table 33.3 Pharmacokinetics and pharmacodynamics of oral and selected parenteral antiplatelet agents

Oral anticoagulant agents							
	MOA	Route	Onset	Half-life	Metabolism	Excretion	Specific reversal agents
Heparin-based							
Unfractionated heparin	Potentiates anti-thrombin III; inhibits factor IIa	IV	Immediate	1–2 h	Metabolized in liver and reticuloendothelial system	Urine	Protamine sulfate
Enoxaparin	Inhibits factor Xa > IIa	SubQ	3–5 h	4.5–7 h	Metabolized in liver	Urine	Protamine sulfate (partial reversal)
Dalteparin	Inhibits factor Xa > IIa	SubQ	1–2 h	3–5 h	Metabolized in liver	Urine	Protamine sulfate (partial reversal)
Tinzaparin	Inhibits factor Xa > IIa	SubQ	4–6 h	1–2 h	Metabolized in liver	Urine	Protamine sulfate (partial reversal)
Vitamin K antagonists							
Warfarin	Depletes functional Vitamim K reserves	PO	24–72 h	20–60 h	Metabolized in liver	Urine	Vitamin K; PCC; FFP
Factor Xa inhibitors							
Rivaroxaban	Direct Xa inhibition	PO	2–4 h	5–13 h	Metabolized in liver	Urine, feces	Andexanet alfa; PCC
Apixaban	Direct Xa inhibition	PO	3–4 h	8–15 h	Metabolized in liver	Urine	Andexanet alfa; PCC
Edoxaban	Direct Xa inhibition	PO	1–2 h	10–14 h	Metabolized in liver	Urine	Andexanet alfa; PCC
Fondaparinux	Indirect Xa inhibition	SubQ	2–3 h	17 h	Not well-established	Urine	None
Direct thrombin inhibitors							
Dabigatran	Direct thrombin inhibition	PO	1–2 h	12–14 h	Prodrug; metabolized in liver	Urine	Idarucizumab
Argatroban	Direct thrombin inhibition	IV	Immediate onset	30–60 min	Metabolized in liver	Urine, feces	None
Bivalirudin	Direct thrombin inhibition	IV	Immediate onset	30 min	Proteolytic cleavage	Urine	None

heart failure, hypertension, age >75, diabetes, or prior stroke/transient ischemic attack) to assess thrombotic risk [28]. High-risk patients are defined as those with greater than a 10% annual risk for thromboembolism. These include patients with a mechanical mitral valve, AF with a $CHADS_2$ score of 5 or 6, history of VTE within the past 3 months, or a severe thrombophilia [1].

Patients on anticoagulation therapy that should be continued perioperatively can be bridged with unfractionated heparin. Normal hemostasis is typically achieved 3–4 h after discontinuing UFH. Low molecular weight heparin should be held at least 24 h prior to surgery and perhaps longer in patients with renal insufficiency [29, 30]. Per the guidelines, Vitamin K antagonists should be stopped 5 days prior to surgery and resumed 12–24 h post-operatively once adequate hemostasis has been achieved [26]. Bridging with heparin-based therapy is recommended for all patients with a mechanical heart valve and those with AF or VTE that are at high risk for thromboembolism but not for patients at low risk [26]. The Effectiveness of Bridging Anticoagulation for Surgery (BRIDGE) Study comparing bridging with dalteparin versus placebo in patients with AF requiring perioperative interruption of warfarin found significantly higher incidence of major bleeding risk associated with bridging than with placebo (3.2% versus 1.3%) with no significant difference in incidence of venous or arterial thromboembolism [31].

Few studies assess perioperative management of the newer anticoagulant therapies. A subgroup analysis of the Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) With Dabigatran Etexilate trial looked at 4591 patients with AF that had anticoagulant therapy interrupted at least once for an invasive procedure. The rates of perioperative bleeding and thromboembolism were not significantly different between dabigatran and warfarin, even in the case of urgent or major surgery [32]. Patients with AF plus an additional risk factor for stroke in the Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) trial that underwent a procedure while on anticoagulation did not have a statistically significant difference in rates of major periprocedural bleeding between the apixaban arm and the warfarin arm (1.625 vs 1.93%). Rates of stroke or systemic embolism in the 30-day post-procedure period were also found to be similar (0.35% versus 0.57%) [33]. Table 33.4 provides summaries of selected studies of peri-procedural interruption of antithrombotic agents.

Clinical Challenges in the Use of Antithrombotic Therapies

Management of antiplatelets and anticoagulants in the perioperative setting can present clinical dilemmas; common challenges include making decisions based on unknown indication for therapy, balancing ideal duration of antithrombotic therapy with timing of surgery, and coordinating interruption of therapy when necessary, including bridging, when indicated, and restarting therapy as soon as feasible from the perspective of postoperative bleeding.

Table 33.4 Selected data on peri-procedural interruption of antithrombotic therapy

Peri-procedural interruption of antithrombotics						
Author (year), reference #	Study type	Study population	Number of patients	Drugs studied	Results	Quality of evidence
Angiolillo (2012) [27]	Randomized controlled trial	Patients undergoing non-emergent CABG previously on thienopyridine for ACS or stent	210	Cangrelor	Patients on cangrelor vs placebo were more likely to have low platelet reactivity (98.8% vs 19.0%, $p < 0.001$). No significant difference in excessive CABG-related bleeding between patients on cangrelor vs placebo (11.8% vs 10.4%, $p = 0.7$)	High
Douketis (2015) [31]	Randomized controlled trial	Patients on warfarin for atrial fibrillation requiring therapy interruption for elective invasive procedure	1884	Low molecular weight heparin	No bridging is non-inferior to bridging with low molecular weight heparin with respect to rates of arterial thromboembolism (0.4% vs 0.3%, $p = 0.01$ for noninferiority). Incidence of major bleeding was lower with no bridging (1.3% vs 3.2%, $p = 0.005$ for superiority)	High
Healey (2012) [32]	Secondary analysis of randomized controlled trial	Patients randomized to dabigatran or warfarin requiring peri-procedural therapy interruption	4591	Dabigatran, warfarin	No significant difference in rates of major periprocedural bleeding between dabigatran 110 mg vs warfarin ($p = 0.28$) or between dabigatran 150 mg vs warfarin ($p = 0.58$). Patients on dabigatran were assigned shorter interruptions in therapy (49 vs 114 h)	Moderate
Garcia (2014) [33]	Secondary analysis of randomized controlled trial	Patients with atrial fibrillation on chronic apixaban or warfarin requiring a procedure	9260	Apixaban, warfarin	In patients treated with apixaban, 30-day all cause mortality was similar whether therapy was interrupted periprocedure or not (1.0% vs 1.4%, OR 0.754 [0.440–1.295]). In patients treated with warfarin, 30-day mortality was lower in patients with therapy interruption than in those continued on treatment periprocedure (0.5% vs 2.0%, OR 0.406 [0.264–0.625])	Moderate

Intensity of antithrombotic therapy must be re-evaluated at regular intervals to match ischemic risk and risk of bleeding, particularly prior to a planned procedure. For instance, continuing a $P2Y_{12}$ inhibitor in addition to aspirin for 30 months versus 12 months after coronary stent placement significantly increases risk of moderate or severe bleeding, though it does decrease risk of major adverse cardiovascular outcomes [34]. The DAPT score can be utilized to assess late ischemic and bleeding risks to help stratify which patients would benefit from extended use of DAPT [35]. Table 33.5 outlines key source data relevant to the duration of DAPT as well as individualized risk/benefit analysis.

Risk assessment tools such as the $CHADS_2$/CHA_2DS_2-VAS_C and HASBLED scores should be utilized to help quantify thrombotic and bleeding risks for patients on anticoagulation. The $CHADS_2$ score has demonstrated validity in predicting thrombotic events after cardiac surgery [36]. It bears recognition that scores often change over time, contingent on the patient's age and accrual of additional risk factors and so, anticoagulation approach may need to be adjusted accordingly. In patients who are on a DOAC, it is also imperative to routinely reassess renal function as bleeding risk can increase significantly with inadvertent overdosing in the setting of decreasing glomerular filtration rate (GFR) [37]. The perioperative setting is a particularly appropriate time to readdress this and encourage adherence to guideline-supported anticoagulation strategies.

Patients with indications for both dual-antiplatelet therapy as well as anticoagulation can present unique challenges; these patients should generally avoid extended triple-therapy or only do so with adequate dose-reduction. In the WOEST trial (What is the Optimal antiplatElet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing), patients on chronic VKA anticoagulation requiring PCI had increased bleeding when both a $P2Y_{12}$ inhibitor and aspirin were added compared to only adding a $P2Y_{12}$; there was no significant difference in thrombotic events [38]. The PIONEER AF-PCI study (A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) assessed various permutations of anticoagulation with VKA versus different doses of rivaroxaban with one or two antiplatelet agents in a similar patient population [39]. Triple therapy with a VKA had the highest bleeding risk; low-dose rivaroxaban (15 mg daily) with a $P2Y_{12}$ inhibitor only or very-low-dose rivaroxaban (2.5 mg twice a day) with dual-antiplatelet therapy were associated with significantly lower bleeding risk and similar efficacy. The Cardiovascular OutcoMes for People Using Anticoagulation StrategieS (COMPASS) trial randomized 27,395 patients with stable atherosclerotic disease to either rivaroxaban 5 mg po BID, rivaroxaban 2.5 mg po BID plus low-dose aspirin or aspirin alone and found that combined therapy with low-dose aspirin plus low-dose rivaroxaban was superior to aspirin alone for MACE reduction but incurred more bleeding risk [40]. At the time of writing however, the aforementioned low-dose rivaroxaban strategies are not FDA-approved.

Table 33.5 Selected data on risks of thrombotic or bleeding events related to length of antithrombotic therapy

Risks associated with duration of antithrombotic therapy						
Author (year), reference #	Study type	Study population	Number of patients	Drugs studied	Results	Quality of evidence
Mauri (2014) [34]	Randomized controlled trial	Patients with drug-eluting stent without major adverse cardiac events over first 12 months of dual antiplatelet therapy	9961	Clopidogrel, prasugrel	Continuation of clopidogrel or prasugrel for an additional 18 months after completion of 12 months of dual-antiplatelet therapy decreased rates of stent thrombosis (0.4% vs 1.4%, $p < 0.001$) and myocardial infarction (2.1% vs 4.1%, $p < 0.001$) but increased rate of moderate/severe bleeding (2.5% vs 1.6%, $p = 0.001$)	High
Yeh (2016) [35]	Secondary analysis of randomized controlled trial	Patients with drug-eluting an/or bare metal stent without major adverse cardiac events over first 12 months of dual-antiplatelet therapy	11,648	Clopidogrel, prasugrel	Patients with high scores on presented prediction tool had significantly fewer ischemic events when clopidogrel/prasugrel was continued an additional 18 months (2.7% vs 5.7%, $p < 0.001$) while difference for patients with low scores did not (1.7% vs 2.3%, $p = 0.07$) (interaction $p < 0.001$). Patients with high risk scores also had smaller increases in bleeding with prolonged dual antiplatelet therapy (1.8% vs 1.4%, $p = 0.26$) than those with low scores (3.0% vs 1.4%, $p < 0.001$) (interaction $p = 0.02$)	Moderate

Reversal Strategies

Patients on antithrombotic agents who develop major bleeding while on therapy or who require an urgent procedure with a high bleeding risk can be particularly difficult to manage. In addition to holding further antithrombotic therapies and initiating supportive care with intravenous fluids and local hemostatic measures, these patients often require transfusion of blood products and may merit reversal of iatrogenic coagulopathies.

Blood Products

Patients with clinically significant bleeding of any etiology typically require transfusion of packed red blood cells. Depending on the extent of bleeding, additional products, including platelets, fresh frozen plasma, and cryoprecipitate may be added due to consumption and dilution of factors as well as underlying coagulopathies [41].

Transfusion of exogenous platelets in the setting of irreversibly-binding antiplatelet agents such as aspirin, clopidogrel, or prasugrel may help improve platelet function but may also potentiate a pro-thrombotic state. It should be noted that ticagrelor binds reversibly to the $P2Y_{12}$ receptor, theoretically limiting the effectiveness of platelet transfusions [3].

Fresh frozen plasma (FFP) contains the procoagulant factors II, V, VII, VIII, IX, X, and XI and fibrinogen, as well as anticoagulant proteins C, S, and antithrombin [42]. It has been utilized in patients with massive bleeding with various underlying coagulopathies, including VKA therapy, liver disease, disseminated intravascular coagulation, and a post-operative state [43].

DOACs tend to be more difficult to reverse with blood product administration, perhaps due to reversible binding to targets which allows for inhibition of exogenously administered factors as well [44]. Prothrombin complex concentrate (PCC) has historically been the agent of choice for reversal of oral factor Xa inhibitors as the high concentration of factors helps overcome this effect. The concentrated formulation also means that smaller volumes of product can be utilized, minimizing risks of volume-overload and allowing for faster reversal times [45]. The CHEST guidelines currently recommend using 4-factor PCC for VKA-associated major bleeding rather than FFP [46]. In a randomized study of patients on a VKA who required reversal prior to cardiopulmonary bypass, PCC was associated with faster and more successful INR reversal than FFP [47]. A randomized controlled trial utilizing surrogate laboratory markers in healthy subjects found that PCC reversed the anticoagulant effect of rivaroxaban (as measured by the activated prothrombin time and endogenous thrombin potential) but had no influence on the anticoagulant effect of dabigatran [48]. The risk of thrombosis with administration of PCC has been reported as 1.8% for 4-factor PCC and 0.7% for 3-factor PCC [15].

In a retrospective study of patients on DOACs (dabigatran, rivaroxaban, or apixaban) or warfarin that presented with clinically significant bleeding, the total amount of blood product received was found to be similar between the two groups; however,

patients on warfarin were more likely to receive PCC and/or fresh frozen plasma while those on DOACs received more packed red blood cells [49].

Specific Reversal Agents

Unfractionated heparin can be reversed with protamine, a cationic protein that binds directly to heparin [3]. Protamine has also been used for patients on low molecular weight heparin but is only partially effective [12].

For patients on VKAs, oral or parenteral vitamin K may be utilized either alone or in conjunction with direct administration of vitamin K-dependent factors. Exogenously administered factors have a short life, while administration of vitamin K has a slower effect and can prolong resistance to VKAs.

Dabigatran is the DOAC with the first commercially available reversal agent. Idarucizumab is a monoclonal antibody that binds to dabigatran with a very high affinity, preventing interaction of dabigatran with thrombin [3]. In patients requiring reversal of anticoagulation prior to an urgent procedure, normal intraoperative hemostasis was achieved in 92% of patients who received idarucizumab preoperatively [50]. In addition to reversal with idarucizumab, hemodialysis has also been shown to be effective at reversing anticoagulation with dabigatran by expediting clearance [51].

Andexanet alfa is a novel injectable agent that is a catalytically inactive form of factor Xa which serves as a decoy receptor with higher affinity for factor Xa inhibitors than native factor Xa [15, 51]. It has demonstrated efficacy at reversing enoxaparin, rivaroxaban, apixaban, and edoxaban in phase II trials. Onset of action occurs within minutes and has a short half-life, allowing for rapid return to anticoagulated state [52]. Andexanet alfa was recently approved by the FDA for rivaroxaban- or apixaban-related uncontrolled or life-threatening bleeding [53].

Risks of Transfusions and Reversal

While transfusion of blood products is often unavoidable in the setting of major bleeding, associated risks must be carefully assessed, including allergic reaction, hemolysis, infection, transfusion-associated volume-overload and transfusion-associated lung injury. For patients in whom the risk of thrombosis is high, simply withholding further antithrombotic therapy may be preferable to transfusion of procoagulant factors. In a retrospective analysis of thirty-one patients with continuous flow left ventricular assist devices on warfarin that developed intracranial hemorrhage, 11 patients did not receive reversal with FFP or PCC; 10 of these patients survived and none developed increasing hemorrhage. Patients who did not receive reversal were noted to have small, stable bleeds with minimal symptoms or deficits, though further analysis is required to better characterize in which patients risks of reversal outweighs the benefits [54]. Table 33.6 offers summaries of selected studies evaluating the risks and benefits of clinically-necessitated antithrombotic reversal.

Table 33.6 Selected data on reversal of antithrombotic therapy

Reversal of antithrombotics						
Author (year), reference #	Study type	Study population	Number of patients	Drugs studied	Results	Quality of evidence
Xu (2017) [49]	Retrospective cohort study	Patients with oral anticoagulant-related hemorrhage	2002	Warfarin, DOACs (rivaroxaban, apixaban, dabigatran)	Patients with DOAC-associated major bleeding were less likely than patients with warfarin-associated bleeding to get fresh frozen plazma (10% vs 18%, aRR 0.53 [0.40–0.73]) or prothrombin complex concentrates (12% vs 41%, aRR 0.31 [0.24–0.40]) and more likely to get packed red blood cells (52% vs 40%, aRR 1.32 [1.18–1.46])	Moderate
Wong (2016) [54]	Retrospective cohort study	Patients with left ventricular assist device (LVAD) presenting with intracranial hemorrhage	31	Vitamin K antagonists	Patients who received 4-factor prothrombin complex (4FPCC) for warfarin reversal had lower fresh frozen plasma transfusion requirements (1.9 vs 3.6 units, $p = 0.05$) and similar rates of thromboembolic events (0% vs 10%, $p = 1.0$) than those who did receive 4FPCC. Of 11 patients who did not receive reversal with either 4FPCC or FFP, 10 survived to discharge and did not have any evidence of increasing hemorrhage	Low

Recommendations
We recommend a guideline-based approach to perioperative management of antithrombotic therapy.

- Decisions regarding choice of antiplatelet and/or anticoagulant agent(s) and duration of therapy should be tailored to each patient's clinical indications, risk profile, and comorbidities. The minimum intensity of antiplatelet and anticoagulant therapy required at a given time point should be utilized. (evidence quality moderate; strong recommendation)
- The risk of thrombosis should be carefully weighed against risk of bleeding, with assistance from validated tools such as CHADS2, HAS-BLED, and the DAPT score. This should be re-evaluated at regular intervals, particularly in the pre-operative setting. (evidence quality strong; strong recommendation)
- Triple-antiplatelet therapy and triple therapy with DAPT and an anticoagulant should generally be avoided due to a prohibitively high bleeding risk. An appropriate period of interruption in antithrombotic therapy prior to elective procedures should be attempted if it is safe to do so, or the procedure may need to be delayed until this can be done. (evidence quality strong; strong recommendation)
- For patients on a VKA, perioperative bridging with heparin is not always necessary and should only be done if clinically indicated. (evidence quality strong; strong recommendation)
- In the event of clinically significant bleeding, judicious use of blood products (including red blood cells, platelets, fresh frozen plasma, cryoprecipitate) as well as specific reversal agents are generally warranted. Risks of transfusions and reversal of anti-thrombotic therapy should be considered. (evidence quality moderate; strong recommendation)

A Personal View of the Data

Anticoagulant and antiplatelet therapy are indispensable and ubiquitous components of the cardiovascular armamentarium. The indications for the various drug classes and individual agents vary considerably, thus it is critical to ascertain the specific indication, dosage and optimal duration of therapy intended prior to surgical planning. A detailed knowledge of the pharmacokinetics and pharmacodynamics of the various compounds along with specific reversal strategies is mandatory for safe navigation of the perioperative period. It should be recognized that reversal of therapeutic antiplatelet and anticoagulant therapies can be associated with significant potential transfusion- and non-transfusion related risks and therefore should be utilized only with due consideration. Reinstitution of necessary oral antithrombotic therapies in suitable patients is often delayed or overlooked entirely and thus should be prioritized at the time of discontinuation.

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Chapter 34
Complex Cardiac Surgery Without Blood Transfusions: Lessons Learned from Managing Jehovah Witness Patients

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Introduction

Jehovah's Witnesses (JW) are well recognized for their refusal of blood transfusion as part of their faith. There are about 1.2 million JW members in the United States and estimated 8 million members in the world [1]. Accordingly, cardiac surgery in JW patients becomes challenging because cardiac surgery is frequently associated with blood transfusion requirement. In fact, since Cooley et al. reported the first case of cardiac surgery in a JW patient in 1964 [2], it has been reported in the early era that the mortality rate of cardiac surgery in JW patients was as high as 10% in 1970s [3–5]. However, due to the development of blood management strategies as well as medical advancement in general, clinical outcomes in JW patients undergoing cardiac surgery have become acceptable [6–13], and even to the extent of mortality and morbidity rates in JW patients comparable to non-JW patients [14–21]. Generally speaking, there are many benefits from minimizing transfusion including reduced risks of transfusion reactions, blood-transmitted infection, and immunosuppression. Given the fact that the avoidance of blood transfusion could provide possible positive effects on clinical outcomes, the blood management strategies for JW patients would be also beneficial to any patients undergoing cardiac surgery.

In this chapter, we review published studies evaluating the clinical outcomes in cardiac surgery of JW patients, and discuss the current blood management strategies in JW patient population.

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Search Strategy

A literature search of English language publications from 1960 to 2017 was used to identity published data on cardiac surgery in JW patients using the PICO outline (Table 34.1) with Pubmed. Terms used in the search were "Jehovah's Witness" AND "cardiac surgery" AND/OR "bloodless surgery". The search strategy revealed 244 articles. Of these, appropriate articles to discuss the optimal management for cardiac surgery in JW patients were selected. One systematic review and 17 retrospective observational/cohort studies were included in our analysis. The data was classified using the GRADE system.

Results

In the Early Era of Cardiac Surgery in JW Patients

It is challenging to safely perform cardiac surgery in JW patients because cardiac surgery inherently has a substantial potential for blood transfusions. The transfusion rate in isolated coronary artery bypass grafting was reported in the range from 10% to greater than 90% [22]. Cardiac surgery in JW patient was firstly reported by Dr. Cooley in 1964 [2]. At around the same time, several case series of cardiac surgery in JW patients were reported [3, 4]. In 1977, Ott et al. published a large series of 542 JW patients undergoing cardiac and vascular surgery. Of these patients, 362 JW patients underwent cardiac surgery with cardiopulmonary bypass, and their mortality was 10.7% [5]. At that time, blood management strategies were limited to the hemodilution perfusion technique with bloodless priming, injectable iron compounds before and after surgery, and avoiding dextran to reduce the risk of bleeding tendency. Since then, many other blood management strategies have been established including preoperative hemoglobin (Hb) optimization, new pharmacological agents, and improved cardiopulmonary bypass (CPB) system, leading to improved clinical outcomes.

Development of Blood Management Strategies in Cardiac Surgery

Current recommended perioperative blood management strategies for JW patients undergoing cardiac surgery are listed in Table 34.2 (adapted from Tanaka, et al. [6]).

Table 34.1 PICO table for cardiac surgery in Jehovah's Witnesses patients

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Jehovah's Witnesses patients	Cardiac surgery	Non-Jehovah's Witnesses patients	Mortality
			Morbidity

Table 34.2 Perioperative blood management strategies for JW patients

Preoperative phase
• Evaluating each patient's individual belief
• Optimization of hemoglobin levels >12 g/dl
– PO iron 60 mg 3 times per day or IV iron sucrose 2 mg/kg/day
– SC epoetin alfa 250–500 U/kg every 48 h or IV epoetin alfa 200 U/kg every 24 h
– PO folic acid 1 mg once per day
– PO cobalamin 1000 μg twice per day
• Withholding aspirin, clopidogrel, vitamin E, fish oil, turmeric, ginger
Intraoperative phase
• Retrograde autologous priming of CPB circuit
• Autologous whole blood sequestration
• Cool to core temperature of 34 °C and rewarm to 37 °C before the termination of CPB
• Minimize crystalloid administration
• Cell saver
• Hemostasis with topical and systemic hemostatic agents
– Hemasorb (Abyrx Inc, Irvington, NY)
– Coseal (Baxter Healthcare Corp, Deerfield, Ill)
– Topical fibrin, thrombin
– Antifibrinolytic administration (Aprotinin, EACA)
– Recombinant factor VII
• Minimally invasive surgical techniques, off-pump surgery
• Meticulous surgical technique, anastomosis reinforcement
Postoperative phase
• Minimize blood lab testing, use of pediatric blood tubes
• Early recognition and low threshold to re-exploration for bleeding
• Optimization of Hb >10 g/dl
– IV Iron sucrose 2 mg/kg/day
– SC epoetin alfa 250–500 U/kg every 48 h or IV epoetin alfa 200–300 U/kg every 24 h
– PO vitamin
• Longer inotrope and ventilator support as needed

Cited from an article by Tanaka et al. [6]

Perioperative Hemoglobin Optimization

One of the most important contributions to blood management strategies in JW patients is perioperative Hb optimization. Preoperative anemia is a predictor of blood transfusion in cardiac surgery, and negatively affects postoperative morbidity and mortality [23, 24]. Perioperative Hb optimization has been focused in every study of JW cardiac surgery since the first case was reported. Tanaka et al. reported improved outcomes in JW patients with preoperative Hb optimization. They concluded that the target preoperative Hb was more than 12 g/dl which was statistically calculated based on clinical outcomes [6]. In contrast, unnecessarily high Hb level produced by medication such as epoetin alfa may be associated with adverse event (e.g. thromboembolism) [25]. Literature review would suggest that a target Hb level

range of 12–14 g/dl would be recommended for cardiac surgery in JW patients. It should be noted that preoperative Hb optimization is time-consuming and optimal timing of surgery may be missed. The duration from hospital admission to surgery in JW patients was reported longer than non-JW patients [15]. In case of urgent/emergent cases, this optimization strategy can not necessarily be utilized.

New Pharmacological Agents

Newly developed pharmacological agents contribute to the improvement of outcomes in cardiac surgery in JW patients. Erythropoiesis-stimulating agents (ESAs) has been widely used for perioperative Hb optimization in JW patients undergoing cardiac surgery, since it was approved by the US Food and Drug Administration for use in anemia in 1989. ESAs is an endogenous glycoprotein hormone, which increases the production of red blood cells. In 1990s, Gaudiani et al. first reported perioperative ESAs use in cardiac surgery in JW patients [26]. In the large study of 500 JW cases, ESAs was used for the preoperative Hb optimization in patients, resulting in significantly decreased mortality in JW patients who received preoperative ESAs compared with patients who did not receive ESAs (1% vs 3%, $P < 0.05$) [11]. Recent report described the benefit of ESAs in a series of cardiac surgery patients who received a single ESA dose 2 days before surgery. ESA in this study reduced the blood transfusion use and showed no increase in adverse events [27]. There is still a concern regarding ESAs treatment related adverse events, most notably thrombosis, which has been observed especially in hemodialysis patients [25]. Therefore, careful ESAs use would be recommended for patients who are anemic (preoperative Hb <12 g/dl, or postoperative Hb <10 g/dl), and further study to determine the safe range of perioperative Hb to perform cardiac surgery would be warranted.

Appropriate use of antifibrinolytic agents which reduce blood loss in patients undergoing cardiac surgery is beneficial in this patient population [28]. Aprotinin was used in several studies until its withdrawal in 2007. Epsilon-aminocaproic acid (Amicar) or trans-exeemic Acid (TEA) are used to reduce the risk of bleeding. Topical hemostatic agents may also play an important role to decrease blood loss. Sternal hemostasis with topical hemostatic agents (i.e. Hemasorb, Abyrx Inc., Irvington, NY), bone wax (Aesculap AG & Co KG Tuttlingen, Germany) is crucial to perform bloodless cardiac surgery. Fibrin sealant as an alternative hemostatic agent to control persistent sternal bleeding was reported to be superior to bone wax in a randomized study [29].

Development of Cardiopulmonary Bypass Circuit System

CPB is one of the main contributing factors causing blood loss and coagulopathy during cardiac surgery. Previous reports demonstrated higher mortality in cardiac surgery performed with on-CPB compared with off-CPB [5, 30]. Several

management techniques and devices have been developed to minimize these negative effects of CPB. Heparin bonded circuits can reduce systemic heparin administration, possibly result in less coagulopathy, decrease in blood loss, and reduction in blood transfusion requirements [31]. Hemodilution, infusion of crystalloid, is a useful technique in avoiding transfusion secondary to red cell priming of CPB. The use of retrograde autologous priming minimizes the impact of initial hemodilution [32]. Ultrafiltration can provide hemoconcentration, concentrate the coagulation factors, and may prevent blood loss [33]. Cell-saver technique is suctioning shed blood from the operating field, centrifuging, washing, mixing with an anticoagulant solution and then re-infusing via a filter as required. Some JW patients accept the cell-saver technique if the blood circuitry is in continuity with the patient's own circulation. Short circuit CPB to decrease priming volume and minimize hemodilution was used effectively in the pediatric field [34]. Recently, similar concept was applied to JW patients. Minimal extracorporeal circulation system (fully-heparin coated closed-loop cardiopulmonary bypass system) was developed, and used in JW patients undergoing cardiac surgery with a favorable result [35, 36].

Latest Outcomes of Cardiac Surgery in JW Patients

Owing to the above-mentioned developments, recent studies showed excellent outcomes of cardiac surgery in JW patients. Articles related with JW cardiac surgery published in the past 10 years are summarized in Table 34.3. Marshall et al. retrospectively reviewed 59 JW patients undergoing coronary artery bypass surgery or aortic valve surgery with an acceptable mortality of 1.7% [7]. Several case series demonstrated no mortality in JW patients [8–10]. Pompei et al. reported no hospital mortality and good mid-term outcomes; actuarial survival of 100% and 80% at 5 and 10 years, respectively [10]. In the largest number study recently published by Vaislic et al., 500 JW patients underwent cardiac surgery with mortality of 2.0% [11]. However, these studies did not involve complex cardiac cases such as emergent case, heart transplantation, and left ventricular assist device (LVAD) implantation. Tanaka and colleagues reported a series of cardiac surgery in JW patients including such complex surgery as emergent cardiac surgery, heart transplantation, and LVAD implantation with a respectable mortality of 6.6% [6]. Moraca et al. reported mortality of JW patients who underwent cardiac surgery was 5.0% (2/40), and both mortality occurred in high-risk group (e.g. third time reoperation) [12]. Emergent/urgent cardiac surgery may not be theoretically feasible for JW patients when their Hb level is too low and there is not enough time for preoperative Hb optimization. However, there is a report of 91 JW patients undergoing cardiac surgery that showed no statistically difference in mortality or major complication rate between the elective and urgent surgery [13]. Nowadays, with proper utilization of updated blood management strategies, cardiac surgery including even complex cases or urgent cases can be safely performed in JW patients.

Table 34.3 Characteristics of studies evaluating the outcomes after cardiac surgery in JW patients

Author	Year	N	Pre-ope Hb (mean ± SD)	Lowest Hb (mean ± SD)	Type of procedure	Mortality (%)	Study type (quality of evidence)
Tanaka [6]	2015	137	12.7 ± 1.7	9.5 ± 2.6	CABG, valve, aortic, redo, transplant, LVAD, emergent	6.6	Retrospective observational study (low)
Marshall [7]	2011	59	14.2	10.7	CABG, Valve, Redo, Urgent	1.7	Retrospective observational study (low)
Emmert [8]	2010	16	14.5 ± 2.0	10.0 ± 1.5 g/dl (POD3)	CABG, valve, aortic, emergent	0	Retrospective observational study (low)
McCartney [9]	2014	45	14.0 ± 1.1	10.3 ± 2.2	CABG, valve	0	Retrospective observational study (low)
Pompei [10]	2010	34	14.2 ± 1.4	9.0 ± 1.7	CABG, valve, aortic, redo, urgent	0	Retrospective observational study (low)
Vaislic [11]	2012	500	N/A	N/A	CABG, valve, aortic, redo	2.0	Retrospective observational study (low)
Moraca [12]	2011	40	14.1 ± 1.6	N/A	CABG, valve, aortic, redo	5.0	Retrospective observational study (low)
Jassar [13]	2012	91	N/A	N/A	CABG, valve, aortic, redo, urgent	5.5	Retrospective observational study (low)

Abbreviations: JW Jehovah's Witnesses, *Hb* hemoglobin, *SD* standard deviation, *CABG* coronary artery bypass grafting, *POD* postoperative day, *LVAD* left ventricular assist device

JW Patients Versus Non-JW Patients Undergoing Cardiac Surgery

Previous retrospective cohort studies comparing JW patients versus non-JW patients undergoing cardiac surgery are summarized in Table 34.4. With appropriate perioperative blood management strategies, comparable morbidity and mortality were achieved in JW patients compared to non-JW patients. Pattakos et al. compared the outcomes in 322 JW patients versus 322 propensity-matched non-JW patients who received blood transfusion. In-hospital mortality was similar between two cohorts (3.1% vs 4.3%), and JW patients had better 1-year survival (95% vs 89%) [14]. Several similar studies in regard to JW versus matched non-JW patients have been published, and they all demonstrated no significant difference in mortality in cardiac surgery between these groups [15–19]. Recently, Bhaskar and colleagues [20]

Table 34.4 Characteristics of studies comparing the outcomes in JW versus non-JW patients undergoing cardiac surgery

Author	Year	Type of procedures	JW	Non-JW	Mortality (%) JW	Mortality (%) Non-JW	P value	Study type (quality of evidence)
Pattakos [14]	2012	CABG, valve, aortic, redo, emergent	322	322	3.1	4.3 (P = 0.40)	0.40	Retrospective cohort study (low)
Guinn [15]	2015	CABG, valve	45	90	0	0	N/A	Retrospective cohort study (low)
Azab [16]	2009	CABG, valve	123	4219	2.7	1.5	0.59	Retrospective cohort study (low)
Stamou [17]	2006	CABG, valve, redo, urgent	49	196	6.1	8.2	0.63	Retrospective cohort study (low)
Reyes [18]	2007	CABG, valve, aortic, redo	59	59	6.8	8.5	N/A	Retrospective cohort study (low)
Vaislic [19]	2003	CABG	40	40	0	0	N/A	Retrospective cohort study (low)
Bhaskar [20]	2010	CABG, valve, emergent	49	196	2	3.1	0.52	Retrospective cohort study (low)
Marinakis [21]	2016	CABG, valve, aortic, redo, urgent	31	62	2.8	2.4	0.55	Retrospective cohort study (low)

Abbreviations: JW Jehovah's Witnesses, *CABG* coronary artery bypass grafting

and Marinakis and colleagues [21] did the similar cohort studies in JW patients versus non-JW patients undergoing cardiac surgery including complex cases, and demonstrated comparable outcomes in JW patients. Systematic review of six studies comparing the outcomes in JW and non-JW patients showed JW patients group had a trend toward decreased early mortality (2.6% vs 3.6%, p = 0.318), and significantly less postoperative blood loss compared to non-JW patients group (402 ml vs 826 ml, p < 0.001) [37]. Preoperative Hb optimization is the most crucial factor in JW patients and used in all analyzed studies. It might be reasonable to apply the blood management strategies for JW patients to non-JW patients, given the possible benefits from non- or less- blood transfusion. Iron supplement could be easily extended to non-JW patients. Use of ESAs for cardiac surgery in all patients is currently still controversial due to an increased risk of thromboembolic events as well as from a cost-effectiveness perspective [27]. Further studies are necessary to clarify the potential benefits and harms related with the use of ESAs in cardiac surgery.

Recommendations

Cardiac surgery can be safely performed in JW patients with the current blood management strategies leading to acceptable mortality and morbidity rate. Even complex, high-risk cardiac surgery in JW patients can be done in well-experienced centers. Preoperative optimization of Hb greater than 12 g/dl would be recommended in JW patients as preoperative Hb less than 12 g/dl is associated with early mortality and morbidity. Perioperative ESAs administration in conjunction with iron therapy would be encouraged for JW patients with preoperative Hb <12 g/dl, or postoperative Hb <10 g/dl.

A Personal View of the Data

Because of their refusal of blood products in JW patients, cardiac surgery is extremely challenging, especially in complex cases. However, as it has been reported by several authors, appropriate multiple blood management strategies through the surgery could make it safely performed even in JW patients without blood transfusion. First and foremost, meticulous surgical technique is critical. While operative time is usually longer in JW patients compare with non-JW patients, surgical skills and techniques are paramount including careful intraoperative observation, complete hemostasis from anastomosis and cannulation sites using pledgeted stitches and appropriate reinforcement stitches, and lower threshold of re-exploration for bleeding. All dissection in reoperations should be done with electrocautery. Raw surfaces should be eliminated using topical hemostatic agents. We often increase the blood pressure and distract anastomoses to absolutely insure hemostasis and prevent late bleeding. Every surgical consideration contributes to acceptable clinical outcomes in this challenging group of patients. Among the blood management strategies, the most important factor is preoperative Hb optimization, and use of ESAs. Future study should focus on how blood management strategies can be applied to all cardiac patients (i.e. non-JW patients). Although, patient with very low Hb (less than 4 g/dl) after cardiac surgery is extremely challenging, it is still manageable. In such case, optimal sedation and mechanical ventilation support would be beneficial to decrease oxygen consumption, and high cardiac output with inotropes maintain appropriate oxygen delivery even in very low Hb level.

Recommendations

- Multiple blood management strategies lead acceptable mortality and less blood loss in JW patients undergoing cardiac surgery compared to non-JW patients (evidence quality low; low recommendation)
- Preoperative target Hb level >12 g/dl should be achieved for cardiac surgery in JW patients (evidence quality low; low recommendation)
- Perioperative ESAs administration is considered if preoperative Hb <12 g/dl, or postoperative Hb <10 g/dl (evidence quality low; low recommendation)

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Part IX
Acute Kidney Injury

Chapter 35
Cardiac Surgery Acute Kidney Injury: Controversy in Renal Support

Aaron M. Cheng and Seth Wright

Introduction

Risk Factors and Management Strategies of AKI

Acute kidney injury (AKI) following cardiac surgery remains a well-recognized complication and has been clearly associated with increased patient morbidity and mortality. It is estimated to occur in as commonly as 20–30% of cardiac surgery patients post-operatively and results in longer ICU and hospital length of stay as well as a threefold increased mortality in those who newly require renal replacement therapy [1–3]. The incidence of AKI does depend on the criteria used for its diagnosis. Clinically, contemporary criteria for AKI diagnosis, notably RIFLE, AKIN, and KDIGO, all use increases in serum creatinine concentrations and oliguria. Currently, most guidelines recommend using the KDIGO (Kidney Disease Improving Global Outcomes) criteria, which defines acute kidney injury as a 0.3 mg/dl increase in serum creatinine (Scr) from baseline within 48 h, or an increase of Scr $\geq$1.5-fold above baseline with known or assumed kidney injury within 7 days, or urine output <0.5 ml/kg/h for 6 h [4]. Following urine output in early post-operative cardiac surgery patients to diagnose acute kidney injury can be misleading as oliguria commonly occurs in the immediate postoperative period and may be related more to poor perfusion than acute loss of intrinsic renal function. Thus,

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clinicians often rely on increases in Scr to define cardiac surgery-associated AKI (CS-AKI) but admittedly, rises in creatinine usually manifest several hours or days from the actual renal insult when damage to the nephrons has already occurred.

The risk factors for the development of CS-AKI are well-known, but most of these risk factors are not easily modifiable in the post-operative setting. Pre-existing chronic kidney disease is one of the greatest risk factors for requiring renal replacement therapy post-operatively after cardiac surgery, and studies indicate that nearly 10–20% of patients with elevated preoperative baseline creatinine between 2 and 4 mg/dl will require RRT post-operatively; whereas, nearly 30% of those patients with preoperative creatinines greater than 4.0 mg/dl will require RRT, potentially indefinitely [5–7]. This possibility should be part of the counseling before surgery. To modify CS-AKI risks, avoiding or holding medications pre-operatively that can alter glomerular hemodynamics are reasonable, including ACE/ARBs. Allowing serum creatinine to return to baseline after acute nephrotoxicity before proceeding with cardiac surgery whenever possible is also recommended. This is particularly relevant as an increasing number of cardiac surgical patients peri-operatively are undergoing cardiac catheter-based procedures which increase their risk of intravenous contrast-induced AKI. Circumstances permitting, patients who already require dialysis should be dialyzed within the 24 h before surgery and planned for dialysis again afterwards, as they have greater susceptibility to fluid overload, metabolic acidosis, and electrolyte derangements after surgery. Intraoperatively, maintaining renal perfusion pressure and renal blood flow to reduce ischemia to the kidneys, and avoiding critically low hemoglobin levels (<6–7 g/dl) while avoiding unnecessary red cell transfusions remain the primary strategies to reduce acute kidney injury during surgery [8]. Considering hemofiltration for chronic hemodialysis patients while on cardiopulmonary bypass also may be necessary to reduce volume overload, particularly in those patients who also have severe concomitant chronic heart failure.

The post-operative setting is typically when surgically-related AKI is first identified; treatment of acute kidney injury is focused on reducing any ongoing renal insult and inflammation and general supportive measures to maintain adequate hemodynamic support to minimize renal ischemia. Prescribed medications should be reviewed and those with known nephrotoxicity should be discontinued. Necessary medications should be appropriately dosed according to the patient's decreased glomerular filtration rate (eGFR), with the caveat that when creatinine is actively rising, creatinine-based GFR estimating equations –which assume a steady-state – can severely overestimate the renal function. The use of low-molecular weight heparin (LMWH) for venous thromboembolism prophylaxis should be administered cautiously, as its decreased renal clearance due to AKI can result in unsuspected systemic anticoagulation and coagulopathy in the acute post-operative recovery from cardiac surgery. Other important interventions in the ICU to prevent ongoing acute kidney injury include blood sugar control and also adequate nutritional support [9]. In addition, though the overwhelming majority of CS-AKI are from the hemodynamic insults pre-, intra-, and post-procedure, when clinically indicated consideration should be given to less common causes of AKI such as interstitial nephritis

from antibiotics or pigment nephropathy from hemolysis due to ventricular assist devices.

Impaired renal perfusion after cardiac surgery should be actively addressed particularly since autoregulation of renal blood flow can be disrupted after cardiopulmonary bypass and AKI. A variety of intraoperative factors contributes to hypotension and hemodynamic instability: bleeding and coagulopathy, poor recovery of ventricular function, and systemic inflammation and vasodilation. These factors often persist in the post-operative period worsening renal function, and should be aggressively managed in the ICU. When tamponade is suspected, bedside interventions such as echocardiography and invasive hemodynamic monitoring should be promptly utilized to confirm diagnosis and guide therapy.

Optimization of post-operative hemodynamics in CS-AKI may be particularly challenging in the early post-operative period. Treatment of hypovolemia for inadequate preload in this setting often requires volume resuscitation, but the choice of fluid may have important effects on renal function. The perennial debate between colloid versus crystalloid resuscitation notwithstanding, albumin has been shown to have a more favorable profile than synthetic hetastarches, which contribute to renal injury and coagulopathy, and restrictive-chloride crystalloid solutions (e.g. Lactated ringers, Plasmalyte) may reduce overall AKI and need for RRT when compared to high-chloride crystalloids such as 0.9% saline [10, 11]. Whether it is the composition of the high-chloride crystalloid solution which intrinsically increases the AKI risk or the development of hyperchloremic metabolic acidosis caused by a liberal-chloride crystalloid resuscitation which contributes to AKI remains unclear [12].

Several studies have been undertaken in the past to examine the role of pharmacological interventions to directly treat AKI, but thus far none, have incontrovertibly demonstrated improvement with relevant clinical outcomes. In particular, the role of "renal-dose" dopamine to directly prevent or treat AKI has not been proven [13–15]. Low-dose dopamine does improve dopaminergic-related renal vasodilation and renal blood flow which will increase renal perfusion pressure; however, the improved urine output associated with dopamine has not correlated with important clinical outcomes, including decreased requirement for renal replacement therapy or decreased mortality in cardiac patients following early AKI [16, 17]. Similarly, while patients who have non-oliguric renal injury fare better than those with oliguric AKI, the routine use of diuretics to directly prevent or treat AKI has not been proven in studies [18–20]. The premise that by administering diuretics to "keep a patient making urine or to convert the patient from oliguric AKI to non-oliguric AKI" to treat renal injury that has occurred should be dispelled. Instead, the observation that those patients who respond with improved urine output to diuretics have better renal outcomes than those who do not, suggests that the "diuretic-responsive" AKI patient has lesser extent of acute nephron damage than AKI patients who are unresponsive to diuretics.

However, as patients who undergo cardiac surgery often are volume-overloaded, and acutely impaired renal function can worsen fluid overload, the use of diuretics to treat volume overload and resultant pulmonary edema is often indicated in CS-AKI patients. An increasing number of studies have shown that volume over-

load has deleterious effects on critically ill patients [18, 21, 22]. Diuretic-responsive cardiac surgical patients with AKI who are or become in a state of fluid-overload or have associated pulmonary edema will benefit from diuretic therapy to decrease fluid gain; also certainly, minimizing unnecessary fluid administration is warranted. The clinical dilemma and controversy in these critically ill cardiac surgical patients is not whether diuretics should be given in the setting of AKI, but rather when and how volume overload should be optimally managed. Good evidence based-studies to guide this decision-making in CS-AKI remain elusive.

Renal Replacement Therapy

In critically ill patients with AKI, progression to requiring renal replacement therapy (RRT) is estimated to occur in 5–10% of general ICU patients [23, 24]. For patients undergoing cardiac surgery, the need for new RRT post-operatively is estimated to be 1–5% [25]. There are various modalities of RRT that are currently available, including intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), and hybrid approaches such as slow low-efficiency dialysis (SLED) and slow continuous ultrafiltration (SCUF). No specific RRT modality has been demonstrated to be more beneficial over another with regards to frequency and dose of dialysis; however in hemodynamically unstable patients with severe AKI requiring RRT, continuous renal replacement therapy is better tolerated than intermittent hemodialysis, although it has not been shown to improve overall mortality. This is particularly evident in critically ill complex cardiac surgical patients who require RRT post-operatively but remain hemodynamically very labile. In addition, the use of continuous therapies has the attraction of allowing continuous adjustments to net fluid balance as hemodynamics and pulmonary status change, as opposed to the single adjustment of volume every 24–48 h provided by intermittent dialysis.

Timing of the initiation of RRT in patients with severe AKI remains highly controversial. The classic life-threatening indications for RRT are hyperkalemia, acidemia, pulmonary edema or difficulty oxygenating, and complications associated with uremia such as pericarditis and bleeding. However, when these conditions are not emergent or residual kidney function with urine output remains, the trigger to initiate RRT for solute control, volume control, and correction of pH abnormalities becomes more arbitrary with less consensus among nephrologists, intensivists, and surgeons. Nevertheless, given the high incidence of acute renal failure in this patient group, the role of renal replacement therapy remains particularly relevant for post-cardiac care management, and therefore, we sought to evaluate the clinical evidence available to guide the role of when to initiate renal replacement therapy once CS-AKI has occurred.

Search Strategy

We used the PICO model depicted in Table 35.1 to frame the clinical question of whether the timing of renal replacement therapy after acute kidney injury associated with cardiac surgery reduces mortality. The search methodology was limited to contemporary clinical studies available on PUBMED in the past 10 years (2007–2017) which focused on the timing of initiating renal replacement therapy for post-cardiac surgery associated acute kidney injury in adult patients (>18 years of age) and the results are listed in Table 35.2. The QUALITY of data in the papers evaluated were then reviewed and classified according the GRADE system.

Results

The cumulative evidence examining clinical outcomes associated with early initiation of renal replacement therapy for CS-AKI remains moderate to low in quality (Table 35.3). Despite some retrospective studies concluding that earlier RRT initiation improved outcomes for acute kidney injury following cardiac surgery, these study results are challenged by their retrospective study design and small patient samples. Further, any conclusions drawn from these studies are confounded by the lack of details regarding which RRT modalities were applied, the variability of indications for starting renal replacement therapy, and the non-uniformity of patient clinical factors among studies [26–29]. Those studies listed in Table 35.3 that were prospectively designed found no difference among relevant clinical outcomes when comparing early versus late initiation of renal replacement therapy, including the only randomized prospective multi-center study, which found no difference in mortality [30–34]. Studies which have not exclusively focused on the cardiac surgical population also have not identified early RRT leading to improved clinical outcomes: most notably, a large recent multi-centered randomized trial investigating the timing of RRT initiation in patients with severe AKI found no significant difference between patients who were started early on RRT versus those who were randomized to a delayed RRT strategy [35]. This trial, albeit, did not examine patients with life-threatening complications from AKI or post-cardiac surgery. Interestingly, 49% of the patients randomized to the delayed-RRT strategy did not require hemodialysis, suggesting that those patients were able to recover renal function

Table 35.1 PICO table of RRT timing for CS-AKI

P	Adult patients diagnosed with CS-AKI who undergo acute RRT after cardiac surgery
I	Early initiation of RRT, dialysis, hemofiltration
C	Late/delayed initiation of RRT, dialysis, hemofiltration
O	Post-operative survival, ICU LOS, Vent days, acute morbidity

Table 35.2 PUBMED search methodology and QUERY results

QUERY (all fields or MeSH terms)	Studies found
((Early OR late) OR (timing OR initiation)) AND (renal replacement therapy OR hemofiltration OR dialysis)	25,575
Studies searched for (acute kidney injury)	2571
Studies searched for (cardiac surgery OR cardiopulmonary bypass OR coronary bypass OR post cardiac surgery)	314
Studies filtered for (published in last 10 years)	237
Authors reviewed titles and abstract for topic study focus on timing of RRT in post cardiac surgery (excluding pediatric population)	13
Authors reviewed published studies which included single-center, multi-center, retrospective, prospective clinical studies (excluding reviews and meta-analysis studies)	9 (Studies listed in Table 35.3)

sufficiently to avoid renal replacement therapy. A notable exception to this conclusion was a recent meta-analysis performed by Zou et al. which included 15 studies examining mortality outcomes following early versus late RRT in CS-AKI [36]. In their meta-analysis, Zou et al. report improved mortality and decreased hospital and ICU LOS in those cardiac patients who received early RRT post-operatively for AKI. An important caveat to their study is that 9 of the 15 studies used for their data meta-analysis were retrospective in design and consequently subject to the same inherent limitations and biases previously mentioned above. As a counterpoint, a separate contemporary meta-analysis – which in contrast selected only randomized control trials on critically ill patients—concluded that early RRT initiation did not reduce mortality compared with a late RRT initiation strategy. In this meta-analysis by Yang et al. the risk ratio of mortality of the pooled studies was 0.98 (CI 0.78–1.23, $p = 0.84$), and no differences were found between those who received early or late RRT initiation in secondary outcomes: ICU LOS, in hospital LOS, or renal recovery [37].

Recommendations Based on the Data

The cardiac surgical patient who sustains severe kidney injury occurring in the context of ongoing multi-system organ injury, circulatory shock, and a low cardiac output state will have a very different mortality outcome compared with the hemodynamically normal post-operative patient who manifests isolated acute renal insult from transient intraoperative hypotension while on cardiopulmonary bypass or post-contrast nephropathy. In these clinical scenarios, conceivably delaying renal replacement therapy in the former patient may be life-ending, whereas, delaying the start of RRT despite oliguria to allow for renal recovery may be entirely feasible in the latter and not affect mortality outcome. Until there are better definitions which account for the varied circumstances in which acute kidney injury and renal failure develop after cardiac surgery and renal replacement therapy is utilized,

Table 35.3 Clinical studies evaluating timing of RRT initiation following CS-AKI

Authors/year	Study design	RRT groups (n = # patients)		Mortality		Morbidity	Comments	Quality of evidence
		"Early"	"Delayed"	"Early"	"Delayed"			
Yang et al. (2016) [29]	Retrospective cohort-Single Center	<24 h onset of AKI w/o traditional indications for RRT (n = 59)	>24 h onset of AKI w/presence of traditional indications for RRT (n = 154)	33.9%	51.95%	No difference in ICU LOS, ventilator duration	Early group with significant better mortality rate (p = 0.018)	Moderate
Combes et al. (2016) (HEROICS Study) [30]	Prospective randomized control-Multi-Center	Severe shock with RRT initiated within 24 h of surgery (n = 112)	Severe shock with RRT initiated when traditional (n = 112)	36%	36%	No difference in ICU LOS, ventilator requirement, renal recovery	No difference in mortality. Trend toward decrease catecholamine requirements in Early group (NS) (p = 1.00)	High
Crescenzi et al. (2015) [31]	Prospective cohort-Single Center	UOP <0.5 ml/kg/h for >6 h 9 (n = 837)	UOP <0.5 ml/kg/h for >12 h (n = 821)	RRT used in 5.5% of cohort with 60.9% death on RRT	RRT used in 1.6% of cohort with 76.9% death on RRT	No signficant differences in hospital and ICU LOS were noted between the two cohorts	No difference in mortality rates between 'early' RRT and 'delayed' RRT (p = 0.286). Fewer patients in the 'delayed' cohort actually received RRT	Moderate

(continued)

Table 35.3 (continued)

Authors/year	Study design	RRT groups (n = # patients)		Mortality		Morbidity	Comments	Quality of evidence
		"Early"	"Delayed"	"Early"	"Delayed"			
Mirhosseini et al. (2013) [33]	Prospective cohort-Single Center	RRT in post-heart transplant patients with UOP <400 ml/day with evidence of volume overload and AKI (n = 15)	Continuous furosemide therapy (20 mg/h) in post-heart transplant patients with UOP <400 ml/day with evidence of volume overload and AKI (n = 15)	40.0% (6/15)	26.6% (4/15)	Significant improved estimated GFR in RRT group compared to furosemide group	No difference was note in mortality between the two groups with small sample size. (p = 0.43) Primary outcome reported is est. GFR which improved with RRT and also at time of discharge in RRT group	Low
[a]Schneider et al. (2012) [34]	Retrospective cohort- Single Center	Severe AKI with Failure (RIFLE-F stage) receiving RRT (n = 48)	Severe AKI with Failure (RIFLE-F stage) NOT receiving RRT (n = 23)	29.2% (14/48)	13.0% (3/23)	Not applicable	[a]Initiation of RRT post cardiac surgery for severe AKI classified by RIFLE criteria did not improve mortality	Moderate
Garcia-Fernandez et al. (2011) [26]	Retrospective cohort-Multi Center	RRT <3 days post cardiac surgery	RRT >3 days post cardiac surgery	53.2%	80.4%	Delayed RRT group with increased LOS	Significant difference in hospital mortality	Low
Ji et al. (2009) [27]	Retrospective cohort- Single Center	RRT <12 h of UOP <0.5 ml/kg/h (n = 34)	RRT >12 h of UOP <0.5 ml/kg/h (n = 24)	8.8% (3/34)	37.5% (9/24)	Significant increase in ICU LOS, sepsis, low CO, pneumonia, and ventilator support >72 h in the delayed group	Significant difference in hospital mortality (p = 0.02)	Low

Iyem et al. (2009) [32]	Prospective cohort-Single Center	RRT initiated <48 h when UOP <0.5 ml/kg/h and 50% increase in preop BUN and creatinine levels (n = 95)	RRT initiated >48 h when UOP <0.5 ml/kg/h and 50% increase in preop BUN and creatinine levels (n = 90)	5.2%	6.6%	Increased major post-op complications (PNA/sepsis ($P < 0.05$), ventilator >5 days ($p < 0.05$), ICU LOS ($p < 0.001$), low cardiac output ($p < 0.001$) in delayed group)	No difference in mortality rates (NS)	Moderate
Manche et al. (2008) [28]	Retrospective cohort-Single Center	Oliguria to RRT 'Early': (average 8.6 ± 8.2 h) (n = 56)	Oliguria to RRT 'Delayed': (average 41.2 ± 22.8 h) (n = 15)	25% (14/56)	87% (13/15)	Not applicable	Significant difference noted in mortality. ($p = 0.00001$)	Low-very low

[a]In the study by Schneider et al. the mortality data shown in the Table compares the percentages of in-hospital death of patients with AKI-FAILURE by RIFLE staging who did receive RRT (shown in "EARLY" column) to those with AKI-FAILURE who did not receive RRT (shown in "DELAYED" column)

consensus to guide decision-making on the optimal time to initiate RRT will remain elusive. Further highlighting the clinical quandary of when to initiate RRT in AKI, it is notable that even the results from well-designed randomized controlled trials examining outcomes of early versus late RRT strategies applied to the broader group of critically ill patients with AKI are not consistent. While the ELAIN randomized clinical trial in Germany found that early RRT initiation decreased 90-day mortality compared to delayed initiation, the multi-center randomized controlled trial by the French AKIKI (Artificial Kidney Initiation in Kidney Injury) study group found no significant difference in mortality between the different initiation strategies [35, 38].

In summary, the current level and quality of evidence does not support an early initiation strategy for RRT that significantly improves clinical outcomes in critically ill patients with acute kidney injury. Better-designed and larger scale studies are needed before an early renal replacement initiation strategy can be incontrovertibly recommended for the specific subset of patients who develop acute kidney injury post-operatively after undergoing cardiac surgery.

Personal View of the Data

What message then should the practicing cardiac surgeon and intensivists extract regarding the optimal timing to start RRT for severe acute kidney injury in the critically ill cardiac surgical patient? From the perspective of these authors (A.C./S.W.), practical application of the various study results should be interpreted in proper clinical context when deciding when to initiate renal replacement therapy after cardiac surgery. Notably, in the ELAIN randomized trial, which did find that mortality improved with early RRT, most of its enrollees were surgical with the largest group comprised of cardiac patients, suggesting that its study conclusion may be relevant to the cardiac surgical group; and although the French AKIKI study did not find significant mortality benefit with early RRT initiation compared to the delayed strategy, certainly, the inverse was not true: more favorable outcomes were not found with the delayed RRT strategy compared to the early strategy of RRT initiation. In fact, post-hoc analysis of the studied groups found that while those who did not receive any RRT fared the best with 60-day mortality (37.1%), the highest mortality rate – at 61.8% – occurred in those who received renal replacement therapy late as compared with an intermediate mortality rate of 48.5% in the group which received RRT early. On balance, though there are other approaches that could be supported by the data, our clinical bias in the presence of CS-AKI is to provide RRT for moderately strong indications and the absence of signs of improvement, rather than wait until the penultimate minute when RRT becomes urgently necessary. In critically ill cardiac surgical patients, early post-operative mortality infrequently is due solely to acute renal impairment. Any clinical evidence of the sequelae of AKI contributing

to hemodynamic or circulatory compromise or other vital organ functional derangement should prompt aggressive intervention for full renal support, including renal replacement therapy.

Recommendations

- Initiation of renal replacement therapy should not be delayed for severe acute kidney injury (AKI) after cardiac surgery which affects post-operative hemodynamic management (Level of Recommendation: Strong; Level of Evidence: Low)
- Routine early initiation of renal replacement therapy solely for cardiac surgery-related AKI does not improve patient-mortality and is not recommended (Level of Recommendation: strong; Quality of Evidence: Moderate)

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Chapter 36
Role of Biomarkers in Predicting AKI in the CT ICU

Jay L. Koyner

Introduction

Acute kidney injury (AKI) is a one of the most common complications following cardio-thoracic surgery. The incidence of post-operative AKI varies based on a variety of factors including the type and timing (elective versus emergent) of the surgical procedure as well as the definition of AKI that is reported. AKI is traditionally defined by either increases in serum creatinine (SCr) from a pre-specified preoperative baseline or sustained decreases in urine output (UOP) over time, with reports estimating the incidence of some form of AKI in 10–40% of all patient undergoing cardio-thoracic surgery [1–3]. The severity of AKI can vary from relatively self-limited changes in SCr or UOP to the need for renal replacement therapy (RRT, e.g. intermittent hemodialysis (IHD) or continuous RRT (CRRT)) AKI. Regardless of severity AKI has been repeatedly associated with increased length of stay, increased inpatient morbidity and short and long term mortality [1–3].

Despite these associations, SCr and UOP remain imperfect biomarkers of AKI. SCr is neither sensitive nor specific for renal tubular injury, as creatinine is a primarily biomarker of glomerular function/filtration. SCr is often delayed and does not increase until 24–72 h after a renal insult and can be impacted by factors such as hemodilution and hemoconcentration [4]. Additionally, urine output can often be

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altered through the administration of diuretics and/ or intravenous fluid. As such over the last decade, there has been increasing investigation of novel biomarkers in the area of cardiac surgery associated AKI. The overwhelming majority of these investigations have been prospective observational studies. These studies have demonstrated promise and subsequently validated the ability of certain biomarkers to improve the AKI prognostication; with several of these new tools being approved for clinical use across the globe [5, 6]. The clinical implementation of these new biomarkers from these original observational studies has slowly led to a limited number of cardiac surgery based interventional trials that have utilized these biomarkers of AKI to improve patient outcomes [3, 7]. As such this chapter will focus on the observational data on the role of biomarkers in predicting AKI following cardiac surgery.

Search Strategy

A literature search of English language publications from 2005 to 2017 was used to identify published data on the performance of biomarkers of AKI after cardiothoracic surgery (Table 36.1). Databases searched were PubMed, Embase, and Cochrane Evidence Based Medicine. Terms used in the search were "Acute kidney injury (AKI)" OR "Acute renal failure (ARF)" AND "biomarkers" OR "neutrophil gelatinase associated lipocalin(NGAL)" OR "tissue injury metalloprotease-2 insulin-like growth factor binding protein-7 (TIMP2-IGFBP7)" OR "interleukin-18" OR "Albuminuria" OR "Proteinuria" OR "urine albumin to creatinine ratio" OR "kidney injury molecule-1" AND "cardiac surgery" OR "cardiothoracic surgery" OR "heart surgery." Our results returned over 230 viable papers the majority of which were observational studies in which biomarkers of AKI were measured to determine their ability to diagnose AKI following cardiothoracic surgery. While we found a selection of randomized control trials in which biomarkers were measured in the setting of CT surgery but not used to define or predict AKI. However, there was only one in which the biomarkers were used to trigger an intervention in the setting of recent CT surgery. As such, this chapter will discuss the larger observational trials which significantly limits our ability to make highly graded recommendations.

Table 36.1 PICO table for biomarkers of post-operative cardiac surgery associated AKI

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients undergoing elective or urgent cardio-thoracic surgery	Measurement of urine or serum biomarkers of renal injury	No comparator-predominantly observational trial	Incidence, severity, duration and morbidity and mortality of acute kidney injury

Defining Biomarkers and AKI

Briefly, a biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic intervention. An ideal biomarker is easily measured, readily reproducible, sensitive and specific to a disease process, easily interpretable, cost effective and readily available in human specimen (e.g. blood and urine). More specifically in the setting of AKI a biomarker should be:

1. Kidney specific
2. Able to detect and prognosticate the outcome of AKI earlier than the current gold standard (Scr and UOP)
3. Able to differentiate between different sources/causes of AKI (e.g. Acute tubular necrosis from obstructive disease)
4. Site specific and inform pathologic changes in various segments of the nephron while correlating with findings on biopsy specimens
5. Easily and reliably measured in a noninvasive manner at the bedside
6. Inexpensive/cost effective

With respect to biomarkers, several have been investigated over the last two decades, this research has been aided by the formulation of consensus definitions of AKI over this same time period. These definitions have evolved over time from the RIFLE (*R*isk, *I*njury, *F*ailure, *L*oss, *E*nd-stage kidney disease) classification [8] and the Acute Kidney Injury Network (AKIN) definition of AKI eventually being harmonized into the Kidney Disease: Improving Global Outcomes (KDIGO) classification [9]. The KDIGO criteria can be found in Table 36.2 and highlight the importance of small changes in serum creatinine or UOP in the diagnosis of AKI. Changes as small as a 0.3 mg/dl increase in 48 h or 50% increase over 7 days have been repeatedly demonstrated to portend adverse outcomes for patients across a variety of clinical settings including CT surgery [6].

Table 36.2 Kidney disease: improving global outcomes (KDIGO) staging of AKI

Stage	Serum creatinine criteria	Urine output criteria
1	1.5–1.9 times baseline	<0.5 mL/kg/h for 6–12 h
	Or	
	≥0.3 mg/dL (26.5 μmol/L) increase within 48 hours	
2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	≥3.0 times baseline or	<0.3 mL/kg/h for ≥24 h or anuria for 12 h
	Increase in serum creatinine to ≥4.0 mg/dL (≥353.6 μmol/) or	
	Initiation of renal replacement therapy or	
	In patients <18 years, decrease in eGFR to <35 ml/min per m^2	

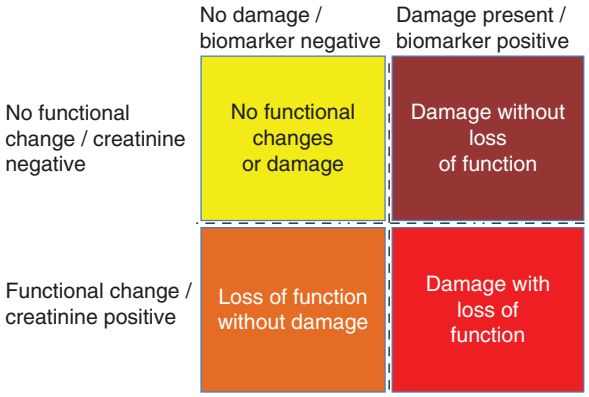

Fig. 36.1 Revised paradigm for acute kidney injury. Currently the definition of AKI is made through changes in urine output, serum creatinine (SCr), or functional kidney biomarkers. Others have delineated a novel criteria for defining AKI in terms of changes in biomarkers of renal function (SCr or urine output) and biomarkers of kidney damage/injury. This paradigm allows for the combination of injury biomarkers with SCr and has proven useful in the discrimination of patients with AKI. (Adapted from Endre et al. [31])

While more recently there have been calls to incorporate biomarkers into the definition of AKI itself this has not gained widespread acceptance at this time [10, 11]. However, in recent years there has been a call to re-evaluate the paradigm of AKI, with calls to replace the traditional pre, post and intra-renal AKI with a classification based on whether there are changes in functional biomarkers and/or damage biomarkers (Fig. 36.1). As discussed in this chapter, this paradigm allows for the combination of injury biomarkers with SCr and has proven useful in the discrimination of patients with AKI.

Results

Biomarkers of AKI

As discussed above there are hundreds of articles published in the last decade investigating several candidate biomarkers of AKI. Table 36.3 provides some functional characteristics and biological role of several biomarkers which have been investigated in the setting of cardiac surgery associated AKI. When possible we will discuss the ability of the biomarker to diagnosis AKI earlier than serum creatinine, predict AKI severity as well as the association of the individual biomarker with long term outcomes following cardiac surgery. The results are compiled in Table 36.3.

Table 36.4 summarizes and grades data on several pre-operative biomarkers and their ability to detect AKI while Table 36.5 summarizes similar data on the ability of post-operative biomarkers to predict AKI and other adverse outcomes.

Table 36.3 Biomarker characteristics, function and performance in detecting cardiac surgery associated AKI from multi-center studies

	Characteristics and function	Pre-op AKI risk	Early post-op AKI	AKI progression	Long term mortality
Urine NGAL	A 25 kDa protein from the lipocalin family which can bind iron-siderophore complexes. Has been shown to be upregulated in the kidney following ischemic injury. Blood and Urine levels have been associated with the development of AKI in adults and children following CT surgery	N/A	+	–	+
Blood NGAL		–	+	+	+
TIMP-2 IGFBP-7	TIMP2- is a 21 kDa protein and endogenous inhibitor of the metalloprotease activity; while IGFBP7 is a 29 kDa cell cycle arrest protein known to inhibit IGF1 receptors. Urine levels of the product of these have been associated with the development of AKI in adults following CT surgery	N/A	+	+	+
Serum cystatin C	13 kDa cysteine protease inhibitor that is freely filtered at the glomerulus and is neither secreted nor reabsorbed by renal tubules. Serum levels serve as an excellent marker for chronic kidney disease but are also associated with increased risk of post-operative AKI following CT surgery	+	+	NA	?
Urine protein/ albumin	66 kDa protein, abundant in the serum and known to be a marker of chronic kidney disease that has been shown to be associated the development of AKI in adults following CT surgery	+	+	+	+
Urine IL-18	A 24 kDa cytokine from the IL-1 family (adaptive immunity). Urine levels have been associated with the development of AKI in adults following CT surgery	N/A	+	+	+
Urine KIM-1	A 38 kDa transmembrane glycoprotein with an ectodomain containing a six-cysteine immunoglobulin-like domains, two *N*-glycosylation sites, and a long mucin domain. Has been shown to be upregulated in the kidney following ischemic injury to the proximal tubule. Urine levels have been associated with the development of AKI in adults following CT surgery	N/A	+	–	+

Adapted and expanded from Koyner and Parikh [30]

+ = data published displays the ability to reliably detect this aspect of AKI

– = data published does not display the ability to reliably detect this aspect of AKI

? = no large multicenter data published on this biomarker/aspect of AKI

N/A not applicable as biomarkers of tubular injury have no role in preoperative risk screening or there have not been large scale investigations of this biomarker in this setting

Table 36.4 Performance of pre-operative albuminuria of AKI in clinical investigation

Biomarker	Author (year)	N	Definition of AKI/ endpoint	Incidence of AKI n(%)	Incidence of RRT n(%)	AUC (SE) or AUC (95%CI) for outcome prediction	AKI rate in those <30 mg/g or negative	AKI rate in 30–300 mg/g or trace to 99 md/ dL	AKI rate in those >300 mg/g or >100 mg/dL	Study type (quality of evidence)
Pre-operative proteinuria (dipstick)	Coca (2012) [24]	1159 adults	>50% or ≥0.3 mg/dl increase in SCr (stage 1)	409 (35%)	N/A	0.57(0.02)	26%	38%	57%	Prospective cohort (low)
Pre-operative albuminuria quantification	Coca (2012) [24]	1159 adults	>50% or ≥0.3 mg/dl increase in SCr (stage 1)	409 (35%)	N/A	0.60(0.02)	30%	42%	47%	Prospective cohort (low)
Pre-operative albuminuria quantification	George (2015) [23]	5968 adults	AKI network criteria	1239 (23.1%)	N/A	N/A	23.9%	29.9%	40%	Retrospective cohort (low)
Pre-operative proteinuria dipstick	Wu (2012) [22]	925 adults	AKI network criteria	140 (15.1%)	33(3.6%)	N/A	9.6%	19.6%	29.4%	Prospective cohort (low)

N/A data not available

Table 36.5 Performance of post-operative albuminuria of AKI in clinical investigation

Biomarker	Author (year)	N	Definition of AKI/ endpoint	Incidence of AKI n(%)	Incidence of RRT n(%)	AUC (SE) or AUC (95%CI) for outcome prediction	Timepoint	Cutoff	Sensitivity	Specificity	Study type (quality of evidence)
Plasma NGAL	Parikh (2011) [1]	1219 adults	100% increase in SCr or receipt of RRT	60 (5%)	18(1.5%)	0.70 (0.04)	ICU 0–6 h post-operatively	293 ng/ml	50%	82%	Prospective cohort (low)
Serum NGAL	Mishra (2005) [12]	71 children	50% increase in SCr from baseline	20 (28%)	N/A	0.91	4 h post CPB	25 ng/ml	70%	802%	Prospective cohort (low
								50 ng/ml	50%	100%	
								80 ng/ml	20%	100%	
Urine NGAL	Parikh (2011) [1]	1219 adults	100% increase in SCr or receipt of RRT	60 (5%)	18(1.5%)	0.67 (0.04)	ICU 0–6 h post-operatively	102 ng/ml	46%	81%	Prospective cohort (low)
Urine NGAL	Mishra (2005) [12]	71 children	50% increase in SCr from baseline	20 (28%)	N/A	0.99	2 h post CPB	25 ng/ml	98%	95%	Prospective cohort (low
								50 ng/ml	98%	95%	
								80 ng/ml	100%	100%	

(continued)

Table 36.5 (continued)

Biomarker	Author (year)	N	Definition of AKI/ endpoint	Incidence of AKI n(%)	Incidence of RRT n(%)	AUC (SE) or AUC (95%CI) for outcome prediction	Timepoint	Cutoff	Sensitivity	Specificity	Study type (quality of evidence)
Urine NGAL	Zarbock (2017) [15]	240 adults	MAKE – Death, RRT or persistent CKD at 90 days	47(19.6%)	26 (10.8%)	0.62(0.52–0.71)	4 h post CPB	52 ng/ml	55%	66%	Post-hoc analysis of randomized controlled trial (moderate)
Urine TIMP2*IGFBP7	Zarbock (2015) [7]	240 adults	50% or 0.3 mg/dl increase in SCr (KDIGO)	108/240 (45%)	26 (10.8%)	0.72 (0.65–0.78)	4 h post CPB	N/A	N/A	N/A	Prospective randomized trial of remote ischemic preconditioning on AKI (moderate)
Urine TIMP2*IGFBP7	Zarbock (2017) [15]	240 adults	MAKE – death, RRT or persistent CKD at 90 days	47(19.6%)	26 (10.8%)	0.64(0.55–0.74)	4 h post CPB	0.36 $(ng/ml)^2/1000$	57%	71%	Post-hoc analysis of randomized controlled trial (moderate)
Urine TIMP2*IGFBP7	Gunnerson (2016) [2]	160 adults	KDIGO stage 2 or higher	14(9%)	N/A	0.83	N/A	N/A	N/A	N/A	Subgroup analysis of prospective cohort (low)

Urine TIMP2*IGFBP7	Meersch (2014) [18]	50 adults	KDIGO stage 1 AKI	26 (52%)	N/A	0.90 (0.79–1.0)	4 h post CPB	0.30	80%	83%	Prospective cohort (low)
								0.4	62%	88%	
								0.5	54%	92%	
								(ng/ml)^2/1000			
Post-operative urine albumin (mg/L)	Molnar (2012) [26]	1198 adults	100% increase in SCr or receipt of RRT	56 (4.7%)	18(1.5%)	0.70 (0.04)	ICU 0–6 h post-operatively	10 mg/L	86%	41%	Prospective cohort (low
								21 mg/L	64%	61%	
								9/mg/L	52%	82%	
Post-operative urine albumin to creatinine ratio (mg/g)	Molnar (2012) [26]	1198 adults	100% increase in SCr or receipt of RRT	56 (4.7%)	18(1.5%)	0.59(0.04)	ICU 0–6 h post-operatively	53 mg/g	66%	40%	Prospective cohort (low)
								100 mg/g	55%	61%	
								190 mg/g	34%	81%	
Post-operative urine proteinuria (dipstick)	Molnar (2012) [26]	1198 adults	100% increase in SCr or receipt of RRT	56 (4.7%)	18(1.5%)	N/A	ICU 0–6 h post-operatively	Trace	65%	50%	Prospective cohort (low)
								30+	52%	72%	
								100–300	30%	90%	

N/A data not available

Neutrophil Gelatinase Associated Lipocalin (NGAL)

NGAL (also known as lipocalin 2 or lcn2) which can be measured in the serum and urine has been extensively studied as a biomarker of AKI since the original seminal paper by Mishra and colleagues [12]. In this prospective observational study, serum and urinary concentrations of NGAL were increased within 2 h of cardiopulmonary bypass (n = 71, children) with a urine NGAL of 50 μg/L supplying a sensitivity of 100% and specificity of 98% for the development of AKI; defined as a 50% increase in serum creatinine for pre-operative baseline (n = 20, 28%). Since this paper which demonstrated an area under the receiver operator characteristic curve (AUC-ROC) of 0.99 there has been a wealth of studies that attempted to replicate these results.

Urine NGAL

Urine NGAL did not provide similar results when it was measured as part of The Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) study [1]. TRIBE-AKI remains one of the largest prospective observational cohorts to investigate biomarkers of AKI in any setting and included 1219 adults who underwent cardiac surgery. TRIBE AKI attempted to increase their AKI event rates by selecting those who were deemed at high risk for AKI by the presence of one of the following: an emergency surgery, a preoperative serum creatinine >2 mg/dl, a preoperative left ventricular ejection fraction <35%, Stage III or IV New York Heart Failure – left ventricular function, age >70, pre-existing diabetes mellitus, concomitant CABG and valve surgery or be going for their second cardiac surgery. Those with preoperative AKI, kidney transplants, ESRD or a preoperative serum creatinine >4.5 mg/dl were excluded.

Urine NGAL was measured within the first 6 post-operative hours after arriving in the ICU. Those subjects in the highest quintile of urine NGAL (>102 ng/ml) at this time point had a significantly increased unadjusted odds ratio for the development of AKI (defined by a doubling of serum creatinine during the hospital stay or the need for RRT, n = 60) (OR (95%CI) 4.7 (1.9–11.7). However, the adjusted odds ratio, after controlling for factors known to be associated with post-operative AKI (age, gender, race, CPB time, diabetes, hypertension, study center and baseline kidney function) was no longer significant (2.5 (0.9–6.8). Urine NGAL provided an AUC(SE) of 0.67(0.04) for the detection of AKI in the early postoperative period. Additionally, in his adult cohort urine NGAL levels in the early post-operative period were associated with an increased length of stay (ICU and total hospitalization) as well as inpatient mortality [1]. In a subsequent post-hoc analysis, they looked at the ability of urine NGAL to predict worsening/progression of AKI (defined as going from Stage 1 to either Stage 2 or 3, or going from Stage 2 to Stage 3) at the time of clinical AKI. In the 480 patients who developed at least Stage 1 AKI, 45 (11.8%) of them had progressive AKI. While urine NGAL was higher in those who went on to develop progressive / more severe AKI, this effect was no

longer significant after adjusting for factors known to be associated with more severe AKI [13]. Not surprisingly urine NGAL was also associated with duration of AKI (days), however this effect was similarly attenuated after adjusting for clinical variables known to predict AKI [14]. Finally, in this adult cohort urine NGAL measured in the early post-operative period was associated with long term mortality in those with AKI following cardiac surgery (n = 407). Those subjects with AKI in the highest tertile of early post-operative NGAL were at increased risk of death during the median 3 year follow up compared to those in the first tertile, adjusted hazard ratio of 2.52 (1.86–3.42), $p < 0.01$. A similar effect was not seen when investigating the association between long term mortality and urine NGAL in those without post-operative AKI.

In a separate randomized control trial Zarbock and colleagues measured urine NGAL in a cohort of 240 high risk cardiac surgery patients (defined as a Cleveland Clinic Score of >6) and looked at its ability to predict 90-day outcomes [15]. They defined their outcome, Major Adverse Kidney Events (MAKE) which consisted of one of three potential outcomes (1) persistent renal dysfunction without RRT, (2) receipt of RRT or (3) all-cause mortality. They demonstrated that urine NGAL measure in the immediate post-operative period was associated with increased risk of MAKE event at 90 days. A cutoff of 51.9 ng/ml 12 h following surgery proved 67% sensitivity and 59% specificity for the development of MAKE-90 days, with other cutoffs at earlier provided much better sensitivity at the expense of specificity (e.g. a pre-procedure cutoff of 4.09 provided 94% sensitivity but was only 30% specific). Importantly, this was a post-hoc analysis of a randomized controlled trial that looked at the impact of remote ischemic pre-conditioning (RIPC) on kidney function in cardiac surgery patients and the data from this investigation is subject to all the limitation of post-hoc analyses of interventional trials [15]. Additionally in this original trial urine NGAL was not a significant predictor of post-operative AKI [7]. Table 36.5 summarizes some of studies and the data around post-operative urine NGAL and AKI.

Plasma NGAL

Similarly, Plasma NGAL has been investigated in the setting of cardiac surgery, and while it provided excellent AKI discrimination in the original Mishra paper subsequent attempts to validate it in larger cohorts have been less successful [12]. Plasma NGAL was also measured in TRIBE AKI adult cohort where it outperformed its urinary counterpart in several aspects of AKI prognostication. Plasma NGAL provided an AUC(SE) of 0.70 (0.04) for the detection of AKI defined by a doubling of serum creatinine during the hospital stay or the need for RRT. Similarly, those in the fifth quintile of plasma NGAL in the immediate post-operative period (>293 ng/ml) had a 7.8 time increased unadjusted odds of developing post-operative AKI compared to those in the first quintile (<105 ng/ml). This association was slightly diminished after adjusting for factors known to

impact the development of AKI (adjusted OR 5.0 (1.6–15.3) [1]. Plasma NGAL measured at the time of clinical AKI (on the day serum creatinine increased) also prognosticated the development of progressive AKI. Plasma NGAL provided an AUC(SE) of 0.74(0.04) for the prediction of progressive AKI. The AUC further increased to 0.80 when biomarker values were combined with a clinical model. Those with a plasma NGAL >322 ng.ml were 7.7 times as likely to develop progressive AKI compared to those with values between 60 and 164 ng/ml (lower quintiles) [13]. Plasma NGAL has also been investigated looking at long term outcomes in the TRIBE AKI adult cohort [16]. Pre-operative plasma NGAL levels >77 ng/ml were associated with a 1.48 (1.04–2.12) increase risk of mortality during the 3.0 year median follow up compare to those with NGAL's <60 ng/ml after adjusting for factors known to impact AKI and mortality. Additionally, early post-operative NGAL levels were also associated with 3-year mortality although this effect was not as strong as the pre-operative biomarker values (adjusted hazard 1.31 (1.0–1.7)).

In addition to TRIBE AKI, plasma NGAL has been measured in several other trials, so much so that Haase and colleagues performed a pooled analysis of prospective studies (n = 10). There final cohort contain 2322 subjects, 1452 of whom underwent cardiac surgery (the remaining 870 were ICU patients) In this study they designated subjects as NGAL(+) or NGAL (−) based on the elevations of the biomarker and did the same for serum creatinine based on a 50% increase in creatinine. They demonstrated that subjects who were NGAL(+)creatinine(−) needed RRT over 16 times more often than subjects who were NGAL(−)creatinine(−). They also demonstrated that length of ICU stay and inpatient mortality incrementally increased across the four study groups. NGAL(−)Creatinine(−) < NGAL(+)Creatinine(−) < NGAL(−)Creatinine(+) < NGAL(+)Creatinine(+) [17]. This concept that biomarkers can be increased in the absences of a change in creatinine is an emerging idea and a variety of non-cardiac surgery related studies have duplicated the finding that biomarker(+)creatinine (−) patients are at increased risk of morbidity and mortality (Fig. 36.1)**.** These markers of renal tubular injury/damage are prognostic of adverse outcomes even in the absence of changes in functional markers such as serum creatinine or urine output.

Despite this wealth of data supporting the use of NGAL (plasma and urine) for the diagnosis and prognosis of AKI following cardiac surgery there is little to no practical data around its real-time use. NGAL remains a clinically available and approved test throughout Canada, much of Europe and other parts of the world, however to date there is little guidance around cutoff values to be employed specifically in the setting of adult cardiac surgery. Based on the amalgam of data from cardiac surgery and non-cardiac surgery settings, it is the author's opinion, that a cutoff of 150 ng/ml for plasma and 100 ng/ml for urine is adequate to demonstrate increased risk for the development of severe AKI (Stage 2 or 3) and other adverse patient outcomes (e.g. prolonged ICU stay, inpatient mortality). Table 36.5 summarizes some of studies and the data around post-operative serum NGAL and AKI.

Urine Tissue Injury Metalloproteinase-2 and Insulin-Like Growth Factor Binding Protein- 7 (TIMP2*IGFBP7)

Urinary concentrations of TIMP2*IGFBP7 (Nephrocheck© – Astute Medical San Diego, Calfornia USA) have been shown to serve as biomarkers of AKI in the setting of ICU and more specifically in those undergoing cardiac surgery [2]. In a pooled analysis from 2 separate prospective observational trials, 160 patients underwent cardiothoracic surgery and had their TIMP2*IGFBP7 measured in the early post-operative period. These cell cycle arrest biomarkers provided and AUC greater than 0.80 for the prediction of Stage 2 or 3 AKI (at least a doubling of serum creatinine from baseline) within the next 12 h. This study enrolled patients who were at increased risk for severe Stage 2 AKI based on either the presence of Stage 1 AKI or abnormal Sequential Organ Failure Assessment Score (SOFA) (cardiovascular or respiratory organ system). Importantly only 14 (9%) of the cohort developed severe AKI, but these severe AKI rates are on par with TRIBE-AKI and other large scale cardiac surgery cohorts. The cohorts used in this analysis were nested within the larger studies that were performed as part of the discovery, validation and replication cohorts that demonstrate the ability of these biomarkers to prognosticate the impending development of severe AKI. It was these studies that led to the clinical implementation of these tests throughout Europe and more recently in the United States. These findings have been subsequently validated in smaller studies [3, 18]. As have the cutoffs employed by Gunnerson and colleagues in the original pooled 160 subject study. They used a high sensitivity cutoff of 0.3 $[ng/ml]^2/1000$ (rough performance across several cohorts 85–90% sensitive, 40–50% specific) and a high specificity cutoff of 2.0 $[ng/ml]^2/1000$ (40–50% sensitive and 80–90% specific) [2]. These values have been used in cardiac surgery studies as well as studies of other critically ill populations at risk for AKI.

Zarbock and colleagues also measured TIMP2*IGFBP7 levels in their post-hoc investigation of the RenalRIP study [15]. They demonstrated that TIMP2*IGFBP7 levels measured 4 h after cardiopulmonary bypass were significantly higher in patients who went on to meet MAKE-90 day outcomes (0.57 $[ng/ml]^2/1000$ in MAKE-negative patients compared to 1.01$[ng/ml]^2/1000$ in MAKE-positive; $p = 0.02$). At this same 4 h timepoint, a TIMP2*IGFBP7 concentration of 0.36 $[ng/ml]^2/1000$ provided a sensitivity of 57% and a specificity of 71%. For MAKE-90 days [15]. This cardiac surgery specific data combined with data from other studies performed in the setting of critical illness point to the ability of TIMP2*IGFBP7 to predict long term renal outcomes in patients at risk of AKI.

However, the true potential strength of these biomarkers come from a recent single-center randomized controlled trial in which TIMP2*IGFBP7 values were used to randomized high risk post-operative cardiac surgery patients to receive an AKI care bundle or usual care in order to improve AKI outcomes [3]. Zarbock and colleagues randomized (1:1) 276 high risk cardiac surgery patients (defined as a TIMP2*IGFBP7 level ≥ 0.3 in the early post-operative period) to receive a KDIGO care-bundle or usual care. The KDIGO care bundle included an algorithm to opti-

mize hemodynamics and volume status (e.g. maintain cardiac index greater than 3 l/min/m^2, or a mean arterial pressure above 65 mmHg) avoidance of hyperglycemia and avoidance of nephrotoxins. Using this care bundle led to a decrease in the total AKI event rate compared to the usual care arm (55.1% vs 71.7%, p = 0.004). Perhaps more impressive was the decrease in Stage 2 and 3 AKI (44.9% in usual care vs 29.7% in the intervention arm, p = 0.009) [3]. While this study did not demonstrate a difference in RRT rates, short or long term mortality, it was not powered to do so and as expected these event rates were low even in a group selected to be at high risk for post-operative AKI. Table 36.5 provides additional data around TIMP2*IGFBP7 and its ability to detect severe AKI following cardiac surgery.

Serum Cystatin C

Cystatin C is a 13 kDa cysteine protease inhibitor that is neither secreted nor reabsorbed by renal tubules but undergoes almost complete catabolism by proximal tubular cells and as such has been highly investigated as both a biomarker of AKI as well as chronic kidney disease. It can be measured in both the blood and urine with serum levels showing promise as a biomarker of AKI, while urinary concentrations have not demonstrated the same success [11, 19]. In 1147 adults from the TRIBE AKI cohort, Shlipak and colleagues demonstrated that preoperative serum cystatin C values outperformed serum creatinine and creatinine based eGFRs in its ability to forecast postoperative AKI. After adjustment for clinical variables known to contribute to AKI, serum cystatin C had a C-statistic of 0.70 compared to serum creatinine (p < 0.001) [20]. However, when this same group investigated sensitivity and rapidity of AKI detection (defined as a 25%, 50%, and 100% increase from preoperative values) by postoperative changes in serum cystatin C, they did not demonstrate a clear advantage over changes in serum creatinine [21]. In a follow up analysis they demonstrated that post-operative elevations of cystatin C (>25%) were associated with an increased risk of death during a 3-year follow up period. This long-term mortality risk was higher in those with changes in cystatin C alone (adjusted hazard ratio 2.2 [1.09–4.47] compared to those with changes in just serum creatinine 1.50 [0.96–2.34] [11]. This ability to predict outcomes even in the absence of changes in serum creatinine has led some to call for including Cystatin C in the definition of AKI, however to date this has not been broadly accepted.

Proteinuria/Albuminuria

Healthy adults excrete less than 150 mgs a day of protein in their urine; however increases in proteinuria can occur in the setting of AKI through several mechanisms; (1) increased permeability/injury to the glomerular filtration barrier as well

as tubular injury (which can decrease tubular absorption of filtered proteins or increased production of tubular proteins by damaged tubules). This proteinuria can be quantified in several methods through urinalysis dipstick, measuring the total protein and urine creatinine in a randomly timed urine sample or more specifically measuring the urine albumin to creatinine ratio (uACR). All of these methods have been utilized to determine the association of proteinuria (pre and post-operatively) with AKI risk following cardiac surgery.

Pre-operative Proteinuria

Several studies have linked pre-operative proteinuria with increased risk of post-operative AKI and other adverse patient outcomes [22–24].) In a prospective observational cohort study of 925 coronary artery bypass grafting (CABG) patients Wu and colleagues demonstrated that AKI (defined by the AKIN criteria) was more common in those with pre-operative dipstick based proteinuria. Only 9.6% of patients with no proteinuria (n = 530 total) developed post-operative AKI as opposed to 19.6% of those with trace to 1+ proteinuria compared to nearly 30% of those with 2-3+ proteinuria [22]. These same patients with pre-operative proteinuria (of any severity) were two times as likely to die during the follow up period compared to those without pre-operative proteinuria. Separately, George et al. published a retrospective cohort study of 17,812 US Veterans who underwent a CABG. They demonstrated that AKI was more likely to occur in those with increased uACR (classified as <30, 30–299 and ≥300 mg/g) with incidence rates of 29.9% in those with no albuminuria and 39.9% in those ≥300 mg/g). In this study as well higher pre-operative uACR was also associated with increased short and long term mortality as well as longer length of hospital stay [23]. Using slightly different urinary albumin (not normalized to urine creatinine), the TRIBE AKI cohort similarly demonstrated that those with increased pre-operative albuminuria were at increased risk for post-operative AKI [24]. After adjusting for factors known to be associated with AKI, those with a uACR ≥300 mg/g were still 2.21 times as likely to develop post-operative AKI compared to those with a <10 mg/g. This same study demonstrated a similar effect when proteinuria was quantified through a urinary dipstick as well as demonstrating that pre-operative proteinuria was associated with increased length of stay [24]. It is important to note that in a follow up TRIBE AKI investigation they demonstrated that pre-operative proteinuria as measured by dipstick was significantly correlated with post-operative biomarker levels with the correlation coefficients being between 0.07 and 0.19 [25]. Given the evidence that the presence of pre-operative proteinuria increases the risk of post-operative AKI and other adverse patient outcomes we recommend using it as a screening tool prior to surgery to help risk stratify patients for AKI so that care team can formulate a care plan to further minimize the risk of future kidney injury. Table 36.4 summarizes several investigations around pre-operative proteinuria and its ability to risk stratify patients for post-operative AKI.

Post-operative Proteinuria

Post-operative proteinuria has similarly demonstrated a significant association with the impending development of AKI. In the TRIBE AKI cohort the urinary albumin concentration (mg/L, not normalized to urine creatinine) and dipstick proteinuria measured within the first six post-operative hours both correlated with the future development of AKI. After adjusting for factors known to impact AKI, the highest quintile of albuminuria (>48.9 mg/L) had an adjusted risk ratio of 3.85 (1.63–4.82) for the development of AKI compared to the first quintile (<5.5 mg/L) [26]. The effect size was diminished and attenuated when the authors investigated the ability of early post-operative uACRs to predict the development of AKI, however urine dipstick values performed on par with urinary albumin. Those with 2–3+ dipstick proteinuria had a 2.94 adjusted relative risk of developing AKI compared to those who were dipstick negative [26]. Additionally, when the TRIBE-AKI group investigated albuminuria for its ability to predict progression of AKI in those who already have early creatinine based AKI they demonstrated that the uACR measured on the day of clinical AKI provided a significant ability to detect the progression to severe AKI (AUC 0.78). The fifth quintile of uACR (>133.0 mg/g) had an adjusted odds of 3.4 (1.2–9.1) for the development of progressive AKI compared to those in the first and second quintile (uAR <35 mg/g) [13]. Thus not only can one use early post-operative albuminuria values to predict the impending development of AKI when AKI is clinically present a follow up test can help determine how likely the AKI is worsen. Lastly, early postoperative urinary albumin values were associated with 3 year long term mortality in patients with AKI. Those patients with a urinary albumin >81.6 mg/g were 2.8 times as likely to die in the mean 3 year follow up compared to those with a value less than 35.8 mg/g; there was no correlation between uACR and mortality in those without AKI [27]. As such, given that uACR is a widely available clinical test, we recommend clinician begin to use it both for screening their pre-operative patients but also as a marker of current/ongoing AKI in the post-operative cardiac surgery patients. Table 36.5 summarizes the data around post-operative proteinuria and the detection of AKI.

Kidney Injury Molecule-1 (KIM-1)

KIM-1 is a 38 kDa transmembrane glycoprotein that has been shown to be upregulated in the kidney following ischemic injury to the proximal tubule and has been investigated as a biomarker of AKI for the last 15 years. In the TRIBE-AKI study, KIM-1 values were associated with an increased risk of post-operative doubling of serum creatinine. Those in the fifth quintile of urinary KIM-1 (>1.19 ng/ml) were at a 6.2 fold increased risk of AKI compared to those in≥ the first quintile (<0.13 ng/ml). This risk remains significant (a 4.8 folks increase) after adjusting for clinical factors which are known to be associated with post-operative AKI (e.g. age, race,

gender, CPB time, non-elective surgery, presence of diabetes and pre-operative kidney function). Importantly, this effect was completely attenuated after controlling for other biomarkers such as urinary IL-18 and plasma and urine NGAL [28]. Similarly, higher urinary KIM-1 concentrations in the early post-operative period were associated with a longer duration of AKI (1–2 days, 3–6 days, >7 days). Those in the fifth quintile of KIM-1 were nearly three times as likely to have longer AKI compared to those in the lowest quintile (unadjusted odds ratio of 2.96[2.01–4.37]); this effect remain relatively unchanged after adjusting of clinical factors known to impact AKI adjusted odds 2.30 [1.51–3.53] [14]. Additionally, while KIM-1 levels measured on the day of clinical AKI could not predict the progression of AKI to higher stages, values measured in the early post-operative period were associated with higher rates of long term mortality [27]. In those without post-operative AKI (n = 792) the third tertile of KIM-1 had an adjusted hazard ratio(95%CI) for the death during the median 3.0 year follow up of 1.83 (1.44–2.33) compared to the lowest tertile. This effect was more pronounced in the cohort with post-operative AKI (n = 407) where the hazard (95%CI) was 2.01 [1.31–3.1] even after adjusting for factors known to contribute to both the development of AKI as well as post-operative mortality. Despite this evidence, KIM-1is not currently available for clinical use, however given the wealth of clinical data around its use, as well as investigations in other AKI clinical settings we anticipate its use in the future.

Interleukin-18 (IL-18)

Il-18 is 18 kilo Daulton pro-inflammatory cytokine that is produced by renal tubule cells and macrophages in response to caspase-1 and has been shown to be a mediator of acute tubular injury. In the TRIBE AKI cohort early post-operative IL-18 values were associated with increased risk of AKI. The fifth quintile of IL-18 (>60 pg/ml) was associated with a 10.9 fold higher risk of AKI, defined as a postoperative doubling of serum creatinine or receiving acute dialysis, when compared to the lowest quintile (<3 pg/ml). This effect was slightly attenuated to an adjusted odds of 6.8 (1.9–24.3) after adjusting for factors known to be associated with AKI [1] The first postoperative concentration of IL-18 (0–6 h) provided and AUC of 0.74 that increased to 0.76 after combining IL-18 with the aforementioned clinical model. Similarly higher IL-18 concentrations measured in the early post-operative period were associated with an increased duration of AKI [14]. Additionally, higher IL-18 levels in the early post-operative period were associated with increased risk of mortality over the 3 year follow up period. In patients who developed AKI, those patients with IL-18 levels between 48 and 133 pg/ml were likely to die compared to those with values <48 pg/ml (adjusted hazard of 1.49 (1.01–2.21); this increased mortality risk was larger in those with a value greater than 133 pg/ml (adjusted hazard 3.16(1.53–6.53). Of note there was a similar effect seen in those who did not develop AKI, where those in the highest tertile (>133 pg/ml) had an adjusted hazard ratio of 1.23 (1.02–1.48) compared to those with values less than 48 pg/ml) [27].

Additionally, Il-18 values measured at the time of clinical AKI demonstrated the ability to predict the progression of AKI. IL-28 measured on the day of an increase in serum creatinine provided an AUC of 0.78 for the development of progressive AKI. And after adjusted for the clinical model those with a value >185 pg/ml were three times as likely to progress to a more severe stage of AKI compared to those with a value <29.6 pg/ml [13]. Thus IL-18 has demonstrated the ability to detect a variety of AKI endpoints across the spectrum of cardiac surgery associated AKI; however at the current time it is not available for clinical use in the United States.

Recommendations

We anticipate further investigation into these biomarkers over the next few years, as they have increasingly been shown to not only detect AKI earlier than serum creatinine but also help identify high risk post-operative patients who benefit from early nephrology focused care [3]. While some may await further validation of these finding in cardiac surgery, similar results have been seen in the setting of other post-surgical (non-cardiac) patients [29]. As such, when available we make the recommendation to consider measuring TIMP2*IGFBP7 or NGAL in post-operative cardiac surgery patients who are at high risk for AKI (hemodynamic instability, increased respiratory distress or early Stage 1 AKI). (Evidence quality: Low to Moderate) Pairing these biomarker results with stratified treatment strategies to mitigate AKI risk as outlined in Table 36.6 is

Table 36.6 Potential use of biomarkers in the setting of cardiac surgery

Interpretation of results and clinical actions			
Post-operative urine NGAL result (ng/ml)	**<100**		**>100**
Post-operative plasma NGAL result (ng/ml)	**<150**		**>150**
Post-operative TIMP2*IGFBP7 result $(ng/ml)^2/1000$	**<0.3**	**0.3–2.0**	**>2.0**
	Standard care	**Optimize kidney-focused care**	**Maximal kidney protective care**
	Continue standard post-operative of care	Record strict ins and outs. Consider maintaining indwelling bladder catheters	Record strict ins and outs. Consider maintaining indwelling bladder catheters
	Continue to monitor for AKI using standard definitions	Continue to monitor renal function – every 12–24 h	Consider nephrology consult

Table 36.6 (continued)

Interpretation of results and clinical actions			
	No restriction on nephrotoxins	Consider discussing drug dosing for AKI w/ pharmacist, with close monitoring of drug levels when feasible (e.g. calcineurin inhibitors or vancomycin)	Monitor renal function – every 12–24 h
	Liberal use fluids/diuretics	Optimize hemodynamics by judicious use fluids/ diuretics to ensure adequate renal perfusion	Discuss drug dosing for AKI with Pharmacist, with close monitoring of drug levels when feasible (e.g. calcineurin inhibitors or vancomycin)
	Standard plans drug dosing	Consider sending Urinalysis with microscopy and consider urine lytes	Optimize hemodynamics by judicious use fluids/ diuretics
	Consider early removal of urinary catheter	Minimize nephrotoxin exposure (e.g. aminoglycosides, ACE, ARB, NSAIDs)	Consider renal imaging
		Consider rechecking biomarkers in 12–24 h	Send Urinalysis with microscopy and urine lytes
			Avoid nephrotoxin exposure (e.g. aminoglycosides, ACE, ARB, NSAIDs)
			Recheck biomarkers in 12–24 h

appropriate. Most of the care of patients with AKI remains supportive and as such recommendations include attempt to avoid further injury through avoidance of nephrotoxins and maintenance of adequate renal perfusion. Further studies will clarify specific novel interventions to minimize the risk AKI following adult cardiac surgery.

Similarly there is a low level of evidence to utilize pre-operative urinary protein excretion (either dipstick or albuminuria quantification) as a marker for post-operative AKI risk. We recommend measuring pre-operative albumin to creatinine ratio as method to identify patients who are higher risk for the development of post-operative AKI. Patients with macro-albuminuria (>300 mg/g) are at the highest risk for AKI and their care should maximize kidney-protective strategies, including ensuring adequate renal perfusion and the upfront avoidance of known nephrotoxic agents (Table 36.4).

A Personal View of the Data

Post-operative AKI remains a common complication of cardio-thoracic surgery and is associated with increased morbidity and mortality. Identifying patients at highest risk for the development of the most severe forms of AKI is the first step in mitigating the impact of post-operative AKI. There is limited data around the use of biomarkers in the pre- and early post-operative period to detect the earliest signs of kidney injury, but this data all points to improved outcomes through the implementation of these new tools. The new biomarkers (NGAL, TIMP2*IGFBP7) are not perfect and their results are hindered by comparison to a flawed gold standard (serum creatinine); however their association with clinically meaningful endpoints such as early AKI, progression of AKI, need for RRT and long-term mortality is clear. As clinicians we need to embrace these novel tools and use them despite their limitations. In an ideal situation all post-operative patients should be receiving care that prevents AKI, but utilizing biomarkers in conjunction with more kidney focused care (Table 36.6) seem appropriate given the current clinical evidence.

- We recommend measuring pre-operative urine albumin to creatinine ratio to improve risk stratification for post-operative AKI (evidence quality low; recommendation weak)
- We recommend measuring TIMP2*IGFBP7 and /or plasma NGAL and/ or urine NGAL in the early post-operative period to improve AKI risk stratification. (evidence quality moderate; recommendation strong)
- Pairing novel biomarkers of AKI with kidney-centered care may lead to a decrease in AKI severity and improved patient outcomes. (evidence quality moderate; recommendation weak)

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Chapter 37
Cardiorenal Syndrome in Heart Failure Patients: ICU Management

Andrew Kowalski and Jonathan D. Rich

Introduction

Fluid balance and blood pressure regulation are the result of an intricate equilibrium between the heart and kidney, mediated by the body's regulation of neurohormonal processes. The coupled malfunction of these two organs has been described in the literature as cardiorenal syndrome (CRS). A working group in 2004 attempted to define CRS as an extreme state of increased circulating volume leading to symptoms of heart failure (HF) and disease progression/exacerbation, where therapy to relieve HF symptoms is limited by the patients overall renal function [1]. This definition negates the bidirectional contribution of these two systems and implies that failure of HF resolution is the result of worsening renal function. More simply, CRS should be viewed as dysfunction of one organ leading or contributing to dysfunction in the other through hemodynamic and neurohormonal feedback pathways [2]. To emphasize this concept, a classification system of CRS was proposed at a Consensus Conference by the Acute Dialysis Quality Group in 2008 to highlight the bidirectional interactions of these organs (Table 37.1) [3]. CRS was subdivided into five subtypes to help illustrate the various potential interactions. Types 1 and 2 are related to the influence of the heart on renal function as a result of acute cardiac decompensation leading to renal injury or chronic cardiac dysfunction contributing to steady and progressive renal dysfunction, respectively. CRS types 3 and 4, alternatively coined 'reno-cardiac syndrome' describes the directional relationship of

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Table 37.1 The five types of cardiorenal syndrome, causes and basic management options

Various types of cardiorenal syndrome			
CRS type	Description	Causes	Management
Type 1	Acute cardiorenal	Acute heart failure, acute coronary syndrome, cardiogenic shock	Supportive care, oxygenation, decongestion via diuretics, inotrope support, vasopressors, ultrafiltration
Type 2	Chronic cardiorenal	Stigmata of chronic heart disease (LV remodeling, diastolic dysfunction, cardiomyopathy, etc.)	Treat HF based on current guidelines, adjust medication dose based on renal function, avoid nephrotoxins as possible, monitor electrolyte disturbances
Type 3	Acute reno-cardiac	Acute kidney injury leading to acute cardiac dysfunction	Supportive care, decongestion via diuretics, identification of renal injury and address reversible causes, monitor electrolyte disturbances, initiate dialysis as clinically indicated
Type 4	Chronic reno-cardiac	Chronic kidney disease leading to chronic cardiac dysfunction	Supportive care, follow current guidelines for CKD management, monitor electrolyte disturbances, initiate dialysis as clinically indicated
Type 5	Secondary cardiorenal	Systemic conditions leading to simultaneous cardiac and renal injury (sepsis, sarcoidosis, amyloidosis, etc.)	Supportive care, management specific based on underlying etiology, diuretics, initiation of dialysis as clinically indicated

Data extrapolated from Ronco et al. [3]
LV left ventricle, *HF* Heart Failure, *CKD* Chronic Kidney Disease

acute renal injury or chronic renal dysfunction and its influence on cardiac function. Finally, CRS type 5 is a subtype that is not related to the acute or chronic dysfunction of either heart or kidney, but to any systemic process that contributes to the simultaneous dysfunction of both organs [3]. Thus, although CRS is a broad and expansive topic, the precise focus of this chapter will be specific to the various approaches to management of CRS as it pertains to patients with acute decompensated heart failure (ADHF) in an intensive care setting.

Search Strategy

A literature search of English language publications from 2002 to present was used to identity published data on cardiorenal syndrome treatment using the PICO outline (Table 37.2). Databases searched were PubMed and Cochrane Evidence Based Medicine. Terms used in the search included “cardiorenal syndrome,” “treatment of cardiorenal syndrome,” “treatment of acute decompensated heart failure,” “bolus versus continuous infusion for heart failure treatment,” “ultrafiltration and acute

Table 37.2 PICO table of ICU management of cardiorenal syndrome

Patients	Intervention	Comparison	Outcome
Adult, cardiorenal syndrome, acute decompensated heart failure	Advanced management of heart failure in an ICU setting	Traditional approach to heart failure management	Mortality, decongestion, renal recovery

decompensated heart failure," "ultrafiltration versus diuretic management in heart failure," and "inotropes and cardiorenal syndrome."

Prevalence of Renal Dysfunction in Heart Failure

Impaired renal function is commonly observed among patients with HF and is a strong predictor of mortality in both acute and chronic HF settings [4, 5]. Additionally, patients with chronic renal dysfunction are commonly underrepresented among cardiac studies despite being at higher risk for cardiovascular diseases and complications [5, 6]. While the exact prevalence of renal impairment in patients hospitalized with ADHF remains poorly characterized, a report looking at 118,465 HF patients from the Acute Decompensated Heart Failure National Registry (ADHERE) database identified 64% of patients with reduced renal function as measured by an estimated glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2. The mean GFR was 55 mL/min/1.73 m^2, and only 9% had a GFR of >90 mL/min/1.73 m^2 [4]. Prior to admission, 33% of men and 27% of women carried a pre-hospitalization diagnosis of renal insufficiency [4]. In a systemic review of 39 studies of CKD patients by Tonelli et al., the absolute risk for death increased exponentially with decreasing renal function, with cardiovascular deaths representing over 50% of the overall mortality [5]. A graded, dose response trend of worsening cardiovascular outcomes in relation to the degree of CKD has also been reported [3].

As shown, worsening renal function is a frequent complication after admission for ADHF and contributes to adverse outcomes. Although worsening renal function may be transient and reversible at times, its occurrence is associated with longer hospitalizations, higher risk of readmission, and decreased survival, irrespective of baseline renal function [7]. Smith et al. illustrated this in a meta-analysis looking at >80,000 hospitalized and non-hospitalized HF patients and the impact of renal impairment on mortality. A total of 63% of patients had some degree of renal impairment, and 29% had moderate to severe impairment as defined by a creatinine >or = 1.5 mg/dL or eGFR <53 mL/min/1.73 m^2. After a 1 year follow-up period, 38% of patients with any renal impairment and 51% with moderate to severe impairment died versus 24% of patients without renal impairment [8]. Thus, renal function should be considered prominently in the risk stratification, evaluation, and therapeutic strategies when treating ADHF patients.

Pathophysiology

Management of CRS, which is interlaced with complex pathophysiologic processes, is more complicated than its simple definition suggests. Cardiac dysfunction, including ADHF, triggers a number of downstream and often maladaptive neurohormonal cascades in an attempt to preserve end organ perfusion. In the kidney, the increase in circulating catecholamines contributes to arterial vasoconstriction and decreased perfusion to the already oxygen poor renal medulla leading to organ dysfunction. Furthermore, potentiation of the renin-angiotensin-aldosterone system (RAAS) and anti-diuretic hormones occurs, leading to a significant increase in both sodium and water retention. These maladaptive responses translate to a vicious cycle of worsening volume overload, increased cardiac afterload, and a further reduction in cardiac output.

Although long presumed to be the reduced cardiac output state as the major contributor to CRS, there has been a renewed focus on the deleterious contribution of increased renal venous congestion leading to a reduction in glomerular filtration, increasing intratubular pressure and decreased tubular flow in CRS [9]. In a study of ADHF by Mullens et al., worsening renal function was more common in patients with elevated central venous pressures (CVP) as compared to patients who achieved lower CVPs. Moreover, an elevated CVP was determined to be a stronger contributor to worsening renal function than was a reduced cardiac output in these same patients [10]. In a separate retrospective study of 2557 HF patients undergoing a cardiac catheterization, increased CVP was the most potent independent hemodynamic predictor of both worsening renal function and mortality [11]. Thus, when approaching the management of CRS in ADHF patients, in addition to restoring or improving cardiac output, an emphasis on reducing systemic venous congestion is of critical importance [9].

Results

Approach to Treatment: Diuretics

Decreasing venous congestion is among the cornerstone treatment strategies in ADHF including in those with CRS. The mode of action and efficacy of loop diuretics in particular occurs in the ascending limb of the Loop of Henle by decreasing the absorption of sodium and chloride [12]. This critical blockade occurs in a section of the renal tubule that is impermeable to water and leads to a steady decrease in renal medullary osmolality. The decreased osmolality contributes to a dysfunction in water absorption in the descending limb of the Loop of Henle, by decreasing the concentration gradient leading to an inability to concentrate urine and a profound diuresis. Intravenous diuretics are often preferred over oral agents in ADHF and CRS as they tend to elicit a stronger diuretic response more rapidly and avoid impediments of gastrointestinal absorption related to gastrointestinal edema.

However, practice differences exist with respect to the preferred method of IV diuresis, i.e. intravenous bolus versus continuous intravenous infusion and a summary of studies addressing this question can be seen in Table 37.3.

Table 37.3 Overview of study design and outcomes comparing IV bolus with IV continuous infusion of loop diuretics in acute decompensated heart failure

Author/ study	Number of patients	Intervention	Comparison	Outcome	Grade
Salvatore (2004) [13]	N: 254 patients Cochrane review of 8 trials	Continuous IV infusion of loop diuretics	Bolus IV administration of loop diuretics	Greater diuresis and similar safety profile with continuous loop diuretics; continuous had greater UOP, shorter hospital stay but with more electrolyte abnormalities and similar all-cause mortality	High
Peacock et al.; ADHERE (2009) [15]	N: 82,540 patients randomized to 62,866 to receive low does furosemide and 19,674 to receive high dose furosemide	Low dose furosemide (<160 mg/ day)	High dose furosemide (>160 mg/day)	Patients receiving the lower doses had a lower risk for in-hospital mortality, ICU stay, prolonged hospitalization, or adverse renal effects	Moderate
Allen et al. (2010) [18]	N: 41 patients randomized to randomized to 21 receiving bolus IV and 20 to continuous infusion of loop diuretic	Twice daily IV bolus furosemide	Continuous IV furosemide infusion	No substantial differences from admission to hospital day 3 or discharge found between bolus injection and continuous infusion of furosemide; mean change in creatinine −0.02 vs 0.13 mg/dL, p = 0.18; urine output 5113 vs 4894 mL, p = 0.78; length of stay 8.8 vs 9.9 days, p = 0.69, respectively	Moderate
Thomson et al. (2010) [19]	N; 56 patients randomized to 26 patients to receive continuous IV and 30 patients to receive bolus dosing	IV bolus furosemide	Continuous IV furosemide infusion	Continuous IV furosemide was well tolerated, had greater UOP (3726 ± 1121 mL/24 h vs 2955 ± 1267 mL/24 h, p = .019), and shorter length of stay (6.9 ± 3.7 versus 10.9 ± 8.3 days, p = .006) than bolus IV furosemide	Moderate

(continued)

Table 37.3 (continued)

Author/ study	Number of patients	Intervention	Comparison	Outcome	Grade
Felker et al.; DOSE-HF (2011) [14]	N: 308 patients randomized in a double-blind study of twice daily IV bolus furosemide and continuous IV infusion and further divided by dose	Twice daily IV bolus of furosemide (stratified to dose equal to oral and 2.5 times oral dose)	Continuous IV infusion of furosemide (stratified to dose equal to oral and 2.5 times oral dose)	No significant differences in patients' global assessment of symptoms (mean AUC, 4236 ± 1440 and 4373 ± 1404, p = 0.47) or change in renal function (0.08 ± 0.3 mg/dL vs 0.04 ± 0.3 mg/dL, p = 0.21) with bolus compared to continuous infusion, or with respect to high vs low dose administration. High dose was notable for a greater diuresis without worsening renal function	High
Shah et al. (2012) [16]	N: 308 patients randomized in DOSE-HF comparing outcome based on outpatient loop diuretic dose (N: 177 high dose; N: 131 low dose)	High dose outpatient diuretic (>120 mg furosemide equivalent)	Low dose outpatient diuretic (<120 mg furosemide equivalent)	Patients on higher outpatient diuretic doses have greater disease severity and worse renal function. Admission diuretic dose was associated with an increased risk of death or rehospitalization at 60 days	Low
Palazzuoli et al. (2014) [17]	N: 82 patients randomized to 43 to receive a continuous infusion and 39 were assigned to bolus treatment	Twice daily IV bolus furosemide	Continuous IV furosemide infusion	Continuous infusion of loop diuretics resulted in greater reductions in BNP (−576 ± 655 vs −181 ± 527 pg/ml, p = 0.02) than bolus treatment from admission to discharge, but was associated with worsening renal failure (change in creatinine; +0.8 ± 0.4 versus −0.8 ± 0.3 mg/dl p = <0.01) and higher rates of rehospitalization from admission to discharge but was associated with worsened renal function and higher rates of rehospitalization or death at 6 months	Moderate

Table 37.3 (continued)

Author/ study	Number of patients	Intervention	Comparison	Outcome	Grade
Alqahtani et al. (2014) [20]	N: 936 patients in a meta-analysis of 7 crossover and 11 parallel-arm randomized controlled trials	IV bolus loop diuretics	Continuous IV loop diuretic infusion	Continuous infusion of loop diuretics preceded by a loading dose resulted in greater diuresis in hospitalized adults with extracellular fluid volume expansion compared with intermittent dosing regimens	High
Wu et al. (2014) [21]	N: 518 patients in a meta-analysis of 10 randomized controlled trials looking at the safety and efficacy of continuous infusion vs bolus injection of intravenous loop diuretics	IV bolus loop diuretics	Continuous IV loop diuretic infusion	There were no significant differences in the safety and efficacy with continuous administration of loop diuretics, compared with bolus injection in patients with acute decompensated heart failure	High

A Cochrane review by Salvador et al. examined eight studies that compared the effects of continuous intravenous infusion versus intravenous bolus administration among patients with ADHF. Seven of the studies reported urine output to be greater in patients who were treated with continuous infusion ($p < 0.01$) and electrolyte abnormalities including hypokalemia and hypomagnesemia were not significantly different in the two treatment groups ($p = 0.5$) [13]. To further evaluate the relationship between bolus and continuous as well as the potential dose effect of diuretic strategies in patients with acute decompensated heart failure (DOSE-AHF), Felker et al. looked at bolus versus continuous and then stratified high dose furosemide versus low dose to evaluate the outcomes. No significant difference was observed in efficacy or safety end points when using bolus or continuous infusion. Although patients assigned to bolus therapy were more likely to require a dose increase at 48 h, the total dose of furosemide in the bolus group was not significantly different from that in the continuous group (592 versus 480 mg, $p = 0.06$) over the span of 72 h. This study also showed that while high-dose furosemide compared with low-dose furosemide, produced greater net fluid loss, weight loss, and relief from dyspnea, this strategy was also associated with more frequent transient worsening of renal function (23 versus 14%) [14]. Following this observation, Peacock et al. showed, perhaps not surprisingly, that heart failure patients who required lower

doses of diuretics had a lower in-hospital mortality, shorter ICU and overall hospitalization lengths of stay, and fewer adverse renal events [15].

A subsequent study from DOSE-AHF, Shah et al. examined the patients' outpatient, pre-hospitalization furosemide regimen, as a surrogate for diuretic resistance and HF severity and found that a higher outpatient diuretic dose (defined as ≥120 mg furosemide) was associated with increased death and rehospitalization for HF. Additionally, patients on a higher outpatient diuretic dose achieved a more potent initial diuresis in response to a bolus of furosemide versus a continuous infusion, supporting the practice of administering an initial bolus dose of furosemide followed by either a continuous infusion or intermittent diuretic strategy [16].

In a separate randomized clinical trial, Palazzuoli et al. also evaluated the mode of delivery of diuretics, bolus versus continuous, on clinical outcomes. After the cumulative daily dose of furosemide was decided upon by the treating physician, patients were randomized in a 1:1 ratio to either twice-daily bolus injections or continuous infusion. Patients were started at daily doses of 80 ± 20 mg of furosemide and increased to 160 ± 40 mg and up to 240 ± 40 mg if diuretic resistance was observed. While patients receiving continuous infusion exhibited greater urine output after 24 h and a larger reduction in BNP after 5 days, other clinical indices including the change in serum creatinine, use of inotropic agents, length of hospital stay, and rehospitalization or death at 6 months favored bolus administration. In addition, there were higher rates of re-admission or death in the continuous infusion group at 6 months, (58% versus 23%, (P = 0.001) [17]. Additional subsequent smaller studies have largely demonstrated findings similar to the above mentioned studies, most notably that a modest increase urine output is typically achieved with continuous diuretic infusions without considerably differences in overall efficacy or safety as compared to bolus adminstrations [18–21]. Thus, on the basis of the totality of available evidence, what appears most consistent is that in patients with ADHF and CRS, what matters most is not necessarily the mode of diuretic administration but rather using a sufficient dose, achieving a clinically relevant diuresis, while closely monitoring renal function. In patients with systolic heart failure in particular who are not achieving sufficient diuresis despite the above strategies, a reassessment of perfusion status is critical as we are reminded that patients must be "first warmed up in order to be dried out." [22]

Approach to Treatment: Ultrafiltration

When patients present with ADHF and diuretic resistance, concerns arise regarding continued escalating diuretic dosing and exposing the patient to the known side effects of high dose loop diuretics and worsening renal function. Ultrafiltration (UF) is a method of volume offloading that has seen mixed results over the past decade as part of the ADHF treatment armamentarium and has declined in popularity of late, but which may still have a role in the management of ADHF and CRS in select patients. Table 37.4 summarizes the recent studies comparing UF to diuretic management.

Table 37.4 Overview of study design and outcomes comparing IV diuretics with peripheral ultrafiltration in the management of ADHF

Author/study	Number of patients	Intervention	Comparison	Outcome	Grade
Bart et al; RAPID-CHF (2005) [23]	N: 40 patients randomized to 20 to receive peripheral UF and usual care and 20 usual care (diuretics)	Usual care with diuretics (median dose 160 mg)	8 h UF (fluid removal determined by physician) followed by diuretics (median dose 80 mg)	Use of a peripheral device for UF fluid removal for patients with ADHF was feasible, well-tolerated, and resulted in significant weight loss and fluid removal	Moderate
Costanzo et al; UNLOAD (2007) [24]	N: 200 patients randomized to UF or IV diuretics	IV furosemide 2 times outpatient oral dose	UF via Aquadex system 100 UF for 48 h	At 48 h UF safely produced greater weight and fluid loss than intravenous diuretics, and reduced 90-day resource utilization for HF. No serum creatinine differences occurred between groups	Moderate
Bart et al; CARRESS-HF (2012) [25]	N: 188 patients with ADHF, worsened renal function, and persistent congestion to stepped pharmacologic therapy (94 patients) or UF (94 patients)	IV loop diuretics with intent to decrease, increase, or continue current doses of diuretics as necessary to maintain a urine output of 3–5 l per day	UF via Aquadex system 100 UF with a set rate of 200 cc/h. with a median duration of 40 h	The use of a stepped pharmacologic-therapy algorithm was superior to a strategy of ultrafiltration for the preservation of renal function at 96 h, with a similar amount of weight loss. Ultrafiltration was associated with a higher rate of adverse events	High
Marenzi et al; CUORE (2014) [26]	N: 56 patients with congestive HF were randomized to receive standard medical therapy (n = 29) or UF (n = 27)	IV diuretics administered via recommendation from the AHA and ESC	UF via Dedyca through a double lumen catheter in a major vessel for a single or double session up to >2 L fluid removal	In HF patients with significant fluid overload, first-line treatment with ultrafiltration was associated with prolonged clinical stabilization and a greater freedom from rehospitalization for ADHF	Low
Costanzo et al; AVOID-HF (2016) [27]	N: 110 patients were randomized to adjustable UF and 114 to adjustable loop diuretics	IV diuretic protocol based on CARRESS-HF: with intent to decrease, increase, or continue current doses of diuretics as necessary to maintain a urine output of 3–5 l per day	UF via Aquadex FlexFlow system. UF fluid removal rates based on SBP; SBP <100 mmHg: 150 cc/h; SBP 100-120 mmHg: 200 cc/h; SBP >120 mmHg: 250 cc/h median time was 70 h	The UF group trended toward a longer time to first HF event within 90 days and fewer HF and cardiovascular events. More patients in the UF group experienced serious treatment-related adverse events. The study was stopped early due to slow enrollment	Moderate

UOP Urine Output, *L* liter, *IV* intravenous, *SBP* systolic blood pressure, *RV* right ventricle, *NTG* nitroglycerine, *LVEF* left ventricle ejection fraction

Initially, the concept of using UF was reserved for patients with advanced renal failure or those unresponsive to pharmacologic management. Over time, however, the concept of employing UF as a treatment modality earlier in the process gained traction. Bart et al. in the Relief for Acutely Fluid-Overloaded Patients with Decompensated Congestive Heart Failure (RAPID-CHF) trial studied 40 patients with ADHF randomized to a single UF session in addition to usual care or usual care alone with goal the primary end point of weight loss at 24-h. The UF armreceived treatment for 8 h with a fluid removal target of up to 500 mL/h and were not given concomitant diuretics during the treatment. Fluid removal after 24 h was 4650 mL in the UF group compared to 2838 mL in the usual care group ($p = 0.001$) without significant differences in electrolyte abnormalities or renal function [23]. This study suggested that ADHF patients can tolerate UF well in the short term.

In 2007 the Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) study compared the safety and efficacy of UF and standard intravenous diuretic therapy in 200 patients with ADHF. The average duration of a single ultrafiltration session was 12 h with an average UF rate of about 241 cc/h and patients averaged two treatments during their hospitalization. After 48 h, there was a greater weight loss achieved in the UF group (5.0 ± 3.1 kg vs. 3.1 ± 3.5 kg; $p = 0.001$) associated with more net fluid loss (4.6 L vs. 3.3 L; $p = 0.001$). In addition to these differences, the UF group was shown to have a reduction in rehospitalizations for HF (18% vs. 32%; $p = 0.037$). Furthermore, there was no difference between groups with respect to changes in creatinine, BUN, sodium, bicarbonate or hypokalemia [24]. The UF group was also discharged on a lower oral diuretic dosing regimen and remained on lower doses at 90 days.

Building on the momentum achieved by UNLOAD, Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) compared the effect of UF with step-wise diuretic therapy on renal function and weight loss in patients with ADHF who had worsening renal function and persistent congestion (i.e. the cardiorenal syndrome). In contrast to the results of UNLOAD, UF was shown to be inferior to pharmacologic therapy with diuretics due to a significant worsening in renal function and without improvements in rehospitalization or survival. More specifically, they showed that at 96 h the change in the creatinine level was worse in the UF group when compared to the pharmacologic-therapy group without any noticeable significant differences in weight changes. A possible explanation for the worsening creatinine seen in the UF arm was the aggressive strategy of volume removal as the duration of UF sessions in this study was considerably longer than in previous studies [25].

Following the results from CARESS-HF, two additional notable studies were performed. The first, the Continuous Ultrafiltration for Congestive Heart Failure (CUORE) trial, randomized 56 patients with ADHF to standard medical therapy or UF. Interestingly, despite no difference in weight change between the two groups, a lower incidence of rehospitalizations for HF was observed favoring the UF arm [26]. The investigators speculate that this decrease in rehospitalizations coupled with a more stable observed renal function may be related to the fact that UF was

initiated early as a first line treatment rather than as a rescue therapy. Subsequently, the Aquapheresis versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF) trial evaluated the time to first HF event in ADHF with UF compared to standard IV diuretic therapy and found the UF group had fewer HF and cardiovascular events. Due to lessons learned from the earlier UF trials, AVOID-HF was unique in that the UF rate was designed to be adjustable in relation to the patients' changes in hemodynamics and renal function. UF rates thus fluctuated between 150 and 250 cc/h and this real-time algorithm may have allowed for greater fluid removal with minimal changes in renal function [27]. Although the trial was stopped prematurely due difficulty achieving target enrolment, the UF group had a non-statistical trend toward achieving a longer time to first HF event when compared to the diuretic group (62 vs 34 days, respectively; P = 0.106). Additionally, at 30 days the UF groups had fewer cardiovascular events when compared to the diuretic group [27]. Yet, adverse events were noted to be common in the UF group, including infection requiring intravenous antibiotics, bleeding requiring transfusion, symptomatic hypotension with some requiring fluid replacement or vasopressor agents, drops in hemoglobin of >3 g/dL, and acute coronary syndrome requiring intervention [27]. Thus, at this time, treatment with UF in ADHF and CRS should be considered carefully and on a case-by-case basis only.

Approach to Treatment: Inotropes

When patients with ADHF present with signs and symptoms of a low cardiac output state, short terms use of intravenous inotropic agents may be needed [28]. Several inotropes exist, including milrinone, dobutamine and dopamine, and each may achieve the desired effect of increasing stroke volume and improving end organ perfusion. However, there are some notable differences between the agents that should be considered in the context of ADHF and cardiorenal syndrome. IV milrinone has a slow onset of action if not administered as a bolus followed by a continuous infusion. Additionally, milrinone has more potent vasodilatory properties which could be beneficial in achieving afterload reduction, but may also be more likely to result in systemic hypotension. Finally, in contrast to either dobutamine or dopamine, milrinone is renally cleared. Cautious dosing should thus be used in the setting of ADHF with worsening renal function if milrinone is chosen.

The role of dopamine in the cardiorenal syndrome deserves special attention. For many years, "low dose dopamine" enjoyed special status designation given its theoretical benefits in not only aiding in augmenting cardiac output, but also improving renal blood flow (and function) owed to its binding to dopaminergic receptors leading to dilatation of renal vessels [29, 30]. Giamouzis et al. looked at the role of dopamine in a small cohort of ADHF patients in the decompensated heart failure (DAD-HF) trial. After giving a furosemide bolus, patients were randomized to a high dose continuous infusion of furosemide or a lower dose furosemide infusion in conjunction with low dose dopamine. They showed that while the mean hourly

urine output and dyspnea score were similar among the two groups, the high dose furosemide group had more frequent worsening renal function when compared to the low dose furosemide and dopamine group (30% vs. 6.7%; p = 0.042). They concluded that the combination of low dose furosemide and low dose dopamine were similarly effective as high dose furosemide in volume removal, but was associated with an improved renal function profile and should be considered in the treatment of ADHF [31]. However, in a more definitive randomized, placebo controlled trial, Chen et al. conducted the Renal Optimization Strategies Evaluation (ROSE-HF) trial to evaluate separately the effects of low dose dopamine and low dose nesiritide in a two by two factorial design in ADHF. Notably, adding low dose dopamine to standard ADHF therapy did not either enhance decongestion or preserve/improve renal function when compared to placebo [32]. Of note, the low dose dopamine dose was lower in ROSE (2 mcg/kg/min) compared to the DAD-HF trial (5 mcg/kg/min). It is thus possible that any benefits realized by the use of dopamine in ADHF and cardiorenal syndrome may be related exclusively to its inotropic properties rather than its dopaminergic actions at low doses that had been historically touted.

Special Populations: Heart Failure with Preserved Ejection Fraction (HFpEF) and Right Heart Failure in Pulmonary Arterial Hypertension (PAH)

Heart Failure with Preserved Ejection Fraction

CRS is common in ADHF related to HFpEF although the physiologic contributors may differ somewhat from those with HFrEF. Moreover, the heterogeneous nature of the HFpEF syndrome makes generalizing treatment strategies challenging. Nonetheless, while it is debatable whether a component of systolic dysfunction might exist in some forms of HFpEF, what is uniformly true is these patients suffer from elevated filling pressures despite a preserved EF. When the HFpEF patient develops ADHF and CRS, a critical evaluation of systemic blood pressure is important when contemplating management strategies. Sometimes overt hypertension is present and judicious blood pressure lowering concomitant with diuresis is most effective in decongesting the patient while also preserving renal function. More challenging however is the HFpEF patient with hypotension. In these instances, inotropic therapy is usually of little benefit unless severe RV systolic dysfunction is present concomitantly. Rather, use of arterial vasopressors (i.e. phenylephrine) is often the treatment of choice to raise blood pressure, ensure adequate renal perfusion pressure, which in turn allows for the effective and safe co-administration of IV diuretics. Interestingly, in a subgroup analysis of ADHERE, patients with HFpEF who were treated with inotropes had significantly longer length of hospital stay (12.9 vs. 5.8 days; $P = <0.0001$) as well as a higher mortality rate (19 vs. 2%; $P = <0.0001$) compared with those who were not treated with inotropes [33]. In

recalcitrant cases of recurrent, symptomatic hypotension upon pressor discontinuation, patients may be weaned from IV to oral vasopressors (i.e. midodrine) which may allow for sustained blood pressure support when transitioned to outpatient status.

Right Heart Failure in Pulmonary Arterial Hypertension

In patients with ADHF related to right heart failure, particularly in the presence of PAH, there is evidence of varying degrees that a state of RV ischemia is present. Thus, any drugs that increase myocardial oxygen demand (i.e. inotropes) may further exacerbate RV failure. Similar to the patients with HFpEF, these patients nearly all have preserved LV systolic function. Thus, in the presence of ADHF (i.e. RV failure) and CRS in this population who do not respond adequately to initial IV diuretic therapy, use of a vasopressor when relative hypotension is present may allow for sufficient renal perfusion without any significant detrimental effects on the RV and, by increasing the right coronary artery perfusion gradient, may also support the ischemic, failing RV. The often-taught point on rounds to not diurese the PAH patient because the RV is "preload dependent" is misguided; to the contrary, aggressive diuresis is often required to decompress the overloaded RV and this rarely leads to hypotension until euvolemia is achieved [34]. Additionally, if an inotrope is used because of concomitant RV dysfunction and hypotension, IV milrinone is a particularly poor choice as it may worsen hypotension and will not have any meaningful impact on pulmonary artery pressure lowering in PAH. Rather, drugs with mixed inotrope and pressor properties (i.e. norepinephrine or dopamine) or the careful use of dobutamine could be considered.

Ongoing Assessments

It is important for clinicians to be consistently re-evaluating ADHF patients with CRS to avoid complications of over diuresis and worsening renal function while also not prematurely concluding that treatment has been adequate. While there is no substitute to a meticulous bedside assessment, some physical examinations may be more limited and such patients may benefit from invasive hemodynamic monitoring with an indwelling pulmonary artery catheter (PAC) [35]. While clinical trials have shown that the *routine* use of a PAC is not recommended, in select cases, the information derived can be of great assistance while meticulously titrating therapies in those patients with relatively narrow therapeutic windows [36]. For instance, aggressive diuresis may lead to intravascular volume depletion and could contribute to worsening renal function during the treatment of ADHF. When the rate of diuresis is greater than the ability of the extracellular space to refill the intravascular space, the concentrations of hemoglobin and plasma proteins increases and

hemoconcentration ensues, consequently leading to decreased renal perfusion. Interestingly, a sub study of 336 patients in Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) sought to determine the effects of hemoconcentration on renal function and outcomes. They showed the patients experiencing hemoconcentration received higher doses of loop diuretics during the study, had a lower baseline cardiac index, and had greater reductions in cardiac filling pressures. While hemoconcentration was strongly associated with worsening renal function (OR 5.3; P = <0.001), those same patients who achieved hemoconcentration had a significantly lower 180-day mortality (HR 0.31; P = 0.013) [37]. These data suggest that aggressive diuresis is likely not primarily responsible for the excess mortality noted in patients with worsening renal function but rather that diuretic resistance and CRS, in general, may be a marker for a higher risk patient population in general. Moreover, a recent analysis of the ROSE-HF trial showed that direct renal tubular injury does not typically occur with diuresis in heart failure patients despite worsening renal function as defined by a >20% decrease in glomerular filtration rate (Ahmad et al. [38]).

While data derived from an indwelling PAC may be useful in select circumstances, ensuring the data derived from the PAC are indeed reflective of the patients' evolving clinical condition should not be taken for granted. Inaccurate data owed to imprecise zero or leveling of the system, not measuring pressures at end expiration, and other common pitfalls can lead to erroneous and detrimental clinical judgements [39].

Recommendations Based on the Data

In the general approach to ADHF the cornerstone in management is based on aggressive decongestion. Venous decongestion with intravenous loop diuretics should be the initial step in managing patients with ADHF, irrespective of the ejection fraction (High Quality/Strong Recommendation). Based on the data discussed, the initial dose of loop diuretic should be greater than the home dose and usually double that of the home dose (High Quality/Strong Recommendation). Due to the lack of clear data, there is no official recommendation on which loop diuretic to use. Although most of the studies used furosemide, we recommend that personal and institutional preference should dictate this practice. Furthermore, the escalation or de-escalation of a diuretic regimen should be based on objective data, such as the urine output of the patient, with a goal daily urine output of 3–5 L reasonable in most cases of significant volume overload. This is further illustrated in Fig. 37.1 and Table 37.5, which offer a step-wise approach to maximizing venous decongestion based on the reviewed data [25, 27]. Although there are limited studies offering suggestions to the initial diuretic regimen, we recommend beginning with bolus dosing

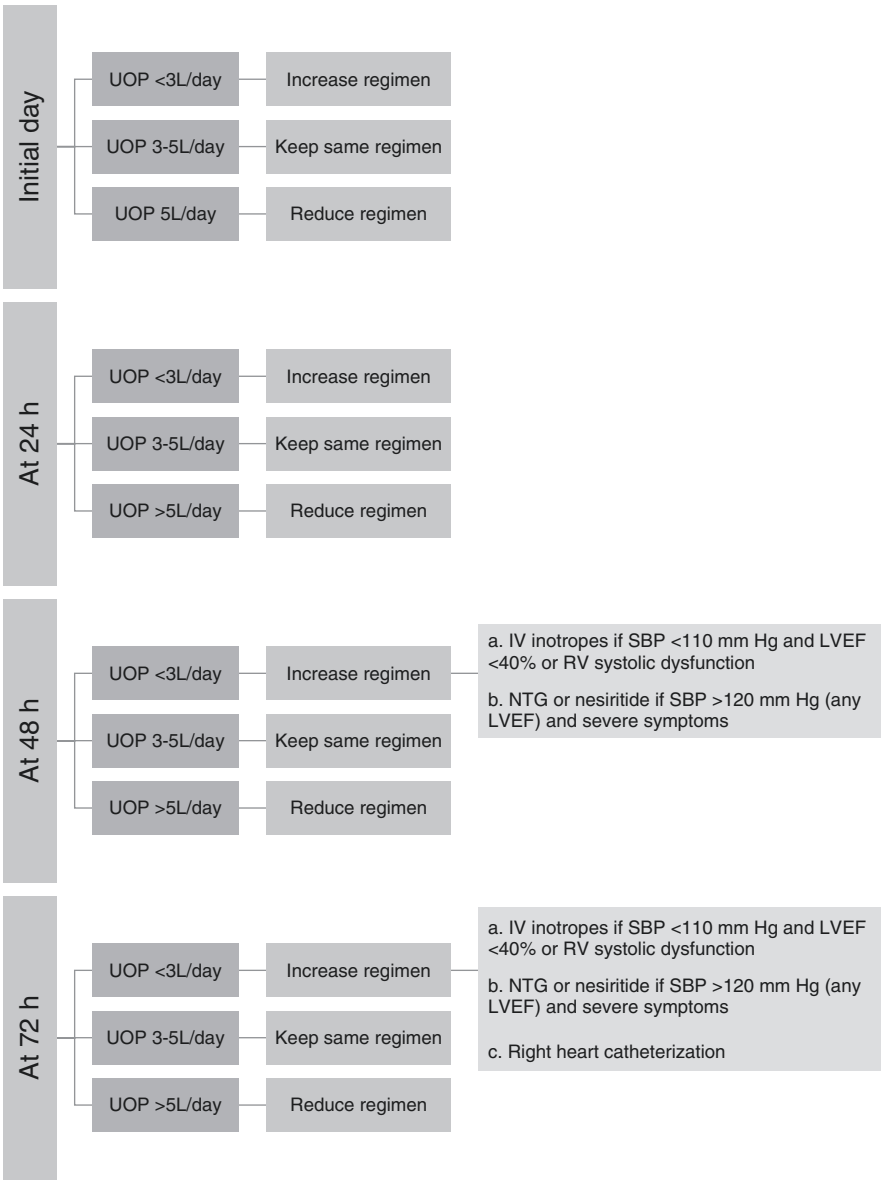

Fig. 37.1 An algorithm based on the CARRESS-HF and AVOID-HF trials suggesting a slow stepwise escalation of diuretic therapy based on daily goal urine output with diuretic dose adjustment recommendations (in Table 37.5) to achieve desired daily UOP [26, 28]

Table 37.5 Recommendations of diuretic dose escalations based on current and suggested doses as pertaining to the algorithm in Fig. 37.1

Recommendations of diuretic escalations based on initial starting dose			
Current dose		Suggested dose	
Loop diuretic	Thiazide diuretic	Loop diuretic	Thiazide diuretic
<80 mg/day	+ or −	40 mg bolus +5 mg/h	0
81–160 mg/day	+ or −	80 mg bolus +10 mg/h	Metolazone 5 mg daily
161–240 mg/day	+ or −	80 mg bolus +20 mg/h	Metolazone 5 mg BID
>241 mg/day	+ or −	80 mg bolus +30 mg/h	Metolazone 5 mg BID

This table is based on the CARRESS-HF and AVOID-HF trials that have shown favorable results with a slow, stepwise, diuretics escalation to achieve adequate diuresis [26, 28]

and observe urine output. The emphasis should therefore not be on the dose of the diuretic, per se, but the careful titration to achieve a targeted degree of hemoconcentration over the course of the initial few days without being overly aggressive (Moderate Quality/Strong Recommendation). Titration of the loop diuretic should be continued and if desired, transition to a continuous infusion to maintain the goal urine output should be considered (Moderate Quality and Strong Recommendation). Following initiation of the loop diuretic it is reasonable to add a thiazide diuretic to maintain urine output via a sequential nephron blockade strategy, particularly when faced with relative diuretic resistance (Moderate Quality/Strong Recommendation). This aggressive strategy is often employed due to the upregulation of receptors in the distal nephron in the setting of chronic loop diuretic use, but aggressive electrolyte repletion will likely be necessary with this combination and thus sequential nephron blockade should be used judiciously.

In the challenging cases of patients with low cardiac output or hypotension accompanying volume overload, inotropes or vasopressors may be necessary to achieve or even augment diuresis in recalcitrant diuretic resistance (Moderate Quality/Strong Recommendation). These methods offer critical circulatory support to achieve and maintain adequate renal perfusion and delivery of filtrate to the nephron segments. In the event of continued diuretic resistance, UF may be considered to address persistent venous congestion. Although there has been a push to begin UF sooner in the management regimen, current literature has simply not established a concrete, proven role in using UF in the early stages of ADHF. We thus view the use of UF as a reasonable final alternative to venous decongestion and recommend consultation with nephrology to aid with UF management (High Quality/Strong Recommendation).

Finally, frequent reassessments of these tenuous patients are imperative, including a careful bedside examination. The use of additional monitoring modalities such as an indwelling PAC should be considered on a case-by-case basis by experienced physicians and nurses to avoid tailoring therapies according to misinterpreted or erroneous data (Moderate quality and Moderate Recommendation).

Personal View of the Data

In ADHF with CRS, resolving venous congestion and symptomatic improvement, while meticulously guarding against unintended, potentially harmful consequences are key principles in patient management. The choice of bolus versus continuous IV diuretics should be at the discretion of the managing physician with the addition of inotropes or vasopressors being employed to further support the circulatory system on an as needed basis. In general, it is only after maximizing decongestion efforts with diuretics should one consider additional aid with the use of UF. A judicious and step-wise approach, based largely on targeted daily urine output, is illustrated in Fig. 37.1 with diuretic dose adjustment recommendations included in Table 37.5 [25, 27]. Careful bedside assessments (and reassessments), coupled with integration of *reliable* additional sources of clinical information (i.e. invasive hemodynamics) are often necessary to achieve a successful outcome in these tenuous patients.

Recommendations

1. Venous decongestion with intravenous loop diuretics should be the initial step in managing patients with ADHF in the absence a severely low cardiac output state – High Quality and Strong Recommendation
2. The dose of loop diuretic should be greater than the home dose – High Quality and Strong Recommendation
3. We recommend beginning with bolus dosing and observing urine output. The emphasis should not be on the dose of the diuretic per se but the careful titration to achieve a targeted degree of hemoconcentration over the course of the initial few days – Moderate Quality and Strong Recommendation
4. Loop diuretic titration should be continued and if desired, transition to a continuous infusion to maintain the goal urine output should be considered– Moderate Quality and Strong Recommendation
5. The addition of a thiazide diuretic could be considered to maintain urine output via a sequential nephron blockade strategy but aggressive electrolyte repletion will be necessary with this combination and should be used judiciously – Moderate Quality and Strong Recommendation
6. Inotropes or vasopressors may be necessary to achieve or augment diuresis in recalcitrant cases with diuretic resistance, particularly in the presence of a low cardiac output or hypotension – Moderate Quality and Strong Recommendation
7. Ultrafiltration is a reasonable final alternative strategy to address venous congestion and consultation with nephrology to aid with ultrafiltration management is advisable – High Quality and Strong Recommendation
8. Frequent reassessments of these tenuous patients are imperative and use of an indwelling PAC should be considered on a case-by-case basis – Moderate quality and Moderate Recommendation

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Chapter 38
Management of Patients with Difficult Vascular Access Issues

Bailey Su and Yolanda Becker

Introduction

There is a high association of cardiac and renal disease. Many patients who subsequently require cardiac surgical procedures are at risk not only for acute kidney injury but also subsequent chronic renal disease. Due to the high likelihood of previous hospitalizations in this population, obtaining intravenous access for cases and subsequent vascular access for dialysis can prove incredibly challenging. In this chapter, we discuss the management of these challenging patients with respect to immediate and long term vascular access.

Epidemiology

Acute kidney injury (AKI) following cardiac surgery is a relatively common postoperative complication associated with serious implications, greater healthcare costs and a significant impact on patient outcomes, including prolonged ICU stays, increased risk of chronic renal failure and increased risk of death. The presence of AKI alone is an independent predictor of early mortality following cardiac surgery [1]. Because there are a wide range of AKI definitions, the true incidence of AKI following cardiac surgery is difficult to delineate. Although

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several attempts at consensus definitions have been described, including the RIFLE (Risk, Injury, Failure, Loss of kidney function, and end stage kidney disease) criteria, AKIN (Acute Kidney Injury Network) definition and KDIGO (Kidney Disease: Improving Global Outcomes) definition, many scientific articles still use their own criteria to define AKI. However, there have been multiple large systematic reviews that have evaluated the pooled incidence of AKI following cardiac surgery, and shown that incidence and prognosis were not significantly altered regardless of definition. Hu et al. performed an extensive systematic review and meta-analysis of 91 observational studies with over 320,000 patients, which demonstrated the pooled incidence rate of AKI following all types of cardiac surgery was 22.3%, with 2.3% of patients requiring renal replacement therapy [2]. The incidence is similar in patients undergoing surgery involving cardiopulmonary bypass (CPB) with a rate of CPB-associated AKI at 18.2%, with 2.1% requiring renal replacement therapy [3]. Lastly, those who require extracorporeal membrane oxygenation are at particularly high risk, with an incidence of AKI >80% [4].

Being able to identify those most at-risk for post-operative AKI has implications for clinical decision-making, pre-operative optimization, post-operative management and patient counseling. Patients requiring cardiac surgery are already susceptible to AKI, secondary to the pathophysiology of most cardiac diseases. Myocardial infarction, cardiogenic shock, use of ace inhibitors and angiotensin receptor blockers (ACEI/ARB), contrast studies and lack of renal reserve can all pre-dispose to kidney injury and are commonly seen in patients requiring cardiac surgery. Additionally, female gender, congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, need for emergent surgery and an elevated preoperative serum creatinine are risk factors that have been repeatedly shown to increase the risk of AKI [5].

Several scoring systems have been developed in order to readily identify and quantify a patient's risk for developing AKI. The Cleveland Clinic model for predicting AKI requiring dialysis in patients undergoing open heart surgery has been validated in multiple cohorts and is the most widely tested of the prediction scores. Thakar et al. included 33,217 patients who underwent open-heart surgery between April 1993 and December 2002. They utilized half of the patients to develop the scoring system and the other half as a data set for validation of the score. Patients were excluded if they were heart transplant recipients, required preoperative extracorporeal membrane oxygenation, preoperative tracheostomy or mechanical ventilation; underwent procedures for automated implantable cardioverter-defibrillator, left ventricular assist devices or sternal work. They derived and validated a scoring system (Tables 38.1 and 38.2) based on 13 risk factors most significant for predicting AKI [6].

While the scoring system was developed from data derived from a single center, it has been tested internationally in multiple cohorts [7]. By utilizing this prediction method in the appropriate scenarios, clinicians can predict which patients are at high risk for AKI requiring dialysis, which can aid in developing strategies for prevention, early diagnosis and early intervention.

Table 38.1 Cleveland clinic acute renal failure score

Risk factor	Points
Female gender	1
Congestive heart failure	1
Left ventricular ejection fraction <35%	1
Preoperative use of IABP	2
COPD	1
Insulin-requiring diabetes	1
Previous cardiac surgery	1
Emergency surgery	2
Valve surgery only (reference to CABG)	1
CABG + valve (reference to CABG)	2
Other cardiac surgeries	2
Preoperative creatinine 1.2 to <2.1 mg/dl (reference to 1.2)	2
Preoperative creatinine ≥2.1 (reference to 1.2)	5
Minimum score, 0; maximum score 17	

Table 38.2 Frequency of ARF requiring dialysis

Score	Frequency of ARF-dialysis
0–2	0.4%
3–5	1.8%
6–8	7.8%

Search Strategy

In May 2017, one author (B.S.) conducted a literature search to identify studies and case reports documenting indications and options for dialysis access in medically complicated patients. A PubMed search was performed using the keywords: "hemodialysis access", "unconventional access", "novel dialysis access", "AKI in cardiac surgery", "ICU dialysis", "ICU vascular access" and "temporary dialysis". The search was limited to articles published in English after 1995.

One author (B.S.) then manually reviewed all titles and abstracts of resultant publications. Full-text papers of appropriate publications were then retrieved and checked. In addition, a hand review of bibliographies of selected articles was performed yielding several more articles. In total, 41 papers were reviewed and 25 were selected for inclusion. These included: 7 retrospective reviews, 4 systematic reviews, 3 randomized control trials, 3 case reports, 2 retrospective cohort studies, 2 cohort studies, 2 meta-analyses, 1 case-control study, and 1 consensus paper. The studies outlining complications of dialysis access are outlined in Table 38.3. The PICO definitions are outlined in Table 38.4.

Table 38.3 Studies showing complications of dialysis access

Author (reference)	Publication year	Duration of study	No. of patients	Total number and type of catheters	Rate of catheter-related infection	Rate of thrombosis	Mean access patency	Procedure-related complications	Exceptions	Type of study (quality of evidence)
Parienti et al. [8]	2008	May 2004 – May 2007	750	370 femoral catheters 366 jugular catheters	(Bacteremia) Femoral: 1.5 per 1000 catheter-days Jugular: 2.3 per 1000 catheter-days	Femoral: 8 of 76 Jugular: 17 of 75 (US exams from 2 participating centers)	–	Jugular catheters required longer insertion times, had more failures on 1 side and more crossovers	BMI >28.4, colonization rates higher in femoral site. BMI <24.2, colonization rates higher at IJ site	Randomized control trial (High)
Younes et al. [9]	2011	Jan 2003 – Oct 2008	22	127 transhepatic catheters (104 exchanges in 14 patients)	(Sepsis) 0.22 per 100 catheter-days	0.18 per 100 catheter-days	450.3 catheter-days	Difficulty advance guide wire due to thrombus (6), intercostal pain (1), bleeding (1)	–	Retrospective review (Low)
Herscu et al. [10]	2013	June 2000 – May 2011	7	4 transhepatic catheters 3 translumbar catheters	(Sepsis) 1 translumbar catheter	1 transhepatic catheter	380 catheter-days	–	–	Retrospective review (Very low)
Liu et al. [11]	2015	June 2006 – June 2013	28	84 translumbar catheters	(Bacteremia) 0.22 per 100 catheter-days	0.02 per 100 catheter-days	381 catheter-days	–	–	Retrospective review (Low)
Kade et al. [12]	2014	2007 – 2012	7	16 translumbar catheters	(Infection) 2.2 per 1000 catheter-days	1.2 per 1000 catheter-days	261 catheter-days	–	2 subcutaneous hematomas	Retrospective review (Very low)

Table 38.4 PICO table for acute renal failure and access for RRT in patients who have exhausted traditional access sites

P	I	C	O
Patients	Intervention	Comparator	Outcome
Patients requiring hemodialysis access who have exhausted traditional access sites	Novel dialysis access techniques (e.g.: transhepatic or translumbar)	Dialysis access via traditional access sites (e.g.: internal jugular vein, femoral vein, etc.)	Incidence of line infection, incidence of thrombosis, mean access patency

Results

Traditional Access Options

While patients who undergo cardiac surgery are at high risk for AKI and subsequently renal replacement therapy, the challenge in this patient population lies in the difficulty of obtaining hemodialysis access. These patients frequently have limited access options for hemodialysis secondary to extensive catheterization/instrumentation for monitoring, venous thrombosis, existing central venous access and mechanical supportive devices. Additionally, the potential need for permanent dialysis access in the future requires clinicians to be thoughtful and proactive about preserving as many access sites as possible.

Historically, the internal jugular site has been preferred over the femoral site for hemodialysis access, secondary to the increased risk of nosocomial complications and catheter dysfunction, however this has largely been disproven [13]. In a large, prospective, multi-center controlled trial of 750 bed-bound patients in the intensive care unit with short-term need for hemodialysis access, patients were randomized to receive jugular or femoral vein catheterization. The study demonstrated that the incidence of catheter colonization at removal was not significantly different between the jugular and femoral groups. Additionally, the rate of catheter-related bacteremia was also not significantly different [8]. Of note, there was a difference in two specific patient populations in regards to catheter colonization: In patients with BMI >28.4, colonization rates were higher at the femoral site, and for patients with BMI <24.2, colonization rates were higher at the internal jugular site. This information should be taken into consideration when choosing a site for hemodialysis access. These results were further validated in a crossover study in which 134 patients of the original study underwent a second catheterization at an alternative site. That is, if the original site of catheterization was the internal jugular, the femoral site was the secondary access site and vice versa. Again, time to catheter-tip colonization was not significantly different and there was no difference in time to dysfunction [14].

Subsequent secondary analysis of this data also demonstrated that in regards to catheter dysfunction and dialysis performance, the jugular site did not significantly outperform the femoral site, however the femoral group had significantly less catheter dysfunction when compared with the left-side jugular site alone. Therefore, in order to limit the risk of dysfunction, the left jugular site should be considered last if the right jugular or femoral sites are not accessible [15].

The subclavian vein site has become less favorable, especially in the setting of the cardiothoracic intensive care unit. There is an increased risk of pneumothorax and hemothorax associated with subclavian vein approach and the risk of central vein stenosis and thrombosis makes the subclavian vein unfavorable [16, 17]. For patients who may progress to chronic kidney disease, the presence of central vein stenosis/thrombosis greatly reduces the availability of permanent dialysis options and impedes arteriovenous fistula creation in the ipsilateral upper extremity. This is significant as it eliminates several of the best options for long term dialysis access.

Novel Access Options

For patients in whom the traditional access sites are not available or have been exhausted, there are several novel options for temporary vascular access. These include transhepatic and translumbar approaches. Placement of these catheters is usually done by an interventional radiologist and can typically be done under conscious sedation. It is important to note, however, that all studies and case reports regarding these novel approaches to hemodialysis access are conducted in patients with chronic kidney disease and not in the emergency setting of AKI in the ICU. Therefore it is difficult to determine whether their results could be translated to acutely ill post-operative patient, however they remain options worthwhile of consideration in patients with difficult access.

Transhepatic Catheters

The transhepatic approach was first described in a 1994 case report by Po et al. [18], and all subsequent studies have been small retrospective reviews. The largest review completed by Younes et al. looked at a 70-month period in which 22 patients with chronic kidney disease who had exhausted all traditional vascular access sites, including inability to recanalize occlusions bilaterally. Among these 22 patients, they had a total of 127 transhepatic catheters placed in 24 access sites. The mean initial service device interval was 141.2 days, the mean cumulative catheter duration in situ was 506.2 days and the mean time catheter in situ was 87.7 days. There was a low sepsis rate of 0.22 per 100 catheter-days, which is comparable to jugular and femoral vein infection rates [8]. Additionally, there was a low thrombosis rate (0.18 per 100 catheter-days) and the most common complication was migration [9]. Although their patients were outpatients with chronic kidney disease, they were able to demonstrate that transhepatic access for hemodialysis is a viable option in patients who have run out of transitional access options. Several small, subsequent studies have also confirmed the viability of transhepatic access for temporary hemodialysis access, but again, the patient population is not specific to those in the intensive care unit with AKI [10]. A radiograph showing the pre placement guidance is shown in Fig. 38.1.

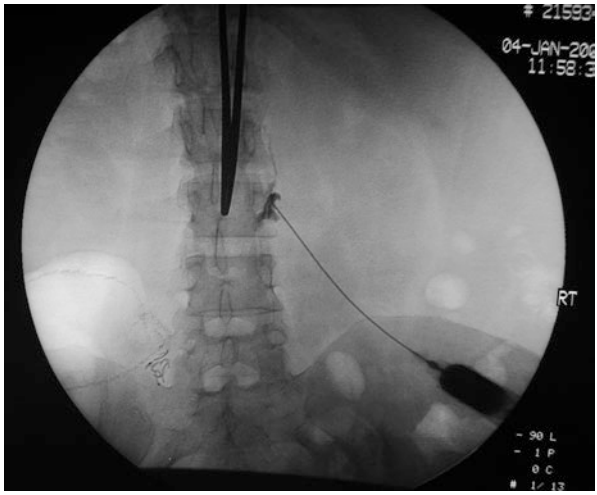

Fig. 38.1 Radiograph of pre transhepatic catheter placement guidance. (Courtesy of Dr. Brian Funaki)

Translumbar Catheters

The translumbar approach for hemodialysis access was first described by Lund et al. in 1995 [19]. Translumbar dialysis catheters have a higher rate of dysfunction when compared to the transhepatic approach and cannot be placed if the IVC is occluded [20]. However, several small studies have confirmed its viability as a route for dialysis access in patients who have exhausted all other traditional options. In the largest series of translumbar dialysis catheter placements to date, Liu et al. retrospectively reviewed records over a 7 year period, of 28 patients who underwent 28 primary insertions and 56 exchanges [11]. The mean initial device interval was 110 days with a rate of bacteremia of 0.22 per 100 catheter days – both of which were similar to that of transhepatic catheters: 141.2 days and 0.22 per 100 catheter days, respectively [9]. The most common reason for catheter exchange was catheter-related infection, followed by poor blood flow. Another retrospective review looked at 13 patients over a 5 year period undergoing translumbar hemodialysis catheter placement. The average time of catheter function was 261 days, and the incidence of catheter-associated infection and thrombosis per 1000 catheter days was 2.2 and 1.2, respectively [12]. Again, the rate of infection and thrombosis was similar to the rate in other translumbar access patients, as well as those undergoing transhepatic catheter placement.

One benefit of the transhepatic approach over the translumbar approach is a decreased risk of bleeding. Bleeding from the transhepatic site can be controlled by embolization of liver parenchyma, where bleeding from the translumbar site can lead to a retroperitoneal bleed from the IVC. Additionally, initial access at the transhepatic site is easier in obese patients [9]. Figure 38.2 shows the proper placement of a translumbar catheter.

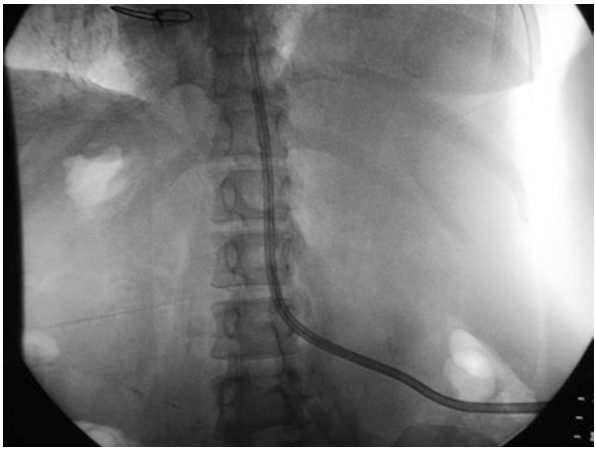

Fig. 38.2 Translumbar catheter. (Courtesy of Dr. Brian Funaki)

Guidewire Exchange

Lastly, if a patient already has hemodialysis access, but the catheter is colonized or malfunctioning, providers should consider a guidewire exchange of the line as opposed to removal. This is preferable to accessing a new site as it preserves as much of the vascular network as possible. Coupez et al. performed a post-hoc cohort study comparing incidence of catheter colonization and dysfunction in dialysis catheters replaced by guidewire exchange versus catheters placed in a new venipuncture insertion site. The most common indication for line replacement was catheter dysfunction, but in many cases the indication was not documented. Regardless, the study showed that catheter placement via guidewire exchange did not increase the risk of catheter colonization, but was associated with more than twofold increase in catheter dysfunction [21]. Very few studies have looked at guidewire exchange in the ICU setting for temporary hemodialysis access and results of existing studies have had conflicting results. Although guidewire exchange should be considered because it allows preservation of the vascular network and decreases risks of complications involved with accessing a new site, additional research in this area is necessary.

Prognosis with AKI

Development of AKI after cardiac surgery increases the length of stay and subsequently increases healthcare costs. Additionally, it is an independent risk factor for increased mortality [1, 22]. The mechanism by which AKI increases mortality is unclear, but is likely linked to an increased incidence of infection. An observational analysis performed by Thakar et al. demonstrated an epidemiologic association between AKI and serious infection, including pneumonia, mediastinitis, wound

Table 38.5 Stepwise effects of creatinine on long-term outcomes after cardiac surgery [24]

Percent change in creatinine[a]	Frequency	Incident CKD[**]	Death[b]
No change	32.5%	25.1%	19.5%
Class I: 1–24%	35.3% (n = 10,369)	33.7%	21.0%
Class II: 25–49%	18.2% (n = 5357)	44.1%	26.4%
Class III: 50–99%	9.5% (n = 2719)	51.1%	31.7%
Class IV: ≥100%	4.5% (n = 1334)	53.4%	33.6%

[**] $p < 0.001$

[a]Percent change calculated by extracting all serum creatinine values obtained over the first 7 days after cardiac surgery and determined based on the percent change comparing the peak creatinine value with the baseline creatinine value

[b]Censoring deaths within 30 days of surgery to eliminate effect of AKI; $p < 0.01$

infection, sepsis syndrome or septic shock. Out of 22,589 patients who underwent open heart surgery from 1993 to 2000, 750 developed a serious infection for an overall incidence of 3.3%. Comparatively, among patients who developed post-operative AKI not requiring dialysis, the frequency of serious infection was 23.7%, and 58.5% for those requiring dialysis [23].

The effect of AKI after cardiac surgery has long-term implications as well. Ishani et al. studied 29,388 individuals who underwent cardiac surgery at VA hospitals between November 1999 and Sept 2005, and found that a rise in creatinine after cardiac surgery was associated, in a graded manner, with increased incidence of chronic kidney disease and death [24].

Risk of both incident CKD and mortality were highest in first 3–24 months of follow-up and attenuated at 5 years but remained elevated and did not return to baseline. The risk of death increases at every stage of kidney disease as shown in Table 38.5. Lastly, and perhaps most importantly when it comes to discussing dialysis access in cardiac surgery patients, the risk of developing a permanent need for dialysis access is extremely high. Leacche et al. found that of patients who underwent cardiac surgery and subsequently developed post-operative AKI requiring RRT, 64% required permanent dialysis [25]. This reinforces the importance of careful and thoughtful planning in regards to selecting locations for hemodialysis access, as preservation of the vascular network is of the utmost importance.

Recommendations and Guidance

For routine access, there are clinical practice guidelines. In patients with renal disease, the right internal jugular site is the preferred first site of central line placement followed by the left internal jugular. Given the higher rate of stenosis, the subclavian site is not recommended [26]. There is no clear guidance in these difficult cases. The care teams must collaborate and use all tools at their disposal to provide life-saving access in patients who have exhausted traditional sites. It is critical to

recognize kidney disease in the cardiac patient population so that vascular sites are chosen with an eye to the need for future access sites.

We make the following recommendations based on the literature available:
Consider needs for future dialysis access:

- Recognize the high incidence of renal insufficiency in patients with cardiac disease
  - (Evidence: Strong Recommendation: Strong)
- Place intravenous lines as distal as possible
  - (Evidence: Moderate Recommendation: Strong)
- Place percutaneous lines in the non-dominant extremity
  - (Evidence: Moderate Recommendation: Moderate)
- Avoid Subclavian access if possible
  - (Evidence: Strong Recommendation: Strong)

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Part X
ICU Catastrophes

Chapter 39
Free Air in the Postoperative CT Patient: Observe or Operate?

Robert Keskey and John Alverdy

Introduction

The finding of pneumoperitoneum in a postoperative cardiothoracic (CT) patient can create a diagnostic and therapeutic dilemma for the clinician. In many cases, some degree of free air is expected postoperatively, but at what point should it be considered pathologic? When is urgent intervention warranted and when can the patient be safely observed? Surgeons have attempted to sort out the duration of benign postoperative pneumoperitoneum for generations including several studies from the early 1920s and 1940s [1].

In the cardiothoracic patient, some degree of postoperative pneumoperitoneum might be expected when the patient has had an operation that has violated the peritoneum. This might be expected in an esophagectomy patient, or a patient with a history of a cardiac or lung transplant who undergoes an abdominal operation and is admitted to the cardiothoracic intensive care unit (CTICU) for close monitoring. More importantly, the clinician must keep in mind that CT patient's can suffer from abdominal pathology that may be unrelated to their recent surgery. This chapter will begin by looking at studies attempting to determine the expected duration of "benign" pneumoperitoneum to aid the clinician in determining times where observation is warranted.

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https://doi.org/10.1007/978-3-030-04146-5_39

Table 39.1 PICO table for CT patients with free air

Patient	Intervention	Comparison	Outcome
CTICU, post operative pneumoperitoneum	Surgery	Observation	Mortality, length of stay

Search Strategy

A literature search was performed in PubMed using MeSH terms outlined in PICO elements: "pneumoperitoneum,", "post-operative," "free air. Studies included were systematic reviews, prospective and retrospective studies. The years of the search were expanded from 1957 to the present, 2018. Approximately seven studies, a combination of retrospective and prospective, were found using this method. The search was originally conducted using "cardiothoracic;" however, no studies specific to cardiothoracic patients were found. Separate searches were conducted to obtain literature regarding pathologic causes of pneumoperitoneum and post-procedureal causes of free air. The quality of the data were classified according to the GRADE system (Table 39.1).

Results

Utility of Imaging Modalities in Detecting Postoperative Pneumoperitoneum

Incidental postoperative pneumoperitoneum can occur in the early postoperative period in CT patients that does not indicate surgical pathology. However, the question at hand is when to determine if the presence of free air is an inadvertent consequence of the CT surgery or the result of new intraabdominal pathology. One must first rule out surgical emergencies such as a perforated viscus or a complication from the surgery requiring emergent intervention. Making this determination may not always be easy – there may be some level of postoperative pain obscuring the clinical picture; the patient may be intubated and sedated, or the patient may be immunosuppressed inhibiting their ability to mount a typical response seen in peritonitis [2]. CTICU postoperative patients often have a more tenuous clinical status, which is reflected by their prolonged stays in the ICU [3]. Given their low physiological reserve, their risk for surgical morbidity and mortality is significantly higher than the general population. Both previous cardiac surgery and emergent operation are known factors for increased postoperative morbidity and mortality, making the decision to return to the OR a difficult one in this particular patient population [4]. Several studies have attempted to outline the extent of "benign" pneumoperitoneum post abdominal surgeries and attempted to determine characteristics when postoperative pneumoperitoneum should no longer be observed (Table 39.2).

Table 39.2 Posoperative pneumoperitoneum

Study	Type of study	Imaging	Study size	Free air (%)	Duration of FA	Conclusion	Quality of evidence
Harrison et al. [1]	Prospective	XR	104	53	1–6 days	Postop free air duration varies by type of operation Patients can be safely observed, unless clinical signs of peritonitis	Low
Milone et al. [5]	Prospective	XR	648	10	<7 days	POD2 sensitivity 77, specificity 97, PPV 94, NPV 89 POD3 sensitivity 90, specificity 100, PPV 100, NPV 95 Free air on POD2/3 should be further investigated if >10 cc and signs of peritonitis	Moderate
Earls et al. [6]	Prospective	CT + XR	17	87 (CT), 53(XR)	N/A	Plain films only detect 47% cases of FA detected by CT	Low
Gayer et al. [7]	Retrospective	CT	89	44	<18 days	Characteristics of benign free air: Small volume (<10 cc), males, surgical drains, and slender patients	Moderate
Chapman et al. [8]	Retrospective	CT	344	39	<24 days	Only 6% of patients with free air required an operation, all had clinical indications (change in clinical status, change in surgical drain output, etc.)	Moderate
Malgras et al. [9]	Retrospective	CT	80	47	<15 days	Average volume 15 cc 85% had free air until POD5, 41% until POD15, 9.5% after POD15	Moderate

Summary of studies regarding duration, and occurrence of postoperative pneumoperitoneum

Postopereative Pneumoperitoneum on Plain Films

Historically, surgeons have attempted to standardize the extent and degree to which pneumoperitoneum can be expected after an abdominal operation. In 1957, Harrison et al. published one of the earliest prospective studies addressing this question. The study was conducted by obtaining daily upright and left lateral decubitus plain films in 104 postoperative open abdominal surgery patients. Approximately 53% of patients in the study exhibited free air on postoperative plain films. The duration of free air in these patients ranged on average from 1 to 6 days. The duration appeared to be dependent on the type of surgery that was performed. Inguinal hernia had the shortest average duration (1 day), and gastrectomy had the longest average duration (6.1 days). They also noted the pneumoperitoneum was significantly higher in upper incisions and as one might expect the duration was also dependent on the initial volume of pneumoperitoneum seen. The study concluded that the vast majority of post-operative pneumoperitoneum is reabsorbed within 2 weeks. They also made an important conclusion that post-operative free air with signs of peritoneal irritation within two to three post operative days should be immediately addressed and not dismissed as trapped air from a recent operation [1].

In 2013, Milone et al. conducted one of the more comprehensive studies examining postoperative pneumoperitoneum. They attempted to determine the diagnostic value of free air on upright chest x-rays in post-operative patients. Plain films were used for the study given that they were deemed more practical than CT scans by the authors. Overall, they studied 648 patients who underwent upright CXR on POD2, POD3, and every 2 days until the free air was no longer detected [5]. In addition to simply monitoring the duration of postoperative pneumoperitoneum, they also attempted to distinguish patients who had concerning signs for a perforated viscous (abdominal pain rated by 0–10 scale, leukocytosis >12,000) by obtaining a CT scan. Of the 645 patients, 10% had postoperative pneumoperitoneum on postoperative day 2, while 7% had pneumoperitoneum on postoperative day 3. Approximately 43% of the patients who had free air on postoperative day 2 underwent exploratory surgery. Only 0.5% of the patients had pneumoperitoneum on postoperative day 4, none of which had signs of GI perforation, and none of which had exploratory surgery. Patients that were found to have perforation had a significantly larger volume of free air than those with benign pneumoperitoneum 12 mL vs 4.8 mL and 17 mL vs 1.9 mL on postoperative day 2 and 3 respectively. Using this knowledge, the sensitivity, specificity, positive predictive value, and negative predictive value when 10 ml of pneumoperitoneum was used as a cutoff was 77%, 97%, 94%, and 89% on postoperative day 2, and 90%, 100%, 100%, and 95% when used on postoperative day 3. The hazard ratio for GI perforation was 21.54 for free air found on POD2 and 23.87 for free air found on POD3. When they analyzed patients with surgically confirmed bowel perforation they found that free air was seen in 68% of patients on postoperative day 2 and 68% seen on postoperative day 3. Comparing this study to previous studies, the number of patients with postoperative pneumoperitoneum is much less; however, they had more laparoscopic patients 357 than the other studies. It is believed that postoperative pneumoperitoneum is less after laparoscopy due to

the rapid absorption of CO2 relative to air [10]. There has also been a previous study showing that on average laparoscopic pneumoperitoneum tends to resolve by post-operative day 2 [11]. In addition to the rapid reabsorption of CO2, plain films study likely underestimate the amount of retained postoperative free air present. Overall, this study concluded that the prevalence of postoperative pneumoperitoneum on upright chest XR was relatively low (about 10%); however, its presence in the setting of clinical signs of peritonitis (fever, abdominal pain, leukocytosis) or large volume (>10 mL) should raise concern for a GI perforation and should be taken to the operating room for exploratory surgery. Additional, imaging such as a CT scan should be forgone at this point as it will only delay definitive surgical correction of the underlying problem [12].

Postoperative Pneumoperitoneum Detected by CT

Following these earlier studies, CT scanning slowly emerged and attempts were made to study the same issues of postoperative pneumoperitoneum comparing CT and plain films. Earls et al. performed a prospective trial in 17 postoperative patients in an attempt to not only compare the duration of postoperative pneumoperitoneum, but also looked at the sensitivity of CT scan versus plain films in detecting pneumoperitoneum. They obtained CT scans and postoperative plain films on postoperative day 3 and day 6. They identified free air in 87% of the CT scans and 53% of radiographs obtained 3 days after surgery and 50% of the CT scan and 8% radiographs 6 days after surgery. When compared to CT scans, plain films were only able to detect 47% of cases with free air [6]. These findings correlated with previous studies that had also shown CT scan was clearly superior at detecting free air than plain films [13]. It is reasonable to conclude from these prospective studies that patients who undergo CT scan in the early postoperative period are more likely to have free air detected when compared to plain films.

With the results of the previous studies showing superior sensitivity to a CT scan for detecting free air than plain films, Gayer et al. reviewed abdominal CT scans of 89 patients who had underwent abdominal operations, and had subsequent CT scans for various indications [7]. The goal of this study was to simply quantify the duration and presence of non-operative pneumoperitoneum. Patients were excluded if they had known gastrointestinal perforations seen on the scan, if the patient was discovered to have an anastomotic leak, or if they patient died within 15 days of the CT scan. The studied included 103 CT scans. The authors showed that approximately 44% of the patients had pneumoperitoneum on CTs done within the first 3 postoperative days, roughly 30% of the scans done within post perative days 4–18, and none of the CT scans done after the 18th post-operative day showed pneumoperitoneum They found that the majority of post-operative pneumoperitoneum was small volume (10 mL in 66% of the studies with free air), more common in males than females (43% vs 12%, $p < 0.001$), and more likely when drains were in place. They demonstrated no significant difference in pneumoperitoneum between types of surgery, and a slightly lower occurrence of in slender versus obese individuals.

Overall, the authors conclude that postoperative pneumoperitoneum is a frequent event after abdominal surgery within the first 18 days; however, its significance should be interpreted with caution, as it is ill-advised to dismiss findings and overlook a perforation [7].

Similarly, Chapman et al. performed a retrospective study looking at CT scans detecting postoperative pneumoperitoneum in 344 patients. The CT scans were obtained for various reasons ranging from abdominal pain to evaluation for possible anastomotic leak. They found pneumoperitoneum in 39% of patients who underwent a CT scan. The majority of the pneumoperitoneum was found in patients POD 0–6, and decreased to the point where no free air was found in patient's more than 24 days post surgery. Up to 23% of patients had evidence of free air up to 3 weeks postoperatively. Only 6% of the patient's that were found to have free air in the study required an operation. Most of which had other concerning findings on CT scan or other clinical indicators to proceed to the operating room which included bloody drain output, feculent material noted from an intraperitoneal drain or incision, and failed conservative management of a bowel obstruction [8].

More recently, Malgras et al. performed a retrospective analysis of patients who underwent a CT scan postoperatively after laparotomy. Pneumoperitoneum was found in 48% of patients. As with previous studies, the amount of pneumoperitoneum decreased over time. They found 100% of patients with a CT scan that showed free air all were before POD3, 81% of patients with free air lasted until POD5, 41% of patients between POD6 and POD15, and 10% of patients after POD15. The average volume of pneumoperitoneum was 15 mL, which was higher than previous studies. They found no association between type of procedure and presence of pneumoperitoneum, and found an association with the presence of intraperitoneal drains [9].

In summary, there have been multiple prospective and retrospective studies attempting to gain a better understanding of the presence of pneumoperitoneum postoperatively. It is not uncommon to find pneumoperitoneum postoperatively both on plain films and CT scans. The percentage of patients that may be noted to have free air on imaging greatly varies based on the type of imaging being used, whether the surgery was open versus laparoscopic, and the timing from surgery. One common theme seen is that the duration is highly variable and can last up to several weeks postoperatively. However, the vast majority of benign postoperative free air will be reabsorbed after 1 week. When evaluating the presence of pneumoperitoneum, the entire clinical picture needs to be taken into account. The studies have shown that a large number of patients have been safely observed with free air noted on postoperative imaging. The one common theme was that these patients did not have any other clinically concerning issues. When factors such as abdominal pain, fever, leukocytosis, free fluid on CT scan, or other evidence of worse abdominal pathology is present then the patient should proceed to the operating room. In the postoperative CTICU patient, who is likely to have multiple of these factors related to their recent operation, clinical judgment will have to dictate this decision.

Common Pathology of Pneumoperitoneum

As previously discussed, postoperative pneumoperitoneum can be a benign finding related to surgery, but more importantly a broad differential of the potential source of the free air must be considered. Sources of surgical complication should be considered such as an iatrogenic GI perforation or an anastomotic leak, both of which can present with free air on postoperative imaging. It is important to remember that patients in the CTICU can also suffer from a perforation of a hollow viscous not related to the CT surgery such as a perforated peptic ulcer or perforated diverticulitis. These are common causes of perforations that affect all patients, including those that are critically ill. This section is to serve as a reminder of all of the sources of pneumoperitoneum outside of those that might be considered iatrogenic from an abdominal operation.

Peptic ulcer perforation is the most common cause of pneumoperitoneum. Perforated peptic ulcers are a surgical emergency and surgical repair should not be delayed. Soreide et al. conducted a recent systematic review in Lancet noting that short-term mortality of perforated ulcers can be as high as 30% [14]. Crofts et al. conducted one of the earliest randomized control trial in the 1980s comparing observation to surgery in patients with perforated peptic ulcer disease. The study consisted of 83 patients randomized to observation versus immediate surgery. They concluded that observation lead to a longer length of stay, but had similar morbidity and mortality (5% mortality in both surgery and observation). It is important to point out despite their conclusions, 28% of the patients in the observation group eventually required an operative repair [15]. More recent studies have found that for every hour delay to surgery after admission there was an association with a decrease of 2–4% survival compared to a previous hour [16]. Given these findings, it is best not to delay treatment if you suspect a perforated ulcer.

Diverticulitis is not an uncommon gastrointestinal disease. In the setting of free air, diverticulitis should be on the differential. Based on a recent retrospective study, approximately 30% of patients had evidence of free air on CT scan [17]. If diverticulitis is noted on a CT scan of a CTICU patient then a general surgeon/colorectal surgeon should be consulted; however, it should be noted a similar approach to surgery versus medical management should be approached. Sallinen et al. showed that when free air is found pericolonic then non-operative management can be successful 99% of the time [17]. As mentioned above, any signs of peritonitis accompanying the presence of free air and associated with a known history of diverticulitis, the treatment team should consider surgical management.

As mentioned, patients admitted to the CTICU can still experience perforated gastrointestinal viscera similar to the general population, and perforated diverticulitis and peptic ulcers should remain on the clinician's differential when free air is noted on imaging. It is important to remember that there are cases where expectant observation of perforated diverticulitis and peptic ulcers is acceptable. This may be particularly important in post-operative CT patients who may not be able to tolerate an operation. For early diverticulitis, observation and antibiotics has been shown to be a successful management option. Whereas, with peptic ulcer disease, observation

is a poor option as mortality increases the longer definitive surgical treatment is delayed. It should again be re-emphasized that free air with any clinical signs of peritonitis should proceed to the operating room [18]. With the advent of laparoscopy, a lower threshold for definitive diagnosis and minimally invasive treatment may allow for earlier treatment and even a negative exploration.

The Immunocompromised patient. As mentioned previously, typical causes of GI and general surgery problems can manifest in all patients, including solid organ transplant patients. A systematic review of emergency abdominal surgery found that 2.5% of solid organ transplant patient underwent emergency abdominal surgery from 1996 to 2015 [19]. An important finding in this study was that in immunosuppressed patients, the findings and symptoms of perforation are often absent or non-specific. This was evident by a delay from clinical presentation to surgery ranging from 2 to 8 days. Regarding lung transplant patients, a study by Larson et al. found that diverticulitis in the lung transplant patient was fairly common, especially in the first 2 years post transplant [20]. There have been several reports looking at colon perforations in the transplant patient which have shown an incidence of perforation ranging from 0.7% to 6.7%. The rate in more recent studies have shown a rate of colon perforation amongst lung transplant patients to be 6.6%, which is significantly higher than other solid organ transplant [21]. When compared to immunocompetent patients, solid organ transplant have increased postoperative mortality (19% vs 0%) and morbidity (51% vs 24%) when undergoing emergent surgery for diverticulitis [22].

Post-procedure Causes of Pneumoperitoneum

Percutaneous Feeding Tubes

It is not uncommon for a post-operative ICU patient to require a percutaneously placed feeding tube. These procedures are not without complications, and have been associated with the development of pneumoperitoneum. There are situations where free air after feeding tube placement should be managed non-operatively. Studies have shown that up to 12–16% of patients undergoing percutaneous gastrostomy tube placement will have free air seen on films taken within the first 5 days after the procedure [23, 24]. Blum et al. performed a retrospective study of patients who underwent PEG/PEJ placement and found that 12% of patients who undergo imaging post procedurally will have some amount of free air. Less than 1% of the patients in the study had serious complications from the percutaneous feeding tube requiring operative intervention. Patients who had serious complications after PEG placement all exhibited signs of peritonitis and were noted to have additional imaging findings aside from free air, particularly free fluid. Similar to the discussion above regarding the presence of postoperative free air, free air following percutaneous feeding tube placement can be observed in the absence of clinical findings of peritonitis.

Alley et al. published a paper looking at the incidence of pneumoperitoneum after percutaneous endoscopic gastrostomy tubes in the ICU. They retrospectively studied PEG placement in 120 ICU patients. Pneumoperitoneum was found in 6.7%

of patients studied. They found complications in 10% of their study population, none of which had evidence of pneumoperitoneum on imaging [25].

Percutaneous feeding tubes are not uncommon in the critical care setting, finding of pneumoperitoneum following placement of PEG can potentially occur. This finding, as with benign postoperative pneumoperitoneum, can be a byproduct of the procedure and can be safely observed if no other signs of peritonitis are present.

Free Air Associated with Peritoneal Dialysis Catheters

Like gastrostomy tubes, patients in the ICU often present with multiple medical comorbidities including ESRD in which peritoneal dialysis may be implemented. The presence of pneumoperitoneum in a patient with peritoneal dialysis requires careful decision-making. If a postoperative patient has free air and is also on peritoneal dialysis, then it is important to consider the relationship to the peritoneal dialysis catheters. Studies have attempted to determine the incidence of pneumoperitoneum in patients undergoing continuous ambulatory peritoneal dialysis. In a retrospective review of 101 PD patients who underwent imaging, it was found that almost one third had evidence of free air on imaging. One third of the cases were within 30 days of peritoneal dialysis catheter placement. Approximately 30% of patients had pneumoperitoneum that was associated with an episode of peritonitis. Only two patients with pneumoperitoneum and peritonitis had gastrointestinal perforation [26]. To summarize it is not uncommon for patients with peritoneal dialysis to exhibit free air. The challenge can occur when the patients are also having signs of peritonitis, which can occur in association with the peritoneal catheter or due to a gastrointestinal perforation. There are occasions where free air is observed in the setting of PD catheter associated peritonitis; therefore, the presence of free air on plain films should lead the clinician to a CT scan and potentially exploratory surgery. As mentioned earlier, with the advent of laparoscopy, definitive diagnosis is now possible that minimizes stress to the patient. Early use of laparoscopy may be indicated in many patients and should be considered.

Free Air Following Transesophageal Echocardiogram

Transesophageal Echocardiogram (TEE) is commonly used in the cardiothoracic patient, and is not completely without risk. Although exceedingly rare, there are reports of gastrointestinal perforation secondary to TEE. A retrospective review of 7200 adult cardiac surgery patients found that the rate of esophageal perforation was 0.01% [27]. A comprehensive review by Hilberath et al. noted the incidence of perforation to be between 0.01% and 0.04% [28]. These patients will not always present with the expected vomiting, pain, subcutaneous emphysema. Additionally, initial radiographs tend to be normal, and presentation of symptoms can be delayed. Perforations tend to occur more often in patients with pre-existing GI pathologies (strictures, diverticulae, etc.), distorted anatomy, and those where there is observed resistance to probe insertion [28]. It is important to note that perforation is exceedingly rare after TEE, but not impossible and if clinical concern is present than further investigation should take place.

Recommendations

Overall, the literature concludes that postoperative pneumoperitoneum is not an uncommon finding. The amount of free air and duration is highly variable as it is dependent on the type of surgery and image modality used to assess the patient. Postoperative pneumoperitoneum without signs of peritonitis or systemic infection can be safely observed with serial abdominal exams and images. The role of diagnostic laparoscopy should be considered when diagnosis is critical [29]. If the patient has any signs of peritonitis, the patient should be taken to the operating room without delay. The following characteristics can be used to determine the ability to safely observe a patient with postoperative free air: small volume (<10 mL), presence of drain, and slender patients. Most importantly, always consider common causes of pneumoperitonuem that may be unrelated to the patient's initial operation. This is absolutely essential in the immunocompromised transplant patient who can have an atypical presentation, and has a higher rate of morbidity and mortality following gastrointestinal perforations.

- Postop Pneumoperitoneum is not uncommon, and when clinical signs of peritonitis are absent then the patient can safely be observed (evidence: moderate, recommendation: strong)
- If clinical signs of peritonitis are present in conjunction with pneumoperitoneum seen on imaging then there should be no delay in taking the patient to the operating room (evidence: moderate, recommendations: strong)
- Characteristics of benign postoperative pneumoperitoneum include small volume (<10 mL), normal WBC, presence of surgical drains, and slender patients (evidence: low, recommendations: weak)
- If perforated peptic ulcer is determined to be the source of free air the patient should undergo surgical intervention. If uncomplicated diverticulitis is diagnosed as the cause of free air then medical management and observation can be pursued. (evidence: high, recommendations: strong)
- Always consider common causes of GI perforation in the immunocompromised, transplant patient as they often have atypical and delayed presentations (evidence: high, recommendations: strong)

A Personal View of the Data

Were the physical exam of the abdomen to be accurate to reliably diagnose peritonitis or the need for surgery, there would be no need for CT scans and other modern imaging modalities. Yet any experienced surgeon recognizes that in complicated clinical scenarios, such as a postoperative cardiothoracic patient who is sedated, ventilated and receiving pain medication, the physical exam is wholly unreliable. The mere presence of free air makes all surgeons take pause as in many cases its significance cannot be determined with reliability. Yet no free fluid on CT, no

stranding fat and no focal pathology, lends itself to expectant observation with a low threshold for operative intervention should the patient display any signs of infection at the systemic level (fever, tachycardia, etc.). In the low risk abdomen (no previous surgery, or minimal previous surgery), laparoscopy should be used liberally [29]. Although the utility of this approach is unconfirmed, if performed properly, it is diagnostically definitive and generally regarded as safe (Table 39.3). In many circumstances it is simply safer to know than to not know. This is particularly true in cases of intestinal ischemia, which invariably does not present as free air, and

Table 39.3 Non-iatrogenic causes of pneumoperitoneum

Peptic ulcer disease			
Study	Type of study	Conclusion	Quality of evidence
Crofts et al. [15]	Randomized control (N = 83)	Found observation to be a safe alternative to surgery in patients under the age of 70 28% of patients being observed eventually required surgery Longer length of stay in observation Small simple size – 83 patients	Moderate
Soreide et al. [14]	Systematic Review	Short term mortality −30% Elderly patients with delay to surgery have highest mortality rate Surgical repair should not be delayed as every hour increases mortality	Strong
Buck et al. [16]	Retrospective Review (N =2668)	26.5% mortality rate Every hour delay to surgery was associated with a decrasae in survival by 2–4%	Strong
Diverticulitis			
Salinen et al. [17]	Retrospective review (N = 132 patients)	Non-operative managment of patients with minimal free air or pericolic air without signs of peritonitis is safe Pericolic air without abscess had a 99% success rate with observation, 0% mortality Patients with retroperitoneal free air had a 43% success rate and 7% mortality	Strong
De' Angelis et al. [19]	Systematic review	Median time from transplant to emergency abdomianl surgery 2.4 years Rate of diverticulitis was 6.2% Morbidity up to 33% for diverticulitis Delay in presentation 2–8 days	Strong
Reshef et al. [22]	Retrospective Review (N = 5329 transplant patients)	Urgent surgery for diverticulitis in solid organ transplant is associated with worse mortality and morbidity compared to immunocompetent patients (19% vs 0% mortality, 51%vs 24% morbidity) Elective surgery for diverticulitis in the transplant patient is associated with equivalent morbidity and mortality as immunocompetent hosts	Strong

therefore was not discussed. That said, free air is always a concern in the postoperative cardiothoracic patient and should be investigated to the full extent possible and never dismissed as insignificant.

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Chapter 40
Ischemic Bowel in the Post Cardiothoracic Patient

Ashley J. Williamson and J. Michael Millis

Introduction

Bowel ischemia remains a rare, but critical surgical consultation. Historically the diagnosis is characterized by abdominal pain out of proportion to exam requiring prompt intervention for resolution. However, in clinical practice, the clinical state of post-operative patients can make diagnosis difficult, leading to a delay and increased morbidity and mortality. Ischemia in the gastrointestinal tract can be acute with sudden onset of pain, or chronic with gradual accumulation of atherosclerotic disease. Pathologies include occlusive ischemia (emboli or thrombus), arterial spasm secondary to low cardiac output or vasoconstrictors, or venous congestion. Each of these pathologies can progress to a common path of necrosis, bowel perforation, peritonitis, sepsis, and in severe instances: death. Acute ischemia remains a particular challenge, with mortality rates ranging from 30% to 90% and largely dependent on time to diagnosis [1].

Post-operative cardiothoracic patients are at a higher risk for non-occlusive ischemia which create particular challenges and questions in how to diagnose and treat these patients. Often these patients are intubated and sedated post-operatively making a physical exam difficult. Further, derangements in laboratory analysis and hemodynamic changes may be secondary to a variety of simultaneous pathologies making the crucial early diagnosis of ischemia particularly difficult.

Their critical illness makes the diagnosis challenging.

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Table 40.1 PICO table for management of bowel ischemia in post cardiothoracic patient

P (Patients)	I (Intervention)	C (Comparator group)	Outcomes (Outcomes measured)
Adult post-operative cardiothoracic patients	Diagnosis and treatment of bowel ischemia: non-surgical intervention (CT-scan, lab analysis)	Surgical intervention (laparoscopy, laparotomy)	Diagnostic sensitivity, complications, mortality

Search Strategy

A Medline comprehensive search was performed in PubMed using the following MeSH terms based on the outlined PICO elements (Table 40.1) "cardiothoracic" "cardiac" "post-operative" "mesenteric" "bowel" "ischemia." Studies included in search included clinical study, clinical trial, comparative studies, meta-analysis, multicenter study, randomized control trial, reviews, and systemic reviews. Initial search reviewed 34 articles which were reviewed for applicability to topic. Only studies with human subjects were included. Given the lack of specific literature available for post-operative patients and non-occlusive mesenteric or low flow ischemia, search was broadened to include studies addressing endovascular and open repair for acute mesenteric ischemia as a whole. The quality of the data provided by the papers evaluated were classified according to the GRADE system.

Results

Mesenteric Ischemia

Broadly, mesenteric ischemia is grouped into occlusive and non-occlusive etiologies. Occlusive disease is the predominant subset of all-comers and accounts for approximately 85% of presentations. Within occlusive disease, roughly 50% is the result of arterial thrombus, 20% embolic etiology, and 15% venous thrombosis [2]. Plaque development most often forms at a site of ulceration or spot of atherosclerotic disease. Patients who are candidates for cardiothoracic surgery represent a population predisposed to peripheral atherosclerotic disease and thus prone to the development of chronic ischemia. However, post-operatively these patients may develop acute ischemia.

Non-occlusive mesenteric ischemia is a rare complication after cardiac surgery with an incidence of approximately 1%, but with a reported mortality of 60–90% [3]. Of the subtypes of ischemia that develop in post-op cardiac patients, non-occlusive mesenteric ischemia rates have been shown to approximate 80% [4]. The pathophysiology of the development of non-occlusive mesenteric ischemia is not well defined but is assumed to be extreme reduction in blood flow resulting in

compromised integrity of intestinal mucosa leading to bacterial translocation, bacteremia, and multiorgan failure. The mechanism of non-occlusive mesenteric ischemia being the delayed presentation of intra-operative microcirculatory changes in the mucosa that progress post-operatively has also been proposed [5]. Classic mechanism of ischemic changes in the mucosa secondary to vasopressor use also remain well hypothesized. Indeed, treatment with alpha adrenergic catecholamines such as norepinephrine have been correlated with an increased incidence of non-occlusive mesenteric ischemia after cardiopulmonary bypass. This has been thought to be the consequence of a hypercontractile response of ileal microvessels after alpha adrenoceptor stimulation [6].

Risk Factors of Post-operative Mesenteric Ischemia

Significant effort has been spent attempting to identify patients about to undergo cardiothoracic surgery who may be particularly at risk for ischemia in an effort to prevent or identify these patients earlier post-operatively.

Mothes et al. conducted a large retrospective study of 9385 patients who underwent major cardiovascular surgery between January 2005 and December 2012 [7]. Co-morbidities and peri-operative risk factors of patients with or without mesenteric ischemia following cardiac surgery were analyzed. In total, 108 patients (1.15%) developed acute mesenteric ischemia within 2 weeks post-op cardiac surgery and underwent laparotomy. Mortality was 68% and similar to other values reported in the literature. Generally studies demonstrate that cardiopulmonary bypass was the only procedure associated with increased rate of ischemia. As expected, a longer time on pump is associated with an increased likelihood of ischemia. Patients with ischemia were matched to controls similar in age and type of cardiac surgery. Extensive pre-operative risk factors were assessed and in multivariate analysis. Liver cirrhosis (OR 13.3 CI95% 3.6–49.3) and emergency cardiac surgery (OR 2.6 CI95% 1.3–5.2) were independent pre-operative risk factors for development of acute ischemia. Post-operative parameters demonstrated higher rates of mesenteric ischemia in patients with the use of norephinephrine (OR 3.5 CI95% 1.6–7.8), epinephrine (OR 2.0 CT 95% 1.1–3.7), and serum lactate levels >3 mmol/L (OR 2.9, CI95%, 1.5–5.6) [7]. Additional studies looking at risk factors for mesenteric ischemia in post-cardiac surgery patients have identified older age, renal insufficiency, peripheral vascular disease, preoperative inotropic support, poor left ventricular ejection fraction, cardiogenic shock, pre-operative intra-aortic balloon pump, cardiopulmonary bypass time, and inotropic support as independent risk factors for developing mesenteric ischemia [8].

A recent study by Guillaume et al. highlighted the importance of having a high level of suspicion for ischemia in post-op cardiac patients who develop multi-organ failure. The retrospective observational study demonstrated that of 4948 patients who underwent cardiac surgery between 2007 and 2013 at a single institution, 320 patients developed multiple organ failure requiring ICU admission [4]. Of those,

acute mesenteric ischemia was confirmed in 33/320 (10%) of patients. Further, 28-day and 90-day mortality approached 64% and 83% respectively. Non-occlusive mesenteric ischemia was again identified as the dominant ischemic pathology, present in 83% of the patients. CABG as primary surgery, need for blood transfusion during bypass, and ASAT >100 UI/L were found to be independent risk factors associated with developing mesenteric ischemia [4].

Many small case series and retrospective trials have investigated potential modifiable intra-operative risk factors for ischemia. Sastry et al. completed the largest retrospective trial in 2014, completed at Papworth Hospital [9]. Between 2006 and 2011, 10,409 patients underwent cardiac surgery and ischemia was found to be associated with recent myocardial infarction (OR 4.98 CI95% 1.58–15.71 P = 0.01), vasopressor dose on bypass (OR 1.28 CI95% 1.04–1.57 P = 0.02), metaraminol (alpha 1 adrenergic agonist) dose on bypass (OR 1.52 CI95% 1.12–2.06 P = 0.01), and lowest documented mean arterial pressure (OR 0.90 CI95% 0.83–0.97 P = 0.01) [9].

While the data is diverse and within multiple different patient populations, statistically significant risk factors have been identified within the literature and are summarized (Table 40.2).

Non-surgical Diagnosis and Management of Ischemia

Early identification of ischemia remains the most pivotal marker for survival. Given the critical state of most of these patients, high morbidity of return to the operating room, and logistics and cost of invasive approach, literature has addressed the utility of using various serum markers and imaging to diagnosis ischemia.

Given the factors identified, risk calculators have been developed which may be of predictive value. Several are used in practice and are beyond the scope of chapter, however both the EuroSCORE/newer EuroSCOREII and GICS are worth noting. The EuroSCORE was developed using a variety of age, frailty, renal, cardiac, pulmonary, and body habitus features in Europe in the early 1990s. It is utilized to predict all morbidity post cardiac surgery. The newer GICS (gastrointestinal complication score) was developed to specifically identify risk factors for GI complications post-operatively and includes factors such as cardiopulmonary bypass time >150 min, post-op atrial fibrillation, post-operative heart failure, post-operative vascular complication, and reoperation due to bleeding. EuroSCOREII was developed after concern was raised that EuroSCORE may be outdated and in fact over predict mortality in the more modern operative era. It was developed in 2010 with prospective risk and outcome data in over 20,000 patients throughout 154 hospitals in 43 countries. The primary outcome was in hospital mortality with secondary outcomes being 30 and 90 day mortality. When compared to patients from the initial EuroSCORE, the population was older, included more women, and higher comor-

Table 40.2 Risk factors for acute mesenteric ischemia

Author, year (reference)	Total # of patients, # of patients w/ ischemia (% w/ischemia)	In-hospital or 30 day mortality of patients with MI	Statistically significant risk factors	Study type/ quality of evidence
Mothes et al. (2016) [7]	9385, 108 (1.2%)	68%	Cirrhosis (OR 13.3, CI95% 3.6–49.3), emergent surgery (OR 2.6 CI95% 1.3–5.2), use of norepinephrine and epinephrine (OR 3.5 CI95% 1.6–7.8), lactate >3 (OR2.9, CI95% 1.5–5.6)	Retrospective, low
Guillaume et al. (2017) [4]	4948, 33 (0.6%)	64%	CABG as primary surgery (OR 2.3 95% CI 1.02–5.1), need for blood transfusion during bypass (OR 2.3 95% CI 1.03–5.1), ASAT >100 uL/L (OR 4.1 95% CI 1.5–11.5)	Retrospective, low
Sastry et al. (2014) [9]	10,409, 30 (0.3%)	100%	MI (OR 4.98 95% CI 1.58–15.71), dose of vasopressor on bypass (OR1.28 95% CI 1.04–1.57), lowest documented MAP (OR0.90 95% CI 0.83–0.97), EuroSCORE (OR 1.12 95% CI 1.03–1.21)	Retrospective, medium
Eris et al. (2013) [8]	6013, 52 (0.9%)	67%	Age, renal insufficiency, peripheral vascular disease, amount of inotropic support, poor LF ejection fraction, cardiogenic shock, intraaortic balloon pump, cardiopulmonary bypass time, dialysis, prolonged ventilator time	Retrospective, low
Nilsson et al. (2013) [10]	18,879 17 (0.09%)	59%	Steroid use (OR 9.4 95% CI 2.1–43), peripheral vascular disease (OR 3.7 95% CI 1.4–9.9), cardiogenic shock (OR 4.9 09% CI 1.2–19), New York Heart Association Class 4 (OR 4.2 95% CI 1.6–13), creatinine >200 umol/L (OR 17.5 95% CI 5.8–53), prolonged ventilator time (OR 6.2 95% CI 1.7–23), intra-aortic balloon pump (OR 3.5 95% CI 1.0–12), cerebrovascular insult (OR 7.8 95% CI 2.3–27)	Prospective case control, medium

bidity demonstrated by more patients with NYHA class IV, renal and pulmonary dysfunction. Changes from the initial score included measuring creatinine clearance rather than serum creatinine, including hepatic function, redefining unstable angina, and "weighting" the procedure or defining the severity and involvement of the proposed procedure. EuroSCOREII is now considered the standard for an appropriate risk score in the modern era, reflecting decreased mortality in older and sicker surgical patients [11]. Nilsson et al. looked at the two scores in 8879 patients who underwent surgical procedures at a single institution between 1996 and 2011 [10]. Patients who experienced gastrointestinal complications were subsequently reviewed (n = 17) with an incidence of 0.09%, slightly less than what is predicted in the literature. The group found that the GICS performed better than the EuroSCORE with recovering operating characteristic curve analysis with (ROC 0.87 CI95% 0.87 0.77–0.98 and ROC 0.74 CI95% 0.61–0.86) respectively [10, 12]. Since the study completed, EuroSCOREII has been described and is worth assessing as comparison for predictive value in the future.

Laboratory Tests for Mesenteric Ischemia

Bowel ischemia has been associated with a variety of laboratory derangements, perhaps most notably elevated C-reactive protein, leukocytosis, lactic acidosis, D-dimer, and renal dysfunction. However, while clinicians often utilize these lab values as reason for operative intervention, there is concern over whether the timing of their abnormalities may in fact be too late in the course to intervene and change the clinical course.

Lactate has long been described both in the literature and as a clinical sign of ischemia, however the utility of the study is just as frequently debated. Hong et al. assessed the reliability of lactate and new laboratory markers for diagnosis nonocclusive mesenteric ischemia in post-operative patients. The small prospective observational study included twenty patients who were recruited after cardiac surgery if they required laparotomy for suspected nonocclusive mesenteric ischemia. The clinical decision for laparotomy was deemed via a consensus of intensivists, cardiac surgeons, and general surgeons. Plasma was collected immediately before each laparotomy. Positive laparotomy for ischemia was defined by full thickness intestinal infarction and was confirmed on histopathology. At initial laparotomy, 13/20 (65%) patients had evidence of full thickness intestinal infarction. Three of the seven patients with an initial negative laparotomy had a subsequent positive laparotomy in their hospital course. When biomarkers were analyzed, elevated D-lactate demonstrated no difference in positive and negative laparotomy, but was found to be strongly associated with mortality after bowel resection likely reflecting the prolonged disease course. However, positive laparotomy was associated with a decreased i-FABP (intestinal fatty acid-binding protein) and increased SMA (smooth muscle actin). Overall in-hospital mortality was 70% (14/20), median time to laparotomy after cardiac surgery was 7 days, and median time to

death after surgery was 13.5 days [13]. This study although small is pivotal to the topic at hand given is specifically assessed values in the patient population described. Further, the length of time to laparotomy potentially suggests the difficulty in diagnosing ischemia in these patients. The major limitation to potential intervention is that laboratory analysis was conducted immediately prior to laparotomy, and markers drawn earlier in the clinical course may demonstrate a different trend.

Imaging for Mesenteric Ischemia

Because of the lack of specificity of physical exam and laboratory analysis, imaging remains a well described and controversial component to non-operative management. Plain films, duplex ultrasound, CT scan, endoscopy, MRI, and angiography have all been evaluated. Angiography is historically described as the gold standard as it remains both a diagnostic and therapeutic option, however this approach is not available at all institutions. Plain films of the abdomen or upright chest remain limited in their utility as features that may be visualized on film including obstruction, pneumoperitoneum, portal venous gas, and pneumatosis intestinalis are often late findings. Earlier in the course plain films may appear normal [14]. Ultrasound with doppler used to evaluate the vasculature can be useful, but is operator dependent. Celiac and SMA are visualized in the sagittal plane while IMA is often hard to see. While specificity of doppler is high (92–100%), sensitivity is lower (70–89%) and less useful in non-occlusive ischemia [14] which should raise question as to the diagnostic utility of this modality in post-op cardiothoracic patients.

In recent years, CT angiography (CTA) has become the imaging modality of choice. CTA is more widely available than angiography and is less invasive, the obvious limitation being that it is not a therapeutic intervention. CTA allows for visualization of the abdominal vasculature in three dimensions. Imaging of the entire abdomen also allows for evaluation of broad differential diagnoses present in these acutely ill patients. CTA's sensitivity for acute ischemia approaches 85–88% while specificity ranges from 61% to 72% making it a better candidate for initial imaging than modalities described above. Characteristics consistent or concerning for ischemia on CTA include vascular luminal filing defects, lack of mural enhancement, bowel wall thickening in addition to the previously described late findings of pneumatosis intestinalis and portal venous air [15]. Menke completed a large systemic review looking at the sensitivity and specificity of acute mesenteric ischemia with abdominal CT described sensitivity and specificity values approaching 90%, however it should be noted that a majority of these studies were performed in the setting of occlusive ischemia [16]. Non-occlusive ischemia, as most often found in post-op cardiothoracic patients is much harder to detect [16] and no trials are available at this time looking at the utility of imaging in this specific pathology. Magnetic resonance imaging and angiography in addition to positron-emission tomography have demonstrated positive results for diagnosis in small and animal studies for the

diagnosis of acute ischemia and may be modalities that are able to better identify non-occlusive ischemia, however they remain time consuming and may not be available at every institution [13].

In the age of relying on imaging for diagnosis and treatment intervention, a word of caution is warranted. Boucier et al. addressed this concern in their 2016 retrospective monocenter study where 147 patients with clinically suspected acute non-obstructive mesenteric ischemia were definitively confirmed or ruled out through endoscopic or surgical intervention and compared to previous imaging modalities [17]. Of the 147 patients, 114 had previously undergone contrast-enhanced abdominal CT-scan. It was found that portal venous gas, pneumatosis intestinalis, and wall enhancement were poorly sensitive but with good specificity (95, 85, and 71%). Of note, 19/75 patients (25.3%) without any radiological signs of ischemia demonstrated mesenteric ischemia, 10 with intestinal necrosis at the time of intervention [17]. While small and retrospective, this study is the best glimpse into the often failed utility of imaging for confirmation of this diagnosis.

Surgical Diagnosis and Management

One of the most important, albeit obvious on initial assessment, points of evidence continues to be that early surgical consultation and intervention remains an independent risk factor for survival. The most compelling of this data comes from a review completed by Kougias et al. in 2007 with a retrospective review of 72 patients in which a low mortality rate of approximately 14% was demonstrated in patients who underwent surgical intervention in less than 12 h following the onset of acute ischemia symptoms, whereas a mortality rate of 75% was demonstrated in patients who underwent surgical intervention more than 12 h following the onset of symptoms ($P = .02$) [18].

However, operative intervention comes with significant morbidity and systems issues. Mobilization to the operating room can take hours and accrues cost with staff and instruments. Further, this endeavor can be criticized if the laparotomy is negative for ischemia and is not an “always” solution.

Diagnostic Laparoscopy

Research has targeted its focus on diagnostic laparoscopy both in the ICU and in the OR for use in ischemia. Hackert et al. specifically looked at the utility and safety of diagnostic laparoscopy in post-operative cardiac surgery patients with clinical condition suggesting mesenteric ischemia [19]. Patients felt to have mesenteric ischemia were taken to the operating room ($n = 17$) and diagnostic laparoscopy was performed prior to laparotomy. While small in number, the study demonstrated a sensitivity of 94% for mesenteric ischemia in laparoscopy, with a complication rate

of 6%, which albeit large appears exaggerated secondary to the sample size. The study suggests that laparoscopy be utilized for earlier diagnosis given its high sensitivity and relatively low complication rate [19]. Newer studies address the utility of diagnostic laparoscopy in the ICU but remain poor in quality and without sound evidence to base decisions.

Surgical approach for ischemia is broad and includes diagnostic laparoscopy as above, laparotomy with embolectomy, resection of necrotic bowel, second look procedures for evaluation of necrotic bowel, mesenteric bypass, or retrograde profusion. Endovascular interventions are newer and significant work has gone into comparing open and endovascular intervention. Success rates, comorbidities within open interventions are beyond the scope of this chapter and difficult to assess given they are necessary based on the clinical situation at hand. However, comparison between endovascular and open technique is important when deciding how to proceed in the operating room.

Endovascular Techniques

Minimally invasive catheter directed therapy using endovascular techniques have emerged as a dominant intervention with multiple techniques described. These agents have wide use in peripheral artery disease within vascular surgery. Schoots et al. completed a systemic review looking at a large patient population spanning the mid 1960s to early 2000s which demonstrated that a majority of patients were able to avoid surgery for acute ischemia after use of thrombolytics [20]. Multiple other reviews demonstrate this, however it is important to recognize and remember that a majority of these studies were conducted on patients with embolic or thrombotic ischemic disease. The utility of angiograms and catheter directed therapy in the dominant pathology of non-occlusive mesenteric ischemia in post-op cardiac patients remains unstudied.

While skill, availability, and use of endovascular intervention for acute ischemia has increased in recent years, expected decline in open surgery has not yet occurred [21]. Nationwide Inpatient Sample, the largest all-payer inpatient care database in the US, demonstrates that between 2000 and 2012 of the 12,517 patients who underwent intervention for acute ischemia: 6311 (50%) underwent open surgery while 6206 (50%) underwent endovascular intervention [22]. Older age and comorbid conditions were more common in patients who underwent endovascular treatment. Of note, patients with atrial fibrillation and history of stroke were more likely to undergo open repair, suggesting that acute ischemia thought to be due to embolism was more likely to be treated with open surgery. Total mortality amongst patients with acute mesenteric ischemia was noted to decline from 12.9 to 5.3 deaths per million over the 12 year period. Of note, in-hospital mortality was found to be higher in patients who underwent open as compared to endovascular intervention, however patients undergoing open surgery were found to be more likely to require bowel resection suggesting the presence of a more advanced disease process. Open

surgery continues to remain an independent predictor of in hospital mortality [22]. Few trials exist directly comparing endovascular vs. open intervention in patients with acute mesenteric ischemia. At this time, no randomized controlled trials have been done likely given the clinical judgement and critical illness of the patients at the time of diagnosis. One of the largest retrospective studies was completed by Arthurs et al. who at a single institution, looked at 70 consecutive patients who underwent intervention for acute mesenteric ischemia. Endovascular treatment was deemed initially successful in 87% of patients, however only 30% were able to avoid a laparotomy, and 13% of the endovascular patients required open revascularization. Endovascular intervention was associated with shorter segments of bowel resected (59 cm vs. 160 cm respectively) [23].

The largest, most inclusive systemic review to date completed by Zhao et al. in 2015 includes 1110 patients and investigated outcomes of endovascular intervention as described above to traditional open surgical laparotomy, revascularization and new hybrid technique [24]. The review's obvious weakness is the selection bias towards endovascular intervention, and the availability of mostly case reports and small case series for review. Endovascular intervention including variations on thrombolysis, embolectomy and angioplasty demonstrates lower in-hospital mortality and morbidity (wound infection, multiple organ dysfunction, pulmonary failure, myocardial infarction) in addition to similar survival rate at a 5 year follow up in comparison to the open surgery group. Primary patency at 5 years in addition to amount of bowel resected rate was lower in the endovascular group. Further, the review discusses a hybrid approach, laparoscopy or laparotomy with endovascular retrograde SMA revascularization as potential approach since viability of the bowel is confirmed and length of operation is decreased in comparison to traditional open repair [24]. This approach may be useful in post-operative cardiac patients as laparoscopy vs. laparotomy would allow for intervention, and retrograde angiogram could confirm lack of embolus or thrombus at time of the operation as would be expected in the dominant non-occlusive subtype.

Along with mortality outcomes, Beaulieu et al. addressed the rates of bowel resection following endovascular vs open repair of acute mesenteric ischemia using the National Inpatient Sample database with admissions from 2005 to 2009 utilizing a search of ICD 9 codes [25]. A total of 679 patients underwent vascular intervention for acute mesenteric ischemia during this time frame: 514 (75.7%) underwent open surgery and 165 (24.3%) underwent endovascular treatment. Endovascular rates expectedly increased over the years with 11.9% of patients undergoing them in 2005 and 30.0% in 2009. Mortality was found to be significantly increased in the open revascularization group as compared to the endovascular arm (39.3% vs 24.9% respectively $P = 0.01$). Length of stay was significantly longer in the open revascularization group. Further, patients undergoing endovascular intervention required bowel resection significantly less than patients requiring open repair (14.4% vs. 39.3% $P < 0.001$) and endovascular repair required less use of total parenteral nutrition support than the open group (13.7% vs. 24.4% $P = 0.025$). Of note, patients

who underwent open repair were found to have a significantly elevated lactic acidosis when compared to the endovascular arm in addition to a higher percentage of ARDS, likely identifying a sicker patient population. Time to vascular intervention did not differ significantly between the groups, critical as time to intervention is likely to be one of the most important factors when it comes to outcome in these patients [25]. Further, it suggests that survival benefit demonstrated in this study cannot be secondary to severity of illness in open population alone. The limitation of the study remains the lack of non-occlusive disease identified.

As made clear by the literature, great limitation exists in a randomized controlled trial, and one likely may never exist given the complexity of the disease process. Direct comparison of diagnostic intervention and success rate is not well defined, however it can be best summarized with current data on mortality and morbidity for various interventions as presented in (Table 40.3).

Table 40.3 Intervention outcomes for mesenteric ischemia

Author, year (reference)	# of patients	Intervention	Mortality	Total morbidity (examples: prolonged intubation, renal failure, cardiac complications, sepsis, gastrointestinal hemorrhage)	Study type, quality of evidence
Kougias et al. (2007) [18]	72	Open surgical intervention (within 24 h of diagnosis)	14% (OR within 12H) 75% (OR after 12H)	68%	Retrospective, very low
Hackert et al. (2003) [17]	16	Diagnostic laparoscopy	NR	6%	Prospective, low
Schermorhoen et al. (2009) [19]	3380	Open surgical intervention	39%	48.2%	Retrospective, medium
Schermorhoen et al. (2009) [19]	1857	Endovascular	16%	36.7%	Retrospective, medium
Arthurs et al. (2011) [21]	14	Open surgical intervention	50%	NR	Prospective, medium
Arthurs et al. (2011) [21]	56	Endovascular	39%	NR	Prospective, medium
Zhao et al. (2017) [22]	234	Endovascular	27%	47.9%	Review, medium
Zhao et al. (2017) [22]	856	Open surgical intervention	40.3%	62.1%	Review medium
Beaulieu et al. (2014) [23]	514	Open surgical intervention	39.3%	NR	Retrospective, medium
Beaulieu et al. (2014) [23]	165	Endovascular	24.9%	NR	Retrospective, medium

Recommendations

Mesenteric ischemia remains a rare but fatal complication in the post-operative cardiac population. The difficulties in diagnosing ischemia patients who are sedated, ventilated, and with many other factors which may predispose them to illness are profound. Clinicians must keep a high index of suspicion particularly when signs of multi-organ failure begin to develop. Surgical intervention should be implemented as soon as a suspicion for ischemia develops as this appears to be the only consistent intervention with improvement in outcomes. No laboratory or imaging study is sensitive enough on its own to diagnose and drive therapy for ischemia. The dominance of non-occlusive mesenteric ischemia within the post-operative cardiothoracic population makes intervention more difficult as endovascular intervention may have a limited role. Medical treatment should be optimized for improvement in systemic blood flow by decreasing vasoconstrictors. Limited literature exists for the utility of diagnostic laparoscopy, but in the studies reviewed it appears feasible and may be the bridge to quicker diagnosis. The most important survival factor continues to be time to diagnosis and early operative intervention when indicated. A multidisciplinary combined approach to streamline diagnosis with early surgical consultation is clearly indicated.

- Surgical assessment should be initiated at first concern for acute mesenteric ischemia. If operative or endovascular intervention is warranted, it should take place within 12 h of diagnosis (evidence quality high; strong recommendation).
- Medical optimization for decreasing risk factors i.e. amount of vasopressor required, optimal ventilator support, etc. is important in decreasing risk (evidence quality medium; moderate recommendation).
- Multi-organ failure in a critically ill post-operative patient may be an indicator of the presence of acute mesenteric ischemia (evidence quality medium; moderate recommendation).
- Diagnostic laparoscopy may play a role in this critically ill patient population with marginal morbidity (evidence quality low; weak recommendation).

Personal View of the Data

The level of evidence regarding a precise management approach to this complication is poor (zero prospective randomized controlled trials), but the goals of management are consistent: maximize systemic perfusion, rapid diagnosis and intervention. The use of endovascular techniques either through interventional radiology or vascular surgery may decrease the amount of bowel resected, but often does not eliminate the need for surgical intervention either via laparoscopic or open techniques. The choice of therapy should be determined by the rapidity with which each pathway can be expected to reach a confirmed diagnosis and definitive therapeutic endpoint.

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Chapter 41
Confusion in the ICU: Anticoagulated VAD Patient with MS Changes

Agnieszka A. Ardelt

Introduction

Acute confusion (also commonly referred to as "acute mental status [MS] change", "encephalopathy", or "delirium") in an anticoagulated cardiothoracic ICU patient with a VAD may be due to systemic decompensation (e.g., hypotension, systemic inflammatory response [SIRS], sepsis, hypoglycemia or other metabolic disorder, organ failure, drug effect or withdrawal, nutritional deficiency, or ICU delirium) or to a primary cerebral disorder (e.g., hemorrhage, ischemia, seizures/status epilepticus, or hydrocephalus). In the literature, conditions besides cerebral ischemia or hemorrhage that present with acute neurologic symptoms and signs are sometimes referred to as "stroke mimics", but this definition tends to de-emphasize the importance of several non-vascular conditions which require immediate treatment and can result in permanent brain injury if missed. Failure to correctly and rapidly diagnose and treat a broad category of conditions including hypoglycemia, cerebral ischemia, cerebral hemorrhage, hydrocephalus, or status epilepticus may result in irreversible brain injury and poor neurologic outcome. The key lies both in recognition and rapid treatment: in acute cerebral ischemia, for example, it is estimated that 1.9 million neurons die per minute [1].

While, arguably, treatment of systemic decompensation may not require an expert on acute neurologic disease, extensive literature shows that expert organized stroke care improves patient outcomes [2]. For this reason, medical centers in the United States striving to provide the best care for stroke patients increasingly become organized and accredited as primary [3] or comprehensive [4] stroke centers, in which the key feature is the rapid availability of expert, protocolized neurologic diagnosis and treatment. With respect to the acute evaluation of patients with

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sudden-onset neurologic symptoms, most of the literature relates to patients who develop symptoms in the community and are evaluated in the Emergency Department (ED); less is known about assessment of hospitalized patients who develop acute neurologic symptoms. This chapter focuses on the approach to the assessment and treatment of anticoagulated patients with VADs presenting with acute confusion while hospitalized in the cardiothoracic ICU.

Management of Hospitalized Patients with Acute Neurologic Changes

Cardiothoracic ICU patients with VADs presenting with acute confusion are, by definition, already hospitalized. Hospitalized patients presenting with acute neurologic changes differ in several critical aspects from outpatients presenting with the same to the ED. Hospitalized patients are more likely to: be diagnosed with non-ischemic and non-hemorrhagic cerebral conditions (i.e., the "stroke mimics"); have different risk factors for cerebral ischemia; not receive thrombolysis or thrombectomy; have higher severity of illness and higher neurologic disability scores; and experience poorer outcomes and higher mortality than ED patients [5–12]. The data suggest that a different approach or skillset may be required for the timely and accurate assessment of patients presenting with acute neurologic changes in the hospital versus in the ED, but responders assessing both hospitalized and ED patients are required to rapidly determine if immediate neuroprotective actions are appropriate, e.g., correction of hypoglycemia or cerebral perfusion; thrombolysis or thrombectomy; administration of anti-epileptic medications; correction of coagulopathy; or treatment of intracranial hypertension or cerebral edema (Fig. 41.1). Typically, community patients with acute neurologic changes presenting to the ED are assessed by ED providers, neurologists, or stroke teams. The responsibility for hospitalized patients presenting with acute neurologic changes is less clear. Studies have found that despite the increased deployment of in-hospital rapid response teams, deficiencies remain in the evaluation and treatment of inpatients presenting with stroke symptoms [6]. Because acute confusion is common in hospitalized patients, some authors have called for the establishment of protocols specifically for the assessment of inpatients presenting with acute MS changes by general rapid response teams so as to provide better care but not overwhelm the stroke team [7].

Search Strategy

Literature searches were performed to identify studies addressing the acute evaluation of anticoagulated cardiothoracic ICU patients with VADs presenting with acute confusion (Table 41.1). Databases searched were PubMed, Scopus, and Cochrane

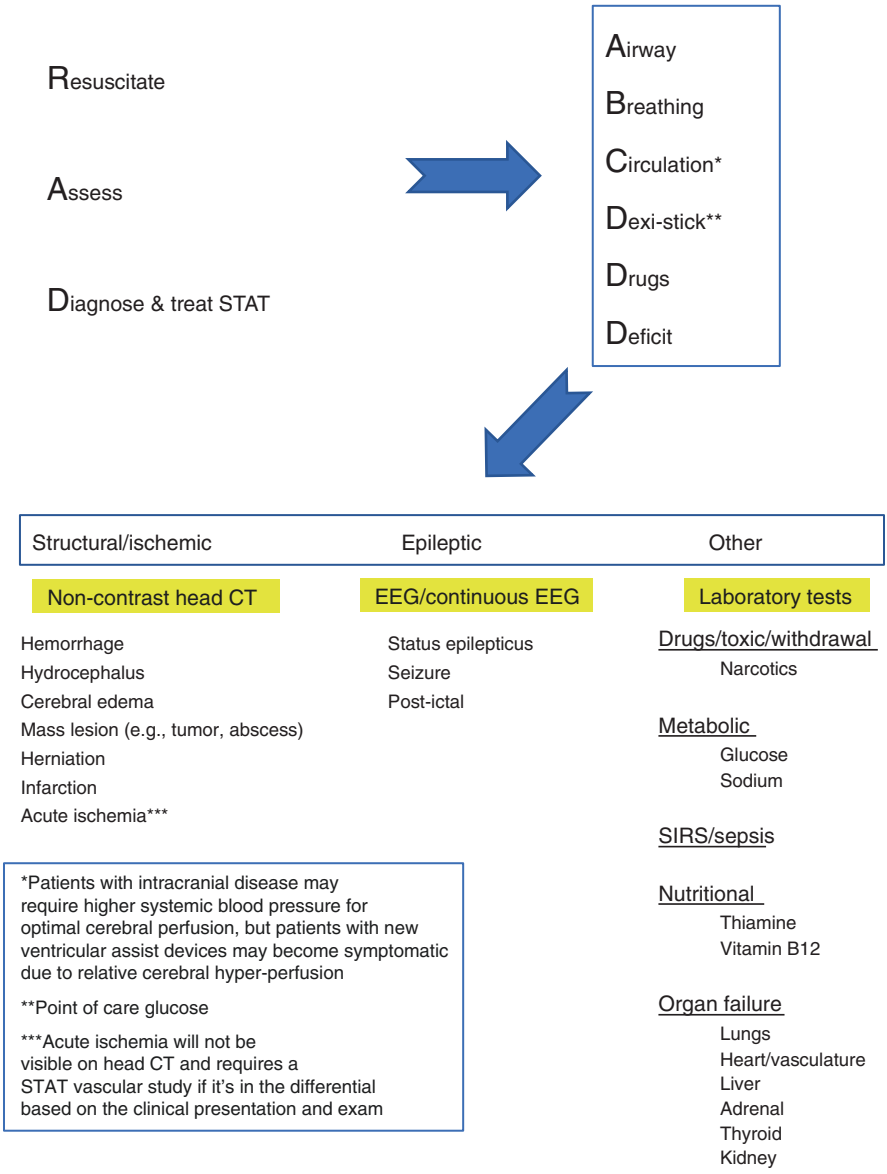


Fig. 41.1 Example of an approach to emergently assess and treat an ICU patient with a VAD presenting with acute confusion. "Drugs" refers to any drug of importance to the current situation, from potential narcotic overdose to the presence of anticoagulants (i.e., need for holding any IV anticoagulant infusions; preparation for possible rapid reversal; and STAT laboratory testing of coagulation) while investigating the etiology of the clinical presentation. "Deficit" refers to neurologic deficit and the localizing value it provides, e.g., prompting early suspicion of a cerebral large vessel occlusion and, therefore, need for STAT vascular imaging or spine imaging. The non-contrast head CT should be performed STAT, as soon as the airway is secured, the patient is hemodynamically stable, and the blood glucose has been assessed

Table 41.1 PICO table for assessment of cardiothoracic ICU patients with VADs presenting with acute confusion

Patient population	Intervention	Comparator	Outcome
Adult, postoperative cardiothoracic ICU, VAD	Rapid neurologic assessment by an expert	Evaluation and treatment by the ICU team	Neurologic function, mortality

Evidence Based Medicine. The following search terms were used: ventricular assist device AND acute neurologic; acute brain; central nervous system; confusion; delirium; rapid assessment; thrombectomy; anticoagulation reversal. Searches which included "ventricular assist device" were not filtered except for English language. Additional search terms were used in various combinations: acute stroke; ventricular assist device; brain; acute evaluation; in-hospital brain attack; in-hospital stroke; ICU; brain attack; code stroke; stroke alert; acute neurologic; rapid assessment; delirium; acute confusion; telehealth. These searches were limited to English language, human, and the time period from January 2007 to July 2017. Resulted titles and abstracts were evaluated for relevance. Relevance was defined as articles focusing on neurologic issues, acute complications, and adults. Excluded from further analysis were case reports, pediatric studies, and non-English language publications.

Results

The searches identified 35 manuscripts which provide the background information and the basis for the recommendations; there were no articles specifically addressing the rapid evaluation of anticoagulated patients with VADs presenting with acute confusion in the cardiothoracic ICU. To generate the recommendations, the following types (and numbers) of articles were evaluated (Tables 41.2 and 41.3): guidelines (4); randomized controlled trials (0); systematic reviews (2); literature reviews (3); multicenter prospective observational studies (1); single center prospective observational studies (2); analyses of administrative claims data, registry data, and other databases (5); multicenter retrospective chart reviews (1); and single center retrospective chart reviews (9).

Acute Confusion in Patients with VADs

Acute confusional states (also referred to as MS changes, encephalopathy, or delirium) are common in the post-operative state and correlate with worse outcomes [24]. Patients with VADs are at risk for neurologic events post-operatively [25, 26]. In one study, 9/23 patients implanted with the Novacor device developed neurologic complications: four patients had strokes, three had seizures, and two had delirium [13].

Table 41.2 Ischemic and hemorrhagic stroke as a complication of VADs

Reference	Study type	Number of subjects	Outcomes	Quality of evidence
Thomas et al. [13]	Retrospective chart review, single center	23	Frequency of cerebral complications in patients with VADs: 9/23; types of complications: strokes (4), seizures (3), delirium (2)	Very low
Genovese et al. [14]	Retrospective chart review of a prospective database, single center	195	Frequency of cerebral complications within 60 days of VAD implantation: 24–31%	Moderate
Kato et al. [15]	Retrospective chart review, consecutive patients, single center	307	Pre-operative characteristics and post-VAD placement neurologic complications: history of pre-implantation cerebral events and post-implantation infection were associated with neurologic complications	Moderate
Coffin et al. [16]	Retrospective chart review, multicenter	497	Neurologic complications in patients implanted with two different types of VADs: advanced age was associated with post-implantation neurologic events	High
Parikh et al. [17]	Analysis of administrative claims data	1813	Frequency of ischemic and hemorrhagic cerebral complications in patients with VADs: stroke incidence 8.7%/year; ischemic stroke incidence approximately double that of hemorrhagic stroke	High
Holman et al. [18]	Analysis of an NIH-sponsored registry	483	Risk factors for death and likelihood of transplantation in VAD patients: central nervous system events were the most common causes of death – 11%	High
Sakaguchi et al. [19]	Retrospective chart review, consecutive patients, single center	110	Frequency of ischemic and hemorrhagic cerebral complications in patients with VADs with a focus on convexity (sulcal) subarachnoid hemorrhage: cerebral infarcts occurred in 35 patients (72 events); hemorrhages in 25 patients (31 events); and subarachnoid hemorrhage in 23 patients (33 events)	Moderate
Willey et al. [20]	Retrospective chart review, single center	301	Ultimate outcome in patients with VADs who experienced either ischemic or hemorrhagic stroke: 50% of 8 patients with hemorrhagic stroke died; 28% of 32 patients with ischemic stroke died and 40% received, or were waiting for, transplants	Moderate

Table 41.3 Management of hospitalized patients, including patients with VADs[a], presenting with acute neurologic changes including ischemic and hemorrhagic stroke

Reference	Study type	Number of subjects	Outcomes	Quality of evidence
Al-Mufti et al. [21][a]	Retrospective chart review, single center	5	Functional outcome and safety of endovascular thrombectomy in VAD patients who developed acute ischemic stroke: no significant complications; all had neurologic improvement; two received transplants	Very low
Benavente et al. [22]	Prospective observational study, single center	139	Functional outcome and safety of mechanical thrombectomy in anticoagulated versus non-anticoagulated patients: anticoagulated patients had higher frequency of symptomatic intracranial hemorrhage (16.7% vs. 8.3%) but lower mortality at 3 months (6.7% vs. 19.0%)	Moderate
Wong et al. [23][a]	Retrospective chart review of a prospective database, single center	237	Safety and efficacy of warfarin anticoagulation reversal with traditional agents versus prothrombin factor concentrates (PCC) in VAD patients: time to reversal was shorter with PCC with no difference in post-reversal thromboembolism rates	Moderate
Cumbler and Simpson [6]	Prospective observational study, six certified Primary Stroke Centers	393	Prevalence of "stroke mimics" (and their treatment) in hospitalized patients with acute neurologic decompensation: 46.1%	High
Husseini and Goldstein [7]	Retrospective chart review, single center	297	Differences in final diagnosis and treatment of emergency department versus in-hospital stroke alerts: hospitalized patient stroke alerts were less likely to be due to cerebral ischemia (26.8% vs. 51.4%) and patients were less likely to receive thrombolytic treatment	Moderate
Emiru et al. [8]	Analysis of the national inpatient survey	134,977	Utilization and functional outcome with IV tPA in hospitalized versus emergency department patients with acute ischemic stroke: hospitalized patients treated with thrombolytics for acute ischemic stroke had higher in-hospital mortality, OR 1.1 (1.0–1.3; p = 0.05)	High

Table 41.3 (continued)

Reference	Study type	Number of subjects	Outcomes	Quality of evidence
Kelley and Kovacs [9]	Prospective observational study, single center	171	Ischemic stroke mechanisms and treatments in hospitalized patients were evaluated: peri-operative thrombosis or thromboembolism and pre-existing risk factors including hypertension and prior stroke were reported	Moderate
Kimuru et al. [10]	Analysis of a multicenter registry	15,815	Classification, treatment, and outcome of in-hospital onset ischemic stroke: neurologic deficits were greater, and outcomes worse, in hospitalized patients presenting with ischemic stroke	High
Masjuan et al. [11]	Analysis of a prospective multicenter registry	367	Safety, efficacy and operational metrics with IV tPA use in hospitalized versus emergency department patients with acute ischemic stroke: operational delays were identified in the evaluation and treatment of hospitalized patients	Moderate
Park et al. [12]	Retrospective chart review, single center	111	Comparison of clinical characteristics and outcomes between emergency department and in-hospital stroke alert patients: the two groups of patients have distinct characteristics and outcomes	Moderate

All three patients with seizures and one of the patients with delirium died. Additionally, patients with VADs are prone to bacteremia, and persistent blood stream infections correlate with increased frequency of central nervous system events [27]. Bacteremia associated with SIRS/sepsis may in and of itself cause acute MS changes; however, acute confusion may be a sign of focal neurologic injury (ischemic or hemorrhagic stroke) either because it is actually an aphasia or another localizing cognitive disturbance. In one study, delirium was the sole manifestation in 3% of 661 patients with imaging or tissue – proven cerebral hemorrhage or infarction [28]. Finally, while global cerebral hypoperfusion is a frequent cause of MS changes in heart failure, the opposite mechanism, i.e., relative cerebral hyperperfusion, has been postulated as a cause of delirium in some post-operative patients with VADs [29].

Ischemic and Hemorrhagic Stroke in VAD Patients

Post-operative ICU patients with VADs are at an increased risk of stroke: 24–31% of patients developed ischemic or hemorrhagic cerebral events within the first 60 days of VAD implantation in one study [14]. More recent studies report overall

stroke (cerebral ischemia and hemorrhage) rates of 14% [15] and between 16% and 19% [16] during longer follow-up periods. The lower rate of clinical events in the contemporary studies probably reflects methodologic differences, as well as improvements in VAD design and management. Another study evaluated administrative claims data between 2003 and 2015 of 1813 patients with VADs from three states: an overall annual stroke (ischemic and hemorrhagic) rate of 8.7% was found [17]. Ischemic stroke was more frequent than hemorrhagic, and in-hospital mortality correlated with stroke occurrence. With respect to mortality in patients with VADs, analysis of a large registry revealed that 18.3% of deaths were caused by central nervous system events [18]. After evaluating autopsy material from 33 patients with VADs, another study reported that the cause of death was related to the central nervous system in eight patients: six patients had catastrophic intracerebral hemorrhages, one had a brain stem infarct, and one had multifocal air embolism [30]. Overall, infarction was present in 23, and hemorrhage in 14, of the 33 brains studied. Many brains exhibited both pathologies: thus, patients with VADs are at risk for both ischemic and hemorrhagic stroke, and injuries are often multifocal. Multifocal small infarcts (or hemorrhages) may present with confusional states rather than gross focal motor deficits and may, therefore, be rather elusive diagnostically to a non-neurologist.

Patients with VADs are at risk for cerebral embolism including embolism to large cerebral vessels. There has recently been a revolution in treatment of patients with acute large vessel occlusions: endovascular thrombectomy after intravenous thrombolysis has dramatically improved outcomes, with number needed to treat to benefit of 4, and is recommended in guidelines [31]. Post-operative patients after VAD implantation presenting with proximal cerebral vessel occlusion do not qualify for intravenous thrombolysis regardless of whether they are anticoagulated or not, but they are potential candidates for endovascular thrombectomy [21]. Crucially, the endovascular thrombectomy option can also be triggered in fully anticoagulated patients [22]. The key to therapeutic success is rapid recognition and rapid reperfusion: time lost is brain lost. Beyond providers with clinical stroke expertise, thrombectomy requires interventional neuroradiology expertise and resources including a 24-7-365 on-call neuro-angiography technical team.

Intracranial hemorrhage comprises intracerebral hemorrhage, subdural hemorrhage, epidural hemorrhage (not relevant to this discussion), and subarachnoid hemorrhage (SAH). In intracerebral (intraparenchymal) hemorrhage, which was a frequent cause of death in the study of autopsies of patients with VADs [30], rapid reversal of anticoagulation, correction of thrombocytopenia, and blood pressure control to a specific range are recommended to decrease the chance of hematoma expansion [32]. Hematoma expansion is an important effector of poor outcome, and the frequency of hematoma expansion is significantly increased with systemic anticoagulation. Although identification of hematomas at risk for expansion is an area of on-going investigation, it is currently not possible to reliably predict which hemorrhages are at risk and, thus, the majority of anticoagulated VAD patients require rapid anticoagulation reversal. There is little data on anticoagulation reversal strategies in anticoagulated patients with VADs. A small retrospective study evaluated three strategies of reversal in warfarin-anticoagulated VAD patients with intracranial hemorrhage and found that there was no difference in outcome between patients

reversed with prothrombin complex concentrates (PCC), conventional approaches without PCC, or just with stopping the anticoagulants in the case of small hemorrhages [23]. The authors found that reversal was faster with PCC, but there were too few patients and too few adverse events to differentiate outcomes. In acute subdural hemorrhage, similarly to intraparenchymal hemorrhage, acute reversal of anticoagulation is recommended. In convexity (sulcal) SAH, reversal of anticoagulation is generally recommended, and because convexity SAH (as well as some intraparenchymal hemorrhages) in patients with VADs may be related to mycotic aneurysms or infectious arteritis, additional interventional and/or surgical expertise should be sought. One study evaluated stroke subtypes in 110 patients with VADs: there were 31 episodes in 25 patients of intracerebral hemorrhage and 33 episodes in 23 patients of SAH [19]. Vascular abnormalities likely related to infection were found in five of the ten patients who underwent angiography: some vascular abnormalities require interventional treatment to exclude them from the circulation and decrease the chance of rebleeding. There is no data to inform the management of VAD patients with anticoagulation-associated intracranial hemorrhage and thrombocytopenia or concomitant treatment with anti-platelet agents. In the aftermath of acute intracerebral or subdural hemorrhage, decisions about the length of time during which anticoagulation is withheld in patients with VADs should be individualized.

Intracranial hypertension and/or acute obstructive hydrocephalus may complicate large hemorrhages or hemorrhages with intraventricular extension: diagnosis and treatment of intracranial hypertension and acute hydrocephalus requires rapid neurologic and neurosurgical expertise.

In summary, patients with VADs are at increased risk for ischemic and hemorrhagic stroke. While the diagnosis of hemorrhagic stroke is relatively straightforward using non-contrast head CT, clinical ischemic stroke presentations, including delirium, may be elusive to non-experts [33] especially in the post-operative setting and with a normal head CT. Given recent revolutionary advances in the management of acute cerebral large vessel occlusion, failure to rapidly consider cerebral ischemia in the differential diagnosis of post-operative delirium in patients with VADs admitted to the ICU may deprive patients of the opportunity for effective treatment. While the outcome from intracerebral hemorrhage in patients with VADs is generally poor, properly treated patients with VADs and ischemic stroke may go on to recover and receive heart transplants [20]. Other conditions, e.g., hypoglycemia, hydrocephalus, and status epilepticus, may present with acute confusion and result in permanent brain injury and poor outcome if not rapidly diagnosed and treated. Given the preceding discussion, it is important to determine the best institutional resources and protocols for the rapid assessment of the anticoagulated cardiothoracic ICU patient with a VAD presenting with an acute confusional state.

Recommendations Based on the Data

The recommendations below are based on literature addressing the clinical characteristics of patients with VADs, stroke systems of care, and hospitalized patients with acute neurologic changes. Acute confusion in an anticoagulated cardiothoracic

ICU patient with a VAD may be a sign of an immediately actionable cerebral condition including acute ischemic or hemorrhagic stroke. Because ischemic stroke is sometimes elusive; potentially devastating; and treatable, it is important that the responding provider be well-versed with neurologic as well as medical resuscitation. Responding providers need to rapidly recognize and operationalize the requirement for advanced cerebral imaging (e.g., cerebral vascular and/or perfusion imaging; Appendix 1) and expert management (e.g., neurointensive care, neurointerventional therapy, or neurosurgical management). Because hemorrhagic stroke is potentially devastating and may be associated with life-threatening complications such as acute obstructive hydrocephalus or intracranial hypertension, responding providers need to understand the need to immediately reverse anticoagulation, correct thrombocytopenia, and organize expert assistance (e.g., a neurointensivist, neurointerventionalist, and/or neurosurgeon).

In summary, for the optimal assessment and treatment of anticoagulated cardiothoracic ICU patients with VADs presenting with acute MS changes, the responding provider needs to have training and experience in the management of acute neurologic disease, including, specifically, an excellent working knowledge of the neurologic exam and evidence-based acute neurologic resuscitation.

Recommendations

- Anticoagulated cardiothoracic ICU patients with VADs presenting with sudden confusion should be rapidly evaluated for the presence of immediately actionable conditions affecting the brain such as airway instability, hemodynamic instability, hypoglycemia, presence of sedatives, acute ischemic stroke, intracranial hemorrhage, or seizures/status epilepticus (evidence quality high, strong recommendation)
- Responding providers should be trained in neurologic assessment and acute stroke response and should follow evidence-based principles of management of acute cerebral vascular occlusion and anticoagulation-related intracranial hemorrhage (evidence quality high, strong recommendation)
- During the initial emergent evaluation, anticoagulant infusions should be stopped until intracranial hemorrhage is ruled out (evidence quality low, strong recommendation)
- A non-contrast head CT should be performed emergently to evaluate for intracranial hemorrhage or early signs-of ischemia; if the non-contrast head CT is negative for acute injury and there is a clinical suspicion of a large vessel occlusion, advanced imaging including a vascular study should be considered (evidence quality high, strong recommendation)
- In the case of intracerebral hemorrhage, any anticoagulant with residual activity and a reversal strategy should be reversed and thrombocytopenia should be corrected (evidence quality moderate, strong recommendation)

A Personal View of the Data

As a neurointensivist and vascular neurologist with 15 years of experience at three different urban academic centers, I have personally observed the gap in care of hospitalized patients presenting with acute confusional states. In my experience, the first problem is failure on the part of bedside primary providers to recognize a neurologic emergency such as a cerebral vascular event as a cause of the confusional state. Failure of recognition leads to failure of activation of providers with acute neurologic expertise, which leads to failure to treat (or treat in a timely fashion) and poor outcome. The second problem is logistical, i.e., inefficient rapid response processes including transport, radiology, expert provider availability, etc.

In my opinion, there are two types of possible responders to acute neurologic changes in hospitalized patients: (1) general rapid response providers trained in acute neurologic assessment; or (2) stroke team trained in the assessment of non-cerebrovascular etiologies of decompensation. The preferred approach depends on the institutional culture and resources. Regardless of the provider type, the first responder to an anticoagulated cardiothoracic ICU patient with a VAD presenting with acute confusion should quickly institute a process like the one outlined in Fig. 41.1 and Appendix 2, which is based on my personal practice, and the goal of which is resuscitation, maintenance of appropriate (i.e., perfusion matched to the metabolic demand) cerebral perfusion, and diagnosis of immediately actionable conditions including catastrophic structural cerebral disease (e.g., cerebral hemorrhage, hydrocephalus, or cerebral edema); acute cerebral ischemia; hypoglycemia; or status epilepticus.

Patients with VADs who experience an intracranial hemorrhage require particularly vexing decision-making acutely and chronically. Acutely, most patients require specific anticoagulation reversal. As the most-often encountered anticoagulant in VAD patients is warfarin, my approach is to use PCC to rapidly achieve a normal INR in most of the intracerebral and subdural hemorrhage cases. PCCs, compared to plasma, result in a more rapid reversal of the INR and require less volume. If the intracerebral hemorrhage is very tiny (e.g., 1 cc or less) or if it's a convexity SAH and the INR is close to normal, I may choose to withhold the anticoagulant or use plasma instead. I do not routinely use vitamin K, as I anticipate that the patient with VAD will require re-anticoagulation with warfarin at some point in the near future, but I do follow the INR daily for at least 3 days to ensure that there is no "bounce-back". In general, patients with VADs who have experienced an intracranial hemorrhage while anticoagulated are thought to be at high risk for ischemic stroke and device thrombosis if not re-anticoagulated and at high-risk for re-hemorrhage if re-anticoagulated. Unfortunately, there is little data to guide the decision-making. In specific cases, I consider vascular imaging to rule out treatable vascular lesions, e.g., mycotic aneurysms, given that VAD patients are prone to bacteremia. In general, I consider re-anticoagulation after 5–10 days of hemorrhage stability in situations of high immediate embolic risk such as the presence of an acute (or mobile) intracardiac thrombus. In these situations, I counsel the patient and family on the

high risk of both types of complications (ischemia if not re-anticoagulated or recurrent hemorrhage if re-anticoagulated) and initially utilize the so-called "neuro protocol" infusion of unfractionated heparin, i.e., infusion without bolusing and with lower PTT targets. Once the patient shows clinical and imaging (non-contrast head CT) stability after 24 h at goal PTT, I initiate warfarin to achieve the goal INR appropriate for the device type. Barring the high-risk situation, I generally prefer to delay re-anticoagulation for 2–4 weeks after hemorrhage stability.

I have personally not encountered a VAD patient with an intracranial hemorrhage while anticoagulated with target-specific oral anticoagulants. Reversal strategies in patients bleeding while on these agents are in development but, currently, only one (dabigatran) has a specific antidote – I refer the reader to their institutional policy on reversal strategies in these cases. Unfractionated heparin, and to some extent enoxaparin, can be reversed with protamine sulfate. The main benefit of unfractionated heparin infusion is, of course, its short half-life – therefore, it is my agent of choice for initial re-anticoagulation in a VAD patient with a recent intracranial hemorrhage.

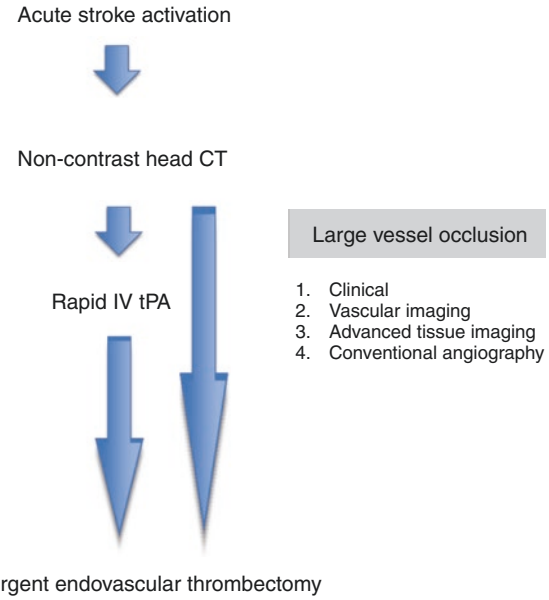
There is no consensus on the management of thrombocytopenia or presence of anti-platelet medications in VAD patients with intracranial hemorrhage. My approach is to initially correct thrombocytopenia to >100,000/microliter (unless contraindicated, e.g., in heparin-induced thrombocytopenia) and maintain platelets at this level for ~48 h, and >50,000/microliter for a week or so, if possible. I do not routinely use ddAVP or transfuse platelets in patients with anticoagulation-related intracerebral hemorrhage and concomitant anti-platelet medications, but others in the field do utilize these options – I refer the reader to their institutional policy on reversal strategies in these cases.

In summary, there is insufficient evidence to provide a more detailed guidance as far as management in specific clinical cases or institutional selection of the optimal type of provider beyond the skills that are needed. Organized stroke response systems and general rapid response systems are structures which can support such expertise and address these difficult decisions. Telehealth is a well-established option for providing high-level, timely stroke expertise and could potentially be adapted to provide this type of service 24-7-365 in the cardiothoracic ICU [34, 35].

Appendix 1

Example of an approach to the patient with VAD presenting with acute confusion focused on determination of potentially actionable cerebral ischemic lesions. Upon the stroke alert, the assessment should proceed as in Fig. 41.1. If the non-contrast head CT is negative for hemorrhage or signs of large territory ischemia, the patient should be screened for intravenous thrombolysis with tissue plasminogen activator (tPA) per institutional protocol. In most institutional protocols, if the INR is 1.7 or greater, the patient is not a candidate for medical thrombolysis. If an acute large vessel occlusion is suspected, the patient can be further evaluated for candidacy for

endovascular thrombectomy. Just how that evaluation is performed depends on physician preference and institutional resources. Options include: proceeding to the angiography suite based on clinical signs suggesting a large vessel occlusion and a normal head CT; obtaining non-invasive vascular imaging with CT angiography or transcranial Doppler (magnetic resonance angiography is usually not an option for patient with a VAD) to demonstrated the vascular occlusion prior to proceeding to angiography; or including tissue-based imaging in addition to the non-invasive vascular study, i.e., CT perfusion, to assess the amount of infarcted versus salvageable tissue before proceeding to angiography (again, magnetic resonance perfusion would not be an option for a patient with a VAD).



Appendix 2

Management of the acutely decompensating ICU patient with a VAD with emphasis on neurologic resuscitation.

Immediately actionable condition	Initial management options
Instability of breathing, respiratory failure	Provide oxygen; non-invasive or invasive ventilatory support as needed
Arrhythmia	Provide entity-specific medical management; cardioversion; pacing

Immediately actionable condition	Initial management options
Hypotension/cerebral hypoperfusion	Place HOB flat; administer IV fluid bolus (unless contraindicated), vasopressors; address etiology of hypotension/relative hypotension (pump-tone-tank)
Hyperperfusion	Lower blood pressure (or cardiac output)
Hypoglycemia	Administer IV thiamine and dextrose; monitor glucose
Drug overdose, over-sedation	Administer antidote, if available; stop sedatives; send toxicology screen
Cerebral vascular occlusion	Augment cerebral perfusion (see hypoperfusion, above); immediately assess for medical thrombolysis (IV tPA) and/or mechanical thrombectomy
Cerebral hemorrhage	Immediately reverse coagulopathy; treat thrombocytopenia; provide neurointensive care; evaluate for surgical and/or interventional options
Seizure/status epilepticus	Administer loading dose of anti-epileptic agent; obtain continuous EEG; schedule anti-epileptic drug levels and maintenance doses
Hydrocephalus	Medically manage elevated ICP; emergently consult a neurosurgeon
Cerebral edema/ herniation	Medically manage elevated ICP; emergently consult a neurosurgeon
Other	Assess presence of other conditions (examples in Fig. 41.1); address specifically with appropriate diagnostics and management Evaluate for underlying chronic conditions contributing to altered mental status, e.g., nutritional deficiencies, chronic organ failure, and dementia Ensure normal metabolic milieu (normoglycemia: blood glucose ~120 to 180 mg/dl; normothermia: body temperature ~36.5 to 38.0 °C)

HOB head of bed, *IV* intravenous, *tPA* tissue plasminogen activator, *EEG* electroencephalogram, *ICP* intracranial pressure, *mg/dl* milligrams per deciliter

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Chapter 42
Acute Ischemic Stroke in the Cardiothoracic Surgery Patient: Thrombolytic Therapy or Mechanical Thrombectomy?

Masoom Desai and Deborah M. Stein

Introduction

Stroke is a devastating complication after cardiac surgery and accounts for substantially higher post-surgical mortality and morbidity. Peri-operative mortality for patients who suffer a stroke post cardiac surgery is considerably higher than those who do not (32.8% vs. 4.9%) [1].

Stroke post cardiac surgery has significant economic consequences with prolonged length of stays in the hospital incurring estimated costs that exceed two to four billion annually worldwide for patients with stroke after CABG [2]. Post-operative stroke significantly increases the number of patients being discharged to long term facilities post cardiac surgery. In addition, there are detrimental effects on quality of life in these patients.

The incidence of stroke post cardiac surgery varies with the risk profile of the patients and the definition of stroke used in different studies. Estimated frequencies are much higher when the radiographic or clinically silent infarcts are included in the definition of stroke. The incidence of peri-operative stroke after cardiac surgery has been reported to be between 0.8% and 9.8% [1]. The incidence of peri-operative stroke varies with the type of the procedure as illustrated in Table 42.1 [3, 4]. In addition, the incidence is higher after an urgent surgery compared to elective surgery. The timing of the stroke has been varyingly reported in the literature as well.

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Table 42.1 Cardio-thoracic surgeries and procedures along with respective incidence of peri-operative stroke [3, 4]

Type of procedure	Incidence of peri-operative stroke (%)
Coronary artery bypass grafting (CABG)	1.7
Ascending aortic graft placement	4.6
Congenital defect correction	1.0
Ventricular assist device	6.2
Cardiac transplant	6.2
Aortic valve surgery	4.8
Mitral valve surgery	8.8
Multiple valvular repair/ replacement surgery	9.7
CABG with valve surgery	3.3–7.4

Approximately 60% of patients present with symptoms immediately after surgery [1]. Thirty to 40% of strokes are reported to occur intraoperatively. Most strokes occur within the first 2 days after surgery and are uncommon after the 1st week [5]. Subtle deficits from strokes may not be detected peri-operatively due to anesthesia and sedation administration. Therefore, the timeline of stroke onset in peri-surgical period can be imprecise.

Risk Factors and Causes of Stroke in Peri-operative Period

To provide appropriate preventative and therapeutic measures, physicians need to be aware of the risk factors and pathophysiology of peri-operative stroke in cardio-thoracic surgery patients.

Pre-operative factors such as history of previous stroke, peripheral vascular disease, hypertension, diabetes, age, sex and presence of carotid stenosis, previous cardiac surgery, pre-operative infection, systolic dysfunction, renal insufficiency and atherosclerosis of the ascending aorta put patients at an elevated risk for neurological complications after cardiac surgery [6].

Contrary to previous belief of hypoperfusion as a leading cause of peri operative stroke, embolic phenomena (cardio-embolic, athero-embolic) are the major etiology of stroke post cardiac surgery. The stroke in the early post-operative period can occur due to manipulation of the aorta and heart, release of emboli from cardiopulmonary bypass pump or less frequently systemic hypotension [4, 6, 7]. Intra-operative risk factors such as prolonged surgical duration and aortic cross clamp time, type of surgical procedure, type of anesthesia and cardiac and metabolic disturbances during the surgery have been described in the literature. Vessel trauma/ dissection, air, fat and paradoxical embolism are some of the other described mechanisms in this population. Post-operative risk factors include myocardial infarction,

atrial fibrillation, heart failure, low ejection fraction, arrhythmias, volume status, blood loss and metabolic derangements.

Uncommonly, intracranial hemorrhages can occur post-cardiac surgery. These are typically due to anti-coagulant/anti-thrombotic usage and/or hypertension. Rarely they are vascular in etiology.

In this chapter, we will review the medical and interventional management of stroke in post-cardiac surgery patients.

Search Strategy

A literature search of English language publications from 2000 to 2017 was used to identify published data on perioperative stroke management after major cardiac/cardiothoracic surgery using the PICO outline (Illustrated in Table 42.2). Databases searched were PubMed, Embase, and Cochrane Evidence-Based Medicine. Terms used in the search were "perioperative stroke treatment", "perioperative stroke management", "post-operative stroke treatment", "post-operative stroke management", "cardio thoracic surgery and stroke", "cardio thoracic surgery and stroke management", "cardiac surgery and stroke" "cardiac surgery and stroke management" "intra operative complications of cardiac surgery", "perioperative complications of cardiac surgery", "stroke and mechanical thrombectomy", "stroke and carotid artery stenting", "stroke and anticoagulation", "cardiac surgery and anticoagulation", "cardiothoracic surgery and anticoagulation", "contraindications to t-PA."

Articles were excluded if they specifically addressed stroke management in non-operative patients or stroke management in non-cardiothoracic surgery. Studies including ≤5 patients were excluded. The data was classified using the GRADE system.

Table 42.2 PICO table for ischemic stroke in CT surgery patients

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Patients undergoing cardiothoracic (CT) surgery	1. Mechanical thrombectomy (MECHANICAL THROMBECTOMY)	Medical management	Improvement in NIHSS, rates of recanalization, modified ranking scale (mRS), rates of secondary intracerebral hemorrhage/ hemorrhagic transformation, rates of complications
	2. Intra-arterial (IA) therapy		

NIHSS NIH Stroke Scale, *ICH* intracerebral hemorrhage

Clinical Evaluation and Diagnostic Studies

Inability of a patient post cardiothoracic surgery to emerge from anesthesia should raise concerns for stroke. Patients who are unable to return to prior baseline neurological exam within first few hours after surgery should prompt a stroke evaluation.

Depending on the availability, either a neurologist or an acute stroke care team should be consulted for a stroke evaluation when there is a concern. After careful consideration of patient factors, suitable treatment plan should be developed promptly and if patient is deemed to be a candidate for mechanical thrombectomy or intra-arterial therapy, an interventional neurology team should receive timely notification.

Computer tomography (CT) scan of the head is an essential screening tool which guides decision- making in emergency management of AIS. It is a AHA/ASA Class 1, Level A recommendation to obtain CT scan emergently before initiating any therapy in acute ischemic stroke [8]. CT was the single imaging tool used in the pivotal **NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE (NINDS) trial** which demonstrated the efficacy of intravenous (IV) tissue plasminogen activator (t-PA) [9].

CT scan is widely available, easy to perform and is an invaluable option in unstable patients. CT scan can aid in excluding an intracranial hemorrhage. CT scan provides an ASPECTS score (Alberta Stroke Program Early CT Score detailed in Table 42.3, Fig. 42.1) which can assist in determining the eligibility of patients with large vessel occlusion for interventional therapy [10].

Randomized control trials (RCT) addressing mechanical thrombectomy in AIS have used different forms of imaging such as CTA head and neck, magnetic resonance angiography (MRA) of the head and neck, digital subtraction angiography (DSA), CT perfusion imaging and diffusion weighted imaging (DWI) magnetic resonance angiography (MRI) as radiographic criteria to determine patient eligibility for mechanical thrombectomy or intra-arterial therapy [8].

Detection of large vessel occlusion (LVO) with the aid of non-invasive vessel imaging, either CTA or MRA can influence decisions on management of AIS in an emergent setting. It is a current AHA/ASA recommendation (Level 1

Table 42.3 Clinical implications of ASPECT score in acute ischemic stroke [8, 64]

ASPECT score (total score = 10)	Clinical implication
ASPECTS <3	Lower chance of good outcome (mRS 0–1 within 90 days)
ASPECTS 3–5	Increased incidence of symptomatic intracerebral hemorrhage post iv t-PA treatment
ASPECTS ≥6	Eligibility criteria for consideration for intra-arterial therapy and mechanical thrombectomy[a]

[a]For different cut-offs for ASPECT score used in MT trials, refer to Table 42.5; *ASPECTS* Alberta Stroke Program Early CT Score

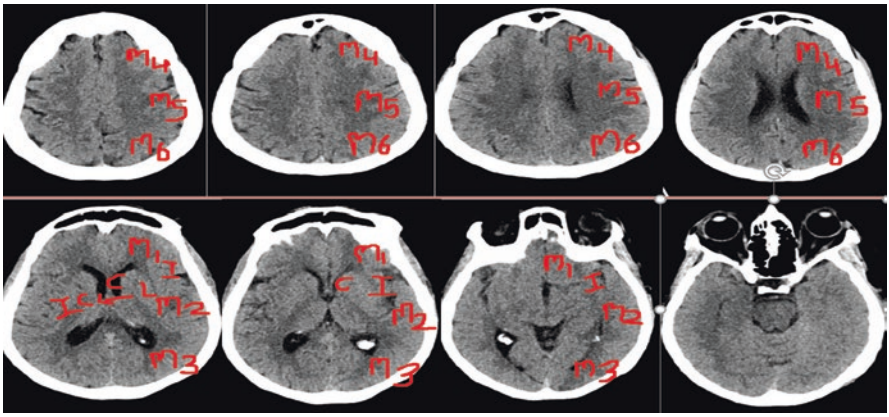

Fig. 42.1 ASPECTS Score derived from non-contrast CT Scan of Head: Illustrated in the figure are axial cut sections of CT scan of head. We are depicting various areas in the brain via a numbering system. ASPECTS score involves ten regions depicted above and is scored based on hypodensities seen in those territories. The total ASPECTS score is out of 10. The ten areas which account for a total of 10 points are described in the picture via numbering. *C* caudate, *I* Insula, *IC* Internal capsule, *L* lentiform nucleus; The above CT scan is obtained from a 70 year old female with RMCA (M1 proximal occlusion). The ASPECTS score was accounted to a seven-tenth after accouding for the hypodensities in M3, M5, M6

recommendation, Class A evidence) to obtain emergent non-invasive imaging in AIS to define eligibility for mechanical thrombectomy [8]. The recent RCTs on mechanical thrombectomy in AIS used non-invasive imaging proven LVO as an inclusion criterion.

CTA head and neck is a preferred choice of imaging in cases where there is concern for a LVO as it is readily available and can be obtained quickly. This form of imaging does need contrast administration, hence would need a careful consideration in patients with prior renal insufficiency. MRA head and neck is another useful imaging modality in AIS. Time of flight protocol MRA can avoid contrast exposure in patients with renal insufficiency. The disadvantage of MRA studies is lack of availability and the time required to obtain the study.

MRI is used to evaluate the acute stroke burden. The DWI sequence is the earliest marker of stroke burden. Acute stroke will appear hyperintense on DWI imaging and hypointense on apparent diffusion coefficient (ADC) imaging, also called as restricted diffusion. Fluid Attenuated Inversion recovery (T2 Flair) appears hyperintense within 6 h post stroke.

CT/MR perfusion studies can be used to identify infarct core size versus ischemic penumbra which is potentially salvageable tissue. The tissue at risk or penumbra will demonstrate a prolonged mean transit time (MTT), reduced cerebral blood flow (CBF) and increased to normal cerebral blood volume (CBV), whereas, the infarcted tissue will have a prolonged MTT, reduced CBF and reduced CBV.

In the recently published DAWN and DEFUSE 3 trials [11, 12], CT perfusion studies in addition to the DWI sequence of MRI were used to define eligibility

Table 42.5 NIH stroke Scale (NIHSS) [8, 9]

Total NIHSS score varies from 0 to 42 points
13 items are tested on NIHSS including Level of consciousness, Answer to questions, performing tasks, extra-ocular movements, visual field assessment, facial palsy, motor exam of all four extremities, limb ataxia/co-ordination, sensory exam on all four extremities, language/aphasia, dysarthria, extinction/inattention
Typically, NIHSS scores >12, especially with cortical signs suggestive of Large vessel occlusion and potential for large hemispheric stroke
Higher scores on NIHSS correlate with greater neurological impairment

criteria for mechanical thrombectomy in patients who presented within 6–24 h of stroke onset in addition to a vessel imaging. An occlusion of the cervical or intracranial internal carotid artery or the proximal middle cerebral artery on CT angiography (CTA) or magnetic resonance angiography (MRA) was a pre-requisite for inclusion in both trials.

Emergent imaging in the form of CT Head should be obtained as a part of stroke evaluation **(high level of evidence; strong recommendation)**. If the case is being considered for a LVO needing mechanical thrombectomy, CTA head and neck should be obtained as non-invasive form of vessel imaging **(high level of evidence; strong recommendation).** Perfusion imaging should be obtained in patients who present beyond the 6-h mark and within 24 h of last known normal **(high level of evidence; strong recommendation).** Clinical core mismatch should be evaluated in these patients to determine eligibility for therapy.

Intravenous t-PA, Intra-arterial t-PA and Mechanical Thrombectomy in Acute Ischemic Stroke

Intravenous t-PA in Acute Ischemic Stroke

The t-PA package insert warns of increased risk of bleeding while using intravenous (IV) t-PA in patients with recent cardiac surgery. The National Institute of Neurological Disorders and Stroke (NINDS) trial excluded patients who had a major surgery within the last 14 days from stroke onset [9]. Patients with a surgery within past 3 months was one of the exclusion criteria for t-PA in the European Co-operative Acute Stroke Study (ECASS) trial as well [13]. Major cardiac surgery in the past 14 days is a relative contraindication for administering intravenous t-PA according the American Heart Association/American Stroke Association (AHA/ASA) guidelines [14].

The risk of bleeding in the surgical bed and the challenge in controlling the potential bleeding are major concerns when delivering t-PA in this population. Careful consideration of the severity of the clinical symptoms and risk of bleeding is required.

The data on using t-PA in post-surgical patients is not robust. There are a few studies that have evaluated the safety of use of t-PA following surgical procedures. In these studies, there is a small subset of patients who received t-PA after a major surgery. In one observational study [15], out of the 51% (n = 499) of the patients received off-label t-PA, eight patients received t-PA post-surgery (not limited to CT surgery). None of these eight patients had systemic hemorrhage but three-eighth patients had poor outcome (mRS 3–6).

One of the largest multi-center retrospective studies analyzing outcomes in acute ischemic stroke post cardiac procedures reviewed 66 cases of AIS and compared the patients who got intravenous t-PA versus those that did not [16]. Twelve (18%) of the patients were treated with thrombolysis, seven with intravenous t-PA and five with intra-arterial t-PA. Neurologic outcomes at 24 h, 7 days and 30 days were assessed with NIHSS (NIH stroke scale Table 42.4) and mRS (modified Rankin Scale Table 42.5).

The median change in NIHSS score from baseline to 24 h, the primary outcome measure of the study, was 6 in the t-PA group and 0 in the non-t-PA group ($p < 0.001$). The improvement in NIHSS score trended toward better outcome with t-PA treatment (median 6.5 vs. 3; $p = 0.07$). There was no statistically significant difference in the rates of discharge mRS 0–1 between the two groups (30% t-PA vs. 28% non-t-PA; $p = 0.72$). No significant differences in cerebral or systemic bleeding events between the two groups was found, and the mortality rate was similar. No symptomatic bleeding complications occurred.

The study had several limitations including too small a sample size to ascertain safety and efficacy in the patient with AIS after cardiac surgery. This retrospective study included patients post all cardiac procedures including cardiac catheterization, hence limits its generalizability to CT surgery population.

In a prospective registry, 134 patients underwent surgery prior to IV t-PA therapy [17]. With reference to the timing of the surgery, the groups were divided into recent

Table 42.4 Categories of modified rankin scale [8, 65]

Modified rankin scale	Patient's ability
0	No symptoms
1	No significant disability despite symptoms; able to carry out usual activities and duties
2	Slight disability; unable to carry out all previous activities but able to look after one's affairs without assistance
3	Moderate disability; requiring some help but able to walk without assistance
4	Moderate severe disability; unable to walk and attend bodily needs without attention
5	Severe disability; incontinent, bed-ridden, and requiring constant nursing care and attention
6	Dead
Pre-stroke mRS (0–1)	Eligibility criteria for mechanical thrombectomy

(within past 1–10 days) which accounted for 49 patients (37%) and non-recent (within past 11–90 days) which accounted for 85 patients (63%). Surgery was classified as major in 86 patients (64%), and in 48 (36%) as minor.

Nine patients (7%) developed surgical site hemorrhage after receiving IV t-PA. Four (3%) had life threatening bleeding requiring intervention; but none were fatal. Rate of intracerebral hemorrhage was 9.7% (13/134). All these patients were however, asymptomatic. Surgical site hemorrhage was prominently higher in recent surgery group compared to non-recent surgery (14.3% versus 2.4%, respectively, odds ratio adjusted 10.73; 95% confidence interval, 1.88–61.27). Overall in-hospital mortality was up to 8.2%.

Limitations of this study include generalizability; selection of patients undergoing general surgical procedure and not limited to CT surgery.

Based on the limited available data, intravenous t-PA is a relative contraindication in patients up to 14 days post cardio-thoracic surgery and cardiac procedures. **(low level of evidence, weak recommendation).**

Intra-arterial Thrombolytic Therapy (Tables 42.6a and 42.6b)

Intra-arterial administration of thrombolytic therapy is an alternative treatment option to intravenous t-PA for stroke in a cardiothoracic surgery patient. Intra-arterial thrombolysis has advantage over intravenous therapy with respect to higher recanalization rate and, possibly, an expanded time window. Lower doses of thrombolytic agent are required, hence there is the theoretical benefit of fewer systemic bleeding complications. This is important in severely affected acute stroke patients with recent surgery or systemic bleeding. Tables 42.6a and 42.6b review studies where intra-arterial thrombolysis was used in post cardiac surgery patients.

A few small retrospective cases studies demonstrated the safety of intra-arterial t-PA within 6 h of onset of peri-operative stroke.

The largest retrospective study by Chalela [18] was a multi-center study involving 6 university hospitals reviewed 36 patients who received intra-arterial therapy within 2 weeks of surgery. Twenty five percent of patients had bleeding complication; three patients had fatal bleeding. Two craniotomy patients had fatal intracerebral hemorrhage and patient had a hemopericardium post CABG resulting in death. The remainder of the patients had minor bleeding at compressible sites.

Good outcome at discharge (defined by Rankin Scale ≤ 2 at discharge) was achieved in 38% of patients who had available data. The median Rankin Scale on discharge, available in 32 of 36 (89%) patients, was 3.5. Mortality occurred in nine (26%) patients; the three with fatal bleeding complications and six (three caused by cerebral edema and three due to systemic issues) unrelated to intra-arterial therapy.

A small retrospective study studied the efficacy and rate of complications of intra-arterial thrombolysis in 13 patients with AIS within 12 days of cardiac surgery, administered in less than 6 h of onset of symptoms [19]. The study demonstrated a similar efficacy of intra-arterial t-PA with 38% (5/13) of patients having improvement

Table 42.6a Intra-arterial t-PA in acute ischemic stroke post cardiac surgery

Author, year of study	Patients/ inclusion criteria	Intervention	Time from stroke onset to intervention	Imaging	Outcomes	Complications	Type of study
Chalela [18]	36 patients with AIS within 2 weeks of surgery Median age-71.5 (45–85) Median NIHSS-17	IA thrombolysis using t-PA or urokinase	Median time of 4.5 h [1–8]	CTH + DSA	Median NIHSS at 24 h – 6.5 and 7-day NIHSS – 8.5. Median ranking score at discharge was 3.5. Rankin score ≤2 achieved by 12 of 32 (38%) of patients at 1 week. Median RS at discharge – 3.5. RS ≤2 achieved by 12 of 32 (38%) of patients at 1 week	9/36 patients had surgical site bleeding out of which 3 were fatal	Multi center retrospective study; very low-quality evidence
Moazami [19]	13 patients; mean age 69±5 years within 12 days of cardiac operation Median NIHSS −18.5	Intra-arterial therapy	Mean of 3.6±1.6 h	CTH + DSA	Recanalization TIMI 3-1, TIMI 2 -6, TIMI 3-6. NIHSS improvement at 1 h occurred in 5/13 patients. 3 patients died	1 patient had hemothorax; 1 patient with incisional bleeding, 3 patients with asymptomatic ICH	Retrospective study; very low-quality evidence

Table 42.6b Intra-arterial t-PA in acute ischemic stroke

Author, year of study	Patients/ inclusion criteria	Intervention	Time from stroke onset to intervention	Imaging	Outcomes	Complications	Type of study
Furlan [20]	180 patients; mean age 64 ± 16; median NIHSS prior to intervention −17	Intra-arterial urokinase in DSA documented MCA occlusion of <6 h duration	Median time to initiation of treatment −5.3 h	CTH+DSA	mRS ≤2 at 90 days -T:40% Vs C:25% – NNT of 7 (p = 0.043). No statistical difference in post intervention NIHSS <1 or less at 90 days between two groups. No statistically significant difference in rate of recanalization between two groups	sICH (11/108) T: 10% Vs C: 2%. Systemic hemorrhage occurred in T: 7% % (9/121) vs 17% (4/59)	Randomized control trial, moderate quality evidence
Ogawa [21]	114 patients mean age 66 ± 9	Intra-arterial urokinase in DSA documented MCA occlusion of <6 h duration urokinase	Mean time to initiation of treatment – 3.75 h	CTH+DSA	mRS 0–2 at 90 days not statistically different between two groups. mRS 0–1 at 90 days (42.1% in the UK group and 22.8% in the control group, $P = 0.045$)	The rates of mortality at 90 days (T:5.3% Vs C:3.5%) and rates of ICH T: 9% & C: 2%	Randomized control trial; moderate quality evidence

AIS acute ischemic stroke, *IA* intra-arterial, *RS* ranking score, *NNT* number needed to treat, *T* treatment group, *C* control group, *DSA* digital subtraction angiography, *TIMI* thrombolysis in myocardial infarction, *sICH* symptomatic intra cerebral hemorrhage

in their NIHSS within 60 min of therapy. Minor systemic bleeding occurred in three patients; asymptomatic intracerebral hemorrhage occurred in three patients.

Two RCTs [20, 21] studied the efficacy and complications of thrombolytic therapy via intra-arterial infusion directly at the site of occlusion. The PROACT II trial evaluated a total of 180 patients with AIS of less than 6-h duration caused by angiographically proven occlusion of the middle cerebral artery [20]. The patients were randomized into two groups, those who received pro-urokinase and the control group. The study demonstrated higher proportion of patients with mRS ≤2 at 90 days (40%) in treatment group than in controls (25%) resulting in a 58% relative benefit and number-needed to treat of 7 (p = 0.043). Symptomatic intracerebral hemorrhage (sICH) rate was 10%.

The MELT trial [21] was stopped early after enrolling 114 patients after t-PA was approved for use in Japan. The patients were randomized into two groups; one group (n = 57) received urokinase and the other group acted as control (n = 57). The primary end-point of favorable outcome (mRS 0–2) at 90 days was higher in the treatment group compared to control but did not reach a level of statistical significance. Secondary end-point of (mRS 0–1) at 90 days was higher in the treatment group than in the control group (42.1% and 22.8%, $P = 0.045$, OR: 2.46, 95% CI: 1.09–5.54). There were notably a higher number of patients with NIHSS 0 or 1 at 90 days in the treatment group than the control group ($P = 0.017$). There was no statistically significant difference between two groups in terms of the 90-day cumulative mortality and intracerebral hemorrhage within 24 h of treatment.

t-PA is the most widely used intra-arterial thrombolytic. Several thrombolytics (urokinase, tenecteplase, reteplase, streptokinase) used in studies in the literature are not approved for use in United States. Moreover, the optimal dose and mode of administration of each thrombolytic is unknown. In the face of a large body of data supporting the safety and efficacy of mechanical thrombectomy in AIS, it has emerged as a preferred choice over intra-arterial therapy.

While intra-arterial t-PA is seldom used as a primary therapy, it might be used as an adjunctive therapy in the management of large vessel occlusion **(low level of evidence, weak recommendation).**

Mechanical Thrombectomy in Anterior Circulation Strokes Due to Large Vessel Occlusion (Table 42.7)

The year of 2015 revolutionized the management of anterior circulation strokes secondary to large vessel occlusion. Five RCTs (reviewed in Table 42.7) favoring mechanical thrombectomy over medical management with intravenous t-PA for large-vessel occlusion in the setting of anterior circulation stroke were published [22–26].

Table 42.7 Mechanical thrombectomy in anterior circulation stroke due to large vessel occlusion

Author, year of study	Patients/inclusion criteria	Intervention	Time from stroke onset to intervention	Imaging	Outcomes	Complications	Type of study
Saver [23]	196 patients; age 18–80;	Solitaire FR (flow restoration) or solitaire 2 device	Median 3.73 h; time window for eligibility– 6 h	CTH +CTP	mRS 0–2 at 90 days: 24.7% ($p < 0.05$)	Mortality: T: 9% vs C: 12% ($p > 0.05$)	RCT; high quality evidence
	NIHSS 8–29;			Rapid soft ware	I:60% Vs C:35% $p < 0.001$; TICI 2b/3 recanalization-88%		
	ASPECTS≥6						
Berkhemer [24]	500 patients; age ≥18; NIHSS≥2	MT with solitaire stent retriever	Median 4.33 h; time window for eligibility- 6 h	CTH+CTA/ MRA/DSA	mRS 0–2 at 90 days: 13.5% ($P < 0.05$)	Mortality: T:44 (18.9%) Vs C:49 (18.4%) ($p > 0.3$)	RCT; high quality evidence
					I:32.6 Vs C: 19.1; $P < 0.05$; TICI 2b/3 recanalization-58.7%	sICH: T: 7.7 Vs C: 6.4% $P > 0.05$	
Goyal [26]	316 patients; NIHSS>5; ASPECTS>5, mod/ good collaterals on CTA	MT with solitaire FR stent retriever	Median 4.1 h; time window for eligibility-12 h	CTH+CTA	mRS 0–2 at 90 days: 23.7% ($p < 0.05$) T: 53% Vs C: 29.3%; $p < 0.001$	Mortality:10.4% Vs 19%	RCT; high quality evidence
						$P = 0.04$	
					TICI 2b/3 re-canalization-72.4%	sICH: T 3.6%vs C:2.7%; $P > 0.05$	
Campbell [22]	70 patients; Eligible for IV t-PA; ischemic core <70 cm^3; evidence of penumbra	MT with solitaire FR stent retriever	Median-3.5 h; time window for eligibility-6 h	CTH+ CTA+CTP	mRS 0–2 at 90 days:31.4% ($p < 0.05$) T: 71% Vs C: 40%; $p = 0.01$; TICI 2b/3 recanalization-84.6%	Mortality T;9% Vs C:20% ($P > 0.05$)	RCT; high quality evidence
				Rapid software		sICH-T:11% Vs 15% $P > 0.05$)	
Jovin [25]	206 patients; Age 18–80; NIHSS≥6; ASPECTS≥7	MT with Solitaire FR stent retriever	Median-4.48 h; time window for eligibility-8 h	CTH+ DWI MRI; ASPECTS >6 on CTH or >5 on DWI	mRS 0–2 at 90 days:15.5% ($p < 0.05$) T:43.7%	Mortality: T:19% Vs C: 16% $P > 0.05$	RCT; high quality evidence
					Vs C: 28.2%	sICH:1.9%Vs 1.9% ($P > 0.05$)	
					TICI 2b/3 recanalization-65.7%		

Nogueira [11]	206 patients; age ≥18; pre-stroke mRS 0–1 divided into three groups based on age, NIHSS and infarct volume[a]	MT with Trevo stent retriever	Median[b]- 4.8 h; time window for eligibility- >6 h and <24 h	CTH+ CTA/ MRA+ CTP/ DWI sequence/MR perfusion using	Mean UmRS- T: 5.5 and C:3.4; functional independence at 90 days- T:49% and C:13%; both outcomes statistically significant; TICI 2b/3 recanalization- 90 (84%)	Mortality: T:20 (19%) and C: 18 (18%)	RCT; high quality evidence
	Median NIHSS -17			RAPID software		sICH: 6 (6%) and 3 (3%), both not statistically significant	
Albers [12]	182 patients; age ≥18; initial infarct volume of <70 cc; a ratio of volume of ischemic tissue to infarct volume of ≥1.8 and an absolute volume of potentially reversible ischemia of ≥15 cc	MT performed with any FDA approved thrombectomy device	Median- 10:53 h; time window for eligibility >6 h and <16 h	CTH+ CTA/ MRA+ CTP/ DWI sequence/MR perfusion using RAPID software	Median mRS 0–2 at 90 days: T: 3 and C: 4; functional independence at 90 days- T:45% and C: 17%; both outcomes statistically significant; TICI 2b/3 recanalization-69(76%)	Mortality: T:13(14%) and C: 23 (26%)	RCT; high quality evidence
						sICH: 6 (7%) and C: 4 (4%)	

Rapid software (iSchemaView ©) for penumbral imaging, *RCT* randomized control trial, *mRS* modified ranking scale, *IAT* intra-arterial therapy, *MRA* magnetic resonance angiography, *DSA* digital subtraction angiography, *T* treatment group, *C* control group, *CTA* CT angiography, *IV* intravenous, *sICH* symptomatic ICH rates, *MT* mechanical thrombectomy, *UmRS* Utility weighted mRS_*, *DWI sequence* Diffusion Weighted imaging, *Mortality* mortality at 90 days, *TICI 2b/3 recanalization* TICI 2b/3 recanalization in treatment group

[a]Group A: Age ≥80; infarct volume <21 ml and NIHSS ≥10. Group B: Age <80; infarct volume <31 ml, NIHSS ≥10 Group C Age >80; NIHSS ≥20; infarct volume 31–51 ml;

[b]Study consists of large number of wake-up strokes and unwitnessed onset; Median time- Median time from first witnessed symptom to randomization

According to the AHA/ASA 2018 guidelines [8] there is a Class I (strong) recommendation (Level of Evidence A) for mechanical thrombectomy in AIS if all the following criteria are met:

1. Pre-stroke modified Rankin Scale (mRS) score of 0–1
2. AIS receiving iv t-PA within 4.5 h of onset
3. Causative occlusion of the internal carotid artery (ICA) or proximal middle cerebral artery (MCA; M1 segment).
4. Age ≥18 years
5. NIHSS score of ≥6
6. Alberta Stroke Program Early CT Score (ASPECTS) of ≥6
7. Time from onset to groin puncture is 6 h

The trials evaluating safety and efficacy of mechanical thrombectomy used it as an adjunct to intravenous t-PA therapy. This is important to note, when generalizing the results of the RCTs to post-cardio thoracic surgery patient cohort.

A recent meta-analysis of the 5 RCTs [22–26] on mechanical thrombectomy therapy was conducted by the HERMES collaborators [27]. In this analysis, the efficacy of mechanical thrombectomy in a subgroup of patients who were ineligible for t-PA was studied. A total of 188 patients who did not receive t-PA but had received endovascular intervention were studied. This subgroup consisted of 108 patients in the intervention arm and 80 patients in the control arm. 43.5% of patients in the intervention arm achieved a mRS of 0–2 compared to 22.3% of patients in the control group. The odds ratio (OR) of 2.43 (1.30–4.55) favored the intervention group with regards to the outcome measure of mRS 0–2 at 90 days. There was no statistical difference between those patients that did not receive t-PA (n = 188) compared to those who did receive t-PA in terms of primary outcome. P value = 0.43.

A recent pooled analysis from the SWIFT and STAR studies comparing combined intravenous t-PA and mechanical thrombectomy versus mechanical thrombectomy alone used data from 291 patients treated with mechanical thrombectomy included in 2 large multicenter trials [28]. Fifty-five percent (n = 160) received intravenous thrombolysis in addition to mechanical thrombectomy, and 45% (n = 131) underwent only mechanical thrombectomy. The study did not find any statistically significant difference between the two groups in terms of functional independence at 90 days, mortality at 90 days, procedural complications and radiographic recanalization.

The DAWN trial compared mechanical thrombectomy to best medical management in patients (age ≥18 and baseline mRS 0–1) who presented between 6 and 24 h of onset of AIS due to large vessel occlusion (middle cerebral artery (MCA)M1 or intracranial internal carotid artery) and had a clinical imaging mismatch, either with CT-perfusion imaging or DWI sequence MRI [11]. A total of 206 patients were enrolled; 107 patients were assigned to the thrombectomy group and 99 patients to the control group. The study showed better co-primary outcomes (utility-based mRS and mRS) at 90 days in the thrombectomy group compared to the control group. The rates of symptomatic intracerebral hemorrhage and 90-day mortality were similar between the two groups.

Extended time limit for mechanical thrombectomy is also supported by the the latest DEFUSE 3 trial which was terminated prematurely due to the results from the DAWN trial supporting intervention past 6 h [12]. In this multi-center trial, 182 patients (age 18–90 years; baseline mRS 0–2 and NIHSS >6) underwent randomization (92 to the endovascular-therapy group and 90 to the medical-therapy group). Additional eligibility criteria for the DEFUSE trial consisted of infarct volume <70 ml on imaging and absolute volume of penumbra ≥15. Endovascular therapy plus medical therapy, as compared with only medical therapy was associated with a statistically significant difference in the percentage of patients who were functionally independent, defined as a score on the mRS of 0–2 (45% vs. 17%, $P < 0.001$). The 90-day mortality rate was 14% in the thrombectomy group and 26% in the medical treatment group ($P = 0.05$). There was no significant between-group difference in the frequency of symptomatic intracranial hemorrhage (7% and 4%, respectively; $P = 0.75$) or of serious adverse events (43% and 53%, respectively; $P = 0.18$).

The best evidence of mechanical thrombectomy with the new devices (Solitaire™ and *Trevo*® retrievers) in patients post cardiothoracic surgery are from case series [29, 30]. Although, the management of patients developing AIS post cardiac surgery compared to general population should be similar other than careful consideration of t-PA. Figures 42.2 and 42.3 illustrate a case of a 60-year old female s/p coronary artery bypass graft who developed a RightMCA stroke due to a RightM1 proximal occlusion. Patient was deemed not a candidate for intravenous t-PA since she was post-operative day 1 from her surgery. The time of onset of the acute stroke in this

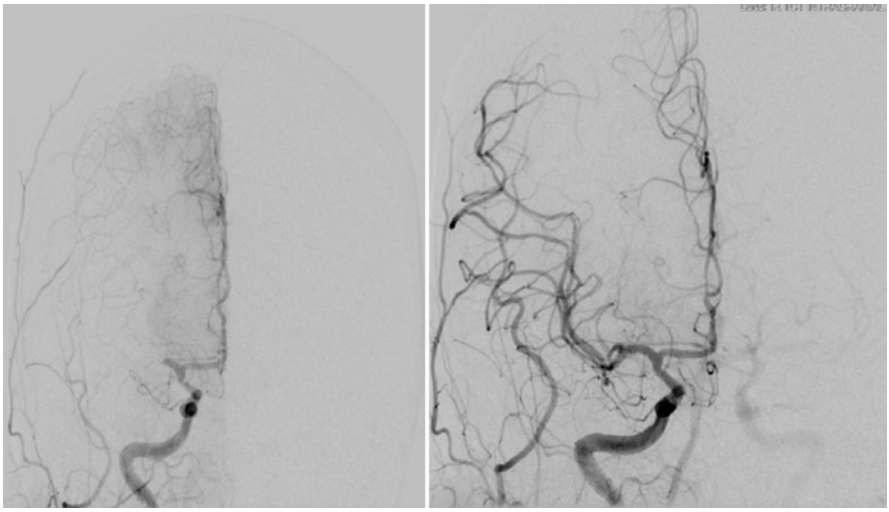

Fig. 42.2 Digital substraction angiography pre and post mechanical thrombectomy in a patient post CABG: The figure is illustrating a rightcommon carotid injection of dye. The first shot is demonstrating a proximal right middle cerebral occlusion. Evident is not only the occlusion but dimished flow in the entire right middle cerebral artery territory. Second shot depicts a post mechanical thrombectomy picture with complete revascularization of the right middle cerebral artery

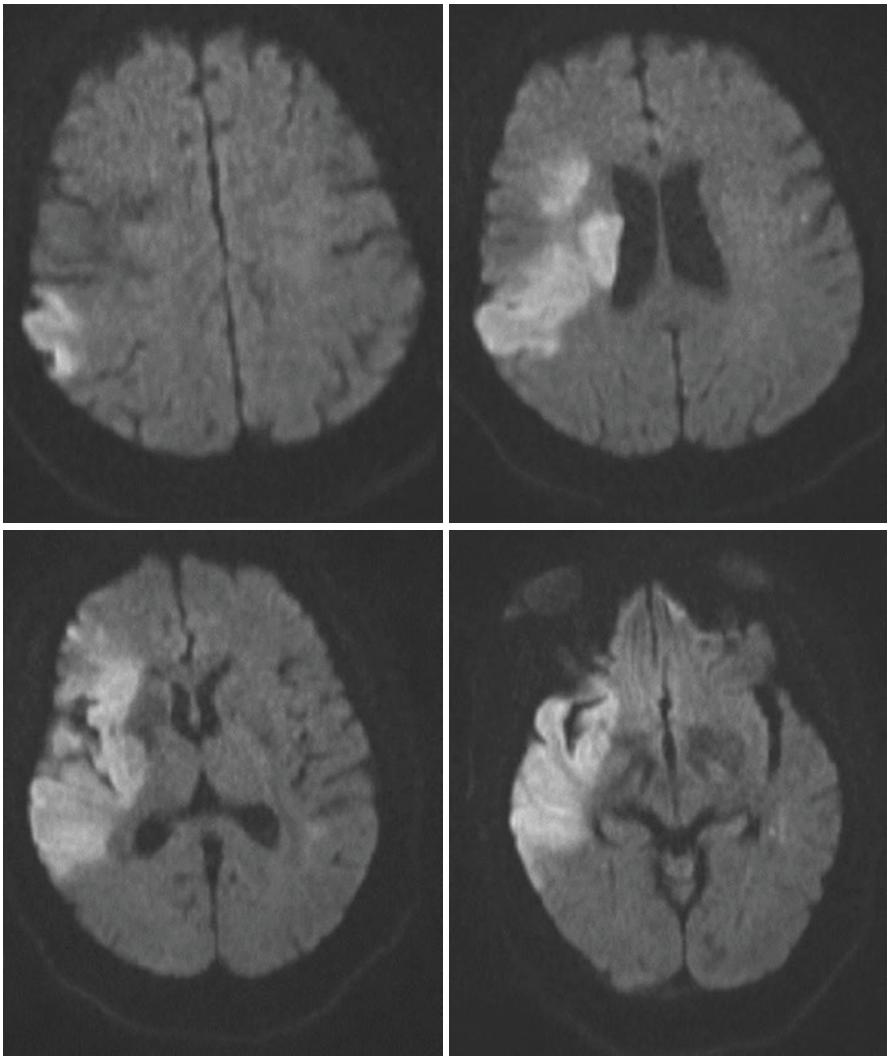

Fig. 42.3 MRI brain diffusion weighted sequence (DWI) of the patient prior to mechanical thrombectomy. Depicted in the picture below are axial cut sections from a DWI sequence of MRI Brain of the patient with right middle cerebral artery infarct. This imaging was performed as a part of evaluation for mechanical thrombectomy since her last known normal was unknown and she was post operative day 1 post surgery.The imaging shows sparing of some of the deeper structures and posterior temporal lobe supplied by the middle cerebral artery

case was unknown. A DWI sequence was obtained to assess for a clinical core mismatch after determining her NIHSS to be 21. As seen on the DWI sequence, the infarcted territory was sparing the deep structures as well as posterior temporal lobe. Patient underwent a mechanical thrombectomy at 16 h from onset of stroke. Over the course of next 24 h, her NIHSS improved 21(left face, arm and leg plegia,

sensory deficits and forced right gaze deviation and visuospatial neglect)→ 12 notable for improvement in the left sided weakness, sensory deficits, visuospatial neglect and ability to cross midline on gaze assessment.

Thus, mechanical thrombectomy is an effective option for patients with AIS post cardiothoracic surgery who meet the eligibility criteria **(high level of evidence, strong recommendation).** Patients who present beyond the 6 h mark with a large vessel occlusion should be assessed for a clinical core mismatch using CT perfusion or DWI sequence MRI. Patients who have a significant clinical core mismatch should be considered for thrombectomy beyond the 6-h cut-off **(high level of evidence, strong recommendation).**

Posterior Circulation Strokes Due to Large Vessel Occlusion (Table 42.8)

Posterior circulation strokes due to large vessel occlusion have the highest morbidity and mortality rates of all strokes.

The American Heart Association/American Stroke Association (AHA/ASA) guidelines [8] for the management of patients with posterior circulation stroke suggests that thrombectomy may be reasonable in carefully selected patients with posterior circulation strokes, when initiated within the first 6 h of stroke onset (Class IIb, Level of Evidence C). Important trials assessing role of mechanical thrombectomy in posterior circulation strokes due to large vessel occlusion are reviewed in the text below as well as in the Table 42.8.

A prospective single-center study [31] included 31 patients with acute ischemic stroke attributable to acute basilar artery occlusion treated within the first 24-h after onset of symptoms with the Solitaire device. Recanalization post-procedural grade 2–3 TICI flow in 23/31(74.2%) of patients. 11/31 patients (35%) of the patients achieved mRS 0–2 at 90 days. 10/32 patients (32%) of the patients died. 5/31 patients (16%) had symptomatic intracerebral hemorrhage.

In addition, a multicenter retrospective analysis [32] consisting of 100 patients, mean age 63.5 ± 14.2 years, mean NIH Stroke Scale 19.2 ± 8.2 reviewed posterior circulation strokes that received mechanical thrombectomy. Favorable outcome at 3 months (mRS ≤2) was achieved in 35% of patients. Successful recanalization was achieved in 80 (80%) cases. Symptomatic intracerebral hemorrhage occurred in five patients (5%). Mortality rate during hospitalization was 30%. Successful recanalization and shorter time from stroke onset to the start of the procedure were significant predictors of favorable clinical outcome at 90 days.

A multicenter observational study [33] using the ENDOSTROKE registry consisting of 148 patients (median age 71, median NIHSS 20) with angiographically confirmed basilar occlusion was performed. Recanalization post procedure TICI 2b-3 grade was achieved by 111 (79%), and mRS (0–2) achieved by 50 (34%). Thirty-five percent of patients had death and rate of ICH was 6%.

Table 42.8 Mechanical thrombectomy in posterior circulation stroke

Author, year of study	Patients/inclusion criteria	Intervention	Time from stroke onset to intervention	Imaging	Outcomes	Complications	Type of study
Mourand [31]	31 patients with basilar occlusion; Mean ± SD age 61 ± 17 years of age; median NIHSS-38; median GCS-7	Mechanical thrombectomy with solitaire stent retriever	<24 h	CTA/MRA followed by DSA	Successful recanalization TICI 3 or 2b: 23/31 (74%) patients. mRS (0–2): 11/31 (35%)	Mortality rate 32% (10/31) sICH:(5/31) 16%	Prospective single center study; low quality evidence
Mokin [32]	102 patients with posterior circulation occlusion; mean age 63.5 ± 14.2; Mean NIHSS 19.2 ± 8.2	Mechanical thrombectomy with stent retriever/primary aspiration thrombectomy	<24 h	CTA/MRA and MRI	Successful recanalization TICI 3/2b: 80/100 (80%). mRS (0–2): 35/100 (35%) at 90 days	Mortality rate: 30/100 (30%); sICH 5/100 (5%)	Multi-center retrospective study; low quality evidence
Singer [33]	148 patients with angiographically confirmed basilar occlusion; median age 71; median NIHSS -20	Mechanical thrombectomy with stent retriever	<24 h	CT/MRI + DSA	Successful recanalization TICI 3/2b: 111/148 (79%) mRS (0–2):50/148 (34%)	Mortality rate:35% ICH: 9/148 (6%)	Multi-center retrospective study; low quality evidence

CTA CT angiogram, *DSA* Digital subtraction angiography, *TICI* thrombolysis in cerebral infarction scale, *mRS* Modified rankin scale, *sICH* Secondary intracranial hemorrhage scor

To summarize, there is no randomized control trial looking at the role of mechanical thrombectomy in posterior circulation strokes. However, considering the high fatality and morbidity associated with posterior circulation strokes, mechanical thrombectomy is a reasonable option in patients with stroke post cardiac surgery within 6 h **(low level of evidence, moderate recommendation).**

If the time of onset of stroke is not known or patients present beyond the 6-h intervention window, imaging modality preferably an MRI brain or CT scan head can be obtained. This can aid in assessing the clinical-core mismatch and determine the eligibility for mechanical thrombectomy.

Acute Ischemic Stroke Due to Internal Carotid Artery Occlusion

Internal carotid artery (ICA) occlusion is a rare etiology for AIS in patients post cardiac surgery. AIS due to ICA occlusion carries significant morbidity and mortality. An occluded ICA puts the patient at high risk of large hemispheric infarct.

In one prospective study, 50 consecutive patients with complete or near-total occlusion of the ICA were treated with aspiration, angioplasty, and/or stent placement in conjunction with retrieval devices [34]. Successful recanalization (TICI grade >2) was achieved in 90%, and mRS score <2 at 6 months was obtained in 30 of 50 patients (60%).

Another retrospective study analyzing the efficacy of endovascular therapy for ICA occlusion evaluated 25 patients with acute and subacute presentations [35]. Ninety percent of patients had successful revascularization with carotid artery stenting. Among the 23 successfully revascularized patients, 10 exhibited an improvement in their NIHSS by >4 points at 24-h follow-up. Out of the ten patients, three had acute presentations within 6 h and seven patients presented in a subacute fashion. Good outcome at 30 days, defined as mRS ≤2, was noted in 5 of 15 patients presenting within 6 h (33%) and 7 of 8 patients (88%) with subacute presentation.

There are no data that directly addresses the treatment of patients with ICA occlusion post cardiac surgery. A patient's prior comorbidities, baseline functional status as well as adequate hemodynamic stability would need to be ascertained before making decisions in these complex cases post cardiac surgery.

Thus, endovascular therapy in proximal internal carotid artery occlusion may be considered based on the individual case. **(very low-level evidence, weak recommendation)**

Medical Management of CABG Patients in Peri-operative Period to Reduce Incidence of Stroke

Pre-operative Period

Does On/Off Pump CABG Matter?

Traditional CABG requires a heart lung machine, cross clamping of the aorta and cardioplegic arrest; all of which carry significant post-operative ramifications. Despite these theoretical concerns, there is no conclusive data that "off- pump" CABG is superior to "on-pump" CABG with respect to neurological complications.

The three major trials comparing on pump and off pump CABG showed similar prevalence of death, stroke, and acute renal failure at 30 days among patients who underwent off-pump CABG and those who underwent on-pump CABG [36]. Both the ROOBY [37] and the CORONARY [38] trials demonstrated that the off-pump group had a higher rate of incomplete vascularization at 1 year. However, the two trials differed in their 5-year outcomes. CORONARY trial showed no significant differences in the prevalence of death, nonfatal stroke, non-fatal myocardial infarction, nonfatal new renal failure, or repeat revascularization, as well as the prevalence of their composite outcomes (consisting of death from any cause, repeat revascularization, and nonfatal myocardial infarction). On the other hand, the ROOBY trial suggested that the 5-year prevalence of death from any cause (15.2% in the off-pump group vs. 11.9% in the on-pump group, $P = 0.02$) and of the composite outcome were higher among patients who underwent off-pump CABG than those who underwent on-pump CABG (31.0% vs. 27.1%, $P = 0.046$).

There are several limitations associated with the above trials including the risk profile of the patients included, the surgeon's experience and selection bias. A recent meta-analysis of studies looking at high risk patients with on-pump and off-pump CABG suggested that the incidence rate of post-operative neurologic complications in patients undergoing off-pump CABG was significantly lower (OR = 0.56; 95% CI: 0.43–0.75; $z = 3.98$ $P < 0.0001$) [39].

Hence, the benefit of on-pump versus off-pump with regards to prevention of neurologic complications is a controversial topic (strong level of evidence, moderate recommendation).

Carotid Artery Stenosis: When to Screen and When to Intervene?

Although symptomatic carotid disease is associated with a greater risk of stroke, >50% of patients suffering stroke after CABG do not have significant carotid disease. Even in patients who suffer strokes after cardiac surgery and have carotid disease, a major proportion of the strokes cannot be explained by the carotid disease or stenosis.

A multidisciplinary team approach consisting of a cardiologist, cardiac surgeon, vascular surgeon, and neurologist is recommended for patients with clinically significant carotid artery disease for whom CABG is planned per the American College of Cardiology/American Heart Association (ACC/AHA) guidelines enlisted in Table 42.9 [40]. Selective non-invasive screening of high risk patients such as age >65 years, left main coronary stenosis, peripheral arterial disease, history of cerebrovascular disease, hypertension, smoking, and diabetes mellitus is reasonable [41, 42].

In patients with a history of prior cerebrovascular events (stroke/transient ischemic attack who have a significant carotid artery stenosis (50–99% in men or 70–99% in women), the likelihood of a post-CABG stroke is high; as a result, they are likely to benefit from carotid re-vascularization [40] .The NASCET (North American Symptomatic Carotid Endarterectomy trial [43] demonstrated significant benefit in patients who had significant carotid stenosis (70–99%) in patients who received medical management plus carotid endarterectomy (CE) compared to those who received medical management alone. The 2-year ipsilateral stroke risk was 26% in the medically managed arm and 9% in the group who received CE in

Table 42.9 ACC/AHA guidelines for coronary artery bypass graft that reduce the incidence of post op strokes [40, 49]

Treatment	ACCF/AHA guidelines 2011
Aspirin	Current guidelines suggest that aspirin should be given pre-operatively and should be resumed within 6 h post-operatively
Statins	All patients undergoing CABG should receive statin unless contraindicated
Beta blockers	Beta blockers should be administered at least 24 h before CABG to all patients without contraindications
	Beta blockers should be reinstituted in all patients without contraindications as soon as possible after CABG if not started in the pre-operative period
Epi-aortic ultrasound imaging	Routine epi-aortic ultrasound scanning is reasonable to evaluate the presence, location, and severity of plaque in the ascending aorta to reduce the incidence of athero-embolic complications
Carotid artery screening	A multi-disciplinary approach for patient with clinically significant carotid artery disease who is planned for a CABG
	Carotid artery duplex scanning is reasonable in selected patients who are considered to have high-risk features
Carotid artery re-vascularization	In the CABG patient with a previous TIA or stroke and a significant (50–99%) carotid artery stenosis, it is reasonable to consider carotid revascularization in conjunction with CABG
	In the patient scheduled to undergo CABG who has no history of TIA or stroke, carotid revascularization may be considered in the presence of bilateral severe (70–99%) carotid stenosis or a unilateral severe carotid stenosis with a contralateral occlusion
Atrial fibrillation and Anti-coagulation	In post-CABG, atrial fibrillation that is recurrent or persists more than 24 h, warfarin anticoagulation for 4 weeks is probably indicated

TIA transient ischemic attack

addition to medical management ($p < 0.001$). In patients with 50–69% symptomatic stenosis, the 5-year rate of ipsilateral stroke was 15.7% in arm treated with medical management + CE and 22.2% in arm who received medical management alone (ARR 6.5%, NNT = 15.4, $p = 0.045$). There was no statistically significant difference in patients with <50% symptomatic stenosis, with a 5-year rate of ipsilateral stroke of 14.9% in the CE group and 18.7% in the medical management group ($p = 0.16$).

The ACAS (Asymptomatic Carotid Atherosclerosis trial) [44] and the ACST (Asymptomatic Carotid Surgery trial) [45] addressed the role of CEA for asymptomatic carotid artery stenosis. In the ACAS trial, 1662 patients with asymptomatic carotid artery stenosis of 60% or greater stenosis were randomized into two groups: CEA+ medical management and medically managed group. The cumulative risk over a 5-year period of ipsilateral stroke; perioperative stroke or death was estimated to be 5.1% for surgical patients and 11.0% for patients treated medically (aggregate risk reduction of 53% [95% CI, 22–72%]).

In addition, ACST [45] randomized 3120 patients with >60% asymptomatic carotid artery stenosis into CEA and medical management versus deferred CEA in addition to medical treatment. In a 10 year follow up of the study, there was no significant difference between the immediate CEA versus the deferred CEA in terms of the peri-operative stroke and death (within 30 days of CEA) at 5 and 10 years. However, there was statistically significant difference between non-peri-operative stroke risk, any stroke and peri-operative death at 5 and 10 years between the two groups ($p < 0.05$). Hence, CABG alone can be performed safely in patients with asymptomatic unilateral carotid stenosis because a carotid revascularization procedure offers no clear benefit in the incidence of peri procedural stroke or death in these individuals.

Recent meta-analysis [46] of randomized control trials comparing CEA versus Carotid artery stenting (CAS) in symptomatic and asymptomatic patients suggested that endarterectomy has more favorable peri-procedural and long-term stroke outcomes, as well as composite primary outcomes (i.e., stroke or death). Peri-procedurally, CAS was associated with a lower risk of myocardial infarction (OR: 0.51; 95% CI: 0.33–0.80; P = 0.003) but a higher risk of death or stroke (the composite endpoint, OR: 1.76; 95% CI: 1.38–2.25; P < 0.0001).

Hence, for symptomatic carotid artery stenosis, CEA should be the first line of management. (High level of evidence, strong recommendation) CAS is a reasonable alternative in high risk patients for CEA (Moderate level of evidence, Moderate recommendation).

Whether the carotid and coronary revascularization procedures are performed simultaneously or in a staged, sequential fashion is a controversial topic, especially since statistically significant benefit of peri-procedural stroke risk reduction has not been established [47].

In summary, a multi-disciplinary team approach consisting of cardiologist, cardiac surgeon, vascular surgeon and neurologist is recommended for patients with clinically significant carotid stenosis prior to surgery.

Intra-operative and Post-operative Period

Anticoagulation in Patients with a Stroke Post Cardio-thoracic Surgery

Aspirin administration within 6 h post-CABG improves outcomes and is currently a AHA Level 1 Class A recommendation for secondary prevention in post-CABG patients [48]. Uncontrolled atrial fibrillation lasting for more than 48 h, venous thrombo-embolism, reduced left ventricular function, left ventricular or atrial thrombus are a few indications for anticoagulation post CABG. In cases of valvular heart disease and surgery, early anticoagulation post-surgery especially in patients at high risk of thrombosis and with mechanical valve is recommended according to the 2017 ACC/AHA guidelines depicted in Table 42.9 [49] on management of patients with valvular heart disease.

This poses a dilemma in patients post cardiac surgery who suffer an ischemic stroke with respect to the following issues: (1) When is it safe to start anticoagulation? (2) What should be the approach of management of patients who are already on anticoagulation? and (3) Are there predictors of hemorrhagic transformation of an AIS?

A recent Cochrane review analyzing 24 trials involving 23,748 participants suggested no benefit of early anticoagulation therapy within first 14 days after stroke onset in terms of odds of death from all causes (OR 1.05; 95% confidence interval (CI) 0.98–1.12) [50]. There was no evidence suggesting that early anticoagulation reduced the odds of being dead or dependent at the end of follow-up (OR 0.99; 95% CI 0.93–1.04). Although early anticoagulant therapy was associated with fewer recurrent ischemic strokes (OR 0.76; 95% CI 0.65–0.88), it was linked to an increase in symptomatic intracranial hemorrhages (OR 2.55; 95% CI 1.95–3.33). Similarly, early anti-coagulation reduced the frequency of symptomatic pulmonary emboli (OR 0.60; 95% CI 0.44–0.81), but this benefit was offset by an increase in extracranial hemorrhages (OR 2.99; 95% CI 2.24–3.99).

In addition, a meta-analysis including 7 randomized trials with 4624 patients comparing anticoagulants started within 48 h, with other treatments (aspirin or placebo) in patients with acute ischemic cardioembolic stroke suggested that anticoagulants were associated with a non-significant reduction in recurrent ischemic stroke within 7–14 days (3.0% versus 4.9%, odds ratio 0.68, 95% CI: 0.44–1.06, P = 0.09, NNT = 53) [51]. There was a significant increase in symptomatic intracranial bleeding (2.5% versus 0.7%, odds ratio 2.89; 95% CI: 1.19–7.01, P = 0.02, NNH = 55). The study showed no substantial difference in death or disability at final follow up (73.5% versus 73.8%, OR 1.01; 95% CI: 0.82–1.24, P = 0.9).

If the patients on anticoagulation suffer a stroke, currently, there lacks robust data addressing the question of reversal of anticoagulation in this population. Risk of further strokes with reversal of anticoagulation and worsening prothrombotic states versus elevated risk of hemorrhagic conversion on therapeutic anticoagulation poses dilemma in management of these patients. The major concern with anticoagulation after AIS is the risk of hemorrhagic conversion. Factors such as poor

collaterals, timing of starting anticoagulation, atrial fibrillation and embolic stroke, hyper-dense vessel sign on imaging have been associated with increased risk of hemorrhagic transformation of ischemic stroke. A retrospective study was performed in patients with AIS who had indications for anticoagulation to evaluate factors associated with hemorrhagic transformation. Among 99 patients anticoagulated for various indications, age (OR 1.50 per 10 years, 95% CI 1.07–2.08), total infarct volume (OR 1.10 per 10 cc's, 95% CI 1.06–1.18), and estimated glomerular filtration rate (eGFR) (both linear OR 1.03 per 1 mL/min/1.73m^2 improvement, 95% CI 1.01–1.06) were associated with hemorrhagic transformation of an AIS [52]. Later in a prospective cohort study these variables were validated and area under the curve (AUC) comparing predicted odds of hemorrhage (HeRS score) to actual hemorrhage was close to 0.854 [53].

To summarize, anticoagulation management in post cardiac surgery patients is challenging in the setting of an AIS. In the setting of cardio-embolic stroke due to a large vessel occlusion with sizeable volume of infarct, withholding anticoagulation for 7–10 days, at times up to 2 weeks, depending on the indication is recommended **(high level of evidence, strong recommendation).**

The decision needs careful clinical judgement, weighing the benefits of anticoagulation versus risks of hemorrhagic transformation of stroke and bleeding.

Optimal Blood Pressure Management

Blood pressure goals during and post cardiac surgery is a controversial topic. Factors such as bleeding from surgical site or other organs, hemodynamic stability and cardiac status, adequate cerebral perfusion and the individual autoregulatory curve should considered while setting blood pressure targets.

In a randomized study, the incidence of cardiac and neurologic complications, including stroke, was significantly lower when the mean systemic arterial pressure was 80–100 mm Hg during CABG, as compared with 50–60 mm Hg, suggesting that a higher mean systemic arterial pressure during CABG is safe and improves outcomes [54]. Another study suggested that intra-operative blood pressure should be targeted in relation to pre-operative baseline blood pressures [55]. Prolonged changes of more than 20 mm Hg or 20% in relation to pre-operative levels result in peri-operative complications. Efforts to sustain intra-operative and early post-operative blood pressure to the patient's pre-operative range can reduce the risks of peri-surgery stroke and mortality [56].

Once a patient has suffered an AIS, there is a lack of robust data to guide management of blood pressure. In one retrospective study involving 3 centers and a total of 228 patients after mechanical thrombectomy (mean age 65.8 ± 14.3; 104 males, 45.6%), maximum systolic blood pressure independently correlated with a worse 90 day mRS and hemorrhagic complications within 48 h (adjusted OR = 1.02 [1.01–1.03], $P = 0.004$; 1.02 [1.01–1.04], $P = 0.002$; respectively) in multi-variable analyses, after adjusting for several possible confounders [57].

Current AHA/ASA guidelines [8] addressing blood pressure management after any AIS directed recanalization suggest targeting a BP goal of <180/105.

Systemic and cerebral perfusion should be kept in mind while deciding on blood pressure goals in patients with AIS post cardiac surgery.

Thus, maintaining a blood pressure goal after MT which optimizes the cerebral perfusion pressure without increasing the risk of hemorrhage and is amenable to patient's cardiac status should be considered **(very low-level evidence, moderate recommendation).**

Beta-Blockade in Cardio-thoracic Surgery Patients

Beta blockers administration is used as a quality metric, both pre-and post-cardiac surgery. The ACA/AHA guidelines [40] recommend using beta-blockers at least 24 h before CABG in all patients without contraindication. However, the benefit of beta blockade has been debated in the literature.

A multi-center observational study [58], using the Society of Thoracic Surgeons National Adult Cardiac Surgery Database to assess beta blocker use and outcomes among 629,877 patients undergoing isolated CABG showed that the patients who received beta-blockers had lower mortality rates than those who did not (unadjusted 30-day mortality, 2.8% vs 3.4%; OR, 0.80; 95% confidence interval [CI], 0.78–0.82). A recent retrospective analysis by Brinkman involving 506,110 patients undergoing non-emergent CABG surgery excluded the patients with recent myocardial infarction [59]. The results of the study contradicted the previous literature suggesting that patients who received pre-operative beta blockers within 24 h of surgery had higher rates of new-onset atrial fibrillation when compared with patients who did not (21.50% vs 20.10%; OR, 1.09 [95% CI, 1.06–1.12]; P < .001). There was no difference in the incidence of stroke (0.97% vs 0.98%; OR, 0.99 [95% CI, 0.89–1.10]; P = .81). The study had several limitations, one being its retrospective nature.

A recent meta-analysis by Wiesbauer included RCTs comparing beta blockers with placebo in a cardiac surgery population suggested that beta blockers reduced the frequency of ventricular tachyarrhythmias (OR 0.28, 95% CI 0.13–0.57), atrial fibrillation/flutter OR (0.37, 95% CI 0.28–0.48) and supraventricular arrhythmias (OR: 0.25, 95% CI 0.18–0.35) and myocardial ischemia (OR: 0.49, 95% CI 0.17–1.4), however did not have any significant effect on myocardial infarction, mortality, or length of hospitalization [60]. A Cochrane review with 89 randomized controlled trials with 19,211 participants suggested no difference in all-cause mortality, cerebrovascular events (relative risk (RR) = 1.52, 95% CI 0.58–4.02) (low quality evidence), myocardial infarction, bradycardia and hypotension. However, beta blockers reduced the burden of supraventricular arrhythmias and ventricular arrhythmias with low quality evidence suggesting reduced length of hospital stay [61].

From a standpoint of stroke prevention, studies do not suggest evidence in support of neuroprotection with beta blockade. However, beta-blockade is efficacious in controlling arrhythmias including atrial fibrillation and hence should be enforced

in a timely fashion to optimize heart rate and blood pressure **(moderate level of evidence, strong recommendation).**

Atrial Fibrillation Management in Cardio-thoracic Surgery Patients

Post-operative atrial fibrillation, occurring in up to 40% of patients after cardiopulmonary bypass, carries a two-four-fold increased risk of embolic events. Some centers utilize pharmacologic prophylaxis with pre-operative amiodarone and beta-blockers and post-operative atrial pacing. Immediate cardioversion may be necessary when atrial fibrillation is hemodynamically compromising or is associated with ischemia or congestive heart failure. Otherwise, the mainstay of therapy is correction of electrolyte abnormalities and attempting ventricular rate control. In the face of recent stroke, cardioversion is delayed while awaiting echocardiographic examination to rule out an atrial embolic source.

A multi-center randomized control trial showed no different between the two strategies of rate control versus rhythm control in post cardiac surgery patients showed no different in terms of days of hospitalization ($p = 0.76$), rates of death ($p = 0.64$), and rates of serious adverse events including bleeding or thromboembolic events ($p = 0.61$) [62]. If a persistent embolic source is documented and there is no severe systemic bleeding, it is reasonable to consider anticoagulation with heparin and then warfarin. Although this certainly increases the risk of bleeding at the surgical site, it can be safely undertaken if done cautiously. Anticoagulation should be initiated in cases of refractory or recurrent atrial fibrillation post operatively that persists for more than 48 h and be continued for at least 4 weeks post restoration of normal sinus rhythm [62].

Other Causes of Stroke in Cardio-thoracic Surgery

Cerebral ischemia caused from an air embolism is one syndrome that is amenable to therapy. A small retrospective study showed benefits of hyperbaric oxygen therapy in cardiothoracic surgery patients who develop cerebral ischemia post-operatively [63]. Even if hyperbaric oxygen is not available, the patient may be placed on 100% oxygen and kept flat to reduce the risk of recurrent air emboli to the brain. (Very low level of evidence, weak recommendation).

Recommendations Based on Facts

- **Timely detection of symptoms of an acute stroke in the post-operative period is challenging and requires vigilance on the part of the team. CT head along with vessel imaging should be pursued based on the clinical presentation,**

especially if patient is being considered for intra-arterial therapy (high level of evidence, strong recommendation)**.**

- **Patient should be immediately evaluated by a neurologist. Major cardiac surgery in the past 14 days is a contraindication for administering IV t-PA** (low level of evidence, weak recommendation).
- **Mechanical thrombectomy is a safe option in patients who have an acute ischemic stroke due to a large vessel occlusion in the anterior circulation post cardiac surgery up to 24 h from onset** (High level of evidence, Strong recommendation)**. In the event, the time of onset is unknown, determination of the eligibility should be based on DWI and perfusion imaging in addition to the clinical exam to determine clinical core mismatch** (High level of evidence, strong recommendation).
- **Mechanical thrombectomy is a reasonable option in patients who have an acute ischemic stroke due to a large vessel occlusion in the posterior circulation post cardiac surgery up to 6 h from onset.** (Low level of evidence, moderate recommendation). **Beyond 6 h from onset in cases of posterior circulation occlusion, clinical infarct mismatch defined by clinical exam and DWI imaging or CT imaging may be considered.** (Low level of evidence, weak recommendation)
- **While intra-arterial t-PA is seldom used as a primary therapy, it might be considered as an adjunctive therapy in cases where revascularization is difficult to achieve with mechanical thrombectomy** (low level of evidence/weak recommendation).
- **Benefit On-pump versus off-pump CABG with regards to prevention of neurologic complications is a controversial topic.** (strong level of recommendation, moderate recommendation).
- **In cases of symptomatic carotid artery stenosis, CEA should be the first line of management.** (high level of evidence, strong recommendation). **Carotid artery stenting is a reasonable alternative in high risk patients for CEA** (moderate level of evidence, moderate recommendation).
- **Maintaining a blood pressure goal after MT which optimizes the cerebral perfusion pressure without increasing the risk of hemorrhage and is amenable to patient's cardiac status should be considered (**very low-level evidence, moderate recommendation**).**
- **In the setting of cardio-embolic stroke due to a large vessel occlusion with sizeable volume of infarct, withholding anticoagulation for 7–10 days is recommended.** (high level of evidence, strong recommendation).

A Personal View of the Data

Post-operative stroke, one of the common complications after cardiac surgery is associated with increased length of stay, morbidity, mortality, and hospital cost. Management of stroke post cardiac surgery should follow the same guidelines as

patients with acute ischemic stroke except that this cohort of patients, is often not eligible for t-PA.

However, mechanical thrombectomy should be offered to patients with stroke detected within 6 h post-cardiac surgery evidence of ASPECTS ≥6 on CT scan/DWI sequence of MRI. Data from upcoming trials extending the timeline for consideration for mechanical thrombectomy could be practice changing in the field of stroke care post cardiac surgery. There is need for more trials to assess outcomes post thrombectomy in posterior circulation strokes. Benefit of stenting in the setting of acute ischemic stroke is unknown.

Thorough assessment of the risk factors should be done before surgery to reduce the damage from complications post-surgery. Vigilance and proactive measures from the surgeons and the ICU team can reduce morbidity from stroke in the perioperative period.

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Chapter 43
Neurologic Catastrophe in the CT ICU: A Neurosurgeon's Dilemma

Emily P. Sieg, Russell A. Carter, and Shelly D. Timmons

Introduction

Cerebral neurological complications after cardiothoracic surgical procedures run the gamut from mild functional problems to surgical lesions, and include metabolic encephalopathies, cognitive dysfunction, seizures, and various often catastrophic forms of "stroke," whether from ischemic infarction or hemorrhagic lesions [1]. As a result, neurosurgeons often are faced with complex decision-making regarding potentially surgical lesions in the background of implanted devices, such as pacemakers or pacing wires, ventricular-assist devices, and artificial valves, as well as antithrombotic therapies and other acquired coagulopathies. Cardiac surgeons must balance the need for antithrombotic therapy to prevent intracardiac thrombus, maintenance of hemodynamic stability, and prevention of dysrhythmias in post-operative patients with the sometimes competing neurophysiological needs of patients with neurological catastrophes.

This chapter will focus on a common problem seen in the CTICU requiring neurosurgical intervention, intracranial hemorrhage (ICH). ICH may occur from a variety of pathologies, and the focus will be on two major etiologies, those related to antithrombotic therapy for chronically implanted ventricular-assist devices, and ICH in the face of anticoagulation for mechanical valve replacement.

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Ventricular Assist Devices

Heart failure is highly prevalent, resulting in over five million patients living with the disease in the United States alone, and over 800,000 new cases diagnosed annually [2]. There are more than one million hospitalizations annually for acute heart failure in the U.S. Prognosis is poor with a 5-year survival rate of just over 50% [3]. The prognosis is even worse in cases of advanced heart failure; patients with New York Heart Association Class IV heart failure have a 1-year mortality rate of 75% [4]. Many CHF patients have right heart failure-induced congestive hepatopathy resulting in a coagulopathic state, in addition to the anticoagulation and antiplatelet therapy required for many post-op patients with implanted valves, VADs, and other etiologies, making management of ICH in this patient population quite complicated.

The use of left ventricular assist devices (LVADs) to augment circulation in the face of heart failure has gained increasing utility in the past two decades. The use of LVADs is extending both life expectancy and quality of life for patients with heart disease, as both bridge to cardiac transplant (BTT) [5] and as destination therapy (DT), effectively doubling survival to 52% at 1 year, as opposed to 24% for those undergoing medical therapy alone. The risks of both ischemic infarction and intracerebral hemorrhage are notable in LVAD patients [6]. While a low risk of cerebral hemorrhagic complications was noted in the intial trials, the consequences of intracranial hemorrhages are high, and warrant an evaluation of treatment options should they occur. VAD patients who suffer hemorrhages resulting in significant neurological deficits may have to be removed from the transplant waiting list due to functional criteria, not to mention the potential for mortality from ICH. The relative rarity of such events, however, makes the study of appropriate interventions difficult. Further research challenges have been encountered as these devices have evolved over time, including the development of both pulsatile and non-pulsatile flow devices [7], questions about optimal blood pressure levels [8], variability in type and dose of antithrombotic medications used during long-term use [9], and the various impacts that these parameters have on hemorrhagic complications.

Valve Replacement Surgery

While ICH after valve surgery in the absence of infection is rare, it does occur. Decision-making regarding antithrombotic therapy depends upon whether or not bioprosthetic valves or mechanical valves are used, and whether the mitral valve or aortic valve are replaced, with higher levels of anticoagulation being required for mitral valves. Long-term anticoagulation is necessary for those with mechanical valves due to their thrombogenicity, although there is variability in practice with regard to timing of initiation [10, 11]. Despite recommendations regarding the use of antithrombotic therapy, clinical variability exists regarding duration and type of

medication used after uncomplicated bioprosthetic mitral and aortic valve replacement and mitral valve repair [12, 13]. With the advent of transcatheter valve replacement procedures, further questions are arising, but this chapter will only consider open valve replacement surgery.

Search Strategy

General

Searches were limited to English-language clinical trials from January 1, 1998 to January 1, 2018 in non-pregnant adults. Case reports and case series were not included. PubMed and Cochrane Database searches were performed. Cochrane Database evidence-based reviews were searched with filters for intervention, and included stroke intervention in the neurologic diseases category. Cardiology topics included surgery, heart transplantation, and valve disease.

Ventricular Assist Devices

PubMed search terms included: "Neurologic Complications AND Cardiac Surgery," OR "Neurologic Complications AND Ventricular Assist Device (OR VAD)" OR "Neurologic Complications AND Cardiac ICU," OR "Intracranial Hemorrhage AND Cardiothoracic Surgery." Non-English, non-human, pediatric/neonatal/fetal subjects, diagnostic studies, and studies related to congenital hemophilias were eliminated. Articles relevant to incidence and treatment of intracranial hemorrhage after VAD or valve replacement surgery and in the face of bacterial endocarditis-associated mycotic aneurysms in adults were screened and reviewed. The reference sections of the relevant articles were reviewed for additional relevant articles for completeness.

The applicable studies were evaluated for clinical relevance to the identified PICO questions (See Table 43.1). Articles were independently graded using the classification of evidence scheme adopted by the American Academy of Neurology (AAN) and the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system [14]. The GRADE system was designed to assess the total body of evidence with attention to study design, inconsistency, risk of bias, indirectness, publication bias, imprecision, effect size, dose response and any plausible residual confounders. The individual studies were assigned AAN Classification of Evidence levels, while the body of evidence reviewed for clinical questions and recommendations was assigned one of the four possible final designations for quality of evidence: high, moderate, low, and very low quality (See Tables 43.2 and 43.3).

Table 43.1 PICO questions

Patients (P)	Intervention (I)	Comparator (C)	Outcomes (O)
Patients with intracranial hemorrhage after placement of a ventricular assist device	What is the incidence?		Hemorrhage type
			Mortality
			Glasgow outcome scale score
			Other functional outcome
Patients with intracranial hemorrhage after placement of a ventricular assist device	Craniotomy	No craniotomy	Mortality
			Glasgow outcome scale score
			Other functional outcome
Patients with intracranial hemorrhage after placement of a ventricular assist device	Cessation or reversal of anticoagulation or antiplatelet therapy	No cessation or reversal of anticoagulation or antiplatelet therapy	Thrombosis rates
			Hemorrhage progression
			Mortality
			Glasgow outcome scale score
			Other functional outcome
Patients with intracranial hemorrhage after placement of prosthetic heart valve	What is the incidence?		Re-hemorrhage
			Mortality
			Glasgow outcome scale score
			Other functional outcome
Patients with intracranial hemorrhage after placement of prosthetic heart valve	Craniotomy	No craniotomy	Re-hemorrhage
			Mortality
			Glasgow outcome scale score
			Other functional outcome
Patients with intracranial hemorrhage after placement of prosthetic heart valve	Anticoagulation or antiplatelet therapy	No anticoagulation or antiplatelet therapy	Re-hemorrhage
			Mortality
			Glasgow outcome scale score
			Other functional outcome

Valve Replacement Surgery

Searches were additionally performed for the following search terms: "Neurologic Complications AFTER Cardiac Surgery," OR "Intracranial Hemorrhage AND Valve Surgery." Transcatheter valve replacement was not considered for this analysis. For completeness, searches were performed with the additional search terminology

Table 43.2 Classification of evidence for ventricular assist devices and intracranial hemorrhage

Ref.	Number of patients	Summary	Type of study	AAN level of evidence[a]
Incidence of intracranial hemorrhage				
Drews et al. [19]	108	10-year period comparing at-home and in-hospital cohorts	Retrospective review	Class III
		At-home 1 death/38 patients from ICH		
		Mean support 454 days		
		In-hospital 7 deaths/70 patients from ICH		
		Mean support 238 days		
Pae et al. [17]	23	Pulsatile LVADs Over 7980 LVAD total days	Prospective, single-arm, non-randomized observational study	Class II
		13 Patients had 30 neurological events		
		1 ICH (Fatal)		
Ramey et al. [18]	58	4 year study	Retrospective review	Class III
		5 patients had ICH		
		7 neurosurgical procedures in 2 patients		
		3 EVDs		
		1 Asymptomatic IVH		
		1 iatrogenic SDH		
		1 later VP shunt		
		2 hemispheric DC		
		1 posterior fossa DC		
		1 hemispheric DC for the iSDH		
		60% mortality		
Saeed et al. [9]	114 CF-LVAD patients	Over 102 months with complications after post-operative day 14; a priori medication regimens compared over 3 consecutive time frames	Retrospective review	Class III
		ASA 81 mg daily + dipyridamole 75 mg daily (n = 26); target INR 2–3		
		ASA 81 mg daily (n = 18); target INR 1.5–2		
		ASA 325 mg daily (n = 18); target INR 2–3		

(continued)

Table 43.2 (continued)

Ref.	Number of patients	Summary	Type of study	AAN level of evidence[a]
Slaughter et al. [22]	200 patients slated for cardiac transplant with either continuous-flow LVAD or pulsatile-flow LVAD placement	CF-LVAD (n = 134 patients randomized)	Randomized trial	Class I
		15/133 patients implanted had an ICH (11%)		
		44/134 deaths within 2 years (33%)		
		9% of ICH-Related deaths		
		PF-LVAD (n = 66 patients Randomized) 5/59 Patients Implanted had an ICH (8%) o 27/66 Deaths within 2 years (41%) o 10% of ICH-Related Deaths		
		5/59 patients implanted had an ICH (8%)		
		27/66 deaths within 2 years (41%)		
		10% of ICH-related deaths		
Steffen et al. [21]	301 LVADs in 285 Patients	Over 105 months: duration of therapy and complication rates	Retrospective review of a prospective database	Class III
		ICH associated with decreased survival		
Wilson et al. [20]	330 LVADS in 330 patients	Over 110 months	Retrospective cohort study	Class III
		36 patients had ICH		
		10 SAH (traumatic)		
		1 IVH (spontaneous)		
		17 IPH (spontaneous)		
Craniotomy vs no craniotomy				

(continued)

Table 43.2 (continued)

Ref.	Number of patients	Summary	Type of study	AAN level of evidence[a]
Wilson et al. [20]	330 LVADS in 330 patients	Of 36 patients with ICH, 6 had surgery, 1 for SDH and 5 for IPH	Retrospective cohort study	Class III
		IPH (All spontaneous)		
		1/9040 LVAD days		
		17/36 (47%)		
		5/16 operated		
		30-day mortality 10/17 (59%)		
		1-year mortality 11/17 (65%)		
		SDH (all traumatic, 6 falls/2MVAs)		
		1/18,081 LVAD days		
		8/36 (22%)		
		30-day mortality 1/8 (13%)		
		1-year mortality 3/8 (38%)		
		SAH (all traumatic, same-level falls)		
		10/36 (28%)		
		0/10 operated		
		30-day mortality 0/10 (0%)		
		1-year mortality 1/10 (10%)		
		IVH (spontaneous) 1/36 (3%)		
Antithrombotic therapies				

(continued)

Table 43.2 (continued)

Ref.	Number of patients	Summary	Type of study	AAN level of evidence[a]
Jennings et al. [25]	122 LVAD patients	Over 55 months: 25 patients had 38 anticoagulation reversal events	Retrospective cohort study	Class III
		29 acute hemorrhage		
		9 supratherapeutic INR		
		7 invasive procedures		
		3 unexplained anemia		
		Mortality rates		
		Overall 5/25 deaths within 30 days of reversal (20%)		
		3/5 30-day deaths due to ICH		
Wong et al. [24]	237 LVAD patients	Over 68 months; 42 with ICH (2 excluded for insufficient data and 9 excluded for INR ≤1.6)	Retrospective study of a prospectively collected database	Class III
		35 spontaneous "hemorrhagic CVAs"		
		7 traumatic		
		31 patients received 4-factor PCC (n = 10), FFP (n = 10), or no correction of INR (n = 11)		

CF Continuous Flow, *CVA* Cerebrovascular Accident, *DC* Decompressive Craniotomy/Craniectomy, *EVD* External Ventricular Drain, *FFP* Fresh Frozen Plasma, *ICH* Intracranial Hemorrhage, *INR* International Normalized Ratio, *IPH* Intraparenchymal Hemorrhage, *IVH* Intraventricular Hemorrhage, *LVAD* Left Ventricular Assist Device, *MVA* Motor Vehicle Accident, *PCC* Prothrombin Complex Concentrates, *PF* Pulsatile Flow, *SAH* Subarachanoid Hemorrhage, *SDH* Subdural Hematoma, *VP* Ventriculoperitoneal

[a]American Academy of Neurology (AAN) 2017 [35]

"Intracranial Hemorrhage" AND "Bacterial Endocarditis" in an attempt to garner additional manuscripts referencing valve surgery. While 24 studies additional were identified, all were specific to the treatmentof mycotic aneurysms and were not considered further for the purposes of this chapter.

Table 43.3 Classification of evidence for valve replacement and intracranial hemorrhage

Reference	Number of patients	Summary	Type of study	AAN level of evidence[a]
Incidence of intracranial hemorrhage				
Akhtar et al. [28]	507	Followed over 10 years	Prospective observational cohort study	Class III
		268 mitral		
		96 aortic and mitral		
		76 aortic		
		345 ball and cage		
		126 bileaflet		
		36 single disc		
		23 thromboembolic events		
		41 hemorrhagic events		
		4 ICH (0.19% patient years)		
		25 (4.9%) 30-day mortality		
		62(12.2%) late deaths		
		37 (7.3%) anticoagulation related		
Nishimura et al. [27]	38 patients identified with ICH and mechanical and bioprosthetic heart valves	Over an 11-year period	Descriptive study	Class IV
		Median ICH volume 22.8 ml		
		50% were Lobar		
		All mechanical valve patients on warfarin		
		46% of bioprosthetic valve patients on Warfarin		
		14 (36.8%) underwent emergent hematoma evacuation within 24 h		
		11 underwent reversal of anticoagulation		
		24 underwent no surgery within 24 h		
		12 Underwent reversal of anticoagulation		

(continued)

Table 43.3 (continued)

Reference	Number of patients	Summary	Type of study	AAN level of evidence[a]
Piper et al. [26]	89 consecutive mechanical valve patients	Over a 10-year period	Retrospective review	Class III
		69 patients had some ICH		
		42 (60.9%) small		
		24 (34.8%) intermediate		
		3 (4.3%) massive		
Craniotomy vs. no craniotomy				
None		None		None
Antithrombotic therapies				
Amin et al. [32]	12 patients undergoing SDH evacuation While anticoagulated following mechanical valve replacement	Over 16-year period	Retrospective single-institution review	Class III
		9 had surgical evacuation within 24 h		
		3 Treated with anticoagulation reversal alone but required later surgery		
		No deaths in-hospital		
		2 had recurrent SDH in 50 months		
Krittalak et al. [33]	652	Patients with mechanical valves	Retrospective descriptive review	Class III
		26 hospitalized due to ICH over 6 years		
		13 SDH		
		7 IPH		
		2 SAH		
		1 EDH		
		2 IPH and IVH		
		1 IPH and SAH		
		5 In-hospital deaths from ICH		
		4 within 3 days		

(continued)

Table 43.3 (continued)

Reference	Number of patients	Summary	Type of study	AAN level of evidence[a]
Wijdicks et al. [34]	39	Patients with ICH and mechanical heart valves	Retrospective review	Class III
		20 SDH		
		10 lobar IPH		
		4 SAH		
		3 cerebellar IPH		
		2 basal ganglia IPH		
		13 died within 2 days		
		15 underwent SDH evacuation		
		1 aneurysm clipping		
		No ICH recurrence In-hospital		
		No ICH recurrence with reinstitution of anticoagulation or antiplatelet therapy		

I*CH* Intracranial Hemorrhage, *IPH* Intraparenchymal Hemorrhage, *SAH* Subarachanoid Hemorrhage, *SDH* Subdural Hematoma
[a]American Academy of Neurology (AAN) 2017 [35]

Results

A total of 522 peer-reviewed articles were screened for inclusion from PubMed Searches. Duplicates were eliminated, as were case reports, case series, and articles not relevant to the topics at hand, yielding the studies assessed as outlined in Tables 43.2 and 43.3. From the 232 Cochrane reviews identified, a total of 185 stroke intervention reviews were assessed with no relevant reviews found. Cardiology topics included surgery (0 of 30 reviews relevant), heart transplantation (0 of 9 relevant), and valve disease (1 of 9 relevant on antiplatelet and anticoagulation for patients with prosthetic heart valves) [15].

Ventricular Assist Devices

Search strategies yielded seven (7) relevant articles regarding the incidence of intracerebral hemorrhage in the face of LVAD usage. One (1) article was identified addressing craniotomy for ICH in LVAD patients and two (2) on the reversal of anticoagulation in the face of ICH.

Incidence of Intracranial Hemorrhage Incidence of ICH in LVAD patients has been widely variably reported with a median incidence of 3% [roughly 0.04 Events Per Patient Year (EPPY)] [16]. While the incidence appears low overall, complications from ICH in LVAD patients are significant with a high chance of fatality. However, holding or reversing antiplatelet and anticoagulant medications in patients with implanted devices risks thromboembolic events, especially as related to the device itself. VAD thromboses may prompt replacement conferring additional risk of morbidity and mortality, as well as thromboembolic cerebral infarction with its own potential for morbidity and mortality. The incidence of all neurological events in the presence of an LVAD is higher than that of hemorrhage alone, but the clinically relevant anticoagulation-related hemorrhage causing death is of major concern for these patients (1/23 patients over 7980 PF-LVAD days in one study) [17]. In a separate retrospective review of 58 consecutive patients in one institution over 4 years [18], five (5) patients had ICH but two (2) of them required seven (7) neurosurgical procedures shortly after ICH: three (3) external ventricular drains (EVDs) [two (2) with hemorrhagic complications, including one (1) asymptomatic IVH and one (1) iatrogenic hyperacute subdural hematoma (SDH) requiring emergent surgery], two (2) hemispheric decompressions, and one (1) posterior fossa decompressive craniectomy for evacuation of intraparenchymal hemorrhage (IPH). Three of these five patients died for a 60% mortality rate. This review highlights that even though the incidence of ICH may be relatively low, the complication rate is quite high, including fatal complications.

The type of antithrombotic medication (ATM) regimen may affect overall hemorrhage rates (all types), particularly as relates to antiplatelet medication. A retrospective review of 114 continuous-flow LVAD patients assessed complications related to ATM regimen in the first 2 weeks after LVAD placement. This study concluded that those on a regimen including 325-mg aspirin (ASA) daily had a threefold higher increased hazard of all hemorrhagic events compared with ASA 81 mg and dipyridamole or ASA 81 mg alone. INRs among groups were similar, demonstrating no warfarin effect [9]. The effect also extended to ICH specifically, and thrombotic events were not different amongst the three regimens.

Successful longer-term treatment has resulted in additional data on ICH risk. As discharge to outpatient care with LVAD therapy has evolved as a safe practice, comparisons between hospitalized and discharged patients have been made. One such analysis highlighted the role of co-morbidities and critical illness in the development of ICH, with in-hospital deaths being higher than outpatient deaths from ICH in at least one retrospective data review [19]. Furthermore, as longer durations of support have become more commonplace over the past two decades, cumulative risk exposure to ICH has been shown with longer durations of use [20]. ICH-related mortality also increases with longer durations of LVAD support [21]. Other considerations include type of LVAD, with no significant differences in ICH-related deaths seen between continuous-flow and pulsatile flow LVADs [22].

Characterization of the etiologies and types of hemorrhage is important to formulate outcome predictions. Aiming to address the incidence of ICH in LVAD

patients not addressed in the REMATCH trial [6], one retrospective cohort study [20] included all adult patients in a single institution (the University of Michigan) who underwent placement of an LVAD over 110 months from 2003 to 2012. During the study period, 330 LVADs were placed and 36 patients developed an intracranial hemorrhage [ten (10) traumatic subarachnoid hemorrhages (SAH) all caused by same-level falls, eight (8) traumatic subdural hematomas (SDH) all caused by trauma with same-level falls in 6 and minor motor vehicle accidents in two (2), one (1) spontaneous intraventricular hemorrhage (IVH), and 17 spontaneous intraparenchymal hemorrhages (IPH)]. One SDH occurred for every 18,081 LVAD days. One IPH hemorrhage occurred for every 9,040 LVAD days.

Patients with IPH had the worst outcomes, with a mortality rate of 59% within 30 days and a median Glasgow Outcome Scale (GOS: Table 43.4) score of 1 (dead) at both 6 months and 1 year. By comparison, SDH and SAH did better; only 13% SDH patients and no SAH patients died by 30 days. SDH and SAH patients also had much better GOS scores at 1 year (median 3.5 and 5, respectively).

With respect to the IPH patients, this study demonstrated that patients' outcome did depend on presenting Glasgow Coma Scale (GCS: Table 43.5) (congruent with a plethora of other literature), but interestingly, the inflection point occurred at GCS 11 with no patients with GCS <11 surviving past 30 days. Surgery did nothing to improve survival (see below), and there were no associations between the international normalized ratio (INR), time since LVAD placement, age, midline shift, or hemorrhage volume (when cerebellar IPH was excluded) and death risk.

Craniotomy for Intracranial Hemorrhage Of the seventeen (17) patients in the Michigan cohort who had an IPH, five (5) underwent operative intervention. Two (2) patients had craniotomies for hematoma evacuation and three had hemicraniectomies. Four (4) of the five (5) IPH patients died within 60 days and the one (1) survivor had GOS of 3 (severe disability) at 6 months. Of the eight (8) SDH patients, one (1) underwent craniotomy for evacuation and ultimately had a good functional outcome. There were no intraoperative deaths during craniotomy. Due to the retrospective nature of this study, indications for surgery could not be determined, and it is possible that selection bias for operations in only the most critically ill was present. The study authors appropriately concluded that an ICH can be a devastating event for an LVAD patient but the outcome depends upon the type of hemorrhage, and further, that data are insufficient to inform surgical decision-making.

While non-cardiac surgery can be safely performed in LVAD patients with low risk of excessive operative bleeding problems [23], VAD patients may require more transfusions than non-VAD patients secondary to complex coagulopathies. These complex coagulopathies increase the risk for catastrophic intracranial hemorrhage above that associated with combined warfarin and antiplatelet therapy alone [18, 23], and should be considered and treated aggressively for any LVAD patient in whom a craniotomy is proposed.

Table 43.4 The glasgow outcome scale (GOS) and the glasgow outcome scale extended (GOS-E)

GOS category	GOS category number	GOS brief definition	GOS-E category	GOS-E category number	GOS-E brief definition
Good recovery	5	Resumption of normal life; may have minor deficits	**Good recovery** *Upper*	8	Minor deficits are not disabling
			Good recovery *Lower*	7	Minor problems that affect daily life; resumes >50% of the pre-injury level of social and leisure activities
Moderate Disability	4	Some disability but independent with activities of daily living. Independent at home but require help outside the home	**Moderate Disability** *Upper*	6	Able to work even with special arrangements; resumes <50% of the pre-injury level of social and leisure activities
			Moderate disability *Lower*	5	Unable to work
Severe disability	3	Dependent on daily support for cognitive or physical disability	**Severe disability** *Upper*	4	Can be left alone >8 h during the day; Unable to travel and/or shop without assistance
			Severe disability *Lower*	3	Cannot be left alone >8 h per day
Vegetative state	2	Unaware of surroundings; reflex responses may have spontaneous eye opening		2	Unaware of surroundings; reflex responses may have spontaneous eye opening
Death	1			1	

Resumption of Antithrombotic Medications In the Michigan cohort [20], all 36 of the patients presenting with IPH were being treated with both aspirin and warfarin at the time of presentation, but management of these medications was variable. For all ICH patients (operated or not), aspirin was held in 47% of patients and warfarin in 61% but no specific criteria for holding were able to be determined. Platelets were given to 39% and fresh frozen plasma to 61%, again with no criteria for administration being attainable. Notably, no pump failures or clinically significant ischemic events were observed in any patients in whom aspirin or warfarin were held. No delayed re-hemorrhages were observed after resuming aspirin or warfarin therapy which was done on average at 7 days for aspirin and 10.5 days for warfarin.

Table 43.5 The glasgow coma scale (GCS)

Behavior	Response	Score
Eye opening response	Spontaneous	4
	To speech/voice command	3
	To painful stimulus	2
	No response	1
Verbal response	Oriented to person, time, and place	5
	Confused speech	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
Motor response	Obeys commands	6
	Motor Localization to Painful Stimulus	5
	Withdrawal from painful stimulus	4
	Abnormal flexion (decorticate posturing)	3
	Abnormal extension (decerebrate posturing)	2
	No response	1

With respect to optimal patient selection for and methods for reversal of vitamin K antagonist anticoagulant medications (warfarin), little data exists. A retrospective study in a single quaternary referral institution (the University of Rochester) [24] examined all continuous-flow LVAD patients over a 68-month period of time between 2008 and 2015 identified by a prospectively collected database. Of 236 LVAD patients identified, 42 sustained an ICH during the study period; only 31 were analyzed, as 9 had sub-therapeutic INRs and two (2) had insufficient data. Etiology was trauma in eight (8) patients, supratherapeutic INR in eight (8), spontaneous in seven (7) patients, hemorrhagic transformation of an infarction in five (5), and mycotic aneurysm in two (2). The type of ICH was SAH in fifteen (15), IPH in thirteen (13), and SDH in three (3). Of these 31 patients, ten (10) received fresh frozen plasma (FFP), ten (10) received 4-factor prothrombin complex concentrates (PCCs) [seven (7) with additional FFP], and eleven (11) underwent no active reversal, but had their Vitamin K antagonist (warfarin) held to allow physiological self-correction of the INR over time. The latter group consisted of those patients with much smaller volumes of hemorrhage than the other two groups. Seven (7) were noted only to have small SAHs; the other four (4) were transferred from outside institutions and had stable ICH on admission CT at the study institution. There were no significant differences between time to initiation of therapy between the PCC and FFP groups, but there was a significant difference in time to INR correction. There were no significant differences in number of units of FFP given (7/10 PCC patients received both). No difference in 30-day neurologic deficits or in-hospital mortality was seen between these two groups. One patient did develop an LVAD thrombus at post-reversal day number 19 requiring a VAD exchange, but had also been given unknown doses of recombinant activated Factor VII and IX at an outside hospital prior to transfer. No data were available about duration of withholding of

warfarin therapy. Progression of ICH volume was not assessed, only initial ICH volume. No conclusions can be drawn about overall timing to reinstate anticoagulation after ICH from this study.

While not specifically assessing anticoagulation reversal for ICH or cranial surgery, a second study of 122 consecutive LVAD patients over a 55-month period [25] revealed that 25 patients had 38 anticoagulation reversal episodes, 29 for acute hemorrhage of all types (5 for ICH). In this cohort, one (1) patient had a thromboembolic event within 30 days of reversal, but 5/25 patients died (20%) within 30 days, with 3 of those deaths attributable to ICH.

These studies highlight the paucity of data obtainable regarding anticoagulation reversal for ICH in LVAD patients, and the need for practical approaches to avoid thromboembolic complications, i.e., avoidance of active reversal in select patients at very low risk of ICH progression or need for surgery and who have a higher likelihood of a good outcome at baseline due to the minor nature of their ICH (typically SAH).

Valve Replacement Surgery

Search strategies yielded three (3) relevant articles regarding the incidence of intracerebral hemorrhage in the face of ATM use for mechanical valves. No articles were identified addressing craniotomy for ICH and three (3) were included regarding reversal of anticoagulation in the face of ICH.

Incidence of Intracranial Hemorrhage A Cochrane review of 13 trials on the use of various antithrombotic medication regimens in cardiac valve replacement [15] concluded that antiplatelet drugs are not effective when used alone to prevent thromboembolic events. Oral anticoagulation and antiplatelet drug combinations are more effective. However, the combination is also associated with increased bleeding complication risks by about 50% overall. Lower-dose aspirin regimens may carry lower bleeding risks, but the overall evidence in the review was of low quality.

In an attempt to ascertain the etiology of "stroke" in mechanical valve patients, one group studied 89 consecutive patients [26] and determined that most neurological events included hemorrhages (69 of 89 or 77.5%). Of these, most were small (42 or 60.9%), 24 (34.8%) were intermediate in size and 3 (4.3%) were massive. The other 20 patients sustained non-hemorrhagic ischemic events.

In a descriptive study of 38 patients identified with ICH and mechanical and bioprosthetic heart valves identified over an 11-year period [27], median ICH Volume was noted to be 22.8 ml and 50% were lobar. All of the mechanical valve patients were on warfarin at the time of presentation, as were 46% of the bioprosthetic valve patients. Mortality or severe disability at discharge was noted in 53% of patients, hematoma enlargement within 24 h in eight (8) patients, and other hemorrhagic complications in three (3).

Finally, in one of the larger studies on this subject, 507 mechanical valve patients were prospectively followed for 10 years (2008.5 patient years) [28]. There were 64 adverse events, of which 23 were thromboembolic (1.13% per patient year), and 41 were hemorrhagic (2.04% per patient year). Of these, only eight had ICH (0.34% per patient year). Again, ICH being a rare event in patients on ATMs for valvular replacement, conclusions about treatment must be based on very limited data.

Craniotomy for Intracranial Hemorrhage No relevant articles were identified comparing craniotomy to non-operative management in the treatment of ICH in mechanical valve patients. With such a limited evidentiary basis, surgical decision-making must be based upon data extrapolated from other clinical scenarios.

Resumption of Antithrombotic Medications Other reviews have concluded that among patients with mechanical valves, inadequate data exist to suggest optimal timing of re-initiation of antithrombotic therapy regimens using warfarin [29]. However, this review showed that the overall incidence of ICH recurrence was 13% compared to valve thrombosis and ischemic stroke risk of 7% regardless of timing. Lower ICH recurrence rates were noted when resumption of warfarin was delayed, with a suggested target for restarting therapy of 4–7 days post-ICH. This same study group surveyed neurosurgeons and "thrombosis specialists" and found, not surprisingly, a wide variation in practices related to re-initiation of therapy [30].

A third review of best evidence on this subject yielded an overall rate of thromboembolic events as low as 5% with a very low incidence of re-hemorrhage or hematoma expansion of 0.5% in ten studies included during periods of withholding ATMs [31]. A period of seven to fourteen (7–14) days was deemed to be safe post-ICH to withhold ATMs in patients at low risk of thromboembolism. Those with mechanical valves were safely anticoagulated with heparin at three (3) days with conversion to warfarin at seven (7) days.

Brief interruptions in anticoagulation therapy for up to 3 weeks post-craniotomy for ICH are likely safe in terms of both thrombotic risk and hemorrhagic recurrence [32]. One small series of 26 mechanical valve patients with ICH out of 652 patients undergoing mechanical valve replacement over six (6) years showed that five (5) in-hospital deaths occurred within three (3) days of sustaining severe ICH [33]. Two intracerebral thromboembolic complications were noted after withholding and correction of anticoagulant medications, one at seven (7) days and one at 76 days. Low thromboembolic risk was noted in the first seven (7) days of withholding ATMs and no valve dysfunction when ATMs were held for less than fourteen (14) days.

Another older small retrospective review of 39 patients with ICH and mechanical heart valves yielded an interesting mix of ICH types [34]. Mortality was high in this cohort, with 13/39 patients dying within two (2) days of admission. Fifteen (15) of twenty (20) SDH patients underwent evacuation. Duration of withholding of ATMs was highly variable, ranging from two (2) days to three (3) months. No thromboembolic complications or recurrences of ICH were noted.

In the small Japanese cohort cited above [27], ATMs were held for a median value of two (2) days, with 4/38 patients suffering from thromboembolic cerebral infarctions despite early resumption of therapy, in contrast to other studies.

Discussion

Ventricular Assist Devices

LVADs have significantly improved survival from heart failure, either as a bridge to transplantation or as destination therapy. However, the need for prolonged dual antithrombotic therapy with antiplatelet and anticoagulant agents does confer a specific risk of both traumatic intracranial hemorrhage and spontaneous intracranial hemorrhage. These lesions are often non-operative, but when they are associated with a poor presenting GCS, clinical evidence of mass effect, or radiographic evidence of mass effect, the neurosurgeon is faced with a difficult decision-making scenario. There are very few data to inform decision-making in this complex patient group, and each case must be considered on the basis of overall co-morbidities, degree of coagulopathy present, presenting neurological and radiographic status, and patient and family wishes.

Valve Replacement Surgery

Despite mechanical valve replacement being more commonly performed, relatively fewer data are available to inform decision-making regarding surgery or ATM re-initiation in patients suffering from ICH. It is likely that more data are available for LVAD patients due to the more recent evolution of this technique and increased scrutiny on such interventions in more recent decades. However, further study should be performed on both groups of patients.

Recommendations

Ventricular Assist Devices

The overall quality of evidence by GRADE criteria is LOW or VERY LOW.

- For LVAD patients on antithrombotic medications with small-volume non-operative lesions, especially with isolated SAH, consideration should be given to allowing physiological self-correction of the INR without active reversal and

without transfusion of platelets for those on dual therapy (evidence quality low, weak recommendation).
- For LVAD patients on antithrombotic medications with SDH, medication and operative decisions should be made in keeping with SDH in other clinical settings (evidence quality low, weak recommendation).
- For LVAD patients on antithrombotic medications with large-volume IPH and/or IPH associated with mass effect, no recommendations regarding surgical decision-making can be made (evidence quality very low, very weak recommendation).
- For LVAD patients with ICH, consideration for early reinstitution of antithrombotic medications should be given as soon as operative and other procedural interventions are no longer expected, and neurological and radiographic evaluations are stable (evidence quality very low, very weak recommendation).

Valve Replacement Surgery

- For patients with mechanical valves suffering from ICH, resumption of ATMs is likely safe at 3–14 days post-hemorrhage (evidence quality very low, very weak recommendation).

A Personal View of the Data

Ventricular Assist Devices

The overall incidence of intracranial hemorrhage in LVAD patients is low, making this a difficult problem to study. Although the overall GRADE quality of evidence is low, themes emerge from the literature and clinical practice suggesting that mortality and morbidity from operative ICH lesions is quite high, prompting detailed counselling of families of patients with large-volume lesions associated with significant midline shift and other signs of major mass effect, and with large-volume intraparenchymal lesions in particular. As with non-LVAD patients, rapid surgical treatment of operative traumatic lesions tends to be associated with better prognosis, as compared to spontaneous hemorrhages which tend to be intraparenchymal. In general, rapid evacuation of traumatic subdural and epidural hematomas should be done.

General indications for surgical evacuation of intraparenchymal lesions include ease of evacuation without contributing to morbidity. Those IPHs that come to the surface are generally amenable. Deep lesions, for example those involving the basal ganglia, may still be evacuated, depending on the clinical scenario. Another factor that argues for surgery is mass effect thought to be the cause of deficit (rather than

the IPH itself as the cause of the deficit), such as often occurs with cerebellar hemorrhages.

Attention to treatment of coagulopathy pre-, intra-, and post-operatively is paramount in the avoidance of complications from cranial surgery in these circumstances. ATM-related coagulopathy may be complicated by other clinical factors, such as congestive hepatopathy.

Lessons learned from the fields of neurotrauma (as many of these hemorrhages result from falls) and cerebrovascular neurosurgery (spontaneous intraparenchymal hemorrhage) can be employed in neurosurgical operative and neurocritical care decision-making, in addition to the small body of literature on LVAD patients. In general, small volume lesions and specifically subarachnoid hemorrhage typically does not warrant active reversal of antithrombotic medication regimens, especially since there is a small but definite incidence of thromboembolic events. These can occur fairly late after correction of coagulation status highlighting the need to reinstitute antithrombotic medication regimens at the earliest time after ICH in the LVAD patient. Once the risk of post-operative bleeding for operated patients has passed, and very soon after CT-proven stabilization of hemorrhage has occurred, medications should be restarted as the risk of progression after a stable CT is low.

In our practice, we tend to withhold antithrombotic medications but not actively correct coagulation status (either with transfusion of platelets or FFP/PCCs) for those patients with implanted mechanical assist devices and SAH, small, non-operative so-called "sliver" acute subdural hematomas or small intraparenchymal hemorrhages—essentially all lesions without significant mass effect. Radiographic operative criteria are based upon lesion volume, lesion thickness in the case of SDH, degree of midline shift, and the presence of other signs of mass effect such as cerebrospinal fluid cisternal and sulcal effacement, as in other clinical situations. Clinical operative criteria for surgery incorporate the GCS, status of brainstem reflexes, and the presence of neurological deficits. One exception may be the patient with a small IPH but rupture into the ventricular system and resultant hydrocephalus requiring placement of an external ventricular drain, as this procedure carries a risk of iatrogenic hemorrhage in the patient on antiplatelet and anticoagulant medications, so reversal should be considered prior to EVD placement. These practices are supported by the low-level evidence presented herein.

Unfortunately, many patients have had ATM correction prior to neurosurgical consultation. We would urge emergency room and other physicians treating patients with LVADs and ICH to consult both the cardiac surgery and neurosurgery teams emergently prior to making decisions about medication reversal, employing image transmission from outside hospitals if at all possible (in addition to reporting on the neurological status). Chronic SDH with admixed acute blood is another commonly seen scenario in anticoagulated patients, and consultation with neurosurgical colleagues prior to reversal should always be employed, as many of these lesions are non-operative.

Transfusion of platelets is generally reserved for operative candidates. Transfusion of FFP and/or PCCs is reserved for patients with definite surgical lesions or for borderline surgical lesions at risk of progression, generally hyperacute or thicker

acute SDH and certain IPHs. Since SDH usually occurs as a result of trauma, there is a risk in the anticoagulated patient of progression due to unsecured bleeding vessels of larger caliber. Therefore, these patients must be watched more closely radiographically and consideration given for reversal, even for a brief period of a few days. However, once stable scans are observed (typically at about 24–48 h after ictus), even if full correction has not been achieved, active correction is generally stopped. IPH, though it carries a high mortality and morbidity, is not as likely to progress. Morbidity occurs from the parenchymal damage at the time of the initial hemorrhage, and mortality risk is from mass effect and herniation. Therefore, we tend to be less aggressive about surgery, and more ambivalent about reversal of anticoagulation. The evidence of reversal in these patients is particularly lacking. Patients with IVH and obstructive hydrocephalus require reversal due to the need for external ventricular drainage as noted above.

For most LVAD patients with ICH, aspirin is generally held for 3–7 days, depending upon the clinical situation. Full anticoagulation is withheld for a similar time frame, but if there are ongoing operative or procedural considerations, or concern that lesions will progress, some further delay may be employed. Furthermore, protection from thromboembolic events and VAD thromboses may be conferred by the utilization of heparin drips in the ICU prior to conversion to warfarin therapy. This can be useful due to the titratability and relative ease of reversibility of heparin drips over warfarin therapy.

Valve Replacement Surgery

The same general considerations are employed for patients with artificial valves, with earlier reinstitution of antithrombotic medications in those with mechanical valves and mitral valves in particular. For those at low risk of thromboembolism, we routinely reinstitute therapy at 3–14 days depending upon the intracranial findings and neurological status. For higher-risk patients, heparin drips are used at 2–3 days post-hemorrhage with conversion to warfarin at 7 days post-ICH. This long-standing practice is in keeping with a recent review on this topic [31].

Summary

In conclusion, far more data are needed to inform clinical decisions regarding the neurological catastrophe of ICH in the CVICU, particularly in the face of antithrombotic medication use in LVAD and valve replacement patients. However principles of management can be extrapolated from other clinical scenarios, and aggressive surgical management of ICH may, in fact, be warranted.

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Chapter 44
Management of Malperfusion Syndrome in Acute Type A Aortic Dissection

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Introduction

Malperfusion is one of the most important conditions that could significantly increase the risk of mortality and need to be diagnosed as soon as possible when assessing ATAAD patients. Malperfusion is defined as diminished or lack of blood perfusion to an organ caused by arterial obstruction due to the dissection. Malperfusion syndrome is defined as irreversible organ dysfunction with infarction due to an arterial blood supply obstruction. The incidence of malperfusion in ATAAD patients is reported in the range from 16% to 33%, and malperfusion syndrome significantly increases the mortality rate in ATAAD patients [1–3]. Malperfusion could occur in any organ in the body leading to a variety of organ ischemia including heart, brain, spinal cord, viscera, or limbs. Theoretically, early peripheral intervention to selectively reperfuse the ischemic organ is critical to avoid malperfusion syndrome. However, as the bottom line, it is also important to perform a proximal aortic repair as soon as possible to save the patient's life. Clinical outcomes of ATAAD are time-dependent from the onset. It is well known that the mortality increases by 1–2% per hour after the onset without surgical intervention (i.e. proximal aortic repair), and up to 90% of patients die within 7 days [4, 5]. Patel et al. reported 33% of ATAAD patients treated with initial peripheral intervention for reperfusion died before achieving proximal aortic repair [6]. Thus, whether prioritizing proximal aortic repair or peripheral intervention for selective treatment of

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malperfusion remains controversial. This chapter reviews surgical outcomes of ATAAD with malperfusion, and discusses the optimal treatment strategy for malperfusion of each organ.

Search Strategy

A literature search of English language publications from 1990 to 2017 was used to identify published data on ATAAD with malperfusion using the PICO outline (Table 44.1) with Pubmed. Terms used in the search were "type A aortic dissection", AND "malperfusion", AND/OR "malperfusion syndrome", AND/OR "endovascular intervention", AND/OR "hybrid". The search strategy revealed 512 articles. Of these, 42 articles to discuss the optimal surgical strategy for ATAAD with malperfusion were selected. The data was classified using the GRADE system.

Results

Optimal Surgical Strategy for ATAAD with Malperfusion by Involved Organ System

Studies comparing surgical outcomes in ATAAD patients with and without malperfusion are summarized in Tables 44.2 and 44.3.

Myocardial Malperfusion

The incidence of myocardial malperfusion is about 10–15% in ATAAD patients [7, 8]. The right coronary artery is affected more frequently than the left coronary artery [9]. It is generally accepted that primary aortic repair is the mainstay to treat myocardial malperfusion in the current era. On the other hand, there are some reports that coronary angiogram might be indicated prior to surgical intervention if there is a concern about coronary malperfusion. Imoto et al. reported that coronary stenting for left coronary artery territory ischemia prior to aortic surgical repair might be beneficial to prevent postoperative low cardiac output syndrome while right coronary artery territory ischemia should be treated with surgical intervention [10].

Table 44.1 PICO table for malperfusion in acute type A aortic dissection

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Patients with acute type A aortic dissection with malperfusion	Hybrid surgery (Early intervention for reperfusion plus proximal aortic repair)	Proximal aortic repair alone	Mortality

Table 44.2 Surgical mortality in acute type A aortic dissection with malperfusion

Author	Year	MPS (+)		MPS (−)		P value	Study type (quality of evidence)
		N	Mortality (%)	N	Mortality (%)		
Yagdi et al. [24]	2006	57	42.1	61	14.8	0.001	Retrospective cohort study (low)
Geirsson et al. [12]	2007	59	30.5	162	6.2	<0.001	
Girdauskas et al. [8]	2009	93	29.0	183	14.0	0.002	Retrospective cohort study (low)
Pacini et al. [22]	2012	103	43.7	399	15.0	0.001	Retrospective cohort study (low)

Abbreviation: MPS malperfusion syndrome

However, catheterization in patients with ATAAD carries significant risks of rupture, extending the aortic dissection, and/or worsening the existing malperfusion. While it is a general consensus that surgical intervention is the first line to treat ATAAD patients with myocardial malperfuion, further investigation would be warranted to assess which ATAAD patients with myocardial malperfusion would benefit from early revascularization by coronary stenting prior to surgical repair.

Cerebral Malperfusion

The brain is the most vulnerable organ for ischemia, and complications secondary to outcome and cerebral malperfusion dramatically impact the postoperative outcome and quality of life of ATAAD patients. According to data from the International Registry of Acute Aortic Dissection (IRAD), stroke was observed in 6.0% of ATAAD patients, and it was associated with longer hospital stay and higher in-hospital mortality [11]. Preoperative cerebral malperfusion significantly worsen also the long-term survival [12]. There have been many surgical strategies investigated to protect and improve the cerebral circulation before/during proximal aortic repair, topics which include cannulation strategy, ante-/retrograde cerebral perfusion, and appropriate temperature of deep hypothermia. It is not scientifically apparent which strategy is the best to treat ATAAD with cerebral malperfusion. A recent meta-analysis of nine clinical studies assessed the effect of cannulation site (femoral vs. axillary artery) used for ATAAD repairs. They summarized that axillary artery cannulation may reduce the short-term mortality and neurological dysfunction [13]. It is always a challenging question if ATAAD patients with cerebral malperfusion should be considered for surgical intervention or not. Prognosis of ATAAD patients with severe neurological dysfunction, especially with coma, is very poor, and therefore proximal aortic repair in such cases may be even considered contraindicated [14]. However, several investigators reported neurological recovery with early cerebral reperfusion by proximal aortic repair in a limited

Table 44.3 Surgical mortality in acute type A aortic dissection with malperfusion of specific organs

Author	Year	Cerebral MP		Myocardial MP		Visceral MP		Limb MP		Without MP	
		N	Mortality (%)	N	Mortality (%)	N	Mortality (%)	N	Mortality (%)	N	Mortality
Yagdi et al [24]	2006	15	46.7	9	22.2	9	100	39	43.6	61	14.8
Geirsson et al [12]	2007	16	50	16	31.3	3	33.3	28	N/A	162	6.2
Patel et al. [6]	2008	7	57.1	N/A	N/A	37	40.5	41	34.1	125	9.5
Girdauskas et al. [8]	2009	29	20.7	41	39.4	8	75	32	34.6	183	14.0

Abbreviation: MP malperfusion, *N/A* not available

number of cases [15, 16]. Estrera et al. reported neurological recovery in 14% of ATAAD patients presented with stroke [15]. Tsukube et al. also reported a series of ATAAD patients with cerebral malperfusion (i.e. coma) undergoing proximal aortic repair that showed full neurological recovery was achieved in 86% of patients who underwent surgery within 5 hours since the onset of neurological symptoms, but only in 17% those patients operated over 5 hours since onset [16]. It is the gold standard strategy to perform proximal aortic repair on as soon as possible basis in order to prevent/improve permanent neurological deficit in ATAAD patients with cerebral malperfusion. However, some investigators have reported efficacy of selective reperfusion of the carotid artery prior to proximal aortic repair both in animal experiments and clinical case reports [17–19]. Recently, Furukawa et al. reported acceptable outcome with quick cerebral reperfusion using cutdown carotid cannulation method in cases with neurological symptoms or cerebral malperfusion, which was monitored by transcutaneous carotid echo and regional oxygen saturation, with subsequent proximal aortic repair in ATAAD patients [20].

Visceral Malperfusion

Visceral malperfusion carries the highest mortality rate among all malperfusion syndromes in ATAADs. The incidence of visceral malperfusion in ATAAD patients is ranging from 2.4% to 6.0%, and the mortality rate in patients with visceral malperfusion is about three times higher than those without malperfusion (63.2% vs 23.8%) [8, 21–23]. Furthermore, visceral malperfusion is reported as the strongest predictor of postoperative mortality among ATAAD patients with organ malperfusion [24]. Even with exploratory laparotomy with/without necrotic bowel resection following the proximal aortic repair, the clinical outcome is not satisfactory. Therefore, visceral malperfusion is the most intensively assessed category if peripheral reperfusion prior to proximal aortic repair would benefit or not. There are several peripheral interventions that have been investigated.

Open surgery is the main treatment option for visceral malperfusion. Open fenestration technique is a procedure to remove a wide portion of the intimal flap in the abdominal aorta expecting reperfusion to organs by changing dynamic blood flow. This technique is the most common open procedure reported for peripheral reperfusion especially in complicated type B aortic dissection [25, 26]. Lauterbach et al. reported no mortality with early open fenestration in ATAAD patients with visceral malperfusion. They suggested ATAAD patients without rupture, but with mesenteric malperfusion would benefit from peripheral intervention before proximal aortic repair [27]. Fenestration technique might not effectively work for static malperfusion. In such a situation, extra-anatomical bypass grafting for direct branch revascularization might be reasonable option [28, 29]. Considering the significant invasiveness of such open surgery, endovascular interventions have been emerging as an alternative strategy for peripheral intervention.

Endovascular interventions recently has become a standard option for visceral malperfusion. Percutaneous fenestration technique with an endovascular balloon is

one of the main endovascular interventions [1, 30]. Deeb et al. proposed that percutaneous fenestration before proximal aortic repair might reduce the mortality of ATAAD patients with visceral malperfusion with end-organ dysfunction [1]. As for endovascular fenestration techniques other than the standard balloon fenestration method, a variety of device and techniques has been reported including the intravascular scissors technique [31], the cheese wire technique [32], and the funnel technique [33, 34]. Intravascular ultrasound (IVUS) is reported useful to distinguish false/true lumens as well as intimal flaps, and is also able to confirm expansion of the true lumen after intervention [35].

While early intervention for malperfusion with open or endovascular procedures prior to proximal aortic repair may contribute to improving the mortality, there is always a dilemma that a delay in proximal aortic repair might lead to a significant increase in the risk of mortality due to aortic rupture, tamponade, etc. [6, 27]. Uchida et al. used simultaneous direct cannulation to the superior mesenteric artery during proximal aortic repair to secure early reperfusion to the endorgans and minimize organ damages. This early reperfusion strategy successfully improved the mortality of ATAAD patients with visceral malperfusion [36]. Recently, hybrid suites have become available and found useful for proximal aortic repair with simultaneous early therapeutic intervention for ATAAD patients with malperfusion. The IRAD data revealed that a hybrid strategy -proximal aortic repair with simultaneous percutaneous treatment of visceral melperfusion- had an improved mortality rate compared to those of endovascular intervention only or medical therapy groups (41.7% vs 72.7% vs 92.5%) [21]. Tsagakis et al. described the efficacy of a hybrid suite for ATAAD patients with malperfusion. In their report, visceral malperfusion was detected in 23% of patients (16/71) who underwent surgery with angiography. Of these, mortality in patients with endovascular intervention before proximal aortic repair was 25%, and those without endovascular revascularization was 75% [37].

The hybrid suite also could facilitate advanced operative interventions such as the frozen elephant trunk technique. The hybrid frozen elephant trunk technique includes proximal aortic repair and intraoperative stenting into the distal true lumen, which result in increased true lumen flow and superior organ reperfusion. Hofferberth et al. reported a comparison between standard proximal aortic repair alone and the hybrid surgery with the frozen elephant technique with a distal bare metal stenting. Of eleven ATAAD patients with preoperative visceral malperfusion, 60% (3/5) of patients with conventional aortic repair and none (0/6) with hybrid surgery had persistent visceral malperfusion postoperatively; the mortality rate was 40% and 0%, respectively [38].

At present, there is not enough data from large cohort studies available to support short- or long-term safety and efficacy of endovascular reperfusion in ATTADs with visceral malperfusion. In addition, the best timing (i.e. before, during, or after proximal aortic repair) of endovascular interventions is still unclear. However, early diagnostic or/and therapeutic peripheral intervention should be considered/investigated to treat ATAADs with visceral malperfusion given the current high mortality when treated with proximal aortic repair alone. The hybrid suite contributes to reducing the delay between early endovascular intervention and subsequent proximal surgical repair and certainly expedites the simultaneous performance of peripheral interventions and/or the frozen elephant trunk technique.

Extremity Malperfusion

Lower limb ischemia occurs in approximately 11% of ATAAD patients [21]. In general, it is considered that limbs have a higher tolerance for ischemia compared to other organs and therefore proximal aortic repairs should be prioritized in ATAAD patients with limb ischemia. The majority of limb malperfusion are resolved only with proximal aortic repair [8, 39, 40]. Charlton-Ouw et al. retrospectively compared the outcomes of proximal aortic repair for a total of 335 ATAAD patients with or without limb ischemia (Table 44.4). Proximal aortic repair resolved the lower limb ischemia in nearly 80% (40/51) of cases. It also showed comparable in-hospital mortality and 5-year survival between ATAAD patients with/without limb ischemia. Early revascularization was required in 9 of the remaining 11 patients following the proximal aortic repair with excellent outcomes [39].

While proximal aortic repair resolves limb ischemia in 70–100% of cases, early diagnostic investigation and therapeutic intervention are crucial for persistent limb ischemia and/or coexisting other malperfusion to prevent further complications [8, 39, 40]. ATAAD patients with lower limb malperfusion have a higher rate of coexisting mesenteric ischemia compared with those without limb malperfusion (16.2% vs 6.2%) [40]. Shiiya et al. reported nine ATAAD patients with lower limb ischemia who underwent proximal aortic repair. Four patients (44.4%) required additional femoro-femoral bypass grafting, and two of them were performed immediately after the proximal aortic repair [41]. Luterbach et al. reported 3 of 14 (21.4%) ATAAD patients with limb ischemia required additional intervention after central aortic repair (aorto-bifemoral bypass N = 1, femoro-femoral bypass N = 2), and all three were discharged uneventfully [27]. It is a reasonable option to perform simultaneous surgical intervention (e.g. femoro-femoral, axillo-bigemoral bypass) during central aortic repair for ATAAD patients with persistent limb ischemia [42, 43]. In conclusion, for extremity malperfusion, peripheral intervention, even after the proximal aortic repair, provides an acceptable outcome.

Recommendations

Malperfusion in ATAAD may involve single or multiple organ systems, and the optimal treatment is variable depending on the affected organ(s). Therefore, treatment strategy should be determined on a case-by-case basis. Early central repair is recommended for ATAAD patients with limb malperfusion, because most of them are resolved only with proximal aortic repair and also the clinical outcomes of peripheral intervention after proximal aortic repair are excellent. Myocardial malperfusion also deserves immediate proximal aortic repair due to the nature of the anatomical location and possible “peripheral” reperfusion treatment (i.e. coronary artery bypass grafting). In case of cerebral malperfusion, if surgery is indicated, proximal aortic repair should be done first. Cerebral perfusion monitoring is important, and if malperfusion is observed or newly occurred during surgery, quick reperfusion with direct cannulation of the carotid artery would be one of the options to

Table 44.4 Surgical mortality in acute type A aortic dissection of surgery with/without adjunctive intervention for peripheral malperfusion

Author	Year	Organ	Type of PI	PAR + PI		PAR alone		P value	Study type (quality of evidence)
				N	Mortality (%)	N	Mortality (%)		
Lauterbach et al. [27]	2001	Multiple	Open surgical fenestration, stenting of abdominal arteries, peripheral bypass grafting	5	20	19	21	N/A	Retrospective cohort study (low)
Patel et al. [6]	2008	Multiple	Percutaneous fenestration, aortic true lumen stenting with/without branch vessel stenting	47	8.5	N/A	N/A	N/A	Retrospective cohort study (low)
Hofferberth et al. [38]	2013	Multiple (Visceral)	Retrograde descending aortic stent grafting plus distal bare metal stenting	19 (5)	5 (40)	18 (6)	12 (0)	0.60 (N/A)	Retrospective cohort study (low)
Tsagakis et al. [37]	2013	Visceral	Percutaneous fenestration, aortic true lumen stenting with uncovered stent, selective stenting of abdominal arteries	12	25	4	75	N/A	Retrospective cohort study (low)
Yamashiro et al. [28]	2015	Visceral	Superior mesenteric artery bypass grafting	8	0	2	100	<0.01	Retrospective cohort study (low)
Charlton-Ouw et al. [39]	2013	Limb	Peripheral bypass grafting	11	27	40	15	N/A	Retrospective cohort study (low)
Charlton-Ouw et al. [40]	2016	Limb	Peripheral bypass grafting	18	N/A	50	N/A	N/A	Retrospective cohort study (low)

Abbreviations: PAR proximal aortic repair, *PI* peripheral intervention for end-organ malperfusion, *N/A* not available

improve neurological outcomes. In visceral malperfusion, because of its high mortality rate with proximal aortic repair alone, early peripheral intervention prior to proximal aortic repair either by open or endovascular technique would be recommended in selective cases. Hybrid suites might facilitate peripheral interventions before/during/after proximal aortic repair, and accommodate new surgical techniques (e.g. the frozen elephant trunk technique).

A Personal View of the Data

Malperfusion in ATAAD is associated with high perioperative morbidity and mortality. While malperfusion in ATAAD patients is an important clinical property, it suffers from a lack of strong clinical evidence of an optimal treatment strategy because of the infeasibility of performing a randomized control trial (due to the nature of this critical disease process). Nevertheless, it is important to seek new techniques/strategies to improve the clinical outcomes. Recently, an advanced surgical technique has emerged. – The frozen elephant trunk technique-consisting of proximal aortic surgical repair along with an open stenting of the true lumen of the distal aorta. This technique could potentially decrease the rate of postoperative malperfusion [38]. Roselli et al. showed the technique might enhance false lumen thrombosis and aortic remodeling after the surgery [44]. On the other hand, while it is a promising technology, it has been reported that this technique is associated with relatively high postoperative paraplegia (5%) [45]. Further intervention of the frozen elephant trunk technique in this acute condition is warranted.

Recommendations

- Immediate proximal aortic repair is recommended for ATAAD patients with limb malperfusion. In case of persistent limb malperfusion after proximal aortic repair, peripheral revascularization then should be considered (evidence quality low; weak recommendation).
- Myocardial malperfusion deserves immediate proximal aortic repair and requires simultaneous revascularizations (i.e. coronary artery bypass grafting). (Evidence quality low; weak recommendation).
- For cerebral malperfusion, it is recommended to do proximal aortic repair first. Cerebral perfusion monitoring may be useful for intraoperative neurological assessment and possible specific treatments (evidence quality low; weak recommendation).
- Open/percutaneous intervention (diagnostic and therapeutic) prior to proximal aortic repair in selected ATAAD patients with visceral malperfusion might be critical. (Evidence quality low; weak recommendation).

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Chapter 45
Ischemic Leg Following IABP Insertion: Timing of Diagnosis and Treatment

Theodore Hart and Ross Milner

Introduction

The published experience with limb ischemia and other vascular complications from intra-aortic balloon pump (IABP) counterpulsation now spans over four decades [1]. There are a variety of causes for limb ischemia in the setting of an IABP including arterial injuries at the time of insertion leading to dissection, arterial insufficiency resulting from the luminal obstruction, vasospasm, or an associated thromboembolic event [2]. The reported incidence varies widely with early and smaller institutional series reporting rates of limb ischemia as high as 25% [3]. The largest registry data published to date reported a 2.9% incidence of limb ischemia with a 0.9% rate of ischemia requiring surgical intervention in 16,909 patients reviewed [4]. An important caveat to this data is the in-hospital mortality is 21.2% and the majority of patients expire with the IABP in place [4]. This illustrates a crucial challenge both with treating this group of patients and interpreting data in this setting – limb ischemia is frequently coupled with hemodynamic instability and is often reported as a secondary endpoint.

Limb ischemia in critically ill patients with mechanical circulatory support devices remains a frequent clinical occurrence and the published data now expands

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beyond IABP. In patients treated with venoarterial extracorporeal membrane oxygenation (VA-ECMO), rates of limb ischemia exceed 10% with even higher associated mortality when compared to IABP [5]. Patient risk factors for limb ischemia in the setting of IABP include peripheral arterial disease, female gender, smaller patients, diabetes, low cardiac index, and history of smoking [4, 6–9]. The strongest risk factor of these is pre-existing peripheral arterial disease. Certain technical considerations including insertion of the IABP with a larger sheath and the use of larger catheter sizes are associated with higher rates of vascular complications in several series as well [4, 10–12]. The propensity for limb ischemia thus depends on a combination of vessel caliber, vessel quality, and the degree of obstruction by a sheath, cannula, or catheter.

This chapter examines those patients who have developed limb ischemia in the setting of an IABP. We review the evidence that exists that focuses directly on the management of this difficult clinical problem once it has arisen. The problem is approached primarily from the perspective of a consulting surgeon with consideration also given to the perspective of a managing intensivist. After reviewing and analyzing the literature, we offer our recommendations pertaining to the management of this challenging presentation.

Search strategy

A search of English language publications in the last 25 years was used to identify published data on limb ischemia following intra-aortic balloon pump placement using the PICO outline (Table 45.1). PubMed and Cochrane databases were searched using the terms “intra-aortic balloon pump” OR “intraaortic balloon pump” OR “IABP” OR “balloon counterpulsation” AND “limb ischemia” OR “vascular complications.” Articles were excluded if the study population was non-human or pediatric, the focus was on chronic rather than acute limb ischemia, the primary focus was a novel technique or alternative mechanical circulatory support device, or the article did not list complications or failed to address the interventions for complications. We analyzed references of major review series for missed publications and reviewed historic papers of interest. The data was classified using the GRADE system.

Table 45.1 PICO table for timing of diagnosis and treatment of acute limb ischemia following intra-aortic balloon pump insertion

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Adult patients with femoral IABP	IABP removal, anticoagulation, revascularization	Supportive care, Expectant management	Amputations, Overall survival

Results

There are no randomized controlled trials or meta-analyses that specifically address management of acute limb ischemia in this setting. Large reviews of the topic also focus primarily on the incidence and risk factors rather than management [13]. Our search yielded 21 relevant observational studies, a third of which collected data prospectively (Table 45.2) [4, 6, 12, 14, 15, 16]. There is significant heterogeneity across the data with most studies representing a single institution's experience with

Table 45.2 Summary of publications addressing management of lower extremity ischemia following intra-aortic balloon pump insertion

Author (year)	Study type, evidence quality	Patients N	Ischemia N (%)	IABP removal only N (%)	Surgery N (%)	Bypass N (%)	Amputation N (%)
Yuksel (2013) [9]	R/SI/OS, Low	148	13 (8.8)	4 (30)	9 (69)	1 (7.7)	1 (7.6)
Kogan (2012) [14]	P/SI/OS, Low	203	7 (3.4)	3 (43)	4 (57)	–	1 (14)
Severi (2012) [17]	R/SI/OS, Low	423	4 (0.9)	N/A	4 (100)	1 (25)	1 (25)
Dick (2009) [18]	R/SI/C, Low	187	19 (10)	5 (26)	10 (53)	–	4 (21)
Laish-Farkash (2009) [15]	P/SI/C, Low	97	2 (2.1)	1 (50)	1 (50)	–	–
Christenson (2007) [19]	R/SI/OS, Low	135	18 (13)	12 (67)	6 (33)	–	1 (5.5)
Erdogan (2006) [20]	R/SI/OS, Moderate	1211	129 (11)	67 (52)	62 (48)	3 (2.3)	1 (0.8)
Meisel (2004) [12]	P/SI/OS, Low	161	4 (2.5)	2 (50)	2 (50)	–	–
Arceo (2003) [21]	P/SI/OS, Low	212	12 (5.7)	6 (50)	4 (33)	–	1 (8.3)
Colyer (2002) [22]	R/SI/OS, Low	35	2 (5.7)	2 (100)	N/A	–	–
Meharwal (2002) [16]	P/SI/OS, Moderate	911	77 (8.5)	33 (43)	34 (44)	4 (5.2)	7 (9.1)
Ferguson (2001) [4]	P/MC/OS, Moderate	16,909	490 (2.9)	338 (69)	152 (31)	–	17 (3.5)
Cohen (2000) [6]	P/MC/OS, Moderate	1119	37 (3.3)	31 (84)	6 (16)	–	1 (2.8)
Sirbu (2000) [23]	R/SI/OS, Low	524	140 (27)	N/A	140 (100)	–	5 (3.6)
Arafa (1999) [24]	R/SI/OS, Low	509	38 (7.5)	3 (7.9)	35 (92)	4 (11)	4 (11)
Davidson (1998) [25]	R/SI/OS, Low	86	3 (3.5)	N/A	3 (100)	–	3 (100)

(continued)

Table 45.2 (continued)

Author (year)	Study type, evidence quality	Patients N	Ischemia N (%)	IABP removal only N (%)	Surgery N (%)	Bypass N (%)	Amputation N (%)
Busch (1997) [26]	R/SI/OS, Low	472	99 (21)	N/A	99 (100)	–	5 (5.1)
Jameson (1995) [27]	R/SI/OS, Low	51	7 (14)	N/A	7 (100)	–	–
Eltchaninoff (1993) [28]	R/SI/OS, Low	231	21 (9.1)	11 (52)	9 (43)	–	1 (4.8)
Makhoul (1993) [29]	R/SI/OS, Low	436	40 (9.2)	N/A	38 (95)	9 (23)	5 (13)
Tatar (1993) [11]	R/SI/OS, Low	126	20 (16)	9 (45)	11 (55)	–	–
Mackenzie (1992) [3]	R/SI/OS Low	100	25 (25)	7 (28)	18 (72)	2 (8)	1 (4.0)

Study types – *R* Retrospective data review, *P* Prospective data collection, *SI* Single institution, *MC* Multiple centers, *OS* Observational study, *C* Cohort. Mortality accounts for lower surgical therapy numbers in some series

IABP complications over several years. Patient populations included both medical and surgical intensive care unit patients and no study described a difference in management strategy for limb ischemia based on the indication for IABP placement.

The definition used for limb ischemia was usually specified and most commonly included loss of pulse or Doppler signal with an associated change in limb temperature and color. However, the initial approach in response to these findings was not specified in the studies and the impact of several available clinical maneuvers such as decreasing vasopressors, passively rewarming the extremity, pulling back on the sheath of the IABP to increase the cross-sectional area of the arterial lumen, and initiation of therapeutic anticoagulation during evaluation and treatment of limb ischemia are not quantified. It should be noted that the selective use of anticoagulation in the IABP patient population as a whole is supported in studies of both medical and surgical intensive care patients, but its role in management specifically for limb ischemia is not addressed in the existing literature [14, 15, 30].

Several studies differentiated between major and minor ischemia, typically classifying minor ischemia as diminished pulse or Doppler signal with resolution after IABP removal. A few studies only reported limb ischemia that required operative intervention [17, 23, 25–27, 29]. A majority of studies specified the average duration of IABP therapy. However, the timing of the diagnosis of limb ischemia relative to the overall duration of IABP therapy was rarely included and data regarding the timing of interventions relative to diagnosis of limb ischemia is conspicuously absent. Similarly, granular data to account for the individualized decisions of increasingly involved interventions ranging from IABP removal to replacement at a different site to surgical revascularization as well as need for fasciotomy or amputation is lacking. A majority of studies included data on mortality but did not discuss

the relationship between mortality and limb ischemia. Mortality as a direct consequence of IABP complications was low with the largest registry data citing a rate of 0.05% [4].

Prolonged duration of IABP therapy has been cited as a risk factor for both overall vascular complications and limb ischemia [19, 31]. Christenson reported significantly higher average IABP duration in 18 patients with limb ischemia compared to 117 without (99.8 ± 54.1 h vs. 34.4 ± 30.4 h); however, the timing to diagnosis of limb ischemia was not specified [19]. Contrasting this, Eltchaninoff reported a shorter IABP duration in 21 patients with limb ischemia compared to 210 patients without (37 ± 24 h vs. 45 ± 39 h) [28]. The mean timing for identification of limb ischemia was reported at 25.3 h (range 1–86.5 h), with 4 of 21 patients developing ischemia after IABP removal [28]. Arceo observed 8 of 12 patients with limb ischemia presented in the initial 24 h, the remaining patients presented at 38 and 55 h with two patients developing symptoms greater than 96 h after insertion [21]. Taken together, this data highlights an uncertain relationship between duration of IABP therapy and development of limb ischemia. The timing of the clinical presentation of ischemia is variable and warrants vigilant observation, including after the IABP is removed.

Removal of the IABP often resolves limb ischemia by alleviating a flow-limiting luminal obstruction. Meisel's illustration of lower profile catheters is extremely helpful with depicting the luminal reduction caused by an IABP (Fig. 45.1) [12]. It is important to note that the removal of the IABP can occasionally herald the onset of limb ischemia. In four of five series with over 500 patients that differentiated major and minor limb ischemia, the majority of patients avoided operative intervention with IABP removal [4, 6, 20, 16, 24]. In addition to the Eltchaninoff series discussed above, three additional series reported instances of limb ischemia that occurred in the period after IABP removal, the largest of which had a rate of 23% [18, 15, 20, 23]. These data confirm that removal of the IABP is successful as the initial management for limb ischemia in the majority of patients, but a percentage are at risk of developing ischemia after removal and these patients still need to be critically assessed for their distal perfusion.

Early experience with operative intervention for acute lower extremity ischemia in the postoperative cardiac surgery population was associated with significant mor-

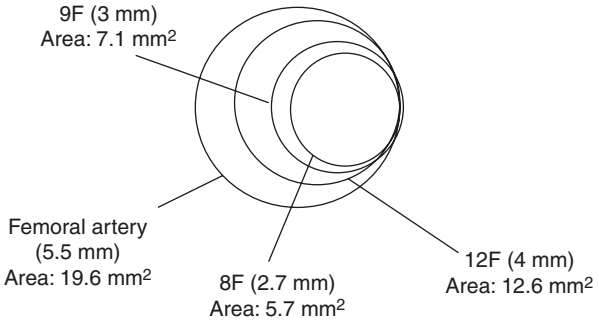

Fig. 45.1 A schema depicting the degree of luminal obliteration of the femoral artery by intra-aortic balloon catheters of varying diameters. (Borrowed with permission from Wiley periodicals [12])

bidity and mortality [32]. Several studies now highlight a trend of a decreasing morbidity associated with IABP placement attributed to changes in technique from an open to percutaneous approach utilizing a smaller diameter catheter with a sheathless insertion technique [10, 18, 24]. However, nearly all studies highlight the continued need for surgical interventions in a percentage of patients, often with risk factors of peripheral arterial disease and diabetes. Our search did not reveal any data to specifically compare surgical revascularization techniques in this setting. The majority of procedures performed included a thromboembolectomy at the IABP insertion site with a lesser percentage requiring additional procedures such as arterial repair, endarterectomy, patch angioplasty, iliofemoral or other bypass including extra-anatomic bypass; these were quantified in best detail in smaller series making the data difficult to compare. Unfortunately, morbidity and mortality data specific to the surgical revascularization procedures is limited.

There are number of additional reported procedures in the literature which deserve mention. Subclavian artery IABP insertion in advanced heart failure and high-risk cardiac surgery patients has been performed with only a 1.1% rate of arterial thrombosis and no additional limb ischemia complications [33–35]. Temporary approaches utilizing percutaneous and open techniques with an external prosthetic graft to treat IABP-related limb ischemia have been described with technical success [36, 37]. Diagnostic angiography with endovascular therapy has been performed with technical success in this setting as well, but this experience is limited a handful of patients [22, 38]. Colyer's experience demonstrates percutaneous endovascular intervention should be a consideration prior to IABP placement in high risk patients [38]. Experience with prophylactic distal perfusion catheters is an important related intervention increasingly utilized to decrease limb ischemia in the setting of VA-ECMO [5]. In Lamb's review of 91 patients on VA-ECMO, placement of distal perfusion catheter prophylactically in 55 patients prevented limb ischemia; a third of the remaining patients went on to develop ischemia and were treated with a combination of subsequent distal perfusion catheter placement and fasciotomy with a limb salvage rate of 91% [5].

Recommendations

The existing literature does little to capture the context of this difficult clinical problem. Critically ill patients with mechanical circulatory support devices are among the most challenging patients to manage and limb ischemia is rarely an isolated issue in these patients. In practice, we evaluate each patient on an individualized basis beginning with an assessment to identify the degree of limb ischemia and its suspected pathophysiology. The history and physical examination, at times combined with an arterial duplex ultrasound, are effective at identifying cases of critical limb ischemia requiring intervention. If the patient's lower extremity condition permits, we initially observe with serial neurovascular exams while attempts are made to medically optimize cardiac output and peripheral perfusion in order to remove

the IABP. If not contraindicated, we recommend therapeutic anticoagulation with heparin. The evidence that guides this initial evaluation, particularly with respect to its timing, is lacking in depth and detail. However, the fact that the vast majority of patients experience resolution of limb ischemia with IABP removal is clear from the larger series and supports our first recommendation. It is our experience that the majority of surgical consults for limb ischemia in this setting do not progress beyond this point.

If the patient is dependent on the device, we next recommend changing the insertion site with preference given to the subclavian artery. Although technically demanding, the subclavian artery approach overcomes limitations of the femoral placement and importantly allows for mobility and ambulation if a longer-term period of mechanical support is necessary [33]. For patients with limb ischemia after IABP removal or re-siting, surgical revascularization beginning with thromboembolectomy is appropriate; this is the most common surgical intervention in the literature and addresses additional causes of ischemia beyond low flow from luminal obstruction. We believe operative extra-anatomic bypass is the preferred surgical intervention for patients with critical limb ischemia in whom IABP removal or re-siting is not feasible. This is typically performed with a femorofemoral bypass below the IABP insertion site utilizing a tunneled prosthetic graft. Although the data regarding surgical interventions is limited to series, there are multiple observational studies supporting its use in comparison to sporadic case reports of alternative techniques.

A Personal View of the Data

While data that dives deeper than simply describing the association between IABP insertion and limb ischemia in the context of risk factors or patient populations is hard to come by, there is a clearly discernable pattern across the published observational studies that most patients with ischemia will not need surgery and those who do most commonly require only thromboembolectomy. With these observations in mind, this complex clinical scenario should remain one in which the management is individualized. The pathophysiology of luminal obstruction, the possibility that an additional thromboembolic complication or trauma from insertion are contributing to ischemia, and the timing and degree to which the ischemia is limb threatening should be placed in the context of the patient's prognosis and his or her ability to tolerate interventions to formulate management recommendations.

Although classically described and evaluated in the context of the IABP, this difficult clinical problem will persist as the technology and experience with additional mechanical circulatory support devices continues to grow. The majority of studies referencing limb ischemia in the context of mechanical circulatory support devices are likely to continue to do so as a secondary endpoint. However, an effort to better specify the degree of ischemia, the timing and criteria used in the clinical assessment, and the interventions required as well as their associated outcomes will help

to advance the care of patients with this complication. We feel that these should be the future directions of research in this area and compel the attention of the practitioners who care for this complex patient population.

Recommendations (Abstracted)

1. Patients with limb ischemia following IABP insertion should undergo removal or re-siting of the IABP (Evidence quality moderate; Strength of recommendation: strong)
2. Patients with limb ischemia following removal of the IABP should undergo revascularization beginning with thromboembolectomy (Evidence quality moderate; Strength of recommendation: strong)
3. Patients with limb ischemia following IABP insertion who are unable to undergo removal or re-siting of the IABP should undergo extra-anatomic surgical bypass (Evidence quality low; Strength of recommendation: weak)

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This chapter was inadvertently published with incorrect figure credit lines in Fig. 1.3 and Fig. 1.4. The correct credit line were updated as follows:

In the original version of chapter 1, the figures credit lines for figures 1.3 and 1.4 were changed from **the Royal Collection Trust** to **the University of Illinois**.

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