# Postoperative Critical Care for Cardiac Surgical Patients

Ali Dabbagh
Fardad Esmailian
Sary F. Aranki
*Editors*

Springer

# Postoperative Critical Care for Cardiac Surgical Patients

Ali Dabbagh • Fardad Esmailian • Sary F. Aranki
Editors

# Postoperative Critical Care for Cardiac Surgical Patients

Springer

*Editors*
Ali Dabbagh, MD
Department of Anesthesiology
and Anesthesiology Research Center
Faculty of Medicine
Shahid Beheshti University
of Medical Sciences
Tehran
Iran

Fardad Esmailian
Heart Transplant and Mechanical
Circulatory Support
Cedars-Sinai Heart Institute
Los Angeles, CA
USA

Sary F. Aranki, MD
Divisions of Cardiac Surgery
Brigham and Women's Hospital
Boston, MA
USA

ISBN 978-3-642-40417-7 ISBN 978-3-642-40418-4 (eBook)
DOI 10.1007/978-3-642-40418-4
Springer Heidelberg New York Dordrecht London

Library of Congress Control Number: 2013955229

*To my wife Samira and to my Parents*

*Ali Dabbagh*

*To my family: Yvonne, Gabriel and Aaron and to my parents*

*Fardad Esmailian*

*To Nadia, Alex, Heather and Abla*

*Sary F. Aranki*

# Foreword

The *Handbook of Postoperative Critical Care for Cardiac Surgeries* is a superb amalgamation of a wide variety of clinical expertise in the perioperative and postoperative care of cardiac surgical patients edited by three very fine academicians from three outstanding medical centers and who are in the position of being able to judge the best perioperative and postoperative cardiac surgical care. The three editors have a wide variety of cardiac surgical interest. Dr. Dabbagh is a cardiac anesthesiologist, who is intimately involved in the intraoperative and postoperative care of cardiac surgery patients; Dr. Esmailian is an expert in the care of patients receiving cardiac assist devices and cardiac transplantation, which are some of the most challenging postoperative patients; and Dr. Aranki is an extremely talented surgeon in all aspects of cardiac surgery, especially coronary artery bypass grafting and valve repair and replacement.

This book brings the entire spectrum of cardiac surgical perioperative treatment and postoperative care under one cover. Postoperative critical care in cardiac surgery is extremely important and I believe this book has the potential to be the gold standard in postoperative care for cardiac surgical patients. The key to good surgical results is the combination of an excellent operation and meticulous perioperative and postoperative care, the essence of this book.

The authors are to be complimented for providing up-to-date, accurate, and intellectual contributions for this most important area of cardiac surgery. This book is an excellent effort in advancing the art and science of perioperative and postoperative surgical care.

Lawrence H. Cohn, MD
Brigham and Women's Hospital
Harvard Medical School,
Boston, MA, USA

# Preface

Cardiac surgery is a process, not an event. Due to the prevalence of cardiac diseases and conditions within society, cardiac surgeries now rank among the most common of all surgical procedures. But they are also the most challenging and complicated, all of which imposes a burden of instructive issues upon students and faculty alike. The following is a handbook encompassing the entire period of postoperative cardiac surgical care, including the basic physiologic and pharmacologic knowledge to clinical aspects of clinical care in different major body organs.

This book stresses on this point that during postoperative period, the patient commences upon a highly complex set of postoperative challenges and will often require lifelong monitoring to ensure that the management of all potential morbidities has been achieved. Surgery is not, therefore, an end, but rather a beginning.

In the often long-term postoperative era, a patient embarks upon a new set of needs for recovery and lifelong follow-up. Towards this end of perioperative care, it is most crucial not to view the surgery and anesthesia as the climax of a patient's experience, but rather as a bridge between a former and a new life for the patient.

While postoperative care plays a crucial role in determining the clinical result for the patient, the success of postoperative care is also directly affected by the quality of the pre- and intraoperative experiences. The chapters of this book, therefore, also survey these seminal periods for the patient, with particular attention given to cardiopulmonary bypass. Other chapters assume an organ-oriented perspective in addressing critical care. This broad, intersystemic approach creates a holistic view of the cardiac domain not only in its functions within itself but also within the entire body, enabling this to become a reliable guidebook for cardiac intensive care. This book can then be used by cardiac surgeons, cardiac anesthesiologists, intensivists, and cardiac intensive care nurses, as well as the students, interns, and residents learning in such environments, in the successful management of the process of cardiac surgery.

This book could not have been come to fruition without the very committed and compassionate teamwork of Springer Company, especially Springer-Verlag Berlin Heidelberg.

The authors should acknowledge among a long list of people especially to the following people:

Dr Ute Heilmann, Meike Stock, Martina Himberger, Dörthe Mennecke-Bühler, Sally Ellyson, Margaret Zuccarini, Megan Hughes, Karthikeyan Gurunathan and Palanisamy Dhanapal.

Also, the author would like to acknowledge the kind assistance of Heather M. Couture, Division of Cardiac Surgery, Brigham and Women's Hospital, Boston, MA, USA and Ann M. Maloney could not be forgotten.

We also have to acknowledge the creative, expressive and cultivated drawings of Majid Ghaznavi which are used in Chapters 1, 4, 5, 7, 8, and 12.

And finally, we have to acknowledge our families who have inspired us with accompaniment, empathy, sacrifice and endless love in such a way that we could promote this effect.

Tehran, Iran — Ali Dabbagh, MD
Los Angeles, CA, USA — Fardad Esmailian
Boston, MA, USA — Sary F. Aranki, MD

# Contents

# Cardiac Physiology

1

Ali Dabbagh

## Contents



**Abstract**

Cardiac physiology is one of the most interesting discussions both in physiology and cardiac-related clinical sciences. Anatomy and physiology of the heart are directly related to the clinical presentations of disease states. The heart is composed of pericardium, endocardium, and myocardium, the last being more

A. Dabbagh, MD
Department of Anesthesiology and Anesthesiology Research Center, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
e-mail: alidabbagh@sbmu.ac.ir

A. Dabbagh et al. (eds.), *Postoperative Critical Care for Cardiac Surgical Patients*,
DOI 10.1007/978-3-642-40418-4_1, © Springer-Verlag Berlin Heidelberg 2014

discussed here and consists of cardiac connective tissue cells, cardiomyocytes (which have contractile function), and cardiac electrical system cells (consisting of "impulse-generating cells" and "specialized conductive cells"). The main cardiac cells are cardiomyocytes with their unique structure having some shared features with both skeletal muscles and smooth muscles, though not completely similar with any of the two.

Cardiac cells have three different but "highly interrelated" aspects: action potential, excitation-contraction coupling (ECC), and contractile mechanisms, each of the three being a complex of many different physiologic chains to create together and as a final outcome a main goal: cardiac contraction leading to cardiac output.

A number of physiologic reflexes are involved in cardiac physiology discussed in the final part of the chapter.

## 1.1 Introduction to Cardiac Physiology

### 1.1.1 The Physiologic Anatomy of the Heart

The normal heart is a physiologic pump composed of two adjacent, parallel pumps (i.e., left and right); each of these separate pumps is composed of two chambers (i.e., atrium and ventricle); each atrium conducts the blood to its related ventricle; the ventricle would in turn pump the blood to the main artery connected to the related outflow tract, i.e., from left ventricle outflow tract to aorta and from right ventricle outflow tract to pulmonary artery. Afterwards, blood is sent forward, to the arterial tree in a propulsive manner. This is known as the cardiac contractile system composed of the cardiac muscle, which in turn is composed of two muscle masses known as "cardiac muscle syncytium": the atrial syncytium and the ventricular syncytium which are separated by a fine part of the cardiac conductive system (see following pages).

Grossly speaking, both right atrium (RA) and left atrium (LA) have a delicate structure mainly composed of two muscle layers and are located above the related ventricle. Meanwhile, right ventricle (RV) and left ventricle (LV) are composed of three gross muscular layers, much thicker than atria. The two atria are separated anatomically by the interatrial septum, while the two ventricles are separated by the interventricular septum. However, the two atria are connected as an electrical unit through the atrial electrical conduction system discussed later. The same is also correct for the ventricles, and they have a common electrical system with its divisions and branches spread throughout the ventricles.

The great veins are attached to the upper chambers of the heart, i.e., atria; in other words, the superior and inferior venae cavae are attached to the right atrium and bring the deoxygenated blood from the upper and lower organs to the right heart, respectively. However, the right and left pulmonary veins bring oxygenated blood from the right and left lung to the left atrium. On the other hand, the deoxygenated blood is sent from the right atrium through the right ventricle to the right ventricular outflow tract (RVOT) to enter the pulmonary artery to go to the lungs to be oxygenated. The oxygenated blood traverses the left atrium to the left ventricle and is

pumped through the left ventricular outflow tract (LVOT) to the ascending aorta, aortic arch, and descending aorta to perfuse the whole body by oxygenated blood.

Each atrium is separated anatomically from its ventricle by an atrioventricular valve; on the right side, the tricuspid valve does this and on the left side; the mitral valve separates the left atrium from the left ventricle; the tricuspid valve has three leaflets (or three cusps), while the mitral (bicuspid) valve has two leaflets (cusps). The leaflets of the atrioventricular valves are strengthened by the chordae tendineae, which are fibrous connective bundles anchoring the ventricular wall to the inferior surface of the same side atrioventricular valve cusps; muscular extensions, named papillary muscles, are located between the ventricular wall and the chordae tendineae. The structure composed of chordae tendineae and papillary muscles prevents prolapse of the atrioventricular valve from the ventricular cavity back to the atrial chamber during ventricular systole.

Also, each ventricle is separated from the related artery by a semilunar 3-leaflet valve; the right ventricle is separated from the pulmonary artery by the pulmonary valve, while the aortic valve separates the left ventricle from aorta (Fig. 1.1).

The heart is a muscular organ; its location is posterior to the sternal bone in the anterior mediastinum, a bit deviated to the left. Anatomically speaking, the heart is composed of three layers:

- "Pericardium": the outermost layer, covers the heart as a tissue sac, and has itself three layers:
  1. Fibrous pericardium (firm, outermost layer).
  2. Parietal pericardium (between fibrous pericardium and visceral pericardium).

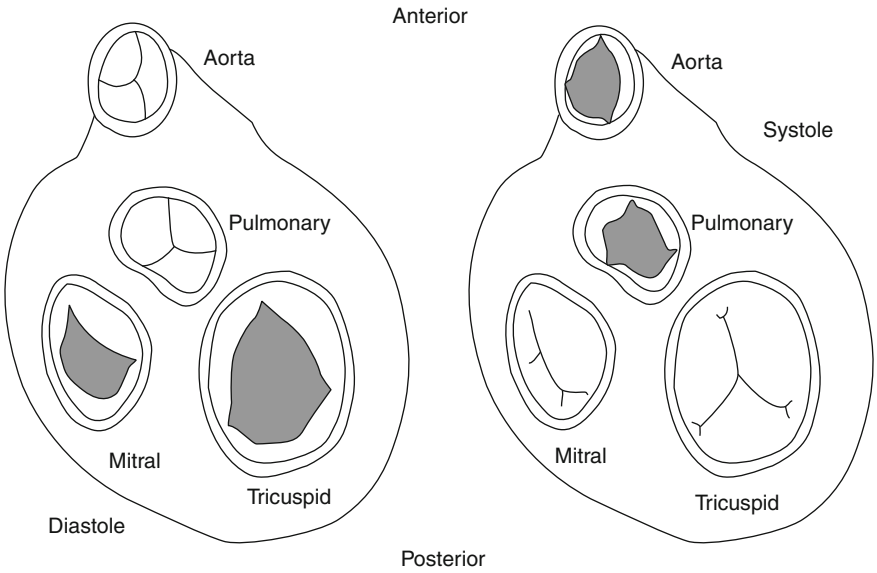



**Fig. 1.1** The apex of the heart when viewed from above in systole and diastole; note the position of the valves and their relationships

3. Visceral pericardium (innermost layer of pericardium) which is attached directly to the outer border of myocardial tissue; normally, a potential space exists between visceral and parietal pericardial layers which are filled with a few milliliters of serous tissue, functioning as a lubricant between the two layers while there is continuous heart rhythm and myocardial contractions.

- "Myocardium": the middle layer, has the main role of contraction, and is composed mainly of:
  1. Myocardial muscle tissue
  2. Coronary vascular system
- "Endocardium": the innermost layer, covers the inner space of the cardiac chambers

(Silver et al. 1971; Anwar et al. 2007; Tops et al. 2007; Haddad et al. 2009; Silbiger and Bazaz 2009; Ho and McCarthy 2010; Rogers and Bolling 2010; Atkinson et al. 2011; Dell'Italia 2012; Silbiger 2012)

Here we discuss more about the myocardial muscle tissue and its ingredients. The cardiac muscle (myocardium) is mainly composed of three cell types:

1. Cardiac *connective* tissue cells
2. *Cardiomyocytes* (which have contractile function)
3. Cardiac *electrical system cells* (consisting of "*impulse-generating* cells" and "specialized *conductive* cells")

#### 1.1.1.1 Cardiac Connective Tissue Cells

The cardiomyocytes are arranged in a cellular bed of protective system and supporting structure known as the cardiac *connective tissue cells*; these cells have the following main functions:

1. Supporting the cardiac muscle fibers as a physical protective structure
2. Transmission of the cardiomyocyte-produced mechanical force to cardiac chambers
3. Adding "tensile strength and stiffness" to the structure of the heart
4. Preventing excessive dilation and overexpansion of the heart
5. Keeping the heart within its original framework, returning the heart to its original shape after each contraction through the elastic fibers

The cardiac connective tissue would be modified according to the function of the related cardiac region; for example, "the amount of collagen in atria is different than in the ventricles" which shows the diversities and dissimilarities of anatomy that are the result of difference in function, both regarding "pressure and volume" work of different cardiac regions (Borg et al. 1982; Robinson et al. 1986, 1988; Rossi et al. 1998; Distefano and Sciacca 2012; Watson et al. 2012).

#### 1.1.1.2 Cardiac Contractile Tissue Cells (i.e., Cardiac Muscle Cells or Cardiomyocytes)

The following hierarchy could lead us to overall order seen in the fine and specialized structure of the myocardial histology:

- The myocardium is composed of myocardial cells called *heart muscle cell, cardiac myocytes,* or, briefly, *cardiomyocytes.*

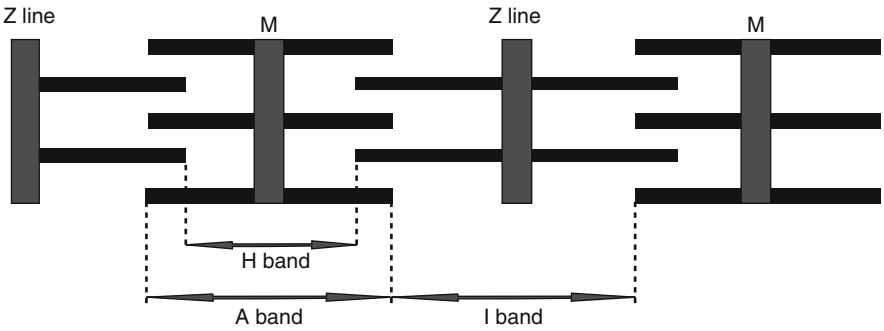



**Fig. 1.2** Microscopic structure of a sarcomere; thin and thick filaments are presented as *thin* and *thick* interspersed horizontal rods; a sarcomere is defined as the part of sarcomere between two *Z lines*

- These cells have contractile function similar to striated muscle cells, with the especial difference that their contraction is involuntary.
- Also, instead of having many nuclei in each cell (like the cellular structure seen in skeletal muscle cells), each cardiomyocyte has only 1–2 nuclei and is 100 μ in length and 25 μ in width.
- The internal structure of each cardiomyocytes is in turn composed of a wealth of cardiac myofibrils.
- And finally, each cardiac myofibril is composed of a vast number of sarcomeres; each sarcomere is located anatomically between two Z lines; thin filaments are attached perpendicularly to Z lines on each side, while thick filaments are in between them in a parallel fashion (Fig. 1.2).

Now let's discuss the above lines in more detail.

The cardiomyocytes are specialized muscle cells, ranging from 25 μm length in atria up to about 140 μm in ventricular cardiomyocytes. About half of a cardiomyocyte is composed of contractile parts (called myofibrils) arranged as contractile units called *sarcomere* (each cardiomyocyte contains a number of sarcomeres); sarcomere is the basic unit of contraction or better to say *contractile quantum of the heart*.

The other half is composed of other cellular structures including nucleus, mitochondria, sarcoplasmic reticulum, and cytosol.

*Sarcolemma, T tubules, and sarcoplasmic reticulum*: each cardiomyocyte is enveloped by a especial membrane called sarcolemma, which not only covers the cardiomyocyte but also has a large network "invaginating" between the cells creating transverse tubules (*T tubules*) having a central role in $Ca^{2+}$ transfer in sarcoplasmic reticulum of the cardiomyocytes. $Ca^{2+}$ has a pivotal role in all the main three cardiac physiologic functions, known among them is *excitation-contraction coupling* which is discussed later; however, in summary, excitation-contraction coupling could be assumed as the "hinge" between the *electrical* and *mechanical* functions of the cardiomyocyte.

The sarcoplasmic reticulum (SR) has a dual function for $Ca^{2+}$ homeostasis; first, SR releases $Ca^{2+}$ after $Ca^{2+}$ influx during depolarization, causing contractility

through junctional SR (JSR), and after that, SR reuptakes $Ca^{2+}$ causing cardiac muscle relaxation through longitudinal SR (LSR).

Intercalated discs: *intercalated disc*s are among the basic cellular structures found in cardiomyocytes, which are "cardiac-specific structures"; these cardiomyocytes structures are the main communication port between adjacent cardiomyocytes.

The main functions of intercalated discs could be categorized as:

1. *Mechanical* connection between adjacent cardiomyocytes
2. *Electrical transport* between adjacent cardiomyocytes (i.e., rapid transduction and transmission of action potential)
3. *Synchronization* of cell contraction

The above main functions of the intercalated discs have an integral role in creating a "physiologic" syncytium. Intercalated discs are special to cardiac muscle cells; adult skeletal muscle cells are devoid of these specialized cellular structures. *Intercalated discs* perform their roles through three types of intercellular junctions:

1. Spot desmosomes
2. Sheet desmosomes
3. Gap junction

*Spot desmosomes* are intercellular connections which "anchor the intermediate-filament cytoskeleton" in the adjacent cells.

*Sheet desmosomes* are the place for contractile structures that connect two neighboring cells; it means that sheet desmosomes fasten and fix the contractile apparatus between the neighboring cells.

*Gap junctions* are primarily responsible for electrical transmission between adjacent cells causing rapid electrical wave progression in "cardiac syncytium" having two roles:

- *Anchorage* which is an integral part of cardiac morphogenesis
- *Communication* which is essential for cardiac conduction and cardiac action potential propagation

Gap junctions are composed of connexins (mainly connexin 43) as one of their main subunits, so the cellular pathologies in gap junctions of cardiomyocytes (especially those related to connexin 43) can have a major role in ischemia and some lethal arrhythmias. In human, connexin 43 is the most common and important type of cardiac connexins. Usually, the Purkinje cells have a high amount of gap junctions, while they do not have considerable amounts of contractile elements.

Each cardiomyocyte is composed of a number of contractile units: let's say *contractile quantum* or as we are more familiar it is called *cardiac sarcomere*. So, sarcomere is the basic unit of contraction (i.e., the *contractile quantum* of the heart). The primary function of cardiomyocyte is produced in each sarcomere.

As mentioned above, the cardiomyocytes are ranging from 25 to 140 μm in diameter; meanwhile, cardiac sarcomeres are "contractile quantum" of the heart and are about 1.6–2.2 μm in length.

Nearly about half of each sarcomere is composed of contractile elements, arranged as contractile fibers, while the other half is composed of all other cellular structures like mitochondria, nucleus, cytosolic structures, and other intracellular organelles.

The contractile fibers are classically divided as thick filaments and thin filaments; however, if the microscopic anatomy of sarcomere is viewed, each sarcomere is defined as the contractile part of the sarcomere located between two Z lines and consists of the following parts:

- Z lines: when seen with a microscope present as thick lines, the margins of each sarcomere is defined by Z line in each side; Z stands for "Zuckung," a German name meaning "contraction" or "twitch"; so, each sarcomere is the region of myofilaments between two Z lines; the Z line is like an "anchor" to which the thin filaments are attached.
- Thin filaments are attached perpendicularly to Z lines on each side; thin filaments are composed of actin, tropomyosin, and troponin.
- Thick filaments are in between them in a parallel fashion; these filaments are composed of myosin and are located in the center of the sarcomere; the two ends of thick filaments are interspersed with thin filaments.
- "I" band is the area of sarcomere adjacent to Z line; during myocardial contraction, "I" band shortens.
- "A" band is the central part of each sarcomere; each "A" band, while located in center, takes two "I" bands (each I band in one side of the single A band) plus two Z lines (each Z line attached to the other side of "I" band); this complex composes a sarcomere (as presented in figure).
- "H" band is the central part of "A" band, composed mainly of thick filaments.

A full description of contractile proteins, thick filament and thin filament, is described in this chapter in later sections and also in Figs. 1.2 and 1.6.

*Histological differences between cardiac muscle and skeletal muscle*: one could find the following differences between cardiac muscle cell and striated muscle cell.

*Cardiac muscle tissue* is a complex of united and combined contractile cells, totally named as a syncytium; this syncytium is:

- Composed of branched cells with the myofibers usually being fused at their ends.
- Connected together through a *relatively unique cardiac cellular structure* called intercalated discs.
- Electrical current is transmitted by an especial electrical link "gap junctions."
- Cardiomyocytes usually have 1 or 2 (rarely 3–4) central nuclei.
- Accompanied with *many mitochondria* having an essential role in *energy production and metabolism regulation,* the energy is delivered as ATP through oxidative phosphorylation for many processes including "excitation-contraction coupling" and the "sarcomere activity" and the relationship between contractile filaments in systole and diastole.
- One of the most important functions of mitochondria is $Ca^{2+}$ homeostasis (see below); this is why in cardiomyocytes, the mitochondria are located near the sarcoplasmic reticulum (SR).
- Both mitochondria and $Ca^{2+}$ have a central role in cardiomyocyte necrosis; the role of mitochondria changes from an "ATP-producing engine" to "producers of excessive reactive oxygen species" which would release "pro-death proteins."
- The high rate of metabolism in these cells necessitates high vasculature with all the cells having aerobic metabolism.

- The special $Ca^{2+}$ metabolism of these cells is the main result for having fewer T tubules, while these T tubules are wider (cardiac T tubules are about 5 times more than skeletal muscles in diameter).
- Thin filaments in cardiac muscles do not have a constant length.

*Skeletal muscle cells* have the following features due to their pattern of contraction; which is a pattern of neuromuscular junction unit:

- Longer, multinucleated, and cylindrical shape.
- Usually not arranged as syncytium; instead, they are located side by side with no tight binding or gap junctions.
- Lower metabolism needs necessitating medium vasculature, with lower amounts of mitochondria (about 2–3 % of the cell).
- Both aerobic and anaerobic metabolism.
- Thick and thin filaments in skeletal muscles have a constant length

(Severs 1985; Peters 1996; Gordon et al. 2000; Kirchhoff et al. 2000; Lo 2000; Alberts 2002, 4th edition, *New York: Garland Science*; Burgoyne et al. 2008; Kobayashi et al. 2008; Meyer et al. 2010; Shaw and Rudy 2010; Workman et al. 2011; Anderson et al. 2012; Balse et al. 2012; Bingen et al. 2013; Delmar and Makita 2012; Eisner et al. 2013; Khan et al. 2012; Kubli and Gustafsson 2012; Miragoli et al. 2013; Orellana et al. 2012; Scriven and Moore 2013; Wang et al. 2012; Zhou and O'Rourke 2012).

#### 1.1.1.3 Cardiac Conductive Tissue Cells

The synchronized *mechanical system* needs a delicate *electrical control* known as *cardiac electrical network* or *cardiac electrical system.* Cardiac electrical system is composed of two main cells:

- Excitatory cells known as "impulse-generating cells" consisting mainly of the sinoatrial (SA) node
- Specialized conduction system known as "conductive cells" composed of the atrioventricular conduction pathways, AV node, the His bundle and its right and left branches, and finally, the Purkinje fiber cells or the Purkinje fiber network distributed all over ventricles to conduct the electrical impulse all over the ventricles effectively and rapidly

This hierarchical pattern is the mainstay for effective mechanical contraction of ventricles leading to an effective cardiac output (Desplantez et al. 2007; Dun and Boyden 2008; Atkinson et al. 2011) (Fig. 1.3).

### 1.1.2 Anatomy of the Coronary Arteries

The coronary arterial system has four main elements (Fig. 1.4):

- Left main coronary artery (LMCA)
- Left anterior descending coronary artery (LAD)
- Left circumflex coronary artery (LCX)
- Right coronary artery (RCA)

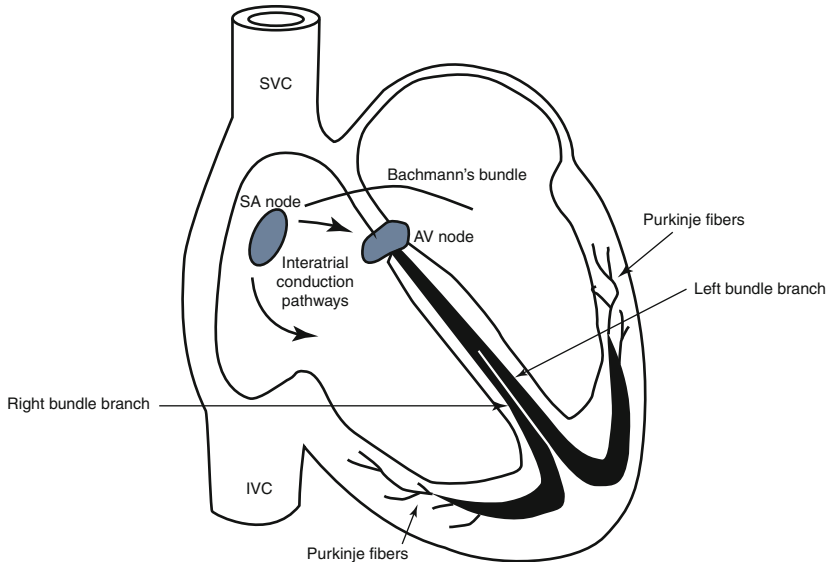



**Fig. 1.3** Cardiac conductive system: different elements of the conduction system

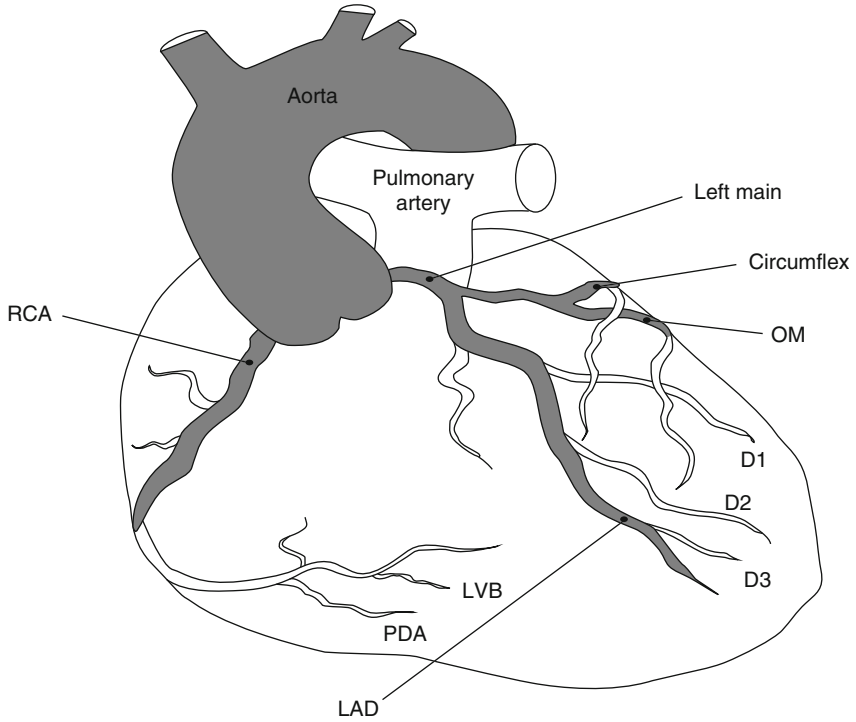



**Fig. 1.4** Anatomy of normal epicardial coronary arteries

#### 1.1.2.1 Left Main Coronary Artery (LMCA)

LMCA starts from the left coronary ostium in left Valsalva sinus and after passing a length (between 0 and 40 mm) is divided to two branches: LAD and LCX. At times, an extra branch is divided from the LMCA and passes parallel to the diagonal arterial system; this arterial branch is called the "ramus" branch.

#### 1.1.2.2 Left Anterior Descending (LAD) Artery

After LCX is separated from LMCA, the remainder of LMCA continues its path as left main coronary artery; LAD goes down the interventricular septum and reaches the apex:

- The *diagonal branches* run as oblique derivations between LAD and LCX; the main role of diagonal branches is to perfuse the lateral wall of the left ventricle; these are demonstrated in Fig. 1.4 as D1 to D3.
- Besides the diagonal branches, there are *septal branches* of LAD which perfuse the anterior two-thirds (2/3) of the interventricular septum.

#### 1.1.2.3 Left Circumflex Coronary Artery (LCX)

LMCA is divided to LAD and LCX often at a 90° angle at the separation point; LCX has a number of ventricular branches which perfuse the lateral and posterior walls of the left ventricle (LV); these branches are called *obtuse marginal* or simply OM; in 40 % of the patients, LCX perfuses the SA node; the other 60 % are perfused by RCA.

#### 1.1.2.4 Right Coronary Artery (RCA)

Right coronary artery (RCA) originates from the right coronary ostium of the Valsalva sinus; so, its origin is from a different coronary ostium compared with the abovementioned coronary arteries; RCA then goes through the right atrioventricular groove (i.e., the groove located between the atria and ventricles) towards right to reach the posterior part of interventricular septum where it gives a branch called acute marginal artery; as mentioned, 60 % are perfused by RCA. Finally, RCA is divided to two main branches:

- *Posterior descending artery* (PDA): to perfuse the posterior 1/3 of the interventricular septum and the inferior wall of LV and also the posteromedial papillary muscle; in the majority of the people (85 %), PDA originates from RCA; these are called *right dominant*; however, in the other 15 %, called *left dominant*, PDA originates from LCX.
- *Posterolateral branch*: to perfuse the posterior part of LV wall.

## 1.2 Cellular Physiology

Among the main characteristic features of cardiomyocytes are their *very specialized* functional and histological features; these subspecialized anatomical and physiological features have a key role in production, propagation, and transmission of "electrical and mechanical" functions of cardiomyocytes. Physiologically speaking, these electrical and mechanical functions are translated to three main domains:

1. Action potential
2. Excitation-contraction coupling (ECC)
3. Contractile mechanisms and their related processes

As mentioned above, the heart muscle is composed of two main syncytia: the atrial syncytium and the ventricular syncytium. It means that in each syncytium, all the cells are interrelated with many widespread intercellular connections. The cardiomyocytes resemble the skeletal muscles, being composed of actin and myosin filaments, contracting and relaxing in a well-cooperated and organized manner in order to produce the cardiac contractile force. The intercellular connections between cardiac muscles are through the "intercalated discs" which are delicate pores located at the proximal and distal parts of each cardiomyocyte; these discs are able to transport great amounts of ions between the cardiomyocytes, transferring the ions from each cell to the next cell through the gap junctions. Hence, the term "syncytium" is not just an anatomical term but also a physiologic term. However, the two syncytia (atrial and ventricular) are separated physiologically by the AV node and AV bundle to act independently.

### 1.2.1 Action Potential

The normal cardiomyocytes have different electrical potentials known as action potentials. However, the resting potential and the action potential of all cells are not the same. Though, the production mechanism is similar and is the result of ion currents across the cellular membrane, the final result is consecutive depolarization and repolarization which produces the cardiac electrical impulse. The impulse is generated and conducted over the cardiac "electrical" and "conduction" system.

Action potential of cardiomyocytes is composed of five phases which are produced due to the influx and efflux of ions; especially $Na^+$, $Ca^{2+}$, and $K^+$ ions, across the cell membrane.

This action potential is about 105 millivolts (mV) starting from about −80 to −90 mV reaching up to +15 to +20 mV, then experiencing a plateau for about 0.2 milliseconds, and finally turning down to the baseline which is −80 to −90 mV (Eisner et al. 2013).

The cardiomyocyte action potential is much similar to the action potential of skeletal muscle; however, it has two main features:

- First of all, the fast $Na^+$ channels are present, both in the skeletal muscles and the cardiomyocyte.
- Second, the slow (L)-type $Ca^{2+}$ channels are present in the cardiomyocytes, but not in the skeletal muscle cells; however, after the start of action potential mainly by the fast $Na^+$ channels, L-type $Ca^{2+}$ channels would open late and also would remain open for a few milliseconds to create the plateau of action potential. These channels have two main effects: first to decrease the heart rate in the physiologically defined range and second to augment cardiomyocyte contractions.

Besides $Na^+$ and $Ca^{2+}$, the third important ion in cardiomyocyte action potential is $K^+$. Just after cardiomyocyte depolarization, due to $Ca^{2+}$ entry to the cell, there is abrupt and considerable decreases in $K^+$ outflux from the cell to the external milieu. This is also an important reason for delayed plateau of the action potential, mainly

created by the slow (L)-type $Ca^{2+}$ channels but also enforced by $K^+$ outflux. The permeability of the cardiomyocyte cell membrane to $K^+$ will return to normal after cessation of $Ca^{2+}$ and $Na^+$ channels to normal potential (about 0.2–0.3 milliseconds) which causes the return of $K^+$ outside the cell and ending action potential.

The phases of action potential in ventricular and atrial cardiomyocytes and also His bundle and Purkinje cells are:

- Phase 0: early rapid upstroke of action potential caused by huge $Na^+$ influx.
- Phase 1: short-term and incomplete repolarization due to $K^+$ outflux.
- Phase 2: slow (L)-type $Ca^{2+}$ channels open and there is $Ca^{2+}$ influx; initiation of the contractions starts immediately afterwards; this phase is also called plateau.
- Phase 3: large amounts of $K^+$ outflux which overcome the $Ca^{2+}$ influx; again the action potential moves to negative levels to reach the resting potential; this phase, named resting potential phase, equals diastole.
- Phase 4: influx of very negligible amounts of $K^+$; however, the "$Na^+$-$Ca^{2+}$ exchanger" also known as "NCX" has a very important role in relaxation phase, since it sends $Ca^{2+}$ against its gradient into the exterior of myocardial cell and sends $K^+$ against its gradient to interior of myocardial cell; the failure of this pump to function properly has been implicated as one of the mechanisms involved in heart failure (Table 1.1, Fig. 1.5).

**Table 1.1** A summary of action potential events in ventricular and atrial cardiomyocytes and also His bundle and Purkinje system

| Phase | Term | Involved ion(s) |
|---|---|---|
| 0 | Rapid upstroke | $Na^+$ influx |
| 1 | Short-term and incomplete repolarization | $K^+$ outflux |
| 2 | Plateau | $Ca^{2+}$ influx and $K^+$ outflux |
| 3 | Repolarization (main part) | Large $K^+$ outflux |
| 4 | Diastole (resting potential) | $K^+$ influx (very negligible amounts) |

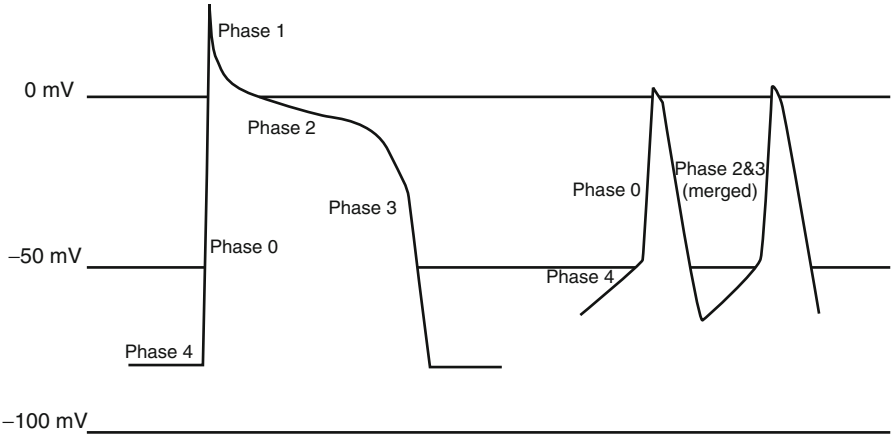



**Fig. 1.5** Action potential in a normal cardiac cell (*left*) and a conducting cell (*right*)

There are a number of differences between "sinoatrial (SA) node and atrioventricular (AV) node cells" on one side with "ventricular and atrial cardiomyocytes and also His bundle and Purkinje cells" on the other side regarding the phases of action potential; these differences are mainly due to increased "$Na^+$ influx" during phase 4 and increased "$Ca^{2+}$ influx" and decreased "$K^+$ influx" during phase 4 which causes:

- Resting potential of pacemaker cells is less negative than the other cardiac cells; it means that if resting potential in majority of cardiac cells is −80 to −90 mV, it would be just −50 to −60 mV in pacemaker cells; the reason for the change is that the flux of $Na^+$ from outside to inside of pacemaker cells (i.e., $Na^+$ influx) continues during repolarization, changing the resting potential level from about −90 mV to upper levels in such a way that it reaches the needed voltage for threshold of repolarization (i.e., about −50 to −60 mV); this $Na^+$ current is called pacemaker *funny current of heart*, i.e., I(f) of the heart; this funny current is responsible for rhythmic, spontaneous, pacemaker activity of the pacemaker cells, especially SA node.
- Phase 4 (diastole) of action potential is more abrupt and head up, i.e., not as much flat of the cardiac muscles' action potential, again due to the same $Na^+$ current in repolarization period.
- Phase 1 of action potential is nearly eliminated.
- Phases 2 and 3 are nearly merged together.

Refractory period of cardiomyocytes: refractory period in cardiac action potential is the time interval after termination of each action potential in which no new impulse could be generated after any stimulus; the role of refractory period is to prevent premature contractions during a definite time interval and also could have a protective role for the heart against "reentrant arrhythmias." However, *the time interval for refractory period* is not constant all over the cardiac cells, being shorter in the atrial cells (0.15 s) than the ventricular cells (0.3 s). Physiologically speaking, the phase 2 (plateau) of action potential is the *main determinant factor* for duration of refractory period.

(Boyden et al. 1988; Szigligeti et al. 1996; Reuter et al. 2005; DiFrancesco 2006, 2010; Bucchi et al. 2007; DiFrancesco and Borer 2007; Zhang and Hancox 2009; Chen et al. 2010; Neco et al. 2010; Pott et al. 2011; Coronel et al. 2012; DiFrancesco and Noble 2012; Ednie and Bennett 2012; Shy et al. 2013; Strege et al. 2012; Torres-Jacome et al. 2013; Brunello et al. 2013; Goldhaber and Philipson 2013; Kim et al. 2013; Ottolia et al. 2013; Papaioannou et al. 2013; Sipido et al. 2013; Weisbrod et al. 2013)

### 1.2.2 Excitation-Contraction Coupling (ECC)

Excitation-contraction coupling (ECC): this term, used in 1952 for the first time, depicts a physiologic process which *transforms an electrical impulse to a mechanical contraction* which is seen in both skeletal and cardiac muscles. In cardiac muscles, ECC acts as a "joint" in cardiomyocytes between the *electrical function* and *mechanical function* of the heart. ECC is one of the most important mechanisms in

cardiac physiology. This very important mechanism is composed of three main delicate cellular and subcellular mechanisms, each having their individual elements; when these structures interact together in a regulated manner, the *electrical action potential* is changed to the *mechanical force* of the cardiomyocyte. These composing aspects are:

1. Functioning organelles of ECC
2. Calcium ion ($Ca^{2+}$)
3. Controllers of ECC

A summary of these composing aspects and their related items are presented in the Table 1.2.

#### 1.2.2.1 Which Parts of Cardiomyocyte Are the Functioning Organelles of ECC?

Which parts of cardiomyocyte are the main components of ECC? The following parts of cardiomyocyte involved in the ECC process are:

1. *Cell membrane* (which is responsible for electrical function, i.e., action potential; discussed before)
2. *Thick and thin filaments* (which are responsible for mechanical function, i.e., contractile function; discussed later in this chapter)
3. *Mitochondria* (ECC needs a great amount of energy; mitochondria are responsible for supporting ECC regarding its energy needs in the form of ATP through oxidative phosphorylation; discussed before)
4. *Sarcoplasmic reticulum* (known as SR; discussed here)
5. *Transverse tubules* of cardiomyocytes (known as T tubules; discussed here)

*Sarcoplasmic reticulum*: SR is divided into longitudinal SR (LSR) and junctional SR (JSR). LSR releases $Ca^{2+}$ reserves into the cell as fast as possible in just a few milliseconds, which would activate cardiomyocyte contractile structures. Junctional SR contains huge "$Ca^{2+}$-releasing channels" called "ryanodine receptors." These receptors form a protein network which would enhance the release of $Ca^{2+}$ in response to the $Ca^{2+}$ influx. The role of "ryanodine receptors" is more recognized when considering this fact:

**Table 1.2** A summary of the composing aspects of ECC and their related items

| | | |
|---|---|---|
| 1 | Functioning organelles of ECC | Cell membrane<br>Thick and thin filaments<br>T tubules<br>Sarcoplasmic reticulum |
| 2 | Calcium ion ($Ca^{2+}$) | $Ca^{2+}$ influx to the cardiomyocytes (by L-type Ca2+ channels in *systole*)<br>$Ca^{2+}$ release inside the cell (by RyR in systole)<br>$Ca^{2+}$ efflux from the cardiomyocytes (by NCX in diastole)<br>$Ca^{2+}$ reuptake from the cell (by SERCA in diastole) |
| 3 | Controllers of ECC | Ryanodine receptor (RyR) family<br>Dihydropyridine receptor (DHPR)<br>Calmodulin |

For *cardiac cell* contraction, nearly 75 % of $Ca^{2+}$ in cardiac cell cytoplasm is released from SR.

*T tubules*: as mentioned before, T tubules are invaginations of the cardiomyocyte cell membrane into the interior space of the cardiac muscle cells and transmit the action potential of the cell membrane to the interior parts of the cardiomyocyte. The role of T tubules is conducting the depolarization phase of action potential, as rapidly as possible, from the cell membrane to the interior of the cell.

Then, the electrical current produced by action potential is transmitted through the T tubules to the interior of the cell, to the "longitudinal sarcoplasmic reticulum." During some cardiac diseases like heart failure or ventricular hypertrophy, the "loss of integrity in transverse tubules" is one of the main etiologies for impaired availability of $Ca^{2+}$ for sarcomere contractile mechanisms, which would impair $Ca^{2+}$ movements and its availability for contraction of the sarcomere myofilaments.

T tubules of cardiomyocytes have some *unique features*:

1. $Ca^{2+}$ is the main mediator playing the most important role in cardiomyocyte action potential, ECC, and finally, muscle contraction. Although the start of action potential in *cardiac muscles* is similar to skeletal muscle, its continuation is dependent on the role of $Ca^{2+}$, as mentioned above (see subtitle of *action potential*). As mentioned above, the role of $Ca^{2+}$ is also important in the release of intracellular $Ca^{2+}$ reservoirs: "the CICR phenomenon"; CICR is one of the mechanisms demonstrating why structural disintegration and disturbance of T tubules is an early happening in heart failure.
2. Although cardiac cell action potential is the main trigger for $Ca^{2+}$ release, the first $Ca^{2+}$ release is from the large $Ca^{2+}$ reservoirs of T tubules, and T tubules would trigger the release of more $Ca^{2+}$ from SR. As mentioned before, the influx of $Ca^{2+}$ from ECF to interior of cardiac cells through slow (L)-type calcium channels located on the T tubule strengthens the depolarization of *cardiac muscle* cells and causes the plateau phase of depolarization; this feature is special to depolarization of cardiac cells, while in skeletal muscle depolarization, the influx of $Ca^{2+}$ to skeletal cells, through T tubule's slow (L)-type calcium channels, *does not* have any significant role.
3. T tubules are invagination of the cell membrane to the cells; it means that T tubules are in fact part of the extracellular fluid (ECF); so, they have continuous exchange of $Ca^{2+}$ with ECF. Any decrease in $Ca^{2+}$ concentration of blood would be associated with a decrease in $Ca^{2+}$ concentration of ECF, which in turn would reduce $Ca^{2+}$ concentration in the intracellular milieu; this is why any decrease in plasma levels of $Ca^{2+}$ is associated with decreased cardiac contractility.

#### 1.2.2.2 $Ca^{2+}$ Homeostasis

$Ca^{2+}$ homeostasis in cardiomyocytes is such an important issue that any perturbation in its equilibrium state would result in cardiac disturbances. Intracellular $Ca^{2+}$ is

considered as a second messenger in cardiac sarcomeres, while its concentration and trends of change exert important effects on "mitochondrial energy," "cell death or apoptosis," and "the intracellular buffering capacity for controlling stress."

To have this equilibrium in a continuous manner for a lifelong time, a delicate balance between $Ca^{2+}$ influx and $Ca^{2+}$ efflux in cardiomyocytes is an obligation: the $Ca^{2+}$ balance has a central role in each cardiac cycle, composed of a systole (contraction) and a diastole (relaxation); although there are a number of states in which influx would exceed efflux or vice versa, a number of subcellular mechanisms work together to modify these fluxes and reach the final equilibrium in such a way to increase the efficacy of myocardial contractions as a result of control in $Ca^{2+}$homeostasis.

$Ca^{2+}$ surge and $Ca^{2+}$ reuptake are both located inside the cardiomyocytes and also, both are among the main features of systole and diastole, respectively. This dual phase is seen in all aspects of $Ca^{2+}$ homeostasis, including cardiac contraction, $Ca^{2+}$ flow direction, $Ca^{2+}$ concentration inside each cell, and $Ca^{2+}$ release and reuptake in all potential intracellular elements like mitochondria.

The *dual phase pattern of* $Ca^{2+}$ with its widespread pattern of distribution and its extensive effects is controlled mainly by four mechanisms:

1. $Ca^{2+}$ influx to the cardiomyocytes (mainly by L-type channels in *systole*: contraction phase)
2. $Ca^{2+}$ release inside the cell (by ryanodine receptor or "RyR" in *systole*: contraction phase)
3. $Ca^{2+}$ efflux from the cardiomyocytes (mainly by $Na^{+}$-$Ca^{2+}$ exchanger "NCX" in *diastole*: relaxation phase)
4. $Ca^{2+}$ reuptake from the cell (by sarcoendoplasmic reticulum $Ca^{2+}$ transport ATPase "SERCA" in *diastole*: relaxation phase)

One of the main etiologic mechanisms for heart failure is "reduced and sluggish $Ca^{2+}$ release and slow removal of $Ca^{2+}$." In these patients, reduced and delayed function of L-type $Ca^{2+}$ channel, slowed release of $Ca^{2+}$ from SR, and "delayed activation" of $Na^{+}$-$Ca^{2+}$ exchanger "NCX" are among the most important mechanisms involved in the pathogenesis of the disease state.

#### 1.2.2.3 What Are the Controllers of ECC?

The exact mechanisms of ECC are delicately controlled and regulated *mainly* by these proteins:

1. Ryanodine receptor (RyR) family (a class of intracellular $Ca^{2+}$ receptors)
2. Dihydropyridine receptor (DHPR)
3. Calmodulin

Let's once more stress on the fact that $Ca^{2+}$ cycling is the ultimate goal of ECC and the main mechanism responsible for its course, including commencement, continuation, and termination of ECC.

$Ca^{2+}$ would enter the cardiomyocyte cytosol through L-type $Ca^{2+}$ channels (also known as dihydropyridine, DHP) in cytosol. This primary $Ca^{2+}$ influx would trigger $Ca^{2+}$ release from subsarcolemma SR (i.e., the specific part of the SR which is under the sarcolemma):

$Ca^{2+}$ cycling is the ultimate goal of ECC and the main managing mechanism.

The functional steps in ECC are as follows:

1. ECC is started by $Ca^{2+}$ entry into cells through L-type $Ca^{2+}$ channels (i.e., DHP).
2. These initial small amounts of $Ca^{2+}$ trigger type 2 of ryanodine receptor (i.e., RyR2).
3. RyR2 is located on the JSR and the triggering RyR2 causes huge amounts of $Ca^{2+}$ to be released from SR (the release of large $Ca^{2+}$ amounts after the initial small $Ca^{2+}$ influx is called $Ca^{2+}$-induced $Ca^{2+}$ release "CICR," a phenomenon first explained by Fabiato).
4. In turn, the necessary $Ca^{2+}$ for contraction is released from SR reservoirs.
5. Immediately afterwards, interaction of $Ca^{2+}$ with contractile proteins of sarcomere occurs.
6. The above interaction between $Ca^{2+}$ and contractile proteins produces mechanical force of contraction.
7. The $Ca^{2+}$ surge would be resolved by later $Ca^{2+}$reuptake.
8. $Ca^{2+}$ reuptake is primarily done through a recycling mechanism in SR (SR acts as a very huge intracellular $Ca^{2+}$ reservoir) which happens after occurrence of the contraction.
9. The rest of $Ca^{2+}$ is effluxed outside the cell by a pump called $Na^{+}/Ca^{2+}$ exchanger (NCX).
10. $Ca^{2+}$ reuptake by SR ends contraction and starts relaxation; $Ca^{2+}$ reuptake is a primary function of a specific protein called sarcoendoplasmic reticulum $Ca^{2+}$ transport ATPase "SERCA" which is an ATP-dependent $Ca^{2+}$ pump in SR; SERCA is also the main protein component of SR.
11. The 2nd main protein of SR is phospholamban which inhibits the function of SERCA; in other words, "phospholamban is a major regulator of SERCA pump."
12. SERCA activates $Ca^{2+}$ reuptake and relaxation, while phospholamban ends the $Ca^{2+}$ reuptake and, hence, ends the relaxation phase.

Besides SERCA, calmodulin, and phospholamban, there are a number of other main proteins involved in $Ca^{2+}$ reserve and adjustment called calsequestrin, calreticulin, and calmodulin.

Calsequestrin is a $Ca^{2+}$-storing reservoir inside the sarcoplasmic reticulum containing large amounts of calcium which keeps calcium inside SR against its gradient; the release of calcium form calsequestrin is among the main triggering factors for contraction.

Calmodulin (CaM) is an abbreviation for *cal*cium-*modul*ated prote*in*, a small-sized protein with the following characteristics:

- Each molecule of calmodulin binds to 4 $Ca^{2+}$ ions.
- Calmodulin controls and modulates (i.e., excites or inhibits) two main $Ca^{2+}$ ports which have essential role in ECC,
- Calmodulin controls both slow (L)-type $Ca^{2+}$ channel (located in transverse tubules of the sarcolemma) and also RyR located at JSR.

- So, calmodulin is a multifunctional protein which does its functions through signal transduction and plays the role of the "boss" who controls all the $Ca^{2+}$ bottlenecks in cardiomyocyte.

(Abbott and Ritchie 1951; Sandow 1952; Hamilton et al. 2000; Periasamy and Huke 2001; Tang et al. 2002; Scoote et al. 2003; Yang et al. 2003; Bickler and Fahlman 2004; Scoote and Williams 2004; Reuter et al. 2005; Vangheluwe et al. 2006; Periasamy et al. 2008; Currie 2009; Kerckhoffs et al. 2009; Koivumaki et al. 2009; Neco et al. 2010; Williams et al. 2010; Malik and Morgan 2011; McDonald 2011; Prosser et al. 2011; Rybakova et al. 2011; Tavi and Westerblad 2011; Eisner et al. 2013; Ibrahim et al. 2013; Jafri 2012; Lu et al. 2013; Nakada et al. 2012; Scriven and Moore 2013; ter Keurs 2012; Goldhaber and Philipson 2013; Shy et al. 2013; Sipido et al. 2013; Solaro et al. 2013)

### 1.2.3 Contractile Mechanisms and Their Related Processes

The contractile function of the heart is a unique function produced in each of the cardiomyocytes. As mentioned in the previous parts of this chapter (Sects. 1.1 and 1.2), the cardiac muscle is composed of two muscle masses: "atrial syncytium" and "ventricular syncytium." We can assume each of the two syncytia as a separate "military band" with all the cardiomyocytes working and acting in a cooperated, regulated, and arranged manner, as each soldier acts in a military group during a "military march." So, the physical outcome of cardiomyocyte function is force generation, and its physiological outcome is cardiac contraction which in turn would produce cardiac output. However, cardiac output (i.e., physiological role of the heart) is set in a widespread spectrum; so, the body demands are met well in severe exercise as well as deep sleep. Such an adaptive and cooperative capacity for fulfilling demands in a wide range of body physiologic needs is directly dependent on the contractile properties of sarcomere. Part of these mechanisms is discussed here; but, the full nature of these mechanisms, in health or in disease, is far beyond the scope of this book.

As described in the previous pages (Sect. 1.1), each cardiomyocyte is composed of a number of contractile units or let's say *contractile quantum* which is called *cardiac sarcomere*. So, the main function of cardiomyocyte is produced in sarcomere. As mentioned, each sarcomere is margined by a line named "Z" line; so, each sarcomere is the region of myofilaments between two Z lines. Thin and thick filaments are the main contractile elements of sarcomere.

It would be worth to know that genetic disturbances (including mutations) are an important source for creating pathologies in sarcomere myofilaments; these pathologies would be the origin for a number of cardiac diseases (named sarcomere diseases with genetic origin); among them, a number of hypertrophic or dilated cardiomyopathies, rhythm disorders, and sudden cardiac death could be mentioned.

However, when considering the cellular mechanisms of contraction, the storey is much more complicated, containing the following steps:

- Contraction of the cardiomyocyte is composed of a repeated and continuous contraction-relaxation process, being the main function of the sarcomeres.
- We should know that the engine of this contractile process is started with an *ignition switch*: $Ca^{2+}$, which is the initiator of the contractile process.
- Cardiomyocyte action potential releases $Ca^{2+}$ from sarcoplasmic reticulum (SR) and T tubules.
- At the next step, $Ca^{2+}$ starts the contraction-relaxation process known as "cross-bridge cycling."
- The contraction-relaxation process is done through the contractile proteins located in thick and thin filaments discussed in previous sections of this chapter.
- $Ca^{2+}$ concentration which is necessary for activation of concentration in cardiomyocytes is always lower than the "saturation" level: it has been demonstrated that *decreased myofilament response* to effects of $Ca^{2+}$ in the contractile system is one of the main mechanisms for heart failure.

The very unique contractile proteins of sarcomere could be classified as "functional classification" and "structural classification."

#### 1.2.3.1 Functional Classification of Sarcomere Proteins

Functional classification of sarcomere proteins divides the sarcomere contractile proteins functionally as two protein classes:

*Contractile proteins*: the contractile proteins are mainly composed of actin, myosin, and titin; cardiac contraction is the final outcome of interactions between myofilaments, presented at cellular level as *cross bridges* of myosin head with actin.

*Regulatory proteins*: contraction of all muscles including cardiac sarcomeres is a very delicate and ordered phenomenon needing precise regulatory and control systems; in sarcomeres, this regulatory function is a duty by the r*egulatory proteins* which work "shoulder to shoulder" of contractile proteins to control their cross-bridge-induced contractions; the main regulatory proteins are "troponin," "tropomyosin," "tropomodulin," and "myosin-binding protein C"; when sarcomere is in relaxation phase, these two proteins attach to actin and myosin to prevent contraction. However, when action potential goes to the activation phase, $Ca^{2+}$ is attached to troponin in order to activate interactions between myosin head and actin; contraction starts immediately afterwards.

#### 1.2.3.2 Structural Classification of Sarcomere Proteins

Structural classification of sarcomere proteins divides the sarcomere contractile proteins in one of the two following classes:

- Thick filament
- Thin filament

These two filaments are formed as interdigit strands going "in between" each other and coming out in a sliding manner; this sliding back-and-forth movement of thin and thick filaments forms the cardiac "systole" and "diastole," respectively (see Figs. 1.2 and 1.6).

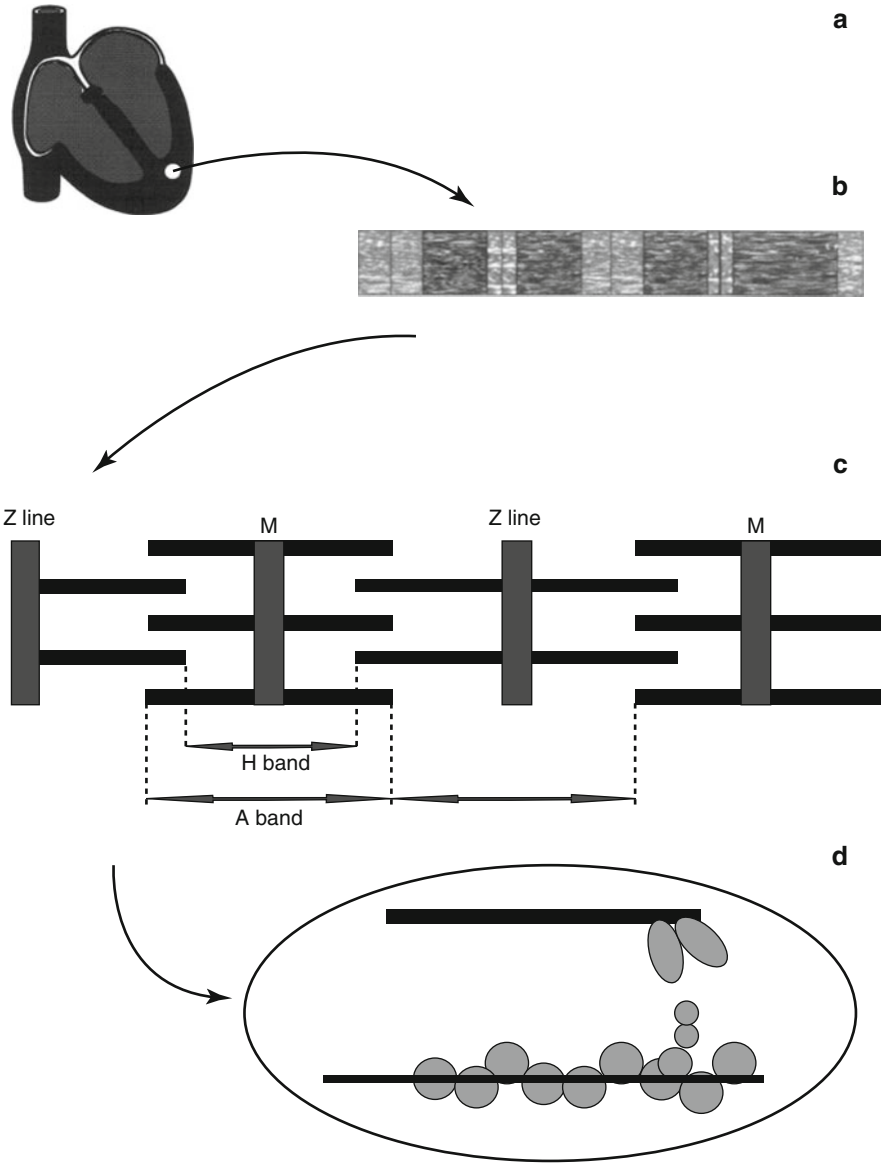



**Fig. 1.6** Detailed sarcomere anatomy in different aspects; also, see Fig. 1.2. (**a**) Macroscopic schematic presentation of the heart. (**b**) Myocardial filaments as seen under microscope. (**c**) Microscopic structure of a sarcomere; thin and thick filaments are presented as thin and thick interspersed horizontal rods; a sarcomere is defined as the part of sarcomere between two Z lines. (**d**) Thick filament with its two myosin light chains and also thin filament with F actin and tropomyosin molecule between actin monomers (see text)

### Thick Filament

The contractile proteins are the "workforce" of the myocardium; the more the *cross bridges* of actin and myosin, the more the contractile force of the sarcomere. Cross bridges are the result of interactions between myosin head and actin after trigger of $Ca^{2+}$.

*Myosin* is the largest and heaviest protein of sarcomere among the others which are in the form of rods; being about 15 nm in diameter, it composes thick filament of myofibrils and interacts with actin during contractions as cross bridges; myosin rods are made of myosin molecules in the following features and characteristics:

- One myosin heavy chain (MHC) plus two myosin light chains (MLC) are composed together as a single strand.
- Two single strands twist round each other to produce one molecule of myosin.
- Each myosin molecule has two functional domains, a head (composed of four MLC's and the lever like end of two MHC's) coming out of the main molecule.
- Myosin heads are the *main location* for interactions with actin and create hinge-shaped features, coming out of the bouquet like "lever arm" and are inhibited by TnI; after interaction with $Ca^{2+}$ they attach to actin in order to produce cross bridges.
- Three hundred molecules of myosin are attached together in a parallel fashion to form the myosin rod, whose microscopic figure is similar to a number of parallel golf clubs forming a bouquet, twisting together in an orderly fashion forming the *body of myosin rod*; while their heads are exposed out of the bouquet, the bodies are attached together.

*Cross bridges* between actin and myosin (the principal mechanism of muscle contraction) are formed repetitively and released after a very short period of time; great amounts of ATP molecules are used for production of actin-myosin interactions and cross bridges leading to muscle contractions. These interactions cause a rotation in myosin along actin filament; the main interaction site is the head and hinge region of myosin.

*Myosin-binding protein C* (MYBPC) is another important and determining protein of sarcomere, being among the regulator proteins; a number of life threatening arrhythmias and some types of hypertrophic cardiomyopathies are the results of genetic impairments in this protein; new treatments of heart failure are in development regarding the role of this protein.

*Titin* is the 3rd most common filament in sarcomere (after actin and myosin), being the main factor for passive features of the myocardium in lower ventricular volumes; this is why the main role of titin is muscular assembly of the heart and its elasticity features. Regarding the molecular structure, titin is a giant filamentous protein, extending as long as "half sarcomere from Z line to M line"; this giant structure of titin provides a continuous link between the Z line and the M line inside each sarcomere; so, titin functions as an extensible filamentous protein to preserve the structural integrity of sarcomere and also to function in sarcomere to reach its

normal length after systolic contraction and returning to normal length in diastole. This is why titin has a central role in patients with ischemic or diastolic heart failure.

As it is demonstrated in Figs. 1.2 and 1.6, the force created by titin helps keep the thick filament in its central position in sarcomere, maintaining the balance inside the sarcomere between sarcomere structures during systole and diastole.

Titin could be divided to two main parts: the *extensible part* which is located in the "I band" area of sarcomere and the *non-extensible part* located in the "A band" area of sarcomere. Also, the extensible parts of titin are mainly composed of two segments, both taking part in passive force development of sarcomere during stretch:

- Immunoglobulin-like segment.
- PEVK segment in which four amino acids are abundant: proline (P), glutamate (E), valine (V), and lysine (K).

Finally, if we want to describe titin in just a two-word phrase, we could name titin as *molecular spring* of the sarcomere which creates elastic properties for the sarcomere.

### Thin Filament

*Thin filament* is composed of the following ingredients discussed here; if we consider an "imaginary unit" for thin filament, this unit consists of:

- 1 F actin strand
- 2 tropomyosin strands (i.e., 2 TM)
- 2 troponin complex (i.e., 2 Tn)

These "imaginary units" are attached together in a row, from head to tail, to compose the thin filament in such a way that:

- F actin (the actin strand) makes the foundation of the filament.
- The two tropomyosin molecules lie in the two groves of the filament as long as the entire thin filament.
- Troponin complexes are attached to actin filament at defined intervals.

*Actin* is one of the main contractile proteins and also a main protein of the thin filament; actin filaments are double-stranded filaments composed of actin molecules, arranged in a special configuration; actin is a 43-kd, 7-nm globular protein *G actin*; 13 G actin monomers are polymerized to form the two-stranded filament *F actin* which is a 360° twisted filament as the contractile element. F actin in cardiomyocytes is mainly "alpha actin" isomer. Pathogenic mutations in actin-related genes are responsible for some cardiac diseases like idiopathic dilated cardiomyopathy.

*Tropomyosin* (TM) is a part of the thin filament, being an inhibitory protein; this protein is formed as α-coiled coil dimmers attached head to tail; in other words, each TM molecule is attached to another TM molecule; then, these two twist round each other to create the first coil and afterwards, the first coil twists once more round itself to produce the coiled coil; this final configuration is repeatedly formed in thin filament and is located inside the groove of F actin between two adjacent lines of actin monomers in such a way that each TM is in attachment with seven actin monomers; however, this line of repeated TM molecules are attached together from the

head of one molecule to the tail of the next and so on. This special configuration of TM has a very determining role in coordination and cooperation of the functions of thin filament.

*Troponin* is part of the thin filament; each troponin complex is attached to one actin monomer after each seven repeated monomers; troponin is in fact a complex of three proteins totally named as troponin complex "Tn":

- Troponin C (TnC) is the $Ca^{2+}$ receptor protein in the contraction-relaxation process; 4Ca2+ could attach to each TnC molecule.
- Troponin I (TnI) binds to actin to inhibit actin-myosin interaction.
- Troponin T (TnT) is responsible for attachment of troponin to TM; it binds to TM on one side and on the other side binds to TnC and TnI.

*Tropomodulin* is a regulatory filament located at the end of actin to prevent excessive elongation of the filament.

Now, let's once go back to $Ca^{2+}$ which is the *ignition switch* of the contraction-relaxation process. When $Ca^{2+}$ binds to TnC, there is a structural change in TnI which would move away from F actin, in such a way to expose the special site on actin for attachment of myosin head; after $Ca^{2+}$ removal from TnC, TnI resumes its primary structural form to inhibit the actin-myosin attachment. TnI-actin interaction has an inhibitory nature; hence, the release of TnI from actin causes detachment of actin from one myosin head and its attachment to another myosin head; the detachment-attachment of actin-myosin head is an ATP-consuming process.

TnC and TnI form the head of Tn, while TnT forms the tail of Tn. These three subunits of troponin have determining roles in contraction-relaxation phases of cardiomyocytes. There are a series of *pathogenic mutations* in amino acid sequence of TnI, resulting in impaired function of TnI as an inhibitory protein in cardiomyocyte contractile system, leading to some type of "diastolic dysfunction" or "hypertrophic/restrictive cardiomyopathies"; also, TnI has the diagnostic role in myocardial infarction.

The specific site for $Ca^{2+}$ in TnC is the unique location and the sole place which has a direct and central role in contraction process of cardiomyocytes through $Ca^{2+}$, performing its function through the following mechanism:

- When $Ca^{2+}$ is attached to TnC, it would induce a "structural change" in troponin.
- This configuration change will result in dissociation of tropomyosin from actin.
- Then, when actin is released, "myosin attachment site" on actin filament is freed.
- Myosin attachment site could start a new the "cross-bridge formation."
- "Inappropriate phosphorylation of sarcomere contractile proteins" especially *troponin* and *myosin* should be mentioned among the important etiologies for heart failure (like ventricular hypertrophy, diabetic cardiomyopathy or heart failure).

The following factors are the main determinants of force generation in cardiac sarcomere:

- $Ca^{2+}$ activation level (i.e., level of sensitivity of sarcomere proteins to $Ca^{2+}$)
- Sarcomere length (i.e., the Frank-Starling relationship)
- Myofilament phosphorylation and other changes in sarcomere proteins (this is why in some cardiac pathologies phosphorylation of cardiac contractile proteins has a central role in progress of the disease)

**Table 1.3** A summary of the main sarcomere proteins

| | Thick filament | Thin filament |
|---|---|---|
| Contractile proteins | Myosin<br>Titin | Actin |
| Regulatory proteins | Myosin-binding protein C | Tropomyosin<br>Troponin<br>Tropomodulin |

On the other hand, the two latter factors could affect the sensitivity of contractile filaments to $Ca^{2+}$ (Table 1.3).

(McLachlan and Stewart 1975; Hill et al. 1980; White et al. 1987; Pan et al. 1989; Schoenberg 1993; Thierfelder et al. 1994; Farah and Reinach 1995; Marston et al. 1998; Redwood et al. 1999; Wick 1999; Gordon et al. 2000; Linke 2000a, b; Morimoto and Goto 2000; Craig and Lehman 2001; Agarkova et al. 2003; Marston and Redwood 2003; Agarkova and Perriard 2005; Granzier et al. 2005; Bragadeesh et al. 2007; LeWinter et al. 2007; Vahebi et al. 2007; Hitchcock-DeGregori 2008; Kobayashi et al. 2008; Ohtsuki and Morimoto 2008; Rice et al. 2008; Teerlink 2009; Campbell 2010; Offer and Ranatunga 2010; Gautel 2011; Kruger and Linke 2011; Malik et al. 2011; Malik and Morgan 2011; McDonald 2011; Posch et al. 2011; Tardiff 2011; Balse et al. 2012; Eisner et al. 2013; Herzog et al. 2012; Kajioka et al. 2012; Knoll 2012; Kuster et al. 2012; ter Keurs 2012)

## 1.3 Cardiac Cycle and Cardiac Work

### 1.3.1 Normal Cardiac Cycle

The final goal of all cardiac treatments (medical, surgical, or interventional) is to change the situation from a diseased pathologic heart towards a normal physiologic heart, which would pump the blood appropriately. In other words, our interventions need to go, as much as possible, towards a normal physiologic heart which could pump the blood appropriately with appropriate force and in appropriate time manner. In other words, we need to go, as much as possible, towards a normal cardiac physiology or, more specifically, a normal *cardiac cycle*, filling normally in diastole (with appropriate time schedule and normal pressure, without overpressurizing the pulmonary vasculature), then ejecting enough blood in systole. The above process could be translated into a 4-phase repetitive cycle, as the following:

Phase 1"Diastolic filling" during which the atrioventricular valves (i.e., mitral and tricuspid) open, while aortic and pulmonary valves are closed. In this phase, the ventricular cavity is filled with blood based on three factors:

- Pressure gradient between atria and ventricles
- Ventricular diastolic compliance
- Atrial contraction (atrial kick)

Phase 2 "Isovolumic systole" during which the ventricular cavity pressure raises without any volume change. The atrioventricular valves are closed in early stages of this phase. However, in a fraction of time, the intracavity pressure increases to a critical level which is more than aortic and pulmonary valves, going to the next phase.

Phase 3 "Systolic ejection" in which blood is pushed with a high pressure to the aorta or pulmonary bed, i.e., blood ejection, to perfuse each of the two vascular beds. The size of the ventricles decreases as blood ejects and their blood content exits as fast as possible.

Phase 4 "Isovolumic relaxation" in which both ventricles are relaxed, starting to increase their size. The aortic and pulmonary valves are closed due to decreased intraventricular pressure, while mitral and tricuspid valves begin to open. Again, the cardiac cycle goes to phase 1 to start a new cycle (Tanaka et al. 1993; Gibson and Francis 2003; Chatterjee 2012).

### 1.3.2 Cardiac Work

Cardiac work implies the product of myocardial performance and is the algebraic sum of two different items: first, the *external work* which is equivalent to the total myocardial energy used for ejecting blood out of the ventricles to the systemic and pulmonary vascular bed. The second parameter is the *internal work* which is the total energy needed by myocardial tissue to maintain cell energy, myocardial integrity, and homeostasis of cardiomyocytes. For calculating the external work, we use the product of "stroke work multiplied by ventricular cavity pressure." However, we usually calculate the external work by calculating the area under curve of pressure-volume loop of left ventricle (i.e., LV pressure-volume AUC). The main myocardial need for energy reserve and its oxygen consumption is for used for external work; however, myocardial ischemia would jeopardize mainly the external work. There are a number of clinical indices for assessment of cardiac work. Since we could not measure the cellular energy easily in clinical practice, we use a number of indices which are discussed here. These are stroke volume, cardiac output, and ejection fraction.

#### 1.3.2.1 Stroke Volume

Each "stroke volume" is the amount of blood ejected from the heart in each cardiac beat. Stroke volume (SV) is the result of "end diastolic volume (EDV) minus end systolic volume (ESV)" or, simply, "SV = EDV – ESV." According to this equation, both EDV and ESV could affect SV. However, which factors could affect EDV and ESV?

- EDV depends directly at two factors:
  1. *Venous return* is the returned blood to the ventricles from veins, i.e., from inferior and superior vena cava (IVC and SVC) to RV and from pulmonary veins to LV.
  2. Diastolic time of ventricular filling or simply "filling time" which is the time in diastole that blood accumulates in ventricles; the longer the filling time, the more the SV would be.

- ESV depends on three factors:
  1. *Preload* is the amount of ventricular stretching; the more stretch in ventricle, the more contractile force; this is discussed more in the Sect. 1.3.3; the relationship between preload and ESV is a converse relationship.
  2. *Contractility* is the contractile force of the myocardium; this factor has a converse relationship with ESV, i.e., the more contractility, the less volume would remain in the ventricle; however, there are a multitude of factors affecting contractility which are discussed later.
  3. *Afterload* is the resistance against the pumping action of ventricles; there is a direct relationship between ESV and afterload; for LV, afterload is mainly the systemic vascular resistance (SVR) which is about 90 % of LV afterload; however, pulmonary vascular resistance (PVR) produces about 50 % of RV afterload, and the RV wall stress is responsible for the other half of RV afterload.

#### 1.3.2.2 Cardiac Output

Cardiac output, abbreviated as CO is the amount of blood which is pumped out of the heart during a 1-min interval; so, CO is the product of SV multiplied by heart rate; so, "cardiac output (mL/min) = stroke volume (mL/beat) × heart rate (beat/min)" or simply: CO = HR × SV.

#### 1.3.2.3 Ejection Fraction

Another important variable is ejection fraction or more commonly known as "EF." EF is calculated based on this equation: EF = SV/EDV. (In this formula, EDV stands for end diastolic volume.) Usually EF is expressed in percentage. Normal EF is usually between 55 and 70 %; though more than 50 % is considered normal for EF and consider patients having EF >50 % as good LV performance. EF is directly a very determining index of cardiac function and global clinical outcome. Patients with EF <30 % are often considered as very high risk cases impressing the global outcome.

Among the above three main factors (i.e., SV, ESV, and EDV), the cardiac work is much related to EDV and less to the other two factors; this is due to the length-tension concept of sarcomere which affects the cardiac contractility, cardiac work, and cardiac output more than the others. To understand this latter fact, we have to discuss Frank-Starling relationship in the next paragraph (Germano et al. 1995; Ababneh et al. 2000; Rozanski et al. 2000; Sharir et al. 2006; Lomsky et al. 2008; Mahadevan et al. 2008).

### 1.3.3 Frank-Starling Relationship

Otto Frank in 1895 and Ernest Starling, two decades later, demonstrated in animal models that the heart has a very important basic and intrinsic characteristic: "length-dependent activation" or the "Frank-Starling relationship."

The Frank-Starling relationship tells us that the more blood accumulated in each of the ventricles in diastole, the more pump output would be pushed out in systole.

This interesting feature is seen even when the heart is removed out from the body to work in a lab environment. So, the Frank-Starling relationship tells us that the heart has a wide range of capacity for adaptation against preload, afterload, and their related imposed work; this fundamental concept of cardiac physiology explains the ability of the heart to change its contractile response under different physiologic and pathologic states, in such a way to save the cardiac output as much appropriate as possible to physiologic body demands. This adaptation capacity is both due to the cellular structure of the heart (especially the sarcomere structure) and also the effects of neurohormonal effectors and the cardiac reflexes. So, considering these length-force changes, we reach to a final conclusion which is the general concept of Frank-Starling relationship: within a defined length of sarcomere, there is a clear and direct "optimal interaction length" for sarcomere; however, in human sarcomere, this "optimal length" between actin and myosin is when the sarcomere length equals 2.2 μ. The cellular basis for Frank-Starling relationship is in general known as "length-dependent activation," which is a mechanism seen in every other sarcomere in all of the cardiomyocytes. In physiologic measurements of the Frank-Starling relationship, any sudden increase in diastolic length of a contractile segment of cardiomyocyte (i.e., sarcomere) would result in a sudden increase of its systolic force reaching a plateau after a short time. Before this plateau, the more length of sarcomere, the more force produced by myocardium; however, after reaching this plateau, the sarcomere could not produce more contraction since the actin and myosin heads start going far from each other and the sarcomere length goes far from its optimal length. Meanwhile, any sudden decrease in diastolic length of the contractile elements would result in decreased systolic force, again reaching a plateau phase after a short time. Though Frank-Starling relationship has been discovered for more than 100 years, its underlying mechanism(s) is not fully clear yet. In other words, its cellular and subcellular mechanisms are not limited to one single mechanism. Instead, Frank-Starling relationship is "the end product of a complex system of interacting elements"; however, there are many different molecular mechanisms cooperating together in each of the cardiac sarcomeres "to produce strain dependent activation." Here, two main classes for its mechanisms have been introduced:

- First, "increased diastolic tension" results in "increased number of cross bridges" which in turn will improve the "myofilament overlap" status, favoring more effective contractions. In other words, the interdigitations of actin and myosin in diastole will become more effective in producing systolic contractions. Though this is the main mechanism, another proposed mechanism seems important.
- Second, improved efficacy of sarcomere contractile function to produce increased contractile force in response to $Ca^{2+}$ concentration is seen when the length of the sarcomere is increased. In other words, according to this mechanism, Frank-Starling relationship is due to improved response of myofilaments to $Ca^{2+}$ when the length of the sarcomere is increased. The interested reader could find more extended explanations in other sources, being beyond the scope of this chapter (Markwalder and Starling 1914; Patterson et al. 1914; Fuchs and Smith 2001; Solaro 2007; Bollensdorff et al. 2011; Campbell 2011; Ribaric and Kordas 2012; Cingolani et al. 2013; Goldhaber and Philipson 2013).

## 1.4 Cardiac Reflexes

### 1.4.1 Bainbridge Reflex

Bainbridge reflex was described first in 1915 by Francis Bainbridge (English physiologist, 1874–1921). He discovered and demonstrated that "saline or blood infusion into the jugular vein of the anesthetized dog" would result in reflex tachycardia. This reflex is also called the "atrial reflex" and involves increased heart rate in response to dilation of "the main systemic veins and left and right atrium." In response to dilation of the right atrium, stretch receptors located in the right atrium (i.e., venoatrial stretch receptors) are activated and send their impulse through the vagus nerve (10th cranial nerve) to CNS; this is why the reflex is blocked if the patient is premedicated with atropine. Also, in animal studies, this reflex is blocked by "bilateral vagotomy or combined cholinergic and beta-adrenergic blockades." After being processed in the CNS, the response to the afferent impulse would result in increased sympathetic tone, which in turn would cause increased contractility and tachycardia which finally helps emptying of the heart. Simply saying, the "Bainbridge reflex" causes "hypervolemia-induced tachycardia." The efferent limb of the reflex is mediated through the sympathetic pathways. In cardiovascular physiologic pathways, the Bainbridge reflex plays an important role and has control over heart rate and other hemodynamic variables; also, the effects of the Bainbridge reflex are in contrary to the effects of the "carotid baroreceptor reflex." This reflex is sensed in the atria through the atrial type B mechanoreceptors; these receptors are located at the junction of venae cavae and the right atria and the junction of pulmonary veins and left atria, which in turn would trigger the neural pathway of the reflex (Vatner and Zimpfer 1981; Boettcher et al. 1982; Hakumaki 1987; Hajdu et al. 1991; Barbieri et al. 2002; Crystal and Salem 2012).

### 1.4.2 Baroreceptors Reflex (or Carotid Sinus Reflex)

This reflex results in regulation of blood pressure, especially if it is highly elevated or severely depressed; however, the reflex is usually elicited in systolic blood pressures over 150–170 mm Hg; the other part of the reflex is not often seen when the systolic blood pressure is below 50–60 mm Hg. However, in patients with underlying hypertension or atherosclerosis, or in the elderly, the reflex thresholds might be altered and at times, the reflex would not be seen partially or totally. The main receptors of this reflex are located in the walls of carotid arteries and aortic arch and its sequence is as follows:

- The circumferential and longitudinal stretch receptors are located in carotid sinus and aortic arch; increased blood pressure triggers these receptors leading to impulse firing.
- The transport of impulse from carotid sinus is through the 9th cranial verve and from the aortic arch through the 10th cranial nerve.
- The impulses from these two locations are sent to the nucleus solitaries in the medullary cardioregulatory and vasomotor centers.

- The nucleus solitaries, however, have two different parts: the first part is lateral and rostral known as the "pressor center," and the second part is located at the central and caudal part which is known as the "depressor" center; in these two parts, the limbic and hypothalamic inputs are integrated to create the final response as either of the two following responses:
- Decreased *sympathetic* tone (mainly through inhibition of sympathetic chain and sympathetic nerves) leading to hypotension and bradycardia and also decreased vascular tone, leading to blood vessel dilation (i.e., systemic vasodilation).
- Increased *parasympathetic* tone (mainly through vagus nerve) leading to decreased heart rate and decreased myocardial contractility.
- These interactions would bring the blood pressure to normal, hence relieving the pressure over the baroreceptors.
- If the initial event is decreased blood pressure, the decreased tone on the baroreceptors would initiate the opposite response (Vasquez et al. 1997; Pilowsky and Goodchild 2002; Campagna and Carter 2003; Kashihara 2009).

### 1.4.3 Bezold-Jarisch Reflex

This reflex, known as a "cardioinhibitory" reflex, was described first by *von Bezold* and *Hirt* in 1867; it was more studied and completed in the late 1930s by *Adolf Jarisch* and *Richter*. Describing the reflex in brief, it is a triad of "bradycardia, hypotension, and peripheral vasodilation" usually accompanied with hypopnea or apnea. Also, coronary artery vasodilation has been mentioned among the items of the reflex. This reflex seems to have some cardioprotective effects; for example, it is seen during some myocardial stress states including during acute phase of myocardial ischemia, infarction, or reperfusion syndrome, especially when involving posterior or inferior myocardial walls.

The main physiologic phenomenon underlying the reflex is *parasympathetic* overactivity; however, some degrees of *sympathetic* inhibition have an etiologic role in the reflex. The sequence of the reflex in brief is as follows:

- The reflex is initiated after mechanical stimuli (like volume overload or pressure) or chemical stimuli (like metabolites of myocardial ischemia or chemicals like veratrum alkaloids) trigger the specific receptors of the reflex in the heart.
- The sensors of the reflex are located in a number of locations over the cardiac walls including the left ventricle wall, the atrial walls, atrial-caval junctions, and other cardiac chambers.
- The majority of the afferent fibers are nonmyelinated C fibers (75 % of the afferent pathways located over all the cardiac chambers) and myelinated fibers (25 % of the afferent pathways located in the atrial walls and the atrial-caval junctions).
- The afferent fibers inhibit the medullary vasomotor center which would have two effects: directly leads to bradycardia and also suppresses the sympathetic output.

- Decreased sympathetic output leads to decreased peripheral vascular tone leading to peripheral vasodilation, presented as systemic hypotension (Robertson et al. 1985; Hakumaki 1987; Meyrelles et al. 1997; Campagna and Carter 2003; Kashihara et al. 2004; Salo et al. 2007; Kashihara 2009).

### 1.4.4 Valsalva Maneuver

The "Valsalva maneuver" first described by Valsalva in 1704 is the name for a cardiac reflex starting with a forced expiration against a "closed glottis"; this act results in sudden increase of intrathoracic pressure resulting in increased central venous pressure (CVP); the increased CVP would cause decreased venous return which leads to decreased "cardiac output" and decreased blood pressure. The decreased blood pressure would be sensed by baroreceptors located in the arterial system and would stimulate the sympathetic pathways leading to tachycardia. After glottis opening, venous return would be resumed leading to increased contractility, and finally, the blood pressure returns to normal which this time would inhibit the baroreceptors leading to "normalized" heart rate; all these changes are as a matter of fact "a sequence of rapid changes in preload and afterload stress" imposed to the heart; this maneuver has a number of clinical therapeutic and diagnostic implications (Sharpey-Schafer 1955; Porth et al. 1984; Smith 2012; Wang et al. 2013).

### 1.4.5 Cushing Reflex

The Cushing reflex was introduced in 1901–1902 by Harvey Cushing (1869–1939) and is presented clinically as a triad of:

- Bradycardia
- Hypertension: presented as increased systolic blood pressure and wide pulse pressure
- Respiratory depression: presented as respiratory irregularity leading to bradypnea and apnea

This reflex is due to increased ICP (often an abrupt increase of ICP), and many times this clinical presentation is associated with cerebral herniation and death; in other words, the Cushing reflex is associated with the cerebral perfusion status; increased cerebrospinal fluid (CSF) production or its decreased reabsorption or, in another way, a mass effect in the CNS would lead to increased intracranial pressure which causes cerebral ischemia; however, cerebral ischemia would trigger sympathetic activity in an attempt to compensate for reduced cerebral perfusion leading to increased heart rate, blood pressure, and myocardial contractility; the increased blood pressure would be sensed by the baroreceptors in the aortic arch and carotid sinus, which leads to reflex bradycardia, well known in Cushing reflex; finally, the triad usually seen after elicitation of Cushing reflex is "increased systolic and pulse pressure with bradycardia and respiratory irregularity," all due to increased intracranial pressure (Grady and Blaumanis 1988; Dickinson 1990; Ayling 2002; Fodstad et al. 2006; Molnar et al. 2008; Wan et al. 2008).

### 1.4.6 Oculocardiac Reflex

This reflex is elicited due to traction on the extraocular muscles (especially rectus medialis) or pain in the eyeball. The pathway of this reflex is as follows:

- The afferent limb of the reflex passes through the ophthalmic division of the 5th cranial nerve (trigeminal nerve); the other branches of the trigeminal nerve (maxillary and mandibular branches) might also be involved.
- The impulses go to CNS, i.e., trigeminal sensory nucleus.
- The efferent limb of the reflex is the 10th cranial nerve (vagus nerve) which causes sinus bradycardia as the final clinical presentation of the reflex; at times, junctional rhythms, asystole, or other types of arrhythmias, atrioventricular blocks, or hypotension may occur.

The frequency of occurrence of the reflex is diminished with aging and also could be somewhat prevented by anticholinergic pretreatment like atropine (Lang et al. 1991; Smith 1994; Gao et al. 1997; Seshubabu 1998; Kim et al. 2000, 2012; Paton et al. 2005; Chung et al. 2008; Yi and Jee 2008; Arasho et al. 2009; Simon 2010; Tsai and Heitz 2012).

### 1.4.7 Chemoreceptor Reflex

This reflex is another important one among the cardiac reflexes:

- Chemoreceptors are located in carotid body and aortic arch.
- Acidosis, hypercarbia (increased $CO_2$ pressure in blood), or a drop in blood oxygen pressure triggers the chemoreceptors.
- Afferent nerves are the 9th (glossopharyngeal) and 10th (vagus) cranial nerves.
- These nerves send the impulses to the medulla.
- The response would be increased sympathetic tone to compensate for hypoxia and hypercarbia.
- However, if hypoxia and hypercarbia do not resolve, the response would be parasympathetic stimulation to decrease heart rate and oxygen demands (Schultz and Sun 2000; Schultz and Li 2007; Ding et al. 2011; Schultz 2011; Campanucci et al. 2012; Schultz et al. 2012; Schultz and Marcus 2012).

## References

Ababneh AA, Sciacca RR, Kim B, Bergmann SR (2000) Normal limits for left ventricular ejection fraction and volumes estimated with gated myocardial perfusion imaging in patients with normal exercise test results: influence of tracer, gender, and acquisition camera. J Nucl Cardiol 7:661–668

Abbott BC, Ritchie JM (1951) Early tension relaxation during a muscle twitch. J Physiol 113:330–335

Agarkova I, Perriard JC (2005) The M-band: an elastic web that crosslinks thick filaments in the center of the sarcomere. Trends Cell Biol 15:477–485

Agarkova I, Ehler E, Lange S, Schoenauer R, Perriard JC (2003) M-band: a safeguard for sarcomere stability? J Muscle Res Cell Motil 24:191–203

Alberts BJA, Lewis J et al (eds) (2002) Molecular biology of the cell, 4th edn. Garland Science, New York

Anderson EJ, Katunga LA, Willis MS (2012) Mitochondria as a source and target of lipid peroxidation products in healthy and diseased heart. Clin Exp Pharmacol Physiol 39:179–193

Anwar AM, Geleijnse ML, Soliman OI, McGhie JS, Frowijn R, Nemes A, van den Bosch AE, Galema TW, Ten Cate FJ (2007) Assessment of normal tricuspid valve anatomy in adults by real-time three-dimensional echocardiography. Int J Cardiovasc Imaging 23:717–724

Arasho B, Sandu N, Spiriev T, Prabhakar H, Schaller B (2009) Management of the trigeminocardiac reflex: facts and own experience. Neurol India 57:375–380

Atkinson A, Inada S, Li J, Tellez JO, Yanni J, Sleiman R, Allah EA, Anderson RH, Zhang H, Boyett MR, Dobrzynski H (2011) Anatomical and molecular mapping of the left and right ventricular His-Purkinje conduction networks. J Mol Cell Cardiol 51:689–701

Ayling J (2002) Managing head injuries. Emerg Med Serv 31:42

Balse E, Steele DF, Abriel H, Coulombe A, Fedida D, Hatem SN (2012) Dynamic of ion channel expression at the plasma membrane of cardiomyocytes. Physiol Rev 92:1317–1358

Barbieri R, Triedman JK, Saul JP (2002) Heart rate control and mechanical cardiopulmonary coupling to assess central volume: a systems analysis. Am J Physiol Regul Integr Comp Physiol 283:R1210–R1220

Bickler PE, Fahlman CS (2004) Moderate increases in intracellular calcium activate neuroprotective signals in hippocampal neurons. Neuroscience 127:673–683

Bingen BO, Askar SF, Schalij MJ, Kazbanov IV, Ypey DL, Panfilov AV, Pijnappels DA (2013) Prolongation of minimal action potential duration in sustained fibrillation decreases complexity by transient destabilization. Cardiovasc Res 97(1):161–170

Boettcher DH, Zimpfer M, Vatner SF (1982) Phylogenesis of the Bainbridge reflex. Am J Physiol 242:R244–R246

Bollensdorff C, Lookin O, Kohl P (2011) Assessment of contractility in intact ventricular cardiomyocytes using the dimensionless 'Frank-Starling Gain' index. Pflugers Arch 462:39–48

Borg TK, Sullivan T, Ivy J (1982) Functional arrangement of connective tissue in striated muscle with emphasis on cardiac muscle. Scan Electron Microsc 4:1775–1784

Boyden PA, Gardner PI, Wit AL (1988) Action potentials of cardiac muscle in healing infarcts: response to norepinephrine and caffeine. J Mol Cell Cardiol 20:525–537

Bragadeesh TK, Mathur G, Clark AL, Cleland JG (2007) Novel cardiac myosin activators for acute heart failure. Expert Opin Investig Drugs 16:1541–1548

Brunello L, Slabaugh JL, Radwanski PB, Ho HT, Belevych AE, Lou Q, Chen H, Napolitano C, Lodola F, Priori SG, Fedorov VV, Volpe P, Fill M, Janssen PM, Gyorke S (2013) Decreased RyR2 refractoriness determines myocardial synchronization of aberrant Ca2+ release in a genetic model of arrhythmia. Proc Natl Acad Sci USA 110:10312–10317

Bucchi A, Barbuti A, Baruscotti M, DiFrancesco D (2007) Heart rate reduction via selective 'funny' channel blockers. Curr Opin Pharmacol 7:208–213

Burgoyne T, Muhamad F, Luther PK (2008) Visualization of cardiac muscle thin filaments and measurement of their lengths by electron tomography. Cardiovasc Res 77:707–712

Campagna JA, Carter C (2003) Clinical relevance of the Bezold-Jarisch reflex. Anesthesiology 98:1250–1260

Campanucci VA, Dookhoo L, Vollmer C, Nurse CA (2012) Modulation of the carotid body sensory discharge by NO: an up-dated hypothesis. Respir Physiol Neurobiol 184:149–157

Campbell KS (2010) Short-range mechanical properties of skeletal and cardiac muscles. Adv Exp Med Biol 682:223–246

Campbell KS (2011) Impact of myocyte strain on cardiac myofilament activation. Pflugers Arch 462:3–14

Chatterjee K (2012) Pathophysiology of systolic and diastolic heart failure. Med Clin North Am 96:891–899

Chen PS, Joung B, Shinohara T, Das M, Chen Z, Lin SF (2010) The initiation of the heart beat. Circ J 74:221–225

Chung CJ, Lee JM, Choi SR, Lee SC, Lee JH (2008) Effect of remifentanil on oculocardiac reflex in paediatric strabismus surgery. Acta Anaesthesiol Scand 52:1273–1277
Cingolani HE, Perez NG, Cingolani OH, Ennis IL (2013) The Anrep effect: 100 years later. Am J Physiol Heart Circ Physiol 304:H175–H182
Coronel R, Janse MJ, Opthof T, Wilde AA, Taggart P (2012) Postrepolarization refractoriness in acute ischemia and after antiarrhythmic drug administration: action potential duration is not always an index of the refractory period. Heart Rhythm 9:977–982
Craig R, Lehman W (2001) Crossbridge and tropomyosin positions observed in native, interacting thick and thin filaments. J Mol Biol 311:1027–1036
Crystal GJ, Salem MR (2012) The Bainbridge and the "reverse" Bainbridge reflexes: history, physiology, and clinical relevance. Anesth Analg 114:520–532
Currie S (2009) Cardiac ryanodine receptor phosphorylation by CaM Kinase II: keeping the balance right. Front Biosci 14:5134–5156
Dell'Italia LJ (2012) Anatomy and physiology of the right ventricle. Cardiol Clin 30:167–187
Delmar M, Makita N (2012) Cardiac connexins, mutations and arrhythmias. Curr Opin Cardiol 27:236–241
Desplantez T, Dupont E, Severs NJ, Weingart R (2007) Gap junction channels and cardiac impulse propagation. J Membr Biol 218:13–28
Dickinson CJ (1990) Reappraisal of the Cushing reflex: the most powerful neural blood pressure stabilizing system. Clin Sci (Lond) 79:543–550
DiFrancesco D (2006) Funny channels in the control of cardiac rhythm and mode of action of selective blockers. Pharmacol Res 53:399–406
DiFrancesco D (2010) The role of the funny current in pacemaker activity. Circ Res 106:434–446
DiFrancesco D, Borer JS (2007) The funny current: cellular basis for the control of heart rate. Drugs 67(Suppl 2):15–24
DiFrancesco D, Noble D (2012) The funny current has a major pacemaking role in the sinus node. Heart Rhythm 9:299–301
Ding Y, Li YL, Schultz HD (2011) Role of blood flow in carotid body chemoreflex function in heart failure. J Physiol 589:245–258
Distefano G, Sciacca P (2012) Molecular pathogenesis of myocardial remodeling and new potential therapeutic targets in chronic heart failure. Ital J Pediatr 38:41
Dun W, Boyden PA (2008) The Purkinje cell; 2008 style. J Mol Cell Cardiol 45:617–624
Ednie AR, Bennett ES (2012) Modulation of voltage-gated ion channels by sialylation. Compr Physiol 2:1269–1301
Eisner D, Bode E, Venetucci L, Trafford A (2013) Calcium flux balance in the heart. J Mol Cell Cardiol 58(1):110–117
Farah CS, Reinach FC (1995) The troponin complex and regulation of muscle contraction. FASEB J 9:755–767
Fodstad H, Kelly PJ, Buchfelder M (2006) History of the cushing reflex. Neurosurgery 59:1132–1137; discussion 1137
Fuchs F, Smith SH (2001) Calcium, cross-bridges, and the Frank-Starling relationship. News Physiol Sci 16:5–10
Gao L, Wang Q, Xu H, Tao Z, Wu F (1997) The oculocardiac reflex in cataract surgery in the elderly. Br J Ophthalmol 81:614
Gautel M (2011) Cytoskeletal protein kinases: titin and its relations in mechanosensing. Pflugers Arch 462:119–134
Germano G, Kiat H, Kavanagh PB, Moriel M, Mazzanti M, Su HT, Van Train KF, Berman DS (1995) Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. J Nucl Med 36:2138–2147
Gibson DG, Francis DP (2003) Clinical assessment of left ventricular diastolic function. Heart 89:231–238
Goldhaber JI, Philipson KD (2013) Cardiac sodium-calcium exchange and efficient excitation-contraction coupling: implications for heart disease. Adv Exp Med Biol 961:355–364

Gordon AM, Homsher E, Regnier M (2000) Regulation of contraction in striated muscle. Physiol Rev 80:853–924
Grady PA, Blaumanis OR (1988) Physiologic parameters of the Cushing reflex. Surg Neurol 29:454–461
Granzier H, Wu Y, Siegfried L, LeWinter M (2005) Titin: physiological function and role in cardiomyopathy and failure. Heart Fail Rev 10:211–223
Haddad F, Couture P, Tousignant C, Denault AY (2009) The right ventricle in cardiac surgery, a perioperative perspective: I. Anatomy, physiology, and assessment. Anesth Analg 108:407–421
Hajdu MA, Cornish KG, Tan W, Panzenbeck MJ, Zucker IH (1991) The interaction of the Bainbridge and Bezold-Jarisch reflexes in the conscious dog. Basic Res Cardiol 86: 175–185
Hakumaki MO (1987) Seventy years of the Bainbridge reflex. Acta Physiol Scand 130:177–185
Hamilton SL, Serysheva I, Strasburg GM (2000) Calmodulin and excitation-contraction coupling. News Physiol Sci 15:281–284
Herzog JA, Leonard TR, Jinha A, Herzog W (2012) Are titin properties reflected in single myofibrils? J Biomech 45:1893–1899
Hill TL, Eisenberg E, Greene L (1980) Theoretical model for the cooperative equilibrium binding of myosin subfragment 1 to the actin-troponin-tropomyosin complex. Proc Natl Acad Sci USA 77:3186–3190
Hitchcock-DeGregori SE (2008) Tropomyosin: function follows structure. Adv Exp Med Biol 644:60–72
Ho SY, McCarthy KP (2010) Anatomy of the left atrium for interventional electrophysiologists. Pacing Clin Electrophysiol 33:620–627
Ibrahim M, Siedlecka U, Buyandelger B, Harada M, Rao C, Moshkov A, Bhargava A, Schneider M, Yacoub MH, Gorelik J, Knoll R, Terracciano CM (2013) A critical role for Telethonin in regulating t-tubule structure and function in the mammalian heart. Hum Mol Genet 22(2):372–383
Jafri MS (2012) Models of excitation-contraction coupling in cardiac ventricular myocytes. Methods Mol Biol 910:309–335
Kajioka S, Takahashi-Yanaga F, Shahab N, Onimaru M, Matsuda M, Takahashi R, Asano H, Morita H, Morimoto S, Yonemitsu Y, Hayashi M, Seki N, Sasaguri T, Hirata M, Nakayama S, Naito S (2012) Endogenous cardiac troponin T modulates Ca(2+)-mediated smooth muscle contraction. Sci Rep 2:979
Kashihara K (2009) Roles of arterial baroreceptor reflex during bezold-jarisch reflex. Curr Cardiol Rev 5:263–267
Kashihara K, Kawada T, Li M, Sugimachi M, Sunagawa K (2004) Bezold-Jarisch reflex blunts arterial baroreflex via the shift of neural arc toward lower sympathetic nerve activity. Jpn J Physiol 54:395–404
Kerckhoffs RC, Campbell SG, Flaim SN, Howard EJ, Sierra-Aguado J, Mulligan LJ, McCulloch AD (2009) Multi-scale modeling of excitation-contraction coupling in the normal and failing heart. Conf Proc IEEE Eng Med Biol Soc 2009:4281–4282
Khan MU, Cheema Y, Shahbaz AU, Ahokas RA, Sun Y, Gerling IC, Bhattacharya SK, Weber KT (2012) Mitochondria play a central role in nonischemic cardiomyocyte necrosis: common to acute and chronic stressor states. Pflugers Arch 464:123–131
Kim HS, Kim SD, Kim CS, Yum MK (2000) Prediction of the oculocardiac reflex from preoperative linear and nonlinear heart rate dynamics in children. Anaesthesia 55:847–852
Kim BB, Qaqish C, Frangos J, Caccamese JF Jr (2012) Oculocardiac reflex induced by an orbital floor fracture: report of a case and review of the literature. J Oral Maxillofac Surg 70:2614–2619
Kim B, Takeuchi A, Koga O, Hikida M, Matsuoka S (2013) Mitochondria Na(+)-Ca (2+) exchange in cardiomyocytes and lymphocytes. Adv Exp Med Biol 961:193–201
Kirchhoff S, Kim JS, Hagendorff A, Thonnissen E, Kruger O, Lamers WH, Willecke K (2000) Abnormal cardiac conduction and morphogenesis in connexin40 and connexin43 double-deficient mice. Circ Res 87:399–405

Knoll R (2012) Myosin binding protein C: implications for signal-transduction. J Muscle Res Cell Motil 33:31–42
Kobayashi T, Jin L, de Tombe PP (2008) Cardiac thin filament regulation. Pflugers Arch 457:37–46
Koivumaki JT, Korhonen T, Takalo J, Weckstrom M, Tavi P (2009) Regulation of excitation-contraction coupling in mouse cardiac myocytes: integrative analysis with mathematical modelling. BMC Physiol 9:16
Kruger M, Linke WA (2011) The giant protein titin: a regulatory node that integrates myocyte signaling pathways. J Biol Chem 286:9905–9912
Kubli DA, Gustafsson AB (2012) Mitochondria and mitophagy: the yin and yang of cell death control. Circ Res 111:1208–1221
Kuster DW, Bawazeer AC, Zaremba R, Goebel M, Boontje NM, van der Velden J (2012) Cardiac myosin binding protein C phosphorylation in cardiac disease. J Muscle Res Cell Motil 33:43–52
Lang S, Lanigan DT, van der Wal M (1991) Trigeminocardiac reflexes: maxillary and mandibular variants of the oculocardiac reflex. Can J Anaesth 38:757–760
LeWinter MM, Wu Y, Labeit S, Granzier H (2007) Cardiac titin: structure, functions and role in disease. Clin Chim Acta 375:1–9
Linke WA (2000a) Stretching molecular springs: elasticity of titin filaments in vertebrate striated muscle. Histol Histopathol 15:799–811
Linke WA (2000b) Titin elasticity in the context of the sarcomere: force and extensibility measurements on single myofibrils. Adv Exp Med Biol 481:179–202; discussion 203–176
Lo CW (2000) Role of gap junctions in cardiac conduction and development: insights from the connexin knockout mice. Circ Res 87:346–348
Lomsky M, Johansson L, Gjertsson P, Bjork J, Edenbrandt L (2008) Normal limits for left ventricular ejection fraction and volumes determined by gated single photon emission computed tomography–a comparison between two quantification methods. Clin Physiol Funct Imaging 28:169–173
Lu X, Ginsburg KS, Kettlewell S, Bossuyt J, Smith GL, Bers DM (2013) Measuring local gradients of intra-mitochondrial [Ca(2+)] in cardiac myocytes during sarcoplasmic reticulum Ca(2+) release. Circ Res 112(3):424–431
Mahadevan G, Davis RC, Frenneaux MP, Hobbs FD, Lip GY, Sanderson JE, Davies MK (2008) Left ventricular ejection fraction: are the revised cut-off points for defining systolic dysfunction sufficiently evidence based? Heart 94:426–428
Malik FI, Morgan BP (2011) Cardiac myosin activation part 1: from concept to clinic. J Mol Cell Cardiol 51:454–461
Malik FI, Hartman JJ, Elias KA, Morgan BP, Rodriguez H, Brejc K, Anderson RL, Sueoka SH, Lee KH, Finer JT, Sakowicz R, Baliga R, Cox DR, Garard M, Godinez G, Kawas R, Kraynack E, Lenzi D, Lu PP, Muci A, Niu C, Qian X, Pierce DW, Pokrovskii M, Suehiro I, Sylvester S, Tochimoto T, Valdez C, Wang W, Katori T, Kass DA, Shen YT, Vatner SF, Morgans DJ (2011) Cardiac myosin activation: a potential therapeutic approach for systolic heart failure. Science 331:1439–1443
Markwalder J, Starling EH (1914) On the constancy of the systolic output under varying conditions. J Physiol 48:348–356
Marston SB, Redwood CS (2003) Modulation of thin filament activation by breakdown or isoform switching of thin filament proteins: physiological and pathological implications. Circ Res 93:1170–1178
Marston S, Burton D, Copeland O, Fraser I, Gao Y, Hodgkinson J, Huber P, Levine B, el-Mezgueldi M, Notarianni G (1998) Structural interactions between actin, tropomyosin, caldesmon and calcium binding protein and the regulation of smooth muscle thin filaments. Acta Physiol Scand 164:401–414
McDonald KS (2011) The interdependence of $Ca^{2+}$ activation, sarcomere length, and power output in the heart. Pflugers Arch 462:61–67
McLachlan AD, Stewart M (1975) Tropomyosin coiled-coil interactions: evidence for an unstaggered structure. J Mol Biol 98:293–304

Meyer T, Stuerz K, Guenther E, Edamura M, Kraushaar U (2010) Cardiac slices as a predictive tool for arrhythmogenic potential of drugs and chemicals. Expert Opin Drug Metab Toxicol 6:1461–1475

Meyrelles SS, Bernardes CF, Modolo RP, Mill JG, Vasquez EC (1997) Bezold-Jarisch reflex in myocardial infarcted rats. J Auton Nerv Syst 63:144–152

Miragoli M, Novak P, Ruenraroengsak P, Shevchuk AI, Korchev YE, Lab MJ, Tetley TD, Gorelik J (2013) Functional interaction between charged nanoparticles and cardiac tissue: a new paradigm for cardiac arrhythmia? Nanomedicine (Lond) 8(5):725–737

Molnar C, Nemes C, Szabo S, Fulesdi B (2008) Harvey Cushing, a pioneer of neuroanesthesia. J Anesth 22:483–486

Morimoto S, Goto T (2000) Role of troponin I isoform switching in determining the pH sensitivity of Ca(2+) regulation in developing rabbit cardiac muscle. Biochem Biophys Res Commun 267:912–917

Nakada T, Flucher BE, Kashihara T, Sheng X, Shibazaki T, Horiuchi-Hirose M, Gomi S, Hirose M, Yamada M (2012) The proximal C-terminus of alpha1C subunits is necessary for junctional membrane targeting of cardiac L-type calcium channels. Biochem J 448:221–231

Neco P, Rose B, Huynh N, Zhang R, Bridge JH, Philipson KD, Goldhaber JI (2010) Sodium-calcium exchange is essential for effective triggering of calcium release in mouse heart. Biophys J 99:755–764

Offer G, Ranatunga KW (2010) Crossbridge and filament compliance in muscle: implications for tension generation and lever arm swing. J Muscle Res Cell Motil 31:245–265

Ohtsuki I, Morimoto S (2008) Troponin: regulatory function and disorders. Biochem Biophys Res Commun 369:62–73

Orellana JA, Sanchez HA, Schalper KA, Figueroa V, Saez JC (2012) Regulation of intercellular calcium signaling through calcium interactions with connexin-based channels. Adv Exp Med Biol 740:777–794

Ottolia M, Torres N, Bridge JH, Philipson KD, Goldhaber JI (2013) Na/Ca exchange and contraction of the heart. J Mol Cell Cardiol 61:28–33

Pan BS, Gordon AM, Luo ZX (1989) Removal of tropomyosin overlap modifies cooperative binding of myosin S-1 to reconstituted thin filaments of rabbit striated muscle. J Biol Chem 264:8495–8498

Papaioannou VE, Verkerk AO, Amin AS, de Bakker JM (2013) Intracardiac origin of heart rate variability, pacemaker funny current and their possible association with critical illness. Curr Cardiol Rev 9:82–96

Paton JF, Boscan P, Pickering AE, Nalivaiko E (2005) The yin and yang of cardiac autonomic control: vago-sympathetic interactions revisited. Brain Res Brain Res Rev 49:555–565

Patterson SW, Piper H, Starling EH (1914) The regulation of the heart beat. J Physiol 48:465–513

Periasamy M, Huke S (2001) SERCA pump level is a critical determinant of Ca(2+)homeostasis and cardiac contractility. J Mol Cell Cardiol 33:1053–1063

Periasamy M, Bhupathy P, Babu GJ (2008) Regulation of sarcoplasmic reticulum $Ca^{2+}$ ATPase pump expression and its relevance to cardiac muscle physiology and pathology. Cardiovasc Res 77:265–273

Peters NS (1996) New insights into myocardial arrhythmogenesis: distribution of gap-junctional coupling in normal, ischaemic and hypertrophied human hearts. Clin Sci (Lond) 90:447–452

Pilowsky PM, Goodchild AK (2002) Baroreceptor reflex pathways and neurotransmitters: 10 years on. J Hypertens 20:1675–1688

Porth CJ, Bamrah VS, Tristani FE, Smith JJ (1984) The Valsalva maneuver: mechanisms and clinical implications. Heart Lung 13:507–518

Posch MG, Waldmuller S, Muller M, Scheffold T, Fournier D, Andrade-Navarro MA, De Geeter B, Guillaumont S, Dauphin C, Yousseff D, Schmitt KR, Perrot A, Berger F, Hetzer R, Bouvagnet P, Ozcelik C (2011) Cardiac alpha-myosin (MYH6) is the predominant sarcomeric disease gene for familial atrial septal defects. PLoS One 6:e28872

Pott C, Eckardt L, Goldhaber JI (2011) Triple threat: the Na+/Ca2+ exchanger in the pathophysiology of cardiac arrhythmia, ischemia and heart failure. Curr Drug Targets 12:737–747

Prosser BL, Hernandez-Ochoa EO, Schneider MF (2011) S100A1 and calmodulin regulation of ryanodine receptor in striated muscle. Cell Calcium 50:323–331
Redwood CS, Moolman-Smook JC, Watkins H (1999) Properties of mutant contractile proteins that cause hypertrophic cardiomyopathy. Cardiovasc Res 44:20–36
Reuter H, Pott C, Goldhaber JI, Henderson SA, Philipson KD, Schwinger RH (2005) Na(+)–Ca2+ exchange in the regulation of cardiac excitation-contraction coupling. Cardiovasc Res 67:198–207
Ribaric S, Kordas M (2012) Simulation of the Frank-Starling Law of the heart. Comput Math Methods Med 2012:267834
Rice JJ, Wang F, Bers DM, de Tombe PP (2008) Approximate model of cooperative activation and crossbridge cycling in cardiac muscle using ordinary differential equations. Biophys J 95:2368–2390
Robertson D, Hollister AS, Forman MB, Robertson RM (1985) Reflexes unique to myocardial ischemia and infarction. J Am Coll Cardiol 5:99B–104B
Robinson TF, Factor SM, Sonnenblick EH (1986) The heart as a suction pump. Sci Am 254:84–91
Robinson TF, Cohen-Gould L, Factor SM, Eghbali M, Blumenfeld OO (1988) Structure and function of connective tissue in cardiac muscle: collagen types I and III in endomysial struts and pericellular fibers. Scanning Microsc 2:1005–1015
Rogers JH, Bolling SF (2010) Valve repair for functional tricuspid valve regurgitation: anatomical and surgical considerations. Semin Thorac Cardiovasc Surg 22:84–89
Rossi MA, Abreu MA, Santoro LB (1998) Images in cardiovascular medicine. Connective tissue skeleton of the human heart: a demonstration by cell-maceration scanning electron microscope method. Circulation 97:934–935
Rozanski A, Nichols K, Yao SS, Malholtra S, Cohen R, DePuey EG (2000) Development and application of normal limits for left ventricular ejection fraction and volume measurements from 99mTc-sestamibi myocardial perfusion gates SPECT. J Nucl Med 41:1445–1450
Rybakova IN, Greaser ML, Moss RL (2011) Myosin binding protein C interaction with actin: characterization and mapping of the binding site. J Biol Chem 286:2008–2016
Salo LM, Woods RL, Anderson CR, McAllen RM (2007) Nonuniformity in the von Bezold-Jarisch reflex. Am J Physiol Regul Integr Comp Physiol 293:R714–R720
Sandow A (1952) Excitation-contraction coupling in muscular response. Yale J Biol Med 25:176–201
Schoenberg M (1993) Equilibrium muscle crossbridge behavior: the interaction of myosin crossbridges with actin. Adv Biophys 29:55–73
Schultz HD (2011) Angiotensin and carotid body chemoreception in heart failure. Curr Opin Pharmacol 11:144–149
Schultz HD, Li YL (2007) Carotid body function in heart failure. Respir Physiol Neurobiol 157:171–185
Schultz HD, Marcus NJ (2012) Heart failure and carotid body chemoreception. Adv Exp Med Biol 758:387–395
Schultz HD, Sun SY (2000) Chemoreflex function in heart failure. Heart Fail Rev 5:45–56
Schultz HD, Del Rio R, Ding Y, Marcus NJ (2012) Role of neurotransmitter gases in the control of the carotid body in heart failure. Respir Physiol Neurobiol 184:197–203
Scoote M, Williams AJ (2004) Myocardial calcium signalling and arrhythmia pathogenesis. Biochem Biophys Res Commun 322:1286–1309
Scoote M, Poole-Wilson PA, Williams AJ (2003) The therapeutic potential of new insights into myocardial excitation-contraction coupling. Heart 89:371–376
Scriven DR, Moore ED (2013) $Ca^{2}$+ channel and Na+/$Ca^{2}$+ exchange localization in cardiac myocytes. J Mol Cell Cardiol 58:22–31
Seshubabu G (1998) The oculocardiac reflex in cataract surgery in the elderly. Br J Ophthalmol 82:589
Severs NJ (1985) Intercellular junctions and the cardiac intercalated disk. Adv Myocardiol 5:223–242

Sharir T, Kang X, Germano G, Bax JJ, Shaw LJ, Gransar H, Cohen I, Hayes SW, Friedman JD, Berman DS (2006) Prognostic value of poststress left ventricular volume and ejection fraction by gated myocardial perfusion SPECT in women and men: gender-related differences in normal limits and outcomes. J Nucl Cardiol 13:495–506

Sharpey-Schafer EP (1955) Effects of Valsalva's manoeuvre on the normal and failing circulation. Br Med J 1:693–695

Shaw RM, Rudy Y (2010) Cardiac muscle is not a uniform syncytium. Biophys J 98:3102–3103; discussion 3104–3105

Shy D, Gillet L, Abriel H (2013) Cardiac sodium channel Na(V)1.5 distribution in myocytes via interacting proteins: the multiple pool model. Biochim Biophys Acta 1833(4):886–894

Silbiger JJ (2012) Anatomy, mechanics, and pathophysiology of the mitral annulus. Am Heart J 164:163–176

Silbiger JJ, Bazaz R (2009) Contemporary insights into the functional anatomy of the mitral valve. Am Heart J 158:887–895

Silver MD, Lam JH, Ranganathan N, Wigle ED (1971) Morphology of the human tricuspid valve. Circulation 43:333–348

Simon JW (2010) Complications of strabismus surgery. Curr Opin Ophthalmol 21:361–366

Sipido KR, Acsai K, Antoons G, Bito V, Macquaide N (2013) T-tubule remodelling and ryanodine receptor organization modulate sodium-calcium exchange. Adv Exp Med Biol 961:375–383

Smith RB (1994) Death and the oculocardiac reflex. Can J Anaesth 41:760

Smith G (2012) Management of supraventricular tachycardia using the Valsalva manoeuvre: a historical review and summary of published evidence. Eur J Emerg Med 19:346–352

Solaro RJ (2007) Mechanisms of the Frank-Starling law of the heart: the beat goes on. Biophys J 93:4095–4096

Solaro RJ, Henze M, Kobayashi T (2013) Integration of troponin I phosphorylation with cardiac regulatory networks. Circ Res 112:355–366

Strege P, Beyder A, Bernard C, Crespo-Diaz R, Behfar A, Terzic A, Ackerman M, Farrugia G (2012) Ranolazine inhibits shear sensitivity of endogenous Na (+) current and spontaneous action potentials in HL-1 cells. Channels (Austin) 6(6):457–462

Szigligeti P, Pankucsi C, Banyasz T, Varro A, Nanasi PP (1996) Action potential duration and force-frequency relationship in isolated rabbit, guinea pig and rat cardiac muscle. J Comp Physiol B 166:150–155

Tanaka Y, Nakamura K, Kuroiwa N, Odachi M, Mawatari K, Onimaru M, Sanada J, Arima T (1993) Isovolumetric relaxation flow in patients with ischemic heart disease. J Am Coll Cardiol 21:1357–1364

Tang W, Sencer S, Hamilton SL (2002) Calmodulin modulation of proteins involved in excitation-contraction coupling. Front Biosci 7:d1583–d1589

Tardiff JC (2011) Thin filament mutations: developing an integrative approach to a complex disorder. Circ Res 108:765–782

Tavi P, Westerblad H (2011) The role of in vivo Ca(2)(+) signals acting on Ca(2)(+)-calmodulin-dependent proteins for skeletal muscle plasticity. J Physiol 589:5021–5031

Teerlink JR (2009) A novel approach to improve cardiac performance: cardiac myosin activators. Heart Fail Rev 14:289–298

ter Keurs HE (2012) The interaction of Ca2+ with sarcomeric proteins: role in function and dysfunction of the heart. Am J Physiol Heart Circ Physiol 302:H38–H50

Thierfelder L, Watkins H, MacRae C, Lamas R, McKenna W, Vosberg HP, Seidman JG, Seidman CE (1994) Alpha-tropomyosin and cardiac troponin T mutations cause familial hypertrophic cardiomyopathy: a disease of the sarcomere. Cell 77:701–712

Tops LF, van der Wall EE, Schalij MJ, Bax JJ (2007) Multi-modality imaging to assess left atrial size, anatomy and function. Heart 93:1461–1470

Torres-Jacome J, Gallego M, Rodriguez-Robledo JM, Sanchez-Chapula JA, Casis O (2013) Improvement of the metabolic status recovers cardiac potassium channel synthesis in experimental diabetes. Acta Physiol (Oxf) 207(3):447–459

Tsai JC, Heitz JW (2012) Oculocardiac reflex elicited during debridement of an empty orbit. J Clin Anesth 24:426–427

Vahebi S, Ota A, Li M, Warren CM, de Tombe PP, Wang Y, Solaro RJ (2007) p38-MAPK induced dephosphorylation of alpha-tropomyosin is associated with depression of myocardial sarcomeric tension and ATPase activity. Circ Res 100:408–415

Vangheluwe P, Sipido KR, Raeymaekers L, Wuytack F (2006) New perspectives on the role of SERCA2's $Ca^{2+}$ affinity in cardiac function. Biochim Biophys Acta 1763:1216–1228

Vasquez EC, Meyrelles SS, Mauad H, Cabral AM (1997) Neural reflex regulation of arterial pressure in pathophysiological conditions: interplay among the baroreflex, the cardiopulmonary reflexes and the chemoreflex. Braz J Med Biol Res 30:521–532

Vatner SF, Zimpfer M (1981) Bainbridge reflex in conscious, unrestrained, and tranquilized baboons. Am J Physiol 240:H164–H167

Wan WH, Ang BT, Wang E (2008) The Cushing Response: a case for a review of its role as a physiological reflex. J Clin Neurosci 15:223–228

Wang Q, Lin JL, Wu KH, Wang DZ, Reiter RS, Sinn HW, Lin CI, Lin CJ (2012) Xin proteins and intercalated disc maturation, signaling and diseases. Front Biosci 17:2566–2593

Wang Z, Yuan LJ, Cao TS, Yang Y, Duan YY, Xing CY (2013) Simultaneous beat-by-beat investigation of the effects of the Valsalva maneuver on left and right ventricular filling and the possible mechanism. PLoS One 8:e53917

Watson CJ, Phelan D, Xu M, Collier P, Neary R, Smolenski A, Ledwidge M, McDonald K, Baugh J (2012) Mechanical stretch up-regulates the B-type natriuretic peptide system in human cardiac fibroblasts: a possible defense against transforming growth factor-beta mediated fibrosis. Fibrogenesis Tissue Repair 5:9

Weisbrod D, Peretz A, Ziskind A, Menaker N, Oz S, Barad L, Eliyahu S, Itskovitz-Eldor J, Dascal N, Khananshvili D, Binah O, Attali B (2013) SK4 Ca2+ activated K+channel is a critical player in cardiac pacemaker derived from human embryonic stem cells. Proc Natl Acad Sci USA 110:E1685–E1694

White SP, Cohen C, Phillips GN Jr (1987) Structure of co-crystals of tropomyosin and troponin. Nature 325:826–828

Wick M (1999) Filament assembly properties of the sarcomeric myosin heavy chain. Poult Sci 78:735–742

Williams GS, Smith GD, Sobie EA, Jafri MS (2010) Models of cardiac excitation-contraction coupling in ventricular myocytes. Math Biosci 226:1–15

Workman AJ, Smith GL, Rankin AC (2011) Mechanisms of termination and prevention of atrial fibrillation by drug therapy. Pharmacol Ther 131:221–241

Yang D, Song LS, Zhu WZ, Chakir K, Wang W, Wu C, Wang Y, Xiao RP, Chen SR, Cheng H (2003) Calmodulin regulation of excitation-contraction coupling in cardiac myocytes. Circ Res 92:659–667

Yi C, Jee D (2008) Influence of the anaesthetic depth on the inhibition of the oculocardiac reflex during sevoflurane anaesthesia for paediatric strabismus surgery. Br J Anaesth 101:234–238

Zhang YH, Hancox JC (2009) Regulation of cardiac Na+−Ca2+ exchanger activity by protein kinase phosphorylation–still a paradox? Cell Calcium 45:1–10

Zhou L, O'Rourke B (2012) Cardiac mitochondrial network excitability: insights from computational analysis. Am J Physiol Heart Circ Physiol 302:H2178–H2189

# Cardiovascular Pharmacology

# 2

Robert Fellin

## Contents



R. Fellin, PharmD, BCPS
Cedars-Sinai Medical Center, West Hollywood, CA, USA
e-mail: robert.fellin@cshc.org

A. Dabbagh et al. (eds.), *Postoperative Critical Care for Cardiac Surgical Patients*,
DOI 10.1007/978-3-642-40418-4_2, © Springer-Verlag Berlin Heidelberg 2014

**Abstract**

Cardiovascular disease is a leading cause of morbidity and mortality in the United States, resulting in an estimated $503 billion in indirect and direct costs in 2010. Annually, there are 1.8 million hospitalizations for acute coronary syndromes. The total number of inpatient cardiovascular operations and procedures increased 27 %, from 1997 to 2007 in the Unites States (National Heart, Lung, and Blood Institute computation based on National Center for Health Statistics annual data). About 10–16 % of patients with coronary artery disease go on to have coronary artery bypass graft surgery (CABG), and each year approximately one million patients worldwide undergo cardiac surgery such as CABG, valve repair or replacement, aneurysm repairs, and arrhythmia surgery. Data for 2008 from the Society of Thoracic Surgeons show that most of these patients require at least an overnight ICU stay, with a mean of about 4 days. Management of cardiovascular surgery patients is complex, encompassing numerous different areas including infectious disease, cardiology, diabetes, and critical care. This chapter reviews the common pharmacologic agents employed by providers in the ICU setting.

## 2.1 Antibiotic Prophylaxis

Cardiothoracic surgery (i.e., CABG, heart valve replacement) is generally considered a clean surgery with the majority of patients having a low risk of infection. Although infrequent, deep organ/surgical site infections (SSI) (i.e., mediastinitis and prosthetic valve endocarditis) are catastrophic complications associated with substantial morbidity and mortality (Edwards et al. 2006).

The shortest effective duration of antimicrobial administration for preventing surgical site infection is not known. Evidence is mounting, however, that postoperative antimicrobial administration is not necessary for most procedures. The duration of antimicrobial prophylaxis should be 24 h or less, with the exception of cardiothoracic procedures (up to 48 h in duration) and ophthalmic procedures (duration not clearly established) (Edwards et al. 2006). The duration of cardiothoracic prophylaxis is based on expert panel consensus because the data does not delineate the optimal duration of prophylaxis. There is no data to support the continuation of antimicrobial prophylaxis until all drains, invasive lines, and indwelling catheters are removed (Edwards et al. 2006; ASHP 1999).

Based on the available literature, there is no conclusive recommendation for weight-based antimicrobial prophylactic dosing needed for clinically relevant decreases in surgical site infection rates (Bratzler and Houck 2004; ASHP 1999, 2012). One recommendation is that the dose of cefazolin for all patients greater than 60 kg body weight is to be 2 g (Engelman et al. 2007).

Limited high-quality data are available for the use of topical antimicrobials, irrigations, and washes. The safety and efficacy of topical antibiotics have not been clearly established and cannot be recommended for routine use in cardiac procedures (ASHP 1999).

**Table 2.1** Recommended surgical antimicrobial prophylaxis

| | Likely pathogens | Recommended regimen | Alternative regimen |
|---|---|---|---|
| Cardiothoracic surgery | *Staph epidermidis*, *Staph aureus*, *Streptococcus*, *Corynebacteria*, enteric-Gram-negative bacilli | Cefazolin 1 g (2 g for patients >60 kg) IV within 60 min prior to surgical incision | Cefuroxime 1.5 g IV within 60 min prior to surgical incision and q12h for up to 48 h |
| Heart transplantation | | 1 g dose every 3–4 h while surgical incision remains open | Vancomycin 1 g IV (with or without gentamicin 3 mg/kg IV×1) within 60 min prior to surgical incision and continued for up to 48 h |
| | | Post-op: 1 g (2 g for patients >60 kg) q8h×48 h | Clindamycin 600 mg IV within 60 min prior to surgical incision and q8h for up to 48 h |
| VAD | Same as above plus *Candida* | Vancomycin 15 mg/kg IV within 60 min prior to surgical incision and q12h×48 h | Gram-negative coverage tailored to patient flora and/or institutional susceptibility×48 h |
| | | Piperacillin-tazobactam 3.375 g IV within 60 min prior to surgical incision and q6h×48 h | Mupirocin (Bactroban®) 2 % nasal ointment to nares BID for 5 days (if nasal culture is positive for *S. aureus*) |
| | | Fluconazole 400 mg IV within 60 min prior to surgical incision and q24h×48 h | |
| | | Mupirocin (Bactroban®) 2 % nasal ointment applied to nares the night before and morning of surgery (if nasal culture is positive for *S. aureus*) | |

Antibiotic dosages may need to be adjusted for renal or hepatic dysfunction

The literature does not support the benefit of routine vancomycin use over cefazolin or cefuroxime for prevention of SSI for any procedure even though guidelines issued by the Surgical Care Improvement Project state that vancomycin is an acceptable antibiotic for surgical prophylaxis (Engelman et al. 2007; ASHP 1999) (Table 2.1).

**Table 2.2** Receptor types targeted by current vasopressor therapy

| Adrenoreceptor type | Primary location(s) | Response when stimulated |
|---|---|---|
| Alpha 1 | Arteries, arterioles, veins | Constriction |
| Alpha 2 | GI tract | Decreased tone, motility, and secretions |
| Beta 1 | Heart | Increased heart rate and force of contraction |
| Beta 2 | Skeletal muscle blood vessels | Dilation |
| | Coronary arteries | Dilation |
| | Bronchial smooth muscle | Relaxation |

## 2.2 Vasoactive Agents (Table 2.2)

### 2.2.1 Norepinephrine

Norepinephrine is a potent alpha-adrenergic agonist and less potent beta-adrenergic agonist. The primary vasoactive effect of norepinephrine is arterial and venous vasoconstriction. The inotropic properties of norepinephrine are usually offset by increases in afterload. Norepinephrine is more potent than dopamine and is commonly considered the first-choice vasopressor to reverse hypotension in vasodilatory shock (Cooper 2008; Poor and Stanke 2005; Kee 2003). Norepinephrine seems to improve parameters of visceral microperfusion when hypotension is reversed in septic shock, compared with epinephrine or dopamine. This may explain why norepinephrine therapy was associated with some survival benefit in septic shock, compared with high-dosage dopamine and epinephrine (Cooper 2008; Poor and Stanke 2005; Kee 2003).

Norepinephrine may be preferential to other catecholamine pressors as first-line therapy for septic shock because it does not substantially worsen end-organ ischemia in most studies of crystalloid-resuscitated septic shock patients. In comparison with epinephrine, norepinephrine demonstrates fewer metabolic adverse effects; however, the use of norepinephrine is not advisable in forms of shock exclusively with low cardiac output (Overgaard and Davík 2008).

### 2.2.2 Dopamine

At low rates of infusion (0.5–5 mcg/kg/min), dopamine causes vasodilation that is presumed to be due to a specific agonist action on dopamine receptors in the renal, mesenteric, coronary, and intracerebral vascular beds (Cooper 2008; Poor and Stanke 2005; Kee 2003). The vasodilation in these vascular beds is accompanied by increased renal blood flow, sodium excretion, and urine flow. The clinical significance of "renal-dose" dopamine is somewhat controversial, however, because it does not increase glomerular filtration rate and a renal protective effect has not been demonstrated (Overgaard and Davík 2008).

At intermediate rates of infusion (5–10 mcg/kg/min), dopamine acts to stimulate the beta1-adrenoceptors, resulting in improved myocardial contractility, increased SA rate, and enhanced impulse conduction in the heart. There is little, if any, stimulation of the beta2-adrenoceptors (peripheral vasodilation). Blood flow to the peripheral vascular beds may decrease while mesenteric flow increases due to increased cardiac output. At low (0.5–5 mcg/kg/min) and intermediate doses (5–10 mcg/kg/min), total peripheral resistance (which would be raised by alpha activity) is usually unchanged (Cooper 2008; Poor and Stanke 2005; Kee 2003).

At higher rates of infusion (>10–20 mcg/kg/min), the predominant effect is on alpha-adrenoceptors, with consequent vasoconstrictor effects and a rise in blood pressure. The vasoconstrictor effects are first seen in the skeletal muscle vascular beds, but with increasing doses, they are also evident in the renal and mesenteric vessels. At very high rates of infusion (above 20 mcg/kg/min), stimulation of alpha-adrenoceptors predominates and vasoconstriction may compromise the circulation of the limbs (Cooper 2008; Poor and Stanke 2005; Kee 2003).

Dosage-dependent effects vary by individual and have not been reproduced in critically ill patients. The alpha- and beta-adrenergic effects of dopamine are generally weaker compared with epinephrine or norepinephrine. Dopamine is used as a vasoconstrictor in vasodilatory shock and as an inotrope in low cardiac output. Low-dose ("renal-dose") dopamine should not be used for renal protection because evidence does not support this practice.

### 2.2.3 Phenylephrine

Phenylephrine is a powerful vasoconstrictor that strongly stimulates alpha-adrenergic receptors but has minimal affects on beta-adrenergic receptors of the heart therefore not arrhythmogenic. Vasoconstrictor properties are similar to norepinephrine and useful for non-cardiogenic hypotension (Cooper 2008; Poor and Stanke 2005; Kee 2003).

### 2.2.4 Vasopressin

Administration of vasopressin reverses vasodilation in vasopressor-resistant shock by activation of vasopressin1 receptors, inhibition of ATP-sensitive potassium channels and nitric oxide, and amplification of vasoconstrictive catecholamine effect (Cooper 2008; Poor and Stanke 2005). The recommended infusion rate for vasopressin in the treatment of shock in adults is 0.01–0.04 units/min (Overgaard and Davík 2008). This dosage range is reported to be effective in about 85 % of patients with norepinephrine-resistant hypotension. Doses greater than 0.04 units/min may lead to myocardial ischemia, peripheral necrosis, and cardiac arrest (Tsuneyoshi et al. 2001).

### 2.2.5 Epinephrine

Because epinephrine is a potent alpha- and beta-adrenoreceptor agonist, it is also a powerful vasoconstrictor, a positive inotrope, and a positive chronotrope. Vasoconstrictor effects of epinephrine become more apparent as the dose is increased. Low-dosage epinephrine infusions primarily stimulate beta-receptors. For this reason, epinephrine at a dosage of <4.0 mcg/min is often considered to be a "pure" inotrope, and this low level of epinephrine infusion is commonly encountered in patients after cardiac surgery. Epinephrine is associated with the induction of pulmonary hypertension, tachyarrhythmia, myocardial ischemia, lactic acidosis, and hyperglycemia. Lactic acidosis and hyperglycemia are caused by epinephrine-induced hypermetabolism, suppression of insulin release, and glycolysis. In addition, epinephrine can compromise hepatosplanchnic perfusion, oxygen exchange, and lactate clearance, especially in septic shock. Epinephrine is the first-line catecholamine in cardiopulmonary resuscitation and anaphylactic shock. As a vasopressor and as an inotrope, epinephrine is usually considered a second-line agent (Cooper 2008; Overgaard 2008; Poor and Stanke 2005; Kee 2003).

### 2.2.6 Vasoactive Agents: Selecting an Agent

There are no large randomized, well-controlled trials to guide the pharmacologic management of hypotension.

Use of vasopressors and positive inotropes are generally based on data from small, often poorly controlled clinical studies. Selection of the appropriate vasoactive agent should be made on a case-by-case basis with attention to the known or suspected underlying cause of hypotension. The ideal vasopressor remains controversial (Havel et al. 2011).

#### 2.2.6.1 Hypotension of Unknown Etiology

For severe hypotension (SBP <70), a more potent alpha1-adrenergic agent such as norepinephrine should be considered. Dopamine in moderate to high doses may be a reasonable first choice given its combined positive inotropic and vasopressor effects.

#### 2.2.6.2 Reduced Systemic Vascular Resistance

Given the superior potency of norepinephrine and data demonstrating worsening splanchnic perfusion with high-dose dopamine, norepinephrine is emerging as the agent of choice for vasodilatory shock in sepsis.

Dopamine may be used as an alternate agent or in cases in which positive inotropic effects are desirable.

The efficacy of phenylephrine is difficult to assess relative to older agents, although its peripheral selectivity and lack of chronotropic effects make it a useful agent in cases of tachycardia or tachyarrhythmias. Vasopressin is emerging as an alternative to adrenergic agents or in combination with other agents. Epinephrine is the least selective of the catecholamines and may be added for refractory shock (Table 2.3).

**Table 2.3** Vasopressor agents

| Drug | Dose | HR | MAP | PCWP | CO | SVR | Adverse effects |
|---|---|---|---|---|---|---|---|
| Norepinephrine | 1–40 mcg/min (0.01–0.5 mcg/kg/min)<br>Increase/decrease rate by minimum of 1 mcg/min at intervals no longer than Q 30 min<br>Titration parameter: MAP and SBP<br>Usual target: MAP>60–65 or SBP 80–100 | + | + | + | + | ++ | Arrhythmias, tissue/myocardial ischemia |
| Epinephrine | 1–10 mcg/min (0.01–0.2 mcg/kg/min)<br>Increase/decrease rate by minimum of 1 mcg/min at intervals no longer than Q 5 min<br>Titration parameter: MAP and SBP<br>Usual target: MAP>60–65 or SBP 80–100 | + | + | + | ++ | + | Tachyarrhythmias, tissue ischemia, myocardial ischemia, hyperglycemia |
| Dopamine | 0.5–5 mcg/kg/min<br>5–10 mcg/kg/min<br>>10–20 mcg/kg/min<br>Increase/decrease rate by minimum of 1 mcg/kg/min at intervals no longer than Q 30 min<br>Titration parameter: MAP and SBP<br>Usual target: MAP>60–65 or SBP 80–100 | 0<br>+<br>+ | 0<br>+<br>+ | 0<br>0<br>+ | 0/+<br>+<br>+ | –<br>0<br>++ | Tachycardia, arrhythmias, myocardial ischemia |
| Phenylephrine | 50–400 mcg/min (0.5–5 mcg/kg/min)<br>Increase/decrease rate by minimum of 10 mcg/min at intervals no longer than Q 15 min<br>Titration parameter: MAP and SBP<br>Usual target: MAP>60–65 or SBP 80–100 | 0 | + | 0/+ | 0 | ++ | Reflex bradycardia, decreased renal perfusion |
| Vasopressin | 0.04 units/min | 0 | + | 0 | 0 | + | Myocardial ischemia, tissue necrosis and end-organ ischemia (doses>0.04 units/min) |

+ increase, – decrease, 0 no change

## 2.3 Inotropic Agents

### 2.3.1 Dobutamine

Dobutamine is a synthetic catecholamine with predominately beta-adrenergic and only limited alpha-adrenergic effects that directly stimulates the myocardium. As a result of beta1-receptor-mediated, positive inotropic, and beta2-receptor-mediated vasodilatory action, dobutamine increases cardiac output and decreases systemic and pulmonary vascular resistance. Dobutamine is the preferred vasoactive agent to treat cardiogenic shock with low output and increased afterload. In combination with norepinephrine, dobutamine is used in septic shock with myocardial dysfunction. As with all catecholamines with a beta-adrenergic effect, dobutamine may cause a mismatch of myocardial oxygen delivery and requirement (Cooper 2008; Poor and Stanke 2005; Kee 2003).

Dobutamine has a short half-life which provides a rapid onset and allows for quick dose escalation.

### 2.3.2 Milrinone

Milrinone, a phosphodiesterase (PDE) inhibitor, increases intracellular cAMP thereby increasing the rate and extent of calcium influx during systole and enhancing contractility. PDE inhibitors have vasodilatory and inotropic actions and improve diastolic ventricular relaxation. PDE inhibitors frequently require the addition of vasopressors because of their substantial vasodilatory action (Cooper 2008; Poor and Stanke 2005; Kee 2003).

Although its physiologic effects are not antagonized by beta-blockade, milrinone's pharmacokinetic profile makes dosing more difficult compared to dobutamine. The long half-life prevents rapid onset, requires slower dose titration/escalation, and necessitates dose reduction for patients with renal impairment. Milrinone improves cardiac output in cardiogenic shock and is generally considered a second-line agent for this indication. Milrinone has shown a greater vasodilatory effect than dobutamine, as demonstrated by further reductions in mean pulmonary artery pressure (MAP), pulmonary capillary wedge pressure (PCWP), and systemic vascular resistance (SVR), improving right-sided heart performance in pulmonary hypertension. Because of these effects, milrinone may be considered as a first-line therapy over dobutamine in patients with more severe pulmonary hypertension (Cooper 2008) (Table 2.4).

### 2.3.3 Inotropic Agents: Selecting an Agent

#### 2.3.3.1 Hypotensive Patient with Significant Cardiac Pump Dysfunction

Dobutamine is the inotropic agent of choice. With cardiogenic shock and concomitant vasodilation, however, a drug with pressor action is usually needed (dopamine

**Table 2.4** Inotropic agents

| Drug | Dose | HR | MAP | PCWP | CO | SVR | Adverse effects |
|---|---|---|---|---|---|---|---|
| Dobutamine | 2.5–20 mcg/kg/min<br>Increase/decrease by 1 mcg/kg/min at intervals no longer than Q 30 min<br>Titration parameter: CO and CI | 0/+ | 0 | – | + | – | Arrhythmogenic, may potentiate hypokalemia, myocardial ischemia, hypotension/ vasodilation |
| Milrinone | 0.125–0.75 mcg/kg/min<br>Increase/decrease by minimum of 0.125 mcg/kg/min at intervals no longer than Q 6 h<br>Titration parameter: CO and CI | 0/+ | 0/– | – | + | – | Arrhythmogenic, thrombocytopenia, myocardial ischemia, hypotension/ vasodilation |

+ increase, – decrease, 0 no change

alone or in combination with dobutamine). For patients with septic shock and myocardial dysfunction, dobutamine can be added to norepinephrine or dopamine for added inotropic support.

Although no single agent is universally superior in this setting, dobutamine's ease of use and better side-effect profile, along with milrinone's pharmacokinetic considerations, render milrinone as a secondary agent. As is the case in heart failure, concomitant vasopressor therapy may be necessary. In select situations, milrinone and dobutamine may be used in combination when an adequate cardiac index cannot be obtained with either agent alone.

An important consideration for use of milrinone over dobutamine in ADHF, however, is for patients admitted on beta-blocker therapy. The use of a beta-agonist with a beta-blocker would be largely counterproductive. In these cases, the use of milrinone during titration or maintenance of beta-blocker therapy would be preferred.

Despite the potentially more favorable hemodynamic profile of milrinone than dobutamine, clinical outcomes between the two agents have not differed.

## 2.4 Vasodilators and Antihypertensives

Vasodilators are used to treat hypertension, heart failure, and angina; however, some vasodilators are better suited than others for these indications.

Dilation of arterial (resistance) vessels leads to a reduction in systemic vascular resistance, which leads to a fall in arterial blood pressure. Dilation of venous (capacitance) vessels decreases venous blood pressure. Vasodilators that act primarily on resistance vessels (arterial dilators) are used for hypertension and heart failure, but not for angina because of reflex cardiac stimulation. Venous dilators are very effective for angina, and sometimes used for heart failure, but are not used as primary therapy for hypertension. Most vasodilator drugs are mixed (or balanced) vasodilators in that they dilate both arteries and veins; however, there are some very

useful drugs that are highly selective for arterial or venous vasculature. Some vasodilators, because of their mechanism of action, also have other important actions that can in some cases enhance their therapeutic utility as vasodilators or provide some additional therapeutic benefit (Koda-Kimble 2006; Rhoney and Peacock 2009).

The potential drawbacks of vasodilators include:

- Systemic vasodilation and arterial pressure reduction can lead to a baroreceptor-mediated reflex stimulation of the heart (increased heart rate and inotropy). This increases oxygen demand, which is undesirable if the patient also has coronary artery disease (Dipiro et al. 2002).
- Vasodilators can impair normal baroreceptor-mediated reflex vasoconstriction when a person stands up, which can lead to orthostatic hypotension and syncope upon standing (Dipiro et al. 2002).
- Vasodilators can lead to renal retention of sodium and water, which increases blood volume and cardiac output and thereby compensates for the reduced systemic vascular resistance (Dipiro et al. 2002) (Tables 2.5 and 2.6).

## 2.5 Intravenous Antiarrhythmic Agents

The ultimate goal of antiarrhythmic therapy is to maintain normal rhythm and conduction in the heart. Antiarrhythmic drugs either decrease or increase conduction velocity, alter the excitability of cardiac cells by changing the duration of the refractory period, or suppress abnormal automaticity. All antiarrhythmic drugs alter membrane ion conduction, which in turn alters the shape of the cardiac action potential (Thireau et al. 2011; Kowey 1998).

Antiarrhythmic medications are used to treat a wide range of cardiac dysrhythmias. Drugs from all of the different classes of antiarrhythmics are, at times, clinically indicated for use in treating atrial fibrillation, atrial flutter, paroxysmal supraventricular tachycardia, ventricular tachycardia, and occasionally premature ectopic beats from either the atrium or the ventricle. The choice of antiarrhythmics is generally based on the specific dysrhythmia or the overall threat to well-being caused by the dysrhythmia (nuisance versus life or death), the underlying substrate (presence or absence of structural heart disease), and the extent of the symptoms associated with the dysrhythmia (Ganjehei et al. 2011; Thireau et al. 2011; Kowey 1998) (Table 2.7).

## 2.6 Analgesic Agents

Pain control in the critical care setting is often inadequate. Critically ill patients may experience pain that is due to their underlying illness or injury and surgery or the result of other nonsurgical interventions. Pain may also be the result of a variety of noxious stimuli present in the critical care setting from monitoring (arterial catheter, central venous catheter), therapeutic devices (ventilator), or routine nursing

**Table 2.5** Intravenous vasodilator and antihypertensive agents

| Drug | Indication | Onset of action | Dosing | Comments |
|---|---|---|---|---|
| Esmolol | Acute MI<br>SVT<br>Atrial fibrillation and atrial flutter<br>Hypertensive urgency/ emergency | 1–5 min | *IV bolus*:<br>500 mcg/kg over 1 min<br>*Continuous infusion*:<br>50–300 mcg/kg/min<br>Titrate by 50 mcg/kg/min every 10 min<br>Titration parameter: SBP and HR | Duration: 15–30 min<br>Short t½ life (2–9 min)<br>Contraindicated in cocaine toxicity (if used alone), LVF, COPD/asthma, and high-grade heart block<br>Hypotension, injection site pain, nausea, heart block, heart failure |
| Hydralazine | Hypertensive urgency/ emergency | 10–30 min | *IV bolus*:<br>10 mg IV push q4h prn<br>Max dose: 20 mg IV push q4h prn<br>Titration parameter: SBP | Duration: 2–4 h<br>Direct arteriolar vasodilator with little or no effect on venous circulation<br>Palpitation, angina, flushing, tachycardia, headache |
| Labetalol | Hypertensive urgency/ emergency | 5–10 min | *IV bolus*:<br>20 mg IV push over 2 min<br>Repeat with 40–80 mg at 10 min intervals up to 150 mg<br>*Continuous infusion*:<br>0.5–8 mg/min<br>Titrate by 0.5 mg every 4 h<br>Titration parameter: SBP and HR | Duration: 2–6 h<br>Combined beta-adrenergic (B1 and B2) and alpha-adrenergic blocker<br>Avoid use in patients with CHF exacerbation, COPD/asthma, bradycardia/heart block<br>Orthostatic hypotension, tingling sensation, nausea, dizziness, nasal congestion |

(continued)

**Table 2.5** (continued)

| Drug | Indication | Onset of action | Dosing | Comments |
|---|---|---|---|---|
| Nicardipine | Hypertensive urgency/ emergency | 5–10 min | *Continuous infusion*:<br>2.5–15 mg/h<br><br>Titrate by 2.5 mg/h every 5–15 min to Max dose of 15 mg/h<br>Titration parameter: SBP | Does not depress LV function<br>Use with caution in heart block, recent MI, CVA, renal failure<br>Hypotension, peripheral edema, tachyarrhythmia, headache<br>Contraindicated in aortic stenosis; may reduce myocardial oxygen balance |
| Nitroglycerin | Antianginal for ischemic pain<br>AMI/CHF<br><br>Hypertensive urgency with ACS | 2–5 min | *IV bolus*:<br>12.5–25 mcg *if no SL or spray given*<br><br>*Continuous infusion*:<br>5–300 mcg/min<br>Titrate by 5–10 mcg/min every 5 min to max of 300 mcg/min<br>Titration parameter: SBP and angina | Tolerance may occur within 24–48 h<br>No phosphodiesterase inhibitors within 24 h or tadalafil within 48 h<br>May increase ICP, use with caution in hypertensive encephalopathy<br>Hypotension, flushing, headache, dizziness |
| Nitroprusside | Hypertensive urgency/ emergency<br><br>CHF (↓ afterload) | Immediate | *Continuous infusion*:<br><br>0.1–5 mcg/kg/min<br>(max: 10 mcg/kg/min)<br>Increase/decrease rate by minimum of 0.5 mcg/kg/min at intervals no longer than Q 15 min<br>Titration parameter: SBP | When treatment is prolonged (>24–48 h) or when renal insufficiency is present, risk of cyanide and thiocyanate toxicity is increased<br>May cause hypotension, $CO_2$ retention<br>Bradyarrhythmia, hypotension, palpitations, tachyarrhythmia |

**Table 2.6** Oral antihypertensive agents

| | Agent | Usual dose/frequency | Comments/adverse effects |
|---|---|---|---|
| Diuretics | | | |
| Thiazide | Chlorothiazide (Diuril®) | 250–500 mg BID | Increased urination, dizziness, possible decrease in potassium, photosensitivity, dehydration, increase in calcium levels |
| | Chlorthalidone (Hygroton®) | 12.5–25 mg daily | |
| | Hydrochlorothiazide | 12.5–50 mg daily | |
| | Indapamide (Lozol®) | 1.25–2.5 mg daily | |
| | Metolazone (Zaroxolyn®) | 2.5–10 mg daily or BID | |
| Loop | Bumetanide (Bumex®) | 0.5–2 mg daily or BID | |
| | Ethacrynic acid (Edecrin®) | 25–100 mg daily | |
| | Furosemide (Lasix®) | 10–40 mg daily | |
| | Torsemide (Demadex®) | 5–10 mg daily | |
| Potassium sparing | Eplerenone (Inspra®) | 50–100 mg daily | |
| | Spironolactone (Aldactone®) | 25–50 mg daily | |
| Beta-adrenergic blocking agents | Acebutolol (Sectral®) | 25–100 mg daily | Dizziness, fatigue, bradycardia, bronchoconstriction (contraindicated in bronchospastic disease, i.e., asthma) |
| | Atenolol (Tenormin®) | 25–100 mg daily | |
| | Betaxolol (Kerlone®) | 5–20 mg daily | |
| | Bisoprolol (Zebeta®) | 2.5–10 mg daily | |
| | Carvedilol (Coreg®) | 12.5–50 mg BID | |
| | Labetalol (Normodyne®) | 200–800 mg BID | |
| | Metoprolol (Lopressor®) | 50–100 mg daily or BID | |
| | Nadolol (Corgard®) | 40–120 mg daily | |
| | Pindolol (Visken®) | 10–40 mg BID | |
| | Propranolol (Inderal®) | 10–120 mg BID | |
| | Timolol (Blocadren®) | 20–40 BID | |

(continued)

**Table 2.6** (continued)

| | Agent | Usual dose/frequency | Comments/adverse effects |
|---|---|---|---|
| ACE inhibitors | Benazepril (Lotensin®) | 10–40 mg daily | Nonproductive dry cough, taste disturbances, increased potassium, rash |
| | Captopril (Capoten®) | 12.5–100 mg BID or TID | |
| | Enalapril (Vasotec®) | 5–40 mg daily or BID | |
| | Fosinopril (Monopril®) | 10–40 mg daily | |
| | Lisinopril (Zestril®) | 5–40 mg daily | |
| | Moexipril (Univasc®) | 7.5–30 mg daily | |
| | Perindopril (Aceon®) | 4–8 mg daily | |
| | Quinapril (Accupril®) | 10–80 mg daily | |
| | Ramipril (Altace®) | 2.5–20 mg daily | |
| | Trandolapril (Mavik®) | 1–4 mg daily | |
| Angiotensin II receptor antagonists | Candesartan (Atacand®) | 8–32 mg daily | Dizziness, diarrhea, cough (lower incidence than with ACE inhibitors) |
| | Eprosartan mesylate (Teveten®) | 400–800 mg daily or BID | |
| | Irbesartan (Avapro®) | 75–300 mg daily | |
| | Losartan (Cozaar®) | 25–100 mg daily | |
| | Olmesartan (Benicar®) | 20–40 daily | |
| | Telmisartan (Micardis®) | 20–80 mg daily | |
| | Valsartan (Diovan®) | 40–320 mg daily or BID | |

| | | | |
|---|---|---|---|
| Calcium channel blocking agents | Verapamil immediate release | 80–320 mg BID or TID | Constipation, bradycardia, heart block, headache, bradyarrhythmia, peripheral edema, pharyngitis |
| | Verapamil (Calan SR®) | 120–240 mg daily or BID | |
| | Diltiazem immediate release | 45–270 mg TID | Nausea, headache, heart block, bradyarrhythmia, peripheral edema, dizziness, fatigue |
| | Diltiazem (Dilacor XR®) | 180–360 mg daily | |
| | Amlodipine (Norvasc®) | 2.5–10 mg daily | Dizziness, headache, flushing, peripheral edema, palpitations |
| | Felodipine (Plendil®) | 2.5–20 mg daily | |
| | Isradipine (Dynacirc®) | 2.5–10 mg BID | |
| | Nicardipine (Cardene SR®) | 60–120 mg BID | |
| | Nifedipine (Adalat CC®) | 30–90 mg daily | |
| | Nisoldipine (Sular®) | 10–40 mg daily | |
| Peripheral $alpha_1$-antagonists | Prazosin (Minipress®) | 1–10 mg BID | First-dose syncope, drowsiness, dry mouth, blurred vision |
| | Terazosin (Hytrin®) | 1–10 mg daily or BID | |
| | Doxazosin (Cardura®) | 1–16 mg daily | |
| Central $alpha_2$-agonists | Clonidine (Catapres®) | 0.1–0.6 mg BID | Dry mouth, sedation, sexual dysfunction, depression |
| | Methyldopa (Aldomet®) | 250–500 mg TID | |
| Arterial vasodilators | Hydralazine (Apresoline®) | 10–100 mg BID or QID | Headache, fluid retention, reflex tachycardia |
| | Minoxidil (Loniten®) | 5–100 mg daily or BID | |

**Table 2.7** Intravenous antiarrhythmic agents

| Drug | Indication | Dosing | Comments/adverse effects |
|---|---|---|---|
| Adenosine | SVT | 6 mg IV rapidly over 1–3 s<br>May repeat with 12 mg IVP up to two more doses Q1–2 min PRN | Must be administered rapidly<br>Patients taking carbamazepine and dipyridamole or cardiac transplant recipients: use initial dose of 3 mg<br>Flushing, chest discomfort, pain of head and neck region, dyspnea, headache, dizziness |
| Amiodarone (Class III agent) | Atrial fibrillation<br>VF<br>Pulseless VT<br><br>VT with pulse | 150 mg IV push<br>300 mg IV × 1 dose in 3–5 min<br>*IV bolus* (*non-ACLS*):<br><br>150 mg IV over 10 min, may repeat Q10 min PRN<br>*Continuous infusion*:<br>1 mg/min IV × 6 h, then 0.5 mg/min × 18 h | Hypotension when given IV push<br>Dose may be repeated PRN to a maximum of 2.2 g/24 h<br>Supplementary boluses of 150 mg can be repeated every 10 min as necessary for recurrent/resistant arrhythmias<br>Many drug-drug interactions<br>Hypothyroidism, pulmonary fibrosis, hepatotoxicity, optic neuritis, bradyarrhythmia, hypotension, photosensitivity |
| Atropine | Bradycardia | 0.5 mg IV and repeat every 3–5 min<br>Maximum dose: 3 mg | Cardiac dysrhythmia, raised intraocular pressure, respiratory depression |
| Diltiazem (Class IV agent) | Atrial fibrillation<br>SVT | *IV bolus*:<br>0.25 mg/kg over 2 min<br>May repeat dose in 15–20 min at 0.35 mg/kg<br>*Continuous infusion*:<br>5–15 mg/h<br>Increase/decrease rate by minimum of 2.5 mg/h at intervals no longer than Q4 h to goal<br>Titration parameter: HR | Bradyarrhythmia, peripheral edema, dizziness, headache, fatigue |

| | | | |
|---|---|---|---|
| Epinephrine | Pulseless VT or VF | 1 mg IV and repeat every 3–5 min | Palpitations, sweating, dizziness, headache, tremor |
| | PEA | 1 mg IV and repeat every 3–5 min | |
| | Asystole | 1 mg IV and repeat every 3–5 min | |
| Isoproterenol | Symptomatic bradycardia refractory torsades de pointes unresponsive to magnesium | *Continuous infusion*: | Do not use for treatment of cardiac arrest |
| | Beta-blocker overdose | 2–10 mcg/min<br>Titration parameter: HR | Do not give with epinephrine (can cause VF/VT)<br>Syncope, tachyarrhythmia, confusion, headache, tremor |
| Lidocaine (Class Ib agent) | Pulseless VT or VF<br>Stable VT | *IV bolus*:<br>1–1.5 mg/kg IV | Maximum cumulative dose: 3 mg/kg<br>Decrease maintenance dose if impaired liver function or left ventricular dysfunction |
| | | May repeat with 0.5–0.75 mg/kg Q5–10 min<br>*Continuous infusion*:<br>1–4 mg/min (15–60 ml/h) | Use with caution in hepatic dysfunction<br>CNS toxicity: paresthesias, confusion, seizure, and tremors<br>Bradyarrhythmia, hypotension, dizziness, headache, lightheadedness, numbness, confusion, somnolence |
| Magnesium Sulfate | Pulseless VT or VF associated with torsades de pointes | *Cardiac arrest* | Use with caution in renal failure |
| | Ventricular arrhythmias due to digitalis toxicity | 1–2 g IV push<br>*Torsades de pointes*<br>1–2 g IV × 1 and follow with 0.5–1 g/h IV and titrate | Hypotension with rapid administration<br>CNS depression, hyporeflexia, vasodilatation, respiratory tract paralysis, heart block |
| Procainamide (Class Ia agent) | Stable VT | *Loading dose* | Administer until arrhythmia is suppressed, hypotension occurs, QRS widens >50 % from baseline, or total of 17 mg/kg has been given |
| | Atrial fibrillation<br>PSVT | 20 mg/min<br>Max dose: 17 mg/kg<br>*Continuous infusion*:<br>1–4 mg/min | Reduce dose for renal dysfunction<br>Use with caution in renal insufficiency<br>Rarely used due to its toxicity and fairly high risk of inducing arrhythmias<br>Hypotension, dysrhythmia, agranulocytosis, bone marrow depression, systemic lupus erythematosus |

(continued)

**Table 2.7** (continued)

| Drug | Indication | Dosing | Comments/adverse effects |
|---|---|---|---|
| Vasopressin | Pulseless VT, VF, or PEA<br>Asystole | 40 units IV push×1 | May replace first or second dose of epinephrine in ACLS algorithm |
| Verapamil (Class IV agent) | Alternate drug (after adenosine) to terminate PSVT narrow QRS | Acute rate control | Maximum cumulative dose: 20 mg |
| | Atrial fibrillation, atrial flutter, or multifocal atrial tachycardia | 2.5–5 mg IV bolus over 2 min (elderly patient: 3 min)<br>Repeat 5–10 mg Q15–30 min<br><br>Alternative dosing<br>5 mg bolus Q15 min | Do NOT use for wide QRS tachycardias or Wolff-Parkinson-White syndrome<br>Hypotension, bradycardia/heart block with concurrent use of beta-blockers (i.e., metoprolol), dizziness, headache<br>Verapamil can worsen heart failure |

care (turning, suctioning). Although some patients may be able to verbally or nonverbally communicate their pain, the critically ill, intubated patient may not communicate their level of pain adequately (Vender et al. 2004; Jacobi et al. 2002).

If intravenous opioid analgesia is required, fentanyl, hydromorphone, and morphine are the recommended agents. Scheduled opioid doses or a continuous infusion is preferred over an "as needed" regimen to ensure consistent analgesia. Fentanyl or hydromorphone are preferred for patients with hemodynamic instability or renal insufficiency. Morphine and hydromorphone are preferred for intermittent therapy because of their longer duration of effect. There are no trials comparing the various opioids to each other in critically ill patients. The choice of agent depends upon the desired onset and duration of action and the potential adverse effects (Vender et al. 2004; Jacobi et al. 2002).

NSAIDs or acetaminophen may be used as adjuncts to opioids in select patients. Ketorolac therapy should be limited to a maximum of 5 days, with close monitoring for the development of renal insufficiency or gastrointestinal bleeding. Other NSAIDs (i.e., ibuprofen) may be used via the enteral route in appropriate patients (Table 2.8).

## 2.7 Sedating Agents

Sedation has become an integral part of critical care practice in minimizing patient discomfort. Consequences of suboptimal sedation include the following: anxiety, patient-ventilator dyssynchrony, agitation, and increased pain response. Adequate sedation reduces the stress response, provides anxiolysis, and improves tolerance of ventilatory support. Patient assessment should include the underlying problems and the role of pain prior to initiation of therapy (Jacobi et al. 2002; Vender et al. 2004; Ostermann et al. 2000).

The use of validated sedation scales improves consistency of medication administration as well as the quality of sedation to enhance patient safety and comfort. The routine use of a standardized assessment scales allow for a more precise medication titration, reduction in the amount of sedative used, less vasopressor support, and shorter duration of mechanical ventilation. Examples of validated ICU sedation scales include the following: Ramsay sedation scale, sedation agitation scale (SAS), Vancouver interactive and calmness scale (VICS), Richmond agitation-sedation scale (RASS), and Minnesota sedation assessment tool (MSAT) (Jacobi et al. 2002; Vender et al. 2004).

The use and titration of sedating agents is complex and requires a working knowledge of the pharmacologic agents employed coupled with the consistent application of validated sedation scales to achieve optimal outcomes. Large variation in dose requirements has been reported due to altered pharmacokinetic/pharmacodynamic properties in the critically ill, tolerance issues, and differences in severity of symptoms. As a result most agents are titrated to effect (i.e., RASS = −2), and therapy should always be individualized for each patient (Jacobi et al. 2002; Vender et al. 2004).

Numerous studies show that sedation algorithms or guidelines decrease drug costs, cause less hypotension and ventilator-associated pneumonia (VAP), decrease aggregate dosing, and often decrease mechanical ventilation duration (Jacobi et al. 2002; Vender et al. 2004; Ostermann et al. 2000) (Table 2.9).

**Table 2.8** Analgesic agents

| Drug | Dosing | Common adverse effects | Comments |
|---|---|---|---|
| Fentanyl | *Intermittent bolus dose*: | Respiratory depression, depressed consciousness, hallucinations, hypotension, nausea/vomiting, decreased GI motility/ileus, urinary retention | Preferred for a rapid onset of analgesia in acutely distressed patients |
| | 25 mcg SQ/IV q2h prn pain (0.35–1.50 mcg/kg) | Withdrawal symptoms when moderate to high doses are used for up to or more than 1 week | Individualize dose for each patient |
| | *Continuous infusion*: | | Virtually devoid of histamine-releasing properties |
| | 25–300 mcg/h (0.7–10 mcg/kg/h) | | More rapid onset of action and a shorter half-life than morphine |
| | Usual starting dose 25–50 mcg/h; increase/decrease rate by minimum of 25 mcg/h at intervals no longer than Q 30 min | | Renal failure does not appear to affect pharmacokinetics |
| | Titration parameter: pain scale | | Rigidity with high doses |
| Hydromorphone | *Intermittent bolus dose*: | Respiratory depression, depressed consciousness, hallucinations, hypotension, nausea/vomiting, decreased GI motility/ileus, urinary retention | Individualize dose for each patient |
| | 0.5 mg SQ/IV q2h prn pain | Withdrawal symptoms when moderate to high doses are used for up to or more than 1 week | Available as PCA |
| | *Continuous infusion*: | | Effect of renal insufficiency on the elimination of hydromorphone is unknown |
| | 1–20 mg/h (7–15 mcg/kg/h) | | More rapid onset of action and a shorter half-life than morphine |
| | Usual starting dose 1 mg/h; increase/decrease rate by minimum of 0.5–1 mg/h at intervals no longer than Q 30 min | | |
| | Titration parameter: pain scale | | |

| | | | |
|---|---|---|---|
| Morphine | *Intermittent bolus dose*:<br><br><br><br>2 mg SQ/IV q2h prn pain (0.01–0.15 mg/kg)<br><br>*Continuous infusion*:<br>1–50 mg/h (0.07–0.50 mg/kg/h)<br>Usual starting dose 1 mg/h; increase/decrease rate by minimum of 0.5–1 mg/h at intervals no longer than Q 30 min<br>Titration parameter: pain scale | Respiratory depression, depressed consciousness, hallucinations, hypotension, nausea/vomiting, decreased GI motility/ileus, urinary retention<br>Withdrawal symptoms when moderate to high doses are used for up to or more than 1 week<br>Histamine release: flushing, tachycardia, pruritus | Individualize dose for each patient<br><br>Available as PCA<br><br>Adjust dose for renal/liver dysfunction<br>Rapid onset |
| Ketorolac | < 65 y.o.:<br><br>30 mg IV/IM × 1 or 30 mg IV/IM q6h (scheduled or PRN)<br>Max dose: 120 mg/day; Max duration: 5 days<br>> 65 y.o. or weight < 50 kg:<br>15 mg IV/IM × 1 or 15 mg IV/IM q6h (scheduled or PRN)<br>Max dose: 60 mg/day; Max duration: 5 days | Injection site pain, abdominal pain, constipation, diarrhea, flatulence, indigestion, nausea/vomiting, headache | Use with caution in patients with preexisting renal insufficiency<br>Use lowest effective dose for the shortest period of time |

**Table 2.9** Sedating agents

| Drug | Onset after IV dose | Dosing | Comments/adverse effects |
|---|---|---|---|
| Dexmedetomidine | 10–30 min | *IV bolus*:<br>*NOT* recommended in ICU patients<br><br>*Continuous infusion*:<br>0.2–0.7 mcg/kg/h<br><br>Increase/decrease rate by 0.1 mcg/kg/h at intervals no shorter than Q 20 min<br>Titration parameter: RASS and BIS (?) | *Duration not to exceed 24 h*<br>Adverse effects: bradycardia, bradyarrhythmia, hypotension<br>Dosage should be individualized<br>Consider dose reduction in patients with renal impairment and/or hepatic impairment due to reduced clearance<br>Consider dose reduction in patients >65 y.o.<br><br>Initial bolus dose NOT recommended due to potentially severe acute changes in heart rate and blood pressure especially when patient is receiving concurrent sedatives/analgesics or when converting from alternate sedative therapy |
| Lorazepam | 5–20 min | *Intermittent bolus dose*:<br>0.02–0.06 mg/kg q2h prn agitation<br>*Continuous infusion*:<br><br>0.5–20 mg/h (0.01–0.1 mg/kg/h)<br>Increase/decrease rate by minimum of 1 mg/h at intervals no longer than Q 2 h<br>Titration parameter: RASS and BIS (?) | Slower onset than midazolam<br>Adjust dose in renal/liver impairment<br>Higher doses and use in patients with renal dysfunction may increase the risk of acidosis from the accumulation of propylene glycol (diluent)<br>Individualize dose for each patient |

**Table 2.9** (continued)

| | | | |
|---|---|---|---|
| Midazolam | 2–5 min | *Intermittent bolus dose*:<br>0.02–0.08 mg/kg q1h prn agitation | Preferred for rapid sedation of acutely agitated patients<br>Produces unpredictable awakening and time to extubation when infusions continue longer than 48–72 h or in patient with renal dysfunction |
| | | *Continuous infusion*:<br>0.5–20 mg/h (0.04–0.2 mg/kg/h)<br>Increase/decrease rate by minimum of 0.5 mg/h at intervals no longer than Q 30 min<br>Titration parameter: RASS and BIS (?) | Active metabolite<br>Individualize dose for each patient |
| Propofol | 1–2 min | *Continuous infusion*:<br>10–75 mcg/kg/min<br>Increase/decrease by minimum of 5 mcg/kg/min at intervals no less than 5 min<br>Titration parameter: RASS and BIS (?) | NO analgesic properties<br>Preferred when rapid awakening is necessary, neurosurgery patients or patients who require neurological assessment<br>Higher doses and sedation >48 h prolongs the awakening time<br>Baseline LFTs and TG level and repeat every 3–5 days<br>Individualize dose for each patient |

The potential for benzodiazepine and propofol withdrawal should be considered after high doses or more than approximately 7 days of continuous therapy. Doses should be tapered systematically to prevent withdrawal symptoms

## 2.8 Neuromuscular Blocking Agents (NMBAs)

Neuromuscular blocking agents play an important but limited role in the ICU. As per the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM) Revised Clinical Practice Guidelines, neuromuscular blocking agents should be used for an adult patient in an ICU to manage ventilation, manage increased ICP, treat muscle spasms, and decrease oxygen consumption only when all other means have been tried without success.

Similar to sedation and analgesia, management of neuromuscular blockade requires individualized approach. Patient-based drug selection, identification of the goal of therapy, and monitoring for safety and effectiveness with titration of drugs to the lowest effective dose for the shortest possible duration are necessary to provide optimal outcomes (Murray et al. 2002; Sessler 2005). Before initiating neuromuscular blockade, patients should be medicated with appropriate sedative and analgesic drugs to provide adequate sedation and analgesia in accordance with the physician's clinical judgment to optimize therapy (Murray et al. 2002; Vender et al. 2004).

Patients receiving neuromuscular blocking agents should be assessed both clinically and by TOF monitoring with a goal of adjusting the degree of neuromuscular blockade to achieve one or two twitches. To ensure deep sedation, neuromuscular blocking agents must be stopped intermittently to observe behavior, and strong consideration should be given to using an objective monitor, such as the bispectral index (BIS). Neuromuscular blocking agents should *never* be used as a substitute for sedation (Murray et al. 2002; Sessler 2005).

In general, use of intermittent dosing to ensure easy return of muscle activity is preferable to continuous infusions. Daily drug interruption is recommended to allow for neurologic evaluations, ensure adequate sedation, and reassess the need for ongoing blockade (Murray et al. 2002; Sessler 2005; Vender et al. 2004).

The most important toxicity of neuromuscular blockade is persistent skeletal muscle weakness, and neuromuscular blocking agents should be stopped as soon as they are no longer required (Murray et al. 2002; Sessler 2005) (Table 2.10).

### 2.8.1 Monitoring

The response to neuromuscular blocking agents can be significantly variable. Variability of response can increase to a greater degree in patients with organ dysfunction or other neuromuscular pathologies. It is imperative that neuromuscular blockade is properly monitored (i.e., determine drug effect, determine the need for additional doses, and confirm recovery) through the use of a peripheral nerve stimulator. Typically, the stimulator is placed over the ulnar nerve, and a train-of-four (TOF) shock pattern (four twitches at half-second intervals and a tetanic stimulus at 50 or 100 cycles per second) is used. Currently, there is no universal standard for twitch monitoring. The choice of the number of twitches necessary for "optimal"

**Table 2.10** Neuromuscular blocking agents (NMBAs)

| | Succinylcholine | Pancuronium | Vecuronium | Cisatracurium | Atracurium |
|---|---|---|---|---|---|
| Initial dose (mg/kg) | 0.6 | 0.06–0.1 | 0.08–0.1 | 0.1–0.2 | 0.4–0.5 |
| Duration (min) | 10 | 90–100 | 35–45 | 45–60 | 25–35 |
| Infusion dose (mcg/kg/min) | N/A | 1–2 | 0.8–1.2 | 1–10 | 2–12 |
| Recovery (min) | 10–20 | 120–180 | 45–60 | 90 | 40–60 |
| Renal failure | No change | Increased effect | Increased effect | No change | No change |
| Hepatic failure | Increased effect (decrease dose) | Mild increased effect | Variable | Minimal to no change | Minimal to no change |
| Active metabolites | Yes | Yes | Yes | No | No |
| Adverse effects | Apnea<br>Bradyarrhythmia<br>Cardiac arrest<br>Cardiac dysrhythmia<br>Hyperkalemia<br>Hypersensitivity reaction<br>Malignant hyperthermia<br>Prolonged neuromuscular block<br>Respiratory depression<br>Rhabdomyolysis<br>Tachyarrhythmia | Apnea<br>Bronchospasm<br>Hypertension<br>Prolonged neuromuscular block<br>Respiratory failure<br>Tachyarrhythmia | Anaphylaxis<br>Apnea<br>Bronchospasm<br>Hypotension<br>Muscle weakness<br>Prolonged neuromuscular block<br>Tachyarrhythmia | Bradyarrhythmia<br>Bronchospasm<br>Hypotension | Anaphylaxis<br>Bradyarrhythmia<br>Bronchospasm<br>Edema<br>Erythema<br>Hives<br>Hypersensitivity reaction<br>Hypotension, at larger than recommended doses<br>Laryngeal spasm<br>Muscle weakness<br>Paralysis<br>Tachyarrhythmia, at higher doses |

blockade is influenced by the patient's overall condition and level of sedation. The goal is two out of four twitches (75–80 % of blockade) (Murray et al. 2002).

The number of twitches counted represents the percentage of neuromuscular blockade:

| | | |
|---|---|---|
| 4 twitches | = | less than 75 % blockade |
| 3 twitches | = | 75 % blockade |
| 2 twitches | = | 75–80 % blockade |
| 1 twitch | = | 90 % blockade |

It is difficult to assess pain and sedation if the patient is receiving NMBA, but patients must be medicated for pain and anxiety, despite the lack of obvious symptoms or signs (Murray et al. 2002).

In common practice, sedative and analgesic drugs are adjusted until the patient does not appear to be conscious and then NMBA are administered.

### 2.8.2 Adjunct Therapy While Receiving NMBAs

DVT prophylaxis (heparin 5,000 units SQ q8–12 h), physical therapy, prevention of keratitis and corneal abrasion (eye patches, taping eyelids shut, application of lubricant eye drops/ointment (i.e., Lacri-lube® to both eyes QID)), as well as repositioning to avoid decubitus ulcers

## 2.9 ICU Delirium

As many as 80 % of ICU patients have delirium, characterized by an acutely changing or fluctuating mental status, inattention, disorganized thinking, and an altered level of consciousness that may or may not be accompanied by agitation. Routine assessment for the presence of delirium is recommended (i.e., CAM-ICU, ICDSC) (http://icudelirium.org/index.html 2012).

Non-pharmacologic options for the prevention and treatment of ICU delirium include removal of deliriogenic drugs, frequent reorientation, restoration of sleep/wake cycles, timely removal of catheters, early mobilization, and minimization of unnecessary noise/stimuli (Bruno and Warren 2010).

*Currently*, *there are no FDA approved drugs for the treatment of ICU delirium*. The American Psychiatric Association guidelines suggest that antipsychotics may be used for delirium; however, there are no formal recommendations for ICU delirium.

Haloperidol is the preferred agent for the treatment of delirium in critically ill patients. Although commonly used in clinical practice on a "prn" basis, limited dosing information for ICU delirium results in variable doses.

Large randomized, placebo-controlled trials with a characteristic ICU population are needed for definitive evidence of efficacy as well as to establish appropriate dosing of atypical antipsychotics. The benefit of these agents is the lower incidence of QTc prolongation and neurologic adverse effects compared with haloperidol (Table 2.11).

**Table 2.11** Agents for ICU delirium

| Drug | Onset | Dosing | Adverse effects/comments |
|---|---|---|---|
| Haloperidol | 3–20 min | 2–10 mg IV push every 30 min then 1–5 mg IVq6h | Monitor for electrocardiographic changes QT interval prolongation and arrhythmias |
| | | 0.03–0.15 mg/kg Q6h | Extrapyramidal side effects |
| | | *Discontinue in patients with QTc* >500 ms | Neuroleptic malignant syndrome (rare) |
| | | | Lowers seizure threshold |
| | | | Black box warning: increased mortality in elderly with dementia-related psychosis |
| | | | Causes sedation |
| Olanzapine | No data | 2.5–5 mg PO QHS | Monitor for electrocardiographic changes QT interval prolongation and arrhythmias |
| | ≤60 min | 5–10 mg IM | Extrapyramidal side effects |
| | | *Discontinue in patients with QTc* >500 ms | Lowers seizure threshold |
| | | | Hyperglycemia |
| | | | Peripheral edema |
| | | | Causes sedation |
| Quetiapine | No data | 25–50 mg PO BID | Monitor for electrocardiographic changes QT interval prolongation and arrhythmias |
| | | *Discontinue in patients with QTc* >500 ms | Extrapyramidal side effects |
| | | | Neuroleptic malignant syndrome (rare) |
| | | | Lowers seizure threshold |
| | | | Neutropenia |
| | | | Hyperglycemia |
| | | | Causes sedation |
| Ziprasidone | No data | 20 mg PO q4h or | Monitor for electrocardiographic changes QT interval prolongation and arrhythmias |
| | ≤60 min | 40 mg PO q6h | Extrapyramidal side effects |
| | | 10 mg IM | Neuroleptic malignant syndrome |
| | | *Discontinue in patients with QTc* >500 ms | Lowers seizure threshold |
| | | | Hyperglycemia |
| | | | Bone marrow depression |
| | | | Many drug-drug interactions |

There is limited trial data establishing safety, efficacy, or appropriate dosing of atypical antipsychotics

## 2.10 ICU Hyperglycemia

Historically, hyperglycemia was not routinely controlled in intensive care units (ICU). More recent evidence indicating that uncontrolled hyperglycemia is associated with poor outcomes has prompted efforts to routinely correct and prevent hyperglycemia in critically ill patients.

Hyperglycemia associated with critical illness (also called stress hyperglycemia or stress diabetes) is a consequence of many factors, including increased cortisol, catecholamines, glucagon, growth hormone, gluconeogenesis, and glycogenolysis. Insulin resistance may also be a contributing factor, since it has been demonstrated in more than 80 % of critically ill patients (Falciglia et al. 2009; Van den Berghe et al. 2001).

Hyperglycemia, defined as a blood glucose level greater than 180–200 mg/dL, is associated with poor clinical outcomes. Intensive insulin therapy (target blood glucose range of 80–110 mg/dL) significantly increases the incidence of severe hypoglycemia. Its effect on mortality is uncertain, since various randomized trials have reported increased mortality, no effect on mortality, or decreased mortality (Falciglia et al. 2009; Griesdale et al. 2009).

Prevention of uncontrolled hyperglycemia is a desirable intervention; however, the optimal blood glucose range remains controversial. As per the 2012 ADA guidelines, insulin therapy should be initiated for persistent hyperglycemia starting at a threshold of no greater than 180 mg/dL with the goal of 140–180 mg/dL recommended for the majority of critically ill patients.

Regularly scheduled administration of insulin is a proactive approach to treat hyperglycemia and is preferable to a reactive administration regimen (i.e., "sliding scale" insulin) in response to an elevated glucose concentration. If a subcutaneous insulin regimen fails to maintain blood glucose within the target range, consider utilizing a continuous infusion of intravenous insulin. Despite the available literature, a widely accepted insulin regimen has not been established.

## 2.11 Miscellaneous

### 2.11.1 Medication Reconciliation

Medication reconciliation is the process of comparing a patient's medication orders to all of the medications that the patient has been taking. Medication reconciliation is intended to identify and resolve discrepancies—it is a process of comparing the medications a patient is taking (and should be taking) with newly ordered medications. This comparison is done to avoid medication errors such as omissions, duplications, dosing errors, or drug interactions and the need to continue current medications. It should be done at every transition of care in which new medications are ordered or existing orders are rewritten.

### 2.11.2 Stress Ulcer Prophylaxis

Stress ulcerations usually occur in the fundus and body of the stomach but sometimes develop in the antrum, duodenum, or distal esophagus. They tend to be shallow and cause oozing of blood from superficial capillary beds. Deeper lesions may also occur, which can erode into the submucosa and cause massive hemorrhage or perforation.

The guidelines recommend stress ulcer prophylaxis (SUP) for ICU patients with any of the following characteristics: coagulopathy, mechanical ventilation for more than 48 h, history of GI ulceration or bleeding within the past year, and two or more minor risk factors. Minor risk factors include sepsis, ICU admission lasting >1 week, occult GI bleeding lasting ≥6 days, and glucocorticoid therapy (ASHP 1999).

**Table 2.12** Agents for stress ulcer prophylaxis

| | Agent | Dosing | Adverse effects/comments |
|---|---|---|---|
| $H_2$ blockers | Ranitidine | 150 mg PO/NG Q12h or | Mental status changes, thrombocytopenia |
| | | 50 mg IV q8h | Dose adjust for renal dysfunction |
| | Famotidine | 20 mg PO/NG/IV q12h | Potential increased risk of nosocomial pneumonia |
| | Cimetidine* | 300 mg PO/NG/IV q6h or | *Only FDA label approved agent for SUP |
| | | 37.5–50 mg/h via continuous infusion | Many drug-drug interactions |
| Proton pump inhibitors (PPI) | Omeprazole | 20 mg PO/NG daily | Headache, diarrhea, constipation, abdominal pain, nausea |
| | Esomeprazole | 40 mg PO/NG/IV daily | No adjustment needed for renal or liver dysfunction |
| | Lansoprazole | 30 mg PO/NG daily | Potential increased risk of nosocomial pneumonia |
| | Pantoprazole | 40 mg PO/NG/IV daily | Potential increased risk of Clostridium difficile infection |
| | Dexlansoprazole | 30 mg PO daily | Many drug interactions |
| | Rabeprazole | 20 mg PO daily | IV administration *ONLY* for patients who cannot tolerate PO/NG administration |

*Cimetidine is the only agent with the FDA-labeled indication for stress ulcer prophylaxis

For ICU patients who are able to receive enteral medications and in whom stress ulcer prophylaxis is indicated, an oral proton pump inhibitor (PPI) rather than an intravenous $H_2$ blocker may be given. In contrast, for those who cannot receive enteral medications, an intravenous $H_2$ blocker rather than an intravenous proton pump inhibitor should be administered (Spirt and Stanley 2006). Antacids and sucralfate are inferior to $H_2$ blockers and PPIs and are therefore not recommended for the prevention of stress ulcers.

Stress ulcer prophylaxis is *not recommended* for medical or surgical patients who are not in an ICU (Grube and May 2007) (Table 2.12).

### 2.11.3 Critical Drug Shortages

Drug shortages are nothing new but have become a growing and critical problem in America. The list of drugs in short supply across all medical specialties is astounding and includes antibiotics, anesthetic agents, antihypertensive medications, chemotherapy agents, and common electrolyte solutions and vitamins.

In 2011, there were a record-high 267 new prescription drug shortages. This is 56 more than in 2010, when there were 211, and more than four times greater than the number of medication shortages in 2004, when just 58 drug shortages were reported.

The shortages have also delayed clinical trials that compare new, experimental drugs to older ones and have led to extraordinary price extortion, causing many hospitals to have to pay extremely large markups for limited drugs.

According to the FDA, the primary cause of the shortages is production shutdowns due to manufacturing disruptions related to problems such as ingredient microbial contamination and impurities or foreign particulates present in medicines that prevent product quality from meeting FDA standards and regulations.

Shortages are also caused by companies that end production of drugs that have small profit margins, consolidation in the generic drug industry, as well as a shortage of the raw materials used to make drugs.

Unfortunately, not many of the current shortages will be resolved soon due to several key manufacturers that have had to shut down production because of contamination or other quality problems. Some medicines may only have one other manufacturer, which lacks the capability to fill the gap immediately or entirely.

The American Society of Health-System Pharmacists (ASHP) created the Drug Product Shortages Management Resource Center (www.ashp.org/shortage) for information related to drug shortages. This site, managed by the University of Utah's Drug Information Service (DIS), maintains the most comprehensive list of scarce or unavailable drugs.

## References

American Psychiatric Association: practice guideline for the treatment of patients with delirium (1999) Am J Psychiatry 156(5 suppl):1–20

American Society of Health-System Pharmacists (1999) ASHP therapeutic guidelines on antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 56(18):1839–1888

ASHP therapeutic guidelines on stress ulcer prophylaxis. ASHP Commission on Therapeutics and approved by the ASHP Board of Directors on November 14, 1998 (1999) Am J Health Syst Pharm 56(4):347

Bratzler DW, Houck PM (2004) Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis 38:1706–1715

Bruno JJ, Warren ML (2010) Intensive care delirium. Crit Care Nurs Clin North Am 22: 161–178

Cooper BE (2008) Review and update on inotropes and vasopressors. AACN Adv Crit Care 19(1):5–15

Dipiro JT, Talbert RL, Yee GC et al (2002) Pharmacotherapy: a pathophysiologic approach, 5th edn. McGraw-Hill Co. Inc., New York

Edwards FH et al (2006) The Society of Thoracic Surgeons practice guideline series: antibiotic prophylaxis in cardiac surgery, part I: duration. Ann Thorac Surg 81:397–404

Engelman R et al (2007) The Society of Thoracic Surgeons practice guideline series: antibiotic prophylaxis in cardiac surgery, Part II: Antibiotic choice. Ann Thorac Surg 83:1569–1576

Falciglia M et al (2009) Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Crit Care Med 37(12):3001

Ganjehei L, Massumi A, Nazeri A, Razavi M (2011) Pharmacologic management of arrhythmias. Tex Heart Inst J 38(4):344–349

Griesdale DE et al (2009) Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-Sugar study data. CMAJ 180:821

Grube RR, May DB (2007) Stress ulcer prophylaxis in hospitalized patients not in intensive care units. Am J Health Syst Pharm 64:1396–1400

Havel C, Arrich J, Losert H, Gamper G, Müllner M, Herkner H (2011). Vasopressors for hypotensive shock. Cochrane Database Syst Rev (5):Art. No. CD003709. doi:10.1002/14651858.CD003709.pub3

http://www.ashp.org/DocLibrary/Policy/PatientSafety/Optimizing-Med-Reconciliation.aspx

http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050792.htm

http://www.forbes.com/sites/dougschoen/2012/02/13/the-drug-shortage-crisis-in-america/

http://www.jointcommission.org/sentinel_event_alert_issue_35_using_medication_reconciliation_to_prevent_errors/

icudelirium.org. Available at: http://icudelirium.org/index.html

Jacobi J et al (2002) Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists (ASHP), American College of Chest Physicians. Crit Care Med 30(1):119

Kee VR (2003) Hemodynamic pharmacology of intravenous vasopressors. Crit Care Nurse 23:79–82

Koda-Kimble MA (2006) Applied therapeutics: the clinical use of drugs, 8th edn. Lippincott Williams & Wilkins, Philadelphia

Kowey P (1998) Pharmacologic effects of antiarrhythmic drugs. Arch Intern Med 158(4): 325–332

Micromedex® 2.0 2012. Accessed August 2012

Murray M et al (2002) Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists (ASHP), American College of Chest Physicians. Crit Care Med 30:142–156

Ostermann ME, Keenan SP, Seiferling RA, Sibbald WJ (2000) Sedation in the intensive care unit: a systematic review. JAMA 283(11):1451–1459

Overgaard CB, Davík V (2008) Contemporary reviews in cardiovascular medicine: inotropes and vasopressors. Circulation 118:1047–1056

Poor K, Stanke S (2005) Understanding adult hemodynamics: a primer for cardiovascular surgery and hemodynamic monitoring. TCHP Education Consortium

Rhoney D, Peacock W (2009) Intravenous therapy for hypertensive emergencies, part 1. Am J Health Syst Pharm 66:1343–1352

Sessler CN (2005) Sedation, analgesia and neuromuscular blockade for high-frequency oscillatory ventilation. Crit Care Med 33(Suppl):S209–S216

Spirt MJ, Stanley S (2006) Update on stress ulcer prophylaxis in critically ill patients. Crit Care Nurse 26(1):18

Standards of Medical Care in Diabetes – 2012. Diabetes Care 35:S11–S63

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII). (2003) JAMA 289(19):2560–2572

Therapeutic guidelines on antimicrobial prophylaxis in surgery section: executive summary (Draft) 2012

Thireau J et al (2011) New drugs vs. old concepts: a fresh look at antiarrhythmics. Pharmacol Ther 132(2):125–145

Thoratec Infection control guidelines for the Heartmate® XVE Left Ventricular Assist System. Available at http://www.transmedic.com.tw/doc/Infection%20Control%20Guidelines-RevB.pdf

Tsuneyoshi I, Yamada H, Kakihana Y, Nakamura M, Nakano Y, Boyle WA (2001) Hemodynamic and metabolic effects of low-dose vasopressin infusions in vasodilatory septic shock. Crit Care Med 29(3):487–493

Van den Berghe G et al (2001) Intensive insulin therapy in critically ill patients. N Engl J Med 345:1359

Vender JS, Szokol JW, Murphy GS et al (2004) Sedation, analgesia, and neuromuscular blockade in sepsis: an evidenced-based review. Crit Care Med 32(suppl):S554–S561

# Principles of Pharmacoeconomics

3

Felice Eugenio Agrò, Marialuisa Vennari,
and Maria Benedetto

## Contents



**Abstract**

Pharmacoeconomics represents about the 15 % of health budgets of many nations (Chunningham 2001). This is particularly relevant for patients with multiple chronic conditions taking on average more medications or critically ill patients that could have a long-term hospital or intensive care units (ICU) stay (Johnson 2002). In this chapter an overview on pharmacoeconomics is presented correlating the choice of i.v. fluid to costs. It is possible to reduce significantly the costs, optimizing clinical benefits.

Pharmacoeconomics represents about the 15 % of health budgets of many nations (Chunningham 2001). This is particularly relevant for patients with multiple chronic conditions taking on average more medications or critically ill patients that could have a long-term hospital or intensive care units (ICU) stay (Johnson 2002).

The key concept in pharmacoeconomics is the opportunity cost, which refers to the added costs and benefits of a new treatment, over and above the already existing ones.

Costs can be classified as follows:

*Direct*: costs spent by health-care funder for a specific service or goods including drug acquisition costs.

F.E. Agrò, MD (✉) • M. Vennari, MD • M. Benedetto, MD
Anesthesia, Department of Intensive Care and Pain Management,
Campus Bio-Medico of Rome, Via A. Del Portillo, 200 00128 Rome, Italy
e-mail: f.agro@unicampus.it; m.vennari@unicampus.it; m.benedetto@unicampus.it

A. Dabbagh et al. (eds.), *Postoperative Critical Care for Cardiac Surgical Patients*,
DOI 10.1007/978-3-642-40418-4_3, © Springer-Verlag Berlin Heidelberg 2014

*Indirect*: costs that are not directly related with a specific object such as costs for administrative staff, equipment rental, and cost of travel to hospital.

*Intangible*: costs that are unquantifiable because they cannot be related to a specific service or good such as engineering costs. These cannot be measured in terms of money, but only in terms of quality of life.

The expected benefits from an intervention might be measured in:

*Natural* units – which refer to tangible events such as years of life saved, strokes prevented

*Utility* units – which refer to the quality of health status

The quality-adjusted life year (QALY) is the most common measure used in health economics, which includes both quality and quantity of life. It corresponds to estimated survival x estimated quality of life (relative to "perfect health") (Agrò 2013).

The costs and benefits or outcome analyses are performed using the following four common types of economic evaluation:

– Cost minimization analysis (CMA): it compares costs of different strategies which are clinically equivalent. As expected, the cheapest therapy is generally preferred.
– Cost-effectiveness analysis (CEA): it is a type of evaluation, through which health benefits are considered in natural units (e.g., years of life saved), whereas the costs are considered in terms of money. The key measure is the incremental cost-effectiveness ratio (ICER) which corresponds to (cost of drug A – cost of drug B)/(benefit of drug A – benefit of drug B).

The four possible results arising in CEA are the following:

1. If costs of a new drug are lower and health benefits are higher, this would be the preferred treatment.
2. If the new drug is more expensive and less effective, this is not recommended.
3. Commonly, a new drug is more effective but more expensive than the standard treatment. Based on ICER, it is necessary to determine if the extra benefits justify the additional costs, i.e., if the new drug is "cost-effective." It could be evaluated by a threshold value previously established.
4. Finally, the new drug is more expensive but more effective than the standard treatment. This case is similar to the third one; it should be assessed that the extra benefits provided by the standard treatment justify the additional costs of retaining it as the preferred drug.

- Cost–utility analysis (CUA): it considers a specific outcome, evaluating the costs to reach the goal measured in money. However, in this analysis, the outcome is measured in terms of survival and quality of life. Thus, the outcome may not be directly related to health status and cost–utility analysis can compare strategies in different areas of medicine.
- Cost–benefit analysis (CEA): it refers to the economic benefits of a strategy, and costs and benefits are expressed in money. Cost–benefit analysis may not account for intangible costs that cannot be measured in terms of money (i.e., relief of anxiety). This approach is rarely used in health economics.

In the critical care of cardiac patients, an important role is exerted by fluid management, besides vasoactive drugs. Cost is one of the main concerns in making decision for fluid therapy (Agrò 2013). Only few reports compared the total costs of

**Table 3.1** Difference in recovery costs using balance or unbalaced solutions. From Agrò et al. (2013)

| | Unbalanced and no plasma-adapted solutions | Balanced and plasma-adapted solutions |
|---|---|---|
| Cost of hospital stay/die | 1,000 € | 1,000 € |
| Cost of FT/die | 21 € | 30 € |
| CostHS for 3 days | (1,000 × 3) = 3,000 € | (1,000 × 3) = 3,000 € |
| CostFT for 3 days | (21 × 3) = 63 € | (30 × 3) = 90 € |
| Total Cost | (3,000 + 63) = 3,063 € | (3,000 + 90) = 3,090 € |

care adopting different fluid therapies (Vincent 2000). In addition, no data exists on costs associated with late outcomes, including those incurred after ICU or hospital discharge. In particular, the widespread use of balanced solutions has caused concerns about their expensiveness. The clinical benefits related to their use, however, are expected to overcome the increased costs. The cost-effectiveness of balanced solutions should be rigorously addressed taking into account potential advantages in outcomes such as morbidity, mortality, and length of ICU or hospital stay, when compared to unbalanced ones (Burchardi and Schneider 2004).

In fact, a large amount of 0.9 % saline and colloids dissolved in isotonic saline (unbalanced) is associated with the development of dilutional–hyperchloremic acidosis. Although moderate, this transient side effect (24–48 h) may increase the length of ICU stay (Guidet 2010). Several reports indicated that this condition may have detrimental effect on patients' clinical course. Patients receiving balanced solutions showed improved gastric and renal perfusion, thus reducing the incidence of renal impairment. In addition, these solutions better preserved the hemostasis when compared to unbalanced ones (Grocott 2005). All these aspects may translate into prolonged length of hospital stay. The cost–benefit ratio of plasma-adapted and balanced fluid therapy can vary from country to country according to the cost of fluids on the market and the clinical condition of the patients.

As an example, assuming that in Europe:

- An ICU stay cost of € 1,000/death
- An unbalanced plasma-adapted colloid or crystalloid cost of € 7
- A balanced plasma-adapted colloid or crystalloid cost of € 10
- A mean of hospital stay length of 3 days and 3 L/day fluid therapy in patients with multiple chronic diseases

The results are expressed in the following Table 3.1:

The use of unbalanced and no plasma-adapted solutions leads to one additional day of hospital stay because of the onset of metabolic and acid–base disorders. The overall cost assuming unbalanced solutions as fluid therapy corresponds to (3,063 + 1,000 + 21) = 4,084 €, with a saving of 4,084 − 3,090 = 994 € using balanced and plasma-adapted ones.

The result of cost–benefit analysis on fluid therapy may be summarized into the following formula that can be used by single institutions to evaluate cost saving related with the use of balanced plasma-adapted solutions (Agrò 2013):

$$\text{Cost saving per year}[€/\$] = n * 0.15 * \text{CDS}[€/\$] - d * L * \text{EXC}[€/\$]$$

**Table 3.2** Presentation of costs according to length of hospital stay and liters of solutions administered per day. From Agrò et al. (2013)

| | Amount of fluid (L/day) | | | |
|---|---|---|---|---|
| Length of stay (day) | 1 L/day | 2 L/day | 3 L/day | 4 L/day |
| 1 Day | 0.15 | 0.075 | 0.05 | 0.0375 |
| 2 Days | 0.075 | 0.0375 | 0.025 | 0.01875 |
| 3 Days | 0.05 | 0.025 | 0.016667 | 0.,0125 |
| 4 Days | 0.0375 | 0.01875 | 0.0125 | 0.009375 |
| 5 Days | 0.03 | 0.015 | 0.01 | 0.0075 |
| 6 Days | 0.025 | 0.0125 | 0.008333 | 0.00625 |
| 7 Days | 0.021428571 | 0.010714 | 0.007143 | 0.005357 |

Assuming that:

- EXC is the extra cost of 1 L of balanced plasma-adapted solutions.
- *L* is the overall amount of fluid therapy per day expressed in liter.
- CSD is the cost of hospital stay per day.
- *n* is the number of patients/year.
- *d* is the average number of hospital stay length.

In addition, we can use the following table reposting the maximum ratio (μ) between extra cost and hospital stay cost for each combination of hospital stay length and average amount of fluid therapy per day. Taking into account site-specific average hospital stay length (day) and average amount of fluid therapy per day (liter), we can obtain site-specific μ.

Multiplying μ * site-specific hospital stay cost per day, we obtain the cutoff value of extra cost in order to gain the cost saving (Agrò 2013) (Table 3.2).

In conclusion, allowing faster patient discharge (hospital stay can be decreased of few hours or even days), we can reduce significantly the costs with optimizing benefits in terms of patient outcome.

## References

Agrò FE (2013) Body fluid management – from physiology to therapy. Springer, Rome

Agrò FE, Benedetto U, Candela C (2013) Pharmaco-economics. In: Agrò FE (ed) Body fluid management – from physiology to therapy. Springer, Milan

Burchardi H, Schneider H (2004) Economic aspects of severe sepsis: a review of intensive care unit costs, cost of illness and cost effectiveness of therapy. Pharmacoeconomics 22(12):793–813

Chunningham S (2001) An introduction to Economic Evaluation of Health Care JO 3:246

Grocott MPW (2005) Perioperative fluid management and clinical outcomes in adults. Anesth Analg 100:1093–1106

Guidet B (2010) A balanced view of balanced solutions. Crit Care 14:325

Johnson RW (2002) Chronic conditions: making the case for ongoing care. Foundation Partnership for Solutions. Princeton, NJ

Vincent JL (2000) Fluid management: the pharmacoeconomic dimension. Crit Care 4(2):S33–S35

# Cardiovascular Monitoring

# 4

Ali Dabbagh

## Contents



A. Dabbagh, MD
Department of Anesthesiology and Anesthesiology Research Center, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
e-mail: alidabbagh@yahoo.com, alidabbagh@sbmu.ac.ir

A. Dabbagh et al. (eds.), *Postoperative Critical Care for Cardiac Surgical Patients*,
DOI 10.1007/978-3-642-40418-4_4, © Springer-Verlag Berlin Heidelberg 2014

**Abstract**

One of the fundamental functions in each intensive care unit is monitoring, while respiratory monitoring, cardiovascular monitoring, and cerebral monitoring are the main three monitoring functions of ICU. In the current world of increasing health technology, though, the exact and sophisticated examinations of the clinicians could not be replaced by any of these technologic improvements. A continual hemodynamic assessment after cardiac operations is a cornerstone of postoperative cardiac surgeries. The main cardiovascular monitoring methods involve – but are not confined to – the following pages, though more detailed explanations could be found in details in related texts. Noninvasive and invasive blood pressure, central venous and pulmonary artery pressure, cardiac output monitoring modalities, and the normal range for measured hemodynamic variables are among the main topics that the reader could be familiar with after reading this chapter.

## 4.1 Noninvasive Blood Pressure Monitoring

In 1896, Scipione Riva-Rocci described for the first time the measurement of systolic blood pressure using a cuff over the upper arm; also, in 1905, Nicolai Sergeivich Korotkoff, a Russian surgeon, described the method of measuring blood pressure by auscultation now well known as the Korotkoff sounds, from I to V, although Korotkoff himself could recognize four stages which were "first sound, then compression murmurs, second tone, and disappearance of sounds" and he could not recognize the muffling which is phase II; these phases are frequently used in the everyday clinic practice. The phase I of Korotkoff sound is equal to the systolic pressure, which is the first stage of sound. During phases II and III of Korotkoff sounds, the quality of the sounds changes. In phase IV of Korotkoff sounds, the sound muffles, and in phase V, the sound disappears; in some pathologies like aortic regurgitation, Korotkoff sound would be never discontinued, and so the final phase is phase IV which is considered as the diastolic pressure. It has been demonstrated that the Korotkoff sounds could be enhanced through a simple maneuver, i.e., "by elevating the arm overhead in a 30-s period, then inflating the sphygmomanometer cuff, and finally returning the arm to the normal position for blood pressure

measurement"; we could listen to Korotkoff sounds louder than normal without any bias of the measurement.

The indirect nature of noninvasive blood pressure measurement poses potential source of measurement errors. Three different sources for bias are possible in indirect blood pressure measurement: "observer bias, faulty equipment, and failure to standardize the techniques of measurement." Very rapid cuff deflation causes rapid "passage" over the Korotkoff sounds which would underestimate the blood pressure. If the sphygmomanometer cuff size is not appropriate, the measurements could be with error, especially when the cuff is undersized; though oversized cuffs do not create a significant error, the cuff is suggested to have a length of 80 % and a width of 40 % of the arm circumference. Also, the cuff should not be fastened so much tightly; otherwise, it would overmeasure the blood pressure (Wiener and Weil 1977; Russell et al. 1989; Bailey and Bauer 1993; Campbell et al. 1994; Eckert et al. 1996; Riva-Rocci et al. 1996; Bur et al. 2000; Manley 2000; Mattoo 2002; Paskalev et al. 2005; Roguin 2006; Verrij et al. 2008, 2009; Amoore et al. 2010; Chio et al. 2011; Sivarajan and Bohn 2011; Amoore 2012; Cheng et al. 2012; Kipnis et al. 2012; Palatini et al. 2012; Roberts et al. 2012; Stirnemann et al. 2012; Truijen et al. 2012; Xiang et al. 2012).

### 4.1.1 Automated Blood Pressure Measurement

Automated noninvasive blood pressure measurement is clinically advantageous over manual measurement in such a way that some believe that "the conventional Riva-Rocci/Korotkoff technique … with a mercury sphygmomanometer and stethoscope is now being relegated to the museum shelves"!

So this method has nowadays replaced the older manual control of blood pressure especially in some places like the intensive care units with which the healthcare personnel would be free to care for the patients. The most common technology used in these devices is the oscillometric technique; so it has a considerable sensitivity for measuring the mean arterial pressure (MAP); however, the measurement of systolic and diastolic blood pressure is not as accurate as the MAP especially in some critical disease states or in some arrhythmias like atrial fibrillation or aortic regurgitation. Since most of the available cuffs for automated blood pressure measurement are made for the upper arm, their use in other parts like thigh or calf would result in errors of measurements. Other technologies for measurement of noninvasive blood pressure have been developed, but none had been able to replace the oscillometry technique.

There are a number of complications due to the effects of noninvasive blood pressure measurement (including automated blood pressure monitoring); among them, the following could be mentioned:

*Compartment Syndrome*: Being the most drastic complication of noninvasive blood pressure monitoring, this syndrome is "a serious potential complication of trauma to the extremities." The following could be considered as the patients at the highest risk for occurrence of compartment syndrome due to noninvasive blood pressure measurements: repeated measurements fastening the cuff against

a bony part or a joint system errors causing repeated unyielding results administration of thrombolytic therapy in coronary artery disease patients having "seizures, movement disorders, hyperactivity, or tremor" obtunded patients are those "having an altered level of consciousness, altered mental status, or altered physical status secondary to injury, illness, or anesthesia; who are dulled or have diminished or absent sensation in the upper extremity due to nerve injury or anesthesia; and, finally, those patients in whom the ability to communicate is impeded, like the mentally ill patients or the disabled patients or infants and young children"; this syndrome will cause an increase in the tissue fluid leading to increased venous pressure and at the same time decreasing the arterial-venous pressure gradient, finally decreasing perfusion pressure of the tissues (Posey et al. 1969; Wiener and Weil 1977; Mauck et al. 1980; Dorlas et al. 1985; Celoria et al. 1987; Whalen and Ream 1988; Parati et al. 1990; Segal and Adair 1990; Block et al. 1991; Gorback et al. 1991; Mabee and Bostwick 1993; Rudoff et al. 1994; Movius et al. 1998; O'Brien 1998, 2003; Ouellette 1998; Saul et al. 1998; Bur et al. 2000; Alford et al. 2002; Schima et al. 2004; Mambelli et al. 2007; Manios et al. 2007; Myers and Godwin 2007, 2012; Agarwal and Light 2009; Chatterjee et al. 2010; Andreadis et al. 2011; Holt et al. 2011; Wax et al. 2011; Hermida et al. 2013; Lakhal et al. 2012; Myers 2012; Myers and Valdivieso 2012; Pavan et al. 2012; Stergiou et al. 2012).

## 4.2 Invasive Blood Pressure Monitoring

"Invasive blood pressure monitoring (IBP)" or "direct blood pressure monitoring" is one of the most commonly used hemodynamic parameters both in operating room and intensive care unit; this fact is especially true in cardiac surgery patients who are exposed to sudden, frequent, and abrupt hemodynamic changes, during both the intraoperative and postoperative period; its feasibility, relatively simple equipment, and the ability for beat-to-beat readings and recordings are among the many favorable features of IBP monitoring. Also, IBP monitoring through arterial line cannula is usually safe with very *few* complications.

Usually, the systolic and diastolic measurements are displayed on the monitoring plane; however, most devices demonstrate the mean arterial pressure (MAP) value simultaneously. For MAP calculation, we use this formula:

$$\mathrm{MAP} = \left[2\left(\text{Diastolic BP}\right) + 1\left(\text{Systolic BP}\right)\right] / 3;$$

(BP stands for blood pressure). MAP is a more accurate index of perfusion in nearly all body tissues except for the coronary perfusion bed in which the diastolic blood pressure is a more important index. However, in cardiac patients undergoing cardiopulmonary bypass, we usually use MAP to assess the overall tissue perfusion.

Although IBP measurement through the arterial line is the most familiar method, it is usually considered as an indirect indicator of the cardiovascular system, since "IBP measurement" depends on two main variables: cardiac output (CO) and

systemic vascular resistance (SVR). However, in critical setting, IBP is more accurate than NIBP: When the patient is hypotensive, the blood pressure values measured with NIBP are usually higher than IBP; however, when the patient is hypertensive, NIBP is lower than IBP.

### 4.2.1 Common Indications and Contraindications for IBP Measurement and Arterial Line Cannulation

#### 4.2.1.1 Indications

1. *Continuous, real-time blood pressure measurement* accompanied with *heart rate* monitoring, like those patients with "impaired hemodynamic status" due to "depressed function of the *left ventricle*," "severe myocardial *ischemia,*" "*coronary ischemic syndromes*," "*septic or hypovolemic shock*," or "*severe right-sided heart failure syndromes,*" in which vigorous hemodynamic monitoring (including IBP) is essential.
2. *Repetitive measurement of BP* (while NIBP is not appropriate or not available, e.g., in patients with multiple, simultaneous *burn* or *fractures* in all extremities or compartment syndrome or in patients with morbid obesity in which NIBP monitoring is not possible).
3. *Need for assessment and evaluation of the BP curve and waveform*, including the components of the arterial waveform; in these cases, the waveform components are used for a number of clinical uses including the adjustment of intra-aortic balloon counterpulsation using the dicrotic notch or measuring the *cardiac output* through the arterial wave contour.
4. *Monitoring the effects of pharmacologic interventions or surgical manipulations* (e.g., those clinical states in which extensive blood pressure changes would happen, like administration of *inotropic* agents, manipulation of the heart, major blood vessels, or cardiopulmonary bypass "CPB").
5. *Severe and/or considerable blood loss* (e.g., in severe trauma with extensive *hemorrhage* or in *surgical* operations with massive bleeding).
6. *Induced hypotension* (due to the nature of the disease and its related surgical operation).
7. *Frequent blood sampling* (e.g., to perform *blood gas* analysis in acid–base or electrolyte disorders).

#### 4.2.1.2 Contraindications

1. Local infection.
2. Proximal obstruction (like coarctation of aorta) which would cause underestimation of blood pressure.
3. Coagulopathies and abnormalities associated with bleeding tendency; these mandate cannulation from more peripheral sites (*relative* contraindication).
4. Peripheral vascular disease like Raynaud's phenomenon and Buerger's disease (*relative* contraindication) which mandates more central arterial cannulation.

### 4.2.2 Technique and Sites of Measurement (Sites of Cannulation), Their Preferences, and Their Potential Complications

*Technique*: For arterial cannulation, either a "needle through catheter" or a "Seldinger method" could be used, depending on the experience and familiarity of the clinician with each technique. In each technique, administration of local anesthetics on the arterial site before needle and catheter insertion is mandatory to prevent the severe pain due to arterial puncture. Even at times, in the awake patient, administration of incremental doses of intravenous analgesics or sedatives accompanied with respiratory monitoring (like pulse oximetry) is necessary.

However, in the first technique (needle through catheter), the needle is inserted in the place where the finger of the clinician best touches the artery; then, the needle is inserted; care must be taken not to withdraw the needle before the tip of catheter lumen is entered into the arterial lumen as demonstrated in Fig. 4.1. In the Seldinger method, first, the needle is inserted, then the guidewire is sent into the lumen and the needle withdrawn, and, finally, the catheter is conducted over the guidewire into the arterial lumen.

*Sites of Cannulation*: Ideally, the root of ascending aorta is the ideal site for IBP measurement. However, in nearly all of the cases, this is not a practical approach. So other arteries are used; usually, among all these arteries, radial, femoral, and axillary arteries are the most common sites for arterial line cannulation and IBP monitoring; in other words, radial artery is the 1st, femoral artery is the 2nd, and axillary artery is the 3rd most frequent site for arterial cannulation and IBP monitoring; however, among all of these sites, the radial artery of the nondominant hand (i.e., usually left radial artery) is more common than any other artery used for arterial cannulation.

Other common arteries include brachial, superficial temporal, dorsalis pedis, posterior tibialis, and ulnar artery; none of the above sites are as accurate as the aortic root pressure. In nearly all of these sites, the systolic measurement of BP is more and the diastolic measurement of BP is lower than the aortic root pressure. However, the MAP amount is usually similar in all of these sites.

#### 4.2.2.1 Radial Artery

Using the radial artery for IBP measurement is the most common site among all the others, since it has a good collateral arterial flow. Also, percutaneous puncture method is the preferred method for insertion of the catheter. Regarding its anatomic features, it is superficial to the distal head of radius bone, between flexor carpi radialis and brachioradialis tendons; also, it has a very rich collateral circulation through the ulnar artery and palmar arch. Since it is a peripheral artery, in hemodynamically unstable patients, its cannulation may not be as easy as femoral artery.

*Complications of radial artery cannulation*:

- *Bleeding* (the most common complication).
  *Temporary occlusion* and temporary *spasm* of radial artery (with about a 20 % mean frequency in different studies) being a negligible and minor complication; "modified Allen's test" has not been proved to have predictive value for hand ischemia, though the controversy about this method still exists and some guidelines support doing this test for all the patients.

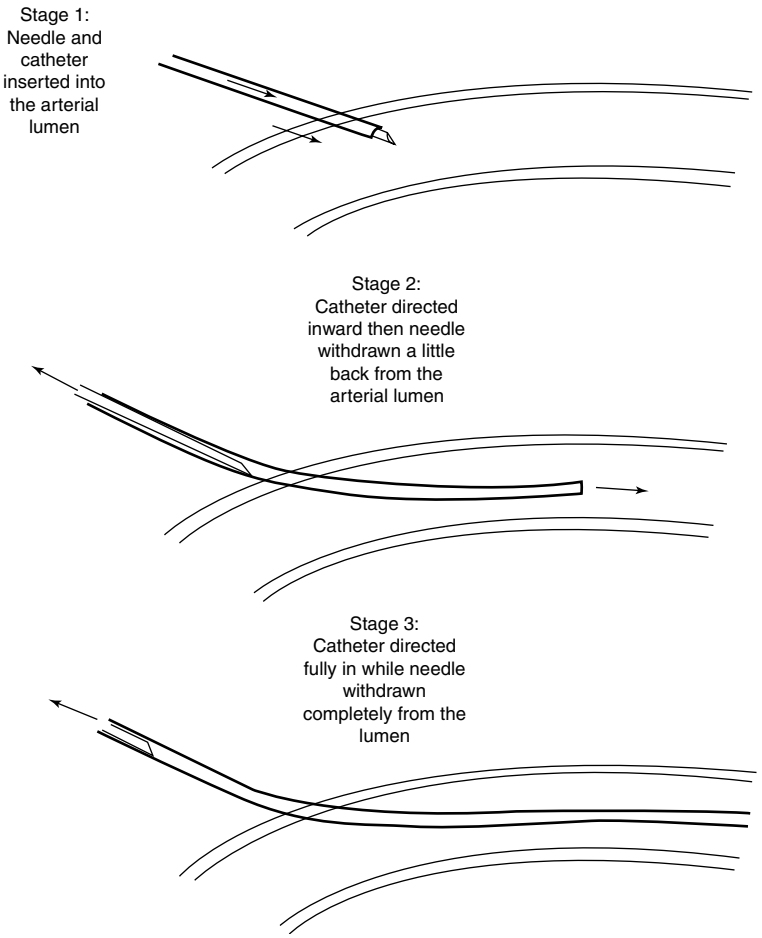



**Fig. 4.1** A schematic presentation of needle through catheter technique in three stages; note that care must be taken not to withdraw the needle before the tip of catheter lumen is entered into the arterial lumen (stage 2)

- *Permanent* occlusion which is a very rare complication.
- Other *mechanical* injuries of the artery rupture (like bleeding, hematoma formation, rupture, and pseudoaneurysm formation).
- *Discrepancy* between radial pressure and the real systolic pressure (especially after some clinical situations like post-CPB period, high-dose administration of vasoactive agents).
- *Thrombus* formation
- *Sepsis* or local *infectious* complications (cellulitis, abscess, suppurative thromboarteritis).
- Local *injury* to other adjacent tissues (compartment syndrome, paralysis of the median nerve, air embolism, catheter fracture, and carpal tunnel syndrome).
- *Air embolization* to the cerebral arterial system after manual flushing (very rare).
- *Regional injuries* to the hand structures (embolization to the fingers, severe ischemia in hand, or skin necrosis in a region proximal to radial artery).

#### 4.2.2.2 Femoral Artery

The femoral artery is located midway between "*anterior superior iliac spine*" and "*pubic symphysis*"; using another anatomic landmark, it is lateral to femoral vein and medial to femoral nerve; it has one of the most accurate arterial waveforms similar to the aortic root (central) arterial wave, regarding both the shape of the wave and the measured values of blood pressure, *even in hypotensive and hypovolemic patients.* Incidence of complications after femoral artery cannulation is equivalent to radial artery; however, some believe the complications, though infrequent, are more complicated to manage; the complications could be listed as:

1. Pseudoaneurysm formation.
2. Bleeding and hematoma formation.
3. Infectious complications (including sepsis and systemic infection and also local infection); there is possibly no more risk of infectious complications for femoral artery than the upper extremities.
4. Massive retroperitoneal bleeding (very *rare*).
5. *Minimal* thrombotic risk (due to the *large arterial lumen* compared with the catheter).
6. Temporary arterial occlusion (*very low* incidence).

#### 4.2.2.3 Axillary Artery

The axillary artery provides IBP measurements very near to the aortic root pressure. Its anatomic location is between the triceps and coracobrachialis tendons, in the armpit; i.e., its landmarks are similar to the landmarks used for axillary block. However, performing this procedure is not technically easy for those who are expert. This artery has also extensive collateral arterial flow. Its complications are as follows:

- Permanent limb ischemia.
- Pseudoaneurysm.
- Sepsis.
- Paresthesia due to mechanical effects of the needle or the catheter.
- Some clinicians have the fear of cerebral air embolism due to retrograde flushing in axillary artery; however, there is no evidence of such complication, and it is a safe approach.

#### 4.2.2.4 Brachial Artery

The brachial artery is subject to inaccuracy, lacks *collateral* circulation, and is associated with the risk of *median nerve* injury and *compartment* syndrome (since it is located in the antecubital fossa); though the occurrence of compartment syndrome is not so much common, it is a *real danger*, since most of the patients are not fully conscious and also they have been exposed to some anticoagulants. The complications of the brachial artery cannulation are injury

- Hematoma
- Local infection
- Arteriovenous fistula
- Pseudoaneurysm
- Paresthesia and median nerve injury

#### 4.2.2.5 Ulnar Artery

Due to the location of the ulnar artery, its proximity and attachment to ulnar nerve, and also the greater anatomical perfusion of the distal hand structures from the ulnar artery, some authors have claimed that ulnar artery cannulation might be associated with a higher risk of vascular and organ injury; however, complications of the ulnar artery cannulation are not so much higher than the radial artery, especially if modified Allen's test is done before arterial puncture and also the radial artery is not injured simultaneously.

#### 4.2.2.6 Dorsalis Pedis

These are the main features of this site:

- Excellent collateral flow
- Easy cannulation
- Minimal patient discomfort
- A very low incidence of complications

However, due to the relatively long distance of the artery with the aortic root, BP readings are not accurate with measurements being 5–20 mm Hg higher than the radial artery.

#### 4.2.2.7 Posterior Tibialis

Posterior tibialis artery cannulation is used mainly for the pediatric patients; however, there are not so many complications reported after cannulation of this artery.

#### 4.2.2.8 Superficial Temporal Artery

The superficial temporal artery is one of the end arteries of the carotid; its cannulation has some "serious" complications; due to its disadvantages, this site is not recommended for IBP measurement.

### 4.2.3 Complications

#### 4.2.3.1 Ischemic Complications

Risk factors for ischemic complications could be classified as female gender:

- Preexisting hypertension
- Arteritis or other vascular diseases
- Size of catheter
- Composition of catheter
- Time duration for cannulation
- Simultaneous use of vasopressors

#### 4.2.3.2 Thrombus Formation

The catheter used for the arterial line could injure the arterial bed and so lead to thrombus formation. There are a number of risk factors which increase the risk of thrombus formation:

- The percentage of the artery surface occupied by the catheter lumen; this occupation percentage is calculated according to the following proportion:
  External diameter of the catheter/internal diameter of the artery; so for radial artery, a 20 G catheter is recommended.
- Teflon catheters are claimed to *decrease* the risk for "thrombus formation," though this issue is controversial.
- Decreased cardiac output *increases* the risk of thrombus formation.
- Hematoma formation *increases* the risk for radial artery occlusion and thrombus formation.
- Systemic administration of aspirin or low-dose heparin *decreases* the chance for thrombus formation.
- Increased time for catheter preservation *increases* the risk of thrombus formation (the risk is especially increased after 48–72 h).

#### 4.2.3.3 Infectious Complications

These include sepsis, local infections, and infectious pseudoaneurysm. The main issue in prevention of these complications, devoid of the site of the arterial line, is to strictly adhere to aseptic techniques, for both the arterial puncture site and the related equipments (including the Luer locks and the connecting tubes). Also, any underlying inflammation or infection should be a warning against using the site for arterial blood pressure monitoring.

### 4.2.4 Technical Considerations in Arterial Line Cannulation

According to the *French Society of Anaesthesia and Intensive Care* (1995) guideline, the following steps should be followed in arterial line cannulation:

1. Use Teflon or polyurethane catheters (maximal size of 18 G for femoral or axillary arteries and 20 G for the other arteries).
2. Maximal length of catheter for small arteries (i.e., radial and dorsalis pedis arteries) is preferred to be 3–5 cm.
3. Heparin coating of catheters for prevention of complications is not proved.
4. Using salts for radiopacity is not useful and may even have thrombogenicity.
5. It is recommended to administer a flush device; the device should have a constant flow of 2 mL/h; at the same time, it is recommended to use a fast flush valve which is connected to normal saline under pressure.
6. Manual intermittent flushing with a syringe is contraindicated.
7. Addition of heparin (2,500 IU.500 $mL^{-1}$ of flush solution) increases the duration of catheter patency and is recommended for catheterizations of more than 24 h duration.
8. Ready-for-use devices are to be preferred.
9. Distortion of pressure wave may be minimized by employing low-volume, low-compliance, and low-resistance devices.
10. The number of connections should be as low as possible and all of Luer-lock type
11. The stopcocks should be clearly identified to minimize the risk of accidental intra-arterial injection.

12. The device should be transparent for disclosure of bubbles, which lead to waveform distortion.
13. For catheter placement, the operator should follow the usual preparation as for any aseptic surgical procedure with cap, mask, gloves, and sterile towel.
14. The insertion site should be prepped either with chlorhexidine or povidone-iodine.
15. In the conscious patient, local anesthesia by injection and/or topical application (EMLA) is recommended.
16. Direct arterial puncture should be preferred rather than transfixion method.
17. It is recommended to use percutaneous cannulation.
18. Needle-catheter assembly should be advanced as slowly as possible to prevent arterial transaction; blood return confirms arterial placement.
19. Resistance against needle advancing is a landmark of error.
20. Catheterization of deep vessels is facilitated by Seldinger technique, which is recommended whatever the site of placement when long-term monitoring and/or difficulties of insertion are foreseen.
21. The radial artery is the site of choice for elective cases. The nondominant hand should be preferred. Puncture must be preceded by assessment of adequacy of the collateral flow by the Allen's test.
22. The femoral artery is a valuable site for emergency situations. Before catheterization, the artery should be auscultated for a murmur.
23. Puncture of a vascular prosthesis is contraindicated.
24. The dressing should be changed every 4 days only.
25. The dressing is recommended to be visible as much as possible to check for any possible leakage of blood; this issue mandates repeated checking of the catheter and its attachments and also minimal application of dressing material.
26. Whether peripheral or central arteries are used, the area distal to the puncture site should be checked for any possible signs or symptoms of ischemia, including change in color, temperature, or distal pulse; of course, it may even mandate Doppler assessment of distal flow.
27. Sites of blood withdrawal should be manipulated with compresses soaked with chlorhexidine or povidone-iodine.
28. The arterial catheter is only changed in case of evidence of local infection or ischemia.
29. The catheter removal should be considered as an aseptic surgical procedure, and the catheter completeness has to be checked.
30. A systematic culture of the catheter is not required.
31. Also, it has been demonstrated that *Doppler ultrasound-guided cannulation* may improve the results and decrease the rate of complications.

### 4.2.5 Arterial Line Transducers and the "Coupling System"

The arterial line transducer and the "coupling system" is the name for the connections from the arterial line catheter connected up to the monitor. Its function is to

change the mechanical data into the electrical data used for the monitor display screen. This system contains the following elements:

1. *Transducer*: The main "exchange system" which transforms mechanical data to electrical data through a delicate diaphragm usually made of silicon.
2. *Tubing*: The mediator between catheter and the transducer.
3. *Flushing System*: Prevents clot formation throughout the catheter-transducer assembly by a continuous infusion of saline (usually 1–3 mL/h). This solution was used to be heparin-rinsed; however, recent studies discourage usage of heparin in such solutions for repetitive washing to prevent the real possibility of heparin-induced thrombocytopenia (see Chap. 6 "postoperative coagulation and bleeding" for explanation of heparin-induced thrombocytopenia).

*Zeroing*: A very important technical consideration is frequent zeroing of the arterial line monitor in order to gain "real" zero readings and then to measure the blood pressure correctly. Each monitor has its recommendations for zeroing based on the manufacturer; however, considering the appropriate level, especially when the patient is in positions other than supine, is an important feature of zeroing. When the patient is in supine position, the level of the transducer should be positioned at the level of the fourth intercostal space which is approximately at the level of midaxillary line; frequent zeroing might increase the accuracy of readings.

*Calibration*: In order to prevent biased readings, calibration should be done in a timely fashion, especially after each episode of blood sampling, when there is a major change in arterial blood pressure, or whenever the readings are doubtful (Mandel and Dauchot 1977; O'Rourke and Avolio 1980; O'Rourke and Yaginuma 1984; Moran 1990; Clark and Kruse 1992; Cockings et al. 1993; Klepper et al. 1993, Ludbrook et al. 1993, Runciman et al. 1993, Franklin 1995a, b; Horlocker and Bishop 1995; Anderson 1997; Kuhn 2001; O'Rourke et al. 2001; McGhee and Bridges 2002; Scheer et al. 2002; Cousins and O'Donnell 2004; Langesaeter et al. 2008; Nichols et al. 2008; Brzezinski et al. 2009; Wilcox 2009; Augusto et al. 2011; Chee et al. 2011; Ranganath and Hanumanthaiah 2011; Wax et al. 2011).

## 4.3 Central Venous Pressure Monitoring

Since its first use in 1929 by Werner Forssmann, central venous pressure catheter (CVP catheter or CVC) has gained widespread use all over the world. CVP is the pressure of blood inside the central intrathoracic veins or the pressure of the right atrium. It is usually measured through a central venous catheter (most commonly known as CVP catheter or CVC). CVP is a very good surrogate for right ventricle pressure and is commonly used as an estimate of left ventricular preload; however, its use as an indicator of right ventricle pressure is not always correct, and many do not rely on the absolute CVP measurement as the index for preload due to many different factors affecting the exact CVP measurement. To compensate for this defect, a number of clinicians rely on the trend of its changes for assessment of the preload status of the patients, though this approach has its own "demerits"; nevertheless, CVP has its own many uses and is among the most commonly applicable devices for critical patients including cardiac surgery patients.

**Table 4.1** Indications and contraindications for central venous catheters (CVCs)

| |
|---|
| Indications |
| Administration of pharmaceuticals (esp. the vasoactive or irritant drugs) |
| Monitoring the hemodynamic parameters (esp. loading status including CVP) |
| Transvenous pacing |
| Rapid fluid administration (in trauma or in procedures mandating large fluid shift or blood loss) |
| Poor peripheral IV access |
| Frequent or rapid aspiration (blood aspiration for frequent venous sampling or rapid air emboli aspiration in specific surgeries) |
| Total parenteral nutrition (TPN) |
| Continuous renal replacement therapy, temporary hemodialysis, plasmapheresis, or apheresis |
| Contraindications |
| *Absolute contraindications* |
| SVC syndrome causes CVC to be useless and possibly increases the CVC risks for the patient |
| *Relative contraindications* |
| Coagulopathies |
| Patients having pacemaker or ICD insertion in the 6 previous weeks |
| Anatomic abnormalities (due to coexisting pathologies or recent surgical manipulations disturbing the normal anatomy of the region) |
| Carotid disease especially in the presence of contralateral carotid involvement |

CVCs are used frequently not only for assessment of CVP but also for administration of drugs and fluids. Of course, CVCs are not considered as the primary route for urgent and rapid fluid replacement. Instead, peripheral large-bore catheters are considered for rapid fluid administration.

Many different indications have been cited for CVP; however, a number of them are mentioned here, and a detailed list could be found in Table 4.1.

### 4.3.1 Indications for CVC Insertion and Usage

1. *Fluid administration and management* (including assessment of loading status, patients with poor peripheral IV access).
2. Continuous renal replacement therapy and/or temporary hemodialysis (although usual multi-lumen 7 F, 20 cm catheters have a much lower capacity for fluid administration compared with usual peripheral IV access).
3. *Diagnostic* measurements (pure values and changing trends of cardiac loading pressures).
4. *Pharmacologic interventions* (especially the vasoactive drugs or irritant drugs and plasmapheresis or apheresis).
5. Other indications (like transvenous pacing).

### 4.3.2 Central Venous Pressure Curves

The CVP curve is composed of five main waves, namely, *a*, *c*, *x*, *v*, and *y* which are the final result of interactions mainly occurring between right atrium (RA), right

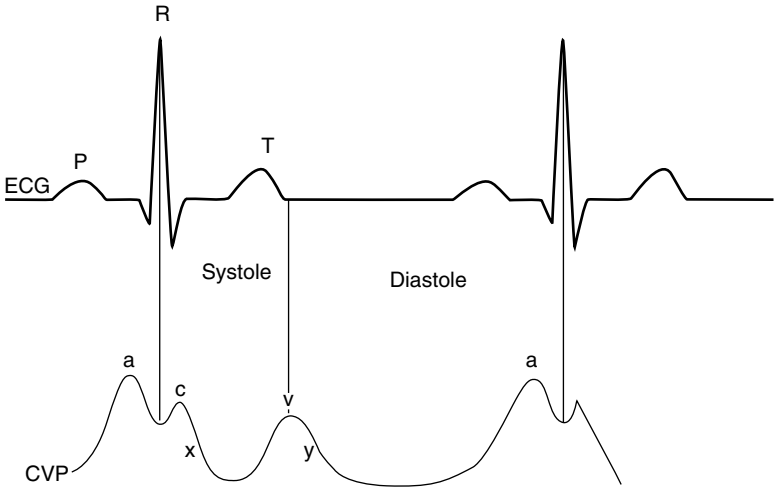



**Fig. 4.2** CVP waves and the relation with ECG

ventricle (RV), and the tricuspid valve (TV); however, among them *a*, *c*, and *v* are upward deflections, while x and y are downward deflections. These waves mainly demonstrate the right atrial pressure (RAP) as the following order (Fig. 4.2):

*a*: Atrial contraction causes an increase in RAP; it appears just after P wave in electrocardiography.

*c*: Isovolemic contraction of RV increases RAP and creates c wave.

*x*: RV contraction pulls TV away from RA and decreases RAP, so we would have a downward deflection wave.

*v*: Blood fills RA during late RV systole which increases RAP and again produces an upward deflection.

*y*: Finally TV opens and causes emptying of RA, so again we see a downward deflection.

### 4.3.3 Technical Considerations for Insertion of CVC

There are a number of well-recognized approaches for CVC insertion, "internal jugular vein" and "subclavian vein" being the two most common approaches while the right internal jugular vein is more common than the left one, while some believe that left internal jugular approach is as easy as the right side.

#### 4.3.3.1 Right Internal Jugular Vein Approach

The internal jugular vein (IJV) was first described by English in the 1960s and is the most frequently used approach for CVC insertion; it causes less complications, has a straight course to the RA, and has lower chance for thoracic duct and pleural dome puncture, both due to anatomic properties of right IJV, although some have claimed

that the left IJV approach is as much easy. It also has a very high success rate (>90 %) even in infants and children accompanied with very low rate of other mechanical complications like arterial puncture, pneumothorax, and hematoma needing surgical intervention compared with all the other methods. Even in anatomically "difficult" patients, the IJV approach has a specific feasibility. The course of IJV especially the right one is straight, short, and with distinct anatomical landmarks; it is without venous valves until superior vena cava and right atrium and could be reached by most anesthesiologist even during the operation time. Its most common and easiest "central approach" described in 1970 by Daily et al. is even the simplest one among all the right IJV access methods in which the needle tip is inserted into the "apex of *Sedillot's triangle*, which is between the sternal and clavicular heads of sternocleidomastoid (SCM) and the related portion of the clavicle located between the two SCM muscle heads." See Fig. 4.3.

Correct sizing of the catheter length is a very challenging issue.

The following steps should be followed for insertion of CVC through right IJV:

1. Put the patient in supine position with a little leftward rotation of the head.
2. Gently extend the neck; excessive extension would distort the "favorable anatomy."
3. Check the anatomic landmark of the neck (*Sedillot's triangle*) once more before draping.
4. Use basic monitoring including electrocardiography (ECG), pulse oximetry ($SpO_2$), and noninvasive or invasive blood pressure measurement.
5. Use a "mild" degree of sedation if the patient is not anesthetized or not sedated accompanied with *supplemental oxygen*.
6. Administer strict aseptic techniques including hand washing, using sterile gown and gloves, and sterile preparation from the mastoid to the sternal notch (2 % chlorhexidine is superior to others like 10 % povidone-iodine).
7. Drape the patient with a *large* drape.
8. Put the patient slightly in head-down position except for patients with cardiovascular or respiratory disease.
9. In awake patients, use 1 % lidocaine solution for local anesthesia using a 25 G needle after another check of landmarks.
10. Use a 22 G finder needle to find IJV.
11. Introduce the 18 G needle from the apex of the *Sedillot's triangle* from between the two heads of SCM towards the ipsilateral nipple with a 30–45° angle from the skin plane.
12. If you could not draw dark blood, relocate the needle a bit laterally or medially in a fanwise model; beware of arterial puncture risk.
13. Check patency of the needle if there is not successful venous puncture yet; also, check the anatomical landmarks once more.
14. The two venous walls of a central vein are at times compressed against the needle; withdrawing the needle gently usually causes sudden filling of the syringe in such cases.
15. After appropriate backflow of relatively dark blood, insert the guidewire through the needle; there should not be any resistance in the course of

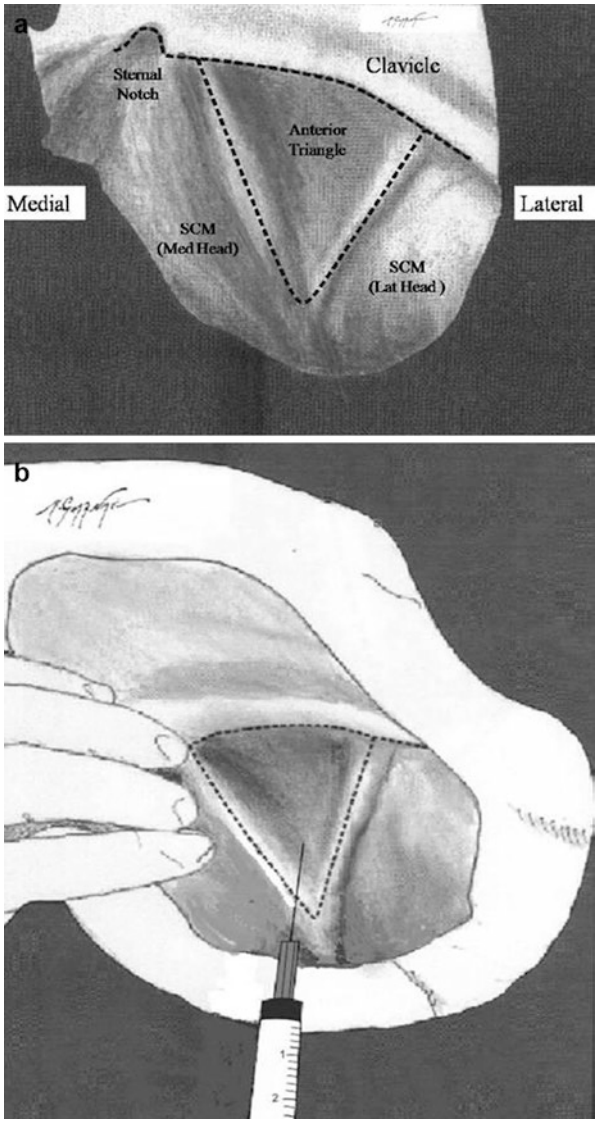



**Fig. 4.3** A schematic presentation of the right anterior triangle (Sedillot's triangle) used for internal jugular vein cannulation when looking from above the patient's head. (**a**) The anatomic landmarks of the triangle, *SCM* sternocleidomastoid muscle, *Lat* lateral, *Med* medial. (**b**) Anatomic location for needle punctures near the apex of triangle towards the ipsilateral nipple

guidewire insertion; otherwise, the guidewire path is not correct; usually the guidewires used for adult CVCs are 0.032–0.035 mm, so the guidewire passage should be never forceful.

16. The blood flow should be non-pulsatile except for cases of severe tricuspid regurgitation or high right ventricular pressure, in which the backflow of IJV would be pulsatile; if you are doubtful regarding the blood flow to be arterial or venous, attach a sterile stopcock to the 18 G needle, which has an extension tube attached to one of its heads; ask a colleague to attach the other head of the extension tube to the pressure monitoring to rule out potential arterial puncture.

17. The guidewire should be always in control, regarding both sterility of its distal end and potential arrhythmias of its proximal head; the former needs protection from contact with the unsterile adjacent objects, and the latter mandates careful ECG monitoring; in most adult cases, guidewire advancement below 20 cm prevents unwanted complications.
18. Withdraw the needle after guidewire installation; use a number 11 scalpel blade before advancing the dilator (especially when a pulmonary artery catheter "PAC" introducer sheath or a large-bore CVC is used); care should be taken not to exert inappropriate force on the catheter; otherwise, guidewire would easily be kinked; on the other hand, excessive dilator advancement would result in unwanted vascular or tissue trauma.
19. After dilator removal, while the guidewire is still in place, insert the catheter while caring to take the distal end of the guidewire out of the port of the CVC before the catheter is fully inserted; loss of control over the distal part of guidewire could result in catheter embolization, an unwanted complication discussed later.
20. Using this approach, CVC should be introduced no more than 15–17 cm in adult men and 13–15 cm in adult women to prevent CVC-induced cardiac tamponade (discussed later).
21. The CVC lines should be de-aired and washed to prevent clotting.
22. Sterile dressings (without any antibiotics) should be used in place.
23. Objective confirmation of the CVC tip which is done by CXR after catheter placement; the tip of the catheter should be above the carina which is approximately at the level of T3–T4 thoracic spines, which is also equal to 3rd rib or azygous vein.

#### 4.3.3.2 Left Internal Jugular Approach (LIJV)

The technique is similar to right IJV; however, the dome of the left pleura is higher than the right pleura, and also, thoracic duct passes from the left; these two anatomic features increase the risk for two important complication: pneumothorax and chylothorax. Chylothorax is exclusive to the left hemithorax. The LIJV is shorter than the right IJV, but the venous path from the left side to superior vena cava is longer than the right side. However, the chance for superior vena cava injury in left IJV is higher than right IJV since the path of right IJV is straightforward compared with left IJV.

#### 4.3.3.3 Subclavian Approach

This approach has some specific features, more patient comfort, an easy approach, and lower infection rate and often used for long-term IV therapy but not monitoring purposes.

Method:

1. Monitor the patient, accompanied with supplemental oxygen and mild sedation.
2. Head-down the patient.
3. Rotate the head laterally.
4. Use a role beneath the two scapulae.
5. Use local anesthesia in a point just below the clavicle, between the lateral and middle thirds of the clavicle.

6. The 18 G needle should be passed below the clavicle being directed to the sternal notch.
7. After appropriate backflow of relatively dark blood, insert the guidewire through the needle.
8. Other steps are similar to internal jugular approach.
9. Due to the potential risk of vascular injury or pneumothorax, one should keep in mind that a maximum of three tries from this approach is allowable, and also, bilateral (right and left subclavian) tries are forbidden since bilateral try would be potentially lethal.

#### 4.3.3.4 External Jugular Vein

A simple, really less risky approach, though having lower chance for success; of course, there are a few concerns for this approach:

1. Never use a dilator for these veins.
2. 90° abduction of the ipsilateral arm increases the success.
3. The vein course is sometimes tortuous, and the venous path could not be used for introduction of the catheter in nearly 20 % of patients.

#### 4.3.3.5 Femoral Vein

Usually used when IJV or subclavian approaches are not available (e.g., in neck injuries or thoracic involvements). The femoral vein is entered in a place just medial to the femoral artery pulse; however, the needle should be introduced to the vein distal to the inguinal ligament to prevent the risk of retroperitoneal bleeding. Besides, femoral artery or femoral nerve injury, infectious complications, and thromboembolic complications are the main other potential complications of this approach. Two different length catheters have been used in this approach: "40–70 cm" and "15–20 cm" catheters; both are near to the SVC measurement but not exactly the same figures.

#### 4.3.3.6 Peripheral CVC

Peripherally inserted catheters as CVC have been used to decrease complications of CVC; but there is no difference between the two methods regarding infection rate. However, peripheral CVCs have more complications like "catheter tip malpositioning, thrombophlebitis, and catheter dysfunction"; hence, central CVCs seem to be preferred over peripheral catheters.

### 4.3.4 Ultrasound-Guided CVC Insertion

This method was introduced for the first time in 1984 and could improve success and decrease the rate of complications, so increasing patient safety, especially in IJV approach and in inexperienced hands. Though adult patients are more frequently said to benefit this method, ultrasound-guided CVC insertion has been shown efficacious in pediatric patients. A 7.5–10 MHz probe, covered by a sterile sheath, used by the nondominant hand, finds the transverse (short) axis at first in order to find IJV

vein lumen, which is larger, laterally located, and non-pulsatile compared with the medially located carotid artery; the transverse axis is also used for detection of the needle entry to IJV lumen. Then, the longitudinal view (long axis) is used to confirm the appropriate passage of the guidewire into the lumen of IJV. However, in other approaches except for IJV, there is not much great utility for ultrasound-guided CVC insertion because of the sonographic "shadows and distances" between the skin and the vein lumen.

### 4.3.5 Complications of CVCs

One of the very common topics in everyday practice of cardiac patients is the minor and major complications of CVCs; many complications have been attributed to CVCs, and too many studies have been published in this topic; the majority of these complications are not common; however, a few could potentially lead to major events and even death. These complications are categorized in four main categories and discussed more in the following paragraphs:

1. Mechanical (vascular injuries, tamponade, nerve injuries, pneumothorax, tissue trauma, etc.)
2. Thromboembolic
3. Infection
4. Other complications

#### 4.3.5.1 Mechanical Complications

These include mainly vascular injuries (arterial puncture, venous injuries), cardiac tamponade, neural injury, *tissue trauma*, pneumothorax, and *catheter or guidewire embolization*. Vascular injuries could be arterial or venous.

*Arterial puncture* is the most frequent among all acute complications, often resulting in local hematoma, which usually resolves after a few minutes of local compression. Few numbers of the patients (especially when major arteries including aorta are injured) need more sophisticated care including emergent consult with a vascular surgeon. If arterial puncture is unintentionally used instead of central vein for catheter placement, the catheter should be removed urgently (except for very unusual circumstances) to prevent unwanted organ embolizations including CNS injuries. However, the risk of arterial bleeding at the puncture site is always potentially serious, needing more vigorous assessments and possible interventions by a vascular surgeon. If a central venous catheter is misplaced anatomically, the location of the catheter tip should be assessed. If it is not in a potentially risky place, we might withdraw the catheter; however, if the catheter tip is located in a risky organ which could not be compressed after catheter removal, or if the course of catheter passes through such an anatomic location, then the catheter should not be removed before an emergent consult with a vascular surgeon.

*Other vascular injuries* are frequent and diverse including minor venous injuries, hemomediastinum, hydromediastinum, hemothorax, hydrothorax, and chylothorax. And finally, *delayed* vascular injuries have been reported including different types

of fistula between veins, arteries, bronchus, or other adjacent tissues, all being rare but needing vigorous attention and care.

*Hemopericardium is the 2nd common and the most lethal complication of CVC placement*. It is usually due to perforation of right ventricle, right atrium, or the segment of superior vena cava located inside the pericardium. The rupture would cause sudden cardiac tamponade blood or fluid tamponade. This is a delayed complication of CVC occurring usually in the 1st week after CVC placement and is usually preceded by arrhythmia unresponsive to anti-arrhythmia treatments. Mortality rates more than 80 % are reported for this complication. Would the clinician perform objective documentation of the CVC tip location (i.e., by CXR), this lethal complication could be prevented in many cases.

*Pneumothorax* is another mechanical complication occurring more commonly after subclavian approach; however, the IJV approach (especially the left IJV) could also lead to pneumothorax though with a lower rate compared with subclavian approach. Minor cases are treated with supportive care, while others need chest tube insertion. Vigorous care should be devoted to high-risk patients especially those underlying mechanical ventilation or those in whom multiple or bilateral punctures have been done to prevent the occurrence of tension pneumothorax which is very lethal.

*Nerve injuries* could be seen mainly at the following sites: brachial plexus, stellate ganglion, and phrenic nerve. Chronic pain syndromes are also possible.

*Tissue Trauma*: Trauma due to needle, guidewire, dilator, or even the catheter had been reported. Dilator-induced tissue or vascular injuries are much more important since the dilators usually cause more harmful injuries than other items used in CVC kits. However, large-bore lumen catheters could lead to tissue injuries; catastrophic results should be anticipated if central vessels or cardiac chambers are injured or, in worst conditions, "*ruptured*" (see above).

*Catheter or guidewire embolization* usually mandates emergent consultation with an interventionist or a surgeon. During CVC placement, guidewire could be introduced inside the venous system unintentionally, so it is necessary that the clinician take control of the distal end of the guidewire before introducing the whole catheter into the venous system. Also, there are reports of partial catheter fracture; both of these states could lead to catheter or guidewire embolization into the venous system, cardiac chambers, or even the pulmonary veins, being dislodged in between the lung tissues. The medical team should check any catheter fractures continually in patients admitted in intensive care wards, especially when the patients are awake and there is the possibility for spontaneous changes in body position. Another critical time for occurrence of this complication is at the time of CVC removal, which mandates careful examination of the whole CVC length, and check for its tip to be intact after withdrawing from the patient.

#### 4.3.5.2 Thromboembolic Complications

These complications are more common in patients with femoral CVC and are lowest in subclavian approach. The primary nidus can change to an infectious complication or may dislodge to the pulmonary vasculature; usually these complications need surgical removal.

#### 4.3.5.3 Infectious Complications

Infectious complications are among the most common late complication of CVC, with 30–50 % mortality. Strict adherence to aseptic techniques during catheter placement is cornerstone of all preventing strategies for CVC infection. Using subclavian approach, application of catheters coated with chlorhexidine and silver sulfadiazine or rifampin and minocycline, and selection of single-use catheters have been demonstrated as methods to decrease the rate of CVC-related infection. Also, the site of catheter insertion could affect the incidence of infectious complications being less in subclavian approach than other routes, though some controversies exist.

#### 4.3.5.4 Other Complications

*Arrhythmia* is a very frequent and usually benign complication during CVC insertion especially in Seldinger technique (due to the guidewire); however, there are reported cases of malignant arrhythmias exactly at the time of CVC insertion, so careful attention to patient's rhythm and hemodynamic status is a main concern during CVC insertion. However, the catheter itself could induce arrhythmias due to its physical effects if not in an appropriate location, which could happen intra- or postoperatively. Careful attention in the length of catheter entry is very important. Also, objective catheter tip confirmation by CXR is an essential job, confirming the CVC tip above the carina bifurcation; otherwise, the catheter should be a bit withdrawn in such a way that its tip is not far beyond carina.

*Bleeding and air emboli* are often related to CVCs with large-bore lumens, though other types of CVC may also have this side effect. Forgetting to secure the lumen ports could result in unnoticed bleeding. If the patient is hypovolemic, this complication would be manifested as air emboli entering the central venous circulation through the nonsecured lumen. Air embolism is also possible during two other situations besides unnoticed nonsecure ports; one is during catheter insertion, which is usually accompanied with small volumes of air going through the needle to the venous system, while the other situation is after CVC withdrawal which could be accompanied with air embolization through the skin lumen and subcutaneous tunnel created by after catheter removal. A compressed dressing with proper sealing could prevent both potential air embolism and CVC site bleeding after CVC removal.

*Misinterpretation of data* and errors in interpretation of data could lead to erroneous results and potential untoward clinical outcomes. For prevention of such erroneous judgments, the clinicians often do not rely only on the results of central venous pressure recordings; instead, the trend of CVP changes, curve of CVP, other measurements of filling pressures, jugular venous pressure figures, etc., are added to the online readings of CVP to prevent such unwanted events (Daily et al. 1970; Knopp and Dailey 1977; Berghella et al. 1979; Tyden 1982; Ferguson et al. 1988; Siradovic et al. 1988; Holmes et al. 1989; Kolodzik 1989; Meyer 1990; Heiss 1992; Mansfield et al. 1994; Tesio et al. 1994; English et al. 1995; Reed et al. 1995; Kuhn 2001; Merrer et al. 2001; Asheim et al. 2002; Keenan 2002; Woodrow 2002; Hind et al. 2003; Unal et al. 2003; Arai and Yamashita 2005; Botha et al. 2006; Di Iorio et al. 2006; Karakitsos et al. 2006; Ash 2007; Chen et al. 2007; Harrigan et al. 2007; Trieschmann et al. 2008; Brusasco et al. 2009; Kujur et al. 2009; Surov et al. 2009;

Ishizuka et al. 2010; Kunizawa et al. 2010a, b; Omar et al. 2010; Furuya et al. 2011; Kang et al. 2011; Kim et al. 2011, 2012; McGee et al. 2011; Uchida et al. 2011; Urban et al. 2011; Boyce 2012; Calabria et al. 2012; Chopra et al. 2012; Ge et al. 2012; Godoy et al. 2012; Guleri et al. 2012; Hewlett and Rupp 2012; Lee and Kamphuisen 2012; Liang et al. 2012; Linnemann and Lindhoff-Last 2012; Marik et al. 2012; Miller and Maragakis 2012; Parienti et al. 2012; Pikwer et al. 2012; Reems and Aumann 2012; Stone et al. 2012; Turi et al. 2013; Vats 2012; Walser 2012; Zhou et al. 2012; Gibson and Bodenham 2013).

## 4.4 Pulmonary Artery Pressure Monitoring

### 4.4.1 History

Pulmonary artery catheter (PAC) was reported first in 1970 by Dr. Swan and Dr. Ganz; hence, the catheter is frequently known as the Swan-Ganz catheter. At that time, this catheter could introduce a new field of online cardiovascular monitoring, controlling the response to therapies and clinical data collection to the clinical world which was not accessible in such a novel way till that time. Due to its novel data, its use was rapidly increased during the following years both inside the operating rooms and intensive care units for cardiac and noncardiac patients. So PAC could help us retrieve a number of useful data which are not retrievable by other monitoring devices like CVC-recorded pressure monitoring; these data are used for diagnostic and/or therapeutic uses, i.e., assessment of the effects of therapies.

### 4.4.2 Clinical Outcome of PAC Usage

During the recent years, there are an increasing number of evidence which question the clinical and final clinical outcome of using PAC, creating an overwhelming load of controversies in using this monitoring device, though some studies have confirm the usefulness of PAC in decreasing mortality in critical patients. Some results of these studies are discussed here briefly.

The negative studies claim that PAC could not decrease the overall mortality or hospital length of stay in critical care patients; also, right heart catheterization in ICU causes increased risk for severe end-organ complications and increased mortality, costs, and length of stay, in such a way that some studies have recommended withdrawal of PAC from current clinical practice in adult ICU patients as a cost-effective strategy; on the other hand, currently, many of the clinicians are seeking newer, less invasive monitoring to be validated and used in practice instead of PAC; among them, transesophageal echocardiography (TEE) could be named as one of the most useful devices for such an application that gives us the needed online data without potential risks of PAC; finally, these data at least recommend us not to use PAC as a routine monitoring, especially in low-risk patients; on the other hand, the positive studies confirm the beneficial role of PAC in decreasing mortality.

### 4.4.3 Indications for PAC Use

PAC is clinically indicated for assessment of these main variables and their response to therapeutic interventions during a wide range of different disease entities:

- Loading status, mainly including right heart failure, pulmonary dysfunction, pulmonary hypertension, severe left ventricular failure needing extra treatments like intra-aortic balloon pump, or shock (septic, cardiogenic, or non-cardiogenic)
- Main hemodynamic parameters of the right heart and the lung, including pulmonary artery pressure (PAP), pulmonary artery occlusion pressure (PAOP), pulmonary vascular resistance (PVR), and mixed venous oxygen saturation ($SvO_2$)
- Monitoring and assessment of cardiac output (CO)

However, risks and benefits of PAC insertion should be assessed before its utilization. Often in low- to moderate-risk cardiac patients, the risks outweigh the benefits, and it is not recommended to use PAC as a "routine" monitoring in such cardiac surgery patients, especially if there is not enough experience and sufficient skill in insertion of PAC and interpretation of its data. In other words, like many other diagnostic devices and technologies, "appropriate patient, sufficient skill in PAC insertion and data analysis, and, finally, appropriate setting" should be present before utilization of PAC.

### 4.4.4 Contraindications of PAC

These are usually due to anatomical causes and include:

- Tricuspid valve stenosis
- Pulmonary valve stenosis
- Previous mechanical prosthesis in any of the two above valves
- Current endocarditis in any of the two above valves
- Tumor and/or mass in right atrium or right ventricle
- Thrombosis in right atrium or right ventricle
- Tetralogy of Fallot due to the potential hyper-reaction of the pulmonary artery in such patients to mechanical stimuli causing spasm and cyanotic spells
- Current underlying severe arrhythmia mandating full preparedness to treat any hemodynamic derangement
- Newly inserted pacemakers which could lead to displacement of the pacemaker wire
- Contraindications to insertion of CVC (see the previous section)

### 4.4.5 Technical Considerations for PAC Insertion

The basic principles for PAC insertion are in essence similar to CVC insertion; however, a few more points should be considered which are discussed here:

- The most preferred approach is right internal jugular vein, while subclavian and femoral veins are not routinely used especially for cardiac surgery patients.

- Guiding the catheter through its path in order to reach to pulmonary artery is used by three ways: the curve of the wave on monitor and its trend, fluoroscopic assessment of catheter tip, and electrocardiography (ECG)-guided approach; however, in intensive care unit, usually the curve of the wave is used for catheter insertion and controlled by chest X-ray.
- Changing the patient position to a head-down and right lateral tilt helps the tip of the PAC to progress from right atrium (RA) to right ventricle (RV) and pulmonary artery (PA).
- An introducer sheath is inserted first, which is mainly like a CVC; this sheath is the conduit for passage of PAC and lets us move PAC back and forth; however, it is a relatively large-bore CVC, nearly 8.5–9 F, and so mandates vigorous caution during its insertion.
- The catheter is 110 cm length and usually 7–8 F. having length markers at 10 cm intervals for accurate and careful back-and-forth movements of the catheter.
- There is a sterile plastic cover on the catheter; this plastic cover should be attached firmly to the distal head of the introducer sheath to prevent contamination, though it is not fully protective and mandates strict adherence to infection prevention methods and, more importantly, avoidance of unnecessary back-and-forth movements.
- Before passing the catheter tip through the introducer sheath and advancing it to the right heart, zeroing of the catheter with the monitoring system at the level of the right atrium should be done while the patient is at supine position; also, the tip of PAC should be raised about 30 cm, and the pressure should be checked with the monitor which equals 22 mm Hg.
- PAC has usually 4–5 lumens for the following purposes (demonstrated in Fig. 4.4):

1. Distal lumen near the tip of catheter for measurement of pulmonary artery pressure.
2. A balloon located 4–5 cm proximal to the tip of catheter and 1.5 mL volume which should be filled for "flow-directed movement of the catheter"; its related lumen should be attached to a specific 2 mL syringe, and the balloon should be checked for symmetrical filling before insertion of PAC; also, the balloon should not be filled when PAC tip is in wedge position to prevent unwanted injuries in lung tissue and pulmonary arterial branches.
3. The most proximal lumen opening nearly 30 cm proximal to the tip of catheter used for measurement of central venous pressure or RA pressure.
4. The 4th lumen having a thermistor for measurement of cardiac output using thermodilution method.
5. Often the 5th lumen being used for assessment of mixed venous blood oxygen saturation (SvO2).

When advancing PAC through introducer sheath from the right internal jugular approach, we should have different related curve patterns at related distance intervals, i.e., for CVP (10–15 cm), RA pressure (15–25 cm), RV pressure (30–35 cm), PA pressure (40–45 cm), and wedge pressure (45–55 cm) as described below and demonstrated in Fig. 4.5:

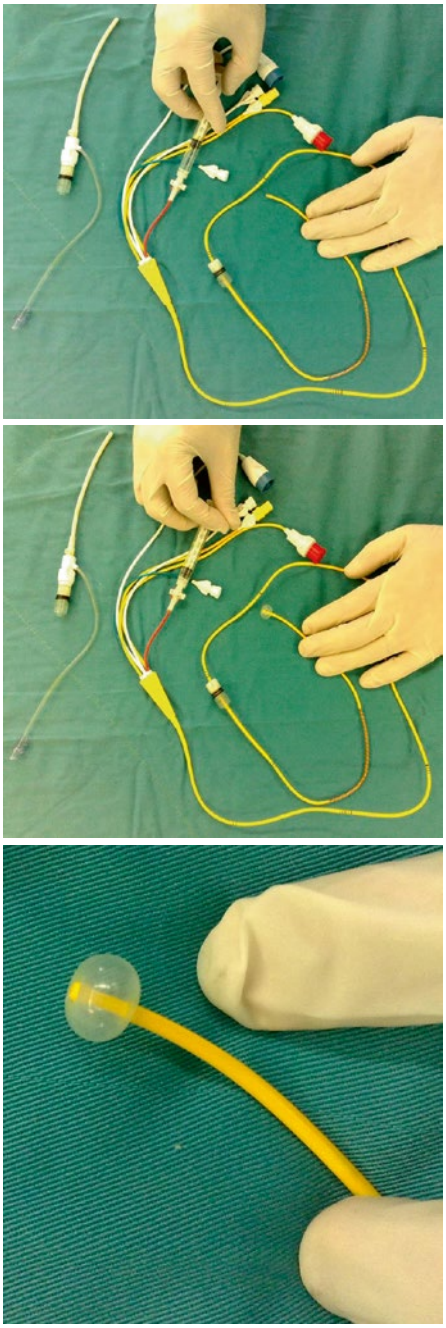


**Fig. 4.4** PAC ingredients: note the tip of the balloon in three subsequent figures to be inflated; the 3rd figure demonstrates a filled balloon in large view

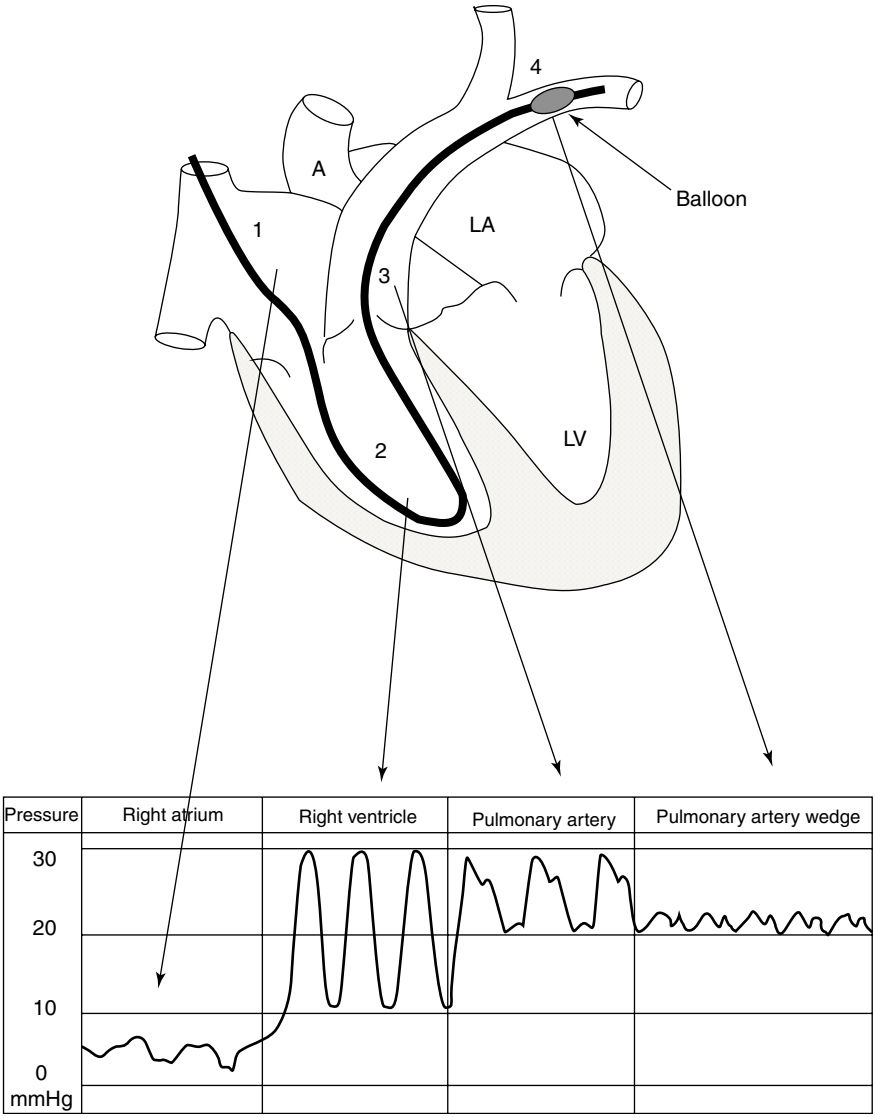



**Fig. 4.5** A schematic presentation of the PAC course and its related pressure waveforms in cardiac chambers, pulmonary artery, and main left pulmonary artery

1. Central venous pressure curve, demonstrating the tip of the catheter being located in central veins and/or RA, for CVP at 10–15 cm and for RA pressure at about 15–25 cm.
2. The catheter tip passes through the tricuspid valve to go to the right ventricle (RV); a significant increase in systolic deflection is seen, and the diastolic deflection does not change so much; this part of the curve belongs to RV when PAC tip goes in as much as 30–35 cm.

3. With catheter progress through the pulmonary valve to reach the entry of pulmonary artery (PA), a dicrotic notch is seen in the point just after the peak of systole, while the bottom of the pressure wave curve increases suddenly showing the diastolic pressure of PA which is higher than the diastole of RV and resembles the wave contour of the systemic arterial pressure; of course in a smaller scale; so PA pressure appears when PAC tip goes in about 40–45 cm.
4. Catheter progression as much as about 5 cm causes another new pattern in wave contour which would be nearly at 45–55 cm from PAC tip; here, there would be another change in the wave contour which indicates pulmonary artery wedge pressure (PAWP) or pulmonary artery occluding pressure (PAOP) which could usually be demonstrated on the monitor screen play after PAC balloon dilatation leading to wedge location of the tip of catheter; of course, PAC tip should not stay in wedge position for more than a few minutes to prevent unwanted complications like rupture of the pulmonary arterial branches or segmental necrosis of lung tissue; frequent withdrawal of PAC as much as 3–5 cm prevents PAC tip lodging, hence preventing such problems.
5. If these curves are not seen in the above length intervals, there is a real chance of catheter coiling, a dangerous complication of PAC discussed in the next paragraph; for prevention of such an event, strictly following the curves is a useful preventive strategy.

### 4.4.6 Complications of PAC

In 2003, the American Society of Anesthesiologists' task force on PAC (2003) stated that "overall deaths attributable to PAC are 0.02–1.5%" and also classified PAC complications in three main categories:

1. PAC complications due to complications of CVC, i.e., "arterial puncture, postoperative neuropathy (pain and sensation deficit), air embolism (air in blood vessels), and pneumothorax (air outside the lungs), reported in less than 3.6 %."
2. The complications mainly related to the mechanical effects of the catheter itself, i.e., "severe dysrhythmias, right bundle branch block, and complete heart block, seen in 0.3–3.8 %."
3. The complications related to persisting catheter in place, i.e., "rupture of the pulmonary artery and its attributed death, infarction of the pulmonary tissue, catheter-related sepsis, positive catheter tip culture, valvular/endocardial vegetation, thrombophlebitis, mural thrombosis, and thrombosis of the veins, i.e., clots in vein, occurring between 0.03 and 3 %."

Sufficient skill, enough experience, and having a high index of suspicion and vigilance in detection of any complication may help the clinician prevent these potentially deadly complications or diagnose them as early as possible. The following comments should be remembered regarding the complications of PAC:

- Atrial or ventricular arrhythmia, often in the form of ventricular premature contractions, is seen during catheter passage from RV; these arrhythmias are usually benign; head-up and right lateral position might decrease the incidence of this complication.

- PAC could lead to right bundle branch block (RBBB); so in patients with underlying left bundle branch block (LBBB), complete atrioventricular block (AV block) would be possible; though not frequent, it could be lethal.
- Pulmonary artery injuries might cause lethal pulmonary artery perforation or rupture mandating emergent surgery or stenting of the rupture; late pulmonary artery false aneurysm is also reported.
- Pulmonary infarction due to catheter dislodgement in segmental or bronchial pulmonary arterial branches is another potential complication.
- Right ventricle rupture, a highly morbid complication needing extreme vigilance for prevention, once occurred, rigorous and prompt surgical treatment in the first minutes is mandatory.
- Endobronchial hemorrhage is a highly morbid complication especially in patients receiving anticoagulants.
- Catheter coiling due to excessive and repetitive back-and-forth movements of the catheter, which might even mandate surgical catheter removal.
- Catheter tip balloon rupture.
- Catheter tip entrapment is RV trabeculae leading to mechanical injury of RV wall, if the balloon is not filled.
- Tricuspid or pulmonary valve mechanical injuries if the catheter is withdrawn without deflation of the catheter tip balloon (Taylor and Tiede 1952; Swan et al. 1970; Swan and Ganz 1974, 1975, 1979; Elliott et al. 1979; Kelly et al. 1981; Sise et al. 1981; Hardy et al. 1983; Mohr et al. 1987; Matthay and Chatterjee 1988; Durbin 1990; Himpe 1990; Ikeda et al. 1991; Urschel and Myerowitz 1993; Westenskow and Silva 1993; Shevde et al. 1994; Zarshenas and Sparschu 1994; Poelaert et al. 1995; Sumita et al. 1995; Connors et al. 1996; Mueller et al. 1998; Rhodes et al. 2002; Cotter et al. 2003; Gibson and Francis 2003; Masugata et al. 2003; Richard et al. 2003; Sandham et al. 2003; Yu et al. 2003; Domino et al. 2004; Monnet et al. 2004; Uzun et al. 2004; Binanay et al. 2005; Harvey et al. 2005; Oransky et al. 2005; Shah et al. 2005; Stevens et al. 2005; Summerhill and Baram 2005; Swan 2005; Harvey et al. 2006; Heresi et al. 2006; Lavine and Lavine 2006; Vender 2006; Wheeler et al. 2006; Williams and Frenneaux 2006; Akima et al. 2007; Bussieres 2007; Leibowitz and Oropello 2007; Mielniczuk et al. 2007; Pirracchio et al. 2007; Frazier and Skinner 2008; Langesaeter et al. 2008; Mathews and Singh 2008; Vincent et al. 2008; de Waal et al. 2009; Katsikis et al. 2009; Ramaswamykanive and Bihari 2009; Renner et al. 2009; Schramm et al. 2009; Hida et al. 2010; Nossaman et al. 2010; Reuter et al. 2010; Takada et al. 2010; Zuffi et al. 2010; Alhashemi et al. 2011; Barmparas et al. 2011; Gurgel and do Nascimento 2011; Hessel and Apostolidou 2011; Richard et al. 2011; Schwann et al. 2011; Trof et al. 2011; Trzebicki et al. 2011; Booth et al. 2012; Godoy et al. 2012; Gologorsky et al. 2012; Pipanmekaporn et al. 2012; Truijen et al. 2012; Kalra et al. 2013; Rajaram et al. 2013; Satler 2013).

## 4.5 Cardiac Output Monitoring

Cardiac output monitoring is performed using a number of invasive and noninvasive approaches. Also, it is a very determining issue in cardiovascular monitoring, especially in critical patients including cardiac surgery patients. A brief discussion of the

currently used methods for cardiac output assessment is presented here, though the interested reader could find detailed discussion in the related textbooks. Also, a great number of clinical and laboratory studies have been performed on this topic due to the importance of this variable especially in critically ill patients to define the benefits and weaknesses of each method.

### 4.5.1 Fick Principle

Fick principle was described in 1870 by the German physiologist and physicist Adolf Eugen Fick, who developed this principle to be used for a number of applications including direct cardiac output measurement. The Fick principle assumes that the amount of oxygen taken up by the lungs (i.e., $O_2$ consumption) is taken up from the air, entirely transferred through the lungs and transported in blood flow (circulation). Based on this fact, we use the Fick principle and calculate how much oxygen is taken from the air and is then transported to the tissues by pulmonary circulation.

So, if we calculate the amount of oxygen transferred from the air to the lungs, we could assume it as the amount of oxygen transported from the lungs to the tissues; hence, we could consider "consumed oxygen" instead of "transported oxygen" to calculate "cardiac output." In other words, we can simply express Fick principle as follows:

$$O_2 \text{ uptake}\left(\text{by the lungs}\right) = O_2 \text{ consumption}\left(\text{by total body}\right) = VO_2$$

We could calculate arterial oxygen content ($CaO_2$) and venous oxygen content ($CvO_2$) and then subtract them ($CaO_2 - CvO_2$); finally, we multiply the result in cardiac output (CO); so we will have the Fick formula:

$$VO_2 = CO \times \left(CaO_2 - CvO_2\right).$$

And then we resolve the above formula for cardiac output:

$$CO = VO_2 / \left(CaO_2 - CvO_2\right).$$

Although the Fick principle seems basically simple and is still considered as the most accurate method of cardiac output measurement, in clinical practice, its calculation is very difficult and mandates sophisticated technical procedures, being used more commonly in experimental labs than the clinical setting.

Other less sophisticated and more practical methods have been developed based on Fick principle with some modifications in practice. One of these is the "partial carbon dioxide rebreathing" method which uses carbon dioxide instead of $O_2$ for calculations discussed here.

### 4.5.2 Indicator Dilution Techniques

Today, mainly two indicators are used for calculation of cardiac output in the clinical setting and include *lithium* and *cold water*; these methods use an indicator

**Table 4.2** Commonly used cardiac output monitoring devices

| |
|---|
| Techniques using cold water and its temperature change including:<br>Thermodilution using PAC (PAC-TD) with application of a bolus of cold water and measurement of cardiac output based on this injection<br>Continuous thermodilution using PAC (continuous thermodilution with PAC)<br>Transpulmonary bolus thermodilution (often using a CVC and an arterial catheter like femoral or radial arterial catheters) |
| Transpulmonary lithium indicator dilution |
| Partial carbon dioxide ($CO_2$) rebreathing |
| Esophageal Doppler |
| Pulse contour analysis |
| Bioimpedance and bioreactance |
| Ultrasonic cardiac output monitor |

(thermal or chemical) and calculate its passage time and/or passage dilution model after passing downstream the blood flow circulation; based on the technical method of measurement, the cardiac output measurement techniques are classified as follows (Table 4.2):

#### 4.5.2.1 Techniques Using Cold Water and Its Temperature Change

- *Thermodilution using PAC (PAC-TD)* with application of a bolus of cold water and measurement of cardiac output based on this injection. Thermodilution method is usually done using a pulmonary artery catheter (i.e., PAC-TD) and is considered the gold standard for cardiac output monitoring, though the technique needs many points to be considered and is also invasive and relatively expensive and needs experience and enough training. Although PAC-TD method has been defined as the superior method for cardiac output assessment, there are studies considering its accuracy and invasiveness, so suggesting other methods including less invasive thermodilution methods, pulse contour cardiac output assessment methods, respiratory-based estimates, esophageal Doppler monitoring, and flow probe and transcutaneous Doppler for cardiac output monitoring.
- *Continuous thermodilution using PAC* (continuous thermodilution with PAC)
- *Transpulmonary Thermodilution*: Conventional thermodilution method mandates using a PAC with a thermistor in its tip; this system has a thermistor inside the CVC and calculates the variables using the curve of arterial line (usually from femoral, axillary, or brachial arteries); so, in this system, a bolus dose of cold water is injected in right atrium, and at the same time, the temperature fluctuations are recorded in the next seconds, measured using a central arterial line. CO is calculated based on these temperature changes to decrease measurements errors, usually three different measurements are done and the average CO is calculated. Also, the measurements are done in 3–10 min to have more accurate data. The "PiCCO" system (Pulsion Medical Systems, Munich, Germany) uses this technology and estimates these variables: "CO, cardiac output"; "ITBV, intra-thoracic blood volume"; "GEDV, global end-diastolic volume"; and "EVLW, extravascular lung water"; the use of transpulmonary thermodilution at bedside is relatively easy; GEDV is a good index of ventricular preload.

#### 4.5.2.2 Transpulmonary Lithium Indicator Dilution

This invasive method involves using a bolus dose of isotonic lithium chloride (150–300 mmol LiCl; 1–2 mL) which is injected inside the right atrium (often through a central venous catheter); then, the arterial concentration of lithium is calculated by the machine. The lithium dose does not have any clinical significant effect.

This method is usually not used in the following:

- Patients below 40 kg (88 lb).
- Patients in the first trimester of pregnancy.
- Patients receiving high doses of neuromuscular blocking agents since they may interfere with the sensor readings of lithium.
- Caution should be taken in patients under lithium therapy.

After injection of lithium dose, the concentration-time curve of lithium dilution in the arterial system is drawn by machine, and cardiac output (CO) is often calculated through a central arterial line and the "Stewart-Hamilton" equation is used to calculate cardiac output:

$$\mathrm{CO} = \mathrm{LiD} \times 60 / \left[ \mathrm{AUC} \times \left(1 - \mathrm{PCV}\right) \right]$$

in which:

CO = calculated cardiac output

LiD = lithium dose (mmol) = the amount of injected lithium

AUC = area under curve for concentration-time curve of lithium

PCV = packed cell volume based on hemoglobin concentration calculated as g/dl; this correction is due to the lack of lithium entry into red blood cells (RBCs) and white blood cells (WBCs) in its first pass. This method is used in LiDCO system, LiDCO Group plc, London, UK

### 4.5.3 Partial Carbon Dioxide ($CO_2$) Rebreathing

This method is based on Fick principle; however, instead of calculating oxygen transport, it calculates cardiac output based on $CO_2$ transport from tissues to the lungs and its excretion, which is done based on 3 min rebreathing intervals. In fact, $CO_2$ is the marker of choice in this method for calculating cardiac output. For this purpose, a disposable rebreathing loop is added to the mechanical ventilation circuit. This rebreathing loop contains three items:

- Air flow measurement device
- Pulse oximeter
- $CO_2$ infrared light absorption sensor

For this method, we could consider the following modification as "Fick formula for calculation of cardiac output using $CO_2$":

$$\mathrm{CO} = \Delta \mathrm{VCO}_2 / \left( \mathrm{S} \times \Delta \mathrm{etCO}_2 \right)$$

in which:
CO = cardiac output
$\Delta VCO_2$ = changes in $CO_2$ elimination
S = correction index
$\Delta etCO_2$ = changes in partial pressure of end-tidal $CO_2$ between normal breathing and $CO_2$ rebreathing

The rebreathing cycles are used in 3-min intervals to calculate the amount of change in $CO_2$ during rebreathing episodes.

The noninvasive cardiac output (NICO) monitor (Novametrix Medical Systems Inc., Wallingford, CT, USA) uses $CO_2$ rebreathing technology. The method is applicable to adults above 40 kg. The accuracy of this method is much more acceptable in ICU and operating room in clinically stable patients under full mechanical ventilatory support. But in patients with intrapulmonary shunt, the accuracy of this method is decreased. So the technique mandates full control of respiration through use of full mechanical ventilatory support, and also, there should not be any intrapulmonary shunts.

### 4.5.4 Esophageal Doppler

The application of this method was first introduced in the 1970s and then developed in the 1980s; it is usually administered through the "esophageal Doppler monitoring" or simply "EDM" which uses ultrasound for calculation of cardiac output. It is noninvasive and uses the pulsatile flow through the ascending thoracic aorta for calculation of cardiac output. The ultrasound transducer is attached to the tip of a flexible probe; this probe is introduced into the esophagus through the mouth; nasal passage while not routine is possible. However, the patient should be anesthetized since its passage is not possible, while the patient is awake. Also, in patients with esophageal disease, EDM probe should not be used unless extreme caution is applied to prevent any possible injury; even the least resistance should prevent further advancement. Usually a depth of 30–35 cm inside the esophagus is acceptable (mid-thoracic level). Then transducer often uses pulsed wave Doppler (5 MHz) or continuous wave Doppler (4 MHz); less frequently, M-mode Doppler is used by some manufacturers. EDM calculates the cross-sectional area of aorta based on age, sex, weight, and height according to the machine software. EDM needs some training before use; about 10–12 probe placements are often enough; however, maintenance of the probe in its place needs care in order to prevent "probe displacement" out of the esophagus (e.g., during routine ICU nursing care).

The blood passing through the lumen of aorta in each heartbeat is about 70 % of stroke volume, while 30 % of the stroke volume goes to head and neck arteries and the coronary vascular bed; so the calculated cardiac output by the machine should be multiplied by a constant of 1.4 to compensate for cerebral and coronary perfusion; some machines automatically compensate this ratio and demonstrate the final figure.

The results of CO assessments with EDM are more useful when the trend of change is considered rather than the punctual readings of CO.

There are a number of limitations for EDM use including:

- In hypovolemic states, cerebral and coronary blood flow is increased compared to total body flow, so the calculated cardiac output may be underestimated.
- The situation is conversed in patients with lower limb vasodilation (like postcardiopulmonary bypass interval or pregnancy).
- Also, surgeries with aortic cross-clamping or having intra-aortic balloon pump (IABP) disturb the turbulent flow of the thoracic aorta, so the calculations of EDM are not correct.
- Patients with thoracic aortic disease and those with underlying aortic stenosis (AS) or aortic insufficiency (AI).
- Personal training and abilities in correct positioning of the probe could affect the results of CO assessments, while inappropriate positioning might give incorrect readings.

*Finally*, EDM is noninvasive and needs minimal training; though it has a few limitations, its efficacy is comparable with PAC-TD technique, both for cardiac output monitoring and for assessment of fluid response in critical patients.

### 4.5.5 Pulse Contour Analysis

Maybe the simplest method for calculation of cardiac output is "pulse contour analysis or PCA." The arterial wave contour is a function of the "interaction between each individual stroke volume and the physical and anatomical characteristics of the arterial tree." There are a number of devices using this method for cardiac output assessment; in all of them, the main basic principle for these methods is analysis of "the systolic portion of curve in the arterial line curve." This analysis is based on "Windkessel model" described first by Otto Frank in 1899 which describes the interaction between the stroke volume and the compliance of the aorta and large elastic arteries known as "Windkessel vessels." Windkessel is a German name which means "air chamber" and uses the following formula for estimation of cardiac output:

$$\mathrm{CO} = \left(\mathrm{SAUC} / \text{aortic impedance}\right) \times \mathrm{HR}$$

in which:

CO: cardiac output

SAUC: systolic portion of area under curve of arterial line

HR: heart rate

Currently the devices which use this method for CO are:

- "PiCCO" system (Pulsion Medical Systems, Munich, Germany) which uses indicator dilution technique and calculates cardiac output based on the Wesseling algorithm by pulse contour analysis; this system uses patient data like age, sex, weight, and height and needs frequent calibrations intervals more than 1 h. The calculation of cardiac output using "pulse contour analysis" in this system is calibrated using the *transpulmonary thermodilution* method.
- "LiDCO" system (LiDCO Group plc, London, UK) and its versions (LiDCOplus, LiDCOrapid) transform pressure wave to volume wave using its algorithm; like

PiCCO system, this device uses indicator dilution technique and calculates cardiac output based on the Wesseling algorithm by pulse contour analysis and so calculates cardiac output based on pulse contour and calibrates the results after comparing them with the measured amounts of cardiac output calculated in each beat by *lithium dilution* methods; this calibration should be done each 8 h

- The FloTrac/Vigileo (Edwards Lifesciences Irvine, CA, USA) was first introduced in 2005 and calculates cardiac output based on the following equation:

$$CO = HR \times SV$$

in which:

CO: cardiac output
HR: heart rate
SV: stroke volume

Stroke volume is estimated based on the contour of the arterial pulse. So this method calculates CO based on heart rate and stroke volume and estimates stroke volume from the "arterial pulse curve," so it calculates the blood flow based on "arterial curve signal and arterial compliance"; also, age, gender, and body surface area are considered in the final machine calculations; however, this system does not need external calibration. This system *does not need* calibration like the other two systems. However, the accuracy of the measurements would be damaged by the following items:

1. Artifacts of the arterial wave
2. Problems in the catheter of arterial line
3. Patients with aortic insufficiency
4. Intense peripheral vasoconstriction
5. Arrhythmias causing irregular pulse
6. Severe left ventricular dysfunction

- Pressure recording analytical method "PRAM" used in "MostCare" system (Vytech Health, Padova, Italy) is not "calibration dependent" like the other methods and calculates cardiac output based on the curve of arterial line pressure.

In all cardiac output assessment methods based on "arterial pressure contour" analysis, the following entities could disturb the results of assessments:

- Aortic insufficiency or aortic regurgitation
- Underdamping or overdamping of the arterial line curve
- Patients with considerable arrhythmia which could disturb the readings
- Vascular leakage syndromes leading to decreased arterial wall compliance

### 4.5.6 Bioimpedance and Bioreactance

These two approaches are "nearly totally" noninvasive methods using physical effects of blood flow on transthoracic variables; for this purpose, they use chest leads attached to the chest wall for assessment of the physical effects of blood flow inside the thorax,

including the changes in impedance of chest (i.e., bioimpedance system) or "blood flow-dependent changes in electrical currents across the thorax" which could be named as the changes in electrical frequencies of the chest (i.e., bioreactance). These systems are noninvasive; however, some believe that their measurements are not yet as accurate as some invasive methods, though their use as devices for "tracking the cardiovascular system responses to treatment in clinical practice" could be much more reliable; also, the noise (especially electrical noise) produced in ICU environment could affect their calculations, and the estimated cardiac output could be flawed.

### 4.5.7 Ultrasonic Cardiac Output Monitor (USCOM; USCOM Ltd., Sydney, Australia)

This system is a completely noninvasive one, which permits serial assessments of cardiac output and is based on "continuous wave Doppler (CWD)" technology, using a Doppler probe to "calculate velocity-time interval." The probe could be placed in one of the two following anatomic positions:

- Suprasternal notch, which measures the blood flow through the aortic outflow tract, hence the transaortic flow
- Left sternal edge, which measures the blood flow through the pulmonary artery outflow tract, hence the transpulmonary flow

This is why appropriate alignment of the probe has an essential role in taking appropriate results; also, this issue mandates time spending for gaining an "appropriate window." Calculation of cardiac output is done by the following equation:

$$CO = CSA \times VTI$$

in which:

CO: cardiac output

CSA: cross-sectional area of the main arterial system which is used for measurement of cardiac output (aorta or pulmonary artery)

VTI: velocity-time integral, which is calculated by the machine

This system may have a useful role in cardiac output estimation based on clinical studies; also, it estimates cardiac output in a real-time model and is also noninvasive; however, the personal training has a main role in the results (Lategola and Rahn 1953; Branthwaite and Bradley 1968; Side and Gosling 1971; Ultman and Bursztein 1981; Singer et al. 1989; Frank 1990; Cohen et al. 1991; Jansen et al. 1996; Lichtwarck-Aschoff et al. 1996; Gan and Arrowsmith 1997; Haryadi et al. 2000; Maxwell et al. 2001; Nilsson et al. 2001; Berton and Cholley 2002; Jonas and Tanser 2002; Murias et al. 2002; Chew and Poelaert 2003; Levy et al. 2004; Moshkovitz et al. 2004; Pearse et al. 2004; Cholley and Payen 2005; Cuschieri et al. 2005; Engoren and Barbee 2005; Ghio 2005; Manecke 2005; Bajorat et al. 2006; Hewitt and Braaf 2006; Ostergaard et al. 2006; Uchino et al. 2006; Fakler et al. 2007; Hofer et al. 2007; Baulig et al. 2008; Compton et al. 2008a, b; Frazier and Skinner 2008; Langesaeter et al. 2008; Mathews and Singh 2008; Missant et al. 2008; Raval et al. 2008; Siu et al. 2008; Benington et al. 2009; Compton and

Schafer 2009; de Waal et al. 2009; Marik et al. 2009; Maurer et al. 2009; Mayer and Suttner 2009; Phillips et al. 2009; Renner et al. 2009; Romagnoli et al. 2009; Bleul et al. 2010; Critchley et al. 2010; Peyton and Chong 2010; Reuter et al. 2010; Takada et al. 2010; Young and Low 2010; Alhashemi et al. 2011; Critchley 2011; Geerts et al. 2011; Jo et al. 2011; Lee et al. 2011; Proulx et al. 2011; Scolletta et al. 2011; Sharma et al. 2011; Vincent et al. 2011; Chong and Peyton 2012; Fagnoul et al. 2012; Jakovljevic et al. 2012; Kiefer et al. 2012; Li 2012; Phillips et al. 2012; Porhomayon et al. 2012; Truijen et al. 2012; Smith and Madigan 2013).

## 4.6 Selection of Cardiac Output Monitoring Modality

Though a detailed list of different monitoring devices is available clinically, none could be nominated as the "best." However, a few criteria could be used to select the appropriate cardiac output monitoring device. Vincent et al. have mentioned a set of ten criteria for appropriate selection of cardiac output monitoring; though this "guideline" is not based on methodologies like meta-analysis and is consensus based, it could be considered as a useful approach for selection of cardiac output monitoring device (Vincent et al. 2011):

1. None of the hemodynamic monitoring devices are able to "improve outcome by itself."
2. "Device availability" and "training" could affect the selection process based on the individual user.
3. None of the monitoring could be "the only best" for all the patients; monitoring each patient should be "tailored" specifically.
4. Integrating different data from different sources could help us improve the quality of data used for monitoring.
5. Mixed venous oxygen saturation ($SvO_2$) is a very useful and decisive indicator; though its measurement is through PAC, using the amount of mixed venous oxygen saturation ($ScvO_2$) from superior vena cava sampling (using a CVC) could be considered as a useful surrogate for $SvO_2$.
6. Though many patients benefit from increased cardiac output, this is not always the rule, since increased cardiac output using any possible treatment could at times be associated with detrimental effects; the same might be true for $SvO_2$ as its increase in critical patients might occur due to maldistribution of perfusion and not necessarily due to improved clinical condition.
7. None of the cardiac output monitoring devices could measure the real values of "CO"; instead, they all estimate cardiac output, though "intermittent thermodilution technique" is usually considered as the "technique of reference" with its own limitations. Maybe using a less invasive monitoring to track "the trend of CO estimations" could be as valuable as directly using PAC-TD method.
8. Ability to respond as fast as possible to pathologic changes is very important; this is why we need "very rapid response" monitoring devices which show the changes as fast as possible to help the clinician and the clinical team respond as

fast as possible; increasing the number of appropriate monitoring may also increase our speed of response.

9. Real-time (beat to beat) CO assessments could guide us in a much better pattern than delayed, intermittent measurements; these real-time results seem superior to methods with delayed measurements in their technique.
10. Although noninvasiveness is a very important issue for selection of monitoring devices, it is not the only determinant factor, as invasive blood pressure monitoring could not be replaced in some patients with indirect blood pressure monitoring (measuring with blood pressure cuff) especially in cardiac surgery patients; also, noninvasive cardiac output monitoring systems using "pulse contour analysis, esophageal Doppler, $CO_2$ rebreathing, and transthoracic bioimpedance" are not as accurate of more invasive methods; this is why we should believe in "noninvasiveness" as one of the many factors and not "the only determining factor" for selection of monitoring.

## 4.7 Normal Values for Hemodynamic Parameters

There are a number of different studies which have assessed and calculated the normal variables of hemodynamic parameters. The following two tables demonstrate a number of the most important hemodynamic variables (Tables 4.3 and 4.4) (Taylor and Tiede 1952; Mohr et al. 1987; Himpe 1990; Cotter et al. 2003; Gibson and Francis 2003; Masugata et al. 2003; Uzun et al. 2004; Lavine and Lavine 2006; Williams and Frenneaux 2006; Akima et al. 2007; Mielniczuk et al. 2007; Pirracchio et al. 2007; Renner et al. 2009; Trof et al. 2011).

**Table 4.3** Normal range for the main pressures in the cardiovascular system

| | Variable | Normal range |
|---|---|---|
| 1 | Heart rate (HR) | 60–100 |
| 2 | Central venous pressure (CVP) | 3–8 mm Hg |
| 3 | Right atrial pressure (RAP) | 2–10 mm Hg |
| 4 | Right ventricular pressure (RVP) | Systolic: 15–30 mm Hg<br>Diastolic: 3–8 mm Hg |
| 5 | Pulmonary artery pressure (PAP) | Systolic: 15–30 mm Hg<br>Diastolic: 6–12 mm Hg |
| 6 | Pulmonary artery wedge pressure (PAWP); pulmonary capillary wedge pressure (PCWP) | 6–12 mm Hg |
| 7 | Left atrial pressure (LAP) | 4–12 mm Hg |
| 8 | Left ventricular end systolic pressure (LVESP) | 90–140 mm Hg |
| 9 | Left ventricular end-diastolic pressure (LVEDP) | 4–12 mm Hg |
| 10 | Aortic pressure | Systolic:<br>90–140 mm Hg<br>Diastolic:<br>60–90 mm Hg |

**Table 4.4** Calculation formulas and normal range of main physiologic variables in the cardiovascular system

| | Variable | Formula | Normal range |
|---|---|---|---|
| 1 | Cardiac output (CO) | CO = SV × HR | 4–6 L/min |
| 2 | Cardiac index (CI) | CI = CO/BSA | 3–5 L/min/$m^2$ |
| 3 | Stroke volume (SV) | SV = (CO × 1,000)/HR | 50–100 mL |
| 4 | Mean arterial pressure (MAP) | MAP = (2DBP + SBP)/3 | 70–100 mm Hg |
| 5 | Systemic vascular resistance (SVR) | SVR = [(MAP − CVP) × 80]/CO | 800–1,200 dyn/s/$cm^5$ |
| 6 | Pulmonary vascular resistance (PVR) | PVR = [(PAP − PAWP) × 80]/CO | 35–250 dyn/s/$cm^5$ |

*HR* heart rate (beats/min), *BSA* body surface area ($m^2$), *DBP* diastolic blood pressure, *SBP* systolic blood pressure

## 4.8 Transesophageal Echocardiography (TEE)

TEE is a noninvasive real-time monitoring used extensively especially for cardiac patients during perioperative period; its application has increased very wide acceptance with the increasing experience and familiarity of anesthesiologists and intensivists in perioperative fields; however, its description needs a separate discussion beyond the scope of this book, and the readers are suggested to refer to perioperative TEE books.

## 4.9 Electrocardiography (EEG)

This monitoring is described in more detail in a separate chapter of the book. Please refer to the related chapter.

## 4.10 Near-Infrared Spectroscopy and Cerebral Oximetry

The full description of this monitoring device is presented in the chapter titled "Central Nervous System Monitoring." Please refer to the related chapter.

## References

(1995) [French Society of Anesthesia and Intensive Care. Arterial catheterization and invasive measurement of blood pressure in anesthesia and intensive care in adults]. Ann Fr Anesth Reanim 14:444–453

(2003) Practice guidelines for pulmonary artery catheterization: an updated report by the American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization. Anesthesiology 99:988–1014

Agarwal R, Light RP (2009) Chronobiology of arterial hypertension in hemodialysis patients: implications for home blood pressure monitoring. Am J Kidney Dis 54:693–701

Akima T, Takase B, Kosuda S, Ohsuzu F, Kawai T, Ishihara M, Akira K (2007) Systemic peripheral vascular resistance as a determinant of functional cardiac reserve in response to exercise in patients with heart disease. Angiology 58:463–471

Alford JW, Palumbo MA, Barnum MJ (2002) Compartment syndrome of the arm: a complication of noninvasive blood pressure monitoring during thrombolytic therapy for myocardial infarction. J Clin Monit Comput 17:163–166

Alhashemi JA, Cecconi M, Hofer CK (2011) Cardiac output monitoring: an integrative perspective. Crit Care 15:214

Amoore JN (2012) Oscillometric sphygmomanometers: a critical appraisal of current technology. Blood Press Monit 17:80–88

Amoore JN, Guehenec M, Scordecchia R, Scott DH (2010) Auditing the technology used to measure blood pressure. J Med Eng Technol 34:209–216

Anderson JS (1997) Arterial cannulation: how to do it. Br J Hosp Med 57:497–499

Andreadis EA, Angelopoulos ET, Agaliotis GD, Tsakanikas AP, Mousoulis GP (2011) Why use automated office blood pressure measurements in clinical practice? High Blood Press Cardiovasc Prev 18:89–91

Arai T, Yamashita M (2005) Central venous catheterization in infants and children–small caliber audio-Doppler probe versus ultrasound scanner. Paediatr Anaesth 15:858–861

Ash SR (2007) Fluid mechanics and clinical success of central venous catheters for dialysis–answers to simple but persisting problems. Semin Dial 20:237–256

Asheim P, Mostad U, Aadahl P (2002) Ultrasound-guided central venous cannulation in infants and children. Acta Anaesthesiol Scand 46:390–392

Augusto JF, Teboul JL, Radermacher P, Asfar P (2011) Interpretation of blood pressure signal: physiological bases, clinical relevance, and objectives during shock states. Intensive Care Med 37:411–419

Bailey RH, Bauer JH (1993) A review of common errors in the indirect measurement of blood pressure. Sphygmomanometry. Arch Intern Med 153:2741–2748

Bajorat J, Hofmockel R, Vagts DA, Janda M, Pohl B, Beck C, Noeldge-Schomburg G (2006) Comparison of invasive and less-invasive techniques of cardiac output measurement under different haemodynamic conditions in a pig model. Eur J Anaesthesiol 23:23–30

Barmparas G, Inaba K, Georgiou C, Hadjizacharia P, Chan LS, Demetriades D, Friese R, Rhee P (2011) Swan-Ganz catheter use in trauma patients can be reduced without negatively affecting outcomes. World J Surg 35:1809–1817

Baulig W, Dullenkopf A, Kobler A, Baulig B, Roth HR, Schmid ER (2008) Accuracy of continuous central venous oxygen saturation monitoring in patients undergoing cardiac surgery. J Clin Monit Comput 22:183–188

Benington S, Ferris P, Nirmalan M (2009) Emerging trends in minimally invasive haemodynamic monitoring and optimization of fluid therapy. Eur J Anaesthesiol 26:893–905

Berghella S, Tempo B, Bernocco A, Neri G, Fiorucci G (1979) Indications, methods and results of bacteriological examinations of central venous catheters in patients admitted to a polyvalent resuscitation center. Minerva Anestesiol 45:379–386

Berton C, Cholley B (2002) Equipment review: new techniques for cardiac output measurement–oesophageal Doppler, Fick principle using carbon dioxide, and pulse contour analysis. Crit Care 6:216–221

Binanay C, Califf RM, Hasselblad V, O'Connor CM, Shah MR, Sopko G, Stevenson LW, Francis GS, Leier CV, Miller LW (2005) Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. JAMA 294:1625–1633

Bleul U, Bircher B, Jud RS, Kutter AP (2010) Respiratory and cardiovascular effects of doxapram and theophylline for the treatment of asphyxia in neonatal calves. Theriogenology 73: 612–619

Block FE Jr, Fletcher MV, Morris TJ, Dzwonczyk R (1991) A clinical evaluation of rapid automatic noninvasive blood pressure determination with the Ohmeda 2120 "return-to-flow" method. J Clin Monit 7:241–244

Booth KL, Mercer-Smith G, McConkey C, Parissis H (2012) Catheter-induced pulmonary artery rupture: haemodynamic compromise necessitates surgical repair. Interact Cardiovasc Thorac Surg 15:531–533

Botha R, van Schoor AN, Boon JM, Becker JH, Meiring JH (2006) Anatomical considerations of the anterior approach for central venous catheter placement. Clin Anat 19:101–105

Boyce JM (2012) Prevention of central line-associated bloodstream infections in hemodialysis patients. Infect Control Hosp Epidemiol 33:936–944
Branthwaite MA, Bradley RD (1968) Measurement of cardiac output by thermal dilution in man. J Appl Physiol 24:434–438
Brusasco C, Corradi F, Zattoni PL, Launo C, Leykin Y, Palermo S (2009) Ultrasound-guided central venous cannulation in bariatric patients. Obes Surg 19:1365–1370
Brzezinski M, Luisetti T, London MJ (2009) Radial artery cannulation: a comprehensive review of recent anatomic and physiologic investigations. Anesth Analg 109:1763–1781
Bur A, Hirschl MM, Herkner H, Oschatz E, Kofler J, Woisetschlager C, Laggner AN (2000) Accuracy of oscillometric blood pressure measurement according to the relation between cuff size and upper-arm circumference in critically ill patients. Crit Care Med 28:371–376
Bussieres JS (2007) Iatrogenic pulmonary artery rupture. Curr Opin Anaesthesiol 20:48–52
Calabria M, Zamboli P, D'Amelio A, Granata A, Di Lullo L, Floccari F, Logias F, Fiorini F (2012) Use of ECG-EC in the positioning of central venous catheters. G Ital Nefrol 29:49–57
Campbell NR, McKay DW, Chockalingam A, Fodor JG (1994) Errors in assessment of blood pressure: sphygmomanometers and blood pressure cuffs. Can J Public Health 85(Suppl 2):S22–S25
Celoria G, Dawson JA, Teres D (1987) Compartment syndrome in a patient monitored with an automated blood pressure cuff. J Clin Monit 3:139–141
Chatterjee A, DePriest K, Blair R, Bowton D, Chin R (2010) Results of a survey of blood pressure monitoring by intensivists in critically ill patients: a preliminary study. Crit Care Med 38:2335–2338
Chee BC, Baldwin IC, Shahwan-Akl L, Fealy NG, Heland MJ, Rogan JJ (2011) Evaluation of a radial artery cannulation training program for intensive care nurses: a descriptive, explorative study. Aust Crit Care 24:117–125
Chen CK, Tan PP, Lee HC (2007) Sternocleoidomastoid muscle length predicts depth of central venous catheter insertion. Acta Anaesthesiol Taiwan 45:211–215
Cheng HM, Sung SH, Shih YT, Chuang SY, Yu WC, Chen CH (2012) Measurement of central aortic pulse pressure: noninvasive brachial cuff-based estimation by a transfer function vs. a novel pulse wave analysis method. Am J Hypertens 25:1162–1169
Chew MS, Poelaert J (2003) Accuracy and repeatability of pediatric cardiac output measurement using Doppler: 20-year review of the literature. Intensive Care Med 29:1889–1894
Chio SS, Urbina EM, Lapointe J, Tsai J, Berenson GS (2011) Korotkoff sound versus oscillometric cuff sphygmomanometers: comparison between auscultatory and DynaPulse blood pressure measurements. J Am Soc Hypertens 5:12–20
Cholley BP, Payen D (2005) Noninvasive techniques for measurements of cardiac output. Curr Opin Crit Care 11:424–429
Chong SW, Peyton PJ (2012) A meta-analysis of the accuracy and precision of the ultrasonic cardiac output monitor (USCOM). Anaesthesia 67:1266–1271
Chopra V, Anand S, Krein SL, Chenoweth C, Saint S (2012) Bloodstream infection, venous thrombosis, and peripherally inserted central catheters: reappraising the evidence. Am J Med 125:733–741
Clark VL, Kruse JA (1992) Arterial catheterization. Crit Care Clin 8:687–697
Cockings JG, Webb RK, Klepper ID, Currie M, Morgan C (1993). The Australian Incident Monitoring Study. Blood pressure monitoring–applications and limitations: an analysis of 2000 incident reports. Anaesth Intensive Care 21:565–569
Cohen IL, Perkins RJ, Bilen Z, Lumb PD (1991) Continuous hemodynamic monitoring: an integrated invasive-noninvasive approach using the Fick principle. Appl Cardiopulm Pathophysiol 3:351–359
Compton F, Schafer JH (2009) Noninvasive cardiac output determination: broadening the applicability of hemodynamic monitoring. Semin Cardiothorac Vasc Anesth 13:44–55
Compton F, Wittrock M, Schaefer JH, Zidek W, Tepel M, Scholze A (2008a) Noninvasive cardiac output determination using applanation tonometry-derived radial artery pulse contour analysis in critically ill patients. Anesth Analg 106:171–174, table of contents

Compton FD, Zukunft B, Hoffmann C, Zidek W, Schaefer JH (2008b) Performance of a minimally invasive uncalibrated cardiac output monitoring system (Flotrac/Vigileo) in haemodynamically unstable patients. Br J Anaesth 100:451–456

Connors AF Jr, Speroff T, Dawson NV, Thomas C, Harrell FE Jr, Wagner D, Desbiens N, Goldman L, Wu AW, Califf RM, Fulkerson WJ Jr, Vidaillet H, Broste S, Bellamy P, Lynn J, Knaus WA (1996) The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. JAMA 276:889–897

Cotter G, Williams SG, Vered Z, Tan LB (2003) Role of cardiac power in heart failure. Curr Opin Cardiol 18:215–222

Cousins TR, O'Donnell JM (2004) Arterial cannulation: a critical review. AANA J 72:267–271

Critchley LA (2011) Validation of the MostCare pulse contour cardiac output monitor: beyond the Bland and Altman Plot. Anesth Analg 113:1292–1294

Critchley LA, Lee A, Ho AM (2010) A critical review of the ability of continuous cardiac output monitors to measure trends in cardiac output. Anesth Analg 111:1180–1192

Cuschieri J, Rivers EP, Donnino MW, Katilius M, Jacobsen G, Nguyen HB, Pamukov N, Horst HM (2005) Central venous-arterial carbon dioxide difference as an indicator of cardiac index. Intensive Care Med 31:818–822

Daily PO, Griepp RB, Shumway NE (1970) Percutaneous internal jugular vein cannulation. Arch Surg 101:534–536

de Waal EE, Wappler F, Buhre WF (2009) Cardiac output monitoring. Curr Opin Anaesthesiol 22:71–77

Di Iorio BR, Mondillo F, Bortone S, Nargi P, Capozzi M, Spagnuolo T, Cucciniello E, Bellizzi V (2006) Fourteen years of hemodialysis with a central venous catheter: mechanical long-term complications. J Vasc Access 7:60–65

Domino KB, Bowdle TA, Posner KL, Spitellie PH, Lee LA, Cheney FW (2004) Injuries and liability related to central vascular catheters: a closed claims analysis. Anesthesiology 100:1411–1418

Dorlas JC, Nijboer JA, Butijn WT, van der Hoeven GM, Settels JJ, Wesseling KH (1985) Effects of peripheral vasoconstriction on the blood pressure in the finger, measured continuously by a new noninvasive method (the Finapres). Anesthesiology 62:342–345

Durbin CG Jr (1990) The range of pulmonary artery catheter balloon inflation pressures. J Cardiothorac Anesth 4:39–42

Eckert S, Gleichmann S, Gleichmann U (1996) Automated blood pressure measurement in special situations: patients with chronic atrial fibrillation or chronic aortic regurgitation. Z Kardiol 85(Suppl 3):92–98

Elliott CG, Zimmerman GA, Clemmer TP (1979) Complications of pulmonary artery catheterization in the care of critically ill patients. A prospective study. Chest 76:647–652

English IC, Frew RM, Pigott JF, Zaki M (1995) Percutaneous catheterisation of the internal jugular vein. 1969. Anaesthesia 50:1071–1076; discussion 1070

Engoren M, Barbee D (2005) Comparison of cardiac output determined by bioimpedance, thermodilution, and the Fick method. Am J Crit Care 14:40–45

Fagnoul D, Vincent JL, Backer DD (2012) Cardiac output measurements using the bioreactance technique in critically ill patients. Crit Care 16:460

Fakler U, Pauli C, Balling G, Lorenz HP, Eicken A, Hennig M, Hess J (2007) Cardiac index monitoring by pulse contour analysis and thermodilution after pediatric cardiac surgery. J Thorac Cardiovasc Surg 133:224–228

Ferguson M, Max MH, Marshall W (1988) Emergency department infraclavicular subclavian vein catheterization in patients with multiple injuries and burns. South Med J 81:433–435

Frank O (1990) The basic shape of the arterial pulse. First treatise: mathematical analysis. 1899. J Mol Cell Cardiol 22:255–277

Franklin CM (1995a) The technique of radial artery cannulation. Tips for maximizing results while minimizing the risk of complications. J Crit Illn 10:424–432

Franklin CM (1995b) The technique of dorsalis pedis cannulation. An overlooked option when the radial artery cannot be used. J Crit Illn 10:493–498

Frazier SK, Skinner GJ (2008) Pulmonary artery catheters: state of the controversy. J Cardiovasc Nurs 23:113–121; quiz 122–113

Furuya EY, Dick A, Perencevich EN, Pogorzelska M, Goldmann D, Stone PW (2011) Central line bundle implementation in US intensive care units and impact on bloodstream infections. PLoS One 6:e15452

Gan TJ, Arrowsmith JE (1997) The oesophageal Doppler monitor. BMJ 315:893–894

Ge X, Cavallazzi R, Li C, Pan SM, Wang YW, Wang FL (2012) Central venous access sites for the prevention of venous thrombosis, stenosis and infection. Cochrane Database Syst Rev 3:CD004084

Geerts BF, Aarts LP, Jansen JR (2011) Methods in pharmacology: measurement of cardiac output. Br J Clin Pharmacol 71:316–330

Ghio S (2005) Pulmonary hypertension in advanced heart failure. Herz 30:311–317

Gibson F, Bodenham A (2013) Misplaced central venous catheters: applied anatomy and practical management. Br J Anaesth 110:333–346

Gibson DG, Francis DP (2003) Clinical assessment of left ventricular diastolic function. Heart 89:231–238

Godoy MC, Leitman BS, de Groot PM, Vlahos I, Naidich DP (2012) Chest radiography in the ICU: part 2, evaluation of cardiovascular lines and other devices. AJR Am J Roentgenol 198:572–581

Gologorsky E, Gologorsky A, Barron ME (2012) Pulmonary artery catheter in cardiac surgery revisited. Anesth Analg 114:1368; author reply 1369

Gorback MS, Quill TJ, Lavine ML (1991) The relative accuracies of two automated noninvasive arterial pressure measurement devices. J Clin Monit 7:13–22

Guleri A, Kumar A, Morgan RJ, Hartley M, Roberts DH (2012) Anaphylaxis to chlorhexidine-coated central venous catheters: a case series and review of the literature. Surg Infect (Larchmt) 13:171–174

Gurgel ST, do Nascimento P Jr (2011) Maintaining tissue perfusion in high-risk surgical patients: a systematic review of randomized clinical trials. Anesth Analg 112:1384–1391

Hardy JF, Morissette M, Taillefer J, Vauclair R (1983) Pathophysiology of rupture of the pulmonary artery by pulmonary artery balloon-tipped catheters. Anesth Analg 62:925–930

Harrigan RA, Chan TC, Moonblatt S, Vilke GM, Ufberg JW (2007) Temporary transvenous pacemaker placement in the emergency department. J Emerg Med 32:105–111

Harvey S, Harrison DA, Singer M, Ashcroft J, Jones CM, Elbourne D, Brampton W, Williams D, Young D, Rowan K (2005) Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. Lancet 366:472–477

Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C, Singer M, Rowan K (2006) An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial. Health Technol Assess 10:iii–iv, ix–xi, 1–133

Haryadi DG, Orr JA, Kuck K, McJames S, Westenskow DR (2000) Partial CO2 rebreathing indirect Fick technique for non-invasive measurement of cardiac output. J Clin Monit Comput 16:361–374

Heiss HW (1992) Werner Forssmann: a German problem with the Nobel Prize. Clin Cardiol 15:547–549

Heresi GA, Arroliga AC, Wiedemann HP, Matthay MA (2006) Pulmonary artery catheter and fluid management in acute lung injury and the acute respiratory distress syndrome. Clin Chest Med 27:627–635; abstract ix

Hermida RC, Ayala DE, Fontao MJ, Mojon A, Fernandez JR (2013) Ambulatory blood pressure monitoring: importance of sampling rate and duration-48 versus 24 hours-on the accurate assessment of cardiovascular risk. Chronobiol Int 30(1–2):55–67

Hessel EA, Apostolidou I (2011) Pulmonary artery catheter for coronary artery bypass graft: does it harm our patients? Primum non nocere. Anesth Analg 113:987–989

Hewitt NA, Braaf SC (2006) The clinical application of pulse contour cardiac output and intrathoracic volume measurements in critically ill patients. Aust Crit Care 19:86–94

Hewlett AL, Rupp ME (2012) New developments in the prevention of intravascular catheter associated infections. Infect Dis Clin North Am 26:1–11

Hida S, Ohashi S, Kinoshita H, Honda T, Yamamoto S, Kazama J, Endoh H (2010) Knotting of two central venous catheters: a rare complication of pulmonary artery catheterization. J Anesth 24:486–487

Himpe D (1990) New approach to systemic vascular resistance calculation and clinical decision making. Acta Anaesthesiol Belg 41:291–295

Hind D, Calvert N, McWilliams R, Davidson A, Paisley S, Beverley C, Thomas S (2003) Ultrasonic locating devices for central venous cannulation: meta-analysis. BMJ 327:361

Hofer CK, Ganter MT, Zollinger A (2007) What technique should I use to measure cardiac output? Curr Opin Crit Care 13:308–317

Holmes SJ, Kiely EM, Spitz L (1989) Vascular access. Prog Pediatr Surg 22:133–139

Holt TR, Withington DE, Mitchell E (2011) Which pressure to believe? A comparison of direct arterial with indirect blood pressure measurement techniques in the pediatric intensive care unit. Pediatr Crit Care Med 12:e391–e394

Horlocker TT, Bishop AT (1995) Compartment syndrome of the forearm and hand after brachial artery cannulation. Anesth Analg 81:1092–1094

Ikeda S, Yagi K, Schweiss JF, Homan SM (1991) In vitro reappraisal of the pulmonary artery catheter balloon volume-pressure relationship: comparison of four different catheters. Can J Anaesth 38:648–653

Ishizuka M, Nagata H, Takagi K, Kubota K (2010) Right internal jugular vein is recommended for central venous catheterization. J Invest Surg 23:110–114

Jakovljevic DG, Moore S, Hallsworth K, Fattakhova G, Thoma C, Trenell MI (2012) Comparison of cardiac output determined by bioimpedance and bioreactance methods at rest and during exercise. J Clin Monit Comput 26:63–68

Jansen JR, Schreuder JJ, Settels JJ, Kornet L, Penn OC, Mulder PG, Versprille A, Wesseling KH (1996) Single injection thermodilution. A flow-corrected method. Anesthesiology 85:481–490

Jo YY, Song JW, Yoo YC, Park JY, Shim JK, Kwak YL (2011) The uncalibrated pulse contour cardiac output during off-pump coronary bypass surgery: performance in patients with a low cardiac output status and a reduced left ventricular function. Korean J Anesthesiol 60:237–243

Jonas MM, Tanser SJ (2002) Lithium dilution measurement of cardiac output and arterial pulse waveform analysis: an indicator dilution calibrated beat-by-beat system for continuous estimation of cardiac output. Curr Opin Crit Care 8:257–261

Kalra A, Heitner S, Topalian S (2013) Iatrogenic pulmonary artery rupture during Swan-Ganz catheter placement–a novel therapeutic approach. Catheter Cardiovasc Interv 81:57–59

Kang M, Ryu HG, Son IS, Bahk JH (2011) Influence of shoulder position on central venous catheter tip location during infraclavicular subclavian approach. Br J Anaesth 106:344–347

Karakitsos D, Labropoulos N, De Groot E, Patrianakos AP, Kouraklis G, Poularas J, Samonis G, Tsoutsos DA, Konstadoulakis MM, Karabinis A (2006) Real-time ultrasound-guided catheterisation of the internal jugular vein: a prospective comparison with the landmark technique in critical care patients. Crit Care 10:R162

Katsikis A, Karavolias G, Voudris V (2009) Transfemoral percutaneous removal of a knotted Swan-Ganz catheter. Catheter Cardiovasc Interv 74:802–804

Keenan SP (2002) Use of ultrasound to place central lines. J Crit Care 17:126–137

Kelly TF Jr, Morris GC Jr, Crawford ES, Espada R, Howell JF (1981) Perforation of the pulmonary artery with Swan-Ganz catheters: diagnosis and surgical management. Ann Surg 193:686–692

Kiefer N, Hofer CK, Marx G, Geisen M, Giraud R, Siegenthaler N, Hoeft A, Bendjelid K, Rex S (2012) Clinical validation of a new thermodilution system for the assessment of cardiac output and volumetric parameters. Crit Care 16:R98

Kim MC, Kim KS, Choi YK, Kim DS, Kwon MI, Sung JK, Moon JY, Kang JM (2011) An estimation of right- and left-sided central venous catheter insertion depth using measurement of surface landmarks along the course of central veins. Anesth Analg 112:1371–1374

Kim WY, Lee CW, Sohn CH, Seo DW, Yoon JC, Koh JW, Kim W, Lim KS, Hong SB, Lim CM, Koh Y (2012) Optimal insertion depth of central venous catheters–is a formula required? A prospective cohort study. Injury 43:38–41

Kipnis E, Ramsingh D, Bhargava M, Dincer E, Cannesson M, Broccard A, Vallet B, Bendjelid K, Thibault R (2012) Monitoring in the intensive care. Crit Care Res Pract 2012:473507

Klepper ID, Webb RK, Van der Walt JH, Ludbrook GL, Cockings J (1993) The Australian Incident Monitoring Study. The stethoscope: applications and limitations–an analysis of 2000 incident reports. Anaesth Intensive Care 21:575–578

Knopp R, Dailey RH (1977) Central venous cannulation and pressure monitoring. JACEP 6:358–366

Kolodzik PW (1989) Guide wire embolization as a potential complication of central line placement. J Emerg Med 7:291

Kuhn CWK (2001) Hemodynamic monitoring. In: Holzheimer RG, Mannick JA (eds) Surgical treatment: evidence-based and problem-oriented. Zuckschwerdt, Munich

Kujur R, Rao MS, Mrinal M (2009) How correct is the correct length for central venous catheter insertion. Indian J Crit Care Med 13:159–162

Kunizawa A, Fujioka M, Mink S, Keller E (2010) Central venous catheter-induced delayed hydrothorax via progressive erosion of central venous wall. Minerva Anestesiol 76:868–871

Lakhal K, Macq C, Ehrmann S, Boulain T, Capdevila X (2012) Noninvasive monitoring of blood pressure in the critically ill: reliability according to the cuff site (arm, thigh, or ankle). Crit Care Med 40:1207–1213

Langesaeter E, Rosseland LA, Stubhaug A (2008) Continuous invasive blood pressure and cardiac output monitoring during cesarean delivery: a randomized, double-blind comparison of low-dose versus high-dose spinal anesthesia with intravenous phenylephrine or placebo infusion. Anesthesiology 109:856–863

Lategola M, Rahn H (1953) A self-guiding catheter for cardiac and pulmonary arterial catheterization and occlusion. Proc Soc Exp Biol Med 84:667–668

Lavine SJ, Lavine JA (2006) The effect of acute hypertension on left ventricular diastolic pressures in a canine model of left ventricular dysfunction with a preserved ejection fraction and elevated left ventricular filling pressures. J Am Soc Echocardiogr 19:1350–1358

Lee AY, Kamphuisen PW (2012) Epidemiology and prevention of catheter-related thrombosis in patients with cancer. J Thromb Haemost 10:1491–1499

Lee AJ, Cohn JH, Ranasinghe JS (2011) Cardiac output assessed by invasive and minimally invasive techniques. Anesthesiol Res Pract 2011:475151

Leibowitz AB, Oropello JM (2007) The pulmonary artery catheter in anesthesia practice in 2007: an historical overview with emphasis on the past 6 years. Semin Cardiothorac Vasc Anesth 11:162–176

Levy RJ, Chiavacci RM, Nicolson SC, Rome JJ, Lin RJ, Helfaer MA, Nadkarni VM (2004) An evaluation of a noninvasive cardiac output measurement using partial carbon dioxide rebreathing in children. Anesth Analg 99:1642–1647, table of contents

Li J (2012) Systemic oxygen transport derived by using continuous measured oxygen consumption after the Norwood procedure-an interim review. Interact Cardiovasc Thorac Surg 15:93–101

Liang SY, Khair H, Durkin MJ, Marschall J (2012) Prevention and management of central line-associated bloodstream infections in hospital practice. Hosp Pract (Minneap) 40:106–118

Lichtwarck-Aschoff M, Beale R, Pfeiffer UJ (1996) Central venous pressure, pulmonary artery occlusion pressure, intrathoracic blood volume, and right ventricular end-diastolic volume as indicators of cardiac preload. J Crit Care 11:180–188

Linnemann B, Lindhoff-Last E (2012) Risk factors, management and primary prevention of thrombotic complications related to the use of central venous catheters. Vasa 41:319–332

Ludbrook GL, Russell WJ, Webb RK, Klepper ID, Currie M (1993) The Australian Incident Monitoring Study. The electrocardiograph: applications and limitations – an analysis of 2000 incident reports. Anaesth Intensive Care 21:558–564

Mabee JR, Bostwick TL (1993) Pathophysiology and mechanisms of compartment syndrome. Orthop Rev 22:175–181

Mambelli E, Mancini E, Santoro A (2007) A continuous and non-invasive arterial pressure monitoring system in dialysis patients. Nephron Clin Pract 107:c170–c176

Mandel MA, Dauchot PJ (1977) Radial artery cannulation in 1,000 patients: precautions and complications. J Hand Surg Am 2:482–485

Manecke GR (2005) Edwards FloTrac sensor and Vigileo monitor: easy, accurate, reliable cardiac output assessment using the arterial pulse wave. Expert Rev Med Devices 2:523–527
Manios E, Vemmos K, Tsivgoulis G, Barlas G, Koroboki E, Spengos K, Zakopoulos N (2007) Comparison of noninvasive oscillometric and intra-arterial blood pressure measurements in hyperacute stroke. Blood Press Monit 12:149–156
Manley L (2000) A look back: the sphygmomanometer. J Emerg Nurs 26:168
Mansfield PF, Hohn DC, Fornage BD, Gregurich MA, Ota DM (1994) Complications and failures of subclavian-vein catheterization. N Engl J Med 331:1735–1738
Marik PE, Cavallazzi R, Vasu T, Hirani A (2009) Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med 37:2642–2647
Marik PE, Flemmer M, Harrison W (2012) The risk of catheter-related bloodstream infection with femoral venous catheters as compared to subclavian and internal jugular venous catheters: a systematic review of the literature and meta-analysis. Crit Care Med 40:2479–2485
Masugata H, Peters B, Lafitte S, Strachan GM, Ohmori K, Mizushige K, Kohno M (2003) Assessment of adenosine-induced coronary steal in the setting of coronary occlusion based on the extent of opacification defects by myocardial contrast echocardiography. Angiology 54:443–448
Mathews L, Singh RK (2008) Cardiac output monitoring. Ann Card Anaesth 11:56–68
Matthay MA, Chatterjee K (1988) Bedside catheterization of the pulmonary artery: risks compared with benefits. Ann Intern Med 109:826–834
Mattoo TK (2002) Arm cuff in the measurement of blood pressure. Am J Hypertens 15:67S–68S
Mauck GW, Smith CR, Geddes LA, Bourland JD (1980) The meaning of the point of maximum oscillations in cuff pressure in the indirect measurement of blood pressure–Part II. J Biomech Eng 102:28–33
Maurer MM, Burkhoff D, Maybaum S, Franco V, Vittorio TJ, Williams P, White L, Kamalakkannan G, Myers J, Mancini DM (2009) A multicenter study of noninvasive cardiac output by bioreactance during symptom-limited exercise. J Card Fail 15:689–699
Maxwell RA, Gibson JB, Slade JB, Fabian TC, Proctor KG (2001) Noninvasive cardiac output by partial CO2 rebreathing after severe chest trauma. J Trauma 51:849–853
Mayer J, Suttner S (2009) Cardiac output derived from arterial pressure waveform. Curr Opin Anaesthesiol 22:804–808
McGee WT, Mailloux PT, Martin RT (2011) Safe placement of central venous catheters: a measured approach. J Intensive Care Med 26:392–396
McGhee BH, Bridges EJ (2002) Monitoring arterial blood pressure: what you may not know. Crit Care Nurse 22:60–64, 66–70, 73 passim
Merrer J, De Jonghe B, Golliot F, Lefrant JY, Raffy B, Barre E, Rigaud JP, Casciani D, Misset B, Bosquet C, Outin H, Brun-Buisson C, Nitenberg G (2001) Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. JAMA 286:700–707
Meyer JA (1990) Werner Forssmann and catheterization of the heart, 1929. Ann Thorac Surg 49:497–499
Mielniczuk LM, Lamas GA, Flaker GC, Mitchell G, Smith SC, Gersh BJ, Solomon SD, Moye LA, Rouleau JL, Rutherford JD, Pfeffer MA (2007) Left ventricular end-diastolic pressure and risk of subsequent heart failure in patients following an acute myocardial infarction. Congest Heart Fail 13:209–214
Miller SE, Maragakis LL (2012) Central line-associated bloodstream infection prevention. Curr Opin Infect Dis 25:412–422
Missant C, Rex S, Wouters PF (2008) Accuracy of cardiac output measurements with pulse contour analysis (PulseCO) and Doppler echocardiography during off-pump coronary artery bypass grafting. Eur J Anaesthesiol 25:243–248
Mohr R, Meir O, Smolinsky A, Goor DA (1987) A method for continuous on-line monitoring of systemic vascular resistance (COMS) after open heart procedures. J Cardiovasc Surg (Torino) 28:558–565

Monnet X, Richard C, Teboul JL (2004) The pulmonary artery catheter in critically ill patients. Does it change outcome? Minerva Anestesiol 70:219–224
Moran J (1990) Chapter 17: Pulse. In: Walker HK, Hall WD, Hurst JW (eds) Clinical methods: the history, physical, and laboratory examinations, 3rd edn. Butterworths, Boston. Available from: http://www.ncbi.nlm.nih.gov/books/NBK278/
Moshkovitz Y, Kaluski E, Milo O, Vered Z, Cotter G (2004) Recent developments in cardiac output determination by bioimpedance: comparison with invasive cardiac output and potential cardiovascular applications. Curr Opin Cardiol 19:229–237
Movius AJ, Bratton SL, Sorensen GK (1998) Use of pulse oximetry for blood pressure measurement after cardiac surgery. Arch Dis Child 78:457–460
Mueller HS, Chatterjee K, Davis KB, Fifer MA, Franklin C, Greenberg MA, Labovitz AJ, Shah PK, Tuman KJ, Weil MH, Weintraub WS (1998) ACC expert consensus document. Present use of bedside right heart catheterization in patients with cardiac disease. American College of Cardiology. J Am Coll Cardiol 32:840–864
Murias GE, Villagra A, Vatua S, del Mar Fernandez M, Solar H, Ochagavia A, Fernandez R, Lopez Aguilar J, Romero PV, Blanch L (2002) Evaluation of a noninvasive method for cardiac output measurement in critical care patients. Intensive Care Med 28:1470–1474
Myers MG (2012) The great myth of office blood pressure measurement. J Hypertens 30: 1894–1898
Myers MG, Godwin M (2007) Automated measurement of blood pressure in routine clinical practice. J Clin Hypertens (Greenwich) 9:267–270
Myers MG, Godwin M (2012) Automated office blood pressure. Can J Cardiol 28:341–346
Myers MG, Valdivieso M (2012) Evaluation of an automated sphygmomanometer for use in the office setting. Blood Press Monit 17:116–119
Nichols WW, Denardo SJ, Wilkinson IB, McEniery CM, Cockcroft J, O'Rourke MF (2008) Effects of arterial stiffness, pulse wave velocity, and wave reflections on the central aortic pressure waveform. J Clin Hypertens (Greenwich) 10:295–303
Nilsson LB, Eldrup N, Berthelsen PG (2001) Lack of agreement between thermodilution and carbon dioxide-rebreathing cardiac output. Acta Anaesthesiol Scand 45:680–685
Nossaman BD, Scruggs BA, Nossaman VE, Murthy SN, Kadowitz PJ (2010) History of right heart catheterization: 100 years of experimentation and methodology development. Cardiol Rev 18:94–101
O'Brien E (1998) Automated blood pressure measurement: state of the market in 1998 and the need for an international validation protocol for blood pressure measuring devices. Blood Press Monit 3:205–211
O'Brien E (2003) Demise of the mercury sphygmomanometer and the dawning of a new era in blood pressure measurement. Blood Press Monit 8:19–21
O'Rourke MF, Avolio AP (1980) Pulsatile flow and pressure in human systemic arteries. Studies in man and in a multibranched model of the human systemic arterial tree. Circ Res 46:363–372
O'Rourke MF, Yaginuma T (1984) Wave reflections and the arterial pulse. Arch Intern Med 144:366–371
O'Rourke MF, Pauca A, Jiang XJ (2001) Pulse wave analysis. Br J Clin Pharmacol 51:507–522
Omar HR, Fathy A, Mangar D, Camporesi E (2010) Missing the guidewire: an avoidable complication. Int Arch Med 3:21
Oransky I, Jeremy H, Swan C (2005) Lancet 365:1132
Ostergaard M, Nielsen J, Rasmussen JP, Berthelsen PG (2006) Cardiac output–pulse contour analysis vs. pulmonary artery thermodilution. Acta Anaesthesiol Scand 50:1044–1049
Ouellette EA (1998) Compartment syndromes in obtunded patients. Hand Clin 14:431–450
Palatini P, Benetti E, Fania C, Malipiero G, Saladini F (2012) Rectangular cuffs may overestimate blood pressure in individuals with large conical arms. J Hypertens 30:530–536
Parati G, Mutti E, Ravogli A, Trazzi S, Villani A, Mancia G (1990) Advantages and disadvantages of non-invasive ambulatory blood pressure monitoring. J Hypertens Suppl 8:S33–S38
Parienti JJ, du Cheyron D, Timsit JF, Traore O, Kalfon P, Mimoz O, Mermel LA (2012) Meta-analysis of subclavian insertion and nontunneled central venous catheter-associated infection risk reduction in critically ill adults. Crit Care Med 40:1627–1634

Paskalev D, Kircheva A, Krivoshiev S (2005) A centenary of auscultatory blood pressure measurement: a tribute to Nikolai Korotkoff. Kidney Blood Press Res 28:259–263

Pavan MV, Saura GE, Korkes HA, Nascimento KM, Madeira Neto ND, Davila R, Rodrigues CI, Almeida FA (2012) Similarity between blood pressure values assessed by auscultatory method with mercury sphygmomanometer and automated oscillometric digital device. J Bras Nefrol 34:43–49

Pearse RM, Ikram K, Barry J (2004) Equipment review: an appraisal of the LiDCO plus method of measuring cardiac output. Crit Care 8:190–195

Peyton PJ, Chong SW (2010) Minimally invasive measurement of cardiac output during surgery and critical care: a meta-analysis of accuracy and precision. Anesthesiology 113:1220–1235

Phillips R, Lichtenthal P, Sloniger J, Burstow D, West M, Copeland J (2009) Noninvasive cardiac output measurement in heart failure subjects on circulatory support. Anesth Analg 108: 881–886

Phillips RA, Hood SG, Jacobson BM, West MJ, Wan L, May CN (2012) Pulmonary artery catheter (PAC) accuracy and efficacy compared with flow probe and transcutaneous Doppler (USCOM): an ovine cardiac output validation. Crit Care Res Pract 2012:621496

Pikwer A, Akeson J, Lindgren S (2012) Complications associated with peripheral or central routes for central venous cannulation. Anaesthesia 67:65–71

Pipanmekaporn T, Bunchungmongkol N, Pin on P, Punjasawadwong Y (2012) Impact of patients' positions on the incidence of arrhythmias during pulmonary artery catheterization. J Cardiothorac Vasc Anesth 26:391–394

Pirracchio R, Cholley B, De Hert S, Solal AC, Mebazaa A (2007) Diastolic heart failure in anaesthesia and critical care. Br J Anaesth 98:707–721

Poelaert JI, Trouerbach J, De Buyzere M, Everaert J, Colardyn FA (1995) Evaluation of transesophageal echocardiography as a diagnostic and therapeutic aid in a critical care setting. Chest 107:774–779

Porhomayon J, Zadeii G, Congello S, Nader ND (2012) Applications of minimally invasive cardiac output monitors. Int J Emerg Med 5:18

Posey JA, Geddes LA, Williams H, Moore AG (1969) The meaning of the point of maximum oscillations in cuff pressure in the indirect measurement of blood pressure. 1. Cardiovasc Res Cent Bull 8:15–25

Proulx F, Lemson J, Choker G, Tibby SM (2011) Hemodynamic monitoring by transpulmonary thermodilution and pulse contour analysis in critically ill children. Pediatr Crit Care Med 12:459–466

Rajaram SS, Desai NK, Kalra A, Gajera M, Cavanaugh SK, Brampton W, Young D, Harvey S, Rowan K (2013) Pulmonary artery catheters for adult patients in intensive care. Cochrane Database Syst Rev 2:CD003408

Ramaswamykanive H, Bihari DJ (2009) Entrapment of the introducing sheath of a pulmonary artery catheter. Anaesth Intensive Care 37:1025–1026

Ranganath A, Hanumanthaiah D (2011) Radial artery pseudo aneurysm after percutaneous cannulation using Seldinger technique. Indian J Anaesth 55:274–276

Raval NY, Squara P, Cleman M, Yalamanchili K, Winklmaier M, Burkhoff D (2008) Multicenter evaluation of noninvasive cardiac output measurement by bioreactance technique. J Clin Monit Comput 22:113–119

Reed CR, Sessler CN, Glauser FL, Phelan BA (1995) Central venous catheter infections: concepts and controversies. Intensive Care Med 21:177–183

Reems MM, Aumann M (2012) Central venous pressure: principles, measurement, and interpretation. Compend Contin Educ Vet 34:E1–E10

Renner J, Scholz J, Bein B (2009) Monitoring fluid therapy. Best Pract Res Clin Anaesthesiol 23:159–171

Reuter DA, Huang C, Edrich T, Shernan SK, Eltzschig HK (2010) Cardiac output monitoring using indicator-dilution techniques: basics, limits, and perspectives. Anesth Analg 110:799–811

Rhodes A, Cusack RJ, Newman PJ, Grounds RM, Bennett ED (2002) A randomised, controlled trial of the pulmonary artery catheter in critically ill patients. Intensive Care Med 28: 256–264

Richard C, Warszawski J, Anguel N, Deye N, Combes A, Barnoud D, Boulain T, Lefort Y, Fartoukh M, Baud F, Boyer A, Brochard L, Teboul JL (2003) Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. JAMA 290:2713–2720

Richard C, Monnet X, Teboul JL (2011) Pulmonary artery catheter monitoring in 2011. Curr Opin Crit Care 17:296–302

Riva-Rocci S, Zanchetti A, Mancia G (1996) A new sphygmomanometer. Sphygmomanometric technique. J Hypertens 14:1–12

Roberts MA, Pilmore HL, Tonkin AM, Garg AX, Pascoe EM, Badve SV, Cass A, Ierino FL, Hawley CM (2012) Challenges in blood pressure measurement in patients treated with maintenance hemodialysis. Am J Kidney Dis 60:463–472

Roguin A (2006) Scipione Riva-Rocci and the men behind the mercury sphygmomanometer. Int J Clin Pract 60:73–79

Romagnoli S, Bevilacqua S, Lazzeri C, Ciappi F, Dini D, Pratesi C, Gensini GF, Romano SM (2009) Most Care®: a minimally invasive system for hemodynamic monitoring powered by the Pressure Recording Analytical Method (PRAM). HSR Proc Intensive Care Cardiovasc Anesth 1:20–27

Rudoff J, Ebner S, Canepa C (1994) Limb-compartmental syndrome with thrombolysis. Am Heart J 128:1267–1268

Runciman WB, Webb RK, Klepper ID, Lee R, Williamson JA, Barker L. 1993. The Australian Incident Monitoring Study. Crisis management--validation of an algorithm by analysis of 2000 incident reports. Anaesth Intensive Care 21:579-592

Russell AE, Wing LM, Smith SA, Aylward PE, McRitchie RJ, Hassam RM, West MJ, Chalmers JP (1989) Optimal size of cuff bladder for indirect measurement of arterial pressure in adults. J Hypertens 7:607–613

Sandham JD, Hull RD, Brant RF, Knox L, Pineo GF, Doig CJ, Laporta DP, Viner S, Passerini L, Devitt H, Kirby A, Jacka M (2003) A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. N Engl J Med 348:5–14

Satler LF (2013) Iatrogenic pulmonary artery rupture: the realities of management. Catheter Cardiovasc Interv 81:60–61

Saul L, Smith J, Mook W (1998) The safety of automatic versus manual blood pressure cuffs for patients receiving thrombolytic therapy. Am J Crit Care 7:192–196

Scheer B, Perel A, Pfeiffer UJ (2002) Clinical review: complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine. Crit Care 6:199–204

Schima H, Boehm H, Huber L, Schmallegger H, Vollkron M, Hiesmayr M, Noisser R, Wieselthaler G (2004) Automatic system for noninvasive blood pressure determination in rotary pump recipients. Artif Organs 28:451–457

Schramm R, Abugameh A, Tscholl D, Schafers HJ (2009) Managing pulmonary artery catheter-induced pulmonary hemorrhage by bronchial occlusion. Ann Thorac Surg 88:284–287

Schwann NM, Hillel Z, Hoeft A, Barash P, Mohnle P, Miao Y, Mangano DT (2011) Lack of effectiveness of the pulmonary artery catheter in cardiac surgery. Anesth Analg 113:994–1002

Scolletta S, Franchi F, Taccone FS, Donadello K, Biagioli B, Vincent JL (2011) An uncalibrated pulse contour method to measure cardiac output during aortic counterpulsation. Anesth Analg 113:1389–1395

Segal LS, Adair DM (1990) Compartment syndrome of the triceps as a complication of thrombolytic therapy. Orthopedics 13:90–92

Shah MR, Hasselblad V, Stevenson LW, Binanay C, O'Connor CM, Sopko G, Califf RM (2005) Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials. JAMA 294:1664–1670

Sharma V, Singh A, Kansara B, Karlekar A (2011) Comparison of transthoracic electrical bioimpedance cardiac output measurement with thermodilution method in post coronary artery bypass graft patients. Ann Card Anaesth 14:104–110

Shevde K, Raab R, Lee P (1994) Decreasing the risk of pulmonary artery rupture with a pressure relief balloon. J Cardiothorac Vasc Anesth 8:30–34
Side CD, Gosling RG (1971) Non-surgical assessment of cardiac function. Nature 232:335–336
Singer M, Clarke J, Bennett ED (1989) Continuous hemodynamic monitoring by esophageal Doppler. Crit Care Med 17:447–452
Siradovic A, Stoll R, Kern F, Haertel M (1988) Optimizing puncture of the internal jugular vein. Effects and advantages of the Valsalva maneuver in catheterization. Anaesthesist 37: 387–391
Sise MJ, Hollingsworth P, Brimm JE, Peters RM, Virgilio RW, Shackford SR (1981) Complications of the flow-directed pulmonary artery catheter: a prospective analysis in 219 patients. Crit Care Med 9:315–318
Siu L, Tucker A, Manikappa SK, Monagle J (2008) Does patient position influence Doppler signal quality from the USCOM ultrasonic cardiac output monitor? Anesth Analg 106:1798–1802
Sivarajan VB, Bohn D (2011) Monitoring of standard hemodynamic parameters: heart rate, systemic blood pressure, atrial pressure, pulse oximetry, and end-tidal CO2. Pediatr Crit Care Med 12:S2–S11
Smith BE, Madigan VM (2013) Non-invasive method for rapid bedside estimation of inotropy: theory and preliminary clinical validation. Br J Anaesth 111:580–588
Stergiou GS, Kollias A, Destounis A, Tzamouranis D (2012) Automated blood pressure measurement in atrial fibrillation: a systematic review and meta-analysis. J Hypertens 30: 2074–2082
Stevens K, McCabe C, Jones C, Ashcroft J, Harvey S, Rowan K (2005) The incremental cost effectiveness of withdrawing pulmonary artery catheters from routine use in critical care. Appl Health Econ Health Policy 4:257–264
Stirnemann JJ, Comte F, Samson A (2012) Density estimation of a biomedical variable subject to measurement error using an auxiliary set of replicate observations. Stat Med 31(30): 4154–4163
Stone PA, Hass SM, Knackstedt KS, Jagannath P (2012) Malposition of a central venous catheter into the right internal mammary vein: review of complications of catheter misplacement. Vasc Endovascular Surg 46:187–189
Sumita S, Ujike Y, Namiki A, Watanabe H, Watanabe A, Satoh O (1995) Rupture of pulmonary artery induced by balloon occlusion pulmonary angiography. Intensive Care Med 21:79–81
Summerhill EM, Baram M (2005) Principles of pulmonary artery catheterization in the critically ill. Lung 183:209–219
Surov A, Wienke A, Carter JM, Stoevesandt D, Behrmann C, Spielmann RP, Werdan K, Buerke M (2009) Intravascular embolization of venous catheter–causes, clinical signs, and management: a systematic review. JPEN J Parenter Enteral Nutr 33:677–685
Swan HJ (2005) The pulmonary artery catheter in anesthesia practice. 1970. Anesthesiology 103:890–893
Swan HJ, Ganz W (1974) Letter: guidelines for use of balloon-tipped catheter. Am J Cardiol 34:119–120
Swan HJ, Ganz W (1975) Use of balloon flotation catheters in critically ill patients. Surg Clin North Am 55:501–509
Swan HJ, Ganz W (1979) Complications with flow-directed balloon-tipped catheters. Ann Intern Med 91:494
Swan HJ, Ganz W, Forrester J, Marcus H, Diamond G, Chonette D (1970) Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. N Engl J Med 283:447–451
Takada M, Minami K, Murata T, Inoue C, Sudani T, Suzuki A, Yamamoto T (2010) Anesthetic management using the arterial pressure-based cardiac output monitor and a central venous oximetry catheter for tricuspid valve replacement in a patient receiving hemodialysis. Masui 59:1016–1020
Taylor HL, Tiede K (1952) A comparison of the estimation of the basal cardiac output from a linear formula and the cardiac index. J Clin Invest 31:209–216

Tesio F, De Baz H, Panarello G, Calianno G, Quaia P, Raimondi A, Schinella D (1994) Double catheterization of the internal jugular vein for hemodialysis: indications, techniques, and clinical results. Artif Organs 18:301–304

Trieschmann U, Kruessell M, Cate UT, Sreeram N (2008) Central venous catheters in children and neonates (part 2) – access via the internal jugular vein. Images Paediatr Cardiol 10:1–7

Trof RJ, Danad I, Reilingh MW, Breukers RM, Groeneveld AB (2011) Cardiac filling volumes versus pressures for predicting fluid responsiveness after cardiovascular surgery: the role of systolic cardiac function. Crit Care 15:R73

Truijen J, van Lieshout JJ, Wesselink WA, Westerhof BE (2012) Noninvasive continuous hemodynamic monitoring. J Clin Monit Comput 26:267–278

Trzebicki J, Lisik W, Blaszczyk B, Pacholczyk M, Fudalej M, Chmura A, Lazowski T (2011) Unexpected fatal right ventricular rupture during liver transplantation: case report. Ann Transplant 16:70–74

Turi G, Tordiglione P, Araimo F (2013) Case report: Anterior mediastinal central line malposition. Anesth Analg 117(1):123–125

Tyden H (1982) Cannulation of the internal jugular vein – 500 cases. Acta Anaesthesiol Scand 26:485–488

Uchida Y, Sakamoto M, Takahashi H, Matsuo Y, Funahashi H, Sasano H, Sobue K, Takeyama H (2011) Optimal prediction of the central venous catheter insertion depth on a routine chest x-ray. Nutrition 27:557–560

Uchino S, Bellomo R, Morimatsu H, Sugihara M, French C, Stephens D, Wendon J, Honore P, Mulder J, Turner A (2006) Pulmonary artery catheter versus pulse contour analysis: a prospective epidemiological study. Crit Care 10:R174

Ultman JS, Bursztein S (1981) Analysis of error in the determination of respiratory gas exchange at varying FIO2. J Appl Physiol 50:210–216

Unal AE, Bayar S, Arat M, Ilhan O (2003) Malpositioning of Hickman catheters, left versus right sided attempts. Transfus Apher Sci 28:9–12

Urban T, Wappler F, Sakka SG (2011) Intra-arterial ECG leads of a positive P-wave potential during central venous catheterization. Anasthesiol Intensivmed Notfallmed Schmerzther 46:94–97

Urschel JD, Myerowitz PD (1993) Catheter-induced pulmonary artery rupture in the setting of cardiopulmonary bypass. Ann Thorac Surg 56:585–589

Uzun M, Erinc K, Kirilmaz A, Baysan O, Sag C, Kilicarslan F, Genc C, Karaeren H, Demirtas E (2004) A novel method to estimate pulmonary artery wedge pressure using the downslope of the Doppler mitral regurgitant velocity profile. Echocardiography 21:673–679

Vats HS (2012) Complications of catheters: tunneled and nontunneled. Adv Chronic Kidney Dis 19:188–194

Vender JS (2006) Pulmonary artery catheter utilization: the use, misuse, or abuse. J Cardiothorac Vasc Anesth 20:295–299

Verrij E, van Montfrans G, Bos WJ (2008) Reintroduction of Riva-Rocci measurements to determine systolic blood pressure? Neth J Med 66:480–482

Verrij EA, Nieuwenhuizen L, Bos WJ (2009) Raising the arm before cuff inflation increases the loudness of Korotkoff sounds. Blood Press Monit 14:268–273

Vincent JL, Pinsky MR, Sprung CL, Levy M, Marini JJ, Payen D, Rhodes A, Takala J (2008) The pulmonary artery catheter: in medio virtus. Crit Care Med 36:3093–3096

Vincent JL, Rhodes A, Perel A, Martin GS, Della Rocca G, Vallet B, Pinsky MR, Hofer CK, Teboul JL, de Boode WP, Scolletta S, Vieillard-Baron A, De Backer D, Walley KR, Maggiorini M, Singer M (2011) Clinical review: update on hemodynamic monitoring–a consensus of 16. Crit Care 15:229

Walser EM (2012) Venous access ports: indications, implantation technique, follow-up, and complications. Cardiovasc Intervent Radiol 35:751–764

Wax DB, Lin HM, Leibowitz AB (2011) Invasive and concomitant noninvasive intraoperative blood pressure monitoring: observed differences in measurements and associated therapeutic interventions. Anesthesiology 115:973–978

Westenskow DR, Silva FH (1993) Device to limit inflation of a pulmonary artery catheter balloon. Crit Care Med 21:1365–1368

Whalen P, Ream AK (1988) A quantitative evaluation of the Hewlett-Packard 78354A noninvasive blood pressure meter. J Clin Monit 4:21–30

Wheeler AP, Bernard GR, Thompson BT, Schoenfeld D, Wiedemann HP, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL (2006) Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. N Engl J Med 354:2213–2224

Wiener F, Weil MH (1977) Cardiovascular monitoring in the medical intensive care unit. Med Instrum 11:268–273

Wilcox TA (2009) Catheter-related bloodstream infections. Semin Intervent Radiol 26:139–143

Williams L, Frenneaux M (2006) Diastolic ventricular interaction: from physiology to clinical practice. Nat Clin Pract Cardiovasc Med 3:368–376

Woodrow P (2002) Central venous catheters and central venous pressure. Nurs Stand 16:45–51; quiz 52

Xiang H, Liu Y, Li Y, Qin Y, Yu M (2012) Noninvasive measurement of beat-to-beat arterial blood pressure by the Korotkoff sound delay time. Blood Press Monit 17:35–41

Young BP, Low LL (2010) Noninvasive monitoring cardiac output using partial CO(2) rebreathing. Crit Care Clin 26:383–392, table of contents

Yu DT, Platt R, Lanken PN, Black E, Sands KE, Schwartz JS, Hibberd PL, Graman PS, Kahn KL, Snydman DR, Parsonnet J, Moore R, Bates DW (2003) Relationship of pulmonary artery catheter use to mortality and resource utilization in patients with severe sepsis. Crit Care Med 31:2734–2741

Zarshenas Z, Sparschu RA (1994) Catheter placement and misplacement. Crit Care Clin 10:417–436

Zhou Q, Xiao W, An E, Zhou H, Yan M (2012) Effects of four different positive airway pressures on right internal jugular vein catheterisation. Eur J Anaesthesiol 29:223–228

Zuffi A, Biondi-Zoccai G, Colombo F (2010) Swan-Ganz-induced pulmonary artery rupture: management with stent graft implantation. Catheter Cardiovasc Interv 76:578–581

# Postoperative Central Nervous System Monitoring

5

Ali Dabbagh

## Contents



A. Dabbagh, MD
Department of Anesthesiology and Anesthesiology Research Center, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
e-mail: alidabbagh@yahoo.com, alidabagh@sbmu.ac.ir

A. Dabbagh et al. (eds.), *Postoperative Critical Care for Cardiac Surgical Patients*,
DOI 10.1007/978-3-642-40418-4_5, © Springer-Verlag Berlin Heidelberg 2014

**Abstract**

The central nervous system (CNS) has the highest rank of priority in all medical interventions including cardiac surgery. Optimal care of the CNS in postoperative period of cardiac surgery mandates appropriate cerebral monitoring to ensure safe course of postoperative care especially when the patient is not fully awake due to residual anesthetics or ongoing effects of sedatives and analgesics.

Implementing CNS monitoring includes a battery of tests from clinical assessments and scoring systems to sophisticated and high-technology invasive and noninvasive monitors. Though for some of these monitors their use is not a common practice for all patients in cardiac surgery ICU, there is a trend to increase using more objective CNS monitoring in these patients especially when considering the ever-increasing rate of higher-risk patients, especially the aging population on one side and the wondrous developments in microprocessor technology and their widespread use in medicine on the other side.

There are some cardiac surgery patients in whom using even more than one modality is suggested, hence using "multimodal CNS monitoring." A number of standard guidelines and statements for CNS modalities are nowadays available; some are discussed here in the chapter.

## 5.1 Role of Central Nervous System (CNS) Monitoring in Postoperative Care of Adult Surgery

The CNS is among the highest priorities for oxygen supplementation in health and disease. However, during the perioperative period, prevention of CNS ischemia would depend on appropriate cerebral oxygen delivery, which in turn is directly dependent on appropriate cardiac output, appropriate cerebral oxygen delivery, and prevention of cerebral hyperactivity causing extraordinary oxygen demand.

CNS monitoring is mainly a matter of concern during the operation; however, there are a number of patients who need more sophisticated postoperative CNS assessments; among them, cardiac surgery patients should be mentioned.

The concept of fast track cardiac surgery has gained much concern during the last decade; however, CNS monitoring has received increased attention and an importance role because of its effects on quality outcomes, making the different techniques used for CNS monitoring an essential part of "anesthesia arsenal"; at the same time, CNS monitoring is advised to be applied as *multimodal monitoring* especially for high-risk patients; this *multimodal* approach includes a number of CNS monitoring devices currently available like the following but not limited to these monitors:

- Clinical assessment of CNS status and of sedation in postoperative period (intensive care unit)
- Classic electroencephalogram (EEG) including multichannel or uni-channel EEG
- Monitoring depth of anesthesia

- Evoked potentials (including motor-evoked potential, somatosensory-evoked potential, and auditory-evoked potential)
- Regional cerebral oximetry ($rSO_2$) by near-infrared spectroscopy technique (NIRS)
- Jugular vein oxygen saturation ($SjvO_2$)
- Transcranial Doppler (TCD)
- Other modes for assessment of cerebral blood flow

Among the above options, the more common devices are discussed in the next pages of this chapter. Multimodal CNS monitoring is demonstrated to improve patient outcome, especially neurologic measures of outcome.

For cardiac surgery patients, the early postoperative period is a critical time interval since these patients have the following characteristics:

1. There are frequent episodes of hemodynamic instabilities in a considerable proportion of these patients.
2. Postoperative hyperthermia is a common unwanted event in many of those undergoing cardiopulmonary bypass (CPB).
3. Usually the anesthetic drugs causing decreased level of consciousness are discontinued causing CNS arousal and increasing oxygen demand.
4. Postoperative pain is usually undertreated; this is also seen in cardiac surgery patients, making the use of analgesics mandatory in such patients.
5. Cardiac surgery patients often have a number of important CNS comorbidities like cerebral vascular or carotid artery diseases which mandate preoperative and postoperative CNS care.
6. Aortic manipulations might dislodge embolic particles mainly into the CNS arterial system which is usually composed of end arteries; such potential ischemic events are presented clinically in the postoperative period.
7. Inflammatory process induced by CPB or the process of surgery is usually continued throughout the early postoperative days.
8. Very high doses of anticoagulants are administered for cardiac surgery patients undergoing CPB; also, many patients receive preoperative anticoagulants; these events might cause postoperative hemorrhagic events, though postoperative CNS dysfunctions are mainly ischemic and not hemorrhagic.
9. Nowadays, an increasing number of patients undergoing cardiac procedures receive hemodynamic support using extracorporeal membrane oxygenation (ECMO); some of them should also be supported by right or left ventricle assist devices (LVAD or RVAD); a number of these patients are at risk of postoperative CNS complications, like ischemia or hemorrhage or indirectly due to hemodynamic instability affecting the CNS; all of these states mandate vigorous postoperative CNS monitoring.

(Johansen and Sebel 2000; Shaaban Ali et al. 2001; White and Baker 2002; Moppett and Mahajan 2004; Cengiz et al. 2005; Dalton et al. 2005; Polito et al. 2006; Wright 2007; Nelson et al. 2008; Brogan et al. 2009; Isley et al. 2009; Palanca et al. 2009; Cogan 2010; Fedorow and Grocott 2010; Rohlwink and Figaji 2010; Edmonds et al. 2011; Hervey-Jumper et al. 2011, 2012; Ghosh et al. 2012; Rollins et al. 2012)

## 5.2 Clinical Assessment of CNS Status and of Sedation in Postoperative Period (Especially Cardiac ICU)

A number of sedation assessment scales have been introduced for use in the clinical setting of ICU. All of these scales are based on clinical assessment of patient arousal state and responsiveness; the response could be to vocal stimulation (simple patient calling) up to mechanical stimulation; also, the agitation level of response is often incorporated in these scales. It is "strongly recommended" to frequently assess the "level of consciousness using a sedation scale," according to Sessler et al. (Carrasco 2000; De Jonghe et al. 2000; Young and Prielipp 2001; Sessler et al. 2002, 2008, 2013; Watson and Kane-Gill 2004; Olson et al. 2007; Thuong 2008; Brush and Kress 2009; Barr et al. 2013).

The American College of Critical Care Medicine has published the "Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit" (Barr et al. 2013). This guideline has assessed ten subjective sedation scales which include:

1. Observer's Assessment of Alertness/Sedation Scale (OAA/S)
2. Ramsay Sedation Scale (Ramsay)
3. New Sheffield Sedation Scale (Sheffield)
4. Sedation Intensive Care Score (SEDIC)
5. Motor Activity Assessment Scale (MAAS)
6. Adaptation to the Intensive Care Environment (ATICE)
7. Minnesota Sedation Assessment Tool (MSAT)
8. Vancouver Interaction and Calmness Scale (VICS)
9. Sedation-Agitation Scale (SAS)
10. Richmond Agitation-Sedation Scale (RASS)

The guideline declares that "RASS and SAS yielded the highest psychometric scores." Also, the guideline announces that "moderate to high correlations were found between the sedation scores and either EEG or BIS values." Also, the guideline stresses on the feasibility of RASS. Moreover, the guideline adds "RASS and SAS to be the most valid and reliable for use in critically ill patients; whereas ATICE, MSAT, and VICS are moderately valid and reliable." Meanwhile, it enunciates that "MAAS, SEDIC, Sheffield, Ramsay, and OAA/S scales had a lower quality of evidence." Based on this newly published guideline, here, the two scales, i.e., RASS and SAS, are described in brief. The interested reader could find the others as needed (Barr et al. 2013).

### 5.2.1 Richmond Agitation-Sedation Scale (RASS)

This scale has ten grades:

- 4 positive scores (+4 to +1) which stand for combative to restless stages
- 1 zero score which stands for an "alert and calm" patient
- 5 minus scores (−1 to −5) which stand for drowsy to unarousable patient

A very important practical point for application of RASS is to determine in the first step of visit if the patient is "alert and calm" which would be scored "zero." If the patient is agitated, the scoring would be above zero (i.e., from +4 to +1); however,

**Table 5.1** A summary of the Richmond Agitation-Sedation Scale (*RASS*)

| Score | Clinical term |
|---|---|
| +4 | Combative |
| +3 | Very agitated |
| +2 | Agitated |
| +1 | Restless |
| 0 | Alert and calm |
| −1 | Drowsy |
| −2 | Light sedation |
| −3 | Moderate sedation |
| −4 | Deep sedation |
| −5 | Unarousable |

**Table 5.2** A summary of the Sedation-Agitation Scale (*SAS*)

| Score | Clinical term |
|---|---|
| 7 | Dangerous agitation |
| 6 | Very agitated |
| 5 | Agitated |
| 4 | Calm and cooperative |
| 3 | Sedated |
| 2 | Very sedated |
| 1 | Unarousable |

if the patient is sedated or drowsy, the score would be negative (i.e., from −1 to −5). A full grading is presented here based on the studies of Sessler and others. The full description of the scale is found at Sessler et al. manuscript (2002) (Table 5.1).

(Sessler et al. 2001, 2002, 2008, 2013; Ely et al. 2003; Turkmen et al. 2006; Khan et al. 2012; Patel and Kress 2012; Barr et al. 2013; Benitez-Rosario et al. 2013)

### 5.2.2 Sedation-Agitation Scale (SAS)

SAS is much easier than RASS; in other words, it is a 7-step scale without negative scores. The "calm and cooperative patient" in SAS gets a score of 4. However, SAS is graded as in Table 5.2. SAS is demonstrated as a valid and reliable scale for assessment of sedation status in postoperative period of adult patients in intensive care unit.

(Riker et al. 1999, 2001; Simmons et al. 1999; Brandl et al. 2001; Barr et al. 2013)

## 5.3 Electroencephalography (EEG) Including Multichannel or Uni-channel EEG

Electroencephalography (EEG) was first introduced by German psychiatrist Hans Berger in 1926 while he presented a number of very exact recordings of the brain electrical activities which are still valid.

Speaking physiologically, the oxygen supply to the CNS is divided as two main categories; the majority (i.e., about 60 %) is provided for specialized neuronal activity including axonal and synaptic transmission; this section is suppressed after administration of anesthetic. Another 40 % of the energy supply is assigned to maintenance of cellular integrity; usually, anesthetics do not affect the latter while hypothermia could depress it. Usually CNS neurons adjust themselves in the ischemic state to be able to continue their basal function, i.e., the portion of their activity related to the 40 % energy requirements for basal homeostasis.

When monitoring the CNS using EEG, we should always consider EEG as a *good* CNS monitoring but not a *perfect* one, since:

- The EEG electrodes record the electrical activity of the neurons just under the scalp (i.e., the cortical neurons); however, these electrodes would not record the electrical activity of thalamus or the subcortical nuclei as well as the cortical neurons; this is why EEG electrodes, even if located directly on the cortical tissue, record mainly the neurologic activity of the cortex and do not assure ischemia prevention in the subcortical brain nuclei.
- Conventional EEG has not been widely used for cardiac operations due to its technical limitations.
- Though the EEG presentations in ischemic insult are often similar, it is not always the same; at times, the ischemic neurons are those which have inhibitory function and their ischemic presentation would be as overactivity of the CNS.
- EEG could demonstrate the ischemic events; however, its role as a CNS monitoring is not to demonstrate the site of ischemia, the etiologic mechanism responsible for ischemia or the anatomic location of injury.
- EEG is a "biorhythm" affected a number of factors like age, environment, and circadian variations, as cited by Constant et al.

In 2009, the American Society of Neurophysiological Monitoring (ASNM) has published the "Guidelines for intraoperative neuromonitoring using raw and quantitative electroencephalography" prepared by Isley et al.; the recommendations presented in this guideline are direct and decisive regarding perioperative EEG monitoring.

In patients undergoing cardiac surgery, especially those with higher risk of CNS injury (including the older patients), perioperative EEG could help in detection, monitoring, and prevention of CNS-related problems. The following are among the most common uses of perioperative EEG in cardiac surgery patients according to Isley et al. and Gugino et al.:

1. Detection and documentation of any preoperative baseline CNS disorder; also, documentation of any possible new event in the perioperative period (including postoperative period).
2. Baseline EEG (i.e., before anesthesia induction) should be documented as the baseline data especially in those at increased risk of CNS injury for comparison with later findings.
3. Intraoperative EEG monitoring and postoperative EEG records both discover new findings and differentiate them from baseline abnormalities while detecting new findings; intraoperative or postoperative new findings should be assessed carefully and cautiously to find potentially treatable new findings.

4. EEG could help us tailor the dosage of anesthetics and sedatives during intraoperative and postoperative period.
5. Monitoring the efficacy of anticonvulsant therapies in patients having seizure in postoperative period.
6. Acute hemodilution due to rapid postoperative bleeding (necessitating volume replacement with large volumes of crystalloids) or hemodilution during cardiopulmonary bypass is an example of state in which cardiac surgery patients are exposed to acute hemodilution; this hematocrit drop needs CNS monitoring to detect any possible regional or global ischemic insult associated with microcirculatory collapse, especially in patients at risk of CNS injury; these patients benefit from EEG monitoring.
7. During the early period after rewarming from CPB, the brain neurons return to the normal temperature, while the CNS perfusing arteries remain partially in some degrees of spam; it means that during early rewarming period, brain oxygen demands would be more than oxygen supply which causes some degrees of brain ischemia; also, this phenomenon could be extended to the postoperative period in which EEG monitoring could help detect these ischemic periods.
8. When hypothermia is administered during the perioperative period as a method of cerebral protection, EEG could help us monitor the efficacy of hypothermia presented as EEG silence.
9. Hyperventilation in postoperative period causes hypocapnia which would in turn lead to cerebral arterial vasoconstriction and reduced CNS perfusion; monitoring the potential ischemic effects of this phenomenon could be done using EEG whenever the patient needs more vigorous care.

### 5.3.1 How EEG Works

EEG is the indicator for CNS activity, mainly the cortex and especially the postsynaptic activity of the cortical neurons; usually, the total brain electrical activity is recorded using the standard 10/20 electrodes placed on different parts of the scalp. EEG electrodes record the electrical activities of those cortical neurons located in the brain cortex just under the scalp; these neurons are "pyramids" with their direction being perpendicular to the scalp; in fact, the cortical neurons are the long ones with elongated axons located vertical to the scalp.

EEG is the summative activity of cortical neurons' functions (both excitatory and inhibitory functions); in other words, *postsynaptic* electrical currents of millions of cortical neurons (called pyramidal cortical cells or Betz cells) are summated and accumulated together to create EEG waves; however, the axonal activity of the cortex does not contribute an important role in EEG wave production.

EEG waves have the following main electrical characteristics:

1. Amplitude: amplitude of waves is decreased with increasing age as a result of aging; the electrical amplitude of EEG waves is in the range of 10–100 μV, about 100 times less than electrical amplitude of electrocardiography.
2. Frequency: the number of times in each second that a wave recurs, presented as waves per second, i.e., Hz; detailed description could be found in Table 5.3.

**Table 5.3** A summary of EEG waves and their brief characteristics

| | Wave category | Symbol | Frequency | Voltage | Related activity | Clinical equivalent |
|---|---|---|---|---|---|---|
| 1. | Beta waves | β | 12.6–25 Hz, in some references 13–30 Hz | In adults 10–20 μV | Cortico-cortical network | Fully awake patient with open eyes |
| 2. | Alpha waves | α | 7.6–12.5 Hz, in some references 8–13 Hz | 30–50 μV; in adults: 10–20 μV | Corticothalamic network | Awake patient but eyes are closed equals drowsy state |
| 3. | Theta waves | θ | 3.6–7.5 Hz, in some references 4–7 Hz | 50–100 μV; in adults: 10–20 μV | Corticothalamic activity and limbic activity | Stage 2 of sleep (light sleep) |
| 4. | Delta waves | δ | 1.5–3.5 Hz, in some references 0.5–3 Hz | 100–200 μV | Corticothalamic dissociation | Deep sleep and coma |
| 5. | Gamma waves | γ | 25.1–55 Hz, in some references 30–50 Hz | | Corticothalamic perception | Involved in the process of perception |

3. Time: the horizontal axis of EEG is always time.
4. Symmetry is an index of normality; even when the patients are anesthetized, the two hemispheres present symmetric EEG changes while pathologic states disturb symmetry.

The EEG electrodes record the "voltage difference" between each of the two different electrodes. The difference in electrode voltages is demonstrated against a time scale as the following pattern:

- If the difference between the 1st and the 2nd electrodes is negative, it would appear as *above the scale deflection* (i.e., up deflection) on EEG.
- If this difference between the 1st and the 2nd electrodes is positive, it would appear as *below the scale deflection* (i.e., down deflection) on EEG.

The EEG electrodes could be metal discs called "cup" electrodes made of "tin, silver, or gold." Also, needle electrodes are available used when sterile application of EEG electrodes is mandatory like neurosurgical operations, though their use should be limited to "obligatory" conditions. The third type of electrodes is called "silver-silver chloride" electrodes. Whatever type of electrode is used, the electrode montage should be from a constant type, with appropriate quality to prevent artifacts and, also, enough gel to guarantee low amount of impedance. We also should be sure that electrodes be well attached.

Another important point is that EEG connection wires and cables should not be in contact or in the vicinity of other cables to improve EEG signal quality. Also, it is recommended to use EEG leads as shielded leads.

Usually, 2–8 channels are used for intraoperative or postoperative CNS recording; even at times, three electrodes are used on the frontal area, two of them for recording the neuronal electrical activity as "differential amplifier with voltage

difference" and the 3rd electrode used as the "mandatory reference signal" electrode. However, some references stress on using not less than eight channels.

The function of EEG is divided into "few seconds" interval; this is why EEG waves are taken in defined time periods called *epochs*. These time periods are usually 2–4 s. The electrical activity waves are taken during these time epochs and are then analyzed by the device microprocessor to be demonstrated as final EEG waves on a time-based scale.

EEG electrode attachment order on the scalp is named *montage* of electrodes. In the standard system of the electrodes, there are four main anatomic landmarks used for electrode attachment over the scalp in different directions:

- One nasion (anterior)
- One inion (posterior)
- Two preauricular points

The location of electrodes is named according to the above anatomic locations and also the standard coding system which uses anatomic, alphabetic, and numeric items (i.e., anatomic and alphanumeric recording); this standard system helps us differentiate the location of any abnormal wave and also to compare similar locations on two hemispheres (Fig. 5.1):

- F for frontal electrodes.
- T for temporal electrodes.
- O for occipital electrodes.
- P for parietal electrodes.
- C for central electrodes.
- A for auricular electrodes.
- M for mastoid electrodes.
- Even numbers as subscripts demonstrate right hemisphere.
- Odd numbers as subscripts demonstrate left hemisphere.
- Z as subscript demonstrates midline electrodes (z: zero).

### 5.3.2 Frequency of EEG Waves and the Changes During Wakefulness, Sleep, and Anesthesia

EEG rhythms during wakefulness, sleep, and anesthesia are the result of balance between cortex and thalamus, depending on the level of consciousness or the stage of anesthesia. However, EEG waves are classified as the five frequency bands; their frequencies are a bit different between different authors; however, according to Gugino et al. the frequencies are classified as demonstrated in Table 5.3 and also, described in the following paragraphs.

### 5.3.3 Normal and Abnormal EEG

Normal and Abnormal EEG in normal EEG, symmetry between hemispheres is clearly evident; also, the EEG waves are according to the category mentioned above without any spike waves; the spike waves suggest epileptic activity.

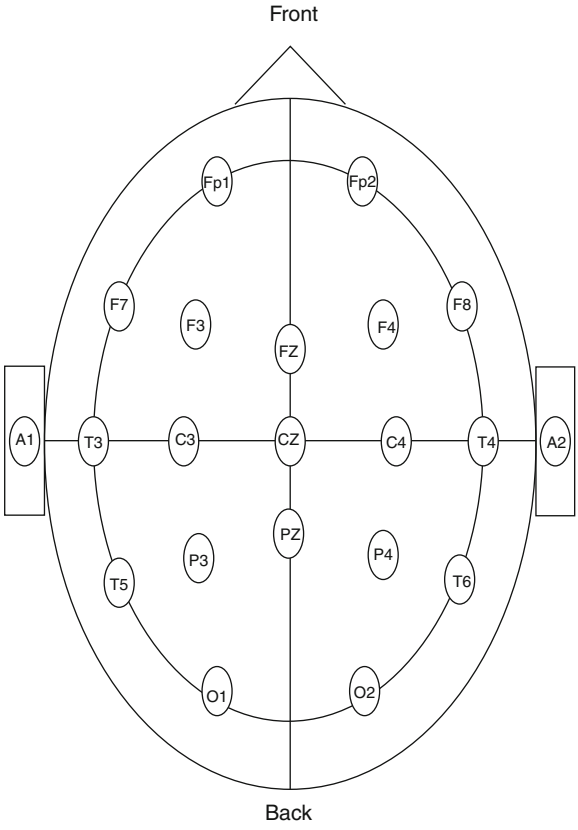



**Fig. 5.1** The standard 10/20 electrode system

However, abnormal EEG may be mainly due to ischemia, infarct, epilepsy, or tumor. For example, these are a number of well-known findings in pathologic EEG:

- Asymmetric patterns between hemispheres (could be sign of ischemia or arterial occlusion).
- Spikes.
- Decreased frequency.
- Decreased voltage.
- Also, if normal waves are seen in abnormal states, it would be suggestive of a pathologic state (like abnormal appearance of delta waves which could be suggestive for a brain lesion).

### 5.3.4 EEG in Cardiac Surgery Patients

The role of EEG in cardiac surgery ICU could be among the following:

- As a *continuous monitoring device* and a real-time neurologic assessment tool and at the same time, to monitor CNS like the other major organ systems which should be monitored in the perioperative period; this is especially important when the hemodynamic status is not stable and there is the risk for impaired CNS perfusion.
- As a *diagnostic tool*, for example, in detection of epilepsy, ischemic or hemorrhagic CNS events, coma, brain death, and drug toxicities or to rule out decreased level of consciousness due to residual anesthetic effects from other etiologies of decreased consciousness.
- As a *therapy tailoring method*, dosage titration tool, or drug adjustment scale, for example, as a tool in clinical approval of the anticonvulsant drugs' efficacy or making any needed change in their dose or in barbiturate-induced or hypothermia-induced coma, for objective approval of their efficacy and confirmation of barbiturate or hypothermia-induced cortical silence.

Also, as discussed in Chap. 10 of this book, cardiac surgery patients tolerate a considerable effect on their CNS due to the process of the disease and the therapeutic approaches. For example, in cardiac surgery patients, postoperative cerebral edema and decreased CNS oxygen delivery due to edema is often seen in the early postoperative days. This finding is seen in nearly all cardiac procedures, though the frequency is not always the same, with the following characteristics:

- EEG findings in cardiac surgery patients are similar to findings in those affected with organic brain syndrome.
- The postoperative changes are more frequent in the left hemisphere.
- These EEG findings are more common after more invasive, complex procedures; so, the prevalence is higher in valve replacement compared with valve repair or CABG.
- More common in on pump CABG's compared with off-pump CABG's, however, seen even in off-pump patients.
- During periods of postoperative CNS ischemia, EEG waves change to ischemic pattern whenever cerebral blood flow (CBF) is <22 mL/100 g/min.
- During early stages of ischemia, frequency of waves decreases while the voltage is preserved.
- If more severe ischemia occurs, both wave frequency and voltage are depressed.
- These changes are especially seen as significant decrease "in the beta and the alpha 2 bands."
- EEG amplitude drop >30 % or duration of EEG changes >30 s have been cited as important indicators of ischemia by Florence et al.
- The effects of anesthetics, analgesic agents, temperature variations, and blood pressure fluctuations in postoperative period should be considered.

(Zeitlhofer et al. 1988; Chabot and Gugino 1993; Hauser et al. 1993; Newburger et al. 1993; Chabot et al. 1997; Nuwer 1997; Pua and Bissonnette 1998; Sebel 1998; Gugino et al. 1999, 2001, 2004; Jacobson and Jerrier 2000; Johansen and Sebel 2000; Rasmussen et al. 2002; Zimpfer et al. 2002; Grimm et al. 2003; Florence et al. 2004; Freye 2005b; Freye and Levy 2005; Jameson and Sloan 2006; Markowitz et al. 2007; Williams and Ramamoorthy 2007; Nelson et al. 2008; Isley et al. 2009; Palanca et al. 2009; Brown et al. 2010; Chakravarthy et al. 2010; Golukhova et al. 2010; Poe et al. 2010; Golukhova et al. 2011; Constant and Sabourdin 2012; Futier et al. 2012)

## 5.4 Monitoring Depth of Anesthesia (Including Bispectral Analysis Index)

Bispectral analysis index could help us deliver an appropriate level of anesthesia and/or sedation. During postoperative period, during the time interval from patient transfer to ICU until tracheal extubation, the overall patient status (including hemodynamic, pulmonary, hematologic, and consciousness) is not yet prepared for extubation. Meanwhile, the residual effects of anesthetics are usually vanished in this time, and the patient needs some degree of sedation.

Besides, frequently it happens in a number of patients that some invasive procedures are needed (like intubation, orotracheal suctioning, central line insertion, and chest tube change), or less frequently, it happens that more time is needed for full recovery: some need prolonged intubation and mechanical ventilatory support or hemodynamic support, mandating additional sedation/analgesia. Level of sedation/analgesia should be monitored to deliver adequate analgesic agents while preventing over-administration. Bispectral analysis index monitor could help us in such cases to improve sedation/analgesia level.

Depth of anesthesia scoring for bispectral analysis index is defined as following:

- >80: awake
- 60–80: sedation state
- 40–60: surgical anesthesia
- <40: deep anesthesia

In some studies, bispectral analysis index is considered as the "most widely used method at the present time" for monitoring sedation as part of an integrated monitoring approach for assessment of sedation/analgesia in critical patients. Also, bispectral analysis index is demonstrated to be a "valid measure of wakefulness after cardiac surgery."

Another important issue is the legal aspects of delivering appropriate level of sedation/analgesia to create both patient satisfaction and amnesia and so prevent patient recall (Simmons et al. 1999; Drummond 2000; Riker et al. 2001; Brocas et al. 2002; Frenzel et al. 2002; Courtman et al. 2003; Deogaonkar et al. 2004; Watson and Kane-Gill 2004; Fraser and Riker 2005; Freye 2005b; Hernandez-Gancedo et al. 2006; Payen et al. 2007; Palanca et al. 2009; Lamas and Lopez-Herce 2010).

## 5.5 Evoked Potentials

Evoked potentials are used as monitoring devices to check the functional integrity of the central and peripheral nervous system, especially the different neural circuits and pathways. Although both EEG and evoked potentials assess the electrical activity of the nervous system, there are some differences between these two neural monitoring, discriminating evoked potentials from EEG:

- Evoked potentials have lower-voltage amplitude compared to EEG.
- Evoked potentials assess the neurologic response to a stimulus (sensory or motor).

- Evoked potentials are not limited to the cortical areas of the nervous system; in other words, evoked potentials monitor cortical areas, deeper neural structures of the CNS, spine, and also peripheral nervous system.
- In periods when EEG is flat (like therapeutic hypothermia), evoked potentials could still work and monitor the functional integrity of the nervous system.

Evoked potentials are divided into three main categories:

1. *Somatosensory-Evoked Potential (SSEP)*: Somatosensory-Evoked Potential (SSEP) which monitors the functional integrity of the ascending pathways, from the peripheral receptors (median or ulnar nerve for upper extremity and posterior tibial nerve or peroneal nerve for lower extremity) up to the multiple spinal segments and then to the contralateral thalamus, reaching finally to cortex; a subtype of this monitoring modality is called visual-evoked potential (VEP) which incorporates visual stimuli as the sensory input.
2. *Motor-Evoked Potential (MEP)*: Motor-Evoked Potential (MEP) which monitors the motor pathway activated in response to electrical stimulus, from the cortical areas down to the related nuclei and corticospinal tracts and finally to motor units.
3. *Auditory-Evoked Potential (AEP)*: Auditory-Evoked Potential (AEP) which objectively monitors the neural pathway involved in hearing from cochlea in ear to the auditory (8th cranial) nerve to brainstem then related brain ganglia and finally to related cortical areas; the first milliseconds of this monitoring controls the brainstem function involved in auditory pathway and is called brainstem auditory-evoked response (BAEP).

The above modes have a relatively wide application in perioperative care, including cardiac surgical procedures. Their application in the postoperative period of cardiac surgery patients could be very useful and help us gather important objective data; however, this is not a common practice; one could stress on the following as the main indications of indications of evoked potentials in postoperative period:

- During periods of postoperative-controlled (therapeutic) hypothermia, EEG becomes flat; however, evoked potentials could monitor functional integrity of the nervous system even at such states.
- Monitoring the physiologic integrity of the neural system while the patient is hemodynamically unstable, deeply sedated, has altered consciousness state, or is comatose; possibly other nervous system monitoring could not assess the functional status of the patients in these periods of time.

In summary, evoked potentials could help the clinicians in assessment of neural system integrity with objective and reproducible data which are a new window besides the routine CNS monitoring; possibly, their postoperative application in cardiac surgery patients would be more common in future years (Hill and Chiappa 1994; Nuwer et al. 1995; Sloan 1995, 2004; Rodriguez 2004; Freye 2005a, b; Toleikis 2005; Sloan and Jameson 2007; Amantini et al. 2008; Martin and Stecker 2008; Sloan et al. 2012).

## 5.6 Cerebral Oximetry

Cerebral oximetry is a relatively new technology for cerebral monitoring though it has passed more than 35 years from the first publication regarding the in vivo application of the technique; however, it has been used in a number of procedures

including cardiac surgery. Successful previous studies have shown the use of this monitor in both animal models and in human studies involving some high-risk procedures like cardiac and vascular surgery and in patients with underlying acute cerebral events though there are still some controversies.

The technology of "near-infrared spectroscopy" (NIRS) was described for this purpose in 1977 by Professor "Frans Jöbsis." NIR light has a specific characteristic which is the power to penetrate a wide range of body tissues (including bone) and, unlike pulse oximetry, utilizes the reflection phenomenon of light rather than the process used in pulse oximetry; transmission of light from a small part of the body (e.g., a finger) is the technology used in pulse oximetry; in other words, this technology utilizes passage of near-infrared (NIR) light in the range of 700–1,000 nm, through skull and underlying tissues using self-adhesive optodes used on the scalp above the eyebrows; part of the NIR light is absorbed by biologic chromophores, especially two main chromophores oxyhemoglobin (OHb) and deoxyhemoglobin (HHb) and cytochrome oxidase, and the rest of the light is returned back; the returned portion of NIR light is used for data collection, processing, calculation, and demonstration of the absorbed fraction of light in each of the above chromophores; in this process, the "modified Beer-Lambert Law" is used for calculations; finally these data are processed by the machine software to demonstrate the figures of $rSO_2$ on the monitor screen. NIR light is produced by "light-emitting diodes" (LEDs) and absorbed by silicon photodiodes. In summary, its mechanism is by differential absorption of near-infrared spectroscopy (NIRS) in the range of 700–1,000 nm, through skin and bone.

One of the key features of cerebral oximetry by NIRS is that $rSco_2$ figures are in appropriate range only if the brain tissue receives adequate oxygenated blood, which mandates not only adequate *cerebral oxygenation* but also appropriate state of *cerebral hemodynamic*, patency of *cerebral arteries*, and efficient cerebral *venous drainage*. Possibly this is why in some high-risk patients like cardiac surgeries (including CABG patients), regional cerebral oxygen saturation monitoring ($rSco_2$) prevents episodes of severe cortical hypoxia; so, application of this monitor has the potential to significantly reduce the *incidence of major organ dysfunction* and "improve outcome," though some controversies exist yet and there are studies questioning the effect of cerebral oximetry application on patient outcome (especially the systematic review recently published by Zheng et al. (2013).

A number of practical notes for utilization of this monitoring are:

- Monitors the in vivo state of the CNS.
- Monitoring is noninvasive, real time, and portable.
- Measures both oxygenation and perfusion of the CNS (i.e., mandates appropriate hemodynamic of the CNS).
- Monitors not only the CNS status but also the hemodynamic status since it monitors both oxygenation and perfusion of the CNS.
- A drop more than 20 % from baseline or an absolute decrease below 50 % in measured $rSco_2$ values is considered as cerebral hypoxia.
- Could be used for preoperative, intraoperative, or postoperative monitoring (all over the perioperative period).

- Does not need pulsatile flow like pulse oximetry for monitoring during CPB.
- Is one important member of the "multimodal CNS monitoring" in cardiac surgery.
- Fine attachment and correct positioning of the probes is very important for its application, and this is a very important application point which could bias the measurements.
- For patients receiving hemodynamic support by ECMO, cerebral oximetry is a very useful and promising CNS monitoring; also, if the patient would be under non-pulsatile flow with ECMO, this device could be more practical than many other CNS monitors.
- Could be used as a predictor for successfulness of extubation in cardiac surgery patients.
- Its application in high-risk patients (like the elderly and the patients undergoing surgery with underlying cerebral vascular disorders) is recommended more than the others.
- Underlying diseases like decreased cardiac output, pulmonary problems, anemia, and underlying disorders of the cerebral vessels are considered as confounders which could decrease the $rSco_2$ readings and create bias.

If a decrease in $rSco_2$ is observed, the following steps are suggested by Murkin et al. and Denault et al. as a useful approach for relieving the etiologic disorder causing cerebral ischemia:

1. Control head position; if head is rotated extensively, turn it to normal position.
2. Check the possibility of arterial or venous occlusion due to arterial or venous cannula physical effects.
3. Check for mean arterial pressure (MAP) and treat it if it is low.
4. Control arterial saturation (by pulse oximeter or blood gas analysis); if it is low, rule out possible causes of systemic desaturation.
5. Treat possible hyperventilation which could decrease arterial $PaCO_2$, especially if it is below 35 mmHg.
6. Treat possible anemia to increase hematocrit above 30 %.
7. Assess the cardiac function including the situation of the heart using methods like echocardiography and also $SjvO_2$; relieve potential underlying etiologies including treatment of failing heart.
8. Check cerebral oxygen consumption; if it is increased, rule out and treat "convulsions" and/or "hyperthermia."
9. But if cerebral oxygen consumption is normal, rule out increased "intracerebral hypertension" and/or "cerebral edema"; for this purpose, use the help of imaging modalities.

(Rolfe 2000; Ferrari et al. 2004; Casati et al. 2005, 2006; Polito et al. 2006; Denault et al. 2007; Hoshi 2007; Murkin et al. 2007; Wolf et al. 2007; Wright 2007; Fischer et al. 2009; Hasegawa and Okita 2009; Huppert et al. 2009; Murkin and Arango 2009; Slater et al. 2009; Vohra et al. 2009; Brady et al. 2010; Erickson and Cole 2010; Fedorow and Grocott 2010; Green and Paklet 2010; La Monaca et al. 2010; Palombo et al. 2010; Sellmann et al. 2010; Svyatets et al. 2010; Veel et al. 2010; Andritsos et al. 2011; Bronicki and Chang 2011; Hoshi 2011; Lampe and

Becker 2011; Lima et al. 2011; Radovanovic and Radovanovic 2011; Rao and Durga 2011; Roggenbach and Rauch 2011; Smith 2011; Cyrous et al. 2012; Ghosh et al. 2012; Hankey 2012; Kertai et al. 2012; Li 2012; Scheeren et al. 2012; Tsygan 2012; Foster et al. 2013; Hampton and Schreiber 2013; Moerman et al. 2013; Murkin 2013; Seule et al. 2013; Zheng et al. 2013; Zulueta et al. 2013)

## 5.7 Jugular Venous Oxygen Saturation ($SjvO_2$)

Monitoring the CNS oxygenation status has been used for more than 60 years: Gibbs et al first in 1942 and then Datsur et al in 1963. Assessment of the jugular venous oxygen saturation ($SjvO_2$) is an "indirect surrogate indicator for global oxygenation of the cortex" and also is an indicator of the balance between cerebral blood flow (CBF) and cerebral metabolism rate of oxygen ($CMRO_2$). $SjvO_2$ monitoring could be used to monitor the trend of change in the following items:

- Oxygen uptake by the brain tissue (i.e., the difference between brain arterial and venous difference which equals CNS oxygen uptake).
- Arterial and venous difference of CNS blood gases and their related parameters.
- Arterial and venous difference of CNS blood glucose levels.
- Arterial and venous difference of CNS blood lactate levels; impaired CNS perfusion leads to decreased cerebral oxygenation which would activate anaerobic metabolism leading to increased lactate level in the jugular venous bulb blood samples.

The normal values for $SjvO_2$ are lower than the normal values for global mixed venous oxygen saturation (which is usually measured by pulmonary artery catheter). This is due to the fact that oxygen uptake and consumption in the cerebral tissue is much higher than the global body oxygen uptake and consumption.

### 5.7.1 Contraindications for $SjvO_2$ Catheter Insertion

According to Shaaban et al. absolute contraindications for $SjvO_2$ catheter insertion are:

- Injuries in the cervical spine
- Bleeding diathesis
- Local neck trauma
- Local infection

Also, relative contraindications could be:

- Compromised drainage of the cerebral venous system
- Patients having tracheostomy

$SjvO_2$ measurements are done either using the *conventional technique* with serial measurements of $SjvO_2$ and other factors or using a fiberoptic catheter with near-infrared light in the catheter tip; however, this conventional technique has the limitation of being "point assessment" needing serial measurements but could not provide real-time data. On the other side, malpositioning of the catheter tip could cause reading errors or the near-infrared light of the fiberoptic catheter may be out of its defined range, and hence, misreading would occur. Also, rotation of the head

to either side could affect the venous return and distort the measurements. The technology used in fiberoptic $SjVO_2$ monitor is similar to the oximetry technology used for some types of pulmonary artery catheters.

### 5.7.2 Technique of Catheter Insertion

$SjvO_2$ is assessed through a catheter introduced to the internal jugular vein using the following technique:

- The technique is through the internal jugular vein, usually the right side.
- Usually, the right IJV is the dominant vein for cerebral venous drainage; however, the mixing pattern between right and left hemispheres is not always the same.
- $SjVO_2$ catheter insertion is exactly the same as central venous catheter (CVC) insertion; the anterior triangle approach is the preferred one; however, the needle and guidewire direction should be a cephalic one (compared to CVC direction).
- Seldinger technique is used for guidewire insertion.
- After guidewire insertion, the catheter should be inserted and conducted upward until resistance is sensed, or in the awake patient, a sense of pressure in skull base is noted by the patient; also, Doppler sonography or sizing the inserted length of the catheter by an external sizer.
- The catheter is sent from the right internal jugular vein over the guidewire to the cephalic direction.
- The catheter tip is sent cephalad to the "common facial vein outlet"; from there, it is sent to the jugular bulb; the jugular bulb is the dilated portion of the internal jugular vein; it is located distal to the jugular foramen (i.e., the anatomic opening in the bony skull from which the jugular vein exits).
- Inside the jugular bulb, the catheter tip should be positioned in the roof of the bulb; this is the site for $SjVO_2$ measurements.
- The location of the catheter tip should be documented by lateral or anteroposterior neck X-ray; it should be located at the level of the mastoid process; in lateral neck X-ray, this location is equal to the lower border of the first cervical spine or the inferior margin of the orbital rim; also, if we draw a line between the two mastoid processes, the tip of the catheter should be just cephalad to this line.
- Another way is the surface landmarks: the surface landmark for jugular vein bulb is 1 cm anterior and 1 cm below the mastoid process.
- The measurements made by the catheter should be calibrated, in vivo or in vitro, per information provided by the manufacturer.
- If the catheter tip is misplaced and attached to the vessel wall or if the catheter tip has move in either direction (cephalic or caudal) more than 2 cm from the bulb of jugular vein, the readings would be biased due to venous sample "contamination" and would fall in the biased range of measurement.
- Also, the speed of sampling should be less than 2 mL/min, to prevent mixing of cerebral venous blood with the venous blood from extra cranial veins; otherwise, mixing of these two samples would result in erroneous over-readings, falsely above the real normal values.

### 5.7.3 Complications of $SjvO_2$ Catheter

Complications of $SjvO_2$ catheter insertion are similar to the complications of central venous catheter insertion and could classified as those related to catheter insertion (like tissue or arterial injuries) and those related to the presence of catheter (like possible increased risk of catheter infection or thrombosis).

### 5.7.4 Data Collection by $SjvO_2$ Catheter

Normal values for $SjvO_2$ are between 55 and 85 %; however, most studies have declared the normal value for $SjvO_2$ in the range of 55–75 %. Anyway, values lower than 50 % are considered abnormal and accompanied with poor outcome in the majority of studies.

As mentioned above, $SjvO_2$ is an indirect surrogate index of global cerebral perfusion; so, it has a high specificity but its sensitivity is low; in other words, $SjvO_2$ could detect global cerebral ischemia but cannot detect exactly the location of the ischemic region in cerebral hemispheres. Also, as mentioned by White and Baker, the following factors could affect the accuracy of $SjvO_2$ readings:

- Simultaneous hemoglobin concentration
- Saturation of the systemic arterial blood
- Core body temperature
- Level of $CO_2$ in the arterial blood

### 5.7.5 Arterial-Jugular Vein Oxygen Gradient ($AjvDO_2$)

Another important index measured by calculating $SjvO_2$ is the gradient between arterial and jugular vein oxygen content, abbreviated as $AjvDO_2$. Schell and Cole have done this calculation using the sequence of following formulas:

$$DO_2 = CBF \times CaO_2$$

$$CMRO_2 = CBF \times \left(CaO_2 - CjvO_2\right)$$

$$AjvDO_2 = CaO_2 - CjvO_2$$

in which:

$DO_2$: cerebral $O_2$ delivery
CBF: cerebral blood flow
$CaO_2$: arterial $O_2$ content
$CMRO_2$: cerebral $O_2$ consumption
$CjvO_2$: jugular vein $O_2$ content
$AjvDO_2$: arterial-jugular vein oxygen gradient

Considering the above equations, $AjvDO_2$ could be calculated by solving the above formulas:

$$AjvDO_2 = \frac{CMRO_2}{CBF}$$

Schell and Cole have declared that normal $AjvDO_2$ values are between 4 and 8 $mLO_2$/100 mL of blood. Values less than 4 denote that $O_2$ delivery is more than $O_2$ consumption (i.e., luxury $O_2$ delivery), while values above 8 demonstrate $O_2$ shortage in brain tissue which could be due to increased $CMRO_2$ or decreased CBF (desaturation state). According to Schell and Cole, each of the above ranges for $AjvDO_2$ is associated with a number of differential diagnoses discussed here.

*$SjvO_2 > 75$ or $AjvDO_2 < 4$* (Luxury $O_2$ Delivery): This is due to decreased $CMRO_2$ (like hypothermia, administration of sedatives), increased CBF (like hypothermia), increased arterial oxygen content, or other causes like bran death.

*$SjvO_2 < 50$ or $AjvDO_2 > 8$* (Desaturation State): This is due to the following etiologies which should be considered and ruled out in the postoperative period for patients undergoing cardiac surgery:

- Increased $CMRO_2$ (like fever, hyperthermia, or seizure)
- Decreased CBF (like systemic hypotension, cerebral arterial vasospasm, hyperventilation-induced hypocapnia)
- Increased intracranial pressure (like brain edema or impaired cerebral venous return)
- Arterial hypoxia (impaired ventilation due to lung pathology or ventilator problems, impaired hemoglobin oxygenation, or impaired transfer and delivery of oxygen to tissues including brain)

According to White and Baker, in cardiac surgery patients, low systemic perfusion pressure during cardiopulmonary bypass, low hematocrit values, and rapid rewarming are the three main causes of intraoperative low $SjvO_2$ (Hatiboglu and Anil 1992; Sheinberg et al. 1992; Dearden and Midgley 1993; Croughwell et al. 1995; von Knobelsdorff et al. 1997; Gupta et al. 1999; Ip-Yam et al. 2000; Nandate et al. 2000; Schell and Cole 2000; Shaaban Ali et al. 2001; Kadoi et al. 2002; Smythe and Samra 2002; White and Baker 2002; Chieregato et al. 2003; Kadoi and Fujita 2003; Kawahara et al. 2003; Perez et al. 2003; Sarrafzadeh et al. 2003; Oh et al. 2004; Stocchetti et al. 2004; Alten and Mariscalco 2005; Shimizu et al. 2005; Wright 2007; Rohlwink and Figaji 2010).

## 5.8 Transcranial Doppler (TCD)

TCD was presented to the clinical practice for the first time by Rune Aaslid and colleagues in 1982 in order to assess blood flow velocities in cerebral arteries. TCD is a noninvasive monitor applicable to either operating room or intensive care unit patients, both in adult or pediatric patients. TCD is used to assess CNS vascular

status through measurement of *cerebral blood flow velocity* (*of course not the blood flow*); usually the mean flow velocity (*FV mean*) is used for assessments. This device is based on using ultrasonic Doppler signal, in the low frequency (1–2 MHz) using pulse-waved Doppler; the Doppler shift in signals gained during passage of red blood cells through the cerebral arteries is calculated by the device to demonstrate the blood flow velocity in the arteries under assessment.

Although electroencephalography (EEG) could assess the integrity of physiologic function in the cortical regions of brain, the subcortical areas are usually neglected by EEG; this is while the cognitive functions are mainly affected by the latter nuclei, while the blood flow to such regions is assessed more effectively by TCD; however, these two technologies assess different aspects of CNS integrity and function, and this is why their complementary use is more justified in higher-risk patients than their competitive comparison. Such high-risk patients may benefit, regarding CNS outcome, in the perioperative period by using both devices.

The following characteristics are among the main features of for assessment of the cerebral blood flow:

- Noninvasiveness
- Fast
- Real-time assessment
- Relatively low price
- Accurate
- Continuous monitoring
- The possibility for repeated assessments (reproducible)
- Indirect information from CNS arteries
- Application both in the operating room and outside of it (including the intensive care unit)
- Application to all age ranges

TCD has been used for cardiac surgery patients mainly during the intraoperative period to detect and prevent sandblasting events, microemboli and macroemboli caused by aortic clamping and manipulations; if there is severe aortic atherosclerosis, preventive surgical methods should be used to prevent stroke in high risk of stroke; even, it may lead to an important change in the surgical strategy to prevent unwanted postoperative CNS insults. However, in postoperative period, more widespread use of TCD could be anticipated. Some of the potential applications of TCD in the perioperative period of cardiac surgery patients could be as:

- Adequacy of CBF and arterial blood flow through the cerebral arteries
- Assessment of the CNS arterial patency (e.g., to rule out cerebral arterial vasospasm)
- Noninvasive monitoring of intracranial pressure (ICP)
- Assessment of brain death
- Assessment of CNS autoregulatory response (i.e., CNS cardiovascular response to a spectrum of stimuli like hypercapnia or blood pressure changes)
- Assessment of postoperative CNS perfusion in patients undergoing cardiac surgery (with or without cardiopulmonary bypass) with underlying borderline carotid stenosis

- Assessing the efficacy of antithrombotic therapies in reducing the platelet embolic load sent to the CNS
- Measurement of effective downstream pressure

The *arterial flow* is mainly determined by the following factors:

- Cerebral blood flow (CBF)
- The inherent vascular anatomy
- The anatomy of the collateral circulation and their perfusion ratio
- The insonation window and hence insonation angle
- The anatomical diameter of the artery

These *confounding factors* could affect the reliability of the assessments:

- Underlying hemodynamic status especially blood pressure (including systolic, diastolic, and mean arterial blood pressure)
- Arterial pressure of $CO_2$
- Gender; female have a bit higher arterial velocity, possibly to compensate for lower hematocrit values than men
- Age (cerebral blood flow has the lowest values after birth, i.e., 25 cm/s; reaching to its peak at the age of 4–6 years, i.e., 100 cm/s and then decreasing gradually with a steady velocity to reach 40 cm/s at the seventh decade of life)
- Diurnal time pattern of blood pressure and CNS perfusion (blood velocity remains the lowest at 11 A.M)
- Patient posture (i.e., the arterial flow is different while the patient is seated compared to supine position)
- Intracranial pressure (ICP)
- Level of consciousness, including administration or discontinuation of analgesic regimens

For gaining the Doppler data, one needs appropriate acoustic (or insonation) window; this window is usually an anatomic area in which the bone plate of the skull is thin or there is a normal anatomic window in the skull; the following locations are the main appropriate acoustic (or insonation) windows in the skull for performing TCD:

1. *Transtemporal* window (the supra-zygomatic portion of the temporal bone) usually used for assessment of anterior, middle, and posterior cerebral arteries (ACA, MCA, and PCA); this is the most commonly used approach for TCD; for performing TCD through this window, the patient should be supine, and an imaginary line is drawn between tragus of ear and the lateral canthus of the eye; the area from this lineup to about 2 cm should be searched while the probe is perpendicular to the bone and gel is applied; MCA blood flow has a good correlation with total cerebral blood flow; this is among the reasons why using this window has gained great popularity.
2. *Transorbital* window (through the eye globe) usually used for assessment of the ophthalmic arteries and also some cavernous portions of the internal carotid artery (i.e., the carotid siphon).
3. *Suboccipital* window used for assessment of the posterior cerebral circulation, mainly the basilar and vertebral arteries used for anterior cerebral artery "ACA" and posterior cerebral artery "PCA."
4. *Retromandibular* window mainly for assessment of cervical segments of the carotid artery.

However, the application of this device needs the following items as its prerequisites by the user:

- Having appropriate training and experience by the user; albeit all tries, 5–10 % of patients remain "poor window" with inadequate access.
- The main cerebral perfusing arteries should be used for assessments.
- Having appropriate Doppler window.
- The probe should be in a fixed position during assessment.
- Stable clinical condition for the patient should be prepared, either in operating room or inside the intensive care unit, including constant blood pressure and other hemodynamic measurements and also a constant level of sedation or anesthesia.

(Aaslid et al. 1982; Sturzenegger et al. 1995; Zurynski et al. 1995; Schmidt et al. 1997; Soustiel et al. 1998; Kaposzta et al. 1999; Markus 1999; Markus and Reid 1999; Fearn et al. 2001; Kumral et al. 2001; Costin et al. 2002; Kral et al. 2003; Moppett and Mahajan 2004; Polito et al. 2006; Radvany and Wholey 2008; Rasulo et al. 2008; Enninful-Eghan et al. 2010; Mok et al. 2012; Horsfield et al. 2013; McDonnell et al. 2013; Mills et al. 2013)

## 5.9 Other Modes for Assessment of Cerebral Blood Flow (Besides TCD)

*Positron emission tomography* (*PET*) is one of the latest imaging techniques based on nuclear medicine technology; in this method, positron-emitting radionuclide is administered to assess the fate of their metabolism in normal and abnormal tissues. PET could demonstrate us many of CNS variables, like cerebral blood flow (CBF) and cerebral oxygen uptake ($CMRO_2$). However, the main disadvantage of PET is its invasiveness (Abraham and Feng 2011; Portnow et al. 2013).

*Dynamic CT scanning* is a method of imaging used for measurement of regional cerebral blood flow (rCBF) based on the clearance of inhaled xenon or intravenous radionuclide contrast (O'Connor et al. 2011; Hochberg and Young 2012).

*Magnetic resonance angiography* (*MRA*) was first introduced in 1986, is noninvasive, and has many application in detection of cerebral vascular disease states like stenosis, occlusion, or aneurysm; some believe that in patients with peripheral vascular disease or history of previous cerebral disease undergoing cardiac surgery, preoperative assessment of cranial arteries using MRA has an effective role in preventing postoperative unwanted cerebral events (Uehara et al. 2001).

*Functional Magnetic Resonance Imaging* (*fMRI*): This technology is based on the fact that cerebral blood flow and cortical activity level are parallel phenomenon; this technology is noninvasive and is a very potent method for CBF assessment, both in research and clinic (Stern and Silbersweig 2001).

*Laser Doppler flowmetry* is used clinically to assess "microvascular blood flow" and in brain for "brain blood flow"; this technique is continuous and real time; however, there are a number of limitations in this technique including choice of bandwidth, patient motion artifact, calibration of the probe, the type of the laser,

and its invasiveness; also, it monitors a small sample of the total brain tissue and finally is not a routine monitor in cardiac postoperative care (Obeid et al. 1990; Leahy et al. 1999; Alvarez del Castillo 2001; Stevens 2004; De Georgia and Deogaonkar 2005).

*Thermal diffusion flowmetry* measures cerebral blood flow based on the thermal conductivity of the brain tissue; however, this method is invasive and has nearly no application in cardiac surgery ICU (Carter 1996; Vajkoczy et al. 2003).

*Intracranial pressure* (*ICP*) *monitoring* is an invasive technique usually used for neurosurgical intensive care; this technique is rarely used in cardiac surgery ICU.

## References

(2012) Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 116:248–273

Aaslid R, Markwalder TM, Nornes H (1982) Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 57:769–774

Abraham T, Feng J (2011) Evolution of brain imaging instrumentation. Semin Nucl Med 41:202–219

Alten J, Mariscalco MM (2005) Critical appraisal of Perez et al: Jugular venous oxygen saturation or arteriovenous difference of lactate content and outcome in children with severe traumatic brain injury. Pediatr Crit Care Med 6:480–482

Alvarez del Castillo M (2001) Monitoring neurologic patients in intensive care. Curr Opin Crit Care 7:49–60

Amantini A, Amadori A, Fossi S (2008) Evoked potentials in the ICU. Eur J Anaesthesiol Suppl 42:196–202

Andritsos M, Singh N, Patel P, Sinha A, Fassl J, Wyckoff T, Riha H, Roscher C, Subramaniam B, Ramakrishna H, Augoustides JG (2011) The year in cardiothoracic and vascular anesthesia: selected highlights from 2010. J Cardiothorac Vasc Anesth 25:6–15

Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, Coursin DB, Herr DL, Tung A, Robinson BR, Fontaine DK, Ramsay MA, Riker RR, Sessler CN, Pun B, Skrobik Y, Jaeschke R (2013) Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 41:263–306

Benitez-Rosario MA, Castillo-Padros M, Garrido-Bernet B, Gonzalez-Guillermo T, Martinez-Castillo LP, Gonzalez A (2013) Appropriateness and reliability testing of the modified Richmond agitation-sedation scale in Spanish patients with advanced cancer. J Pain Symptom Manage 45:1112–1119

Brady KM, Mytar JO, Kibler KK, Hogue CW Jr, Lee JK, Czosnyka M, Smielewski P, Easley RB (2010) Noninvasive autoregulation monitoring with and without intracranial pressure in the naive piglet brain. Anesth Analg 111:191–195

Brandl KM, Langley KA, Riker RR, Dork LA, Quails CR, Levy H (2001) Confirming the reliability of the sedation-agitation scale administered by ICU nurses without experience in its use. Pharmacotherapy 21:431–436

Brocas E, Dupont H, Paugam-Burtz C, Servin F, Mantz J, Desmonts JM (2002) Bispectral index variations during tracheal suction in mechanically ventilated critically ill patients: effect of an alfentanil bolus. Intensive Care Med 28:211–213

Brogan TV, Thiagarajan RR, Rycus PT, Bartlett RH, Bratton SL (2009) Extracorporeal membrane oxygenation in adults with severe respiratory failure: a multi-center database. Intensive Care Med 35:2105–2114

Bronicki RA, Chang AC (2011) Management of the postoperative pediatric cardiac surgical patient. Crit Care Med 39:1974–1984
Brown EN, Lydic R, Schiff ND (2010) General anesthesia, sleep, and coma. N Engl J Med 363:2638–2650
Brush DR, Kress JP (2009) Sedation and analgesia for the mechanically ventilated patient. Clin Chest Med 30:131–141, ix
Carrasco G (2000) Instruments for monitoring intensive care unit sedation. Crit Care 4:217–225
Carter LP (1996) Thermal diffusion flowmetry. Neurosurg Clin N Am 7:749–754
Casati A, Fanelli G, Pietropaoli P, Proietti R, Tufano R, Danelli G, Fierro G, De Cosmo G, Servillo G (2005) Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. Anesth Analg 101:740–747, table of contents
Casati A, Spreafico E, Putzu M, Fanelli G (2006) New technology for noninvasive brain monitoring: continuous cerebral oximetry. Minerva Anestesiol 72:605–625
Cengiz P, Seidel K, Rycus PT, Brogan TV, Roberts JS (2005) Central nervous system complications during pediatric extracorporeal life support: incidence and risk factors. Crit Care Med 33:2817–2824
Chabot RJ, Gugino VD (1993) Quantitative electroencephalographic monitoring during cardiopulmonary bypass. Anesthesiology 78:209–211
Chabot RJ, Gugino LD, Aglio LS, Maddi R, Cote W (1997) QEEG and neuropsychological profiles of patients after undergoing cardiopulmonary bypass surgical procedures. Clin Electroencephalogr 28:98–105
Chakravarthy M, Holla S, Jawali V (2010) Index of consciousness and bispectral index values are interchangeable during normotension and hypotension but not during non pulsatile flow state during cardiac surgical procedures: a prospective study. J Clin Monit Comput 24:83–91
Chieregato A, Calzolari F, Trasforini G, Targa L, Latronico N (2003) Normal jugular bulb oxygen saturation. J Neurol Neurosurg Psychiatry 74:784–786
Cogan J (2010) Pain management after cardiac surgery. Semin Cardiothorac Vasc Anesth 14:201–204
Constant I, Sabourdin N (2012) The EEG signal: a window on the cortical brain activity. Paediatr Anaesth 22:539–552
Costin M, Rampersad A, Solomon RA, Connolly ES, Heyer EJ (2002) Cerebral injury predicted by transcranial Doppler ultrasonography but not electroencephalography during carotid endarterectomy. J Neurosurg Anesthesiol 14:287–292
Courtman SP, Wardurgh A, Petros AJ (2003) Comparison of the bispectral index monitor with the comfort score in assessing level of sedation of critically ill children. Intensive Care Med 29:2239–2246
Croughwell ND, White WD, Smith LR, Davis RD, Glower DD Jr, Reves JG, Newman MF (1995) Jugular bulb saturation and mixed venous saturation during cardiopulmonary bypass. J Card Surg 10:503–508
Cyrous A, O'Neal B, Freeman WD (2012) New approaches to bedside monitoring in stroke. Expert Rev Neurother 12:915–928
Dalton HJ, Rycus PT, Conrad SA (2005) Update on extracorporeal life support 2004. Semin Perinatol 29:24–33
De Georgia MA, Deogaonkar A (2005) Multimodal monitoring in the neurological intensive care unit. Neurologist 11:45–54
De Jonghe B, Cook D, Appere-De-Vecchi C, Guyatt G, Meade M, Outin H (2000) Using and understanding sedation scoring systems: a systematic review. Intensive Care Med 26:275–285
Dearden NM, Midgley S (1993) Technical considerations in continuous jugular venous oxygen saturation measurement. Acta Neurochir Suppl (Wien) 59:91–97
Denault A, Deschamps A, Murkin JM (2007) A proposed algorithm for the intraoperative use of cerebral near-infrared spectroscopy. Semin Cardiothorac Vasc Anesth 11:274–281

Deogaonkar A, Gupta R, DeGeorgia M, Sabharwal V, Gopakumaran B, Schubert A, Provencio JJ (2004) Bispectral Index monitoring correlates with sedation scales in brain-injured patients. Crit Care Med 32:2403–2406

Drummond JC (2000) Monitoring depth of anesthesia: with emphasis on the application of the bispectral index and the middle latency auditory evoked response to the prevention of recall. Anesthesiology 93:876–882

Edmonds HL Jr, Isley MR, Sloan TB, Alexandrov AV, Razumovsky AY (2011) American society of neurophysiologic monitoring and American society of neuroimaging joint guidelines for transcranial Doppler ultrasonic monitoring. J Neuroimaging 21:177–183

Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, Francis J, Speroff T, Gautam S, Margolin R, Sessler CN, Dittus RS, Bernard GR (2003) Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA 289:2983–2991

Enninful-Eghan H, Moore RH, Ichord R, Smith-Whitley K, Kwiatkowski JL (2010) Transcranial Doppler ultrasonography and prophylactic transfusion program is effective in preventing overt stroke in children with sickle cell disease. J Pediatr 157:479–484

Erickson KM, Cole DJ (2010) Carotid artery disease: stenting vs endarterectomy. Br J Anaesth 105(Suppl 1):i34–i49

Fearn SJ, Pole R, Wesnes K, Faragher EB, Hooper TL, McCollum CN (2001) Cerebral injury during cardiopulmonary bypass: emboli impair memory. J Thorac Cardiovasc Surg 121:1150–1160

Fedorow C, Grocott HP (2010) Cerebral monitoring to optimize outcomes after cardiac surgery. Curr Opin Anaesthesiol 23:89–94

Ferrari M, Mottola L, Quaresima V (2004) Principles, techniques, and limitations of near infrared spectroscopy. Can J Appl Physiol 29:463–487

Fischer GW, Torrillo TM, Weiner MM, Rosenblatt MA (2009) The use of cerebral oximetry as a monitor of the adequacy of cerebral perfusion in a patient undergoing shoulder surgery in the beach chair position. Pain Pract 9:304–307

Florence G, Guerit JM, Gueguen B (2004) Electroencephalography (EEG) and somatosensory evoked potentials (SEP) to prevent cerebral ischaemia in the operating room. Neurophysiol Clin 34:17–32

Foster CB, Spaeder MC, McCarter RJ, Cheng YI, Berger JT (2013) The use of near-infrared spectroscopy during an extubation readiness trial as a predictor of extubation outcome. Pediatr Crit Care Med 14:587–592

Fraser GL, Riker RR (2005) Bispectral index monitoring in the intensive care unit provides more signal than noise. Pharmacotherapy 25:19S–27S

Frenzel D, Greim CA, Sommer C, Bauerle K, Roewer N (2002) Is the bispectral index appropriate for monitoring the sedation level of mechanically ventilated surgical ICU patients? Intensive Care Med 28:178–183

Freye E (2005a) Cerebral monitoring in the operating room and the intensive care unit – an introductory for the clinician and a guide for the novice wanting to open a window to the brain. Part II: Sensory-evoked potentials (SSEP, AEP, VEP). J Clin Monit Comput 19:77–168

Freye E (2005b) Cerebral monitoring in the operating room and the intensive care unit: an introductory for the clinician and a guide for the novice wanting to open a window to the brain. Part III: Spinal cord evoked potentials. J Clin Monit Comput 19:169–178

Freye E, Levy JV (2005) Cerebral monitoring in the operating room and the intensive care unit: an introductory for the clinician and a guide for the novice wanting to open a window to the brain. Part I: The electroencephalogram. J Clin Monit Comput 19:1–76

Futier E, Chanques G, Cayot Constantin S, Vernis L, Barres A, Guerin R, Chartier C, Perbet S, Petit A, Jabaudon M, Bazin JE, Constantin JM (2012) Influence of opioid choice on mechanical ventilation duration and ICU length of stay. Minerva Anestesiol 78:46–53

Ghosh A, Elwell C, Smith M (2012) Review article: cerebral near-infrared spectroscopy in adults: a work in progress. Anesth Analg 115:1373–1383

Golukhova EZ, Polunina AG, Zhuravleva SV, Lefterova NP, Begachev AV (2010) Size of left cardiac chambers correlates with cerebral microembolic load in open heart operations. Cardiol Res Pract 2010:143679

Golukhova EZ, Polunina AG, Lefterova NP, Begachev AV (2011) Electroencephalography as a tool for assessment of brain ischemic alterations after open heart operations. Stroke Res Treat 2011:980873

Green D, Paklet L (2010) Latest developments in peri-operative monitoring of the high-risk major surgery patient. Int J Surg 8:90–99

Grimm M, Zimpfer D, Czerny M, Kilo J, Kasimir MT, Kramer L, Krokovay A, Wolner E (2003) Neurocognitive deficit following mitral valve surgery. Eur J Cardiothorac Surg 23:265–271

Gugino LD, Chabot RJ, Aglio LS, Aranki S, Dekkers R, Maddi R (1999) QEEG changes during cardiopulmonary bypass: relationship to postoperative neuropsychological function. Clin Electroencephalogr 30:53–63

Gugino LD, Chabot RJ, Prichep LS, John ER, Formanek V, Aglio LS (2001) Quantitative EEG changes associated with loss and return of consciousness in healthy adult volunteers anaesthetized with propofol or sevoflurane. Br J Anaesth 87:421–428

Gugino LD, Aglio LS, Yli-Hankala A (2004) Monitoring the electroencephalogram during bypass procedures. Semin Cardiothorac Vasc Anesth 8:61–83

Gupta AK, Hutchinson PJ, Al-Rawi P, Gupta S, Swart M, Kirkpatrick PJ, Menon DK, Datta AK (1999) Measuring brain tissue oxygenation compared with jugular venous oxygen saturation for monitoring cerebral oxygenation after traumatic brain injury. Anesth Analg 88: 549–553

Hampton DA, Schreiber MA (2013) Near infrared spectroscopy: clinical and research uses. Transfusion 53(Suppl 1):52S–58S

Hankey GJ (2012) Anticoagulant therapy for patients with ischaemic stroke. Nat Rev Neurol 8:319–328

Hasegawa T, Okita Y (2009) Intraoperative monitoring of the brain and spinal cord ischemia during thoracic aortic surgery. Kyobu Geka 62:655–660

Hatiboglu MT, Anil A (1992) Structural variations in the jugular foramen of the human skull. J Anat 180(Pt 1):191–196

Hauser E, Seidl R, Rohrbach D, Hartl I, Marx M, Wimmer M (1993) Quantitative EEG before and after open heart surgery in children. A significant decrease in the beta and alpha 2 bands postoperatively. Electroencephalogr Clin Neurophysiol 87:284–290

Hernandez-Gancedo C, Pestana D, Pena N, Royo C, Perez-Chrzanowska H, Criado A (2006) Monitoring sedation in critically ill patients: bispectral index, Ramsay and observer scales. Eur J Anaesthesiol 23:649–653

Hervey-Jumper SL, Annich GM, Yancon AR, Garton HJ, Muraszko KM, Maher CO (2011) Neurological complications of extracorporeal membrane oxygenation in children. J Neurosurg Pediatr 7:338–344

Hill RA, Chiappa KH (1994) Electrophysiologic monitoring in the intensive care unit. Can J Neurol Sci 21:S12–S16

Hochberg AR, Young GS (2012) Cerebral perfusion imaging. Semin Neurol 32:454–465

Horsfield MA, Jara JL, Saeed NP, Panerai RB, Robinson TG (2013) Regional differences in dynamic cerebral autoregulation in the healthy brain assessed by magnetic resonance imaging. PLoS One 8:e62588

Hoshi Y (2007) Functional near-infrared spectroscopy: current status and future prospects. J Biomed Opt 12:062106

Hoshi Y (2011) Towards the next generation of near-infrared spectroscopy. Philos Transact A Math Phys Eng Sci 369:4425–4439

Huppert TJ, Diamond SG, Franceschini MA, Boas DA (2009) HomER: a review of time-series analysis methods for near-infrared spectroscopy of the brain. Appl Opt 48:D280–D298

Ip-Yam PC, Thomas SD, Jackson M, Rashid A, Behl S (2000) Effects of temperature strategy during cardiopulmonary bypass on cerebral oxygen balance. J Cardiovasc Surg (Torino) 41:1–6

Isley MR, Edmonds HL Jr, Stecker M (2009) Guidelines for intraoperative neuromonitoring using raw (analog or digital waveforms) and quantitative electroencephalography: a position statement by the American Society of Neurophysiological Monitoring. J Clin Monit Comput 23:369–390

Jacobson S, Jerrier H (2000) EEG in delirium. Semin Clin Neuropsychiatry 5:86–92

Jameson LC, Sloan TB (2006) Using EEG to monitor anesthesia drug effects during surgery. J Clin Monit Comput 20:445–472

Johansen JW, Sebel PS (2000) Development and clinical application of electroencephalographic bispectrum monitoring. Anesthesiology 93:1336–1344

Kadoi Y, Fujita N (2003) Increasing mean arterial pressure improves jugular venous oxygen saturation in patients with and without preexisting stroke during normothermic cardiopulmonary bypass. J Clin Anesth 15:339–344

Kadoi Y, Saito S, Goto F, Fujita N (2002) Slow rewarming has no effects on the decrease in jugular venous oxygen hemoglobin saturation and long-term cognitive outcome in diabetic patients. Anesth Analg 94:1395–1401, table of contents

Kaposzta Z, Young E, Bath PM, Markus HS (1999) Clinical application of asymptomatic embolic signal detection in acute stroke: a prospective study. Stroke 30:1814–1818

Kawahara F, Kadoi Y, Saito S, Goto F, Fujita N (2003) Slow rewarming improves jugular venous oxygen saturation during rewarming. Acta Anaesthesiol Scand 47:419–424

Kertai MD, Whitlock EL, Avidan MS (2012) Brain monitoring with electroencephalography and the electroencephalogram-derived bispectral index during cardiac surgery. Anesth Analg 114:533–546

Khan BA, Guzman O, Campbell NL, Walroth T, Tricker J, Hui SL, Perkins A, Zawahiri M, Buckley JD, Farber MO, Ely W, Boustani MA (2012) Comparison and agreement between the Richmond Agitation-Sedation Scale and the Riker Sedation-Agitation Scale in evaluating patients' eligibility for delirium assessment in the ICU. Chest 142:48–54

Kral MC, Brown RT, Nietert PJ, Abboud MR, Jackson SM, Hynd GW (2003) Transcranial Doppler ultrasonography and neurocognitive functioning in children with sickle cell disease. Pediatrics 112:324–331

Kumral E, Balkir K, Yagdi T, Kara E, Evyapan D, Bilkay O (2001) Microembolic signals in patients undergoing coronary artery bypass grafting. Effect of aortic atherosclerosis. Tex Heart Inst J 28:16–20

La Monaca M, David A, Gaeta R, Lentini S (2010) Near Infrared Spectroscopy for cerebral monitoring during cardiovascular surgery. Clin Ter 161:549–553

Lamas A, Lopez-Herce J (2010) Monitoring sedation in the critically ill child. Anaesthesia 65:516–524

Lampe JW, Becker LB (2011) State of the art in therapeutic hypothermia. Annu Rev Med 62:79–93

Leahy MJ, de Mul FF, Nilsson GE, Maniewski R (1999) Principles and practice of the laser-Doppler perfusion technique. Technol Health Care 7:143–162

Li J (2012) Systemic oxygen transport derived by using continuous measured oxygen consumption after the Norwood procedure-an interim review. Interact Cardiovasc Thorac Surg 15:93–101

Lima A, van Bommel J, Sikorska K, van Genderen M, Klijn E, Lesaffre E, Ince C, Bakker J (2011) The relation of near-infrared spectroscopy with changes in peripheral circulation in critically ill patients. Crit Care Med 39:1649–1654

Markowitz SD, Ichord RN, Wernovsky G, Gaynor JW, Nicolson SC (2007) Surrogate markers for neurological outcome in children after deep hypothermic circulatory arrest. Semin Cardiothorac Vasc Anesth 11:59–65

Markus HS (1999) Transcranial Doppler ultrasound. J Neurol Neurosurg Psychiatry 67:135–137

Markus HS, Reid G (1999) Frequency filtering improves ultrasonic embolic signal detection. Ultrasound Med Biol 25:857–860

Martin WH, Stecker MM (2008) ASNM position statement: intraoperative monitoring of auditory evoked potentials. J Clin Monit Comput 22:75–85

McDonnell MN, Berry NM, Cutting MA, Keage HA, Buckley JD, Howe PR (2013) Transcranial Doppler ultrasound to assess cerebrovascular reactivity: reliability, reproducibility and effect of posture. Peer J 1:e65

Mills JN, Mehta V, Russin J, Amar AP, Rajamohan A, Mack WJ (2013) Advanced imaging modalities in the detection of cerebral vasospasm. Neurol Res Int 2013:415960

Moerman A, Denys W, De Somer F, Wouters PF, De Hert SG (2013) Influence of variations in systemic blood flow and pressure on cerebral and systemic oxygen saturation in cardiopulmonary bypass patients. Br J Anaesth 111:619–626

Mok V, Ding D, Fu J, Xiong Y, Chu WW, Wang D, Abrigo JM, Yang J, Wong A, Zhao Q, Guo Q, Hong Z, Wong KS (2012) Transcranial Doppler ultrasound for screening cerebral small vessel disease: a community study. Stroke 43:2791–2793

Moppett IK, Mahajan RP (2004) Transcranial Doppler ultrasonography in anaesthesia and intensive care. Br J Anaesth 93:710–724

Murkin JM (2013) Is it better to shine a light, or rather to curse the darkness? Cerebral near-infrared spectroscopy and cardiac surgery. Eur J Cardiothorac Surg 43:1081–1083

Murkin JM, Arango M (2009) Near-infrared spectroscopy as an index of brain and tissue oxygenation. Br J Anaesth 103(Suppl 1):i3–i13

Murkin JM, Adams SJ, Novick RJ, Quantz M, Bainbridge D, Iglesias I, Cleland A, Schaefer B, Irwin B, Fox S (2007) Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. Anesth Analg 104:51–58

Nandate K, Vuylsteke A, Ratsep I, Messahel S, Oduro-Dominah A, Menon DK, Matta BF (2000) Effects of isoflurane, sevoflurane and propofol anaesthesia on jugular venous oxygen saturation in patients undergoing coronary artery bypass surgery. Br J Anaesth 84:631–633

Nelson DP, Andropoulos DB, Fraser CD Jr (2008) Perioperative neuroprotective strategies. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 11:49–56

Newburger JW, Jonas RA, Wernovsky G, Wypij D, Hickey PR, Kuban KC, Farrell DM, Holmes GL, Helmers SL, Constantinou J et al (1993) A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. N Engl J Med 329:1057–1064

Nuwer M (1997) Assessment of digital EEG, quantitative EEG, and EEG brain mapping: report of the American Academy of Neurology and the American Clinical Neurophysiology Society. Neurology 49:277–292

Nuwer MR, Dawson EG, Carlson LG, Kanim LE, Sherman JE (1995) Somatosensory evoked potential spinal cord monitoring reduces neurologic deficits after scoliosis surgery: results of a large multicenter survey. Electroencephalogr Clin Neurophysiol 96:6–11

O'Connor JP, Tofts PS, Miles KA, Parkes LM, Thompson G, Jackson A (2011) Dynamic contrast-enhanced imaging techniques: CT and MRI. Br J Radiol 84 Spec No 2:S112–S120

Obeid AN, Barnett NJ, Dougherty G, Ward G (1990) A critical review of laser Doppler flowmetry. J Med Eng Technol 14:178–181

Oh YJ, Kim SH, Shinn HK, Lee CS, Hong YW, Kwak YL (2004) Effects of milrinone on jugular bulb oxygen saturation and cerebrovascular carbon dioxide reactivity in patients undergoing coronary artery bypass graft surgery. Br J Anaesth 93:634–638

Olson DM, Thoyre SM, Auyong DB (2007) Perspectives on sedation assessment in critical care. AACN Adv Crit Care 18:380–395

Palanca BJ, Mashour GA, Avidan MS (2009) Processed electroencephalogram in depth of anesthesia monitoring. Curr Opin Anaesthesiol 22:553–559

Palombo G, Stella N, Faraglia V, Taurino M (2010) Aortic arch catheterization during transfemoral carotid artery stenting: an underestimated source of cerebral emboli. Acta Chir Belg 110:165–168

Patel SB, Kress JP (2012) Sedation and analgesia in the mechanically ventilated patient. Am J Respir Crit Care Med 185:486–497

Payen JF, Chanques G, Mantz J, Hercule C, Auriant I, Leguillou JL, Binhas M, Genty C, Rolland C, Bosson JL (2007) Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. Anesthesiology 106:687–695, quiz 891–682

Perez A, Minces PG, Schnitzler EJ, Agosta GE, Medina SA, Ciraolo CA (2003) Jugular venous oxygen saturation or arteriovenous difference of lactate content and outcome in children with severe traumatic brain injury. Pediatr Crit Care Med 4:33–38

Poe GR, Walsh CM, Bjorness TE (2010) Cognitive neuroscience of sleep. Prog Brain Res 185:1–19

Polito A, Ricci Z, Di Chiara L, Giorni C, Iacoella C, Sanders SP, Picardo S (2006) Cerebral blood flow during cardiopulmonary bypass in pediatric cardiac surgery: the role of transcranial Doppler–a systematic review of the literature. Cardiovasc Ultrasound 4:47

Portnow LH, Vaillancourt DE, Okun MS (2013) The history of cerebral PET scanning: from physiology to cutting-edge technology. Neurology 80:952–956

Pua HL, Bissonnette B (1998) Cerebral physiology in paediatric cardiopulmonary bypass. Can J Anaesth 45:960–978

Radovanovic D, Radovanovic Z (2011) Awareness during general anaesthesia–implications of explicit intraoperative recall. Eur Rev Med Pharmacol Sci 15:1085–1089

Radvany MG, Wholey M (2008) Expanding use of embolic protection devices. Semin Interv Radiol 25:27–36

Rao GS, Durga P (2011) Changing trends in monitoring brain ischemia: from intracranial pressure to cerebral oximetry. Curr Opin Anaesthesiol 24:487–494

Rasmussen LS, Sperling B, Abildstrom HH, Moller JT (2002) Neuron loss after coronary artery bypass detected by SPECT estimation of benzodiazepine receptors. Ann Thorac Surg 74:1576–1580

Rasulo FA, De Peri E, Lavinio A (2008) Transcranial Doppler ultrasonography in intensive care. Eur J Anaesthesiol Suppl 42:167–173

Riker RR, Picard JT, Fraser GL (1999) Prospective evaluation of the sedation-agitation scale for adult critically ill patients. Crit Care Med 27:1325–1329

Riker RR, Fraser GL, Simmons LE, Wilkins ML (2001) Validating the sedation-agitation scale with the bispectral index and visual analog scale in adult ICU patients after cardiac surgery. Intensive Care Med 27:853–858

Rodriguez RA (2004) Human auditory evoked potentials in the assessment of brain function during major cardiovascular surgery. Semin Cardiothorac Vasc Anesth 8:85–99

Roggenbach J, Rauch H (2011) Type A dissection. Principles of anesthesiological management. Anaesthesist 60:139–151

Rohlwink UK, Figaji AA (2010) Methods of monitoring brain oxygenation. Childs Nerv Syst 26:453–464

Rolfe P (2000) In vivo near-infrared spectroscopy. Annu Rev Biomed Eng 2:715–754

Rollins MD, Hubbard A, Zabrocki L, Barnhart DC, Bratton SL (2012) Extracorporeal membrane oxygenation cannulation trends for pediatric respiratory failure and central nervous system injury. J Pediatr Surg 47:68–75

Sarrafzadeh AS, Kiening KL, Unterberg AW (2003) Neuromonitoring: brain oxygenation and microdialysis. Curr Neurol Neurosci Rep 3:517–523

Scheeren TW, Schober P, Schwarte LA (2012) Monitoring tissue oxygenation by near infrared spectroscopy (NIRS): background and current applications. J Clin Monit Comput 26:279–287

Schell RM, Cole DJ (2000) Cerebral monitoring: jugular venous oximetry. Anesth Analg 90:559–566

Schmidt B, Klingelhofer J, Schwarze JJ, Sander D, Wittich I (1997) Noninvasive prediction of intracranial pressure curves using transcranial Doppler ultrasonography and blood pressure curves. Stroke 28:2465–2472

Sebel PS (1998) Central nervous system monitoring during open heart surgery: an update. J Cardiothorac Vasc Anesth 12:3–8

Sellmann T, Winterhalter M, Herold U, Kienbaum P (2010) Implantation of cardioverter-defibrillators. How much anesthesia is necessary? Anaesthesist 59:507–518

Sessler CN, Grap MJ, Brophy GM (2001) Multidisciplinary management of sedation and analgesia in critical care. Semin Respir Crit Care Med 22:211–226

Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK (2002) The Richmond agitation-sedation scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 166:1338–1344

Sessler CN, Grap MJ, Ramsay MA (2008) Evaluating and monitoring analgesia and sedation in the intensive care unit. Crit Care 12(Suppl 3):S2
Sessler CN, Riker RR, Ramsay MA (2013) Evaluating and monitoring sedation, arousal, and agitation in the ICU. Semin Respir Crit Care Med 34:169–178
Seule M, Muroi C, Sikorski C, Keller E (2013) Monitoring of cerebral hemodynamics and oxygenation to detect delayed ischemic neurological deficit after aneurysmal subarachnoid hemorrhage. Acta Neurochir Suppl 115:57–61
Shaaban Ali M, Harmer M, Latto I (2001) Jugular bulb oximetry during cardiac surgery. Anaesthesia 56:24–37
Sheinberg M, Kanter MJ, Robertson CS, Contant CF, Narayan RK, Grossman RG (1992) Continuous monitoring of jugular venous oxygen saturation in head-injured patients. J Neurosurg 76:212–217
Shimizu N, Gilder F, Bissonnette B, Coles J, Bohn D, Miyasaka K (2005) Brain tissue oxygenation index measured by near infrared spatially resolved spectroscopy agreed with jugular bulb oxygen saturation in normal pediatric brain: a pilot study. Childs Nerv Syst 21:181–184
Simmons LE, Riker RR, Prato BS, Fraser GL (1999) Assessing sedation during intensive care unit mechanical ventilation with the bispectral index and the sedation-agitation scale. Crit Care Med 27:1499–1504
Slater JP, Guarino T, Stack J, Vinod K, Bustami RT, Brown JM III, Rodriguez AL, Magovern CJ, Zaubler T, Freundlich K, Parr GV (2009) Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. Ann Thorac Surg 87:36–44, discussion 44–35
Sloan TB (1995) Electrophysiologic monitoring in head injury. New Horiz 3:431–438
Sloan TB (2004) Electrophysiologic monitoring during surgery to repair the thoracoabdominal aorta. Semin Cardiothorac Vasc Anesth 8:113–125
Sloan TB, Jameson LC (2007) Electrophysiologic monitoring during surgery to repair the thoracoabdominal aorta. J Clin Neurophysiol 24:316–327
Sloan TB, Edmonds HL Jr, Koht A (2013) Intraoperative electrophysiologic monitoring in aortic surgery. J Cardiothorac Vasc Anesth [Article in Press]
Smith M (2011) Shedding light on the adult brain: a review of the clinical applications of near-infrared spectroscopy. Philos Transact A Math Phys Eng Sci 369:4452–4469
Smythe PR, Samra SK (2002) Monitors of cerebral oxygenation. Anesthesiol Clin North America 20:293–313
Soustiel JF, Bruk B, Shik B, Hadani M, Feinsod M (1998) Transcranial Doppler in vertebrobasilar vasospasm after subarachnoid hemorrhage. Neurosurgery 43:282–291, discussion 291–283
Stern E, Silbersweig DA (2001) Advances in functional neuroimaging methodology for the study of brain systems underlying human neuropsychological function and dysfunction. J Clin Exp Neuropsychol 23:3–18
Stevens WJ (2004) Multimodal monitoring: head injury management using $SjvO_2$ and LICOX. J Neurosci Nurs 36:332–339
Stocchetti N, Canavesi K, Magnoni S, Valeriani V, Conte V, Rossi S, Longhi L, Zanier ER, Colombo A (2004) Arterio-jugular difference of oxygen content and outcome after head injury. Anesth Analg 99:230–234
Sturzenegger M, Mattle HP, Rivoir A, Baumgartner RW (1995) Ultrasound findings in carotid artery dissection: analysis of 43 patients. Neurology 45:691–698
Svyatets M, Tolani K, Zhang M, Tulman G, Charchaflieh J (2010) Perioperative management of deep hypothermic circulatory arrest. J Cardiothorac Vasc Anesth 24:644–655
Thuong M (2008) Sedation and analgesia assessment tools in ICU patients. Ann Fr Anesth Reanim 27:581–595
Toleikis JR (2005) Intraoperative monitoring using somatosensory evoked potentials. A position statement by the American Society of Neurophysiological Monitoring. J Clin Monit Comput 19:241–258
Tsygan NV (2012) The algorithm of the comprehensive assessment of the brain during cardiac surgery with cardiopulmonary bypass. Voen Med Zh 333:42–46

Turkmen A, Altan A, Turgut N, Vatansever S, Gokkaya S (2006) The correlation between the Richmond agitation-sedation scale and bispectral index during dexmedetomidine sedation. Eur J Anaesthesiol 23:300–304

Uehara T, Tabuchi M, Kozawa S, Mori E (2001) MR angiographic evaluation of carotid and intracranial arteries in Japanese patients scheduled for coronary artery bypass grafting. Cerebrovasc Dis 11:341–345

Vajkoczy P, Horn P, Thome C, Munch E, Schmiedek P (2003) Regional cerebral blood flow monitoring in the diagnosis of delayed ischemia following aneurysmal subarachnoid hemorrhage. J Neurosurg 98:1227–1234

Veel T, Bugge JF, Kirkeboen KA, Pleym H (2010) Anaesthesia for open-heart surgery in adults. Tidsskr Nor Laegeforen 130:618–622

Vohra HA, Modi A, Ohri SK (2009) Does use of intra-operative cerebral regional oxygen saturation monitoring during cardiac surgery lead to improved clinical outcomes? Interact Cardiovasc Thorac Surg 9:318–322

von Knobelsdorff G, Hanel F, Werner C, Schulte am Esch J (1997) Jugular bulb oxygen saturation and middle cerebral blood flow velocity during cardiopulmonary bypass. J Neurosurg Anesthesiol 9:128–133

Watson BD, Kane-Gill SL (2004) Sedation assessment in critically ill adults: 2001–2004 update. Ann Pharmacother 38:1898–1906

White H, Baker A (2002) Continuous jugular venous oximetry in the neurointensive care unit–a brief review. Can J Anaesth 49:623–629

Williams GD, Ramamoorthy C (2007) Brain monitoring and protection during pediatric cardiac surgery. Semin Cardiothorac Vasc Anesth 11:23–33

Wolf M, Ferrari M, Quaresima V (2007) Progress of near-infrared spectroscopy and topography for brain and muscle clinical applications. J Biomed Opt 12:062104

Wright WL (2007) Multimodal monitoring in the ICU: when could it be useful? J Neurol Sci 261:10–15

Young CC, Prielipp RC (2001) Benzodiazepines in the intensive care unit. Crit Care Clin 17:843–862

Zeitlhofer J, Saletu B, Anderer P, Asenbaum S, Spiss C, Mohl W, Kasall H, Wolner E, Deecke L (1988) Topographic brain mapping of EEG before and after open-heart surgery. Neuropsychobiology 20:51–56

Zheng F, Sheinberg R, Yee MS, Ono M, Zheng Y, Hogue CW (2013) Cerebral near-infrared spectroscopy monitoring and neurologic outcomes in adult cardiac surgery patients: a systematic review. Anesth Analg 116:663–676

Zimpfer D, Czerny M, Kilo J, Kasimir MT, Madl C, Kramer L, Wieselthaler GM, Wolner E, Grimm M (2002) Cognitive deficit after aortic valve replacement. Ann Thorac Surg 74:407–412, discussion 412

Zulueta JL, Vida VL, Perisinotto E, Pittarello D, Stellin G (2013) The role of intraoperative regional oxygen saturation using near infrared spectroscopy in the prediction of Low output syndrome after pediatric heart surgery. J Card Surg 24(4):446–452

Zurynski YA, Dorsch NW, Fearnside MR (1995) Incidence and effects of increased cerebral blood flow velocity after severe head injury: a transcranial Doppler ultrasound study II. Effect of vasospasm and hyperemia on outcome. J Neurol Sci 134:41–46

# Postoperative Bleeding Disorders after Cardiac Surgery

6

Sylvia Martin-Stone

## Contents



S. Martin-Stone, PharmD, BCPS
Department of Pharmacy Services, Cedars-Sinai Medical Center,
8700 Beverly Blvd., Room A-903, Los Angeles, CA 90048, USA
e-mail: sylvia.martin@cshs.org

A. Dabbagh et al. (eds.), *Postoperative Critical Care for Cardiac Surgical Patients*,
DOI 10.1007/978-3-642-40418-4_6, © Springer-Verlag Berlin Heidelberg 2014

**Abstract**

Maintaining the delicate balance of thrombostasis postoperatively requires attention to preoperative, intraoperative, and postoperative effects on the coagulation cascade. Identifying preoperative risk factors for bleeding including medication history, comorbid conditions, and prior bleeding complications is an integral part of preventing postoperative bleeding complications. Outpatient anticoagulant therapies are rapidly evolving with the development of novel medications targeting specific coagulation factors such as thrombin and factor Xa. These agents require an understanding of their effects and limitations in the perioperative period. Additionally, an understanding of the interplay between the coagulation cascade and external factors affecting platelet quantity and function can help direct management of postoperative bleeding complications. Applying appropriate monitoring techniques and result interpretation can guide therapy especially in coagulopathic disease states such as disseminated intravascular coagulopathy (DIC) and thrombocytopenia due to a variety of medications and specifically heparin.

## 6.1 Overview of Postoperative Bleeding

Cardiac surgery is associated with particular acquired hemostatic derangements due primarily to the interaction of blood components with the surfaces of the cardiopulmonary bypass (CPB) circuit. The primary effects are due to hemodilution, excessive fibrinolysis, and platelet dysfunction (Ozier and Bellamy 2010). During CPB, anticoagulation with heparin is required to avoid clot formation, while post-CPB, hemostasis must be reestablished. Hemodilution during the procedure results in a 30–50 % decrease from baseline in platelets, coagulation factors, and packed cell volume (Koh and Hunt 2003). Platelet dysfunction develops as a result of CPB-related activation/degranulation, heparin exposure, and hypothermia (<36 °C). These abnormalities are likely the most important early postoperative hemostatic defect (Despotis and Goodnough 2000). Additionally pH and plasma calcium levels should be optimized to maintain >7.3 and 1 mmol/L, respectively (Weber et al. 2013).

## 6.2 Preoperative Medication-Related Risk Factors

An assessment of risk factors for postoperative bleeding begins preoperatively. Factors to consider include medication history, surgical history, documented coagulopathies, baseline coagulation values, and comorbid conditions. Among the most preventable risks of postoperative bleeding is an accurate medication history and discontinuation of any anticoagulant, antiplatelet, or other medications affecting the

coagulation cascade or platelet function within the appropriate time frame. A risk/benefit assessment must be made with respect to patients at highest risk of thrombosis (i.e., recent stent placement, history of recurrent venous thromboembolism, mechanical valves). In some cases alternative anticoagulant therapy (i.e., unfractionated heparin) must be provided through the day of surgery due to the unacceptably high risk of thrombosis following discontinuation of a longer acting antithrombotic (Halasynski et al. 2004).

### 6.2.1 Oral Anticoagulants

Anticoagulants are a mainstay of cardiac medicine. Patients are prescribed with oral antithrombotic agents for a variety of indications including prophylaxis/treatment of venous thromboembolism (VTE), valve replacement, and atrial fibrillation. Over the last 10 years, other oral agents with unique mechanisms of action have been brought to market.

- Warfarin (Coumadin®) is perhaps the most well known of the oral anticoagulants but is associated with many drug interactions (primarily involving the cytochrome P450 enzyme system) and requires close monitoring. Its anticoagulant effect involves *inhibition of vitamin K dependent blood factors* including factors II, VII, IX, and X. In patients with VTE, therapy with warfarin requires concurrent parenteral therapy for a period of 4–5 days and a therapeutic international normalized ratio (INR) to allow for adequate inhibition of factor II, which has a half-life of approximately 60 h. Side effects include bleeding, microvascular thrombosis, and, rarely, nonhemorrhagic cholesterol embolization to the feet and toes. Risk factors for bleeding include age >65, history of gastrointestinal (GI) bleeding or stroke, hematocrit <30 %, creatinine >1.5, malignancy, hepatic disease, and diabetes (Ageno et al. 2012). In patients previously stable on warfarin who are unable to take medications enterally, the IV formulation can be administered at the same dose. Lower doses of the IV formulation may be required in the hospitalized patient due to decreased intake of vitamin K, acute illness, and interacting medications. Higher doses may be required in patients receiving vitamin K containing enteral nutritional supplements (Dager 2011; Wittkowsky 2011).
- Dabigatran (Pradaxa®) is a *direct thrombin* (*factor IIa*) *inhibitor* that requires no monitoring, has limited drug interactions [involving mainly the p-glycoprotein (P-gp) efflux transporter present in the GI tract versus the cytochrome P450 (CYP) system], and is dosed twice daily. Onset of anticoagulation occurs between 30 and 120 min post dose (Brighton 2010). Plasma levels of this agent are affected by age and renal function. Age >65, female gender, and renal dysfunction are factors associated with higher plasma levels and bleeding risk. The primary drawback of this agent is the lack of a reversal agent or routinely available monitoring parameters. The primary side effects are bleeding (particularly GI)

and dyspepsia. Significant drug interactions involve induction or inhibition of the P-gp transporter and include inhibitors such as amiodarone, dronedarone, diltiazem, verapamil, ketoconazole, quinidine, and clarithromycin and inducers such as rifampin. Absorption of dabigatran etexilate can be reduced postoperatively due to decreased GI motility and use of proton pump inhibitors such as pantoprazole (Ageno et al. 2012).

- Rivaroxaban (Xarelto®) is a *direct factor Xa inhibitor* that has no monitoring requirements, comparatively minimal drug interactions, and is dosed once daily. The onset of action is between 2 and 4 h post dose (Brighton 2010). *Combined* strong *inhibitors* of CYP3A4 and P-gp, including ketoconazole, itraconazole, voriconazole, posaconazole, and HIV protease inhibitors may increase systemic levels of rivaroxaban and potential risk of bleeding. *Combined* strong CYP3A4 and P-gp *inducers* can reduce rivaroxaban levels and include rifampin, phenytoin, carbamazapine, phenobarbital, and St. John's wort (Ageno et al. 2012).
- Apixaban (Eliquis®) is the newest *direct factor Xa inhibitor* approved by the FDA and, as with rivaroxaban, has no monitoring requirements and has limited drug interactions. Coadministration of apixaban with strong *dual inhibitors* of CYP3A4 and P-gp, including but not limited to ketoconazole, itraconazole, ritonavir, and clarithromycin can result in increased levels of apixaban. Similarly, coadministration of this agent with strong *dual inducers* of CYP3A4 and P-gp (i.e., rifampin, carbamazepine, phenytoin, St. John's wort) can result in subtherapeutic levels of apixaban. This agent is dosed twice daily and has an onset of action between 3 and 4 h post dose (Table 6.1).

### 6.2.2 Parenteral Anticoagulants

Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), direct thrombin inhibitors, and indirect factor Xa inhibitors are parenteral agents with varying dosing schedules and clinical uses. Heparin and LMWH are used for the treatment of acute coronary syndromes (ACS), VTE, and for prophylaxis of thrombotic events. Both UFH and LMWH indirectly inhibit factor IIa and Xa, with LMWH having a higher affinity for factor Xa. Fondaparinux is an *indirect* factor Xa inhibitor used for treatment and prophylaxis of VTE. Direct thrombin inhibitors (DTIs) are used in the treatment of heparin-induced thrombocytopenia (HIT) and include argatroban and bivalirudin (Angiomax®). Of the available DTIs, bivalirudin has been used in patients with a history of HIT requiring cardiac surgery. Of the agents listed in Table 6.2, heparin and the DTIs are the primary parenteral anticoagulants in the cardiac surgery setting and will therefore be the focus in this section.

- Heparin is the anticoagulant of choice in the cardiac surgery setting due to its fast onset/offset, reversibility with protamine, and point of care (POC) monitoring option. Benefits during CPB include inactivation of thrombin and factor Xa thereby reducing the risk of clot formation in the circuit. Typical doses

**Table 6.1** Oral anticoagulant dosing, monitoring, and preoperative discontinuation

| Anticoagulant | Half-life ($t_{1/2}$)/dose | Monitoring | Discontinue prior to surgery (days)/reversal agent |
|---|---|---|---|
| Dabigatran (Pradaxa®). https://www.pradaxa.com/. Accessed 17 July 2012 | 12–17 h in healthy subjects | No readily available method | CrCl ≥50 mL/min: 1–2 days |
| | CrCl >30 mL/min: 150 mg BID | Activated partial thromboplastin time (aPTT) demonstrates presence but not degree of anticoagulation | CrCl 30–50 mL/min: 2–4 days |
| | CrCl 30–50 mL/min + dronedarone or ketoconazole: 75 mg BID | Prothrombin time (PT) insensitive | CrCl <30 mL/min: ≥5 days |
| | CrCl 15–30 mL/min: 75 mg BID | Thrombin time (TT)—normal value rules out presence of dabigatran | No reversal agent available; dialysis may remove up to 62 % within 2 h (Ageno et al. 2012; van Ryn et al. 2010) |
| | | Ecarin clotting time (ECT)—linear dose relationship; not routinely available | |
| Rivaroxaban (Xarelto®). http://www.xareltohcp.com/. Accessed 17 July 2012 | 5–9 h in healthy subjects | No readily available method | At least 1 day (24 h) |
| | Atrial fibrillation | Prolongs aPTT, PT/INR | No reversal agent available and unlikely to be dialyzable due to high protein binding (Ageno et al. 2012) |
| | CrCl >50 mL/min: 20 mg daily with evening meal | No direct effect on platelet aggregation | |
| | CrCl 15–50 mL/min: 15 mg daily with evening meal | | |
| | VTE prophylaxis: 10 mg daily ± food | | |
| | VTE treatment: 15 mg PO twice daily × 21 days, then 20 mg daily | | |
| Apixaban (Eliquis®). http://packageinserts.bms.com/pi/pi_eliquis.pdf. Accessed 27 February 2013 | ~12 h following repeated dosing | No readily available method | 24–48 h prior to surgery depending on risk, location, and ability to control bleeding |
| | Atrial fibrillation | Prolongs aPTT, PT/INR | No reversal agent and unlikely to be dialyzable due to high protein binding |
| | 5 mg twice daily | No direct effect on platelet aggregation | Activated charcoal may be useful in overdose situations |
| | 2.5 mg twice daily in patients with any two of the following characteristics: ≥80 years of age, weight ≤60 kg, serum Cr ≥1.5 mg/dL | | |
| | 2.5 mg twice daily in patients taking strong dual inhibitors of CYP3A4 and P-gp (ketoconazole, itraconazole, ritonavir and clarithromycin) | | |
| | No data in patient with CrCl <15 mL/min | | |

(continued)

**Table 6.1** (continued)

| Anticoagulant | Half-life ($t_{1/2}$)/dose | Monitoring | Discontinue prior to surgery (days)/ reversal agent |
|---|---|---|---|
| Warfarin (Coumadin®). http://packageinserts.bms.com/pi/pi_coumadin.pdf. Accessed 17 July 2012 | 20–60 h<br>Individualized dosing | PT/INR | Minimum of 5 days without reversal agents<br>Reversal agents<br>*Vitamin K*<br>10 mg PO/IVPB for emergent *normalization* of PT/INR; IVPB initial effect at 2 h and full correction within 24 h<br>5 mg PO and 1 mg IVPB produce similar effects on INR at 24 h<br>0.5–1 mg orally for reducing PT/INR into *therapeutic range* (for <2.5 mg use IV form administered orally)<br>Ineffective in hepatic disease due to inability to produce factors<br>*Oral* route not effective in biliary disease<br>SQ not recommended due to unpredictable absorption and reversal characteristics<br>*Prothrombin complex concentrate* (PCC, Factor IX complex, Profilnine®)<br>25–50 units/kg *with* vitamin K to prevent rebound increase in INR (Ageno et al. 2012; Schulman and Bijsterveld 2007)<br>*Recombinant activated factor VII*<br>For intracranial hemorrhage—doses vary; 20–40 μg/kg have been used; available as 1, 2, 5, and 8 mg vial sizes; use lowest dose rounded to nearest vial size and repeat if needed due to risk of arterial and venous thrombotic and thromboembolic events |

**Table 6.2** Parenteral anticoagulants and monitoring (Douketis 2010; Douketis et al. 2012; Bojar 2011)

| Anticoagulant | Half-life ($t_{1/2}$)/dose | Monitoring | Discontinue prior to surgery (hours)/ reversal agent |
|---|---|---|---|
| Unfractionated heparin (UFH) | 60–90 min | aPTT | 4–6 h |
| | VTE: 80 unit/kg bolus, then 18 units/kg/h | Anti-factor Xa activity level (UFH levels) | Protamine 1 mg/100 units of heparin (max 50 mg at a rate not to exceed 5 min) |
| | ACS: 60 unit/kg bolus, then 12 units/kg/h | Activated clotting time (ACT; intraoperatively) | Dose adjust based on time since heparin held: >60 min 0.5 mg/100 units; >2 h 0.25 mg/100 units |
| | Prophylaxis: 5,000 units SQ BID or TID | | |
| *Low-molecular-weight heparin* | 4.5–7 h | Anti-factor Xa activity level (LMWH level) | 24 h |
| Dalteparin (Fragmin®). www.pfizer.com/files/products/uspi_fragmin.pdf. Accessed 18 July | *VTE treatment* | Dalteparin treatment doses should not be used in patients with CrCl ≤30 mL/min | Protamine |
| | *Dalteparin*: 200 units/kg SQ daily | Enoxaparin 1 mg/kg SQ daily may be considered in patients with chronic stable kidney disease and CrCl ≤30 mL/min who are not dialysis dependent; anti-factor Xa and serum creatinine monitoring is highly recommended | <8 h after last dose: 1 mg/1 mg enoxaparin or per 100 units of dalteparin |
| | *Enoxaparin*: 1 mg/kg SQ BID or 1.5 mg/kg SQ daily | | 8–12 h after last dose or if repeat is necessary: 0.5 mg/1 mg enoxaparin or per 100 units of dalteparin |
| Enoxaparin (Lovenox®). http://products.sanofi.us/lovenox/lovenox.html#section-14.1. Accessed 18 July | *VTE prophylaxis* | | >12 h after last dose: administration of protamine may not be necessary |
| | *Dalteparin* 5,000 units SQ daily | | The anti-factor Xa activity is never completely reversed (typically 60 % is reversed) |
| | *Enoxaparin* 30 mg SQ BID or 40 mg SQ daily | | |
| | *ACS* | | |
| | *Dalteparin* 120 units/kg SQ every 12 h | | |
| | *Enoxaparin* 1 mg/kg SQ every 12 h | | |

(continued)

**Table 6.2** (continued)

| Anticoagulant | Half-life ($t_{1/2}$)/dose | Monitoring | Discontinue prior to surgery (hours)/ reversal agent |
|---|---|---|---|
| *Direct thrombin inhibitors* | *Argatroban* 50 mins | aPTT | 2 h |
| Argatroban®. http://us.gsk.com/products/assets/us_argatroban.pdf. Accessed 31 July 2012 | *Treatment of HIT*: 2 mcg/kg/min initial dose; adjust for hepatic insufficiency and critically ill patients with multisystem organ failure | | |
| Bivalirudin (Angiomax®). www.angiomax.com/Downloads/Angiomax_PI_2010_PN1601-12.pdf. Accessed 18 July 2012 | *Bivalirudin* 25 mins<br>*CPB dosing in setting of HIT*<br>*On pump*:1 mg/kg bolus, 50 mg for pump then 2.5 mg/kg/h; goal ACT >2.5x baseline<br>*Off pump*: 0.75 mg/kg bolus, 1.75 mg/kg/h: goal ACT >300 s | | No reversal agent<br>Case reports suggest that recombinant factor VIIa 90 μg/kg×1 may reverse the anticoagulant effect (Schulman and Bijsterveld) |
| *Factor Xa inhibitor*<br>Fondaparinux (Arixtra®). http://us.gsk.com/products/assets/us_arixtra.pdf. Accessed 31 July 2012 | 17–21 h<br>VTE<br>*Prophylaxis*: 2.5 mg SQ daily<br>*Treatment:*<br><50 kg: 5 mg SQ daily<br>50–100 kg: 7.5 mg SQ daily<br>>100 kg: 10 mg SQ daily | Not routinely available. International standards for anti-factor Xa activity for UFH/LMWH do not apply | 48 h<br>No reversal agent<br>Case reports suggest that recombinant factor VIIa 90 μg/kg×1 reverse the anticoagulant effect (Schulman and Bijsterveld) |

include 20,000–30,000 units to achieve a target ACT of 300–350 s, although this varies widely among cardiac surgery centers. Rarely, patients may require doses of heparin exceeding 500 units/kg without achieving the target ACT. These patients may have a reduced response to heparin due to low levels of antithrombin (AT), excessive factor VIII, or excessive fibrinogen (Dager 2011). Antithrombin is a required cofactor for the anticoagulant effect of heparin. Risk factors for antithrombin deficiency include preoperative heparin, placement of an intra-aortic balloon pump (IAPB), elevated platelet counts, and infective endocarditis (Ranucci et al. 1999). Repletion of AT and subsequent goal ACT can be achieved with administration of fresh frozen plasma (FFP) or commercially available concentrates (i.e., Thrombate®) (Lemmer and Despotis 2002).

- Argatroban and bivalirudin are DTIs and are the primary agents used in the treatment of HIT. Bivalirudin has been used as the intraoperative anticoagulant in patients with a history of HIT or those who require surgical intervention in the presence of active HIT.

### 6.2.3 Antiplatelet Agents

Antiplatelet therapy is a cornerstone of primary and secondary prevention of cardiovascular disease in patients with a history of myocardial infarction, ACS, and some valvulopathies. Thienopyridines (clopidogrel and prasugrel) are hepatically or enzymatically metabolized to active metabolites which bind to the platelet $P2Y_{12}$ receptor causing irreversible platelet inhibition. Antiplatelet therapy should be evaluated perioperatively with respect to dose, duration, last dose administered, and hemorrhagic side effects.

- *Aspirin* irreversibly inhibits platelet cyclooxygenase-1 (COX-1) which prevents production of thromboxane A2. This results in inhibition of platelet activation and aggregation. At any given point, the age of circulating platelets ranges from 1 to 10 days. New platelets with functioning COX-1 are continually being produced and replace 10–15 % of inhibited platelets daily allowing overall platelet function to return gradually over a period of 7 days (Gibbs et al. 2001).
- *Clopidogrel* is a prodrug hepatically metabolized in two-step process to an active form which inhibits ADP binding to the platelet $P2Y_{12}$ receptor. This results in inhibition of ADP-mediated activation of the glycoprotein IIb/IIIa (GP IIb/IIIa) complex and resultant platelet aggregation. The amount of the active form in circulation varies due to genetic variation in hepatic metabolism (CYP2C19) and drug interactions affecting CYP2C19 (i.e., proton pump inhibitors). These factors may contribute to the variable response associated with this agent. Data evaluating the concurrent administration of omeprazole demonstrated no clinically relevant interaction; however, the manufacturer recommends the use of pantoprazole due to less inhibitory effect on CYP2C19 (Wallentin 2009; Wallentin et al. 2009; Patrono et al. 2011).

- *Prasugrel* is a prodrug similar to clopidogrel and exhibits antiplatelet effects by the same mechanism. However, it is unaffected by polymorphisms in CYP2C19 or interactions with proton pump inhibitors. Additionally, the active component is produced following a one-step hepatic conversion resulting in a greater amount of metabolite formed following a loading dose. Prasugrel is 10x more potent than clopidogrel with a more rapid onset (30 min vs 1 h with 600 mg loading dose of clopidogrel) and less variation in response (Eikelboom et al. 2012; Patrono et al. 2011).
- *Ticagrelor* undergoes enzymatic degradation to an active metabolite. Onset of action is approximately 30 min post loading dose of 180 mg (Weitz et al. 2012).
- Intravenous antiplatelet agents administered primarily during percutaneous coronary intervention (PCI) include *abciximab, eptifibatide, and tirofiban*. These agents block the binding of fibrinogen to the GP IIb/IIIa receptor and subsequent platelet aggregation. Abciximab is a monoclonal antibody which acts as a non-competitive inhibitor while eptifibatide and tirofiban are competitive inhibitors and therefore require high plasma levels for adequate antiplatelet effect (Patrono et al. 2011; Bojar 2011) (Table 6.3).

## 6.3 Other Agents

Supplements such as fish oil, vitamin E (>400 units/day) and herbal supplements can significantly impact coagulation and platelet function and should be discontinued at least 5 days prior to surgery. Examples of herbal supplements with anticoagulant or antiplatelet activity include chamomile, garlic, chondroitin, evening primrose oil, ginger, feverfew, ginseng, kava, mate, and goldenseal (Halasynski et al. 2004).

## 6.4 Monitoring Coagulation Status

The final product of a functioning coagulation cascade is the dynamic harmony between clot formation and dissolution known as hemostasis. Achieving hemostasis involves not only blood factors and platelets but also proteins (i.e., cytokines) and non-platelet cells (i.e., endothelial cells). Instability in the coagulation system due to interaction between these factors, often released in situations of vascular injury (i.e., surgery) or various illnesses (i.e., malignancy), increases the risk of hemorrhage or thrombosis. Within the coagulation system are two pathways known as the extrinsic pathway and the intrinsic pathway. Pathway function can be assessed by common laboratory tests (Table 6.4).

Thromboelastography, via either inpatient laboratory or point-of-care reporting, is becoming more widely available. This type of monitoring provides a graphic representation of a patient's complete coagulation status. Tracings demonstrating hemorrhagic and thrombotic states are shown in Figs. 6.1 and 6.2

**Table 6.3** Antiplatelet agent properties

| Antiplatelet agent | Mechanism of action/dose | Duration of effect | Discontinue prior to surgery (days) |
|---|---|---|---|
| *Oral agents* | | | |
| Aspirin | Cyclooxygenase inhibitor<br>81–325 mg daily | 7 days—affected platelets must be replaced | 3–5 days depending on residual aspirin effect desired |
| Clopidogrel (Plavix®). http://www.plavix.com/Index.aspx. Accessed 8 August 2012 | Irreversible ADP-P2Y12 receptor inhibitor<br>Loading dose (LD): 300–600 mg PO × 1; omit in patients ≥75 years of age<br>Maintenance dose (MD): 75 mg PO daily | 7 days—affected platelets must be replaced | 5–7 days |
| Prasugrel (Effient®). http://www.effient.com/Pages/index.aspx. Accessed 8 August 2012 | Irreversible ADP-P2Y12 receptor inhibitor<br>LD: 60 mg PO × 1<br>MD: 10 mg PO daily; reduce to 5 mg PO daily in patients < 60 kg | 7 days—affected platelets must be replaced | 7 days |
| Ticagrelor (Brilinta®). http://www.brilinta.com/. Accessed 8 August 2012 | Reversible ADP-P2Y12 receptor inhibitor<br>LD: 180 mg × 1<br>MD: 90 mg PO BID | 48 h ($t_{1/2}$ 6–13 h including active metabolite) (Wallentin 2009) | 3–5 days |
| *Intravenous agents* | | | |
| Abciximab (Reopro®). http://www.reopro.com/Pages/index.aspx. Accessed 8 August 2012 | Irreversible glycoprotein IIb/IIIa inhibitor<br>PCI: 0.25 mg/kg bolus followed by infusion of 0.125 μg/kg/min × 12 h<br>PCI within 24 h: 0.25 mg/kg bolus followed by infusion of 10 μg/kg/min concluding 1 h post PCI | 24 h | 24 h |
| Eptifibatide (Integrilin®). http://www.integrilin.com/integrilin/index.html. Accessed 8 August 2012 | Reversible glycoprotein IIb/IIIa inhibitor<br>180 μg/kg bolus followed by infusion of 2 mcg/kg/min<br>CrCl <50 mL/min:180 μg/kg bolus followed by infusion of 1 mcg/kg/min | 4 h | 4 h |
| Tirofiban (Aggrastat®). http://www.aggrastat.com/. Accessed 8 August 2012 | Reversible glycoprotein IIb/IIIa inhibitor<br>0.4 μg/kg/min × 30 mins, then 0.1 μg/kg/min<br>CrCl <30 mL/min: reduce dose by 50 % | 4 h | 4 h |

**Table 6.4** Laboratory assays/tests (O'Conner et al. 2009; Dager et al. 2011; Sie and Steib 2006)

| Assay/test | Normal range/values | Pathway/factors assessed | Disease states affecting results |
|---|---|---|---|
| *Plasma assays* | | | |
| Prothrombin time/ international normalized ratio (PT/INR) | INR 2–3.5 (*Higher goals may be indicated in patients with hypercoagulability disorders*) | *PT/INR*: Factors II, V, VII, and X (*extrinsic and common pathways*) | Coagulation disorder (hereditary or acquired factor VII, X, V, and II deficiencies ↑ INR)<br>Medications<br>Warfarin, rivaroxaban, dabigatran (↑ INR)<br>Argatroban and daptomycin associated with *falsely* ↑ INR<br>Factor deficiency due to hepatic disease, malabsorption, malnutrition, and chronic antibiotic therapy (*PT/INR in patients with cirrhosis may not reflect bleeding risk due to overall deficiency in both pro- and anticoagulant factors*) (O'Conner 2009)<br>Anti-phospholipid syndrome (APLS) ↑ INR<br>Hemodilution ↓ factor concentration |
| Activated partial thromboplastin time (PTT) | 1.5–2.5 upper limit of normal reference range (*therapeutic aPTT corresponds to the above but varies by institution due to reagents and instrumentation*) | *aPTT*: II, V, VIII, IX, X, XI (intrinsic and common pathways) | Coagulation disorder<br>Hereditary or acquired factor XII, XI, IX, VIII, X, V, and II deficiencies, APLS ↑ aPTT<br>Medications which ↑ aPTT<br>Rivaroxaban, DTIs, hydroxyethyl starch (HES) |
| Anti-factor Xa activity assay | Range varies based on indication<br>Treatment of VTE with UFH: 0.3–0.7 units/mL<br>Treatment of VTE with LMWH twice daily dosing: 0.5–1 units/mL<br>LMWH daily dosing: 1–2 units/mL | Amount of heparin or LMWH in specimen via factor Xa inhibition | Substantially fewer uncontrolled variables versus PTT monitoring<br>Independent of other coagulation factors in the intrinsic pathway (Winkler and Zimring 2009) |

| | | | |
|---|---|---|---|
| *Whole blood assays* | | | |
| Activated clotting time (ACT) | Goal ranges vary for CPB (i.e., 300–450 s) | Measures intrinsic pathway factors | Used with high doses of heparin (i.e., during PCI or CPB) when aPTT is insensitive<br>Prolonged by<br>Hemodilution<br>Heparin<br>Hypothermia<br>Hyperfibrinogenemia<br>Thrombocytopenia |
| Thromboelastography (TEG®/Rotem®) | Evaluates viscoelastic properties of whole blood and is unaffected by hypothermia (*normal values vary by institution*) | Intrinsic, extrinsic, common pathways, and platelet function | Most valuable in the bleeding patient vs preoperative prediction of bleeding |
| See Figs. 6.1 and 6.2 for depiction of tracings and values | Reaction time (R)—time to first fibrin strand formation (6–8 min) | | May aid in distinguishing medical from surgical bleeding |
| | Clot formation time (K)—time for fibrin/platelets to initiate cross-linking (3–6 min) | | TEG results must always be considered in conjunction with the clinical picture |
| | Alpha angle (α angle)—speed at which solid clot forms (50°–60°) | | ↑ R/K—hypocoagulability related to factor deficiency or heparin/warfarin therapy |
| | Maximum amplitude (MA)—absolute strength of fibrin clot which is dependent on fibrin and platelets (50–70 mm) | | ↓ R/K plus ↑ MA/α —hypercoagulability |
| | Clot lysis index (CLI)—loss of clot due to lysis 60 min after MA (85–100 %) | | ↓ CLI—hyperfibrinolysis<br>(Sie and Steib 2006) |

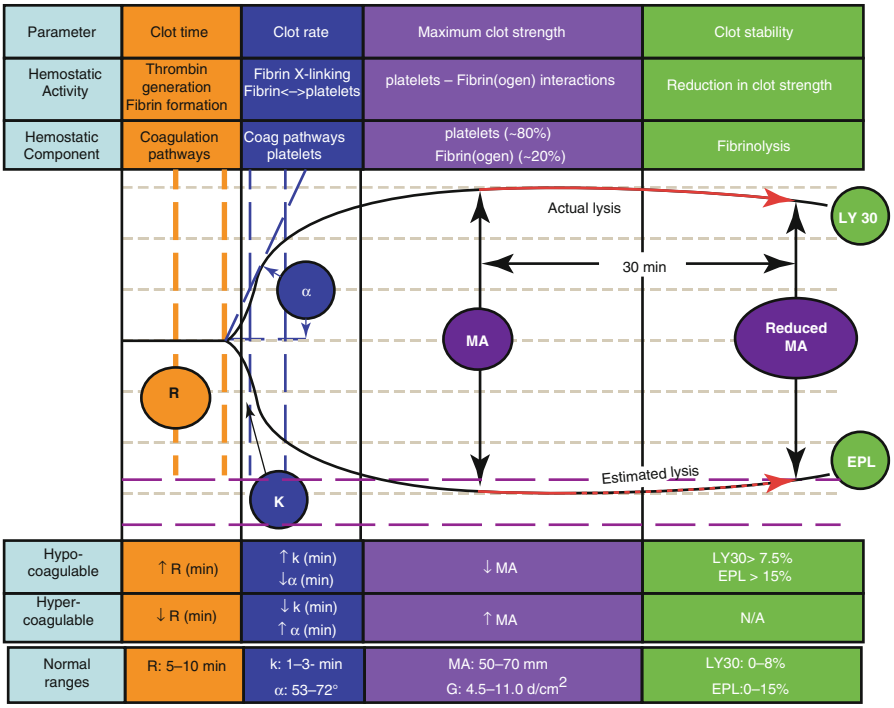



**Fig. 6.1** Thromboelastograph parameters (Reproduced with permission from Haemonetics Corporation, Braintree, MA)

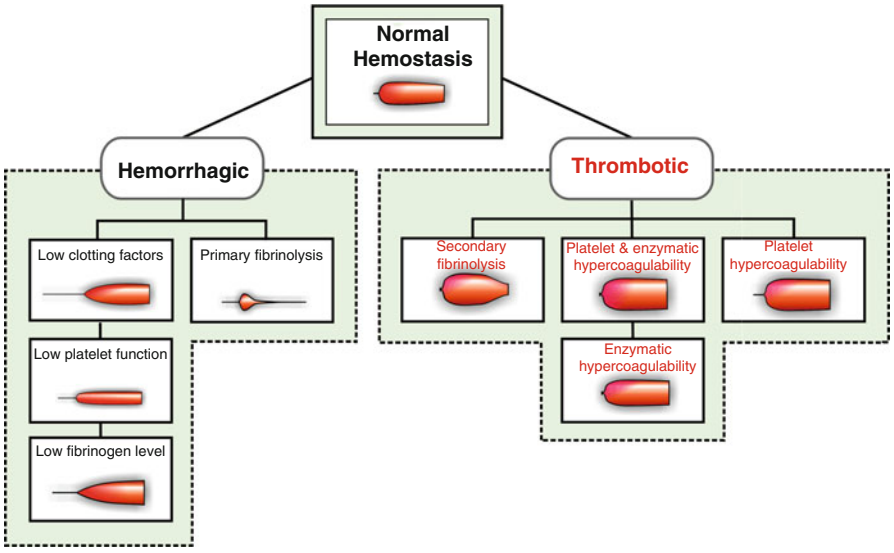



**Fig. 6.2** Thromboelastograph tracing patterns for hemorrhagic and thrombotic conditions (Reproduced with permission from Haemonetics Corporation, Braintree, MA)

## 6.5 Postoperative Considerations

### 6.5.1 Medications

Heparin is the primary anticoagulant of concern in the immediate postoperative period. Initial reversal with protamine is performed in the operating room with a variety of dosing regimens (i.e., 1:1 or 0.5:1 ratio to the dose of heparin, dose based on ACT). Residual heparin can redistribute following reversal in the operating room ("heparin rebound") requiring additional doses of protamine in the postoperative care area (i.e., 25 mg × 2 doses). Given that the elimination of protamine from the circulation occurs within 30 min ($t_{1/2} = 5$ min) from a bolus dose, a low-dose postoperative infusion of 25 mg/h for 6 h is an alternative dosing regimen that has demonstrated a reduction in postoperative bleeding, but not transfusion rate (Teoh et al. 2004). Conservative dosing will avoid the anticoagulant effect associated with high-dose protamine (Bojar 2011).

Following hemostasis postoperatively and depending on the procedure performed (coronary artery bypass, valve replacement, etc.), a variety of anticoagulant agents may be recommended to decrease the risk of postoperative VTE. Timing of initiation is patient-specific and dependent on a variety of factors including risk of bleeding/thrombosis, efficacy/tolerance of therapy preoperatively, and preoperative/preexisting thrombotic risk factors. Options include UFH 5,000 units subcutaneously (SQ) twice or three times daily, enoxaparin SQ 40 mg daily or 30 mg twice daily, or dalteparin 5,000 units SQ daily. In patients in whom pharmacologic VTE prophylaxis is deemed too risky, sequential compression devices should be initiated preoperatively.

### 6.5.2 Coagulopathies

Various coagulopathies (either transient or chronic) can complicate postoperative management. Prompt initiation/resumption of anticoagulant/antiplatelet therapy postoperatively may decrease risk of thrombosis (i.e., stent thrombosis). Table 6.5 describes the most common hypercoagulopathic states (Dager 2011; Bojar 2011).

#### 6.5.2.1 Disseminated Intravascular Coagulopathy

Disseminated intravascular coagulopathy (DIC) is an acquired *hyper*coagulable hematological complication resulting in activation of the coagulation system. Microthrombi deposit in various organs ultimately resulting in reduced blood supply and organ failure. Once circulating blood factors and platelets have been consumed, a *hypo*coagulable status prevails resulting in bleeding. Several disease states are associated with a risk of DIC and include sepsis, transplant rejection, severe hepatic failure, trauma, and hemolytic transfusion reactions (Franchini et al. 2006). Laboratory parameters associated with DIC are listed in Table 6.6.

Primary treatment of DIC should focus on correcting the inciting factor (i.e., appropriate dose/antimicrobial organism causing sepsis) and providing support for

**Table 6.5** Prothrombotic coagulopathies

| Syndrome | Pathology | Considerations |
|---|---|---|
| Antiphospholipid syndrome (APLS) | Autoantibodies bind phospholipids<br>Anticardiolipin antibody<br>Anti-β2-glycoprotein I antibody<br>Lupus anticoagulant<br>Arterial and venous thrombosis | Paradoxically elevated aPTT<br>Intraop: ACT may not be reliable; consider heparin-protamine titration with goal heparin of 3.4 units/mL; consider bivalirudin (Weiss 2008) |
| Increased function/level of native procoagulants | Activated protein C resistance resulting in ↑ concentrations of activated factor V (factor V Leiden mutation)<br>Prothrombin G20210A mutation resulting in ↑ concentrations of prothrombin<br>↑ levels of factors VIII, IX, and XI | Provide postoperative anticoagulation as soon as possible |
| Deficiencies of native anticoagulants | Protein C and S and antithrombin (AT) | AT deficiency: administer fresh frozen plasma or AT concentrate (Thrombate®) intraoperatively if using heparin<br>Dosing based on AT level, clinical status, and setting<br>Consider argatroban (AT independent) |

**Table 6.6** Laboratory parameters in DIC

| Parameter | Value |
|---|---|
| Platelets | Normal or decreased |
| Schistocytes | Present |
| Prothrombin time (PT/INR) | Prolonged |
| Fibrinogen | Decreased; <150 mg/dL—consumption +/− production; <100 mg/dL increased risk of bleeding |
| Fibrin monomers (degradation products or split products) | Increased |
| D-dimer | Increased |

bleeding via plasma, platelet, and cryoprecipitate repletion. Heparin infusions at 500 units/hour can be considered in patients demonstrating thrombosis; adequate AT levels should be verified to assure efficacy of heparin (Dunn 2009).

### 6.5.3 Drug-Induced Thrombocytopenias

A number of medications are known to cause thrombocytopenia potentially associated with bleeding complications due to platelet destruction. Onset, duration, and degree of thrombocytopenia vary. On discontinuation of the suspected medication, symptoms and thrombocytopenia typically resolve within 1–2 and 7 days, respectively. Drug-induced thrombocytopenia can also present as disseminated

**Table 6.7** Drugs associated with thrombocytopenia (Dager 2011)

| | | | |
|---|---|---|---|
| Abciximab | Diazepam | Hydrochlorothiazide | Procainamide |
| Acetaminophen | Diatrizoate meglumine (contrast) | Ibuprofen | Quinidine |
| Amiodarone | Diazepam | Interferon α | Ranitidine |
| Aspirin | Diclofenac | Isoniazid | Rifampin |
| Amphotericin B | Digoxin | Linezolid | Simvastatin |
| Ampicillin | Eptifibatide | Lopinavir/ritonavir | Sulfasalazine |
| Captopril | Ethambutol | Methyldopa | Sulfonamides |
| Carbamazepine | Famotidine | Minoxidil | Sulfisoxazole |
| Chlorothiazide | Fluconazole | Nitroglycerine | Terbinafine |
| Chlorpromazine | Glyburide | Octreotide | Tirofiban |
| Danazol | Haloperidol | Phenytoin | Valproic acid |
| Deferoxamine | Heparin | Piperacillin | Vancomycin |

intravascular coagulopathy (DIC), hemolytic uremic syndrome (HUS), or thrombotic thrombocytopenic purpura (TTP); the mechanisms of which are unclear (Table 6.7).

#### 6.5.3.1 Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia is a rare but potentially catastrophic thrombotic complication of heparin therapy. High intravenous doses of heparin present the highest risk for the development of HIT. Cardiac surgery patients often experience non-HIT-related thrombocytopenia postoperatively due to dilutional effects and platelet consumption. This decline continues for 1–2 days before gradually increasing to preoperative counts. However, in cases where thrombocytopenia *persists* >4 days postoperatively or *begins* >4 days postoperatively, the possibility of HIT should be considered.

Given the clinicopathologic nature of HIT, an accurate diagnosis includes clinical criteria and laboratory assessment of the presence of platelet factor 4 (PF4)/heparin antibody complexes. Enzyme-linked immunoassay (ELISA) allows for detection of platelet factor 4 (PF4)/heparin antibody complexes including IgG, IgM, and IgA and is therefore a sensitive assay. Of these antibodies, only IgG is associated with the pathologic syndrome of HIT, and the PF4 is therefore associated with a high false-positive rate. The serotonin release assay (SRA) is a functional assay that confirms with high sensitivity the presence of platelet-activating antibody complexes associated with the thrombotic complications associated with HIT. A positive SRA should prompt discontinuation of all forms of heparin and initiation of alternative anticoagulant therapy with intravenous DTIs (Linkins et al. 2012). Because of their complexity, these tests are usually sent to an outside laboratory. In an effort to proactively determine the probability of HIT prior to laboratory results being available, a "4-T" score has been developed which allows for assessment of clinical parameters associated with HIT (Warkentin 2004; Linkins et al. 2012). A more detailed discussion on this issue is presented in the annex of this chapter (Table 6.8).

**Table 6.8** The four "Ts" and laboratory test interpretation

| Parameter | 2 points | 1 point | 0 points |
|---|---|---|---|
| **T**hrombocytopenia | >50 % decrease and nadir ≥ 20,000/ul and no surgery within preceding 3 days | 30–50 % decrease or nadir of 10–19,000/ul | <30 % decrease or nadir <10,000/ul |
| **T**iming of onset of platelet decrease | Days 5–10; or ≤1 day with heparin exposure within prior 5–30 days | Day 10 or timing unclear; or day 1 with heparin exposure within past 31–100 days | <day 4 (no recent heparin) |
| **T**hrombosis | Skin necrosis or new arterial or venous thrombosis (MI, VTE, stroke) | Progressive, recurrent thrombosis<br>Suspected thrombosis<br>Skin lesions at infusion site | None |
| O**T**her cause of platelet decrease | None evident | Possible | Definite |
| *Interpretation*: Total points for each of the four parameters (maximum score of 8); T-score 6–8 high probability; 4–5 intermediate; 0–3 low | | | |
| *Laboratory test interpretation* | | | |
| | *Result* | | *Comments* |
| *Elisa PF4 antibody test* (Reported as optical density, OD) | <0.4—negative<br>0.4–0.84—borderline negative<br>0.85–2.79—positive<br>≥2.8—strongly positive | | Probability of HIT<br>0.4–1: <5 %<br>>1–1.4: 18 %<br>>1.4–2: 50 %<br>>2: 90 %<br>(Warkentin et al. 2008) |
| *Serotonin release assay* | ≥20 % release of serotonin with *low*-dose heparin *and* <20 % release in presence of high concentration of heparin (Blood Center of Wisconsin 2009) | | Any inconclusive PF4 or SRA value with a suggestive clinical picture should be reassessed due to potential for "HIT in evolution" |

## 6.6 Medical Management of Bleeding

### 6.6.1 Antifibrinolytics

Epsilon-aminocaproic acid (EACA) and tranexamic acid (TA) are agents which inhibit the conversion of plasminogen to plasmin, thereby minimizing fibrin degradation. Tranexamic acid is 10x more potent and has a longer half-life (80 min) than EACA. Available data indicate that either of these agents are appropriate antifibrinolytic patients in the setting of cardiac surgery with EACA typically being the least costly. Additionally, studies suggest that local application of TA administered as a 1 g/100 mL normal saline solution instilled into the pericardial cavity before closure of the sternotomy while chest tubes were clamped decreased postoperative bleeding (Fawzey et al. 2009; De Bonis et al. 2000) (Table 6.9).

**Table 6.9** Dosing antifibrinolytic agents (Ozier and Bellamy 2010)

| Agent | Available dosing regimens |
|---|---|
| Epsilon-aminocaproic acid (Amicar®) | Varying dosing regimens—10 g loading dose IV, then 2 g/h infusion; no dose ranging study available |
| Tranexamic acid (Cyclokapron®) | 30 mg/kg loading dose IV, then 16 mg/kg/h infusion |

### 6.6.2 Desmopressin

Desmopressin is an analog of antidiuretic hormone that increases release of von Willebrand factor from endothelial cells. This results in increased adhesion of platelets to areas of vascular injury and mediates the procoagulant effects of factor VIII. The primary limitation of this agent is tachyphylaxis as it causes release of von Willebrand factor from storage sites rather than increasing production. Cardiac surgery patients with suspected platelet dysfunction due to platelet inhibiting medications, prolonged on-pump time, excessive postoperative bleeding, and/or high preoperative bleeding risk are likely to benefit the most from this agent (Ozier and Bellamy 2010). When monitoring patients via TEG, an MA value <50 mm may indicate a higher risk for bleeding due to platelet dysfunction. Such a scenario may benefit from prophylactic administration of desmopressin to mitigate bleeding risk (Despotis and Goodnough 2000; Mongan and Hosking 1992).

### 6.6.3 Exogenous Blood Products and Factors

The goal of appropriate mitigation of perioperative risk factors for bleeding is the avoidance of blood product administration. Risk factors for postoperative bleeding include but are not limited to age >70, preoperative anemia, female gender, small body size, multiple comorbidities, urgent cardiac surgery, and clotting abnormalities. The most recent iteration of the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines provides evidence-based recommendations for blood conservation techniques and appropriate transfusion (Ferraris et al. 2011). A summary of blood products and blood factors is provided in Table 6.10.

## 6.7 Surgical Bleeding

Postoperative bleeding is due to surgical causes, coagulopathies, or a combination thereof. Nonsurgical bleeding can be due to small vessels at the tissue surface (i.e., sternal edges, bed of internal mammary artery) that in a state of normal coagulation do not contribute to significant postoperative bleeding. In patients undergoing cardiac surgery, the following criteria are associated with an increased risk of postoperative bleeding:

- Preoperative use of antiplatelet agents
- Quantitative and qualitative abnormality in platelets
- Altered status of coagulation factors

**Table 6.10** Blood products and factors (Callum et al. 2009; Weber et al. 2013)

| Product | Components/unit | Considerations |
|---|---|---|
| Packed red blood cells (pRBC) | 200 ml of red cells<br>100 mL of stabilizing solution to extend shelf life<br>30 mL of plasma | Transfusion triggers vary depending on clinical state/stability of patient (i.e., hematocrit <26 %, hemoglobin < 6–7 g/dL) |
| Fresh frozen plasma (FFP) | 250 mL of volume<br>No red or white cells or platelets | Usual initial dose 2–4 units<br>Contains all blood factors but reduced amounts of factor V and factor VIII |
| Platelets | $8 \times 10^{10}$ platelets per unit<br>60 mL of plasma | Usual initial dose 1–2 packs<br>↑ platelets 7,000–10,000/μL<br>Administer if platelet count <100,000/μL or in setting of bleeding following exposure to antiplatelet agents, GP IIb/IIIa agents, or CPB<br>*Note*: transfused platelets administered with 6 h or 4 h of a loading dose or maintenance dose, respectively, of clopidogrel or pasugrel may be less effective |
| Cryoprecipitate | Concentrate of 6 units FFP equal to ~100 ml of volume<br>100–250 mg of fibrinogen per unit<br>80–100 units of factor VIII per unit<br>von Willebrand factor<br>Fibronectin<br>10–15 mL of plasma | Usual initial dose 6–10 units<br>Replaces fibrinogen which is converted to fibrin by thrombin |
| Fibrinogen concentrate | Alternative to cryoprecipitate for fibrinogen <150 mg/dL | Initial dose 25–50 mg/kg |
| Prothrombin complex concentrate (PCC) | Typical dose for elevated INR 20–30 international units/kg<br>Concentrate of factors II, VII, IX, and X ± protein C and S, heparin, and antithrombin depending on product | Used in setting of elevated INR or presumed deficiency of factors II, VII, IX and X (i.e., warfarin reversal)<br>Available products are either "3-factor" or "4-factor" products depending on the amount of factor VII<br>4-factor PCC potentially effective in reversing rivaroxaban |
| Recombinant activated factor VII (rFVIIa) | 40–60 μg/kg; consider lower doses, round down to nearest vial size and repeat if needed<br>Half-life 2.9 h | Indicated for intractable nonsurgical bleeding post CPB unresponsive to usual therapies<br>Optimal dose is not well established<br>Associated with clinically significant increase in thrombotic events, including ischemic stroke (Gill et al. 2009)<br>Available as 1, 2, 5, and 8 mg vial sizes; use lowest dose rounded to nearest vial size and repeat if needed due to risk of arterial and venous thrombotic and thromboembolic events |

- Increased fibrinolysis activity by cardiopulmonary bypass
- Surgical damage to blood vessels
  - Cannulation sites
  - Internal mammary artery bed and anastomosis
  - Vein graft branches
  - Soft tissue suture lines
  - Arterial anastomoses
  - Sternal wiring site

Reoperation for postoperative bleeding is associated with increased morbidity and mortality and is seen in 2–9 % of patients after cardiac surgery (Vivacqua et al. 2011; Charalambous et al. 2006; Choong et al. 2007; Moulton et al. 1996). In more than half of the patients returning to operating room, the surgeon can locate an obvious bleeding site (Karthik et al. 2004). Studies have identified the following factors as some of the main predictors for postoperative bleeding leading to surgical reexploration (Karthik et al. 2004; Biancari et al. 2012):

- Advanced age
- Left ventricular dysfunction
- Chronic renal failure
- Lower body mass index (BMI)
- Preoperative use of antiplatelet medication
- Prolonged CPB time
- Urgent/emergent operation
- Reoperations

The primary indications for returning to the operating room for bleeding include:

- Sudden massive bleeding at any time in postoperative period
- Continuous chest tube drainage according to the Kirklin criteria (Karthik et al. 2004)
  1. >500 ml in the first hour postoperatively
  2. >400 ml during each of the first 2 h postoperatively
  3. 300 ml during each of the first 3 h postoperatively
  4. 1,000 ml (total bleeding) during the first 4 h postoperatively
- Evidence of excessive pleural or pericardial effusion by chest X-ray or echocardiography
- Signs of tamponade on clinical exam (including, but not restricted to, increased central venous pressure (CVP), decreased urinary output, hypotension, mediastinal widening on chest X-ray accompanied with sudden reduction of chest tube drainage)

The time interval between surgery and resternotomy is the main predictor of outcome. A delay of > 12 h to reoperation is associated with additional complications such as prolonged mechanical ventilation, high blood transfusion rate, stroke, need for intra-aortic balloon pump (IABP) placement, sternal wound infections, and renal failure (Vivacqua et al. 2011; Karthik et al. 2004; Choong et al. 2011).

## 6.8 Appendix A Heparin-Induced Thrombocytopenia

Marzia Leacche, John G. Byrne, and Sary F. Aranki

### 6.8.1 Abstract

HIT is a potentially fatal side effect of heparin that is more common with Unfractionated Heparin (UFH) than Low Molecular Weight Heparin (LMWH). HIT is a clinical-pathologic syndrome: its diagnosis is based on compatible clinical features and presence of HIT antibodies. Antibodies against PF4/heparin are formed commonly during heparin treatment; HIT occurs in the subset of patients with strong platelet-activating IgG antibodies. Binding of HIT antibodies to PF4/heparin complexes on the platelet surface results in platelet activation, thrombocytopenia, and increased risk of thrombosis, mainly venous but also arterial. Platelet, monocyte, and endothelial cell activation results in a hypercoagulable state and increased risk of venous thrombosis. HIT-associated thrombosis occurs in some patients 1–2 days before platelet counts decrease. Platelet count monitoring is important to diagnose isolated HIT and thus has the potential to prevent thrombosis. Recognizing a relative decrease of platelet count is important since platelets do not always fall below $150 \times 10^9$/L, especially in cardiac surgery patients who have had exposure to unfractioned heparin. Platelet count monitoring is recommended in most patients receiving UFH and in some patients receiving LMWH. Heparin should be stopped immediately in all situations where HIT is strongly suspected. Coumadin should also be stopped since it results in reduction of the levels of protein C. Due to the high risk of thrombosis in patients with HIT, anticoagulation with a non-heparin anticoagulant should be started even in the absence of overt thrombosis. A number of conditions should be considered in the differential diagnosis of pseudo-HIT—conditions that closely mimic both the signs and symptoms of HIT and occur in a clinical context that makes the diagnosis of HIT likely, heparin-associated thrombocytopenia (HAT), cancer-associated DIC, pulmonary embolism, DIC/sepsis, EDTA-induced pseudo-thrombocytopenia, and drug-induced thrombocytopenia.

### 6.8.2 Introduction

Heparin-induced thrombocytopenia (HIT) is caused by heparin-induced antibodies that activate platelets and monocytes through the Fcγ IIa receptor. Thrombotic complications can occur in half of the untreated patients mostly in the venous system (Kelton et al. 2013). Thrombocytopenia occurs only after exposure of heparin, typically 5–10 days after the initial exposure. Many cardiac surgery patients, however, have been previously exposed to heparin and may have developed IgG antibodies against the complex platelet factor 4 (PF4)-heparin; thus, a sudden new onset, after hours from reexposure of heparin, is possible with different degree of thrombocytopenia, sometimes with sudden decrease of more than 50 % in the platelet count. The third manifestation of HIT is a delayed manifestation which occurs weeks after

heparin exposure. Because in cardiac patients there might be alternative causes of thrombocytopenia and because the tests available are sensitive but not specific, HIT may be undertreated or underdiagnosed.

### 6.8.3 Pathophysiology

The process is initiated when the patient receives heparin. Low-molecular-weight heparin is much less likely to be associated with HIT than unfractionated heparin. Less frequently 2 non-heparin polyanions, pentosan polysulfate (used in interstitial cystitis) and polysulfated chondroitin sulfate (used in arthritis), may be associated with the condition. Antibodies develop against a multimolecular complex of heparin and PF4 which become accessible after it binds heparin (Greinacher et al. 1992; Goad et al. 1994). PF4 is a small cytokine released by activated platelets which binds heparin. Although IgG, IgM, and IgA antibodies have been described in HIT, it appears likely that most patients with the HIT syndrome have IgG antibodies (Amiral et al. 1992; Visentin et al. 1994).

The newly formed complex (IgG-PF4-heparin) binds to FcϒRIIa receptor located on platelets, monocytes, and other cell surfaces which results in intense platelet activation and release of procoagulant microparticles from platelets and monocytes. Platelet microparticles provide a negatively charged phospholipid surface that promotes procoagulant activity and thrombin generation (Warkentin et al. 1996; Giles et al. 1982). Increased levels of thrombin-antithrombin (TAT) complexes and D-dimer levels reflect the hypercoagulable state. The induction of further release of PF4 further compromises the situation by neutralizing heparin's anticoagulant activity (Fig. A.1).

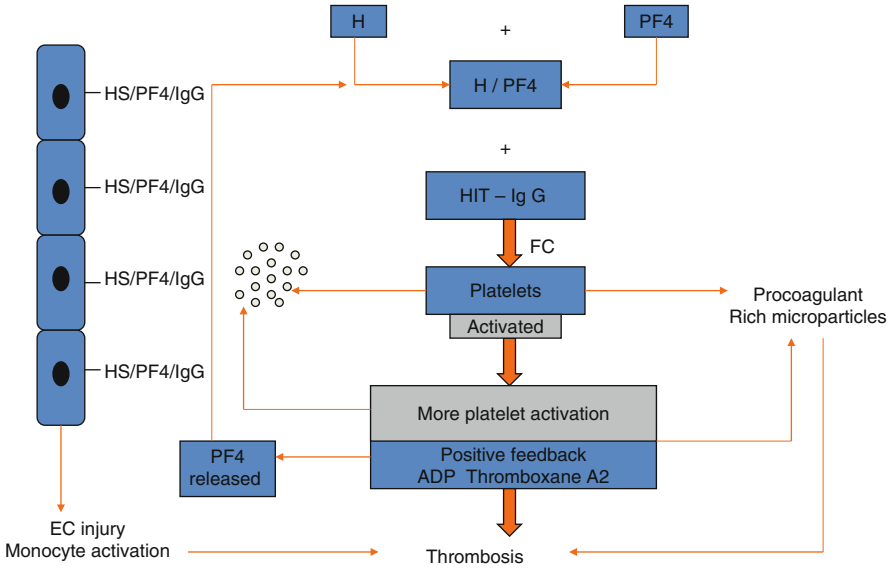



**Fig. A.1** Mechanism of thrombin formation in HIT

There is evidence that binding of PF4/HIT-IgG complexes to the endothelium occurs and results in endothelial cell injury (Visentin et al. 1994; Kwaan et al. 1999). Binding of PF4/HIT-IgG to monocytes results in monocyte activation and release of tissue factor which supports additional thrombin generation reflected by further increase in TAT and D-dimer levels (Arepally et al. 2001; Pouplard et al. 1999). Platelet and monocyte microparticles activate the coagulation cascade by releasing tissue factor which binds factor VIIa leading to activation of factors IX and X.

### 6.8.4 Incidence of HIT

The risk of heparin-induced thrombocytopenia is higher in patients receiving unfractionated heparin because the formation of the complex PF4-heparin depends on the concentration of both, but also the length of the heparin chain and the degree of sulfating. UFH forms larger complex with PF4 than low-molecular-weight heparin. Thus, the risk of HIT in patients receiving UFH is 5 %, while is 1 % in patients receiving low-molecular-weight heparin. Fondaparinux (which has a lower molecular weight) is unlikely to bind to form complex large enough to activate platelets (Gruel et al. 2003).

There are several factors influencing the frequency of HIT.

Patient Variables

- Medical disorder/treatment—it is more frequent in surgical than medical patients and uncommon in obstetric patients.
- Gender—it is more common in females than males (Warkentin et al. 2002).

Product Variables

- Source of heparin—it is more frequently associated with the use of heparin derived from bovine lung than porcine intestine (Francis et al. 2003).
- Type of heparin—it is more frequently associated with the use of unfractionated than low-molecular-weight heparin.

Management Variables

- Duration of heparin therapy—platelet count falls within 5–10 days and thrombocytopenia develops within 7–14 days.
- Dose of heparin—increase from low- to full-dose heparin.

Although various factors have been associated with a high risk for the development of HIT, HIT has occurred with the following: all types of heparin, all routes of heparin administration, and all heparin dose levels (Fig. A.2).

### 6.8.5 Consequences of HIT

While almost all patients develop PF4-heparin antibodies, the incidence of clinical manifestation of HIT varies. In coronary artery bypass surgery, almost 20–50 % of patients at some point will develop antibodies, but only about 1 % of them will manifest the clinical feature of heparin-induced thrombocytopenia. The variation between patients may depend on antibody titers but also on the size of PF4-complexes. The treatment of HIT is heparin cessation, thrombotic complications

| Factors influencing frequency of HIT | |
|---|---|
| **Factor** | **Influence** |
| **Type of heparin** | Bovine UFH > porcine UFH > LMWH |
| **Patient population** | Post-surgery > medical > obstetrical |
| **Duration of heparin** | 5 or more days heparin use > 1–4 days |
| **Dose of heparin** | Change from low to full dose can lead abrupt platelet ↓ in immunized patient |
| **Gender** | Female > male |
| **Definition of thrombocytopenia** | Proportional platelet count fall (e.g. >50 %) more sensitive than absolute platelet ↓ |

**Fig. A.2** Factors influencing frequency of HIT

still however can develop, including deep venous thrombosis (DVT), pulmonary embolism (PE), stroke, or myocardial infarction (MI). Since thrombotic events have been observed even after cessation of heparin exposure, early recognition and initiation of appropriate therapy are essential steps in management (Levine et al. 2004). About half of patients who present with HIT have DVT. Patients presenting with PE while on heparin should be evaluated for HIT—pulmonary emboli are the presenting complication in 25 % of cases.

Between 10 and 20 % of patients may present with erythematous plaques or skin necrosis at the site of heparin injection. About 25% of patients can develop a systemic reaction to injection of heparin. In this clinical scenario, the patient had already been exposed to heparin within the past 5–100 days and already developed IgG antibodies. This reaction can include fever or chills and tachycardia, hypertension, dyspnea, and, very rarely, cardiopulmonary arrest (Warkentin et al. 2004).

HIT patients who are treated prematurely with warfarin may also develop warfarin-induced venous limb gangrene about 5–10 % of the time.

In addition to the classic presentation of HIT, there are several less-common ways that HIT may present.

Acute limb ischemia due to aortic or iliofemoral thrombosis can developed in 5–10 % of the patients; in rare cases (<3 %), an adrenal hemorrhagic infarction may develop.

In a small percentage of patients (3–5 %), HIT presents as an acute thrombotic stroke or myocardial infarction (MI) following the development of an arterial thrombus. In HIT, arterial thrombi most commonly present as acute limb ischemia, stroke, or MI (Warkentin et al. 1996; Hirsh et al. 2004).

The mortality rate due to thrombi associated with HIT ranges from about 30 % to 50 %. Limb amputation or disability occurs in about 20 %. While venous thrombi outnumber arterial thrombi in most patients, either one or both may occur. If HIT is left untreated, the overall risk of thrombosis is 38–76 % in HIT patients (Warkentin et al. 2004; Hirsh et al. 2004; Warkentin et al. 1998).

This evidence supports that heparin cessation alone is inadequate due to high-risk morbidity and mortality. Alternative therapy with a rapidly acting anticoagulant should be initiated when heparin therapy is discontinued.

#### 6.8.5.1 Diagnosis

The recognition of HIT is important to optimal management, yet diagnosis of HIT is complicated. Several clinical clues suggest HIT in patients receiving heparin therapy. Timing of onset of HIT and degree of thrombocytopenia are the two most important clinical clues to exclude/include HIT (Warkentin et al. 1998).

##### Timing

In most patients, HIT develops between 5 and 14 days after heparin treatment is started. However, it is important to remember that HIT can develop quickly in patients reexposed to heparin. Thus, a patient's history of heparin exposure is crucial. Delayed onset HIT has been reported to occur 9–45 days after heparin discontinuation (Rice et al. 2002).

##### Degree of Thrombocytopenia

The actual platelet counts in patients with HIT are rarely <15,000/mol; more important is the occurrence of a sudden drop in platelet count of 30–50 % from the patient's baseline. Drops >50 % seem particularly relevant to HIT diagnosis. Other causes of thrombocytopenia such as sepsis, DIC, and drug therapy (such as Glib/IIIa inhibitors, antibiotics) should be also ruled out.

Two general types of assays are used to make the diagnosis of HIT: functional assay which detect platelet activation and quantitative direct binding assay to detect antibodies.

$^{14}$C-Serotonin Release Assay (SRA) (Sheridan et al. 1986; Warkentin et al. 1992)

- The basis of the SRA is that antibodies from patients with HIT will cause platelet activation and release of 14C-serotonin from platelet-dense granules when HIT serum is incubated with normal donor platelets at therapeutic concentrations of heparin.
- Disadvantages of this test are the use of radioactive substances and it is technically demanding.
- The assay can be used to determine cross-reactivity with other anticoagulant polysaccharides.

The Heparin-Induced Platelet Aggregation Assay (HIPAA) (Greinacher et al. 1992)

- The HIPAA, like the SRA, employs washed platelets from normal donor's platelet aggregation in the presence of heparin rather than serotonin release is used as an indicator of the presence of HIT antibodies.
- The assay is rapid, does not use a radioactive isotope, and is less technically demanding than SRA.
- The assay can be used to determine cross-reactivity with other anticoagulant polysaccharides.

Platelet-Rich Plasma (PRP) Aggregation (Greinacher et al. 1991; Greinacher et al. 1994; Favaloro et al. 1992)

- Platelet-rich plasma (PRP) aggregation is simple, rapid, and widely performed to test for HIT.

PF4 Antigen Assays (Amiral et al. 1992; Arepally et al. 1995; Warkentin et al. 2004)

- The discovery that the major antigen of HIT was the platelet factor 4 (PF4)/heparin complex led to development of an enzyme-linked immunosorbent assay to detect HIT-specific antibodies.
- This assay can detect IgG, IgM, and IgA antibodies.
- These assays *cannot* be used to investigate cross-reactivity of HIT sera for other anticoagulant polysaccharides.
- Has high sensitivity but low specificity.

The antigen assays correlate much less with clinical HIT than the functional assays does.

- The SRA, HIPAA, and PF4 antigen assays:
  (a) Have high negative predictive value (negative test usually rules out HIT *) applies to solid-phase EIAs and washed platelet activation assays
  (b) Have moderate positive predictive value (stronger test result = higher chance of HIT)
  (c) Are not recommended for routine antibody testing in the absence of:
    - Thrombocytopenia or >50 % ↓ in platelet count
    - Thrombosis
    - Heparin-induced skin necrosis
    - Other sequelae of HIT

[Recommendation Grade 1C] (Warkentin et al. 2004; Guyatt et al. 2001)

A commonly used score to predict the likelihood of HIT is the "4 Ts" score introduced in 2003 by Warkentin et al. A score of 0–8 points is generated; if the score is 0–3, HIT is unlikely. If the score is 4–5 a minority will have HIT (10–30 %), while with a score 6–8 (20–80 % will have HIT).

#### 6.8.5.2 Management

If HIT is suspected the use of heparin, including flushing of arterial and venous lines, should be discontinued immediately—(*Recommendation Grade 1C+*) (Greinacher et al. 2004; Warkentin et al. 2004; Guyatt et al. 2001). There are numerous case reports of progressive, new, or recurrent thromboembolic events if heparin is continued or restarted. The thrombocytopenia is also likely to persist if heparin is not stopped:

- HIT is a strong independent risk factor for venous and arterial thrombosis (Girolami et al. 2003), and a substantial number of HIT patients will develop a thrombotic event some time after the cessation of heparin therapy (Girolami et al. 2000). Moreover, many patients will be receiving heparin to either prevent or treat a thrombotic disorder—usually venous thromboembolic disease (VTE). Consequently, continuation of antithrombotic therapy with an alternative non-heparin anticoagulant is recommended—*Recommendation Grades 1B (danaparoid), 1C+ (lepirudin), 1C (argatroban), and 2C (bivalirudin*) (Warkentin et al. 2004; Guyatt et al. 2001).
- Specific serological tests should be performed to confirm or reject the diagnosis of HIT. It should be emphasized that, due to the significant morbidity and mortal-

ity associated with HIT, the previously outlined treatment decisions of stopping heparin and initiating alternative antithrombotic therapy should not be delayed pending the results of confirmatory tests (Greinacher et al. 2004).

- If appropriate confirmatory tests are negative, heparin may be restarted but regular monitoring of platelet counts should be reinstituted—*Recommendation Grade 2C*. Alternatively, where a non-heparin antithrombotic has been substituted, this may be continued at full or low dose depending on the presence or absence of a primary thrombotic disorder (Greinacher et al. 2004; Warkentin et al. 2004; Guyatt et al. 2001).

Patients should not be converted from heparin therapy to VKA therapy—*Recommendation Grade 1C* (Warkentin et al. 2004; Guyatt et al. 2001):

- It is ineffective.
- This may precipitate venous gangrene due to a precipitous fall in the levels of protein C (Warkentin et al. 1997; Warkentin et al. 1991).
- If started prior to diagnosis of HIT it should be reversed by vitamin K (5–10 mg) PO or IV—*Recommendation Grade 2C* (Warkentin et al. 2004; Guyatt et al. 2001).
- Low-molecular-weight heparin should not be substituted for unfractionated heparin due to the high risk of in vivo cross-reactivity despite its low frequency of causing this syndrome—*Recommendation Grade 1C+* (Gruel et al. 2003; Warkentin et al. 2004; Guyatt et al. 2001; Warkentin et al. 1996; Warkentin et al. 1997).
- Platelet transfusions are relatively contraindicated unless absolutely required to manage life-threatening bleeding—*Recommendation Grade 2C* (Gruel et al. 2003; Warkentin et al. 2004; Guyatt et al. 2001; Warkentin et al. 1991; Warkentin et al. 2003).

### 6.8.6 Agents Used in the Treatment of HIT

A number of non-heparin antithrombotic agents may be considered for substitution therapy in suspected or confirmed HIT. The recommendations for their use have been graded at the most recent Consensus Meeting on Antithrombotic Therapy of the American College of Clinical Pharmacy—*Recommendation Grades 1B (danaparoid), 1C+ (lepirudin), 1C (argatroban), 2C (bivalirudin)* (Warkentin and Greinacher 2004; Guyatt et al. 2001). Only danaparoid has been evaluated in a randomized clinical trial in HIT:

- Danaparoid—Xa/IIa inhibitor (anti-factor Xa >> anti-IIa).
- Danaparoid provides an option for anticoagulation in either prophylactic or therapeutic doses.
- Danaparoid has been used in at least 100,000 treatment episodes in patients with HIT.
- Clinical studies in HIT suggest a 94 % success rate (investigator reported).
- It can be given by both IV and SQ routes with 100 % bioavailability.
- Direct thrombin inhibitor (DTI):
- Lepirudin
  Indicated for anticoagulation in patients with HIT and associated thromboembolic disease to prevent further thromboembolic complications

- Argatroban
  Indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with HIT
  Indicated as an anticoagulant in patients with or
  At risk for HIT undergoing PCI

Bivalirudin*
  Indicated as an anticoagulant in patients undergoing percutaneous transluminal coronary angioplasty (PTCA)
  Recently approved for patients with or at risk HIT patients undergoing PCI (December 2005):

- Angiomax® (bivalirudin) for injection [package insert]. Parsippany, NJ: The Medicines Company; 2005; Argatroban Injection [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2005.

Given the high risk category of HIT for thromboembolism, alternative non-heparin anticoagulant therapy should be continued even when not initially complicated thrombosis (Kelton et al. 2013). This should be continued until the platelet count shows recovery to $>100 \times 10^9$. Venous thromboembolism VTE develops early in HIT and may not be detected clinically. Consequently, lower limb ultrasonography should be performed to detect occult DVT and monitor antithrombotic treatment response—*Recommendation Grade 1C* (Fig. A.3) (Warkentin et al. 2004; Guyatt et al. 2001).

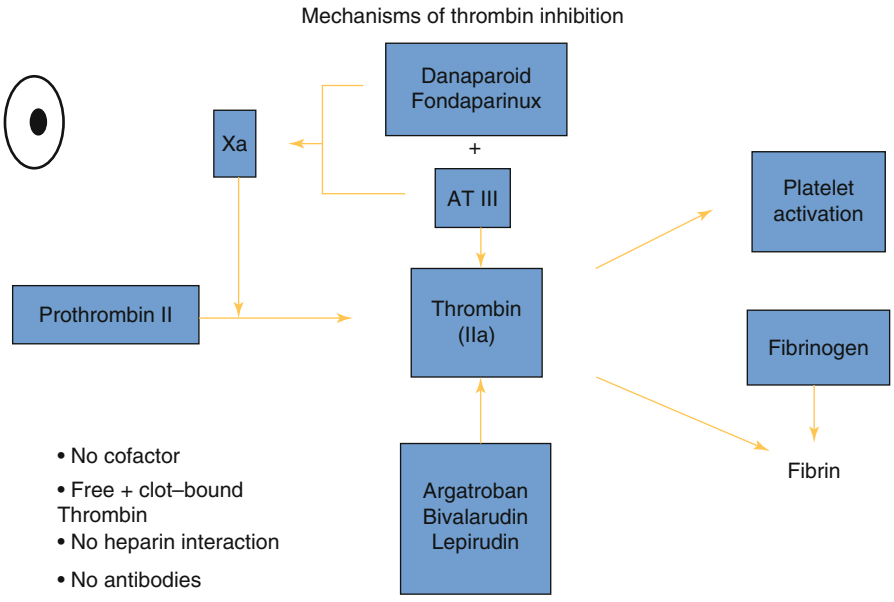



**Fig. A.3** Argatroban and hirudin-related agents inhibits thrombin, while fondaparinux and danaproid inhibit factor Xa

**Case Study Number 1**

A 64-year-old female with severe aortic stenosis and coronary artery disease underwent uneventful aortic valve replacement with 23 mm pericardial valve and saphenous vein graft to the right coronary artery. The patient was transferred to the step-down on POD 1.

On postoperative day 6, the patient had paroxysmal atrial fibrillation and unfractionated heparin infusion was started. The same day, also warfarin was started. On postoperative day 9, the patient suffered from delirium and was transfer back to the intensive care unit. The platelet count was 20,000× $10^3$ per $mm^{3,}$ while the INR was 9 and she developed right upper anterior chest wall necrosis. Heparin and Coumadin were discontinued, and PF4/IgG assay was sent. Bivalirudin was started. PF4/IgG was elevated but borderline (0.4 anti-platelet factor 4 (PF4)/heparin antibody OD value). When the platelet count was >100,000 × $10^3$ per $mm^3$, Coumadin was restarted.

The patient was discharged day 35 and continued Coumadin for 6 months (Fig. A.4).

Figure A.4 summarizes the relationship of platelet count and days of hospitalization.

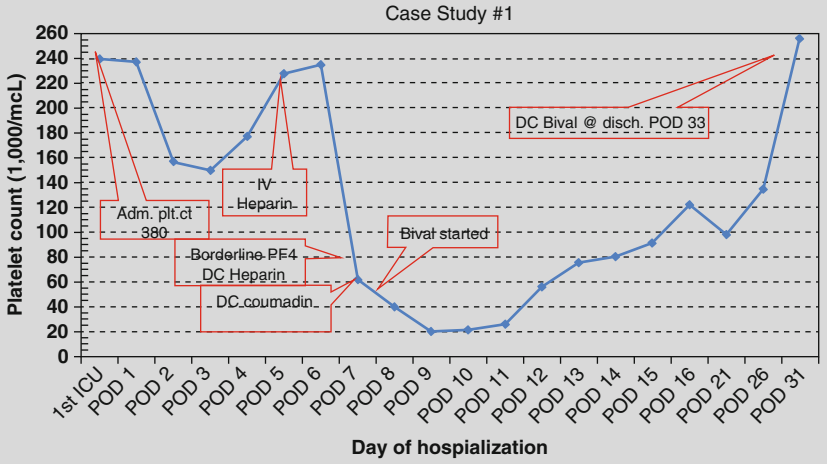
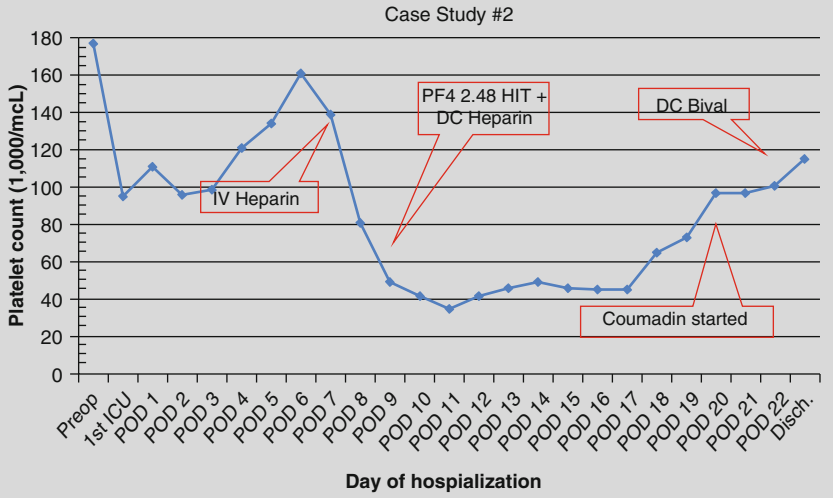



**Fig. A.4** Relationship of platelet count and days of hospitalization

**Case Study Number 2**

A 63-year-old male with symptomatic severe aortic stenosis underwent aortic valve replacement with a 23 mm pericardial valve. His postoperative course was complicated by asystolic cardiac arrest due to complete heart block requiring temporary pacing, agitation, confusion altered mental status, and aspiration requiring re-intubation. On postoperative day 7, the patient was started on unfractioned heparin for atrial fibrillation.

On postoperative day 9, the patient platelet count dropped to 45,000 × $10^3$ per $mm^3$, the patient developed tachypnea and hypoxemia. The PF4/IgG assay was sent and came back (with a value of 2. 48 anti-heparin/PF4 antibody OD value). Bivalirudin was started. The clinical presentation included RUL/LLL PE, left gastrocnemius DVT, and seizures due to embolic events confirmed by tiny punctate infarcts on MRI in the right frontal lobe. Platelet count recovered over 100,000 on postoperative day. Coumadin was started and overlapped with intravenous bivalirudin until the INR was therapeutic. The patient was discharged on postoperative day 23 and continued on Coumadin for 6 months.



### 6.8.7 Discussion

These two cases illustrate the clinical course of HIT. Both patients had recent exposure to unfractionated heparin with drop in platelet count and the presence of thromboembolic complications. In case #1, the clinical picture was so overwhelming for the diagnosis of HIT (sudden drop in platelets count, unexplained symptoms, skin necrosis) that we decided to treat the patient accordingly even though the anti-PF4-heparin Ab level was a borderline value.

These two patients summarizes that HIT is associated with high morbidity and prolonged hospital stay. The financial implications of HIT are significant.

### 6.8.8 Future Directions

Unfractionated heparin will continue to be used in cardiac surgical patients because it is safe for cardiopulmonary bypass. Future advances may be directed toward the treatment of HIT. The introduction of oral direct thrombin inhibitors may be used as an alternative to the intravenous and subcutaneous counterparts. In addition they can be continued to the outpatient setting without the need for Coumadin combined with intravenous therapies. Such an strategy undoubtedly will result in reduced hospital stay and cost.

## References

Amiral J, Bridey F, Dreyfus M et al (1992) Platelet factor 4 complexed to heparin is the target for antibodies generated in heparin-induced thrombocytopenia [letter]. Thromb Haemost 68:95–96

Arepally GM, Mayer IM (2001) Antibodies from patients with heparin-induced thrombocytopenia stimulate monocytic cells to express cells to express tissue factor and secrete interleukin-8. Blood 98:1252–1254

Arepally G, Reynolds C, Tomaski A et al (1995) Comparison of PF4/heparin ELISA with the [14] C-serotonin release assay in the diagnosis of heparin-induced thrombocytopenia. Am J Clin Pathol 104:648–654

Favaloro EJ, Bernal-Hoyos E, Exner T et al (1992) Heparin-induced thrombocytopenia: laboratory investigation and confirmation of diagnosis. Pathology 24:177–183

Francis JL, Palmer GJ III, Moroose R et al (2003) Comparison of bovine and porcine heparin in heparin antibody formation after cardiac surgery. Ann Thorac Surg 75:17–22

Giles AR, Nesheim ME, Hoogendoorn H et al (1982) Stroma free human platelet lysates potentiate the in vivo thrombogenicity of factor Xa by the provision of coagulant-active phospholipid. Br J Haematol 51:457–468

Girolami B, Prandoni P, Stefani PM et al (2003) The incidence of heparin-induced thrombocytopenia in hospitalized medical patients treated with subcutaneous unfractionated heparin: a prospective cohort study. Blood 101:2955–2959

Goad KE, Horne MK III, Gralnick HR (1994) Pentosan induced thrombocytopenia: support for an immune complex mechanism. Br J Haematol 88:803–808

Greinacher A, Warkentin TE (2004) Treatment of heparin-induced thrombocytopenia: an overview. In: Warkentin TE, Greinacher A (eds) Heparin induced thrombocytopenia, 3rd edn. Marcel Dekker, New York, pp 335–370

Greinacher A, Michels I, Kiefel V et al (1991) A rapid and sensitive test for diagnosing heparin-associated thrombocytopenia. Thromb Haemost 66:734–736

Greinacher A, Michels I, Schäfer M et al (1992) Heparin-associated thrombocytopenia in a patient treated with polysulphated chondroitin sulphate: evidence for immunological crossreactivity between heparin and polysulphated glycosaminoglycan. Br J Haematol 81:252–254

Greinacher A, Pötzsch B, Amiral J et al (1994a) Heparin-associated thrombocytopenia: isolation of the antibody and characterization of a multi-molecular PF4-heparin complex as the major antigen. Thromb Haemost 71:247–251

Greinacher A, Amiral J, Dummel V et al (1994b) Laboratory diagnosis of heparin-associated thrombocytopenia and comparison of platelet aggregation test, heparin-induced platelet activation test, and platelet factor 4/heparin enzyme-linked immunosorbent assay. Transfusion 34:381–385

Greinacher A, Eichler P, Lubenow N et al (2000) Heparin induced thrombocytopenia with thromboembolic complications: meta-analysis of 2 prospective trials to assess the value of parenteral treatment with lepirudin and its therapeutic aPTT range. Blood 96:846–851

Gruel Y, Pouplard C, Nguyen P et al (2003) Biological and clinical features of low-molecular-weight heparin-induced thrombocytopenia. Br J Haematol 121:786–792

Guyatt G, Schunëmann H, Cook D et al (2001) Grades of recommendation for antithrombotic agents. Chest 119:3S–7S

Hirsh J, Heddle N, Kelton JG (2004) Treatment of heparin-induced thrombocytopenia: a critical review. Arch Intern Med 164:361–369

Kelton JG, Smith JW, Warkentin TE et al (1994) Immunoglobulin G from patients with heparin-induced thrombocytopenia binds to a complex of heparin and platelet factor 4. Blood 83:3232–3239

Kelton JG, Arnold DM, Sm B (2013) Nonheparin anticoagulants for heparin-induced thrombocytopenia. N Engl J Med 368:737–744

Kwaan HC, Sakurai S (1999) Endothelial cell hyperplasia contributes to thrombosis in heparin-induced thrombocytopenia. Semin Thromb Hemost 25:23–27

Lee DH, Warkentin TE (2004) Frequency of heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A (eds) Heparin induced thrombocytopenia, 3rd edn. Marcel Dekker, New York

Levine RL, Hursting MJ, Drexler A et al (2004) Heparin-induced thrombocytopenia in the Emergency Department. Ann Emerg Med 44:511–515

Pouplard C, May MA, Iochmann S et al (1999) Antibodies to platelet factor 4–heparin after cardiopulmonary bypass in patients anticoagulated with unfractionated heparin or a low-molecular-weight heparin: clinical implications for heparin-induced thrombocytopenia. Circulation 99:2530–2536

Rice L, Attisha WK, Drexler A et al (2002) Delayed onset heparin induced thrombocytopenia. Ann Intern Med 136(3):210–215

Sheridan D, Carter C, Kelton JG et al (1986) A diagnostic test for heparin-induced thrombocytopenia. Blood 67:27–30

Visentin GP, Ford SE, Scott JP et al (1994) Antibodies from patients with heparin-induced thrombocytopenia/thrombosis are specific for platelet factor 4 complexed with heparin or bound to endothelial cells. J Clin Invest 93:81–88

Warkentin TE (1996) Heparin-induced thrombocytopenia: IgG-mediated platelet activation, platelet microparticle generation, and altered procoagulant/anticoagulant balance in the pathogenesis of thrombosis and venous limb gangrene complicating heparin-induced thrombocytopenia. Transfus Med Rev 10:249–258

Warkentin TE (1998) Limitations of conventional options for heparin induced thrombocytopenia. Semin Hematol 35(4 suppl 5):9–16

Warkentin TE (2003) Heparin-induced thrombocytopenia: pathogenesis & management. Br J Haematol 121:535–555

Warkentin TE (2004) Clinical picture of heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A (eds) Heparin- induced thrombocytopenia, 3rd edn. Marcel Dekker, New York, pp 53–106

Warkentin TE, Greinacher A (2004) Heparin-induced thrombocytopenia: recognition, treatment, and prevention – the 7th ACCP conference on antithrombotic & thrombolytic therapy. Chest 126:311S–337S
Warkentin TE, Heddle NM (March 2003) Laboratory diagnosis of immune heparin-induced thrombocytopenia. Curr Hematol Rep 2(2):148–157
Warkentin TE, Kelton JG (1996) A 14-year study of heparin-induced thrombocytopenia. Am J Med 101:502–507
Warkentin TE, Sigouin CS (2002) Gender and risk of immune heparin-induced thrombocytopenia. Blood 100:17a
Warkentin TE, Hayward CP, Smith CA et al (1992) Determinants of donor platelet variability when testing for heparin-induced thrombocytopenia. J Lab Clin Med 120:371–379
Warkentin TE, Levine MN, Hirsh J et al (1995) Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 332:1330–1335
Warkentin TE, Sheppard JA, Horsewood P et al (2000) Impact of the patient population on the risk for heparin-induced thrombocytopenia. Blood 96:1703–1708

### 6.8.9 Appendix A.1 Agents Used for Treatment of HIT

| Agents | Dosage |
|---|---|
| **Danaproid** | IV bolus (1,500 U if patient is 60 Kg, 2,250 U if 60–75 kg, 3,000 U if 75–90 Kg, 3,750 U if >90 Kg) |
| | Intravenous infusion 400 U per hour for 4 h, 300 U per hour for 4 h, 150–200 U per hour |
| *Monitoring* | Adjust to anti-factor Xa activity of 0.5–0.8 U per milliliter |
| **Argatroban** | IV infusion 2.0 μg per kilogram; decrease in patients with liver disease or critical illness (to 0.5–1.2 μg per kilogram) |
| *Monitoring* | Adjust to maintain activated partial thromboplastin time at 1.5–3.0 times baseline value |
| **Bivalirudin** | 0.15–2.0 mg per kg/h |
| *Monitoring* | Adjust to maintain activated partial thromboplastin time at 1.5–2.5 times baseline value |
| **Fondaparinux** | 5.0 mg SQ qday for patients, 50 kg; 7.5 mg for 50–100 kg; 10 mg for patients >100 kg |
| *Monitoring* | None |

## References

Abciximab (Reopro®). http://www.reopro.com/Pages/index.aspx. Accessed 8 Aug 2012
Ageno W, Gallus AS, Wittkowsky A (2012) Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141:e44S–e88S
Apixaban (Eliquis®). http://packageinserts.bms.com/pi/pi_eliquis.pdf. Accessed 27 Feb 2013
Argatroban®. http://us.gsk.com/products/assets/us_argatroban.pdf. Accessed 31 July 2012
Biancari F, Mikkola R, Heikkinen J, Lahtinen J, Airaksinen KE, Juvonen T (2012) Estimating the risk of complications related to re-exploration for bleeding after adult cardiac surgery: a systematic review and meta-analysis. Eur J Cardiothorac Surg 41(1):50–55
Bivalirudin (Angiomax®). www.angiomax.com/Downloads/Angiomax_PI_2010_PN1601-12.pdf. Accessed 18 July 2012

Bojar RM (2011) Manual of perioperative care in adult cardiac surgery, 5th edn. Wiley-Blackwell, West Sussex
Brighton T (2010) New oral anticoagulant drugs – mechanisms of action. Aust Prescr 33:38–41
Callum JL, Karkouti K, Lin Y (2009) Cryoprecipitate: the current state of knowledge. Transfus Med Rev 23:177–188
Charalambous CP, Zipitis CS, Keenan DJ (2006) Chest reexploration in the intensive care unit after cardiac surgery: a safe alternative to returning to the operating theater. Ann Thorac Surg 81(1):191–194
Choong CK, Gerrard C, Goldsmith KA, Dunningham H, Vuylsteke A (2007) Delayed re-exploration for bleeding after coronary artery bypass surgery results in adverse outcomes. Eur J Cardiothorac Surg 31(5):834–838
Clopidogrel (Plavix®). http://www.plavix.com/Index.aspx. Accessed 8 Aug 2012
Dabigatran (Pradaxa®). https://www.pradaxa.com/. Accessed 17 July 2012
Dager W (2011) Unfractionated heparin. In: Dager W, Gulseth M, Nutescu E (eds) Anticoagulation® therapy: a point of care guide. American Society of Health-System Pharmacists, Bethesda
Dalteparin (Fragmin®). www.pfizer.com/files/products/uspi_fragmin.pdf. Accessed 18 July
De Bonis M, Cavaliere F, Alessandrini F (2000) Topical use of tranexamic acid in coronary artery bypass operations: a double-blind, prospective, randomized, placebo controlled study. J Thorac Cardiovasc Surg 119:575–580
Despotis GJ, Goodnough LT (2000) Management approaches to platelet-related microvascular bleeding in cardiothoracic surgery. Ann Thorac Surg 70:S20–S32
Douketis JD (2010) Pharmacologic properties of the new oral anticoagulants: a clinician-oriented review with a focus on perioperative management. Curr Pharm Des 16:3436–3441
Douketis JD, Spyropoulos AC, Spencer FA et al (2012) Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141:e326S–e350S
Dunn AL (2009) Disseminated intravascular coagulopathy. In: Hillyer CD, Shaz BH, Zimring JC, Abshire TC (eds) Transfusion medicine and hemostasis: clinical and laboratory aspects. Elsevier, Burlington
Eikelboom JW, Hirsch J, Spencer FA (2012) Antiplatelet drugs: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141:e89S–e119S
Enoxaparin (Lovenox®). http://products.sanofi.us/lovenox/lovenox.html#section-14.1. Accessed 18 July
Eptifibatide (Integrilin®). http://www.integrilin.com/integrilin/index.html. Accessed 8 Aug 2012
Fawzey H, Elmistekawy E, Bonneau D et al (2009) Can local application of tranexamic acid reduce post-coronary bypass surgery blood loss? A randomized controlled trial. J Cardiothorac Surg 4:25. http://www.cardiothoracicsurgery.org/content/4/1/25
Ferraris VA, Brown JR, Despotis GJ et al (2011) Update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 91:944–982
Fondaparinux (Arixtra®). http://us.gsk.com/products/assets/us_arixtra.pdf. Accessed 31 July 2012
Franchini M, Lippi G, Manzato F (2006) Recent acquisitions in the pathophysiology, diagnosis and treatment of disseminated intravascular coagulation. Thromb J 4:4. doi:10.1186/1477-9560-4-4
Gibbs N, Weightman W, Thackray NM et al (2001) The effects of recent aspirin ingestion on platelet function in cardiac surgical patients. J Cardiothorac Vasc Anesth 15(1):55–59
Gill R, Herbertson M, Vuylsteke A et al (2009) Safety and efficacy of recombinant activated factor VII: a randomized placebo controlled trial in the setting of bleeding after cardiac surgery. Circulation 120:21–27
Halasynski TM, Juda R, Silverman DG (2004) Optimizing postoperative outcomes with efficient preoperative assessment and management. Crit Care Med 32:S76–S86
Karthik S, Grayson AD, McCarron EE, Pullan DM, Desmond MJ (2004) Reexploration for bleeding after coronary artery bypass surgery: risk factors, outcomes, and the effect of time delay. Ann Thorac Surg 78(2):527–534; discussion 34
Koh MBC, Hunt BJ (2003) The management of perioperative bleeding. Blood Rev 17:179–185

Lemmer JH, Despotis GJ (2002) Antithrombin III concentrate to treat heparin resistance in patients undergoing cardiac surgery. J Thorac Cardiovasc Surg 123:213–217
Linkins L, Dans AL, Moores LK et al (2012) Treatment and prevention of heparin-induced thrombocytopenia: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141:e495S–e530S
Mongan PD, Hosking MP (1992) The role of desmopressin acetate in patients undergoing coronary artery bypass surgery. Anesthesiology 77:38–46
Moulton MJ, Creswell LL, Mackey ME, Cox JL, Rosenbloom M (1996) Reexploration for bleeding is a risk factor for adverse outcomes after cardiac operations. J Thorac Cardiovasc Surg 111(5):1037–1046
O'Conner SD, Taylor AJ, Williams EC et al (2009) Coagulation concepts update. AJR 193:1656–1664
Ozier Y, Bellamy L (2010) Pharmacological agents: antifibrinolytics and desmopressin. Best Pract Res Clin Anesthesiol 24:107–119
Patrono C, Andreotti F, Arnesen H et al (2011) Antiplatelet agents for the treatment and prevention of atherothrombosis. Eur Heart J 32:2922–2932
Prasugrel (Effient®). http://www.effient.com/Pages/index.aspx. Accessed 8 Aug 2012
Ranucci M, Isgro G, Cazzaniga A et al (1999) Predictors for heparin resistance in patients undergoing coronary artery bypass grafting. Perfusion 14:437
Rivaroxaban (Xarelto®). http://www.xareltohcp.com/. Accessed 17 July 2012
Schulman S, Bijsterveld NR (2007) Anticoagulants and their reversal. Transfus Med Rev 2:37–48
Sie P, Steib A (2006) Central laboratory and point of care assessment of perioperative hemostasis. Can J Anesth 53:S12–S20
Teoh KH, Young E, Blackall MH et al (2004) Can extra protamine eliminate heparin rebound following cardiopulmonary bypass surgery. J Thorac Cardiovasc Surg 128:211–219
Ticagrelor (Brilinta®). http://www.brilinta.com/. Accessed 8 Aug 2012
Tirofiban (Aggrastat®). http://www.aggrastat.com/. Accessed 8 Aug 2012
Van Ryn J, Stangier J, Sebastian H et al (2010) Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 103:1116–1127
Vivacqua A, Koch CG, Yousuf AM, Nowicki ER, Houghtaling PL, Blackstone EH et al (2011) Morbidity of bleeding after cardiac surgery: is it blood transfusion, reoperation for bleeding, or both? Ann Thorac Surg 91(6):1780–1790
Wallentin L (2009) P2Y12 inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. Eur Heart J 30:1964–1977
Wallentin L, Becker RC, Budaj A et al (2009) Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 361:1045–1057
Warfarin (Coumadin®). http://packageinserts.bms.com/pi/pi_coumadin.pdf. Accessed 17 July 2012
Warkentin TE (2004) Heparin induced thrombocytopenia: diagnosis and management. Circulation 110:e454–e458
Weber CF, Klages M, Zacharowski K (2013) Perioperative coagulation management during cardiac surgery. Curr Opin Anaesthesiol 26:60–64
Weitz JI, Eikelboom JW, Samama MM (2012) New antithrombotic drugs: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141:e120S–e151S
Winkler AM, Zimring JC (2009) Laboratory support for heparin monitoring. In: Hillyer CD, Shaz BH, Zimring JC, Abshire TC (eds) Transfusion medicine and hemostasis: clinical and laboratory aspects. Elsevier, Burlington
Wittkowsky A (2011) Warfarin. In: Dager W, Gulseth M, Nutescu E (eds) Anticoagulation therapy: a point of care guide. American Society of Health-System Pharmacists, Bethesda

# Cardiovascular Complications and Management After Cardiac Surgery

7

Mahnoosh Foroughi and Antonio Hernandez Conte

## Contents



**Abstract**

The essential principle in post-cardiac surgical care is ensuring optimal hemodynamic preservation and tissue perfusion through the utilization of continuous hemodynamic monitoring, adequate volume repletion, and, if necessary, use of inotropic agents and/or pressors. Cardiopulmonary resuscitation (CPR) for

M. Foroughi, MD (✉)
Cardiovascular Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
e-mail: mahnoosh.foroughi@gmail.com, m_foroughi@sbmu.ac.ir

A.H. Conte, MD, MBA
Perioperative Transesophageal Echocardiography Education, Division of Cardiothoracic Anesthesiology, Department of Anesthesiology, Cedars-Sinai Medical Center, Los Angeles, CA, USA
e-mail: antonio.conte@cshs.org

A. Dabbagh et al. (eds.), *Postoperative Critical Care for Cardiac Surgical Patients*,
DOI 10.1007/978-3-642-40418-4_7, © Springer-Verlag Berlin Heidelberg 2014

cardiac arrest after cardiac surgery is different from cardiac arrest in other settings as its causes are usually reversible with associated improved outcomes.

Due to aging of the cardiac surgical population and broader application of interventional cardiologic interventions before admission for cardiac surgery, the profile of patients has changed. Cardiac surgical patients in the twenty-first century are older and sicker, possess diminished physiologic reserve, manifest decreased ventricular function, are referred for more complex procedures, and are at high risk for postoperative major cardiac complications in comparison with other patient populations. The main insult sustained by the patient is related to inadequate myocardial contraction that results in a low cardiac output syndrome. Inability to wean from cardiopulmonary bypass created more emphasis in evaluating means of more prolonged supportive measures. Innovative techniques for circulatory support devices have developed, and different types are now available. Initially intra-aortic balloon pumps (IABP) and centrifugal pumps were developed, whereas now rapidly evolving technical changes have led to new and improved pneumatic and electrically driven internal assist devices. These devices are being increasingly inserted in an effort to provide supportive assistance to one or both ventricles with increased safety and durability.

## 7.1 Cardiac Monitoring

Upon arrival to the ICU, the post-cardiac surgical patient requires intense adequate hemodynamic monitoring; this is accomplished via continuous ECG, arterial blood pressure measurement via arterial catheter, frequent arterial blood gas sampling, central venous pressure (CVP) measurement via central venous catheter, pulse oximetry, and evaluation of chest tube drainage. The use of a pulmonary artery catheter is validated in pulmonary hypertension, severe low cardiac output, and partition of right and left ventricular failure; however, its use is associated with multiple risks and higher morbidity and mortality when inappropriately utilized.

The main aim in post-cardiac surgical care is to maintain optimal hemodynamics with resultant normal tissue perfusion achieved by sufficient intravascular volume and cardiac output. Although, during CPB there is increased weight gain due to water retention, it is distributed to the extravascular component. However, the hypovolemic condition postoperatively is common. CVP is considered an approximate indicator of preload status. It is recommended to keep CVP >10 mmHg by volume repletion; by the same respect, a CVP >20 mmHg may warrant diuresis. Before volume administration, hemodynamic response to increasing preload can be assessed by passive leg rising.

After cardiac surgery reduced myocardial function may be due to inadequate valve repair or insufficient revascularization, ischemic reperfusion injury, myocardial edema, reduced preload, and increased afterload. The adequacy of cardiac performance during the postoperative period in the ICU is assessed by cardiac index, arterial blood pressure, pedal pulses, skin temperature, mixed venous oxygen saturation level, urinary volume, and metabolic acidosis. Possible indicators of insufficient cardiac performance are:

*Mean arterial pressure < 60 mmHg*
*Serum lactate > 2 mmol/L*
*Urinary output < 0.5 mL/h*
*$Svo_2$ < 60 % with $Sao_2$ > 95 %*

Central-mixed venous oxygen saturation ($SVO_2$) is a very accurate indicator of tissue perfusion, as it demonstrates the relationship between oxygen supply (determined by cardiac output) and demand (metabolic state).

Some causes of low cardiac output after cardiac surgery are evaluated by electrocardiogram, chest X-ray, hemodynamic data, and echocardiography. ECG changes may be suggestive of myocardial ischemia or infarction, significant chest tube drainage, and blood collection, or signs of tamponade may be noted through chest X-ray, and echocardiography can delineate new ventricular wall motion abnormalities, decreased ejection fraction (EF), and new or residual valvular pathology (Wasir et al. 2003; Joshi et al. 2005; Overgaard and Džavík 2008).

### 7.1.1 Cardiovascular Effects of Common Inotropic Agents

The primary treatment for low cardiac output states has been pharmacologic interventions. Catecholamines exert their cardiovascular effects through α-, $\beta_1$–, $\beta_2$–, and dopaminergic receptors. α-receptor activation causes arterial vascular smooth muscle contraction and rising in systemic vascular resistance (SVR). $\beta_1$-receptor stimulation in myocardium causes increased contractility and conduction velocity. $\beta_2$-receptor activation causes vascular smooth muscle relaxation and reduction in SVR. Dopaminergic receptor in kidney and splanchnic circulation causes vasodilation. Epinephrine in low dose acts in $\beta_1$-receptors and in high dose acts in α-receptors. Norepinephrine is a potent α-receptor agonist, enhancing SVR via vasoconstriction. Phenylephrine as α-receptor agonist is used in bolus setting to correct hypotension.

Pharmacologic support in patients with low cardiac output may be obligatory in the postoperative period. However, before starting inotropes, improvement of preload status and SVR reduction must be considered because cardiac output is a function of myocardial contractility and hemodynamic conditions (afterload and preload).

## 7.2 Cardiac Complications

### 7.2.1 Postoperative Myocardial Ischemia

While a large majority of cardiothoracic surgery is performed in order to optimize vascular supply to the heart via coronary artery bypass grafting, postoperative myocardial ischemia (PMI) and associated myocardial infarct (MI) continue to remain a significant complication in the postoperative setting. The Society of Thoracic Surgeons (STS) maintains a clinical database for every cardiothoracic surgical procedure performed; the STS has defined perioperative ischemia as the occurrence of at least one of the following markers: (1) electrocardiographic changes consistent

with ischemia, (2) elevation of serum markers (i.e., troponin), and (3) reduced systolic ejection fraction. The incidence of PMI in the STS database is 1 %.

#### 7.2.1.1 Diagnosis

The diagnosis of postoperative myocardial ischemia is based upon detection of the aforementioned markers. The most common laboratory tool for assessment of PMI is measurement of troponin I or cardiac troponin. Patients who manifested elevated preoperative levels of troponin may not necessarily imply PMI in the postoperative period. In addition, patients who underwent coronary artery bypass grafting (CABG) with the use of cardiopulmonary bypass (CPB) were more likely to have elevated levels of troponin compared to patients who were "off-pump"; troponin levels were more apt to remain within normal limits if CPB during CABG is not utilized. Elevation of the MB fraction of creatine kinase may also be measured and may be indicative of PMI. Since the majority of PMI may occur while a postsurgical patient is still intubated, symptoms associated with angina may not be elicited; therefore, electrocardiographic detection with follow-up laboratory assessment is paramount.

The type of cardiac surgery performed may allow the clinician to more accurately assess the etiology for PMI. In cases where coronary artery bypass grafting has been conducted, patients may be prone to closure of newly created vascular coronary conduits, as well as residual myocardial injury secondary to poor myocardial protection. Patients having undergone valve repair or replacement, especially aortic valve replacement, as well as aortic root surgery may be prone to anatomic disturbances in coronary blood flow originating at the coronary ostia. Diagnosis may require invasive cardiac catheterization to rule out reocclusion or new occlusion of coronary ostia or their tributaries.

#### 7.2.1.2 Management

Treatment of coronary myocardial ischemia is targeted at maneuvers to improve or restore coronary perfusion and resultant myocardial perfusion. In the absence of arterial hypotension, the initiation of intravenous venodilators (i.e., nitroglycerin) and arterial vasodilators (sodium nitroprusside) may yield significant improvement. In addition, the administration of calcium channel blockers (nifedipine, nicardipine) may ameliorate vasospasm in cardiac arterial blood vessels. The need to augment oxygen-carrying capacity may also require the administration of red blood cell transfusion. Patients not responding to restoration of arterial diastolic pressure concomitant with use of preferential vasodilators may necessitate further evaluation with cardiac catheterization or invasive assessment with a pulmonary artery catheter. Efforts should be made to initiate the appropriate treatment intervention as soon as possible.

### 7.2.2 Hemodynamic Instability

Patients undergoing cardiac surgery undergo significant alterations in temperature, circulating blood volume, initiation of cardiopulmonary bypass, myocardial

protection with plegic solutions, and total circulatory arrest that render this patient population extremely susceptible to residual hemodynamic lability upon arrival in the intensive care unit.

#### 7.2.2.1 Low Cardiac Output

Afterload, preload, and myocardial contractility are the main determinants of heart performance. Cardiac contraction cannot be considered independent from the vascular system, and manipulation of both afterload and preload is necessary for optimal cardiac function. Review of the Starling Curve is important in understanding this relationship. Low cardiac output is the most critical complication after cardiac surgery. It is defined as the need for inotropic infusion support (for longer than 30 min), IAPB, or both to achieve cardiac output >2.2 L/m$^2$/min and preserve systolic blood pressure >90 mmHg despite afterload reduction, optimization of preload, and correction of electrolytes and blood gases. Low cardiac output plays an important role in morbidity and mortality after cardiac surgery.

Some causes of low cardiac output syndrome include incomplete myocardial revascularization, insufficient myocardial protection during aortic cross clamp, reperfusion injury, and systemic inflammatory response. During aortic cross clamp, myocardial perfusion is interrupted; a bloodless field is provided at the expense of potential myocardial ischemia. A cardioplegic solution is used to arrest the heart and decrease the ischemic damage of myocardium during these intervals. Although there is no consensus about type, time, temperature, route, and volume of cardioplegic solution, many studies had shown that inadequate myocardial preservation during surgery leads to postoperative low cardiac output. Therefore, improved ways of cardiac protection can minimize myocardial injury.

Studies have shown that there are multiple independent predictors of low cardiac output after aortic valve and mitral valve replacement. These include:

- Preoperative renal disease
- Increasing age
- Female sex
- Redo surgery and small aortic valve
- Urgency of the operation and CPB time

The most important predictor of low cardiac output after CABG is preoperative left ventricular dysfunction (EF < 20 %). Management of low cardiac output due to left heart failure consists of increasing contractility, afterload reduction, and preload limitation. For right heart failure, in addition to inotropic agents, adequate preload status and reduction in pulmonary vascular resistance are recommended. In low cardiac output states that do not respond to inotropic support and IABP, the use of a ventricular assist device as a bridge to recovery or transplantation may be advised.

#### 7.2.2.2 Diagnosis

The critical care team should accurately and efficiently review the patient's preoperative hemodynamic and intraoperative hemodynamic history as well as noting significant events which may have deviated from the usual and customary management of a cardiothoracic surgical patient.

Diagnosis should include assessment of systolic and diastolic blood pressure trends as well as calculation of perfusion pressure, total peripheral resistance, and possible cardiac output or cardiac index. Changes in the patient's cardiac rhythm and rate should also be conducted to determine if deviations from the intraoperative status have occurred. Loss of circulating blood volume should also be determined by assessing chest tube drainage or reductions in urinary output.

#### 7.2.2.3 Management

The implementation of pressors, vasodilators, or inotropic agents may be necessary based upon the specific hemodynamic disturbance. However, definitive therapy should be aimed at determining the underlying etiology for the respective change (i.e., hypovolemia causing hypotension). Persistent hypotension despite pressor therapy may warrant further support such as administration of colloids or blood products. Hypertension may denote inadequate pain relief or lack of adequate sedation; therefore, opioids or sedatives may be warranted. Transesophageal echocardiography may be of assistance in delineating cardiac-specific pathology contributing to hemodynamic compromise.

Implementation of inotropic support should be based upon more specific findings delineated by use of a pulmonary artery catheter or echocardiogram. Low cardiac output states secondary to diminution of stroke volume can be augmented by the use of fluids or pharmacologic therapy (i.e., epinephrine, norepinephrine, dobutamine, dopamine, or milrinone). The insertion of an intra-aortic balloon pump should be reserved only for instances of refractory hemodynamic compromise unresponsive to pharmacologic support (Mair and Hammerer-Lercher 2005; Noora et al. 2005; Maganti et ak. 2010; Algarni et al. 2011 Hausenloy et al. 2012; Likosky et al. 2012).

### 7.2.3 Arrhythmias

Numerous rhythm disturbances may manifest themselves in patients' status post-cardiac surgery. Electrophysiologic cardiac abnormalities may be secondary to manual manipulation of the heart, arrest with plegic solutions, anatomic/mechanical disruption of electrical pathways, and/or impaired cardiac perfusion resulting in ischemia. A more detailed discussion about arrhythmias could be found in this book in the related chapter.

#### 7.2.3.1 Diagnosis

The diagnosis of rhythm disturbances is most accurately assessed with a minimal of two-lead electrocardiographic monitoring; however, more occult arrhythmias may necessitate 12-lead electrocardiographic evaluation. Arrhythmias may include but are not limited to bradyarrhythmias, tachyarrhythmias, malignant tachyarrhythmias, and multiple degrees of heart block.

The most common arrhythmia occurring in both the acute and later phases of postoperative recovery is the appearance of atrial fibrillation. A recent study of the

STS database revealed an annual incidence of 20 % with the mean occurrence on postoperative day three, but the range was from 0 to 21 days after surgery. Predictors of atrial fibrillation during hospitalization include age greater than 65, history of intermittent atrial fibrillation, atrial pacing, and chronic obstructive pulmonary disease. Predictors after discharge were atrial fibrillation during hospitalization, valve surgery, and pulmonary hypertension. Patients with atrial fibrillation had almost twice the hospital mortality of patients without atrial fibrillation.

#### 7.2.3.2 Management

Sinus rhythm is the rhythm of choice with respect to optimizing cardiac performance and ventricular filling. Electrical cardioversion or pharmacologic intervention with pacing may be necessary to establish and maintain normal sinus rhythm. Bradycardia can be treated with external or internal pacing and/or the administration of anticholinergics or catecholamines. Atropine (10–40 mcg/kg) and glycopyrrolate (10–20 mcg/kg) are two useful anticholinergics, but they are usually not effective in the postoperative setting. Catecholamines such as epinephrine, norepinephrine, isoproteronol, and ephedrine may also be used to treat symptomatic bradycardia. Sinus bradycardia with an adequate stroke volume may respond to anticholinergics; however, bradycardic patients with depressed ventricular performance should likely receive a more potent catecholamine such as epinephrine. More serious bradycardias (e.g., ventricular escape or idioventricular rhythms) will require more aggressive therapy.

Perioperative tachycardia responds well to electroversion and pharmacologic therapy. Post-electroversion pacing can also help to control dysrhythmias. In the absence of electrolyte disturbances, new onset atrial flutter and atrial fibrillation are receptive to synchronized cardioversion. Beta-blockers (e.g., metoprolol and propranolol), calcium channel blockers (e.g., verapamil and diltiazem), and digoxin can also be used to help control the rate. Ventricular tachycardia can be treated with magnesium, lidocaine, bretylium, procainamide, and direct-current cardioversion. The treatment of ventricular fibrillation is immediate asynchronous cardioversion.

Often times after initial rhythm correction maneuvers, intravenous medications such as lidocaine (1–3 mg/kg), procainamide (250–500 mg load then 15–60 mcg/kg/min), bretylium (5–10 mg/kg), and amiodarone (1–5 mg/kg) may need to be started to help suppress further rhythm disturbance, and infusions of these medications are often necessary. The onset of atrial fibrillation may be mitigated by the use of beta-blockers, angiotensin-converting enzyme (ACE) inhibitor, supplemental potassium, or nonsteroidal anti-inflammatory drug (Mathew et al. 2004; Bradley et al. 2005; Bagshaw et al. 2006).

## 7.3 Vasoplegic Syndrome

Vasoplegia is one form of vasodilatory shock occurring in up to 10 % of patients after cardiac surgery. It is defined as profound hypotension associated with low systemic vascular resistance (SVR), reduced filling pressure, and normal or high cardiac output; vasoplegia may contribute to death in the perioperative period.

The cause of reduced vascular tone is a matter of controversy, but it is postulated that endothelial dysregulation during CPB leading to an inflammatory response may play an important role. Known risk factors for developing vasoplegia include preoperative use of certain drugs (β-blockers, ACE inhibitors, calcium channel blockers, and amiodarone), valve surgery, low pre-CPB mean arterial pressure, length of CPB, administration of pre-CPB vasopressors, core temperature on CPB, and the intraoperative use of aprotinin.

Vasoplegia does not usually respond to volume expansion. Norepinephrine, phenylephrine, high-dose dopamine, and vasopressin can increase systemic vascular resistance and maintain perfusion pressure after CPB. Whenever there is resistance to vasoconstrictor agents, methylene blue is recommended (2 mg/kg intravenously through a period of 20 min); an infusion may be necessary for refractory vasoplegia (Levin et al. 2004; Egi et al. 2007; Levin et al. 2009; Skuza et al. 2009; Langlet et al. 2011).

## 7.4 Postoperative Cardiac Tamponade (POCT)

POCT is a specific type of circulatory failure due to compression of right heart (and sometimes left heart) chambers by blood accumulation in pericardial sac after cardiac surgery; it is seen up to 8 % of cardiac surgeries. This accumulation of fluid leads to increased pressure in the pericardial cavity and a decreased systemic venous return. It is typically secondary to either surgical bleeding (i.e., suture lines, cannulation site, and branches of internal mammary artery) or CPB-related coagulation abnormalities.

The diagnosis of cardiac tamponade is based on clinical presentation, central venous pressure monitoring, chest X-ray, and echocardiography. It should be suspected in any patients with clinical hemodynamic instability (elevated central venous pressure, decreased systemic blood pressure and urine output) in association with increased need for inotropic agents in the setting of significant chest tube drainage. Echocardiograph finding may demonstrate diastolic collapse of right atrium (and right ventricle) and lack of IVC collapse during inspiration. Diastolic collapse of left heart chambers may occur in the presence of discrete localized fluid accumulation.

Independent risk factors for POCT are type of surgery (aortic aneurysm, heart transplant, valve surgery in comparison with CABG alone), renal failure, prolonged CPB time, pulmonary thromboembolism, and elevated BSA.

Some studies have shown that posterior pericardiotomy during cardiac surgery prevents blood accumulation in posterior of left ventricular wall. Resternotomy and

mediastinal re-exploration, clot removal, and search for the probable site(s) of bleeding are the only efficient treatment after cardiac surgery. Late pericardial effusion and delay tamponade may occur after cardiac surgery. Diagnosis may be difficult. In this entity due to pericardial adhesion, effusion is localized often in posterior portion of the heart. Transesophageal echocardiography is able to show the presence, size, and site of localized effusion and guide the approach to drainage. POCT is seen especially in valve surgery where oral chronic anticoagulant agents were usually utilized preoperatively (Kuvin et al. 2002; Mackay et al. 2002; Seferovi et al. 2006; Ashikhmina et al. 2010; Canadyova et al. 2012).

## 7.5 CPR After Cardiac Surgery

The incidence of cardiac arrest after cardiac surgery is less than 3 %. The outcome is better than other causes of cardiac arrest due to its reversible causes and typically witnessed arrest. The most common causes of perioperative cardiac arrest are ventricular fibrillation, major bleeding, and tamponade; all of them are usually treated immediately as they are recognized promptly in the ICU. As multiple hemodynamic indices (i.e., arterial pressure, pulse oximetry, ECG monitoring, and central venous pressure line) are observed continuously in the ICU, this allows for rapid identification of a critical event and rapid response. Because of better outcome and survival in these patients (if they are treated promptly), ICU staff must be trained to manage cardiac arrest.

Among the predisposing factors leading to cardiac arrest, myocardial infarction has the worst prognosis. Hence it is rational that the guideline of CPR after cardiac surgery is different from cardiac arrest in other settings. The last guideline protocol for resuscitation after cardiac surgery was in 2009 and recommended for use in ICU for all patients with sternotomy. Its brief summary follows:

(a) *Diagnosis of cardiac arrest*
- Because of full monitoring of intubated patients in ICU, observation of any "flat line" in monitors must be checked by central pulse palpation (femoral, carotid) for 10 s.
- As a clinical point, ECG lead displacement will not imitate VF or asystole pattern; it causes "flat line" with preserved pressure lines.

*(b) Defibrillation attempts*
- A precordial thump may be recommended within 10 s of VT/VF onset, but does not replace defibrillation. As VF is recognized, three consecutive biphasic defibrillation shocks (between 150 and 360 J) are recommended to restore cardiac output. It must be done consecutively without intervening CPR. Its time sequence is emphasized before starting external cardiac massage.
- If defibrillation fails, a bolus of intravenous amiodarone (300 mg) is recommended. If amiodarone is not available, 1 mg/kg of lidocaine may be given.

- If the patient had severe bradycardia or asystole and cannot be treated by cardioversion, a single dose of 3 mg of atropine is recommended. Epicardial pacing should be instituted at 90 beats/min.
- If adequate cardiac output is not achieved, CPR should be started. In pulseless electrical activity, the pacemaker must be set off to rule out VF.

*(c) Timing of external cardiac massage*

- With VF or VT, if defibrillation either was not accessible or was unsuccessful (after three failed attempts), external cardiac massage must be started. Techniques should apply pressure in the middle of sternum 100 beats/min and press down 4–5 cm in depth. The efficacy of cardiac massage can be assessed by arterial trace on monitor; systolic impulse must be over 60 mmHg.
- In the presence of a balloon-expandable valve stent (i.e., TAVR), there is the risk of valve damage during external cardiac massage.

*(d) Airway control*

- The second person to attend during a cardiac arrest is responsible for respiratory state. In intubated patient, oxygen on ventilator is raised to 100 % and PEEP is omitted. If the patient is not intubated, 100 % oxygen with a bag/valve mask should be initiated, 2 breaths for every 30 chest compressions. Bilateral and equal lung expansion must be checked.
- Capnography confirms position of endotracheal tube and quality of CPR. A rough way to assess lung compliance is disconnection from the ventilator and to continue with bag/valve ventilation; if there is adequate ventilation, reconnect to the ventilator.
- Occlusion or malposition of endotracheal tube must be ruled out whenever lung inflation is not easy; in this condition the endotracheal tube should be removed, and bag/valve ventilation with airway is continued.
- If tension pneumothorax is suspected, a large-bore angiocath catheter is placed in second intercostal space at anterior-midclavicular line with immediate insertion of a chest tube.

*(e) Emergent sternotomy*

- After failed defibrillation or pacemaker activation, there is proven benefit for resternotomy in the ICU. If the pressure generated by compression is not enough, the cause of arrest may be massive bleeding, tamponade, or tension pneumothorax, and emergent resternotomy should be accelerated. It is a common belief among cardiac surgeons that if initial resuscitation is not successful, resternotomy should be performed.
- Location of internal mammary artery and other grafts should be considered before internal massage.
- Resternotomy could be considered in the most common causes of cardiac arrest (i.e., tension pneumothorax, cardiac tamponade, hypothermia, hyper-/hypokalemia).
- Internal cardiac massage can improve coronary and cerebral perfusion pressure more than doubling of external massage. Return of spontaneous circulation may be increased as well.

*(f) Administration of drugs*

- During CPR all medication infusions must be stopped. Although concern about severe hypertension and major bleeding after adrenaline use is justifiable, adrenaline is nonetheless recommended when reversible causes of cardiac arrest are excluded; 1 mg of adrenaline should be administered for asystole/pulseless electrical activity and after the second failed cardioversion in VT/VF is used.
- All drugs should be administered via the central line when available.

*(g) Cardiac arrest in the setting of IABP*

- When pacemaker is activated, cardiac arrest may be identified by changes in pressure trace of CVP, pulse oximetry on monitor. Pressure trigger of IABP is turned on during cardiac massage with maximum augmentation with 1:1 counter pulsation to increase cardiac massage effect. Internal trigger must be set up whenever there is a period without cardiac massage.

*(h) Mechanical circulatory support after cardiac arrest*

- Mechanical circulatory support (CPB, extracorporeal membrane oxygenation) may be effective when spontaneous circulation has not been started by internal massage (Twomeya et al. 2008; Dunning et al. 2009; Ngaage and Cowen 2009; Segesser 2009).

## 7.6 Assist Devices

### 7.6.1 Intra-Aortic Balloon Pump (IABP)

The intra-aortic balloon pump (IABP) is the most commonly utilized mechanical circulatory assist device in cardiac surgery and has been used since the late 1960s. It is used after cardiac surgery, coronary angioplasty, myocardial infarction, and other low output conditions, as the first step in the treatment of cardiogenic shock. IABP increases coronary artery perfusion pressure (and thus improves oxygen supply) during diastole by inflation and decreases the metabolic demand of myocardium (afterload reduction) in systole by deflating. The drive mechanism is pneumatic (helium). This volume replacement during cardiac cycles may increase cardiac output by 20 %, but it cannot provide complete mechanical support.

IABP is used to facilitate CPB weaning intraoperatively when hemodynamic stabilization is not adequate despite adequate preload and afterload and use of inotropic agents. It provides a protective method against hemodynamic deterioration during the early postoperative period in the ICU. It is believed that use of preoperative IABP has better outcomes compared to later insertion in the intraoperative or postoperative period. Studies had suggested that prophylactic IABP (instead of rescue therapy for cardiovascular instability) may decrease mortality and morbidity and improve outcome in high-risk cardiac surgery patients who have at least two of following conditions: unstable angina at the time of surgery, redo operations,

congestive heart failure in spite of full-dose medical treatment, EF <30 %, and left main artery stenosis >75 %.

There is controversy that levosimendan can be as effective as IABP in high-risk cardiac surgery patients. Levosimendan is the only inotropic agent that increases the sensitivity of myocardial contractile protein to calcium (others act by raising intracellular calcium). It decreases myocardial demand and afterload and increases cardiac index.

The insertion technique for IABP is either percutaneously or insertion under direct visualization by surgical exposure of femoral artery (retrograde approach). When there is no access through femoral artery (due to aortic occlusion or previous surgery), transthoracic arch, axillary, subclavian, and iliac arteries are suggested (antegrade approach). The complication rate for IABP is low, and distal embolic event (and limb ischemia) is the most common complication with frequent need for vascular intervention (Fogarty arterial embolectomy catheter). Size of balloon pump catheter, female sex, presence of peripheral arterial diseases, and duration of IABP use are predictors of IABP-related complications. Limitations of IABP are small body size, right ventricular failure, profound heart failure, and tachyarrhythmia (Baskett et al. 2002; Christenson et al. 2007; Lorusso et al. 2010; Lomivorotov et al. 2011; Litton and Delaney 2012).

### 7.6.2 Ventricular Assist Device (VAD)

While the IABP is very helpful for hemodynamic instability, it only increases cardiac output by 10–20 %, the only way to survive in severe decompensated conditions is the use of ventricular assist device. Circulatory assist devices have been designed and utilized to support the heart by providing forward flow, bridge to recovery, heart transplant, or destination therapy; they have been shown to improve quality of life and outcome. VADs may be used for short- and long-term support, without removal of the native heart. VADs are commonly labeled as LVAD (left), RVAD (right), BiVAD (biventricular), and TAH (total artificial heart). VADs may be implantable intracardiac or externally (abdominal wall or intraperitoneal); a midsternotomy and aid of CPB are necessary for insertion of inlet tube from the heart to device and outlet tube from device to the aorta. The device power source may be electrical or pneumatic; forward flow may be pulsatile or continuous. VADs require long-term anticoagulation; however, patients have nearly unlimited mobility. Newer generation of assist devices are smaller, require less complex surgical implantation, have less blood-surface contact, and provide longer durability.

In cardiac surgery, VADs are used in reversible ventricular dysfunction. It was shown that patients who underwent elective assist device had better outcomes than when inserted in emergent or urgent situations. VADs are not recommended in patients with terminal severe comorbidities (severe hepatic or pulmonary dysfunction, chronic dialysis), sepsis, and metastatic cancer. The most common complications are bleeding, infection, and thromboembolic events.

### 7.6.3 Extracorporeal Membrane Oxygenation (ECMO)

Extracorporeal membrane oxygenation (ECMO) is used instead of conventional cardiopulmonary bypass for reversible respiratory or cardiac failure, whenever there is no response to usual therapies (optimized preload state, use of inotropic agents, and ventilator support). The sole ECMO advantage is its application in emergency situation (at the bedside and operating room) and as a satisfactory partial cardiopulmonary support for both heart (left and right) and lung for severe, acute, and reversible dysfunction.

In less than 1 % of patients after routine cardiac surgery operations, there is failure to wean off CPB in spite of high-dose inotropic agents, pressors, and IABP. Emergency surgery, redo surgeries, severe LV dysfunction, renal failure, and younger age are predictors of postcardiotomy pump failure and need for ECMO support. The cause of this low cardiac output syndrome may be the systemic inflammatory response during CPB, myocardial ischemia, and reperfusion injury. Other indications for implementing ECMO include cardiogenic shock with correctable pathology, bridge to transplantation, myocarditis, postpartum cardiomyopathy, and cardiac arrest. ECMO is not suggested in the presence of sepsis, multiorgan failure, and severe neurologic deficit and absolutely contraindicated in active bleeding and whenever recovery of cardiac function due to severe underlying disease is not expected.

The ECMO circuit is composed of a blood-pumping device (roller/centrifugal pump), inflow and outflow cannula, membrane oxygenator, hemofilter, heparin-coated circuit, and heat exchanger. There are two methods of cannula insertion: peripheral and central (transthoracic). Peripheral arterial and venous cannulations are performed percutaneously (by Seldinger technique), cut-down, or both. Central cannulation can be accomplished by sternotomy or thoracotomy. Whenever there is lung dysfunction with normal circulatory state, venovenous type of ECMO is applied. Venoarterial ECMO is recommended in acute heart failure or needed to both heart and lung. The adequacy of perfusion is determined by serum lactate level, mixed venous oxygen saturation, and arterial base deficit.

Activated clotting time must be kept around 180–200 s during use of ECMO in order to prevent thrombosis and hemorrhagic events. Other described complications and causes of inhospital death with ECMO include ischemia of lower limbs, organ system dysfunction (lung, renal, and neurologic), sepsis, DIC, myocardial failure, and oxygenation failure. Vascular complications with venovenous cannulation are less than arterial cannulation. Open vascular exposure, use of antegrade catheter to increase limb perfusion, rapid clinical diagnosis, and intervention to remove cannula and replace vascular access reduce ischemic events (Hirsch and Cooper 2003; Doll et al. 2004; Wilhelm et al. 2005; Wagner et al. 2007; Luo et al. 2009; Formica et al. 2010; Lund et al. 2010; Dalton 2011; Peura et al. 2012).

## References

Algarni KD, Maganti M, Yau TM (2011) Predictors of low cardiac output syndrome after isolated coronary artery bypass surgery: trends over 20 years. Ann Thorac Surg 92:1678–1684

Ashikhmina EA, Schaff HV, Sinak LJ et al (2010) Pericardial effusion after cardiac surgery: risk factors, patient profiles, and contemporary management. Ann Thorac Surg 89:112–118

Bagshaw SM, Galbraith PD, Mitchell LB et al (2006) Prophylactic amiodarone for prevention of atrial fibrillation after cardiac surgery: a meta-analysis. Ann Thorac Surg 82(5):1927–1937

Baskett RJF, Ghali WA, Maitland A et al (2002) The intraaortic balloon pump in cardiac surgery. Ann Thorac Surg 74:1276–1287

Bradley D, Creswell LL, Hogu CW et al (2005) Pharmacologic prophylaxis: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest 128(2_suppl):39S–47S

Canadyova J, Zmeko D, Mokracek A (2012) Re-exploration for bleeding or tamponade after cardiac operation. Interact Cardiovasc Thorac Surg 14(6):704–707

Christenson JT, Sierra J, Romand J et al (2007) Long intraaortic balloon treatment time leads to more vascular complications. Asian Cardiovasc Thorac Ann 15:408–412

Dalton HJ (2011) Extracorporeal life support: moving at the speed of light. Respir Care 56(9):1445–1453

Doll N, Kiaii B, Borger M et al (2004) Five-Year results of 219 consecutive patients treated with extracorporeal membrane oxygenation for refractory postoperative cardiogenic shock. Ann Thorac Surg 77:151–157

Dunning J, Fabbri A, Kolh Ph H et al (2009) Guideline for resuscitation in cardiac arrest after cardiac surgery. Eur J Cardiothoracic Surg 36:3–28

Egi M, Bellomo R, Langenberg C et al (2007) Selecting a vasopressor drug for vasoplegic shock after adult cardiac surgery: a systematic literature review. Ann Thorac Surg 83:715–723, Nomenclature

Formica F, Avalli L, Colagrande L et al (2010) Extracorporeal membrane oxygenation to support adult patients with cardiac failure: predictive factors of 30-day mortality. Interact Cardiovasc Thorac Surg 10:721–726

Hausenloy DJ, Boston-Griffiths E, Yellon DM (2012) Cardioprotection during cardiac surgery. Cardiovasc Res 94(2):253–265

Hirsch DJ, Cooper JR (2003) Cardiac failure and left ventricular assist devices. Anesthesiol Clin N Am 21:625–638

Joshi P, Fraser JF, Mullany DV et al (2005) The high risk cardiac surgical patient. Curr Anaesth Crit Care 16:369–383

Kuvin JT, Harati NA, Pandian NG et al (2002) Postoperative cardiac tamponade in the modern surgical era. Ann Thorac Surg 74:1148–1153

Langlet S, Mach F, Montecucco F (2011) Methylene blue: potential use of an antique molecule in vasoplegic syndrome during cardiac surgery. Expert Rev Cardiovasc Ther 9(12):1519–1525

Levin RL, Degrange MA, Bruno GF et al (2004) Methylene blue reduces mortality and morbidity in vasoplegic patients after cardiac surgery. Ann Thorac Surg 77(2):496–499

Levin MA, Lin H, Castillo JG et al (2009) Early on–cardiopulmonary bypass hypotension and other factors associated with vasoplegic syndrome. Circulation 120:1664–1671

Likosky DS, Goldberg JB, DiScipio AW et al (2012) Variability in surgeons' perioperative practices may influence the incidence of low-output failure after coronary artery bypass grafting surgery. Circ Cardiovasc Qual Outcomes 5:638–644

Litton E, Delaney A (2012) Preoperative intra-aortic balloon pump in high-risk coronary bypass grafting. Asian Cardiovasc Thorac Ann 20:146–152

Lomivorotov VV, Cherniavsky AM, Boboshko VA et al (2011) Levosimendan vs. intra-aortic balloon pump in high-risk cardiac surgery. Asian Cardiovasc Thorac Ann 19:154–159

Lorusso R, Gelsomino S, Carella R et al (2010) Impact of prophylactic intra-aortic balloon counter-pulsation on postoperative outcome in high-risk cardiac surgery patients: a multicentre, propensity-score analysis. Eur J Cardiothorac Surg 38:585–591

Lund LH, Matthews J, Aaronson K (2010) Patient selection for left ventricular assist devices. Eur J Heart Fail 12:434–443

Luo X, Wang W, Sh H et al (2009) Extracorporeal membrane oxygenation for treatment of cardiac failure in adult patients. Interact Cardiovasc Thorac Surg 9(2):296–300

Mackay JH, Powell SJ, Osgathorp J et al (2002) Six-year prospective audit of chest reopening after cardiac arrest. Eur J Cardiothorac Surg 22:421–425

Maganti M, Badiwala M, Sheikh A et al (2010) Predictors of low cardiac output syndrome after isolated mitral valve surgery. J Thorac Cardiovasc Surg 140:790–796

Mair J, Hammerer-Lercher A (2005) Markers for perioperative myocardial ischemia: what both interventional cardiologists and cardiac surgeons need to know. Heart Surg Forum 8:E319–E325

Mathew JP, Fontes ML, Tudor IC, James Ramsay J, Duke P, Mazer CD et al (2004) A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA 291:1720–1729

Ngaage DL, Cowen ME (2009) Survival of cardiorespiratory arrest after coronary artery bypass grafting or aortic valve surgery. Ann Thorac Surg 88:64–68

Noora J, Ricci C, Hastings D, Hill S, Cybulsky I (2005) Determination of troponin I release after CABG surgery. J Cardiac Surg 20:129–135

Overgaard CB, Džavík V (2008) Review of physiology and clinical use in cardiovascular disease. Circulation 118:1047–1056

Peura JL, Colvin-Adams M, Francis GS et al (2012) Recommendations for the use of mechanical circulatory support: device strategies and patient selection: a scientific statement from the American Heart Association. Circulation 126:2648–2667

Seferovi PM, Risti AD, Imazio M et al (2006) Management strategies in pericardial emergencies. Herz 31:891–900

Segesser LK (2009) Post-cardiac surgery arrest: what to do in the ICU (intensive care unit). Eur J Cardiothorac Surg 36(1):1–2

Skuza K, Chmielniak S, Dziuk W et al (2009) Methylene blue therapy for vasoplegia after cardiac surgery. Anaesthesiol Intensive Ther XLI(3):129–132

Twomeya D, Dasa M, Subramaniana H et al (2008) Is internal massage superior to external massage for patients suffering a cardiac arrest after cardiac surgery? Interact Cardiovasc Thorac Surg 7:151–157

Wagner K, Risnes I, Abdelnoor M et al (2007) Is it possible to predict outcome in cardiac ECMO? Analysis of preoperative risk factors. Perfusion 22(4):225–229

Wasir H, Mehta Y, Mishra YK et al (2003) Transesophageal echocardiography in hypotensive post-coronary bypass patients. Asian Cardiovasc Thorac Ann 11:139–142

Wilhelm MJ, Hammel D, Schmid C et al (2005) Long-term support of 9 patients with the DeBakey VAD for more than 200 days. J Thorac Cardiovasc Surg 130:1122–1129

# Noncardiac Complications After Cardiac Surgery

8

Antonio Hernandez Conte and Mahnoosh Foroughi

## Contents



**Abstract**

Surgical, technological, and pharmacologic advances during the past 25 years have enabled complex cardiac surgery to become more routine; however, one cannot underestimate the multiple potential complications that can still arise in the postoperative setting. The anesthesiologist, physician intensivist, and critical care nurse should be thoroughly familiar with a wide range of issues that can arise in the postoperative course in the intensive care unit after a patient has undergone cardiothoracic surgery.

A.H. Conte, MD, MBA (✉)
Perioperative Transesophageal Echocardiography Education,
Division of Cardiothoracic Anesthesiology, Department of Anesthesiology,
Cedars-Sinai Medical Center, Los Angeles, CA, USA
e-mail: antonio.conte@cshs.org

M. Foroughi, MD
Cardiovascular Research Center, Shahid Beheshti University
of Medical Sciences, Tehran, Iran
e-mail: mahnoosh.foroughi@gmail.com, m_foroughi@sbmu.ac.ir

A. Dabbagh et al. (eds.), *Postoperative Critical Care for Cardiac Surgical Patients*,
DOI 10.1007/978-3-642-40418-4_8, © Springer-Verlag Berlin Heidelberg 2014

The widespread use of large long-term clinical databases has led to a greater understanding of the most common complications facing cardiothoracic surgical patients and has allowed the delineation of comorbidities or factors associated with significant and commonly occurring postoperative events. Although an extremely vast myriad of noncardiac-related postoperative complications may occur after a patient has undergone cardiac surgery, this chapter will focus on the most common noncardiac complications after the patient has left the cardiac surgical operative arena and entered into the postoperative phase of care, typically provided in the intensive care unit.

## 8.1 Respiratory Complications

During cardiac surgery, patients experience multiple physiologic and mechanical alterations in respiratory function due to endotracheal intubation, positive-pressure mechanical ventilation, initiation of cardiopulmonary bypass (CPB), and subsequent termination of CPB. All of these respiratory insults are coupled with complex cardiac surgical alterations further exacerbating respiratory mechanics. Therefore, the respiratory system is prone to multiple complications after cardiac surgery, most notably prolonged intubation and/or potential infectious processes.

### 8.1.1 Prolonged Intubation and Failure to Extubate

After cardiac surgery, virtually all patients present to the intensive care unit with an in situ endotracheal tube and require mechanical ventilation for a short period of time before weaning can be initiated. In the last 20 years, improved surgical techniques and shorter-acting anesthetic agents have allowed extubation after cardiac surgery to occur in a shorter period of time. Early extubation is defined as within 8 h of arrival in the ICU.

Because of the success of early extubation, anesthesiologists and surgeons have been able to identify preoperative, intraoperative, and postoperative risk factors for prolonged intubation or failure to extubate. Prolonged intubation not only extolls additional morbidity and mortality upon patients, but it also creates noteworthy economic costs upon the health-care system. Early extubation may result in shorter ICU length of stays and earlier discharge, as well as lower perioperative morbidity and mortality. While early extubation is not associated with higher complications, it may be more beneficial in low-risk patients. Early extubation can be accelerated by modifying anesthetic agents selected intraoperatively. In particular, lower doses of opioid and/or benzodiazepines can be administered and concomitantly receive propofol or dexmedetomidine. In the ICU, reversal of neuromuscular blockade and rapidly decreasing levels of sedation can accelerate extubation.

Early extubation is not impacted by preoperative routine lung function tests such as spirometry, and this does not predict the length of postoperative intubation. While patients who have a history of smoking may have increased pulmonary

**Table 8.1** Predictors for prolonged intubation and/or respiratory failure after cardiac surgery

| Patient-related factors | Surgical factors | Other factors |
|---|---|---|
| Advanced age >70 | Internal mammary artery dissection | Aspiration pneumonia |
| Endocarditis | Increased number of bypass grafts | CPB >120 min |
| Gastrointestinal bleeding | Multiple valve procedures | Deep sternal wound infection |
| Hypoalbuminemia | Operative priority (emergent) | Inpatient hospitalization prior to surgery |
| NYHA Class | Reoperation for bleeding | Use of inotropes |
| Pulmonary hypertension | Need for intraoperative aortic balloon pump | Perioperative cerebrovascular accident (CVA) |
| Sepsis | Topical myocardial cooling | Pleural effusion |
| | | Pulmonary edema |

*NYHA* New York Heart Association

complications, these patients do not necessarily have prolonged intubation periods. However, if patients with a history who smoke remain intubated for greater than 6 h, respiratory complications will increase. There are multiple factors which are predictive of prolonged intubation and respiratory failure post-cardiac surgery. Patients with any one or more of the following may have difficulty with early extubation: advanced age >70, higher New York Heart Association (NYHA) classification, patients who undergo multiple valve procedures, need for emergent surgery, or who require an intra-aortic balloon pump (See Table 8.1).

Consideration should be given to developing rapid extubation protocols in all patients who undergo cardiac surgery; however, additional protocols should be implemented to identify patients who possess high-risk factors that could prolong the time to extubation or lead to respiratory failure.

### 8.1.2 Tracheostomy

Despite decades of experience in ICUs, there is still controversy over the specific indications, techniques, and timing of tracheostomy. Not only the optimal timing (i.e., early versus delayed) and the most appropriate technique remain subjects of debate, but also the actual clinical value (benefit/risk ratio) of tracheostomy is unknown. Typically, the most common indication for tracheostomy in the intensive care unit (ICU) setting has been the need for prolonged mechanical ventilation. However, this is also a controversial indication because of the potential complications and costs associated with the performance of a tracheostomy in this patient population. In addition to the need for prolonged ventilation, ICU patients may require a tracheostomy due to development of nosocomial pneumonia, the administration of aerosol treatments, having a witnessed aspiration event, and after requiring reintubation.

Benefits attributed to tracheotomy versus prolonged translaryngeal intubation include improved patient comfort, more effective airway suctioning, decreased airway resistance, enhanced patient mobility, increased potential for speech, ability

to eat orally, a more secure airway, accelerated ventilator weaning, reduced ventilator-associated pneumonia, and the ability to transfer ventilator-dependent patients from the ICU. However, none of these benefits have been demonstrated in large-scale, prospective, randomized studies.

Patients requiring a tracheostomy usually have significantly longer lengths of stay in the ICU and hospital, a longer duration of mechanical ventilation, and more acquired organ-system derangements compared with patients without a tracheostomy. The duration of mechanical ventilation before tracheostomy was also significantly longer than the overall duration of mechanical ventilation for patients without a tracheostomy. However, mechanically ventilated patients in the ICU setting who received a tracheostomy have a higher hospital survival rate compared with mechanically ventilated patients without a tracheostomy. This difference in hospital survival usually occurs during the first 2 weeks of intensive care and does not appear to be attributable to the tracheostomy procedure.

The optimal timing for tracheostomy and the impact of tracheostomy on patient outcomes in the ICU setting are controversial and very important in optimally managing this subset of patients. Patient-specific variables that were independently associated with subsequent tracheostomy may allow earlier identification of individuals who are at increased risk for prolonged ventilatory support. These variables or risk factors offer clinicians the opportunity to identify more objectively patients who may benefit from earlier placement of a tracheostomy to improve potentially their outcomes (e.g., reduction of pain associated with the prolonged presence of an oral endotracheal tube) and to reduce the use of ICU beds. Earlier placement of a tracheostomy may be justified if it improves patient tolerance of prolonged ventilatory support, even if it does not reduce the total duration of mechanical ventilation compared with translaryngeal intubation.

## 8.1.3 Pneumonia

### 8.1.3.1 Aspiration Pneumonia

Most patients with depressed consciousness may experience pharyngeal aspiration, which, in the presence of underlying diseases that impair host defense mechanisms and alterations in oropharyngeal flora, may manifest as aspiration pneumonia. Patients having undergone cardiac surgery may have residual effects from sedation or may be receiving opioids that may depress protective reflexes. Additionally, cardiac surgical patients may sustain a neurologic injury that could also predispose them to an aspiration event. Concomitantly, patients with diabetes or morbid obesity are prone to delayed gastric emptying, thereby also increasing the risk for aspiration of gastric contents. *K. pneumoniae* is frequently implicated in aspiration pneumonia.

Clinical manifestations of pulmonary aspiration depend in large part on the nature and volume of aspirated material. Aspiration of large volumes of acidic gastric fluid (Mendelson's syndrome) produces fulminating pneumonia and arterial hypoxemia. Aspiration of particulate material may result in airway obstruction, and

smaller particles may produce atelectasis. Radiographically, infiltrates are most common in dependent areas of the patient's lungs. Penicillin-sensitive anaerobes are the most likely cause of aspiration pneumonia. Clindamycin is an alternative to penicillin and may be superior for treating necrotizing aspiration pneumonia and lung abscess. Hospitalization or antibiotic therapy alters the usual oropharyngeal flora such that aspiration pneumonia in hospitalized patients often involves pathogens that are uncommon in community-acquired pneumonias. There are limited data to suggest that treatment of aspiration pneumonia with antibiotics improves outcome.

#### 8.1.3.2 Lung Abscess

Lung abscess may develop after bacterial pneumonia. Alcohol abuse and poor dental hygiene are important risk factors. Septic pulmonary embolization, which is most common in intravenous drug abusers, may also result in formation of a lung abscess. A finding of an air–fluid level on the chest radiograph signifies rupture of the abscess into the bronchial tree, and foul-smelling sputum is characteristic. Antibiotics are the mainstay of treatment of a lung abscess. Surgery is indicated only when complications such as empyema occur. Thoracentesis is necessary to establish the diagnosis of empyema, and treatment requires chest tube drainage and antibiotics. Surgical drainage is necessary to treat chronic empyema.

#### 8.1.3.3 General Postoperative Pneumonia

Postoperative pneumonia occurs in approximately 20 % of patients undergoing major thoracic, esophageal, or major upper abdominal surgery but is rare in other procedures in previously fit patients. Chronic respiratory disease increases the incidence of postoperative pneumonia threefold. Other risk factors include obesity, age older than 70 years, and operations lasting more than 2 h.

##### Diagnosis

An initial chill, followed by abrupt onset of fever, chest pain, dyspnea, fatigue, rigors, cough, and copious sputum production often characterize bacterial pneumonia, although symptoms vary. Nonproductive cough is a feature of atypical pneumonias. A detailed history may suggest possible causative organisms. Hotels and whirlpools are associated with Legionnaires' disease (*L. pneumoniae*) outbreaks. Fungal pneumonia may occur with cave exploration (*Histoplasma capsulatum*) and diving (*Scedosporium angiospermum*). *Chlamydia psittaci* pneumonia may follow contact with birds and Q fever (*Coxiella burnetii*) contact with sheep. Alcoholism may increase the risk of bacterial aspiration such as *K. pneumoniae*. Patients who are immunocompromised, such as those with AIDS, are at risk of fungal pneumonia, such as *Pneumocystis jiroveci* pneumonia (PCP).

Posteroanterior and lateral chest radiographs may be extremely diagnostic in detecting pneumonia. Diffuse infiltrates are suggestive of an atypical pneumonia, whereas a lobar radiographic opacification is suggestive of a typical pneumonia. Atypical pneumonia occurs more frequently in young adults. Radiography is useful

**Table 8.2** Clinical pulmonary infection score calculation

| Parameter | Options | Score |
|---|---|---|
| Temperature (°C) | ≥36.5 and ≤38.4:0 | 0 |
| | ≥38.5 and ≤38.9:1 | 1 |
| | ≥39 or ≤36:2 | 2 |
| Blood leukocytes ($mm^3$) | ≥4,000 and ≤11,000:0 | 0 |
| | <4,000 or >11,000:1 | 1 |
| | + band forms ≥50 %, add 1 | Add 1 |
| Tracheal secretions | Absence of tracheal secretions: 0 | 0 |
| | Presence of non-purulent tracheal secretions: 1 | 1 |
| | Presence of purulent tracheal secretions: 2 | 2 |
| Oxygenation: $PaO_2/FIO_2$ (mm Hg) | >240 or ARDS: 0 | 0 |
| | ≤240 and no ARDS: 2 | 2 |
| Pulmonary radiography | No infiltrate: 0 | 0 |
| | Diffuse (or patchy) infiltrate: 1 | 1 |
| | Localized infiltrate: 2 | 2 |
| Progression of pulmonary infiltrate | No radiographic progression: 0 | 0 |
| | Radiographic progression (after cardiac failure and ARDS excluded): 2 | 2 |
| Culture of tracheal aspirate | Pathogenic bacteria cultured in rare or light quantity | 0 |
| | Pathogenic bacteria cultured in moderate or heavy quantity | 1 |
| | Same pathogenic bacteria seen on Gram stain | Add 1 |

Data from Luyt (2004)
*ARDS* acute respiratory distress syndrome

for detecting pleural effusions and multilobar involvement. Polymorphonuclear leukocytosis is typical, and arterial hypoxemia may occur in severe cases of bacterial pneumonia. Arterial hypoxemia reflects intrapulmonary shunting of blood owing to perfusion of alveoli filled with inflammatory exudates.

Microscopic examination of sputum plus culture and sensitivity testing may be helpful in suggesting the etiologic diagnosis of pneumonia and in guiding the selection of appropriate antibiotic treatment. *S. pneumoniae* and gram-negative organisms, such as *H. influenzae*, may be seen on sputum stain or culture. Unfortunately, sputum specimens are frequently inadequate, and organisms do not invariably grow from sputum. Interpretation of sputum culture may be challenging, as there is frequent normal nasopharyngeal carriage of *S. pneumoniae*. If there is suspicion, sputum specimens should be sent for acid-fast bacilli (*M. tuberculosis*). Antigen detection in urine is a good test for *L. pneumophila*, whereas blood antibody titers are helpful in diagnosing *M. pneumoniae*. Sputum polymerase chain reaction is useful for chlamydia. Blood cultures are usually negative but are important to rule out bacteremia. Table 8.2 displays a useful clinical pulmonary infection score calculator.

## Treatment

For severe pneumonia, empirical therapy is typically a combination such as a cephalosporin (e.g., cefuroxime or ceftriaxone) plus a macrolide

(e.g., azithromycin or clarithromycin) antibiotic. However, local patterns of antibiotic resistance should always be considered prior to initiating therapy. There may be an increasing role for newer quinolones such as moxifloxacin in the treatment of community-acquired pneumonia, especially as "atypical" bacteria are becoming increasingly responsible for community-acquired pneumonia.

Therapy is advised for 10 days for *S. pneumoniae* and for 14 days for *M. pneumoniae* and *C. pneumoniae*. Therapy should be narrowed and targeted when the pathogen is identified. When symptoms resolve, therapy can be switched from intravenous to oral. The inappropriate prescription of antibiotics for nonbacterial respiratory tract infections is common and promotes antibiotic resistance. It has recently been demonstrated that even brief administration of macrolide antibiotics to healthy subjects promotes resistance of oral streptococcal flora that lasts for months. Resistance of *S. pneumoniae* is becoming a major problem.

### Prognosis

The Pneumonia Severity Index (http://www.mdcalc.com/psi-port-score-pneumonia-severity-index-adult-cap/) is a useful tool for aiding clinical judgment, guiding appropriate management, and suggesting prognosis. Old age and coexisting organ dysfunction have a negative impact. Physical examination findings associated with worse outcome are:

*T* temperature >40 °C or <35 °C
*R* respiratory rate >30/min
*A* altered mental status
*S* systolic blood pressure <90 mmHg
*H* heart rate >125/min

Laboratory findings and special investigations that are consistent with poorer prognosis include:

*H* hypoxia ($PO_2$ < 60 mmHg or saturation <90 % on room air)
*E* effusion
*A* anemia (hematocrit <30 %)
*R* renal: BUN (urea) >64 mg/dL (23 mmol/L)
*G* glucose >250 mg/dL (14 mmol/L)
*A* acidosis (pH <7.35)
*S* sodium <130 mmol/L

### Management

Patients with acute pneumonia are often dehydrated and may have renal insufficiency. However, overly aggressive volume resuscitation may worsen gas exchange and morbidity. Fluid management is therefore extremely challenging. The anesthesiologist and critical care provider should conduct aggressive pulmonary toilet including actively removing secretions during the period of intubation via bronchoscopy. If possible, the anesthesiologist should also send distal sputum specimens for Gram stain and culture and ensure that appropriate antibiotics are administered for both the coverage of aspiration pneumonia and surgical prophylaxis.

### 8.1.3.4 Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in the ICU and makes up one third of the total nosocomial infections. VAP is defined as pneumonia developing more than 48 h after patients have been intubated and mechanically ventilated. Ten percent to 20 % of patients with tracheal tubes and mechanical ventilation for more than 48 h acquire VAP, with mortality rates between 5 and 50 %. Anesthesiologists and intensive care physicians play critical roles in the prevention, diagnosis, and treatment of VAP. Several simple interventions may decrease the occurrence of VAP, including meticulous hand hygiene, oral care, limiting patient sedation, positioning patients semi-upright, repeated aspiration of subglottic secretions, limiting intubation time, and considering the appropriateness of noninvasive ventilation support.

### 8.1.3.5 Diagnosis

VAP is difficult to differentiate from other common causes of respiratory failure, such as acute respiratory distress syndrome and pulmonary edema. VAP is usually suspected when a patient develops a new or progressive infiltrate on chest radiograph, leukocytosis, and purulent tracheobronchial secretions. A tracheal tube or a tracheostomy tube provides a foreign surface that rapidly becomes colonized with upper airway flora. The mere presence of potentially pathogenic organisms in tracheal secretions is not diagnostic of VAP. A standardized diagnostic algorithm for VAP employing clinical and microbiologic data is used in the National Nosocomial Infections Surveillance System and the clinical pulmonary infection score to promote diagnostic consistency among clinicians and investigators. A clinical pulmonary infection score greater than 6 is consistent with a diagnosis of VAP (see Table 8.2).

In approximately half the patients suspected on clinical grounds of having VAP, the diagnosis is doubtful, and distal airway cultures do not grow organisms. Arbitrary thresholds that have been proposed to suggest a diagnosis of VAP are $10^3$ colony-forming units/mL (cfu/mL) of organisms grown from protected specimen brush, $10^4$ cfu/mL of organisms grown from bronchoalveolar lavage, or $10^5$ to $10^6$ cfu/mL of organisms grown from tracheal aspirates. Therefore, the accurate diagnosis of VAP is difficult and elusive at best.

### 8.1.3.6 Treatment and Prognosis

The treatment of VAP includes supportive care for respiratory failure plus therapy for the organisms most likely to be implicated. Principles to apply when choosing appropriate therapy for VAP include knowledge of organisms likely to be present, local resistance patterns within the ICU, a rational antibiotic regimen, and a rationale for antibiotic de-escalation or stoppage. The most common pathogens are *P. aeruginosa* and *S. aureus*. Prognosis is improved if treatment is initiated early. Therefore, despite the high rate of false-positive diagnoses, broad-spectrum therapy should be initiated to cover resistant organisms such as methicillin-resistant

*S. aureus* and *P. aeruginosa*. If known multidrug-resistant organisms, such as *A. baumannii* and extended-spectrum β-lactamase-producing organisms, a carbapenem antibiotic may be appropriate pending culture results. Treatment should be narrowed to target specific organisms according to cultures and sensitivities and should be stopped at 48 h if cultures are negative. Eight days of therapy are usually sufficient, except for non-lactose-fermenting gram-negative organisms, for which a 14-day course is recommended.

#### 8.1.3.7 Postoperative Management

One of the major goals for the critical care health team is to ensure that patients with VAP do not experience a setback following surgery. Because patients with respiratory failure may be PEEP dependent, a PEEP valve should be used to decrease the likelihood of "de-recruitment" of alveoli when they are transported to the operating room. In the operating room, protective mechanical ventilation should be used, with tidal volumes of 6–8 mL/kg of lean body mass. Ideally, the same ventilator settings that were used in the ICU should be used, including mode of ventilation and PEEP. The lowest inspired oxygen should be administered to achieve adequate oxygen saturation (e.g., >95 %). If the ventilator in the operating room is limited in its capabilities, consideration should be given to bringing an ICU ventilator into the operating room. If pneumonia is suspected and body fluids (e.g., pleural effusion, empyema, bronchial washing) are drained or suctioned, specimens should be sent to the laboratory for culture and identification of pathogens. Important findings regarding VAP are listed in Box 8.1.

**Box 8.1. Ventilator-Associated Pneumonia (VAP)**

- There is no gold standard for the diagnosis of VAP.
- Patients undergoing general anesthesia are at risk for aspiration pneumonia.
- Patients undergoing major abdominal and thoracic surgery are at significant risk for postoperative pneumonia.
- Early focused or broad-spectrum antibiotic therapy decreases mortality with VAP.
- When organisms are cultured, therapy should be narrowed and targeted to the particular pathogen.
- Eight days of therapy for VAP is sufficient, except for non-lactose-fermenting gram-negative organisms, for which a 14-day course is recommended.
- When no organisms grow from tracheal aspirates or bronchoalveolar lavage after 48 h, antibiotics should generally be stopped.
- If patients with VAP require anesthesia, a protective ventilation strategy should be adopted, similar to that in the ICU.

## 8.2 Renal Complications

Acute kidney injury (AKI) is one of the most difficult-to-predict complications occurring after cardiac surgery. Much emphasis has been placed in attempting to elucidate the physiologic mechanisms for AKI and to develop methods to minimize its occurrence. Because patients who develop AKI after cardiac surgery have a significantly higher mortality rate than those who do not, AKI is a major focus of current research.

### 8.2.1 Acute Kidney Injury

Acute kidney injury (AKI), also known as acute renal failure, after cardiac surgery is one of the most serious complications during the postoperative period of the patient having undergone cardiac surgery. The definition of AKI has been quite variable for many years. Recently, the Acute Kidney Injury Network (AKIN) defined AKI as the new need for institution of hemodialysis within 30 days of surgery. However, other definitions of AKI in past literature may include milder degrees of kidney injury; these may be defined as a 50 % drop in estimated glomerular filtration rate (GFR) or an analogous rise in serum creatinine. Therefore, it is important to consider the multiple definitions that may comprise AKI when evaluating the literature.

Although the incidence of postoperative AKI is relatively low (approximately 5–7 %), it is associated with high mortality rates during hospitalization and may exceed 50 %. The incidence of AKI appears to be fairly stable across institutions in the United States. Compared with patients who do not have postoperative renal dysfunction, patients with renal dysfunction (who do not need dialysis) remain twice as long in both the intensive care unit and hospital wards and have significantly higher mortality rates (1 % compared with 19 %). Furthermore, approximately 1 in 6 patients with renal dysfunction will need dialysis; 2 of 3 of these patients will not survive their hospitalization. Finally, patients with renal dysfunction are three times as likely to require continued, costly extended care after hospital discharge.

Etiology for AKI during cardiac surgery may be secondary to loss of pulsatile blood flow during CPB, increases in levels of circulating catecholamines and inflammatory mediators, macroembolic and microembolic events to the kidney, and release of free hemoglobin from damaged red blood cells. Patients undergoing cardiac surgery may develop maldistribution of renal blood flow, increases in renal vascular resistance, and substantive decreases (25–75 %) in renal blood flow and glomerular filtration rate. Predisposing factors that have been associated with acute kidney injury in cardiac surgical patients are multifactorial, and most are independently associated with AKI (see Table 8.3). Many of the conditions leading to AKI do not occur in isolation; therefore, it is difficult to isolate a specific critical period or inciting event. In addition, patients undergoing valve surgery or valve surgery with coronary artery bypass grafting (CABG) or multiple valve procedures are more likely to sustain AKI compared to CABG alone.

**Table 8.3** Risk factors for acute kidney injury after cardiac surgery

| Patient-related factors | Surgical factors | Others |
|---|---|---|
| Advanced age: 70–79 | Cardiopulmonary bypass >3 h | Left ventricular dysfunction |
| Severely advanced age: 80–89 | Use of intra-aortic balloon pump | Red blood cell transfusion |
| Congestive heart failure | Surgical re-exploration | |
| Diabetes mellitus | | |
| Elevated preoperative serum creatinine (124–177 mmol/L) | | |
| Female gender | | |
| Preoperative anemia | | |
| Previous myocardial revascularization | | |

#### 8.2.1.1 Diagnosis

Renal dysfunction after cardiac surgery is typically defined as a postoperative serum creatinine level of 177 micromol/L or greater and an increase in serum creatinine level of 62 micromol/L or greater from preoperative to maximum postoperative values. Postoperative renal failure is defined by the need for dialysis within 30 days after surgery. Additionally, emerging evidence is demonstrating that urinary interleukin-18 (IL-18) is an early, predictive biomarker of AKI after CPB and that urinary neutrophil gelatinase-associated lipocalin (NGAL) and IL-18 are increased in tandem after CPB. The combination of these two biomarkers may allow for the reliable early diagnosis and prognosis of AKI at all times after CPB, much before the rise in serum creatinine.

#### 8.2.1.2 Management

There is currently no specific method to prevent AKI from occurring in the postoperative period in patients undergoing cardiac surgery. Three major variables are highly predictive of mortality, and those include (1) preoperative intra-aortic balloon pump, (2) prolonged CPB time, and (3) emergent surgery. Unfortunately, there is no way to alter those variables in order to mitigate AKI. However, multiple additional variables have been identified that may be modifiable during the operative period. These include (1) optimizing anemia preoperatively, (2) avoiding intraoperative red blood cell transfusions, and (3) preventing surgical re-exploration. Avoidance of the aforementioned variables may serve to diminish the occurrence of AKI.

Specific pharmacologic therapies, such as vasoactive agents (i.e., low-dose dopamine, fenoldopam, or theophylline), have been utilized in the treatment of postoperative AKI. None of these agents has shown conclusive benefits in ameliorating kidney function. Diuretics (i.e., furosemide) have not been shown to improve or protect kidney function and have, in some cases, worsened outcomes. Proinflammatory cytokines have been extensively studied as mediators or markers of acute ischemia–reperfusion injury in experimental models of AKI. Their role in patients undergoing cardiac surgery is of particular interest due to the potential stimulation of inflammatory mediators upon exposure to the extracorporeal circuit.

Use of therapeutic agents to interfere with these mediators, however, has not been promising in terms of reducing risk for AKI in the clinical setting of cardiac surgery. Both steroid use and N-acetylcysteine use have been examined in cardiac surgery patients without any conclusive benefits.

## 8.3 Infectious Complications

### 8.3.1 Surgical Site Infections

Surgical site infections (SSIs) have been the focus of much attention during the past 30 years, and the major emphasis has been to completely prevent the occurrence of operative-related surgical infections and their associated morbidity and mortality. The key interventions that should be performed and subsequently monitored in the intensive care unit include (1) the proportion of patients who have parenterally administered antibiotics within 1 h before incision (within 2 h for vancomycin and fluoroquinolones), (2) the proportion of patients who are given a prophylactic antimicrobial regimen consistent with published guidelines, and (3) the proportion of patients whose prophylactic antimicrobial is discontinued within 24 h after surgery end time (48 h for cardiac surgical patients).

Despite multiple pharmacologic and procedural policy guidelines implemented in the last three decades, SSIs continue to occur at a rate of 2–5 % for extra-abdominal surgeries, inclusive of mediastinal wound infections. SSIs are among the top three causes of nosocomial infection, accounting for 14–16 % of all nosocomial infections among hospitalized patients. SSIs are a major source of morbidity and mortality rendering patients 60 % more likely to spend time in ICU, five times more likely to require hospital readmission, and twice as likely to die. In the United States, the increased cost per patient who experiences an infectious complication has been reported to be approximately $1,398 per occurrence. A recent resurgence in SSIs may be attributable to bacterial resistance, the increased implantation of prosthetic and foreign materials, as well as the poor immune status of many patients undergoing surgery. The universal adoption of simple measures including frequent hand decontamination with alcohol and appropriate administration of prophylactic antibiotics has been emphasized as a method of dramatically decreasing the incidence of SSIs.

SSIs are divided into superficial (involving skin and subcutaneous tissues), deep (fascial and muscle layers), and organ or tissue spaces (any area opened, manipulated during surgery); see Table 8.4. *S. aureus*, including methicillin-resistant *S. aureus* (*MRSA*), is the predominant cause of SSIs. Other causative organisms are coagulase-negative staphylococci, enterococci, coliforms, and *Clostridium perfringens*. Organ or tissue space infection after gastrointestinal surgery presents as peritonitis or intra-abdominal abscess. Common causative organisms are coliforms, *P. aeruginosa*, *Candida* spp., and *Bacteroides fragilis*. The increased proportion of SSIs caused by resistant pathogens and *Candida* spp. may reflect increasing

**Table 8.4** Types of surgical site infections

| Type of SSI | Time course | Criteria (at least one) |
|---|---|---|
| Superficial incisional SSI | Within 30 days of surgery | Superficial pus drainage<br>Organisms from superficial tissue or fluid<br>Signs and symptoms (pain, redness, swelling, heat)<br>Diagnosis by surgeon |
| Deep incisional SSI | Within 30 days of surgery or within 1 year if prosthetic implant is present | Deep pus drainage<br>Dehiscence or wound opened by surgeon (for fever >38 °C, pain, tenderness)<br>Abscess (e.g., radiographically diagnosed)<br>Diagnosis by surgeon or attending physician |
| Organ/space SSI | Within 30 days of surgery or within 1 year if prosthetic implant is present | Pus from a drain in the organ/space<br>Organisms from aseptically obtained culture of fluid or tissue in the organ/space<br>Abscess involving the organ/space<br>Diagnosis by a surgeon or attending physician |

*SSI* surgical site infection

numbers of severely ill and immunocompromised surgical patients and the impact of widespread use of broad-spectrum antimicrobial agents.

Mediastinitis is a particularly concerning postoperative infectious complication and may occur with or without sternal wound dehiscence. The STS database indicates that 25 % of wound infections in cardiac patients are related to mediastinal wounds. Clinical predictors of sternal infections are diabetes, obesity, preoperative hemodynamic instability, preoperative renal failure on dialysis, use of bilateral internal mammary arteries, sepsis, and transfusions of more than four units of packed red blood cells after surgery. Preoperative patient management and optimization may lessen the impact of these risk factors.

#### 8.3.1.1 Risk Factors for Surgical Site Infections

The risk of SSI is a multifactorial issue and is related to the following factors:

*Patient-Related Factors*

Chronic illness, extremes of age, baseline immune-competence or inherent/acquired immunocompromise, diabetes mellitus, and corticosteroid therapy are associated with an increased risk of developing an SSI. The American Society of Anesthesiologists' Risk Stratification Classification score of 2 or more when combined with the type and duration of surgery has been shown to be predictive of an increased rate of SSIs.

*Microbial Factors*

Enzyme production (*S. aureus*), possession of polysaccharide capsule (*B. fragilis*), and the ability to bind to fibronectin in blood clots (*S. aureus* and *Staphylococcus epidermidis*) are mechanisms by which microorganisms exploit weakened host defenses and initiate infection. Biofilm formation, exemplified by *S. epidermidis*, is particularly important in the etiology of prosthetic material infections (i.e., prosthetic joint infection). Coagulase-negative staphylococci

**Table 8.5** Risk factors for surgical site infections (SSIs)

| Patient-related factors | Microbial factors | Wound-related factors |
|---|---|---|
| Age | Enzyme production | Devitalized tissue |
| Nutritional status | Polysaccharide capsule | Dead space |
| ASA score >2 | Bind to fibronectin | Hematoma |
| Diabetes | Biofilm and slime | Contaminated |
| Smoking | | Foreign material |
| Coexisting infections | | |
| Bacterial colonization | | |
| Immunocompromise | | |
| Length of preoperative hospital stay | | |

*ASA* American Society of Anesthesiologists

produce glycocalyx and an associated component called "slime," which physically shields bacteria from phagocytes or inhibits the binding or penetration of antimicrobial agents.

*Wound-Related Factors*

Devitalized tissue, dead space, and hematoma formation are factors associated with the development of SSI. Historically, wounds have been described as *clean*, *contaminated*, and *dirty* according to the expected number of bacteria entering the surgical site. The presence of a foreign body (i.e., sutures, mesh) reduces the burden of organisms required to induce SSI; however, the implantation of major devices such as foreign material and cardiac devices does not necessarily yield expected SSIs. Risk factors for SSIs are summarized in Table 8.5.

#### 8.3.1.2 Signs and Symptoms

SSIs typically present within 30 days of surgery with localized inflammation of the surgical site and evidence of poor healing. Systemic features of infection, such as fever and malaise, may occur soon thereafter. Erythema, pain, and purulent discharge may develop at the sternal site; dressings should be routinely removed from the sternum to inspect for possible development of mediastinitis.

#### 8.3.1.3 Diagnosis

There may be nonspecific evidence of infection in patients with surgical site infections, including but not limited to elevated white blood count, poor blood glucose control, and elevation of inflammatory markers, such as C-reactive protein and procalcitonin. However, surgery itself is a great confounder leading to inflammation, thus rendering surrogate markers of infection unreliable. Purulence at the wound sight is suggestive, but not invariable. The "gold standard" in documenting infection is by growing organisms from an aseptically obtained culture. Approximately one third of organisms cultured are staphylococci (*S. aureus* and *S. epidermidis*), *Enterococcus* spp. makes up more than 10 %, and *Enterobacteriaceae* (*Escherichia coli*, *P. aeruginosa*, *Enterobacter* spp., *Proteus mirabilis*, and *K. pneumoniae*) make up the bulk of the remaining culprits.

#### 8.3.1.4 Treatment

It was recognized many years ago that prophylactic antimicrobial agents prevent postoperative wound infections. The organisms that are implicated in SSIs are usually those that are carried as colonizers, for example, in the nose or on the skin, by the patient at the time of surgery. Unless the patient has been in the hospital for some time prior to surgery, these are usually community organisms that have not developed multiple drug resistance; gram-positive organisms are typical. Timing of antibiotic prophylaxis (within 1 h) of surgical incision is important as these organisms are introduced into the bloodstream at the time of incision. Ideally, antibiotics should be given within 30 min of surgical incision to achieve peak effect. Currently, this recommendation is being evaluated as part of surveillance measures by the CDC as there is tremendous variation in the timing of prophylactic antibiotics. For most procedures, a single dose is adequate. Prolonged surgery (>4 h) may necessitate a second dose. Prophylaxis should usually be discontinued within 24 h of the procedure. For cardiac surgery, the Joint Commission on Accreditation of Healthcare Organizations (TJC) has recommended that the duration of prophylaxis be increased to 48 h. A first-generation cephalosporin such as cefazolin is effective for many types of surgery. In general, the antibacterial spectrum, low incidence of side effects, and tolerability of cephalosporins have made them the ideal choice for prophylaxis. Refer to Boxes 8.2 and 8.3 for surgical infection prevention guidelines and methods to decrease surgical site infections.

**Box 8.2. Surgical Infection Prevention Guidelines**

- Prophylactic antibiotics received within 1 h of surgical incision.
- Stop prophylactic antibiotics at 24 h (or 48 h for cardiac surgery).
- Increase dose of antibiotics for larger patients.
- Repeat dose when surgery exceeds 4 h.
- Administer antibiotic(s) appropriate for local resistance patterns.
- Follow American Heart Association guidelines for patients at risk for endocarditis, regardless of surgery.
- Adhere to procedure-specific antibiotic recommendations.

**Box 8.3. Methods to Decrease Surgical Site Infection**

- Ensure hand hygiene with alcohol.
- Observe strict asepsis.
- Mask, sterile gloves, and sterile gown for invasive procedures.
- Perform proper hair removal (use of hair clippers only, no razors, or no hair removal).
- Maintain tight glucose control, especially in patients undergoing cardiac surgery.
- Maintain normothermia via active measures.
- Promote adequate tissue oxygenation.

### 8.3.2 Bloodstream Infections

Bloodstream infections (BSIs) are among the top three nosocomial infections. Anesthesiologists have an important role in the prevention and often the treatment of BSIs. Central venous catheters are the predominant cause of nosocomial bacteremia and fungemia. Catheter-related bloodstream infections are common, costly, and potentially lethal; these infections are monitored by the National Nosocomial Infections Surveillance (NNIS) system of the CDC. A total of 80,000 cases of central venous catheter-associated BSIs have been estimated to occur annually in the United States with an attributable mortality rate estimated at 12–25 % for each infection with an average cost of $45,000.00 per infection per patient. The NNIS recommends that the rate of catheter-associated BSIs be expressed as the number of catheter-associated BSIs per 1,000 central venous catheter days. This parameter is more useful than the rate expressed as the number of catheter-associated infections per 100 catheters (or percentage of catheters studied) because it accounts for BSIs over time and, therefore, adjusts risk of the number of days that the catheter is in use.

#### 8.3.2.1 Signs and Symptoms

Patients typically have nonspecific signs of infection with no obvious candidate source, no cloudy urine, purulent sputum, pus drainage, wound inflammation, other than an indwelling infected catheter. Inflammation at the catheter insertion site is suggestive. A sudden change in a patient's condition should alert an astute clinician to the possibility of a BSI. Important signs include mental status changes, hemodynamic instability, altered tolerance for nutrition, and generalized malaise.

#### 8.3.2.2 Diagnosis

Catheter-associated BSIs are defined as bacteremia/fungemia in a patient with an intravascular catheter with at least one positive blood culture with a recognized pathogen not related to another separate infection, clinical manifestations of infection, and no other apparent source for the BSI except the catheter. Bloodstream infections are considered to be associated with a central line if the line was in use during the 48-h period before the development of the BSI. If the time interval between the onset of infection and device use is greater than 48 h, there should be compelling evidence that the infection is related to the central line; however, other sources must always be considered. The diagnosis is more compelling if, when a catheter is removed, the same organisms that grow from blood grow abundantly from the catheter tip.

#### 8.3.2.3 Treatment

The best treatment of central venous catheter-related BSIs is prevention; see Box 8.4 for overview of BSIs. The source of the bloodstream infection, usually a central venous catheter, should be removed as soon as possible, and broad-spectrum empirical antimicrobial therapy should be initiated pending the results of the cultures, at which point therapy should be appropriately narrowed and targeted. Resistance

patterns (both in general and in individual hospitals) may dictate initial therapy. Data from the United States are very concerning. Most coagulase-negative staphylococci and more than 50 % of *S. aureus* from ICUs are oxacillin resistant. More than 25 % of enterococci isolates from ICUs are vancomycin resistant, and this proportion is increasing. As for the gram-negative ICU isolates, many of them produce extended-spectrum β-lactamases, particularly *K. pneumoniae*, rendering them resistant to most antibiotics including even fourth-generation cephalosporins and extended-spectrum penicillins, such as piperacillin/tazobactam. Half of the *Candida* BSIs are associated with non-*Albicans* species, such as *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida krusei*, which are likely to be resistant to fluconazole and itraconazole. Based on these resistance patterns, it is difficult to strike a compromise between appropriate initial empirical coverage and not exhausting the last-line antimicrobial agents with the first salvo. Clinical judgment should be based on the severity of the patient's condition, the known susceptibility patterns of organisms at a particular institution, and the organisms that are currently implicated in infection in a particular environment. In order to delay widespread resistance to all antimicrobial agents, therapy *must* be narrowed as soon as organisms are identified and susceptibility is known. The principles of management for patients with BSIs are as for other causes of sepsis.

**Box 8.4. Bloodstream Infections (BSIs)**

- Bloodstream infections are among the top three causes of nosocomial infections.
- Central venous catheters are the predominant cause of BSIs.
- Resistant organisms are commonly implicated in BSIs.
- Asepsis, masks, sterile gowns, and gloves during central line insertion decrease the likelihood of BSI.
- Blood component transfusion causes immunosuppression and often leads to BSIs; avoid blood component transfusion if possible.
- Remove sources of possible infection (i.e., invasive catheters) as soon as possible.
- Management principles are same as for general sepsis.

#### 8.3.2.4 Central Venous Catheter Insertion Strategies

Anesthesiologists have an essential role to play in the prevention of BSIs. Many central venous catheters are placed by anesthesiologists who may be unaware about BSIs that develop days later. Therefore, anesthesiologists may often be unaware that a particular erroneous practice pattern is contributing to the development of BSIs. Preventing BSIs related to central venous catheters can be minimized by implementing a series of evidence-based steps shown to reduce infections as well as fostering an environment of teamwork and safety.

A recent interventional study targeted *five* evidence-based procedures recommended by the CDC and identified as having the greatest effect on the rate of

catheter-related BSIs and the lowest barriers to implementation. The five interventions were (1) hand washing with soap and water or an alcohol cleanser, (2) the use of full-barrier precautions (hat, mask and sterile gown, sterile area covering) during central venous catheter insertion, (3) cleaning the skin with chlorhexidine, (4) avoiding the femoral site and peripheral arms if possible, and (5) routine daily inspection of catheters with removal as soon as deemed unnecessary. This evidence-based interventional study resulted in a large and sustained reduction (up to 66 %) in rates of catheter-related BSIs that was maintained throughout the 18-month study period. The subclavian and internal jugular venous routes carry less risk of infection than the femoral route, but the decision regarding anatomic location selection has to be balanced against the higher risk of pneumothorax with a subclavian catheter. During insertion, catheter contamination rates can be further reduced by rinsing gloved hands in a solution of chlorhexidine in alcohol prior to handling the catheter. Sterility must be maintained with frequent hand decontamination and cleaning catheter ports each time with alcohol prior to accessing them. Central venous catheters may be coated or impregnated with antimicrobial or antiseptic agents, such as silver/platinum/carbon impregnation or chlorhexidine/silver sulfadiazine or rifampicin/minocycline coating; these catheters have been associated with a lower incidence of BSIs. Concerns about widespread adoption of drug-impregnated catheters are increased costs and promotion of further microbial resistance; however, such catheters and their associated costs may be indicated for the most vulnerable patients, such as those with severe immunocompromise.

### 8.3.3 Sternal Wound Infections

Deep sternal wound infection and dehiscence occurs in up to 5 % of patients undergoing median sternotomy and cardiac surgery and contributes to significant morbidity and mortality. A superficial sternal wound infection (limited to skin and subcutaneous tissue) may be accompanied by sternal instability, purulent discharge, and signs of sepsis. Risk factors for developing sternal wound infection include diabetes, renal failure, and prolonged mechanical intubation. If purulent discharge is evident from a sternal wound infection, cultures should be immediately performed to treat the specific pathogen. Close follow-up by the surgical team is necessary in order to prevent further infectious complications by other potential infectious sites.

Noninfectious sternal dehiscence may occur secondary to obesity, chronic pulmonary disease, osteoporotic sternum, inaccurate technique and fixation of sternum, excess bone wax use, steroid therapy, and history of chest radiation. In this condition, wound reopening, debridement, and primary sternal rewiring is an adequate treatment whenever the sternal bone remains intact. If the sternum has multiple fractures, bone excision and defect closure by pectoral flap is suitable treatment. In cases of deep sternal wound infection and bony nonunion, sternal wound reconstruction is performed with continuous antibiotic mediastinal irrigation, extensive serial sternal debridement, plate fixation, and delay closure by using pectoral

muscle or omental flap. In addition, should wound dehiscence lead to breakdown of muscle tissue, muscle flaps may be indicated. Utilization of a wound vacuum device may assist in wound healing and prevention of entry of exogenous organisms.

## Reference

Luyt CE, Chastre J, Fagon JY (2004) Value of the clinical pulmonary infection score for the identification and management of ventilator-associated pneumonia. Intensive Care Med 30: 844–852

## Suggested Reading

Bando K, Sun K, Binford RS, Sharp TG (1997) Determinants of longer duration of endotracheal intubation after adult cardiac operations. Ann Thorac Surg 63:1026–1033

Bartzler DW, Hunt DR (2006) The surgical infection prevention and surgical care improvement projects: national initiatives to improve outcomes for patients having surgery. Clin Infect Dis 43:322–330

Canver CC, Chanda J (2003) Intraoperative and postoperative risk factors for respiratory failure after coronary bypass. Ann Thorac Surg 75:853–857

Chertow GM, Levy EM, Hammermesiter KE, Grover F, Daley J (1998) Independent association between acute renal failure and mortality following cardiac surgery. Am J Med 104:343–348

Chertow GM, Burdick E, Honour M, Bonventure JV, Bates DW (2005) Acute kidney injury, mortality, length of stay and costs in hospitalized patients. J Am Soc Nephrol 16:3365–3370

Dellinger EP (2007) Prophylactic antibiotics: administration and timing before operation are more important than administration after operation. Clin Infect Dis 44:929–930

Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J et al (2008) Surviving sepsis campaign: guidelines for management of severe sepsis and shock. Intensive Care Med 34:17–60

Guller U, Anstrom KJ, Holman WL, Allman RM, Sansom M, Peterson ED (2004) Outcomes of early extubation after bypass surgery in the elderly. Ann Thorac Surg 77:781–788

Heffner JE (1989) Medical indications for tracheotomy. Chest 96:186–190

Heffner JE (2001) The role of tracheotomy in weaning. Chest 120:477S–481S

Karkouti K, Beattie WS, Wijeysundara DN, Rao V, Chan C, Dattilo DM et al (2005) Hemodilution during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery. J Thorac Cardiovasc Surg 129:391–400

Karkouti K, Wijeysundara DN, Yau TM, Callum JL, Cheng DC, Crowther M et al (2009) Acute kidney injury after cardiac surgery: focus on modifiable risk factors. Circulation 119:495–502

Kollef M, Ahrens T, Shannon W (1999) Clinical predictors and outcomes for patients requiring tracheostomy in the intensive care unit. Crit Care Med 27:1714–1720

Kowdley GC, Maithal S, Ahmed S, Naftel D, Karp R (2005) Non-dialysis-dependent renal dysfunction and cardiac surgery: an assessment of perioperative risk factors. Am Heart J 62:64–70

Lee JH, Graber R, Popple CG, Furey E, Lyons T, Murrell HK et al (1998) Safety and efficacy of early extubation of elderly coronary artery bypass surgery patients. J Cardiothorac Vasc Anesth 12:381–384

Lok CE, Austin PC, Wang H, Tu JV (2004) Impact of renal insufficiency on short- and long-term outcomes after cardiac surgery. Am Heart J 148:430–438

Lutfiyya MN, Henley E, Chang LF, Reyburn SW (2006) Diagnosis and treatment of community-acquired pneumonia. Am Fam Physician 73:442–450

Mair J, Hammerer-Lercher A (2005) Markers for perioperative myocardial ischemia: what both interventional cardiologists and cardiac surgeons need to know. Heart Surg Forum 8: E319–E325

Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT (1994) Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes and hospital resource utilization. Ann Intern Med 128:194–203

Mathew JP, Fontes ML, Tudor IC, James Ramsay J, Duke P, Mazer CD et al (2004) A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA 291:1720–1729

Mauermann WJ, Nemergut EC (2006) The anesthesiologist's role in the prevention of surgical site infections. Anesthesiology 105:413–421

Meade MO, Guyatt G, Butler R, Elms B, Hand L, Ingram A et al (2001) Trials comparing early versus late extubation following cardiovascular surgery. Chest 120:445s–453s

Milot J, Perron J, Lacasse Y, Lettourneau L, Cartier PC, Maltais F (2001) Incidence and predictors of ARDS after cardiac surgery. Chest 119:884–888

Mohamed R, Thomas R (1999) Perioperative predictors of extubation failure and the effect on clinical outcome after cardiac surgery. Crit Care Med 27:340–347

Ngaage DL, Martins E, Orkell E, Griffin S, Cale AR, Cowen ME et al (2002) The impact of the duration of mechanical ventilation on the respiratory outcome in smokers undergoing cardiac surgery. Cardiovasc Surg 10:345–350

Noora J, Ricci C, Hastings D, Hill S, Cybulsky I (2005) Determination of troponin I release after CABG surgery. J Cardiac Surg 20:129–135

Parikh CR, Mishra J, Thiessen-Philbrook H, Dursun B, Ma Q, Kelly C et al (2006) Uninary IL-18 is an early predictive biomarker for acute kidney injury after cardiac surgery. Kidney Int 70:199–203

Porzecanski I, Bowton DL (2006) Diagnosis and treatment of ventilator-associated pneumonia. Chest 130:597–604

Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S et al (2006) An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 355:2725–2732

Rajakaruna C, Rogers CA, Angelini GD, Ascione R (2005) Risk factors and economic implications of prolonged ventilation after cardiac surgery. J Thorac Cardiovasc Surg 130:1270–1277

Shenkman Z, Shir Y, Blueuberg B, Gross D (1997) The effects of cardiac surgery on early and late pulmonary functions. Acta Anaesthesiol Scand 41:1193–1199

Thakar CV (2008) Acute kidney injury after cardiac surgery. US Nephrol 3:46–50

Weissman C (2004) Pulmonary complications after cardiac surgery. Semin Cardiothorac Vasc Anesth 8:185–211

Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M et al (2007) Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and the Kawasaki Disease Committee Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation 116:1736–1754

Wynne R, Botti M (2004) Postoperative pulmonary dysfunction in adults after cardiac surgery with cardiopulmonary bypass: clinical significance and implications for practice. Am J Crit Care 13:384–393

# Postoperative Rhythm Disorders After Adult Cardiac Surgeries

9

Majid Haghjoo

## Contents



**Abstract**

New-onset arrhythmias are a common complication of cardiac surgery. Atrial fibrillation is the most common arrhythmia encountered postoperatively, although ventricular arrhythmias and conduction disturbances can also occur. Postoperative arrhythmias are an important cause of increased morbidity, prolonged

M. Haghjoo, MD
FESC, FACC, Cardiac Electrophysiology Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran

Rajaie Cardiovascular Medical and Research Center, Vali-e-Asr street, Niayesh Blvd, Tehran 1996911151, Iran
e-mail: majid.haghjoo@gmail.com

A. Dabbagh et al. (eds.), *Postoperative Critical Care for Cardiac Surgical Patients*,
DOI 10.1007/978-3-642-40418-4_9, © Springer-Verlag Berlin Heidelberg 2014

hospitalization, and higher medical costs. Prophylactic pharmacological and non-pharmacological treatments are highly useful in avoiding these problems.

## List of Abbreviations

| | |
|---|---|
| ACCF | American College of Cardiology Foundation |
| AF | Atrial fibrillation |
| AFL | Atrial flutter |
| AHA | American Heart Association |
| AT | Atrial tachycardia |
| AV | Atrioventricular |
| AVB | Atrioventricular block |
| BiA | Biatrial pacing |
| CABG | Coronary artery bypass grafting |
| ESC | European Society of Cardiology |
| PVC | Premature ventricular complex |
| SND | Sinus node dysfunction |
| VA | Ventricular arrhythmia |
| VT | Ventricular tachycardia |

New-onset arrhythmias are a common complication of cardiac surgery. Atrial fibrillation (AF) is the most common arrhythmia encountered postoperatively, although ventricular arrhythmias and conduction disturbances can also occur. Postoperative arrhythmias are an important cause of increased morbidity, prolonged hospitalization, and higher medical costs. Prophylactic pharmacological and non-pharmacological treatments are highly useful in avoiding these problems. This chapter discusses the incidence, prognosis, pathogenesis, preventive strategies, and management of these arrhythmias in adult patients undergoing cardiac surgery.

## 9.1 Supraventricular Arrhythmias

### 9.1.1 Incidence and Prognosis

Supraventricular tachycardias are recognized as the most common arrhythmia to occur after coronary artery bypass grafting (CABG) with the reported incidence of 20–40 % after CABG surgery (Creswell et al. 1993) and even higher following valvular surgery (Asher et al. 1998). AF (Fig. 9.1) and atrial flutter (AFL) are the most prevalent supraventricular arrhythmias; however, atrial tachycardias (AT) occurred as well. Most cases of AF occur between the second and fourth postoperative days (Almassi et al. 1997). Although this arrhythmia is usually benign and self-limiting, it may result in hemodynamic instability, thromboembolic events, a longer hospital stay, and increased health-care costs (Hakala et al. 2002; Lahtinen et al. 2004).

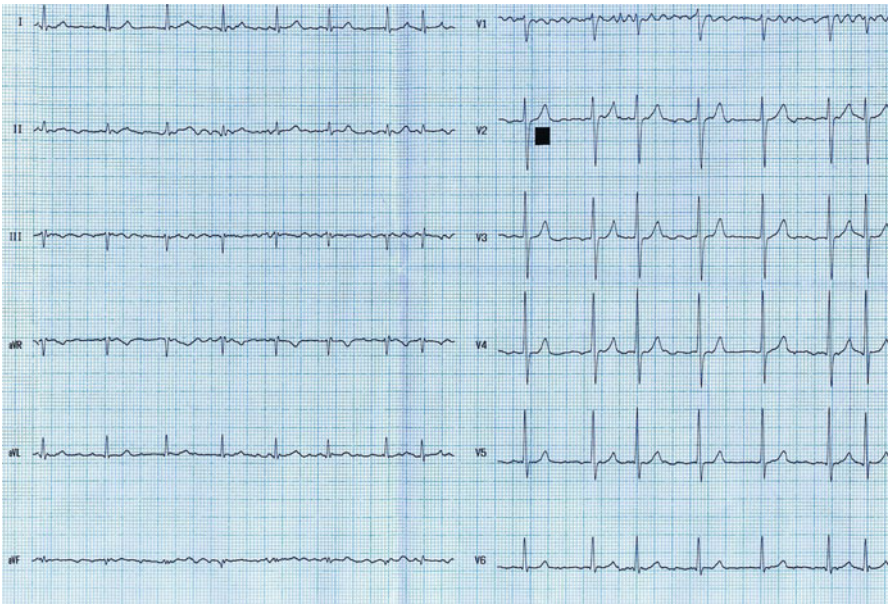



**Fig. 9.1** This figure shows atrial fibrillation with undulating atrial activity and irregular ventricular response

### 9.1.2 Pathogenesis

The mechanism of postoperative AF is not well described and is probably multifactorial. It is suggested that endogenous adenosine, inflammation, and oxidative injury may play a mechanistic role in this arrhythmia (Yavuz et al. 2004; Chung et al. 2001; Korantzopoulos et al. 2006). The perioperative period is also characterized by acute ischemic reperfusion injury and delayed inflammatory response that together result in a net depletion at plasma antioxidants (De Vecchi et al. 1998). Furthermore, patients undergoing cardiac surgery often have underlying atrial enlargement or increased atrial pressures that may predispose to AF. Age-related structural or electrophysiological changes also appear to lower the threshold for postoperative AF in elderly patients (Leitch et al. 1990). Other reported predisposing conditions for development of the postoperative AF included left main or proximal right coronary artery stenoses, chronic obstructive pulmonary disease, beta-blocker withdrawal, history of AF or heart failure, and preoperative electrocardiographic findings of PR interval of 185 ms or longer, P wave duration of 110 ms or longer in lead V1, and left atrial abnormality (Passman et al. 2001; Amar et al. 2004).

Considering the peak incidence of AF in the first 2–3 days after surgery, inflammatory mechanisms have been suggested. The idea has also been supported by the efficacy of anti-inflammatory agents in decreasing the incidence of postoperative AF (Ho and Tan 2009). However, there are other electrophysiological explanations for the higher incidence of AF in this period. Nonuniform atrial conduction is

greatest on postoperative days 2 and 3, and longest atrial conduction is on day 3 (Ishii et al. 2005). Perioperative hypokalemia has been shown to be associated with postoperative AF partly via changes in atrial conduction and refractoriness (Wahr et al. 1999).

There are recent evidences indicating that minimally invasive cardiac surgery or surgery without cardiopulmonary bypass has been associated with lower incidence of postoperative AF. In a prospective randomized study, 200 patients were randomly assigned into on-pump CABG and off-pump CABG. The results of this study clearly indicated postoperative AF occurs with lower frequency in patients who underwent off-pump beating heart surgery compared to those with on-pump CABG (Ascione et al. 2000).

### 9.1.3 Prophylaxis

Several pharmacological and non-pharmacological strategies have been employed to prevent postoperative AF after cardiac surgery. Efficacy of beta-blockers, amiodarone, sotalol, magnesium, and atrial pacing has been assessed in several randomized and nonrandomized clinical trials.

Because patients recovering from cardiac surgery often have enhanced sympathetic tone, the risk of postoperative AF is increased. Beta-blockers antagonize the effects of catecholamines on the myocardium and are, thus, expected to prevent AF after cardiac surgery. Multiple clinical trials and three landmark meta-analyses have shown a significant reduction in postoperative AF by beta-blocker prophylaxis in cardiac surgery patients (Crystal et al. 2002). Following these remarkable results, updated American Heart Association/American College of Cardiology Foundation (AHA/ACCF) 2006/2011 and recent European Society of Cardiology (ESC) 2010 guidelines recommended beta-blocker prophylaxis to prevent AF in cardiac surgery patients in the absence of contraindications (Fuster et al. 2011; Camm et al. 2010). Oral carvedilol, with its unique antioxidant and antiapoptotic properties, appears to be the most effective beta-blocker in the prevention of postoperative AF (Haghjoo et al. 2007). It has been demonstrated that both prophylactic oral and intravenous amiodarone are effective and safe agents in reducing the incidence of AF and its related cerebrovascular accident and postoperative ventricular tachyarrhythmia (Bagshaw et al. 2006). Currently, preoperative administration of amiodarone is deemed class IIa indication for prophylactic therapy in patients at high risk for postoperative AF in the latest AHA/ACCF and ESC guidelines for AF management (Fuster et al. 2011; Camm et al. 2010). Sotalol is a class III antiarrhythmic agent with potent beta-blocking activity. As a result, it would be a suitable drug for AF prevention after cardiac surgeries. Sotalol has been proven to be an effective agent across all the clinical trials using this drug (Pfisterer et al. 1997; Weber et al. 1998). The only issue is related to its safety profile.

Hypomagnesemia has been suggested as a cause of both supraventricular and ventricular tachycardias, and it is an independent risk factor for the development of AF in cardiac surgery patients. Therefore, it has been hypothesized that magnesium

**Table 9.1** Recommendations for prevention of atrial fibrillation after cardiac surgery

| Recommendation | Class | Level |
|---|---|---|
| Unless contraindicated, treatment with an oral beta-blocker to prevent postoperative AF is recommended for patients undergoing cardiac surgery | I | A |
| Preoperative administration of amiodarone reduces the incidence of AF in patients undergoing cardiac surgery and represents appropriate prophylactic therapy for patients at high risk for postoperative AF | IIa | A |
| Prophylactic administration of sotalol may be considered for patients at risk of developing AF following cardiac surgery | IIb | A |
| Biatrial pacing may be considered for prevention of AF after cardiac surgery | IIb | A |
| Corticosteroids may be considered in order to reduce the incidence of AF after cardiac surgery but are associated with risk | IIb | B |

Camm et al. (2010) and Fuster et al. (2011)

supplementation may reduce the incidence of AF after heart surgery. Several clinical trials have examined the use of intravenous magnesium sulfate for the prevention of AF after CABG (Fanning et al. 1991; Kaplan et al. 2003). A meta-analysis of eight identified randomized controlled trials revealed that the use of intravenous magnesium supplementation was associated with a significant reduction in the AF incidence after CABG (Alghamdi et al. 2005).

Overdrive atrial pacing may exert its preventive effect on postoperative AF by suppressing bradycardia-induced irregular heart rate, overdrive suppression of atrial premature beats, suppressing compensatory pauses after atrial premature beats, and resynchronizing atrial activation (Fan et al. 2003). Efficacy of right atrial, left atrial, and biatrial (BiA) pacing has been studied in several randomized studies (Archbold and Schilling 2004). It appears that BiA pacing is more effective than single-site pacing; be that as it may, available data do not permit a firm recommendation on the application of this intervention in a postoperative setting. Recently, the ESC 2010 guidelines on AF management considered BiA pacing as a class IIB recommendation for AF prevention after cardiac surgery (Camm et al. 2010). Latest AHA/ACCF and ESC recommendations for AF prevention in cardiac surgery are summarized in Table 9.1.

### 9.1.4 Management

Considering the self-limited course of the postoperative AF or AFL, treatment begins with pharmacological control of the heart rate (Table 9.2). Beta-blockers should be first-line agents for the rate control because of rapid onset of action and 50 % likelihood of conversion to sinus rhythm. Both metoprolol and esmolol are available in intravenous (IV) formulation. Calcium-channel antagonists are less effective than beta-blockers and considered as second-line agents. Calcium-channel antagonists result in rate control of AF more rapidly than does digoxin. These latter agents may be useful when beta-blockers are contraindicated (i.e., bronchospasm).

**Table 9.2** Antiarrhythmic medications used for rate and rhythm control in postoperative atrial fibrillation

| Antiarrhythmic | Loading dose | Maintenance dose |
|---|---|---|
| Beta-blockers | | |
| Esmolol | 500 μg/kg IV over 1 min | 50–200 μg/kg/min IV[a] |
| Metoprolol | 5 mg IV every 5 min<br>max 15 mg | 25–100 mg PO bid or tid |
| Propranolol | 1 mg IV every 2–5 min<br>max 0.1–0.2 mg/kg | 10–80 mg PO tid or qid |
| Calcium-channel antagonists | | |
| Verapamil | 5–10 mg IV over 1–2 min | 5 μg/kg/min IV or 40–160 mg PO tid |
| Diltiazem | 0.25 mg/kg IV over 2 min | 5–15 mg/h IV or 30–90 mg PO qid |
| Digitalis | | |
| Digoxin | 0.25–0.5 mg IV, then<br>0.25 mg every 4–6 h<br>max 1 mg/day | 0.125–0.25 mg/day |

Abbreviations: *IV* intravenous, *PO* orally, *bid* twice a day, *tid* three times a day, *qid* four times a day, *max* maximum

[a]After initial maintenance infusion, depending upon the desired ventricular response, the maintenance infusion may be continued at 50 μg/kg/min or increased stepwise to 100 μg/kg/min, 150 μg/kg/min, and finally to a maximum of 200 μg/kg/min with each step being maintained for 4 min

Conversion of postoperative AF is not needed in the majority of patients after cardiac surgery because of high recurrence rate and self-limited nature. However, this approach may be useful in high-risk patients who are refractory to or intolerant of atrioventricular (AV) nodal blocking agents. Conversion of AF, AFL, and AT can be accomplished using electrical cardioversion, pharmacological cardioversion, and overdrive pacing (if AFL or AT present). Pharmacological cardioversion should be considered in the setting of unstable respiratory status or other contraindication for anesthesia. Drugs proven to be useful for cardioversion include procainamide, amiodarone, propafenone, ibutilide, and dofetilide. Latter two agents carry a risk of torsades de pointes about 2–4 % (VanderLugt et al. 1999). This risk is higher in the setting of bradycardia, female gender, hypokalemia, and hypomagnesemia. Rapid atrial pacing using epicardial wires implanted during surgery was proved to be safe and effective in conversion of postoperative AFL and AT. Rapid atrial pacing is highly desirable in the patients unsuitable for electrical cardioversion such as patients with chronic obstructive pulmonary disease. Electrical cardioversion is reserved for patients exhibiting acute hemodynamic instability. For elective cardioversion, anterior-posterior paddles are preferred with the posterior paddle placed at the lower tip of the scapula. It has been shown that there is a higher risk of stroke in cardiac surgery patients with AF. Accordingly, anticoagulation with heparin or oral anticoagulation is appropriate when AF persists longer than 48 h, as recommended for nonsurgical patients (Fuster et al. 2011). The duration of anticoagulation must be based on individual clinical situation.

## 9.2 Ventricular Arrhythmias

### 9.2.1 Incidence and Prognosis

New-onset ventricular arrhythmias (VA) are uncommon after cardiac surgery (El-Chami et al. 2012). The highest incidence was observed between 3 and 5 postoperative days (Brembilla-Perrot et al. 2003). The prognosis of postoperative VAs is highly dependent on the type of arrhythmia and the severity of structural heart disease. Patients with simple premature ventricular complex (PVC) usually exhibit a benign prognosis (Huikuri et al. 1990). Complex ventricular arrhythmias, including frequent PVC and nonsustained ventricular tachycardia (VT), have no effect on short-term prognosis but predict a poor long-term prognosis if ventricular function is impaired (Smith et al. 1992; Pinto et al. 1996). The occurrence of sustained VT (Fig. 9.2) always predicts a poor short- and long-term prognosis (Tam et al. 1991). Traditionally, early (<48 h) postoperative VA was considered to have little if any long-term prognostic value and should be ignored after treating the acute episode. Recently, this traditional notion has been challenged by recent data indicating that VAs occurring within 48 h of cardiac surgery resulted in similar long-term outcomes as those occurring >48 h after surgery (El-Chami et al. 2012).

### 9.2.2 Pathogenesis

Etiologies for postoperative VAs include hemodynamic instability, electrolyte abnormalities, hypoxia, hypovolemia, ischemia and infarction, acute graft closure, reperfusion after cessation of cardiopulmonary bypass, and proarrhythmia caused by inotropic and antiarrhythmic drugs (Chung 2000).

### 9.2.3 Prophylaxis

In contrast to atrial arrhythmia, there is no clear recommendation for prevention of VA after cardiac surgery. However, some measures such as correcting electrolyte/metabolic disturbance (especially potassium), volume replacement, better myocardial protection, and special attention to use of inotropic and antiarrhythmic drugs may be useful in reducing the incidence of postoperative VAs. In addition, it has been recently shown that off-pump surgery is protective against the VAs after cardiac surgery (El-Chami et al. 2012).

### 9.2.4 Management

Patients with asymptomatic and hemodynamically stable PVC and even short runs of nonsustained VT usually do not require any specific treatment. All reversible

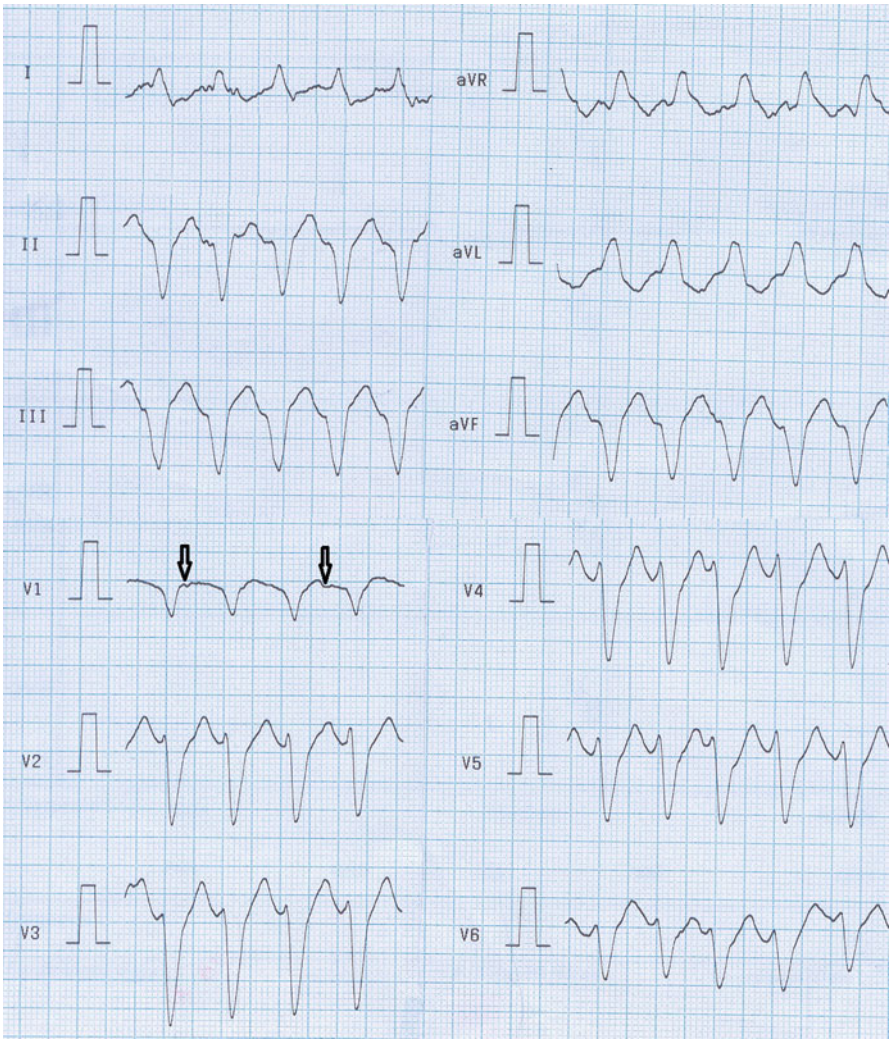



**Fig. 9.2** A 12-lead electrocardiogram (*ECG*) was recorded from a patient with three-vessel disease and severe left ventricular dysfunction after coronary bypass surgery. This ECG shows wide QRS tachycardia with clear atrioventricular dissociation (*arrow*) compatible with ventricular tachycardia

underlying causes should be corrected. In case of the symptomatic or hemodynamically significant PVC or nonsustained VT, lidocaine and overdrive pacing are recommended. For hemodynamically stable sustained VT, IV antiarrhythmic medication is the first-line treatment approach (Fogel and Prystowsky 2000). Dosages of common antiarrhythmic medications are listed in Table 9.3. Lidocaine is usually the first-choice drug and can be tried in dosage recommended in the nonsurgical setting. Procainamide is often the second choice. This drug should be used

**Table 9.3** Antiarrhythmic medications for control of postoperative ventricular arrhythmia

| Antiarrhythmic | Loading dose | Maintenance dose |
|---|---|---|
| Lidocaine | 1–1.5 mg/kg up to 3 mg/kg in two divided doses 15 min apart | 2–4 mg/min |
| Procainamide | 20–50 mg/min up to 15 mg/kg | 1–4 mg/min |
| Amiodarone | 150 mg over 10 min, additional bolus of 150 mg for recurrent arrhythmia | 1 mg/min for 6 h and 0.5 mg/min for 18 h |

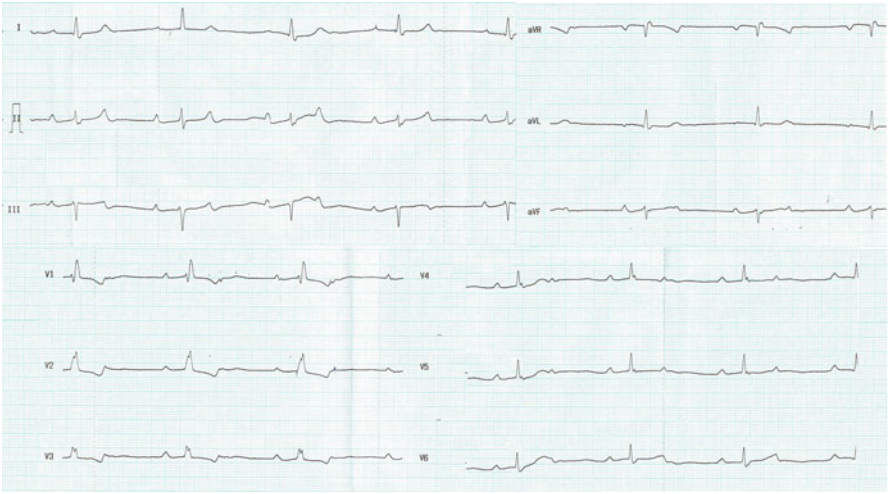



**Fig. 9.3** This electrocardiogram was taken from a patient who recently underwent aortic valve replacement. Underlying rhythm is sinus with wide complex and 2:1 atrioventricular conduction

with caution or not at all in patients with renal dysfunction. In patients with left ventricular dysfunction, amiodarone is better choice than other antiarrhythmics. In this group of patients, overdrive ventricular pacing using epicardial wires placed at the time of surgery may be attempted. In patients with hemodynamically unstable or drug-refractory VT, electrical cardioversion or defibrillation with energy level of 200–360 J is recommended.

## 9.3 Bradyarrhythmias

### 9.3.1 Incidence and Prognosis

Bradyarrhythmias are a common complication following cardiac surgery. Permanent pacemaker is required for sinus node dysfunction (SND) or atrioventricular block (AVB) in 0.6–4.6 % of patients after CABG (Goldman et al. 1984). Varying degrees of AVB (Fig. 9.3) are more common after valve replacement (up to 24 %) than other types of cardiovascular surgery (Jaeger et al. 1994; Brodell et al. 1991).

Bradyarrhythmia due to SND and to lesser extent AVB is relatively common after orthotopic heart transplantation and leads to permanent pacemaker implantation in up to 21 % of patients with SND and 4.5 % of patients with AVB (Grant et al. 1995). Improvement in postoperative bradyarrhythmia may occur in significant number of patients. Rate of recovery is less common after complete AVB than SND (Merin et al. 2009).

### 9.3.2 Pathogenesis

Postoperative bradyarrhythmias can be caused by incomplete washout of cardioplegia solution, antiarrhythmic drugs, or their toxicity. In addition, it may be caused by trauma or surgical manipulation in the area of the AV node or bundle of His.

### 9.3.3 Prophylaxis

In order to reduce the incidence of postoperative conduction disorder, special attention to the anatomy of the conduction system, careful administration of sinus or AV nodal blocking agents, and complete washout of cardioplegia solution are warranted.

### 9.3.4 Management

According to the American College of Cardiology/American Heart Association guidelines, "permanent pacemaker implantation is indicated for third-degree and advanced second-degree AVB at any anatomic level associated with postoperative AVB that is not expected to resolve after cardiac surgery" (Tracy et al. 2013). Generally, it is recommended to implant a permanent pacemaker if symptomatic complete AVB or SND persists longer than 5–7 days after cardiac surgery (Merin et al. 2009). Any decision regarding timing of implantation of a permanent pacemaker will be impacted by the stability of the temporary pacing system. Therefore, patients with no intrinsic underlying rhythm or those with failure of temporary pacing leads, permanent pacing may be performed even sooner. In patients with resolved or resolving bradyarrhythmias, electrophysiological study or exercise stress testing is useful to determine the need for permanent pacemaker implantation.

## References

Alghamdi AA, Al-Radi OO, Latter DA (2005) Intravenous magnesium for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and meta-analysis. J Card Surg 20:293–299

Almassi GH, Schowalter T, Nicolosi AC et al (1997) Atrial fibrillation after cardiac surgery. A major morbid event? Ann Surg 226:501–513
Amar D, Shi W, Hogue CW Jr, Zhang H et al (2004) Clinical prediction rule for atrial fibrillation after coronary artery bypass grafting. J Am Coll Cardiol 44:1248–1253
Archbold RA, Schilling RJ (2004) Atrial pacing for the prevention of atrial fibrillation after coronary artery bypass graft surgery: a review of the literature. Heart 90:129–133
Ascione R, Caputo M, Calori G et al (2000) Predictors of atrial fibrillation after conventional and beating heart coronary surgery: a prospective, randomized study. Circulation 102:1530–1535
Asher CR, Miller DP, Grimm RA et al (1998) Analysis of risk factors for development of atrial fibrillation early after cardiac valvular surgery. Am J Cardiol 82:892–895
Bagshaw SM, Galbraith PD, Mitchell LB et al (2006) Prophylactic amiodarone for prevention of atrial fibrillation after cardiac surgery: a meta-analysis. Ann Thorac Surg 82:1927–1937
Brembilla-Perrot B, Villemot JP, Carteaux JP et al (2003) Postoperative ventricular arrhythmias after cardiac surgery: immediate- and long-term significance. Pacing Clin Electrophysiol 26:619–625
Brodell GK, Cosgrove D, Schiavone W et al (1991) Cardiac rhythm and conduction disturbances in patients undergoing mitral valve surgery. Cleve Clin J Med 58:397–399
Camm AJ, Kirchhof P, Lip GY et al (2010) Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 31:2369–2429
Chung MK (2000) Cardiac surgery: postoperative arrhythmias. Crit Care Med 28(Suppl): N136–N144
Chung MK, Martin DO, Sprecher D et al (2001) C-reactive protein in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation 104:2886–2891
Creswell LL, Schuessler RB, Rosenbloom M et al (1993) Hazards of postoperative atrial arrhythmias. Ann Thorac Surg 56:539–549
Crystal E, Connolly SJ, Sleik K et al (2002) Intervention on prevention of postoperative atrial fibrillation in patients undergoing heart surgery: a meta-analysis. Circulation 106:75–80
De Vecchi E, Pala MG, Di Credico G et al (1998) Relation between left ventricular function and oxidative stress in patients undergoing bypass surgery. Heart 79:242–247
El-Chami MF, Sawaya FJ, Kilgo P et al (2012) Ventricular arrhythmia after cardiac surgery: incidence, predictors, and outcomes. J Am Coll Cardiol 60:2664–2671
Fan K, Lee K, Lau CP (2003) Mechanisms of biatrial pacing for prevention of postoperative atrial fibrillation – insights from a clinical trial. Card Electrophysiol Rev 7:147–153
Fanning WJ, Thomas CS Jr, Roach A et al (1991) Prophylaxis of atrial fibrillation with magnesium sulfate after coronary artery bypass grafting. Ann Thorac Surg 52:529–533
Fogel RI, Prystowsky EN (2000) Management of malignant ventricular arrhythmias and cardiac arrest. Crit Care Med 28(Suppl):N165–N169
Fuster V, Ryden LE, Cannom DS et al (2011) 2011 CCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 123:e269–e367
Goldman BS, Hill TJ, Weisel RD et al (1984) Permanent cardiac pacing after open-heart surgery: acquired heart disease. Pacing Clin Electrophysiol 7:367–371
Grant SC, Khan MA, Faragher EB et al (1995) Atrial arrhythmias and pacing after orthotopic heart transplantation: bicaval versus standard atrial anastomosis. Br Heart J 74:149–153
Haghjoo M, Saravi M, Hashemi MJ et al (2007) Optimal beta-blocker for prevention of atrial fibrillation after on-pump coronary artery bypass graft surgery: carvedilol versus metoprolol. Heart Rhythm 4:1170–1174
Hakala T, Pitkanen O, Hippelainen M (2002) Feasibility of predicting the risk of atrial fibrillation after coronary artery bypass surgery with logistic regression model. Scand J Surg 91:339–344
Ho KM, Tan JA (2009) Benefits and risks of corticosteroid prophylaxis in adult cardiac surgery: a dose–response meta-analysis. Circulation 119:1853–1866

Huikuri HV, Yli-Mayry S, Korhonen UR et al (1990) Prevalence and prognostic significance of complex ventricular arrhythmias after coronary arterial bypass graft surgery. Int J Cardiol 27:333–339
Ishii Y, Schuessler RB, Gaynor SL et al (2005) Inflammation of atrium after cardiac surgery is associated with inhomogeneity of atrial conduction and atrial fibrillation. Circulation 111:2881–2888
Jaeger FJ, Trohman RG, Brener S et al (1994) Permanent pacing following repeat cardiac valve surgery. Am J Cardiol 74:505–507
Kaplan M, Kut MS, Icer UA et al (2003) Intravenous magnesium sulfate prophylaxis for atrial fibrillation after coronary artery bypass surgery. J Thorac Cardiovasc Surg 125:344–352
Korantzopoulos P, Kolettis TM, Galaris D et al (2006) The role of oxidative stress in the pathogenesis and perpetuation of atrial fibrillation. Int J Cardiol 115:135–143
Lahtinen J, Biancari F, Salmela E et al (2004) Postoperative atrial fibrillation is a major cause of stroke after on-pump coronary artery bypass surgery. Ann Thorac Surg 77:1241–1244
Leitch JW, Thomson D, Baird DK et al (1990) The importance of age as a predictor of atrial fibrillation and flutter after coronary artery bypass grafting. J Thorac Cardiovasc Surg 100:338–342
Merin O, Ilan M, Oren A et al (2009) Pacing. Clin Electrophysiol 32:7–12
Passman R, Beshai J, Pavri B et al (2001) Predicting post-coronary bypass surgery atrial arrhythmias from the preoperative electrocardiogram. Am Heart J 142:806–810
Pfisterer ME, Klöter-Weber UC, Huber M et al (1997) Prevention of supraventricular tachyarrhythmias after open heart operation by low-dose sotalol: a prospective, double-blind, randomized, placebo-controlled study. Ann Thorac Surg 64:1113–1119
Pinto RP, Romerill DB, Nasser WK et al (1996) Prognosis of patients with frequent premature ventricular complexes and nonsustained ventricular tachycardia after coronary artery bypass graft surgery. Clin Cardiol 19:321–324
Smith RC, Leung JM, Keith FM et al (1992) Ventricular dysrhythmias in patients undergoing coronary artery bypass graft surgery: incidence, characteristics, and prognostic importance. Am Heart J 123:73–81
Tam SK, Miller JM, Edmunds LH Jr (1991) Unexpected, sustained ventricular tachyarrhythmia after cardiac operations. J Thorac Cardiovasc Surg 102:883–889
Tracy CM, Epstein AE, Darbar D et al (2013) 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 61:e6–e75
VanderLugt JT, Mattioni T, Denker S et al (1999) Efficacy and safety of ibutilide fumarate for the conversion of atrial arrhythmias after cardiac surgery. Circulation 100:369–375
Wahr JA, Parks R, Boisvert D et al (1999) Preoperative serum potassium levels and perioperative outcomes in cardiac surgery patients. Multicenter Study of Perioperative Ischemia Research Group. JAMA 281:2203–2210
Weber UK, Osswald S, Buser P et al (1998) Significance of supraventricular tachyarrhythmias after coronary artery bypass graft surgery and their prevention by low-dose sotalol: a prospective double-blind randomized placebo controlled study. J Cardiovasc Pharmacol Ther 3:209–216
Yavuz T, Bertolet B, Bebooul Y et al (2004) Role of endogenous adenosine in atrial fibrillation after coronary artery bypass graft. Clin Cardiol 27:343–346

# Postoperative CNS Care

# 10

Ali Dabbagh

## Contents



**Abstract**

CNS dysfunction after cardiac surgery is considered among the most important etiologies for morbidities and mortalities after cardiac surgery, and patients undergoing cardiac surgery might be affected by unwanted CNS complications; this is a well-established finding in many studies.

Although postoperative period-related factors constitute only about one fifth (20 %) of etiologies of postoperative CNS complications of cardiac surgery, the CNS complications are not usually seen intraoperatively; those CNS complications seen first during the hospitalization period are usually encountered in ICU.

Two main classifications are used for categorizing postoperative CNS injuries in cardiac surgery patients. The first is mainly a clinical classification (including type I and type II disorders), while the second is a time-based classification (including early and late disease).

A. Dabbagh, MD
Department of Anesthesiology and Anesthesiology Research Center, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
e-mail: alidabbagh@yahoo.com, alidabagh@sbmu.ac.ir

A. Dabbagh et al. (eds.), *Postoperative Critical Care for Cardiac Surgical Patients*,
DOI 10.1007/978-3-642-40418-4_10, 

Advanced age, high preoperative creatinine level, prior neurologic event, prolonged cardiopulmonary bypass time, and female gender are considered as early risk factors, while prior neurologic event, diabetes mellitus, unstable angina, previous cerebral vascular disease, need for inotropic support, and postoperative atrial fibrillation are considered as delayed risk factors. Aortic atherosclerosis is considered as both an acute and a chronic risk factor. The underlying mechanisms are classified in 5 main classes: patient-related etiologies, intraoperative surgical etiologies, intraoperative anesthetic etiologies, intraoperative extracorporeal circulation (ECC) etiologies, and postoperative period-related etiologies; a number of potential etiologies have been proposed in each class. Prevention strategies include pharmacologic neuroprotection and CPB-related techniques. Novel and older technologies are used to improve the CNS outcome.

## 10.1 Classification and Mechanisms of CNS Dysfunction After Cardiac Surgery

### 10.1.1 General Considerations of CNS Dysfunction After Cardiac Surgery

CNS dysfunction after cardiac surgery is considered among the most important etiologies for morbidities and mortalities after cardiac surgery, and patients undergoing cardiac surgery might be affected by unwanted CNS complications; this is a well-established finding in many studies.

Postoperative cerebral dysfunction after cardiac surgery is one of the most devastating complications and the least desired morbidity after cardiac surgery; it would affect not only the short-term clinical outcome adversely but also the long-term quality of life; in such a way that "*neurocognitive decline after cardiac surgery might be seen in up to three quarters of patients at hospital discharge and persist in a third of patients up to 6 months after surgery…and also, are associated with decreased quality of life*." As the population of elderly undergoing cardiac surgery increases, these complications are seen more frequently. Although postoperative period-related factors constitute only about one fifth (20 %) of etiologies of postoperative CNS complications of cardiac surgery, the CNS complications are not usually seen intraoperatively; those CNS complications seen first during the hospitalization period are usually encountered in ICU (Roach et al. 1996; Newman et al. 2001; Sato et al. 2002; Hogue et al. 2008a, b, c; Mathew et al. 2009; Lombard and Mathew 2010; Hedberg et al. 2011; Bartels et al. 2013; Mashour et al. 2013).

### 10.1.2 Classification of CNS Injuries After Cardiac Surgery

Two main classifications are used for categorizing postoperative CNS injuries in cardiac surgery patients. The first is mainly a clinical classification, while the second is a time-based classification.

#### 10.1.2.1 Type I and Type II Injuries

Cerebral complications after cardiac surgery have been categorized as type I and type II injuries (Roach et al. 1996; Newman et al. 2001; Carrascal et al. 2005; Marasco et al. 2008; Liu et al. 2009; Lombard and Mathew 2010).

*The incidence of type I injuries* is not high, but its severity and poor outcome could never be neglected; the incidence of stroke following CABG is about 1 %; these injuries are usually neurologic deficits and include the following:

- Fatal and nonfatal stroke (motor, sensory, or language deficit or a combination of them)
- Hypoxic encephalopathy
- Focal neurologic injury
- TIA (transient ischemic attack)
- Coma at discharge
- Stupor at discharge

Type I injury could happen in 1–4 % of closed chamber cardiac surgery and 8–9 % of open chamber cardiac surgery.

*Type II injuries* are neurologic disorders other than type I which are also more common than the previous class of disorders and include the following:

- New deterioration of intellectual function.
- Confusion.
- Agitation.
- Memory deficit.
- Seizures without evidence of focal injury.
- Disorientation.
- Problem solving ability deficit.
- Attention and concentration impairment.
- Language problems.
- Psychomotor performance problems.
- Learning and memory problems.
- Mental processing speed deficit.
- Intelligence deficit.
- Usually, delirium is among the most common acute presentations of CNS disorders (detailed discussion about postoperative delirium and its management is presented in another chapter of the book titled "Cardiovascular Pharmacology" (Chap. 2)).

Type II injury could happen in over 50 % of the patients at the time of discharge from hospital and about 30 % of the patients six times after operation.

#### 10.1.2.2 Time-Based Classification of Postoperative CNS Injuries

Another classification involves the time interval after surgery, based on the fact that "early and delayed stroke differ in their related risk factors." The risk factors for early and late CNS disorders are discussed in the next section. Early postoperative cognitive dysfunction is an important predictor of "late postoperative cognitive dysfunction" 5 years later after surgery. It has been mentioned that early stroke has right cerebral hemisphere predominance rather than the left hemisphere, while

delayed stroke involves a uniform distribution. About one fifth (20 %) of postoperative CNS complications of cardiac surgery occur due to postoperative events, while 80 % are directly related to intraoperative events (Hogue et al. 1999, 2008a, b, c; Nathan et al. 2007; Hedberg et al. 2011; Hedberg and Engstrom 2012; Bartels et al. 2013; Mashour et al. 2013).

### 10.1.3 Risk Factors of CNS Injuries

Usually, a time-based classification is considered for classification of the risk factors, having the following two categories for classifications of risk factors for postoperative cerebral disorders after cardiac surgery (Hogue et al. 1999; Hedberg et al. 2011).

*Early* stroke risk factors are:

- Advanced age
- High preoperative creatinine level
- Prior neurologic event
- Aortic atherosclerosis area of involvement
- Longer duration of cardiopulmonary bypass
- Female gender with a seven-fold increased risk of early stroke and a 1.7-fold increased risk of delayed stroke

*Delayed* stroke risk factors are:

- Prior neurologic event
- Diabetes
- Aortic atherosclerosis
- Unstable angina
- Previous cerebral vascular disease
- Need for inotropic support
- Atrial fibrillation in postoperative period (combined end points of low cardiac output and atrial fibrillation)
- Low cardiac output (combined end points of low cardiac output and atrial fibrillation)
- Female gender

### 10.1.4 Mechanisms and Potential Etiologies of CNS Injuries

One of the most prominent features in "post-cardiac surgery cerebral disorders" is that their etiologies are not distinct, but a number of interrelated factors are responsible in occurrence of these clinical disorders; however, a general classification could be as follows:

- Patient-related factors.
- Intraoperative surgical factors.
- Intraoperative anesthetic factors.
- Intraoperative extracorporeal circulation (ECC) factors.

- Postoperative period-related factors: about one fifth (20 %) of postoperative CNS complications of cardiac surgery occur due to postoperative events, while 80 % are directly related to intraoperative events.
- First of all, postoperative CNS complications after cardiac surgery are usually *ischemic* type; less than 5 % of them have a hemorrhagic origin. However, "*CPB-related inflammation, microemboli, and hypoperfusion*" are related mainly to acute (short-term) neurocognitive disorders, and "*underlying cerebrovascular disease in CABG candidates*" is mainly responsible for the late neurocognitive impairments (occurring 1–5 years postoperatively).
- There is a direct relationship between aortic atherosclerosis and postoperative CNS problems: "*aortic atherosclerosis and cerebral atherosclerosis are concomitant pathologies*." Till now, the main possible etiology for postoperative CNS complications is the underlying atherosclerotic process of the patient involving all the arterial system including the coronary arteries and the cerebral vascular system. Aortic atheroma (even when it is not as a plaque) is disrupted during thoracic aortic manipulations, including aortic cannulation, aortic cross clamping, and proximal anastomosis of grafts. Also, perfusion through the arterial cannula of CPB has a "sandblasting effect" which increases the risk of CNS injury; epi-aortic scanning is the most sensitive method for detecting aortic atherosclerosis to find appropriate place for cannulation, while palpation of the aorta by surgeon's finger is not as effective.
- *CNS hypoperfusion* during CPB is an important risk factor. MAP between 50 and 80 mmHg is a target blood pressure for maintaining cerebral autoregulation functioning; the role of MAP is especially important in maintaining both cortical end arteries and cerebral collateral arteries. However, patients undergoing cardiac surgery usually have comorbidities; so, their cerebral autoregulation would function in higher pressures, and upper limit of blood pressure for MAP during CPB is considered more appropriate for these patients. Even in patients undergoing off-pump cardiac surgery, any blood pressure derangement might have a great impact on CNS outcome. It seems that cerebral oximetry could help us control cerebral perfusion with much more exactness.
- *Hypothermia* during cardiac surgery has been used as an organ-protective strategy; however, its effect on CNS outcome is yet to be defined since it has not been demonstrated to be effective in protecting CNS. On the other side, *hyperthermia* is a potent CNS risk factor usually occurring if slow rewarming strategies are not used for CPB weaning: 2 °C difference of CPB perfusate temperature and nasopharyngeal temperature improve outcome compared with 6 °C.
- *As* mentioned earlier, *time interval after surgery* is another factor since the risk factors of "early and delayed stroke" are different.
- The main CNS insult happens during the operation; however, about 20 % of the strokes are the result of *postoperative events*, which mandates enough vigilance during postoperative period.
- *Particle emboli*: Both *macroemboli* (atherosclerotic debris originating from the thoracic aorta) and *microemboli* (fatty particles or gaseous emboli) are considered as important etiologies for cerebral injuries.

- Microemboli are originated both from *fatty nature* of embolic particles and also the presence of aluminum and silicone in the aspirates of the cardiotomy suction; both types could occlude CNS end arteries. Lipid microemboli cause small capillary and arteriolar dilatations (SCADs), generally in the range of 10–70 μm; most of the lipid microemboli are shed into brain end arteries through cardiotomy suction.
- Using or avoiding *CPB* has been considered as a potential mechanism of injury with extensive studies assessing its effects. From one aspect, *off-pump surgery* has less aortic manipulations and prevents CPB-related microemboli and inflammation. However, on the other hand, "*aortic manipulations by the surgeon during proximal grafting*" and "*hypotension episodes at the time of cardiac maneuvering for distal grafting*" are two possible mechanisms which could cause CNS injury in off-pump patients. Possibly this is why no significant difference (regarding postoperative CNS events) has been demonstrated between on-pump and off-pump groups. Finally, "*CPB alone does not cause enough neuro-inflammatory changes leading to increased long-term cognitive dysfunction.*"
- Against the discussions related to on-pump and off-pump procedures, *the time interval for using extracorporeal circulation* and CPB is considered as a real risk factor for postoperative CNS dysfunction, since it boosts the inflammatory response.
- *Tight glycemic control* in diabetic and nondiabetic adult patients undergoing cardiac surgery was considered as a neuroprotective strategy; however, during recent years, evidence demonstrated "tight glycemic control" as an equivocal strategy regarding *patient outcome* and *mortality rate*, compared with conventional glucose management; a possible mechanism is the relatively high resistance against insulin during cardiopulmonary bypass with latent hypoglycemia after CPB, especially kin postoperative period which could induce cerebral hazards.
- *Anemia* is another major potential risk factor for postoperative CNS injury, especially if the hematocrit level during CPB is below 22 % in patients at risk of CNS injury; in such a way that for each 1 % fall in the level of hematocrit, a 10 % increase in CNS injury chance has been shown; the possible mechanism for this finding is decreased cerebral oxygen delivery accompanied with increased embolic load due to compensatory cerebral arterial dilatation; however, it is not still proved that packed cell transfusion in order to compensate for anemia could prevent CNS injury, so we have to weigh the risk and benefit of transfusion in such cases.
- *Genetic predisposition* is another potential mechanism explained in a number of studies, including genetic variants of CRP and interleukin 6 and also apolipoprotein E (APOE) genotype.
- *Atrial fibrillation* is the most common arrhythmia in postoperative period of cardiac surgery, occurring in >30 % of the patients and has a clear and direct relationship with postoperative CNS injury.
- *Advanced age* is "the main predictive factor which could foresee the occurrence of permanent postoperative neuropsychological defects" (mainly type II injury).

- *Gender* Female gender is associated with a 5- to 7-fold increased risk of early stroke and a 1.5- to 2-fold increased risk of delayed stroke.
- *Previous history* of cerebrovascular events.
- Impaired *left ventricular function*: Heart failure is associated with impaired cognitive function (primarily presented as delirium in hospitalized patients).
- *Valvular surgery* is an important risk factor for increased prevalence of postoperative cognitive decline than other cardiac procedures; it is possible that microembolic events are the major reason for this fact.
- Postoperative neurocognitive disorders would affect the *cortical white matter of the brain* mainly due to inflammatory mechanisms with a number of markers like "Alzheimer-associated amyloid-β." (Table 10.1)

**Table 10.1** Proposed risk factors for post-cardiac surgery cerebral dysfunction

| Patient-related factors |
|---|
| 1. Risk factors related to *patient pathophysiologic status* |
| CPB-related inflammatory response |
| Intraoperative hypoperfusion |
| Intraoperative cerebral oxygenation status |
| Intraoperative anesthetics used during operation |
| 2. Risk factors related to *underlying patient status* |
| Perioperative comorbid states (diabetes mellitus, hypertension, atherosclerosis especially in ascending aorta, previous cerebrovascular pathologies) |
| Preoperative cerebral blood flow (CBF) velocity, which demonstrates cerebral perfusion status (even, preoperative left-sided hypoperfusion could be a risk factor) |
| Old age |
| Perioperative sleep status |
| Perioperative administration of medications |
| 3. Risk factors related to *patient social status* |
| Underlying social class and social status |
| Postoperative administration of rehabilitation care |
| Underlying level of education |
| Gender |
| Ethnic differences |
| *Procedure-related factors* (intraoperative and postoperative surgical factors, anesthetic factors, and extracorporeal circulation (ECC) factors) |
| Using cardiotomy suction (time of using suction during surgery, using cell saver and arterial filter) |
| Duration of aortic cross clamp |
| Using hypothermia, optimal rewarming, severity and duration of hypothermia (especially if using DHCA) |
| Hyperthermia after CPB |
| Deairing management during surgery |
| Type of surgery (especially valve surgery or involving the aortic root) |
| Intraoperative use of epi-aortic scanning by the surgeon for aortic cannulation |
| Unstable hemodynamic status before, during, or after CPB |
| Location of the possible side of hypoperfusion during operation (left vs. right carotid system) |
| Using or avoiding CPB (on pump vs. off pump) |

(continued)

**Table 10.1** (continued)

| |
|---|
| Duration of CPB |
| Amount of bleeding and the volume of transfused blood |
| Readmission to the operating theater for control of acute postoperative bleeding |
| Only one fifth (20 %) of postoperative CNS complications of cardiac surgery occur due to *postoperative events* |
| Hyperthermia after CPB |
| Hypotension |
| Amount of bleeding and the volume of transfused blood |
| Readmission to the operating theater for control of acute postoperative bleeding |

## 10.2 Prevention Strategies

### 10.2.1 Pharmacologic Neuroprotection

Though a number of pharmaceutical agents have been proposed as neuroprotective agents, none has been fully proved yet; however, the following agents have been demonstrated to be effective in suppressing the ischemic penumbra in some studies (Hogue et al. 2007; Nelson et al. 2008; Mitchell et al. 2009; Lombard and Mathew 2010; Benggon et al. 2012; Dabbagh and Rajaei 2012; Zhang et al. 2012; Bruggemans 2013):

- Intraoperative lidocaine might have neuroprotective effects through suppressing the inflammatory response in cardiac surgery patients.
- Thiopental mainly decreases the embolic load (possibly due to cerebral vasoconstriction).
- Propofol might decrease the oxygen consumption during ischemic period.
- Postoperative donepezil might have therapeutic (rather than preventive) effects for postoperative cognitive dysfunction.
- 17β-estradiol might limit ischemic injury of the neuronal tissue in women undergoing cardiac surgery.
- In some studies, antagonists of N-methyl-D-aspartate have been demonstrated as neuroprotective agents; among them, anesthetics could be mentioned as the prototype of these drugs used for cardiac surgery patients. Usually, these pharmaceuticals are blamed for their neuroapoptotic effects; however, some agents like *xenon* and *dexmedetomidine* may have neuroprotective effects; on the other hand, although *ketamine* might have adverse neurodevelopmental effects in neonatal animal brain studies, it might be effective in decreasing postoperative neurocognitive dysfunction after cardiac surgery. Magnesium is another agent with potential have anti-inflammatory effects, being an antagonist of NMDA.
- Dextromethorphan, nimodipine, aprotinin, remacemide, beta blockers, pexelizumab, and a number of other agents have been proposed; however, none have been conclusive yet.

### 10.2.2 CPB-Related Equipment

A full description of the CPB-related factors affecting the CNS is discussed in detail in this book in a separate chapter titled "Cardiopulmonary Bypass: Postoperative Effects" (Chap. 12).

## 10.3 Neurologic Monitoring

Novel and older technologies are used to improve the CNS outcome. These monitoring are used more commonly nowadays. A full description of the neurologic monitoring in cardiac surgery is discussed in detail in this book in a separate chapter titled "Central Nervous System Monitoring" (Chap. 5). However, a brief discussion is presented here. The main currently available CNS monitoring are the following:

- Clinical assessment of CNS status and of sedation in postoperative period (Intensive Care Unit)
- Classic electroencephalogram (EEG) including multichannel or uni-channel EEG
- Monitoring depth of anesthesia
- Evoked potentials (including motor evoked potential, somatosensory evoked potential, and auditory evoked potential)
- Regional cerebral oximetry ($rSO_2$) by near-infrared spectroscopy technique (NIRS)
- Jugular vein oxygen saturation ($SjvO_2$)
- Transcranial Doppler (TCD)
- Other modes for assessment of cerebral blood flow

A full description of these devices is found in this book in the chapter discussing "Central Nervous System Monitoring" (Chap. 5).

## References

Bartels K, McDonagh DL, Newman MF, Mathew JP (2013) Neurocognitive outcomes after cardiac surgery. Curr Opin Anaesthesiol 26:91–97

Benggon M, Chen H, Applegate R, Martin R, Zhang JH (2012) Effect of dexmedetomidine on brain edema and neurological outcomes in surgical brain injury in rats. Anesth Analg 115:154–159

Bruggemans EF (2013) Cognitive dysfunction after cardiac surgery: pathophysiological mechanisms and preventive strategies. Neth Heart J 21:70–73

Bucerius J, Gummert JF, Borger MA, Walther T, Doll N, Falk V, Schmitt DV, Mohr FW (2004) Predictors of delirium after cardiac surgery delirium: effect of beating-heart (off-pump) surgery. J Thorac Cardiovasc Surg 127:57–64

Carrascal Y, Casquero E, Gualis J, Di Stefano S, Florez S, Fulquet E, Echevarria JR, Fiz L (2005) Cognitive decline after cardiac surgery: proposal for easy measurement with a new test. Interact Cardiovasc Thorac Surg 4:216–221

Coburn M, Fahlenkamp A, Zoremba N, Schaelte G (2010) Postoperative cognitive dysfunction: incidence and prophylaxis. Anaesthetist 59:177–184, quiz 185

Dabbagh A, Rajaei S (2012) Xenon: a solution for anesthesia in liver disease? Hepat Mon 12:e8437
Fahy BG, Sheehy AM, Coursin DB (2009) Glucose control in the intensive care unit. Crit Care Med 37:1769–1776
Funder KS, Steinmetz J, Rasmussen LS (2009) Cognitive dysfunction after cardiovascular surgery. Minerva Anestesiol 75:329–332
Grigore AM, Murray CF, Ramakrishna H, Djaiani G (2009) A core review of temperature regimens and neuroprotection during cardiopulmonary bypass: does rewarming rate matter? Anesth Analg 109:1741–1751
Grocott HP (2009) PRO: Temperature regimens and neuroprotection during cardiopulmonary bypass: does rewarming rate matter? Anesth Analg 109:1738–1740
Heckman GA, Patterson CJ, Demers C, St Onge J, Turpie ID, McKelvie RS (2007) Heart failure and cognitive impairment: challenges and opportunities. Clin Interv Aging 2:209–218
Hedberg M, Engstrom KG (2012) Stroke after cardiac surgery – hemispheric distribution and survival. Scand Cardiovasc J 47(3):136–144
Hedberg M, Boivie P, Engstrom KG (2011) Early and delayed stroke after coronary surgery – an analysis of risk factors and the impact on short- and long-term survival. Eur J Cardiothorac Surg 40:379–387
Hogue CW Jr, Murphy SF, Schechtman KB, Davila-Roman VG (1999) Risk factors for early or delayed stroke after cardiac surgery. Circulation 100:642–647
Hogue CW Jr, Freedland K, Hershey T, Fucetola R, Nassief A, Barzilai B, Thomas B, Birge S, Dixon D, Schechtman KB, Davila-Roman VG (2007) Neurocognitive outcomes are not improved by 17beta-estradiol in postmenopausal women undergoing cardiac surgery. Stroke 38:2048–2054
Hogue CW, Fucetola R, Hershey T, Freedland K, Davila-Roman VG, Goate AM, Thompson RE (2008a) Risk factors for neurocognitive dysfunction after cardiac surgery in postmenopausal women. Ann Thorac Surg 86:511–516
Hogue CW, Gottesman RF, Stearns J (2008b) Mechanisms of cerebral injury from cardiac surgery. Crit Care Clin 24:83–98, viii–xi
Hogue CW Jr, Fucetola R, Hershey T, Nassief A, Birge S, Davila-Roman VG, Barzilai B, Thomas B, Schechtman KB, Freedland K (2008c) The role of postoperative neurocognitive dysfunction on quality of life for postmenopausal women 6 months after cardiac surgery. Anesth Analg 107:21–28
Karkouti K, Djaiani G, Borger MA, Beattie WS, Fedorko L, Wijeysundera D, Ivanov J, Karski J (2005) Low hematocrit during cardiopulmonary bypass is associated with increased risk of perioperative stroke in cardiac surgery. Ann Thorac Surg 80:1381–1387
Knipp SC, Kahlert P, Jokisch D, Schlamann M, Wendt D, Weimar C, Jakob H, Thielmann M (2013) Cognitive function after transapical aortic valve implantation: a single-centre study with 3-month follow-up. Interact Cardiovasc Thorac Surg 16:116–122
Lazar HL, McDonnell M, Chipkin SR, Furnary AP, Engelman RM, Sadhu AR, Bridges CR, Haan CK, Svedjeholm R, Taegtmeyer H, Shemin RJ (2009) The Society of Thoracic Surgeons practice guideline series: blood glucose management during adult cardiac surgery. Ann Thorac Surg 87:663–669
Liu YH, Wang DX, Li LH, Wu XM, Shan GJ, Su Y, Li J, Yu QJ, Shi CX, Huang YN, Sun W (2009) The effects of cardiopulmonary bypass on the number of cerebral microemboli and the incidence of cognitive dysfunction after coronary artery bypass graft surgery. Anesth Analg 109:1013–1022
Lombard FW, Mathew JP (2010) Neurocognitive dysfunction following cardiac surgery. Semin Cardiothorac Vasc Anesth 14:102–110
Marasco SF, Sharwood LN, Abramson MJ (2008) No improvement in neurocognitive outcomes after off-pump versus on-pump coronary revascularisation: a meta-analysis. Eur J Cardiothorac Surg 33:961–970
Mashour GA, Avitsian R, Lauer KK, Soriano SG, Sharma D, Koht A, Crosby G (2013) Neuroanesthesiology fellowship training: curricular guidelines from the Society for Neuroscience in Anesthesiology and Critical Care. J Neurosurg Anesthesiol 25:1–7

Mathew JP, Mackensen GB, Phillips-Bute B, Grocott HP, Glower DD, Laskowitz DT, Blumenthal JA, Newman MF (2009) Randomized, double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery. Stroke 40:880–887

McKhann GM, Grega MA, Borowicz LM Jr, Bailey MM, Barry SJ, Zeger SL, Baumgartner WA, Selnes OA (2005) Is there cognitive decline 1 year after CABG? Comparison with surgical and nonsurgical controls. Neurology 65:991–999

McKhann GM, Grega MA, Borowicz LM Jr, Baumgartner WA, Selnes OA (2006) Stroke and encephalopathy after cardiac surgery: an update. Stroke 37:562–571

Messerotti Benvenuti S, Zanatta P, Longo C, Mazzarolo AP, Palomba D (2012a) Preoperative cerebral hypoperfusion in the left, not in the right, hemisphere is associated with cognitive decline after cardiac surgery. Psychosom Med 74:73–80

Messerotti Benvenuti S, Zanatta P, Valfre C, Polesel E, Palomba D (2012b) Preliminary evidence for reduced preoperative cerebral blood flow velocity as a risk factor for cognitive decline three months after cardiac surgery: an extension study. Perfusion 27:486–492

Mitchell SJ, Merry AF, Frampton C, Davies E, Grieve D, Mills BP, Webster CS, Milsom FP, Willcox TW, Gorman DF (2009) Cerebral protection by lidocaine during cardiac operations: a follow-up study. Ann Thorac Surg 87:820–825

Moller CH, Penninga L, Wetterslev J, Steinbruchel DA, Gluud C (2012) Off-pump versus on-pump coronary artery bypass grafting for ischaemic heart disease. Cochrane Database Syst Rev 3, CD007224

Nathan HJ, Rodriguez R, Wozny D, Dupuis JY, Rubens FD, Bryson GL, Wells G (2007) Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: five-year follow-up of a randomized trial. J Thorac Cardiovasc Surg 133:1206–1211

Nelson DP, Andropoulos DB, Fraser CD, Jr. 2008. Perioperative neuroprotective strategies. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu:49–56.

Newman MF, Grocott HP, Mathew JP, White WD, Landolfo K, Reves JG, Laskowitz DT, Mark DB, Blumenthal JA (2001) Report of the substudy assessing the impact of neurocognitive function on quality of life 5 years after cardiac surgery. Stroke 32:2874–2881

Reinsfelt B, Westerlind A, Blennow K, Zetterberg H, Ricksten SE (2013) Open-heart surgery increases cerebrospinal fluid levels of Alzheimer-associated amyloid beta. Acta Anaesthesiol Scand 57:82–88

Roach GW, Kanchuger M, Mangano CM, Newman M, Nussmeier N, Wolman R, Aggarwal A, Marschall K, Graham SH, Ley C (1996) Adverse cerebral outcomes after coronary bypass surgery. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation Investigators. N Engl J Med 335:1857–1863

Rudolph JL, Schreiber KA, Culley DJ, McGlinchey RE, Crosby G, Levitsky S, Marcantonio ER (2010) Measurement of post-operative cognitive dysfunction after cardiac surgery: a systematic review. Acta Anaesthesiol Scand 54:663–677

Sato Y, Laskowitz DT, Bennett ER, Newman MF, Warner DS, Grocott HP (2002) Differential cerebral gene expression during cardiopulmonary bypass in the rat: evidence for apoptosis? Anesth Analg 94:1389–1394, table of contents

Selnes OA, McKhann GM (2005) Neurocognitive complications after coronary artery bypass surgery. Ann Neurol 57:615–621

Selnes OA, Grega MA, Borowicz LM Jr, Barry S, Zeger S, Baumgartner WA, McKhann GM (2005) Cognitive outcomes three years after coronary artery bypass surgery: a comparison of on-pump coronary artery bypass graft surgery and nonsurgical controls. Ann Thorac Surg 79:1201–1209

Sheehy AM, Coursin DB, Keegan MT (2009) Risks of tight glycemic control during adult cardiac surgery. Ann Thorac Surg 88:1384–1385; author reply 1385–1386

Sun X, Lindsay J, Monsein LH, Hill PC, Corso PJ (2012) Silent brain injury after cardiac surgery: a review: cognitive dysfunction and magnetic resonance imaging diffusion-weighted imaging findings. J Am Coll Cardiol 60:791–797

van Dijk D, Spoor M, Hijman R, Nathoe HM, Borst C, Jansen EW, Grobbee DE, de Jaegere PP, Kalkman CJ (2007) Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. JAMA 297:701–708

Zhang XY, Liu ZM, Wen SH, Li YS, Li Y, Yao X, Huang WQ, Liu KX (2012) Dexmedetomidine administration before, but not after, ischemia attenuates intestinal injury induced by intestinal ischemia-reperfusion in rats. Anesthesiology 116:1035–1046

# Postoperative Pain Management in Cardiac Surgery

# 11

Ali Dabbagh

## Contents



A. Dabbagh, MD
Department of Anesthesiology and Anesthesiology Research Center, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
e-mail: alidabbagh@yahoo.com, alidabagh@sbmu.ac.ir

A. Dabbagh et al. (eds.), *Postoperative Critical Care for Cardiac Surgical Patients*,
DOI 10.1007/978-3-642-40418-4_11, © Springer-Verlag Berlin Heidelberg 2014

**Abstract**

Postoperative pain management is not only a medical concern but also among the human rights; this challenging issue would be much more difficult in postoperative period of cardiac surgery patients in whom the burden of the cardiac disease and the complex perioperative events impose their heavy shadow on the decision-making process for selection of analgesic remedies for acute pain suppression.

In this chapter, a brief discussion about the pathologic mechanisms of pain and their possible risk factors and potential mechanisms is presented first, and then, analgesia methods are discussed in two main categories: pharmacologic methods (including opioids, alpha 2 agonists, nonsteroidal anti-inflammatory drugs "NSAIDs," paracetamol, ketamine, MgSO4, gabapentin, pregabalin, multimodal analgesia, and patient-controlled analgesia) and non-pharmacologic interventions (mainly infiltration of local anesthetics, intercostal nerve block, intrapleural infiltration of local anesthetics, and neuraxial blocks, "paravertebral, intrathecal, thoracic epidural").

## 11.1 Introduction: The Effects of Acute Postoperative Pain and the Benefits of Acute Pain Management in Postoperative Period

Today, a considerable number of patients experience acute postoperative pain and it has been demonstrated that between 30 and 80 % of patients complain of acute "moderate to severe postsurgical pain"; so the health-care team still have to consider postoperative pain as a challenge of care making acute postoperative pain management among the highest priorities, both for the patients and the health-care team. According to the NIH report, the annual pain-related health-care costs in the United States was more than one hundred billion dollars ($100,000,000,000) in 1998, estimated to be doubled now. According to the thirteenth World Congress on Pain in Montreal, Quebec, Canada, *Access to Pain Management is a Fundamental Human Right*; it has been mentioned in Article 3, "*The right of all people with pain to have access to appropriate assessment and treatment of the pain by adequately trained health care professionals*", while there are millions of patients who tolerate pain without experiencing the unpleasant sensation of acute pain unnecessarily due to acute, chronic, or cancer pain. The importance of acute pain management is that lack of its treatment would change in a considerable number of patients to chronic pain, finally causing "irreversible changes in the nervous system" ending in "progressive biopsychosocial epiphenomena" with further impairments, incapacities, and chronic health (Dolin et al. 2002; Popping et al. 2008b; Lippe et al. 2010; International Pain Summit of the International Association for the Study of Pain 2011).

Besides, it should be kept in mind that among a number of factors which could affect the patient outcome, the quality of "acute postoperative pain management" is an important and considerable one; since if we manage acute postoperative pain in a qualitative manner, we could help prevent a number of unwanted

hemodynamic, neuroendocrine, hemostatic, and immunologic side effects, possibly decreasing the prevalence of postoperative morbidities (Peters et al. 2007; Caputo et al. 2011).

In 2012, The American Society of Anesthesiologists has published the updated version of "the American Society of Anesthesiologists' Practice Guideline for Acute Pain Management in the Perioperative Setting." According to this guideline, "*Anesthesiologists and other healthcare providers should use standardized, validated instruments to facilitate the regular evaluation and documentation of pain intensity, the effects of pain therapy, and side effects caused by the therapy*." Also, the guideline emphasizes that "*Anesthesiologists responsible for perioperative analgesia should be available at all times to consult with ward nurses, surgeons, or other involved physicians*" (2012).

In this chapter a brief explanation of the pathophysiologic mechanisms in patients is explained first. Then, different pharmacologic and non-pharmacologic approaches of acute pain management are discussed with a brief explanation of their usage methods, risks, and benefits.

## 11.2 The Effects of Acute Postoperative Pain and the Benefits of Acute Pain Management in Postoperative Period

Acute postoperative pain imposes undesirable perioperative surgical stress response; the effects of perioperative insults to the body causes modifications in a number of body systems including the immune system and its inflammatory components and, also, the metabolic and neurohormonal systems; the collective response is called "the stress response"; this response would directly and indirectly affect many of the body organs. The sympathetic system is affected by the effects of acute pain – though age and sex could significantly influence the sympathetic response – although some studies have neglected the exact relationship between postoperative pain and sympathetic tone to consider other factors such as the severity of surgical lesion and "surgical trauma" much more important than the amount of sympathetic tone severity (Liu and Wu 2007; Ledowski et al. 2011; Wolf 2012a, b).

Suppressing acute postoperative pain would alter patient satisfaction, prevent unnecessary patient discomfort, and decrease the duration of postoperative hospital length of stay, patient costs, overall morbidity, and even mortality; most are alleviated after adequate postoperative pain management. Hence, postoperative analgesia is a major indicator of postoperative care needing "early aggressive perioperative care" (Jayr 1998; Popping et al. 2008a).

Acute postoperative pain in adult cardiac surgery has some special features compared with the other patients, both regarding the patient factors and the analgesic methods, while often severe and undertreated which might cause severe and prolonged chronic pain; hence, the pain management strategy should be "tailored" to each patient in order to have satisfactory results. However, the newly adopted fast-track anesthesia approach in cardiac surgeries necessitates more

aggressive postoperative pain management in these patients. Multimodal analgesic methods are highly effective and possibly *the best technique* in the management of acute postoperative pain. However, this approach has very important considerations due to the specific type of cardiac procedures. For example, neuraxial analgesia has its own limitations due to the coagulation disturbances after administration of anticoagulation and antiplatelet agents to be discussed later in this chapter (Schwann and Chaney 2003; Milgrom et al. 2004; Stritesky et al. 2004; Lena et al. 2008; Popping et al. 2008a, b; Campos 2009; Katz and Seltzer 2009; Cogan 2010; Muehling et al. 2011; Huffmyer et al. 2012; Mugabure Bujedo 2012; Nishimori et al. 2012; Romeyke and Stummer 2012; Usichenko et al. 2013).

## 11.3 Patient Satisfaction and Patients' Expectations

When dealing with pain in cardiac surgery patients, it should be considered that cardiac surgery patients usually expect a greater amount of postoperative pain than the real pain. So, when they make a comparison between *anticipated pain* and *experienced pain* (which is the actual pain), the patients usually express an acceptable and high level of satisfaction, although they really experience severe pain. So, there is a good level of *patient satisfaction* in such patients in the postoperative period. However, the health-care team should describe all aspects of postoperative pain with each patient, especially the potential for occurrence of chronic pain syndromes and its risk factors before the surgery. Of course, the different activities of the patients have different pain thresholds. One study demonstrated the following decreasing order of postoperative pain in cardiac surgical patients: "coughing, moving or turning in bed, getting up, deep breathing or using the incentive spirometer, and resting," while the pain intensity was decreased after removal of chest tubes. Also, the patients expect the health-care team to help them improve the tolerance of acute pain in order to gain their normal life (Simpson et al. 1996; Aida et al. 2002; Milgrom et al. 2004; Leal et al. 2005; Anderson and Cutshall 2007; Ballan and Lee 2007; Lee 2008; Aslan et al. 2009; Azzopardi and Lee 2009; Parry et al. 2010).

## 11.4 The Pathophysiology of Acute Pain in Cardiac Surgery Patients

It should be always considered as an alerting note that in patients undergoing cardiac surgery, the acute postoperative pain could be due to residual ischemia and/or incomplete revascularization; so acute postoperative pain in these patients should always lead the health-care team to a very important differential diagnosis: residual ischemia. *This differentiation is so much important*. After ruling out the above condition, we would focus on the most common source of acute postoperative pain in these patients which is mainly with a myofascial origin and originates from many

sources, most commonly originating from the chest wall (including the muscles, bony structures, tendons, and ligaments) (Jayr 1998; Acharya and Dunning 2010; Borgermann et al. 2010).

Usually in patients undergoing surgical procedures, the perioperative surgical stress response will increase to its uppermost levels just in the immediate postoperative period when it produces its many major pathophysiologic effects (including postoperative pain). This is the same after cardiac surgery with even more severe degrees of stress response due to the nature of cardiac surgery patients; most of them often tolerate the imposed inflammatory response due to cardiopulmonary bypass.

In patients undergoing cardiac surgery, there are considerable homeostatic disturbances which could lead to a number of great pathophysiologic changes in many of the major organ systems, including (but not limited to) the cardiovascular system, the lungs, the gastrointestinal system, the urinary system, the endocrine system, oxygen consumption, the immunologic system, and, finally, the central nervous system; these unwanted effects of cardiac surgery may lead to substantial postoperative morbidity and possibly to increased mortality. On the other hand, there are many studies that have clearly demonstrated potentially improved clinical benefits after adequate postoperative analgesia, which is due to increased level of stability in hemodynamic, metabolic, immunologic, and homeostatic factors and also more levels of stress response attenuation (Jayr 1998; Ledowski et al. 2011, 2012; Bodnar 2011; Brock et al. 2012; Nishimori et al. 2012; Oderda 2012; Torigoe et al. 2012; Urell et al. 2012; van Ojik et al. 2012).

## 11.5 The Etiologic Factors Aggravating Pain After Cardiac Surgery

There are a number of different potential etiologic risk factors for acute pain in these patients which are presented in Table 11.1.

Usually the pain location varies being a function of time; in other words, during the early postoperative days (usually the three postoperative days), the pain is mainly in the thoracic area, while, afterwards, it immigrates to the legs (i.e., the location of vein harvesting in CABG patients) and would be dominant there up to the end of the first postoperative week. During this transition, the type of pain will often change from a radicular chest pain to osteoarticular type leg pain at the end of the first week.

**Table 11.1** A summary of etiologic risk factors for acute pain in cardiac surgery patients and their pain sources

| Etiologic factor | |
|---|---|
| 1 | Incision site pain after sternotomy or thoracotomy |
| 2 | Intraoperative tissue retraction and surgical dissection |
| 3 | The arterial and venous vascular cannulation sites |
| 4 | The site of vein harvesting |
| 5 | The chest and abdominal sites for chest tubes |

The etiology for thoracic pain is usually the injuries of the rib cage, which is a very common source of postoperative pain in cardiac surgery. It will produce *an unexplained* postoperative non-incisional pain which is the physical result of sternal retraction. In clinical evaluation, the patients often have normal routine CXR, and the potential rib fracture (usually the posterior or lateral parts of the lower ribs) could be mainly detected in bone scans. These fractures are due to sternal retraction during the surgical procedure, which causes posterior or lateral rib fracture; also, there is the possibility for brachial plexus injury *leg pain*: leg pain due to vein-graft harvesting could be also problematic in cardiac surgery patients. This phenomenon, limited to patients with conventional saphenous vein harvesting, usually occurs in the *late postoperative days*; the possible explanation for this delayed presentation of pain could be patient mobilization in the 3rd or 4th postoperative days, while there is a decrease in sternotomy-related pain which would unmask the leg pain. There are current evidence that demonstrate the minimally invasive vein-graft harvesting method (endoscopic harvesting) which claim this harvesting method "reduces" the intensity and duration of postoperative leg pain.

There are a number of underlying factors including gender, age, and some ethnic groups; young age, prolonged surgical duration, and anatomical surgery location increase the chance of acute postoperative pain. Acute postoperative pain has been demonstrated to be much more severe in patients below 60 years (compared with those above 60). Also, it is experienced much more severely in women compared with men, though chronic discomfort after discharge is seen more frequently in men (Meehan et al. 1995; Moore 1995; Wipke-Tevis and Stotts 1998; Mueller et al. 2000a; Greenfield et al. 2001; Kalso et al. 2001; Bruce et al. 2003; Gallagher et al. 2004; Hudcova et al. 2006; Lahtinen et al. 2006; Koukis et al. 2008; Rubens and Boodhwani 2009; Garvin et al. 2010; Parry et al. 2010; Tennyson et al. 2010; Kiani and Poston 2011; Mazzeffi and Khelemsky 2011; Ucak et al. 2011; van Gulik et al. 2011; Papadopoulos et al. 2013).

## 11.6 Chronic Pain in Cardiac Surgery Patients

Chronic pain is not infrequent after cardiac surgery; its incidence has been reported to be about 20–55 %, though recent studies have demonstrated high prevalence rates for chronic pain. Chronic pain and its related depressive states could affect the clinical outcome of cardiac surgical patients. Even patient sleep pattern, physical and emotional status, and chronic postoperative pain states are all interrelated in these patients. There are some patients being affected by chronic pain after cardiac surgery mainly due to *chronic thoracic chest pain* or *chronic leg pain*; so, in one way, sternotomy could induce chronic pain in a number of patients with many referrals to pain clinics for managing chronic post-sternotomy pain mainly in the thoracic area; on the other hand, a number of patients undergoing CABG would refer for relief of chronic leg pain due to

**Table 11.2** A summary of the main potential risk factors for chronic pain after cardiac surgery

| | Possible etiologic chronic pain factor |
|---|---|
| 1 | Patients undergoing extensive surgical procedures (e.g., CABG plus valve surgery is associated with increased incidence of postoperative chronic pain than CABG alone) |
| 2 | Prolonged time of the procedure (especially surgeries more than 3 h) |
| 3 | Severe acute postoperative pain (with numeric rating scale ≥4) |
| 4 | Patients with ASA classifications >III |
| 5 | Any underlying history of preoperative or postoperative depression |
| 6 | Any underlying history for psychological vulnerability; preoperative or postoperative |
| 7 | Nonelective operations |
| 8 | Redo operations needing sternotomy |
| 9 | Increased needs for analgesic use during the first few postoperative days |
| 10 | Female patients |

**Table 11.3** A summary of the main etiologic mechanisms involved in chronic pain after cardiac surgery

| | Possible etiologic chronic pain factor |
|---|---|
| 1 | Physical effects of sternotomy |
| 2 | Surgical dissection and harvesting of the IMA, either skeletonized or pedicled |
| 3 | Direct damage to the trauma to the thoracic nerve branches including the anterior rami of intercostals nerve branches nerves |
| 4 | Pressure of the retractor |
| 5 | Surgical tissue destruction, fractures of the ribs |
| 6 | Separation of the costochondral junction |
| 7 | Surgical scar formation |
| 8 | Postoperative infection of the sternum |
| 9 | Sternal stainless-steel wire sutures |
| 10 | Inappropriate positioning of the body organs or suboptimal positioning of the arms before commencement of the surgical procedure |
| 11 | Intraoperative or postoperative injury to the brachial plexus |
| 12 | Pressure effects of rib fracture fragments |
| 13 | Placement of central venous catheter |

cardiac harvesting. These painful events should be differentiated from residual cardiac pain. Many studies have assessed post-cardiac surgery chronic pain to elucidate the related mechanisms, risk factors, and their treatment; a summary is presented here (Jonjev et al. 2000; Mueller et al. 2000a, b; Kalso et al. 2001; Bruce et al. 2003; Hirose et al. 2003; Bar-El et al. 2005; Lima Canadas et al. 2005; Hassan et al. 2006; Lahtinen et al. 2006; De Cosmo et al. 2009; Peivandi et al. 2009; Cogan 2010; Gjeilo et al. 2010; Lee et al. 2010; Dick et al. 2011; Farrell and McConaghy 2012).

There are a number of potential risk factors for occurrence of postoperative chronic pain in cardiac surgery patients during the postoperative period. Table 11.2 is a summary of the main factors among these possible etiologies; these should be differentiated from etiologic factors mentioned later in Table 11.3.

### 11.6.1 Chronic Chest Pain

Although maybe rare, this type of chronic pain could be *problematic*; it is usually manifested as *prolonged and severe chest wall pain*, which presents as a persistent pain after cardiac surgery. It is often localized to the arms, shoulders, or legs. The clinician should differentiate this type of pain from residual cardiac diseases which cause cardiac pain due to possible *residual ischemia or graft failure*. This syndrome is neuropathic in origin, would cause significant morbidity and discomfort for the patients, and occurs occasionally; but it is really difficult to treat. It is more frequent in the thoracic area after CABG, due to its etiologic factors discussed in the next paragraph. The patients who have severe acute pain in the first 10 days after surgery or who have "negative beliefs" about treatment of acute pain with opioids are at increased risk for chronic pain

There are a great number of possible etiologic factors mentioned as potential mechanisms for chronic pain in cardiac surgery patients, which might contribute to the appearance of chronic postoperative pain and postoperative neuropathies including a summary of etiologic mechanisms which is presented in Table 11.3; however, these should be discriminated from the risk factors presented in Table 11.2.

Among the above etiologies, IMA harvesting (either skeletonized or not) has been reported to cause neuropathic pain with a burning and sharp feature, which aggravates at night and would increase in severity by *stretching*, since it is due to neuritis of IMA harvest. Harvesting of IMA (thermal or mechanical injury) causes a number of dysesthesia areas presented as numbness and/or hypersensitivity located on the anterior chest region. It may even become so much worse that it would be aggravated by *usual daily activities* like putting on the clothes or showering. The patients would usually complain of the following words for describing the pain: "annoying, persistently recurring, dull, cutting and sharp, exhausting, tender, and tight." The temporal nature of pain is almost reported as brief, transient, and intermittent

### 11.6.2 Chronic Leg Pain

Chronic pain may also occur in the leg, primarily due to postoperative neuralgia of the saphenous nerve which happens after saphenous veins harvesting for CABG. It is more prevalent in the younger patients, while the correlation of severity of acute post-op pain and development of chronic pain syndromes is still vague.

## 11.7 Different Analgesic Methods

The American Society of Anesthesiologists' Practice Guideline for Acute Pain Management in the Perioperative Setting defines acute pain as "*pain that is present in a surgical patient after a procedure. Such pain may be the result of trauma from the procedure or procedure related complications*" and "*Pain management in the*

*perioperative setting refers to actions before, during, and after a procedure that are intended to reduce or eliminate postoperative pain before discharge*" (2012).

*Preoperative Pain Management Techniques*: According to the guideline text, it is very important to start the analgesic approaches from the preoperative period. Also, preoperative expectations of the patients would influence postoperative patient satisfaction level. The preoperative patient preparation steps include (but are not limited to) the following (Aslan et al. 2009; Guo et al. 2012):

- Reducing underlying pain and anxiety by effective treatments
- Restoration or adjusting those medications which are used by the patients and their abrupt discontinuation could provoke signs or symptoms of withdrawal
- Administration of multimodal analgesic pain management program as preoperative medications before the operating room
- Application of patient and family education programs, which could be as pain control techniques and behavioral adaptations

*Perioperative Pain Management Techniques*: Among all the pain management techniques used during the perioperative period, the following are the most common; however, these are not the only options:

- Neuraxial administration of opioid analgesics (including epidural and intrathecal administration of analgesics and local anesthetics).
- Peripheral regional analgesic techniques (including intercostal blocks, intrapleural blocks, plexus blocks, paravertebral block, local anesthetic infiltration into the incisions).
- Patient-controlled analgesia (PCA) with systemic opioids and NSAIDs.
- Traditional intravenous administration of analgesics (especially opioids analgesics, with their prototype being morphine); however, intravenous opioids have their well-known side effects, including nausea, vomiting, pruritus, urinary retention, respiratory depression, and delayed tracheal extubation; other agents like NSAIDs and α-adrenergic agents could also be added.

## 11.8 Pharmacologic Alternatives Used for Treatment of Acute Cardiac Surgery Patients

The pharmacologic methods used for alleviation of acute pain are very vast and include a large list, from opioids to nonopioids. In Table 11.4, a summary is presented and more discussions could be found in the text.

**Table 11.4** A brief summary of pharmacologic methods for treatment of acute pain in cardiac surgery

| | |
|---|---|
| 1 | Opioids |
| 2 | Alpha 2 agonists |
| 3 | Nonsteroidal anti-inflammatory drugs (NSAIDs) |
| 4 | Paracetamol |
| 5 | Other pharmaceutical agents (ketamine, $MgSO_4$, gabapentin, pregabalin) |
| 6 | Multimodal analgesia |
| 7 | Patient-controlled analgesia |

### 11.8.1 Opioids

Morphine was detected by Friedrich Sertürner in 1803–1806, and its analgesic activity was used afterwards (Klockgether-Radke 2002; Jurna 2003; Rachinger-Adam et al. 2011). However, the routine clinical administration of opioids for acute pain suppression began in 1960s, when administration of very high doses of intravenous opioids (especially morphine) was a standard care for cardiac anesthesia. However, in the following years it was elucidated that even administration of very large intravenous doses of opioids could not induce complete anesthesia (including full unconscious state and amnesia); so other inhalational or intravenous anesthetics were added to the anesthetic regimens for surgical anesthesia.

#### 11.8.1.1 Opioid Receptors

The clinical effects and side effects of the opioid agents are classified – like many other drugs – based on their receptors; the opioids interact with many different body systems through these receptors. The current opioid receptors are classified as three distinct ones, μ, κ, and δ, and the analgesic effects of opioids in the central nervous system (both at the spinal and supraspinal level) are exerted through these receptors. Primarily, the μ-receptor is classified as μ1 and μ2; however, μ1 is a high-affinity receptor mainly with supraspinal analgesia, while μ2 is a low-affinity receptor predominantly with spinal anesthesia. The μ-agonists cause a dose-related respiratory depression which would mainly act via μ2 receptor activities. However, kappa (κ) receptors have potential analgesic role both at the spinal and supraspinal level with possibly lower drug side effects and complications related to μ-receptors, though pure κ-agonists have little effect on respiration. The third type of opioid receptors known as delta (δ) receptors present modulatory role than analgesic role, at both the spinal level δ1 and supraspinal level δ2. Peripheral terminals for opioid receptors have been also demonstrated with their special role in some clinical findings like pruritus, also, cardioprotection, and wound healing However, it seems that the greatest advantage of peripheral terminals of opioid receptors would possibly be used as a common practice in near future, in such a way that we would be able to administer opioids peripherally without the fear of their risks on the CNS; this clinical use of peripheral opioid receptors has now appeared practically in some tissues like joints, bone, and teeth for postoperative pain relief; possibly other surgical operations (like cardiovascular) would be able to use these new molecules of analgesics (Leung 2004a, b; Waldhoer et al. 2004; Rachinger-Adam et al. 2011; Vadivelu et al. 2011; Awad et al. 2012; Bortsov et al. 2012; Granier et al. 2012; Sacerdote et al. 2012).

#### 11.8.1.2 Opioid Effects on the Body Systems

Analgesics and sedatives (especially opioids) have many important interactions with body homeostasis including the body stress modulating systems like "hypothalamus-pituitary-adrenal (HPA) axis and the extrahypothalamic brain stress system"; so opioids could have many beneficial effects in counteracting the unwanted effects of surgical stress response after cardiac surgery, which would help

the body in maintenance of homeostasis; however, opioid-related adverse drug events affect the postoperative recovery (Barletta 2012; Glaser et al. 2012; Hertle et al. 2012; Laorden et al. 2012).

Opioids are used extensively for suppression of acute postoperative pain in cardiac surgery and are known as the "gold standard" of pharmacologic acute pain suppression, mainly as intravenous and/or neuraxial routes. Morphine has more effective analgesic properties than the other opioids. Pharmacologically speaking, opioids have two distinct locations for their analgesic effects: supraspinal and spinal, i.e., neuraxial. Neuraxial administration of hydrophilic opioids (e.g., morphine sulfate) could create excellent postoperative analgesia, lasting at least 24 h for intrathecal and 48 h for epidural route with a number of clinical benefits; however, a very high degree of vigilance is needed to prevent possible side effects, mainly respiratory complications, hypoventilation and apnea being the most lethal ones. A maximum dose of 300 μg intrathecal morphine sulfate is considered the safety margin for prevention of postoperative respiratory depression. Morphine, used in different modes, has many potential benefits compared with other analgesic drugs (Nikoda et al. 1994; Bell et al. 2004; Gehling and Tryba 2009; Meylan et al. 2009; Mota et al. 2010; Mugabure Bujedo 2012; Nishimori et al. 2012; Walker and Yaksh 2012).

### Respiratory System

Opioids cause *respiratory depression* which could be known as the most important side effect of these very potent analgesics. The main mechanism is decreased sensitivity of the brain respiratory center to arterial pressure of $CO_2$, in which its mechanism is through decreased sensitivity of both medullary and peripheral chemoreceptors. Rostral ventromedial medulla is the region implicated in pain modulation and homeostatic regulation. Opioids could inhibit the chemoreceptors through the μ-receptors especially μ2-receptor, while their respiratory depressant effect in medulla is exerted through μ- and δ-receptors. It has been demonstrated that among the many CNS neurotransmitters involved in respiratory depression, the major neuroexcitatory and neuroinhibitory transmitters are glutamate and GABA, respectively. A third mechanism of obstructive apnea due to airway obstruction of opioids has been mentioned as the mechanism of opioid-induced apnea. The clinical steps in this process are as follows which are the steps of the effect of opioids on respirations:

1. Decreased respiratory rate.
2. Decreased tidal volume would happen after respiratory rate decrease.
3. Disturbed rhythmic function and generation of the respiration.
4. Change in the pattern of respiration from normal regular breath to irregular gasping pattern of spontaneous ventilation; this pattern is the characteristic pattern for the patients with diagnosis of opioid overdose.
5. Decreased sensitivity to hypoxia leading to decreased ventilator drive to hypoxia.
6. Apnea.

The opioid compound with active metabolites (e.g., morphine-6-β-glucuronide) has increased respiratory depressant effects. Also, elderly patients are at higher risk

of respiratory depression after opioid administration, since their central respiratory center is more sensitive to the respiratory depressant effects of opioids than the younger patients. Besides, when other anesthetics (like benzodiazepines, barbiturates, or inhalation anesthetics) are used simultaneously, the respiratory depressant effects of opioids would be more severe. And finally, genetic, environmental, and demographic factors may play a role in the severity of opioid-induced respiratory depression (White and Irvine 1999; George et al. 2010; Olofsen et al. 2010a; Geller 2011; Jungquist et al. 2011; Macintyre et al. 2011; Angst et al. 2012; Hicks et al. 2012; Phillips et al. 2012; Yamanaka and Sadikot 2013).

### Cardiovascular System

The opioids and their metabolites, including morphine, improve the analgesic effects of opioids in treatment of acute pain in patients with a history of ischemic heart disease undergoing major surgical operations. In patients undergoing cardiac surgery with extracorporeal circulation, due to increased volume of drug distribution, the required dose is increased (Everts et al. 1998; Hanna et al. 2005; Bodnar 2011; Due et al. 2012; Shekar et al. 2012).

Other systems are also affected by the effects of opioids:

### Immune System

Demonstrated as opioid-induced immunomodulation, both acquired and innate immunity, which can even affect the surgical outcome of the patients. The role of the immune system changes in creation of acute and chronic pain could be negligible. Among many cellular structures and receptors, the role of Toll-like receptor subtypes in many fields, including their interactions with opioids and their role in myocardial ischemia and acute coronary syndrome, has gained a great importance during the last years (Bodnar 2011; Bortsov et al. 2012; Hutchinson et al. 2012; Kwok et al. 2012; Lewis et al. 2012; Saadat et al. 2012)

### Gastrointestinal Tract

Opioids, especially morphine, not only decrease the mobility of the GI tract ending in constipation but also at times aggravate the centrally mediated nausea and vomiting, which are well-recognized unwanted side effects of opioids especially in the old age. The treatment of opioid-induced bowel dysfunction is not yet satisfactory though a number of traditional laxatives (bulking laxatives, stimulant agents, etc.) or newer prokinetic agents like "prucalopride and lubiprostone" have been tested with different clinical results. Prucalopride is a selective, high-affinity agonist of 5-HT(4) receptor used for treatment of chronic constipation, and lubiprostone is a prostaglandin $E_1$ derivative which could increase the activity of chloride channels in the apical aspect of epithelial cells to produce a very high chloride content fluid secretion inside the bowel lumen to soften the stool and increase motility and defecation (Cuthbert 2011; Bodnar 2011; Bove et al. 2012; Brock et al. 2012; Ishihara et al. 2012; Kapoor 2012; Smith et al. 2012; Tack and Corsetti 2012; Valdez-Morales et al. 2013).

#### Urinary Retention

The opioid agents, especially morphine, could induce urinary retention which is accompanied with increased bladder pressure and urinary bladder sphincter pressure; also, histological damage of bladder and the sphincter of bladder is possible. There are some clinical risk factors for increased risk of urinary retention like male sex and intrathecal morphine use; possibly the use of continuous peripheral nerve block could decrease the chance of this complication (Griesdale et al. 2011; Brock et al. 2012; Holzer 2012; Oderda 2012; Shi et al. 2012).

#### Cell Growth and Cell Death

The opioid agents have some effects in suppressing the cell growth. This might be at times against the tumor cells; however, in the recent years, there is an increasing concern regarding the apoptotic effects of anesthetics including opioids (Bortsov et al. 2012; Djafarzadeh et al. 2012; Eschenroeder et al. 2012; Polanco et al. 2012; Tsai et al. 2012; Allegaert et al. 2013).

#### Other Effects

There are a number of other side effects of opioids, namely, nausea and vomiting, pruritus, and urinary retention, which could be decreased by concomitant use of adjuvant analgesic agents, leading to decreased side effects of opioids while maintaining adequate postoperative analgesia. Opioids also affect appetite, thermoregulation, and mental features of the patients (Andrieu et al. 2009; Blaudszun et al. 2012; Bodnar 2011; Engelman and Marsala 2013; Ishihara et al. 2012; Na et al. 2012; Oderda 2012; Torigoe et al. 2012).

### 11.8.1.3 Opioid Compounds

Currently, opioids are classified as two main groups: natural agents and synthetic agents; morphine is the prototype of opioid agents and known as the gold standard (i.e., the benchmark of opioid analgesics). More detailed description of these agents is presented in the "Cardiovascular Pharmacology" chapter (Chap. 2).

#### Morphine

Morphine is the prototype opioid agonist and the most popular analgesic used in patients after cardiac surgery. Also, many synthetic and semisynthetic opioid compounds are made by simple modifications of morphine. Morphine is a lipid-soluble agent and for therapeutic purposes has been changed to some compounds like morphine sulfate which are more water soluble. Morphine has 30–40 % plasma protein binding and has primarily hepatic metabolism being conjugated to water-soluble glucuronides like morphine-3-glucuronide and morphine-6-glucuronide. Elimination half-life of morphine is 2–3 h but would be increased in liver diseases like liver cirrhosis, though the half-life of morphine is normal in renal disease. Morphine has also extrahepatic clearance through gut, brain, and kidneys, which comprises about 30 % of the total clearance of the drug (Bosilkovska et al. 2012; Hughes et al. 2012; Ishii et al. 2012; Swartjes et al. 2012; van Ojik et al. 2012).

### Synthetic Opioid Agents

Currently, we have four main synthetic opioid agonists used in clinic for acute pain management in anesthesia and/or analgesia: fentanyl, sufentanil, alfentanil, and remifentanil. These compounds are synthetic chemical derivatives of phenylpiperidine, which are chemical derivatives of meperidine.

Fentanyl, sufentanil, alfentanil, and remifentanil are very fast-equilibrating agents; alfentanil and remifentanil equilibrate "very fast" having an equilibrium half-life of just 1 min in order to equilibrate between plasma and CNS; fentanyl and sufentanil have a half-life of about 6 min for such an equilibration followed by methadone half-life being 8 min; however, the equilibration half-life of morphine is very much longer, 2–3 h, and morphine 6 glucuronide (an active metabolite of morphine) near 7 h; it means that alfentanil, remifentanil, fentanyl, and sufentanil have a higher speed for reaching from plasma to their effect site (mainly CNS) compared with morphine and its metabolites (Lotsch 2005; Ing Lorenzini et al. 2012).

Another concept considered important for opioid infusions used as acute pain management is the context-sensitive half-life (CSHL) considered as the time interval from discontinuation of the infusion until gaining a plasma level of the drug half as much of the time of infusion discontinuation; of course, the infusion should be discontinued after gaining a steady-state plasma level of the drug; among some other pharmacokinetic and pharmacodynamic indicators, *time to equilibrate after start of infusion* and "CSHL" are two very important factors that could help us chose a more appropriate analgesic in acute postoperative pain management. In this regard, remifentanil and alfentanil have both short "plasma-CNS equilibration time" and short CSHL; the lowest CSHL among all the opioids belongs to remifentanil; also, due to their metabolism, none of these four compounds would impose much considerable problem due to drug overdosage in patients with *renal impairment*; studies have shown that administering infusion of short-acting opioids could decrease the time necessary for postoperative mechanical ventilation and help earlier ventilator weaning so they could decrease the "ICU length of stay" (Bennett and Stanley 1979; Hachenberg 2000; Servin 2003, 2008; Murphy 2005; Guggenberger et al. 2006; Servin and Billard 2008; Futier et al. 2012).

#### Fentanyl

Fentanyl is a very potent opioid being about 80–120 times more potent than morphine, though its receptor affinity is three times more than morphine. Since fentanyl is highly lipid soluble (about 150 times more lipid soluble than morphine), it can bypass the blood–brain barrier (BBB) so much faster than the water-soluble morphine, hence, creating its analgesic effects more rapidly than morphine (either administered as IV, IM, intrathecal, or other routes).

Fentanyl is metabolized by the liver and does not have an active metabolite. This is why its clearance is not impaired in renal diseases but prolonged effects of the drug are well anticipated in liver diseases. Another interesting issue regarding fentanyl is that the drug undergoes active storage in lungs; so nearly two thirds of fentanyl is inactivated in the first pass of the lung.

Bolus doses of fentanyl create their analgesic effect so soon without much residual effects. On the other hand, the effects of infusion doses of fentanyl are not much similar. In other words, due to its high lipophilicity, fentanyl infusion leads to accumulated amounts of drug in adipose tissues, and when the infusion is disconnected, the infused amounts of fentanyl are released into plasma. This is why the effects of prolonged fentanyl infusion are not offset immediately after discontinuation of the infusion; this is especially very important after prolonged infusion of the drug, which could lead to very prolonged drug effects after longtime infusion. Pharmacologically speaking, context-sensitive halftime of fentanyl increases along with the saturation of inactive sites.

However, it is recommended to use fentanyl infusion as the following dosage for having adequate sedation while preventing prolonged residual effects (Hachenberg 2000; Hudson et al. 2002; George et al. 2010):

- Start fentanyl administration drug with a primary bolus dose of 1–2 μg/kg of the drug.
- At the same time, start an IV infusion of 1–3 μg/kg/h.
- Depending on patient needs, adjust the infusion dose, especially if the patient has a history of preoperative drug use.
- Adding patient-controlled analgesia (PCA) route with a dose of 0.1–1 μg/kg for each bolus (depending on patient needs) and a lock time interval about 15 min to the background IV infusion for the relatively awake patient leads to excellent analgesia with good satisfaction and cooperation with limited side effects.
- This method mandates extreme cautious and close monitoring regarding respiratory depression, including respiratory rate, pulse oximeter, and end tidal $CO_2$.
- Fentanyl is accumulated in patients with hepatic impairment due to drug accumulation, though this is not a major problem in patients with renal impairment.

### Sufentanil

Sufentanil is another opioid synthetic compound which is about 5–10 times more potent than fentanyl. Being extremely lipid soluble with a very high plasma protein-binding capacity, sufentanil is metabolized mainly in the liver. So sufentanil pharmacokinetics (like fentanyl and alfentanil) is not very much affected in patients with renal disease; however, its effects are significantly prolonged in patients with hepatic disease due to impaired hepatic metabolism and the resulting drug accumulation. Prolonged infusions of sufentanil are offset much sooner than comparable analgesic doses of fentanyl or alfentanil. This is why IV sufentanil infusions do not demonstrate as much long sedation effects as fentanyl. Of course, the clinical effects of alfentanil are presented sooner than sufentanil and fentanyl; i.e., the time lag between plasma levels and effect site (CNS) is shorter in alfentanil (about 1 min) compared with sufentanil (about 6 min) and fentanyl (about 7 min); however, CSHL of sufentanil is shorter than alfentanil and of course fentanyl; the CSHL order after 3 h of IV infusion is sufentanil (30 min), alfentanil (50–60 min), and fentanyl (250 min) in increasing order; in other words, after discontinuation of equivalent doses of IV infusion, the drug effects would

disappear first in sufentanil, then alfentanil, and finally, fentanyl; this effect is mainly due to larger sufentanil volume of distribution. Of course, as discussed later, the effects of remifentanil would disappear very much sooner than all the other three compounds; *vide infra* (Kapila et al. 1995; Bosilkovska et al. 2012; Jeleazcov et al. 2012).

### Alfentanil

Alfentanil is another opioid compound similar to fentanyl but 5–10 times less potent than fentanyl. Its clinical effects are presented very shortly, 1 min after IV administration, mainly due to its very high lipid solubility which could bypass the BBB very fast; its lipid solubility is even more than fentanyl. So, alfentanil pharmacokinetics (like fentanyl and sufentanil) is not very much affected in patients with renal disease; however, its effects are significantly prolonged in patients with hepatic disease due to impaired hepatic metabolism and the resulting drug accumulation. As mentioned in the previous paragraph, its CSHL is shorter than fentanyl and longer than sufentanil (Kapila et al. 1995; Bosilkovska et al. 2012; Jeleazcov et al. 2012).

### Remifentanil

Remifentanil is the newest version of synthetic opioids, being a potent mu agonist, having an analgesic potency "equal to fentanyl and 20–30 times more potent than alfentanil." However, remifentanil has a very short start time lag (1 min); more importantly, it has the shortest possible time (among all the opioids) for its effects to be offset after discontinuation of drug infusion. The following are among the most important pharmacologic and clinical features of remifentanil (Kapila et al. 1995; Hachenberg 2000; Servin 2003; Lotsch 2005; Murphy 2005; Scott and Perry 2005; Lahtinen et al. 2008; Servin and Billard 2008; Staahl et al. 2009; Olofsen et al. 2010a, b; Ing Lorenzini et al. 2012):

- Time interval from start of drug administration until presentation of its clinical effects is about 1 min (i.e., very fast onset).
- Its CSHL being as short as 3–5 min irrespective of the duration of IV infusion (the shortest CSHL among all the opioid compounds).
- The drug must be used as a continuous infusion as long as the patient has pain.
- The opioid effects of the drug, including respiratory depression, are offset in just 3–5 min after discontinuation of infusion irrespective of the duration of the infusion.
- Acute postoperative pain management in patients under anesthesia using remifentanil as the main opioid mandates considering an appropriate agent as soon as the remifentanil infusion is set off, or remifentanil infusion with its analgesic dose (and not the anesthetic dose) should be continued postoperatively.
- The main mechanism of remifentanil metabolism is *rapid hydrolysis* by nonspecific esterase found in both tissue and plasma, which takes a very short time for drug disappearance and leaves inactive drug metabolites.
- The drug metabolism mandates infusion of the drug as the main effective mechanism of action; its bolus administration should be done very cautiously since

bolus dose has the possibility for severe bradycardia, hypotension, decreased cardiac output, and cardiac arrest.
- Its analgesic dose is 0.05–1 μg/kg/min based on ideal body mass.
- Only IV route is recommended; never use intrathecal or epidural routes for its administration due to glycine added to drug combination.
- Remifentanil is the only opioid with no special consideration in patients with either renal or hepatic regarding its metabolism.

### 11.8.2 Alpha 2 Agonists

α2 adrenergic agonists can cause analgesia, sedation, and sympatholysis. These agents are primarily known in practice as clonidine (natural) and its synthetic analog, dexmedetomidine, which is a pure α2 adrenergic agonist and has a half-life of 2–3 h. They could be administered orally, intrathecally, or through intravenous administration. The mechanism of action in these agents is creation of sedation through stimulation of α2-receptors in the locus ceruleus and creation of analgesia through stimulation of α2-receptors within the locus ceruleus and the spinal cord; also, these agents could enhance the analgesic effects of the opioids via an unknown mechanism of action. Their clinical effects could be classified after systemic administration (antinociception and sedation) and intrathecal administration (only antinociception). There are reports that have mentioned tolerance to these agents after their prolonged administration. Their perioperative effects include increased stability of the hemodynamic parameters accompanied with decreased perioperative myocardial ischemia; also, decreased need for analgesic agents is another potential benefit of these agents while these agents could decrease postoperative opioid consumption, pain intensity, and nausea, accompanied with decreased use of analgesics, beta-blockers, antiemetics, epinephrine, and diuretics when used as sedative for post-CABG patients. Also, they might have some protective effects in a number of organs. However, overdose of these agents could induce excessive postoperative sedation accompanied with postoperative hemodynamic instability, bradycardia, and/or hypotension with bradycardia, at times mandating pharmacologic treatment (Hogue et al. 2002; Herr et al. 2003; Buvanendran and Kroin 2009; Blaudszun et al. 2012; Lin et al. 2012).

### 11.8.3 Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Having analgesic and anti-inflammatory properties, a number of agents are categorized in this class of analgesics. Their main mechanism of action is blockade of cyclooxygenase (COX) enzyme leading to prostaglandin synthesis inhibition described by Vane in 1971 for the first time. Their analgesic mechanism is theoretically classified as two main groups: traditional NSAIDs inhibiting COX in a nonselective manner and relatively newer class of NSAIDs which inhibit COX-2 in a selective manner. Selective COX-2 inhibitors were produced in order to decrease

the unwanted effects of nonselective inhibition of COX-1 by traditional NSAIDs, especially regarding the GI mucosa; however, their merit was not completely fulfilled because of the deep concern of potential unwanted cardiac effects of COX-2 inhibitors. NSAIDs are used frequently in the perioperative period; however, they are used usually in combination with other analgesic methods (mainly in combination with opioids, local anesthetics, or regional techniques) as a multimodal analgesic technique. NSAIDs are clinically effective in suppression of acute postoperative pain; in decreasing the need for postoperative opioid use, an effect named as opioid-sparing effect; and also, in improving the clinical outcome. If contraindications of NSAIDs are considered logically, accompanied with close observation of their potential side effects, these agents could be used cautiously and safely. Potential contraindications of NSAIDs are elderly people, heart failure, hypovolemic states, cirrhotic patients, renal failure, history of active GI tract disease and peptic ulcer disease, active bleeding diathesis, and pregnant patients (Griffin 1998; Tenenbaum 1999; Visser et al. 2002; Aldington et al. 2005; Brown et al. 2006; Langford and Mehta 2006; Munir et al. 2007; Rainsford 2007; Dajani and Islam 2008; McCormack 2011; Moore et al. 2011; Barletta 2012; Derry and Moore 2012; Khan and Fraser 2012).

The most important adverse effects of NSAIDs are as follows:

1. Gastrointestinal complications which could lead to serious and life-threatening hemorrhage, especially in postoperative period of cardiac surgery due to concomitant administration of anticoagulants.
2. Increased risk of bleeding which could be a potential complication in patients receiving neuraxial block for postoperative pain suppression.
3. Acute renal ischemia, especially if administered concomitantly with diuretics, angiotensin converting enzyme inhibitors ("ACE inhibitors"), and/or angiotensin receptor antagonists "ARA"; this drug combination is known as the "triple whammy" (Loboz and Shenfield 2005).

NSAIDs as adjuvant analgesics could reduce the dose of opioids needed for acute pain suppression in postoperative period; the concomitant administration of NSAIDs with opioids helps us to administer them, while this method of NSAID use does not create clinically important renal impairments, though they might be able to decrease renal function during the early postoperative period in a transient and insignificant mode; meanwhile, these agents do not boost the risk of postoperative renal failure in cardiac surgery patients would they be prescribed within a logical dose range and avoiding their contraindications (Bainbridge et al. 2006a; Ong et al. 2007; Buvanendran and Kroin 2009; Frampton and Quinlan 2009; Acharya and Dunning 2010; Barletta 2012).

#### 11.8.3.1 Paracetamol

Paracetamol (*N*-acetyl-*p*-aminophenol) is one of the most common analgesics used worldwide, mainly acting through central blockade of acute pain pathways and creating mild to moderate analgesia and mild anti-inflammatory effects. Its mechanism is not fully elucidated yet; however, some clinicians consider paracetamol as one of NSAIDs, though it does not have the same mechanism as classic drugs of this

category. Its main toxicity could be after large doses to create hepatotoxicity, manifested much earlier in alcoholics. Its analgesic properties are not so much considerable, especially in cardiac surgery patients and the drug is recommended just as part of a multimodal analgesic regimen (Lahtinen et al. 2002; Fayaz et al. 2004; Pettersson et al. 2005; McDaid et al. 2010; Maund et al. 2011; Tzortzopoulou et al. 2011).

### 11.8.4 Other Pharmaceutical Agents

Among the other pharmaceuticals used for acute pain suppression in cardiac surgery patients, a number of other agents could be mentioned, including the following:

#### 11.8.4.1 Ketamine

This is an intravenous anesthetic, mainly acting through "N-methyl-D-aspartate receptor" blockade; this drug could suppress acute pain effectively by a mechanism completely different from opioids: it acts mainly through dissociative anesthesia, "i.e., a combination of analgesia, hallucination, catalepsy, and some degrees of amnesia"; so ketamine does not cause respiratory depression as much as opioids and also does not perturb the hemodynamic status as much. However, due to unwanted clinical experience of the patients (known as emergence reactions), it is strongly recommended that ketamine should *not be used solely* unless preceded by an amnestic agent (like one of the benzodiazepine family); otherwise, the patients would have a *very bad experience* from the effects of the drug; however, a number of studies have demonstrated fewer unwanted effects of ketamine when administered as the S(+)-ketamine isomer. Currently, smaller doses of the drug are used as a part of a multimodal analgesic regimen, especially for thoracic incisions, in such a way that the needed amount of other analgesic drugs, especially opioids, is decreased, possibly improving the respiratory function. Ketamine could be used through many different routes including intravenous or intravenous patient-controlled analgesia (IV or IV-PCA). Some studies have claimed an anti-inflammatory effect for ketamine in patients undergoing CPB, possibly through its mechanism of action: NMDA antagonism (Lahtinen et al. 2004; Bell et al. 2006; Michelet et al. 2007; Buvanendran and Kroin 2009; Suzuki 2009; Carstensen and Moller 2010; Mathews et al. 2012).

#### 11.8.4.2 Magnesium sulfate ($MgSO_4$)

This ionic compound has gained frequent attention during recent years; its analgesic mechanism is mainly through calcium channel antagonism and NMDA antagonism; however, bolus doses of the drug could lead to asystole and accumulation of the drug in the blood, "i.e., overdose" could lead to severe afterload reduction and, hence, hypotension. Anti-inflammatory effects of magnesium sulfate in patients undergoing CPB have been observed in a number of studies (Ferasatkish et al. 2008; Buvanendran and Kroin 2009; James 2009).

#### 11.8.4.3 Gabapentin or Pregabalin

This is mainly an anticonvulsant agent belonging to a class of drugs known as "alpha-2-delta receptor modulators," also used for management of chronic pain; its mechanism of action is inhibition of glutamate release through NMDA antagonism. Gabapentin has been used for treatment of acute pain as an adjuvant in the multimodal analgesia regimen (Ucak et al. 2011). Pregabalin is also an anticonvulsant agent inhibiting the voltage-dependent calcium channel in CNS leading to inhibition of release of a number of agents including glutamate. Its use as an analgesic for acute pain suppression is off-label and as one of the agents in multimodal analgesia regimen (Buvanendran and Kroin 2009; Dauri et al. 2009; Graterol and Linter 2012).

### 11.8.5 Multimodal Analgesia

Multimodal or "balanced" analgesia is a method of analgesia which considers the multistep nature of pain. In acute pain management, this method involves administration of analgesics throughout the perioperative period; so pain management is performed through administration of more than one single drug (opioids plus nonopioids), or even we can add non-pharmacologic analgesia methods to our list of pharmacologic analgesics. Adjuvant analgesics (i.e., drugs which their primary effect is not necessarily analgesia) and non-pharmacologic analgesia methods are mainly added to our battery of opioid compounds and the wide range of opioid administration. The main goals of multimodal analgesia are (Kehlet and Dahl 1993; White 2008; Buvanendran and Kroin 2009; Gandhi et al. 2011):

- Create additive analgesia from administration of different classes of analgesic methods.
- Decrease the dose of each analgesic modality.
- Experience less unwanted side effects of each drug or non-drug method.
- Counteract pain at different levels, i.e., at the level of CNS, spinal cord, peripheral nerves, wound site, etc.
- Decrease time duration of recovery from surgery.

### 11.8.6 Patient-Controlled Analgesia

During the last decades, patient-controlled analgesia (PCA) has been proposed to replace the conventional method of analgesia prescription, in order to increase the efficacy of analgesic methods. Among its benefits, increased patient autonomy, decreased time from pain sensation until receiving analgesics, more matching of analgesics with patient demands, and decreased frequency of some complications of opioids like nausea and vomiting have been mentioned; however, the efficacy of the method is not yet proved. Compared with intramuscular analgesics, PCA is more effective; however, compared with nurse-administered intravenous (IV) analgesia or epidural PCA, it is not yet determined which method is more effective. Anyway, in order to have a successful PCA, some studies suggest (Dolin et al. 2002; Bainbridge et al. 2006b; Hudcova et al. 2006; Mota et al. 2010) the following:

- Using a baseline analgesic infusion added by PCA which could prevent unwanted effects of delayed analgesia administration with concomitant effective analgesia.
- Baseline opioids added to other analgesics could increase the efficacy of pain management.
- Respiratory depression should always be considered as a potential risk.
- Usually, a baseline appropriate PCA dose accompanied with lockout interval should be adjusted for each patient.
- If there is no sufficient patient cooperation, the method would not work effectively, and so its use should be discouraged.

## 11.9 Regional Anesthetic Techniques for Acute Pain Suppression in Cardiac Surgeries

There are a number of regional anesthetic techniques used for acute pain suppression in cardiac surgery patients, each having their benefits and drawbacks. These techniques include the following; however, they are not limited just to the following list:

- Infiltration of local anesthetic in wound
- Intercostal nerve block
- Intrapleural infiltration of local anesthetics
- Neuraxial analgesia (paravertebral, intrathecal, thoracic epidural)

### 11.9.1 Infiltration of Local Anesthetics in Wound

This is an effective method in cardiac surgery patients especially when used as an adjunct to other analgesic methods for controlling acute postoperative pain and administered as parasternal approach or, possibly, directly into the surgical wound; we could control sternotomy-related acute pain and also pain related to chest tubes and thoracic pain. This method has two characteristics in order to be effective for pain control:

- It is better to use this technique as "post-incision infiltration method" of local anesthetic; however, pre-incision local anesthetic infiltration is "equivocal" since acute postoperative pain in cardiac surgery patients is originated mainly from sternotomy.
- It should be used primarily in patients after sternotomy.

Infusion of local anesthetic directly into the surgical wound is another possible method, with tissue necrosis being the most common potential complication; however, cellulitis, infection, and tissue necrosis of the wound are very rare after cardiac surgery. In cardiac surgery patients, it is possible that the use of bilateral catheters for continuous infusion of local anesthetics could be even more effective, when used as a part of multimodal analgesia technique (Dowling et al. 2003; White et al. 2003; Chaney 2005b; McDonald et al. 2005; Kocabas et al. 2008; Buvanendran and Kroin 2009; Eljezi et al. 2012).

### 11.9.2 Intercostals Nerve Block

This is a simple and efficient method for administration of local anesthetic agents into the intercostals neurovascular bundle, which could be as an effective adjuvant analgesic method for acute postoperative pain suppression, causing pain temporal blockade; however, it would last between 6 and 12 h unless an indwelling catheter is placed adjacent to the intercostal nerves or repeated injections are needed. The block is better to be performed under direct vision, i.e., before chest closure by the surgeon or after the operation by injecting the local anesthetics into intercostal nerves through the subcostal approach for each of the nerves. However, prophylactic administration (i.e., before surgical incision) is equivocal. Ropivacaine (0.5–0.75 %) or bupivacaine (0.25–0.5 %) is usually used for this purpose (Barr et al. 2007; Chaudhary et al. 2012).

### 11.9.3 Intrapleural Infiltration of Local Anesthetics

This method involves administration of local anesthetics between the visceral and parietal pleura. The main origin of pain is parietal pleura; however, the proposed mechanism of analgesia in this method is diffusion of local anesthetics in the potential space between the two pleural layers leading to diffusion of a very thin layer of local anesthetics distributed between the two pleura layers and, finally, blocking pain, though some studies are controversial regarding its clinical outcome. Local anesthetics may be administered as a single shot or continuous infusion through a catheter. The method has a number of limitations:

- Intact anatomy and physiology of the pleural layers.
- If the patient has chest tubes, it may lead to leakage of local anesthetics into the chest bottle.
- The lung is not damaged (e.g., after lung surgery).
- There is the possibility for systemic absorption of local anesthetics (Chaney 2005b; May and Bartram 2007; Ogus et al. 2007; Mansouri et al. 2011; Esme et al. 2012).

### 11.9.4 Neuraxial Blocks (Paravertebral, Intrathecal, Thoracic Epidural)

#### 11.9.4.1 Thoracic Paravertebral Block

Thoracic paravertebral block is considered as one of the neuraxial analgesia techniques by some authors; being considered an old technique, it was reappraised just in the last two to three decades used for local anesthetic blockade through the paravertebral spaces, so to some clinicians it is not as much familiar as intrathecal and epidural techniques. Paravertebral spaces are located bilaterally, in each side; they are anatomically located lateral to the spine, where the nerve endings pass through them to go from spine to end in their related nerve fibers (Fig. 11.1). Thoracic epidural

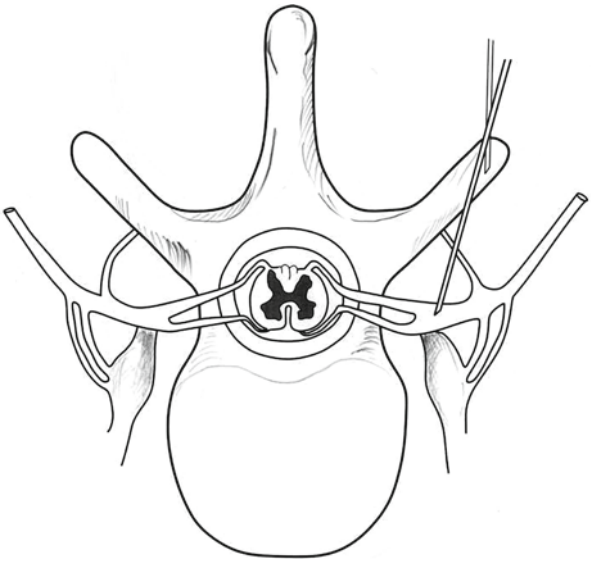


**Fig. 11.1** A schematic representation of thoracic paravertebral block, demonstrating the spine body and other parts of the spine, spinal cord, and its nerve roots and the location where paravertebral needle is introduced (*on right*)

analgesia usually considered as the gold standard of care for acute postoperative pain management, namely, in some procedures like thoracic and cardiac surgeries, especially regarding cardiovascular and pulmonary outcomes; however, thoracic paravertebral block could be a good potential alternative when performed appropriately. The interested reader is referred to study the related referenced for the classic approach of Eason and Wyatt in performing thoracic paravertebral block; however, a summary of the technique is described and includes a step-by-step process:

- Placing the patient in sitting position with the spine being curved as a "C" letter or in lateral decubitus position, i.e., "fetal position"
- Using strict aseptic technique
- Finding and localizing the 6th cervical vertebra (C6)
- Localization of the spinous process at the level of 4th thoracic vertebra (T4)
- Going 3–6 cm laterally in horizontal direction
- Creating a local wheal by local anesthetics in awake patients
- Inserting the needle in a perpendicular direction
- Reaching the transverse process (Fig. 11.1)
- Walking downward and lateral until a sense of "loss of resistance" is reached
- Injection of local anesthetic slowly

The main benefits of thoracic paravertebral block compared with thoracic epidural could be considered as the following:

- Being less invasive
- Very lower risk for epidural hematoma formation
- Less hemodynamic derangement (albeit some degrees of sympathetic block exist)
- Fewer contraindications

- Easier technique
- Lower incidence of complications (especially neurologic complications)
- Very few reports of postoperative complications like nausea, vomiting, and urinary retention
- Very rare reports of systemic toxicity due to local anesthetics, though very high doses are used in this technique

Some clinicians believe that bilateral thoracic paravertebral block is not as effective as thoracic epidural analgesia in suppressing acute pain-induced stress response, especially in major procedures like cardiac surgery, while there are others who believe exactly vice versa and consider thoracic paravertebral block as effective as and even at times more effective than thoracic epidural analgesia improving clinical outcomes with reduced rate of complications (Eason and Wyatt 1979; Davies et al. 2006; Daly and Myles 2009; Scarci et al. 2010; Thavaneswaran et al. 2010; Richardson et al. 2011; Rawal 2012).

#### 11.9.4.2 Spinal (Intrathecal) Analgesia

Postoperative analgesia through intrathecal (IT) administration of drugs is a very popular method among clinicians for noncardiac surgeries of the abdominal and pelvic area and/or lower extremities used for more than 100 years. However, in cardiac surgeries, the idea of IT analgesia was first described in 1980 which included IT morphine administration (Mathews and Abrams 1980). Later, IT administration of local anesthetics was also used which was performed through lumbar interspaces accompanied with downward positioning of the patient (usually after induction of general anesthesia) to deliberately create a high level of spinal block. Theoretically, this method appeared effective, since spinal receptors of pain are located in substantia gelatinosa of Rolando, posterior horn of the spinal cord (Wu et al. 1999; Furue et al. 2004; Fujita and Kumamoto 2006); hence, the drug could attach the receptors with much easier access and higher efficacy than the intravenous route of drug administration of analgesics. Potential benefits of this method would be possibly the following:

- Improved postoperative analgesia with better quality of pain control
- Fewer postoperative respiratory problems
- Decreased level of postoperative stress response
- Improved clinical outcome

The first studies favored IT morphine usage for cardiac surgery, and even during the recent years, some studies approved it. These studies have usually administered a wide range of IT opioid "from 0.3 to 10 mg IT morphine as single shot" administered just before induction of general anesthesia, just after induction of anesthesia, or, even, during the early postoperative period; however, further studies have demonstrated that IT opioid for cardiac surgery could not suppress the level of stress response. Also, improved postoperative analgesia and decreased respiratory problems are gained at the expense of unwanted opioid effects in the postoperative period including pruritus, respiratory depression (early or delayed), urinary retention, nausea and vomiting, and delayed extubation. To the above should be added the fact that shorter-acting opioids are possibly less effective during the

postoperative period, shifting the choice for IT opioids to opioid compounds like morphine with a longer time profile in order to have adequate postoperative analgesia which at the same time would result in increased chance for postoperative opioid complications, especially delayed postoperative respiratory depression (which is usually due to delayed or cephalad migration of water-soluble opioids like morphine) and delayed extubation; also, we should add to the above items that the unwanted respiratory depression and delayed extubation are aggravated by concomitant use of other sedatives and anesthetics; besides, some other factors like underlying age could not be neglected; elderly people are at increased risk for unwanted postoperative respiratory depression of IT opioids (Stoelting 1989; Chaney et al. 1997, 1999; Boulanger et al. 2002; Liu et al. 2004; Jacobsohn et al. 2005; Parlow et al. 2005; Chaney 2006; Meylan et al. 2009; Sultan et al. 2011).

On the other hand, IT administration of local anesthetics in a way to create high spinal levels of block covering the spinal thoracic nerve roots could create a sufficient sensory block to decrease the level of stress response; however, simultaneous widespread sympathetic block associated with this method leads to repeated episodes of hypotension and hemodynamic instability mandating administration of vasopressors and inotropes. Finally, most studies have claimed that benefits of IT local anesthetics could not clearly outweigh its risks. Besides, the effects of IT local anesthetics usually last shorter duration and often disappear or vanish during the early postoperative hours.

Finally, though the risk of neurologic complications (including epidural hematoma) is much lower in spinal technique compared to thoracic epidural technique, it is not negligible and could be as high as 1:1,500 up to 1:220,000. Detailed discussion about prevention and management of this complication is presented just in the next pages, and the reader is addressed to refer there (Horlocker et al. 2010).

In summary, creating analgesia through administration of IT opioids or IT local anesthetics in cardiac surgery patients could not improve the clinical outcome sharply and is not usually considered as a main analgesic method in such patients.

#### 11.9.4.3 Thoracic Epidural Analgesia

Thoracic epidural analgesia (TEA) is considered by many as the *gold standard* of care for acute postoperative pain management in adult cardiac surgery mainly for nearly two decades, because of the following features:

- Adequate and qualitative analgesia (both intraoperative and postoperative).
- Efficient suppression of stress response (induced by CPB and the surgery).
- Thoracic sympathectomy which is relatively selective in TEA and does not involve total sympathetic block as seen in total spinal anesthesia.
- Improved myocardial blood flow (mainly due to thoracic sympathetic block which covers cardiac sympathetic nerves, T1–T5) is associated with increased diameter of the coronary arteries (especially the stenotic epicardial coronary arteries).
- Improved left ventricular function due to the previous item.
- Decreased level of myocardial ischemia mainly due to cardiac sympathetic block (T1–T5).

- Cardiac sympathetic blockade (T1–T5) would lead to decreased need for postoperative use of beta-blockers.
- Decreased incidence of cardiac arrhythmias mainly after improved myocardial perfusion status.
- Earlier postoperative extubation time comparable or even earlier than conventional general anesthesia mainly due to decreased need for rescue analgesia in postoperative period.
- Improved postoperative pulmonary function possibly due to decreased level of stress response, improved postoperative analgesia, improved patient ability for deep breath, and earlier postoperative ambulation.
- The possibility to perform "awake" off-pump coronary bypass surgery using TEA as the main anesthetic method (Karagoz et al. 2000; Schachner et al. 2003; Campos 2009; Royse 2009; Breivik et al. 2010; Bedirli et al. 2011; Caputo et al. 2011; Watanabe et al. 2011; Toda et al. 2013).

However, during the last years, some clinicians have seriously criticized TEA for cardiac surgery and questioned its validity as "gold standard of care" for cardiac surgery. Their reason is mainly the very serious associated risk of "epidural hematoma" which could heavily outweigh the above detailed list of benefits. The issue is that in patients undergoing cardiac surgery receiving very high doses of perioperative anticoagulants and also under full systemic heparinization, TEA is potentially much more "risky" than all the other surgical patient groups. Based on a variety of studies, the risk of epidural hematoma after TEA for cardiac surgery is widely divergent, ranging from 1:1,500 to 1:150,000, though in some patient groups, the risk is *increasing* as much as 1:3,000 (upper). Also, during the postoperative period, when trying to normalize the coagulation profile in order to remove the catheter, there is an increased risk of thromboembolic events which should be considered as another potential complication (Schwann and Chaney 2003; Chaney 2005a, b, 2006, 2009; Chaney and Labovsky 2005; Breivik et al. 2010; Horlocker et al. 2010; Moen 2010; Svircevic et al. 2011a, b; Gu et al. 2012; Rawal 2012).

Most importantly, clinicians should have sophisticated care accompanied with vigilance and a very high degree of suspicion during early postoperative hours in order to be able to detect new onset epidural hematoma through surgical evacuation in its "golden time" of neurologic recovery. This golden time is good if less than 8 h, partial if between 8 and 24 h, and poor if no intervention is performed (Horlocker et al. 2010). Occurrence of epidural hematoma is possible during needle introduction, bolus drug injection, catheter insertion, systemic heparinization period until restoration of coagulation profile, and, finally, during or after catheter removal; however, we always have to keep in mind that occurrence of epidural hematoma and its neurologic complications is a *catastrophe*.

Based on the 3rd version of the "American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guideline: Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy" released in 2010 and also the 2009 version of "Nordic guidelines for neuraxial blocks in disturbed haemostasis" released by "the Scandinavian Society of Anaesthesiology and Intensive

Care Medicine," the following items could help us prevent potential high risk patients:

- Underlying hemostatic disorders
- Dose and preoperative "drug-free" interval for anticoagulants
- Any preexisting anatomical disorders and malalignments in spine, spinal cord, vertebrae, and spinal arteries and vessels
- Elderly
- Technical problems when introducing the epidural needle or the catheter
- Underlying liver or kidney disorders imposing patient to abnormal coagulation profile (Breivik et al. 2010; Horlocker et al. 2010)

Also, according to the 2010 American Society of Regional Anesthesia and Pain Medicine guideline and the 2009 the Scandinavian Society of Anaesthesiology and Intensive Care Medicine, the following recommendations should be kept in mind if there is the possibility of epidural hematoma after neuraxial block:

1. Do not use neuraxial blocks if the patient has a "known underlying coagulopathy" no matter what the etiology is.
2. If the epidural needle tap is traumatic, surgery should be postponed for at least 24 h.
3. Time interval from the end of the epidural technique (including needle tap and drug administration) until start of systemic heparinization should be at least more than 60 min.
4. The clinicians should adhere strictly to the administration doses of heparin and its reversal agents (try strictly to administer as low as possible doses of heparin which are adjusted for the *shortest duration* for the desired *therapeutic objective*).
5. Removing the epidural catheter is permitted only when the coagulation profile tests are resumed to normal values; besides, catheter removal should be followed by strict control of signs and symptoms for any potential epidural hematoma (Breivik et al. 2010; Horlocker et al. 2010).

## References

(2012) Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 116:248–273

Acharya M, Dunning J (2010) Does the use of non-steroidal anti-inflammatory drugs after cardiac surgery increase the risk of renal failure? Interact Cardiovasc Thorac Surg 11:461–467

Aida N, Shibuya M, Yoshino K, Komoda M, Inoue T (2002) Respiratory muscle stretch gymnastics in patients with post coronary artery bypass grafting pain: impact on respiratory muscle function, activity, mood and exercise capacity. J Med Dent Sci 49:157–170

Aldington S, Shirtcliffe P, Weatherall M, Beasley R (2005) Increased risk of cardiovascular events with parecoxib/valdecoxib: a systematic review and meta-analysis. N Z Med J 118:U1755

Allegaert K, Tibboel D, van den Anker J (2013) Pharmacological treatment of neonatal pain: in search of a new equipoise. Semin Fetal Neonatal Med 18:42–47

Anderson PG, Cutshall SM (2007) Massage therapy: a comfort intervention for cardiac surgery patients. Clin Nurse Spec 21:161–165, quiz 166–167

Andrieu G, Roth B, Ousmane L, Castaner M, Petillot P, Vallet B, Villers A, Lebuffe G (2009) The efficacy of intrathecal morphine with or without clonidine for postoperative analgesia after radical prostatectomy. Anesth Analg 108:1954–1957

Angst MS, Lazzeroni LC, Phillips NG, Drover DR, Tingle M, Ray A, Swan GE, Clark JD (2012) Aversive and reinforcing opioid effects: a pharmacogenomic twin study. Anesthesiology 117:22–37

Aslan FE, Badir A, Arli SK, Cakmakci H (2009) Patients' experience of pain after cardiac surgery. Contemp Nurse 34:48–54

Awad H, Abas M, Elgharably H, Tripathi R, Theofilos T, Bhandary S, Sai-Sudhakar C, Sen CK, Roy S (2012) Endogenous opioids in wound-site neutrophils of sternotomy patients. PLoS One 7:e47569

Azzopardi S, Lee G (2009) Health-related quality of life 2 years after coronary artery bypass graft surgery. J Cardiovasc Nurs 24:232–240

Bainbridge D, Cheng DC, Martin JE, Novick R (2006a) NSAID-analgesia, pain control and morbidity in cardiothoracic surgery. Can J Anaesth 53:46–59

Bainbridge D, Martin JE, Cheng DC (2006b) Patient-controlled versus nurse-controlled analgesia after cardiac surgery–a meta-analysis. Can J Anaesth 53:492–499

Ballan A, Lee G (2007) A comparative study of patient perceived quality of life pre and post coronary artery bypass graft surgery. Aust J Adv Nurs 24:24–28

Bar-El Y, Gilboa B, Unger N, Pud D, Eisenberg E (2005) Skeletonized versus pedicled internal mammary artery: impact of surgical technique on post CABG surgery pain. Eur J Cardiothorac Surg 27:1065–1069

Barletta JF (2012) Clinical and economic burden of opioid use for postsurgical pain: focus on ventilatory impairment and ileus. Pharmacotherapy 32:12S–18S

Barr AM, Tutungi E, Almeida AA (2007) Parasternal intercostal block with ropivacaine for pain management after cardiac surgery: a double-blind, randomized, controlled trial. J Cardiothorac Vasc Anesth 21:547–553

Bedirli N, Akyurek N, Kurtipek O, Kavutcu M, Kartal S, Bayraktar AC (2011) Thoracic epidural bupivacaine attenuates inflammatory response, intestinal lipid peroxidation, oxidative injury, and mucosal apoptosis induced by mesenteric ischemia/reperfusion. Anesth Analg 113:1226–1232

Bell G, Dickson U, Arana A, Robinson D, Marshall C, Morton N (2004) Remifentanil vs fentanyl/morphine for pain and stress control during pediatric cardiac surgery. Paediatr Anaesth 14:856–860

Bell RF, Dahl JB, Moore RA, Kalso E (2006) Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev:CD004603

Bennett GM, Stanley TH (1979) Cardiovascular effects of fentanyl during enflurane anesthesia in man. Anesth Analg 58:179–182

Blaudszun G, Lysakowski C, Elia N, Tramer MR (2012) Effect of perioperative systemic alpha2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. Anesthesiology 116:1312–1322

Bodnar RJ (2011) Endogenous opiates and behavior: 2010. Peptides 32(12):2522–2552

Borgermann J, Kanashnik A, Sossdorf M, Gummert J, Losche W (2010) Individual variability of response and non-response to acetyl salicylic acid after cardiac surgery. Platelets 21:610–615

Bortsov AV, Millikan RC, Belfer I, Boortz-Marx RL, Arora H, McLean SA (2012) mu-Opioid receptor gene A118G polymorphism predicts survival in patients with breast cancer. Anesthesiology 116:896–902

Bosilkovska M, Walder B, Besson M, Daali Y, Desmeules J (2012) Analgesics in patients with hepatic impairment: pharmacology and clinical implications. Drugs 72:1645–1669

Boulanger A, Perreault S, Choiniere M, Prieto I, Lavoie C, Laflamme C (2002) Intrathecal morphine after cardiac surgery. Ann Pharmacother 36:1337–1343

Bove A, Bellini M, Battaglia E, Bocchini R, Gambaccini D, Bove V, Pucciani F, Altomare DF, Dodi G, Sciaudone G, Falletto E, Piloni V (2012) Consensus statement AIGO/SICCR diagnosis and treatment of chronic constipation and obstructed defecation (Part II: Treatment). World J Gastroenterol 18:4994–5013

Breivik H, Bang U, Jalonen J, Vigfusson G, Alahuhta S, Lagerkranser M (2010) Nordic guidelines for neuraxial blocks in disturbed haemostasis from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine. Acta Anaesthesiol Scand 54:16–41

Brock C, Olesen SS, Olesen AE, Frokjaer JB, Andresen T, Drewes AM (2012) Opioid-induced bowel dysfunction: pathophysiology and management. Drugs 72:1847–1865

Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, Rostom A, Symmons D (2006) A comparison of the cost-effectiveness of five strategies for the prevention of non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling. Health Technol Assess 10:iii–iv, xi-xiii, 1–183

Bruce J, Drury N, Poobalan AS, Jeffrey RR, Smith WC, Chambers WA (2003) The prevalence of chronic chest and leg pain following cardiac surgery: a historical cohort study. Pain 104:265–273

Buvanendran A, Kroin JS (2009) Multimodal analgesia for controlling acute postoperative pain. Curr Opin Anaesthesiol 22:588–593

Campos JH (2009) Fast track in thoracic anesthesia and surgery. Curr Opin Anaesthesiol 22:1–3

Caputo M, Alwair H, Rogers CA, Pike K, Cohen A, Monk C, Tomkins S, Ryder I, Moscariello C, Lucchetti V, Angelini GD (2011) Thoracic epidural anesthesia improves early outcomes in patients undergoing off-pump coronary artery bypass surgery: a prospective, randomized, controlled trial. Anesthesiology 114:380–390

Carstensen M, Moller AM (2010) Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomized trials. Br J Anaesth 104:401–406

Chaney MA (2005a) Cardiac surgery and intrathecal/epidural techniques: at the crossroads? Can J Anaesth 52:783–788

Chaney MA (2005b) How important is postoperative pain after cardiac surgery? J Cardiothorac Vasc Anesth 19:705–707

Chaney MA (2006) Intrathecal and epidural anesthesia and analgesia for cardiac surgery. Anesth Analg 102:45–64

Chaney MA (2009) Thoracic epidural anaesthesia in cardiac surgery–the current standing. Ann Card Anaesth 12:1–3

Chaney MA, Labovsky JK (2005) Thoracic epidural anesthesia and cardiac surgery: balancing postoperative risks associated with hematoma formation and thromboembolic phenomenon. J Cardiothorac Vasc Anesth 19:768–771

Chaney MA, Furry PA, Fluder EM, Slogoff S (1997) Intrathecal morphine for coronary artery bypass grafting and early extubation. Anesth Analg 84:241–248

Chaney MA, Nikolov MP, Blakeman BP, Bakhos M (1999) Intrathecal morphine for coronary artery bypass graft procedure and early extubation revisited. J Cardiothorac Vasc Anesth 13:574–578

Chaudhary V, Chauhan S, Choudhury M, Kiran U, Vasdev S, Talwar S (2012) Parasternal intercostal block with ropivacaine for postoperative analgesia in pediatric patients undergoing cardiac surgery: a double-blind, randomized, controlled study. J Cardiothorac Vasc Anesth 26:439–442

Cogan J (2010) Pain management after cardiac surgery. Semin Cardiothorac Vasc Anesth 14:201–204

Cuthbert AW (2011) Lubiprostone targets prostanoid EP(4) receptors in ovine airways. Br J Pharmacol 162:508–520

Dajani EZ, Islam K (2008) Cardiovascular and gastrointestinal toxicity of selective cyclo-oxygenase-2 inhibitors in man. J Physiol Pharmacol 59(Suppl 2):117–133

Daly DJ, Myles PS (2009) Update on the role of paravertebral blocks for thoracic surgery: are they worth it? Curr Opin Anaesthesiol 22:38–43

Dauri M, Faria S, Gatti A, Celidonio L, Carpenedo R, Sabato AF (2009) Gabapentin and pregabalin for the acute post-operative pain management. A systematic-narrative review of the recent clinical evidences. Curr Drug Targets 10:716–733

Davies RG, Myles PS, Graham JM (2006) A comparison of the analgesic efficacy and side-effects of paravertebral vs epidural blockade for thoracotomy–a systematic review and meta-analysis of randomized trials. Br J Anaesth 96:418–426

De Cosmo G, Aceto P, Gualtieri E, Congedo E (2009) Analgesia in thoracic surgery: review. Minerva Anestesiol 75:393–400

Derry S, Moore RA (2012) Single dose oral celecoxib for acute postoperative pain in adults. Cochrane Database Syst Rev 3, CD004233

Dick F, Hristic A, Roost-Krahenbuhl E, Aymard T, Weber A, Tevaearai HT, Carrel TP (2011) Persistent sensitivity disorders at the radial artery and saphenous vein graft harvest sites: a neglected side effect of coronary artery bypass grafting procedures. Eur J Cardiothorac Surg 40:221–226

Djafarzadeh S, Vuda M, Takala J, Jakob SM (2012) Effect of remifentanil on mitochondrial oxygen consumption of cultured human hepatocytes. PLoS One 7:e45195

Dolin SJ, Cashman JN, Bland JM (2002) Effectiveness of acute postoperative pain management: I. Evidence from published data. Br J Anaesth 89:409–423

Dowling R, Thielmeier K, Ghaly A, Barber D, Boice T, Dine A (2003) Improved pain control after cardiac surgery: results of a randomized, double-blind, clinical trial. J Thorac Cardiovasc Surg 126:1271–1278

Due MR, Piekarz AD, Wilson N, Feldman P, Ripsch MS, Chavez S, Yin H, Khanna R, White FA (2012) Neuroexcitatory effects of morphine-3-glucuronide are dependent on Toll-like receptor 4 signaling. J Neuroinflammation 9:200

Eason MJ, Wyatt R (1979) Paravertebral thoracic block-a reappraisal. Anaesthesia 34:638–642

Eljezi V, Duale C, Azarnoush K, Skrzypczak Y, Sautou V, Pereira B, Tsokanis I, Schoeffler P (2012) The analgesic effects of a bilateral sternal infusion of ropivacaine after cardiac surgery. Reg Anesth Pain Med 37:166–174

Engelman E, Marsala C (2013) Efficacy of adding clonidine to intrathecal morphine in acute postoperative pain: meta-analysis. Br J Anaesth 110(1):21–27

Eschenroeder AC, Vestal-Laborde AA, Sanchez ES, Robinson SE, Sato-Bigbee C (2012) Oligodendrocyte responses to buprenorphine uncover novel and opposing roles of mu-opioid- and nociceptin/orphanin FQ receptors in cell development: implications for drug addiction treatment during pregnancy. Glia 60:125–136

Esme H, Apiliogullari B, Duran FM, Yoldas B, Bekci TT (2012) Comparison between intermittent intravenous analgesia and intermittent paravertebral subpleural analgesia for pain relief after thoracotomy. Eur J Cardiothorac Surg 41:10–13

Everts B, Karlson BW, Herlitz J, Hedner T (1998) Morphine use and pharmacokinetics in patients with chest pain due to suspected or definite acute myocardial infarction. Eur J Pain 2:115–125

Farrell C, McConaghy P (2012) Perioperative management of patients taking treatment for chronic pain. BMJ 345:e4148

Fayaz MK, Abel RJ, Pugh SC, Hall JE, Djaiani G, Mecklenburgh JS (2004) Opioid-sparing effects of diclofenac and paracetamol lead to improved outcomes after cardiac surgery. J Cardiothorac Vasc Anesth 18:742–747

Ferasatkish R, Dabbagh A, Alavi M, Mollasadeghi G, Hydarpur E, Moghadam AA, Faritus ZS, Totonchi MZ (2008) Effect of magnesium sulfate on extubation time and acute pain in coronary artery bypass surgery. Acta Anaesthesiol Scand 52:1348–1352

Frampton C, Quinlan J (2009) Evidence for the use of non-steroidal anti-inflammatory drugs for acute pain in the post anaesthesia care unit. J Perioper Pract 19:418–423

Fujita T, Kumamoto E (2006) Inhibition by endomorphin-1 and endomorphin-2 of excitatory transmission in adult rat substantia gelatinosa neurons. Neuroscience 139:1095–1105

Furue H, Katafuchi T, Yoshimura M (2004) Sensory processing and functional reorganization of sensory transmission under pathological conditions in the spinal dorsal horn. Neurosci Res 48:361–368

Futier E, Chanques G, Cayot Constantin S, Vernis L, Barres A, Guerin R, Chartier C, Perbet S, Petit A, Jabaudon M, Bazin JE, Constantin JM (2012) Influence of opioid choice on mechanical ventilation duration and ICU length of stay. Minerva Anestesiol 78:46–53

Gallagher R, McKinley S, Dracup K (2004) Post discharge problems in women recovering from coronary artery bypass graft surgery. Aust Crit Care 17:160–165

Gandhi K, Heitz JW, Viscusi ER (2011) Challenges in acute pain management. Anesthesiol Clin 29:291–309

Garvin S, Muehlschlegel JD, Perry TE, Chen J, Liu KY, Fox AA, Collard CD, Aranki SF, Shernan SK, Body SC (2010) Postoperative activity, but not preoperative activity, of antithrombin is associated with major adverse cardiac events after coronary artery bypass graft surgery. Anesth Analg 111:862–869

Gehling M, Tryba M (2009) Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis. Anaesthesia 64:643–651

Geller AS (2011) Opioid overdose-related deaths. JAMA 306:379; author reply 380–371

George JA, Lin EE, Hanna MN, Murphy JD, Kumar K, Ko PS, Wu CL (2010) The effect of intravenous opioid patient-controlled analgesia with and without background infusion on respiratory depression: a meta-analysis. J Opioid Manag 6:47–54

Gjeilo KH, Klepstad P, Wahba A, Lydersen S, Stenseth R (2010) Chronic pain after cardiac surgery: a prospective study. Acta Anaesthesiol Scand 54:70–78

Glaser AM, Reyes-Vazquez C, Prieto-Gomez B, Burau K, Dafny N (2012) Morphine administration and abrupt cessation alter the behavioral diurnal activity pattern. Pharmacol Biochem Behav 101:544–552

Granier S, Manglik A, Kruse AC, Kobilka TS, Thian FS, Weis WI, Kobilka BK (2012) Structure of the delta-opioid receptor bound to naltrindole. Nature 485:400–404

Graterol J, Linter SP (2012) The effects of gabapentin on acute and chronic postoperative pain after coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 26:e26; author reply e26

Greenfield GT, Whitworth WA, Tavares LL, Wittenbraker MT, Wallace DM, Valdivia JA, Campbell K, Williams L, Black E, Pillai R, Caskey MP, Bladergroen MR (2001) Minimally invasive vein harvest and wound healing using the SaphLITE Retractor System. Ann Thorac Surg 72:S1046–S1049

Griesdale DE, Neufeld J, Dhillon D, Joo J, Sandhu S, Swinton F, Choi PT (2011) Risk factors for urinary retention after hip or knee replacement: a cohort study. Can J Anaesth 58:1097–1104

Griffin MR (1998) Epidemiology of nonsteroidal anti-inflammatory drug-associated gastrointestinal injury. Am J Med 104:23S–29S; discussion 41S–42S

Gu WJ, Wei CY, Huang DQ, Yin RX (2012) Meta-analysis of randomized controlled trials on the efficacy of thoracic epidural anesthesia in preventing atrial fibrillation after coronary artery bypass grafting. BMC Cardiovasc Disord 12:67

Guggenberger H, Schroeder TH, Vonthein R, Dieterich HJ, Shernan SK, Eltzschig HK (2006) Remifentanil or sufentanil for coronary surgery: comparison of postoperative respiratory impairment. Eur J Anaesthesiol 23:832–840

Guo P, East L, Arthur A (2012) A preoperative education intervention to reduce anxiety and improve recovery among Chinese cardiac patients: a randomized controlled trial. Int J Nurs Stud 49:129–137

Hachenberg T (2000) Perioperative management with short-acting intravenous anesthetics. Anaesthesiol Reanim 25:144–150

Hanna MH, Elliott KM, Fung M (2005) Randomized, double-blind study of the analgesic efficacy of morphine-6-glucuronide versus morphine sulfate for postoperative pain in major surgery. Anesthesiology 102:815–821

Hassan I, Jacobs AG, Baig ME, Van der Meyden CH (2006) Bilateral axillary and suprascapular neuropathy after coronary artery bypass surgery. Cardiovasc J S Afr 17:259–261

Herr DL, Sum-Ping ST, England M (2003) ICU sedation after coronary artery bypass graft surgery: dexmedetomidine-based versus propofol-based sedation regimens. J Cardiothorac Vasc Anesth 17:576–584

Hertle DN, Dreier JP, Woitzik J, Hartings JA, Bullock R, Okonkwo DO, Shutter LA, Vidgeon S, Strong AJ, Kowoll C, Dohmen C, Diedler J, Veltkamp R, Bruckner T, Unterberg AW, Sakowitz OW (2012) Effect of analgesics and sedatives on the occurrence of spreading depolarizations accompanying acute brain injury. Brain 135:2390–2398

Hicks RW, Hernandez J, Wanzer LJ (2012) Perioperative pharmacology: patient-controlled analgesia. AORN J 95:255–262, quiz 263–255

Hirose H, Amano A, Takanashi S, Takahashi A (2003) Skeletonized bilateral internal mammary artery grafting for patients with diabetes. Interact Cardiovasc Thorac Surg 2:287–292

Hogue CW Jr, Talke P, Stein PK, Richardson C, Domitrovich PP, Sessler DI (2002) Autonomic nervous system responses during sedative infusions of dexmedetomidine. Anesthesiology 97:592–598

Holzer P (2012) Non-analgesic effects of opioids: management of opioid-induced constipation by peripheral opioid receptor antagonists: prevention or withdrawal? Curr Pharm Des 18(37):6010–6020

Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, Brown DL, Heit JA, Mulroy MF, Rosenquist RW, Tryba M, Yuan CS (2010) Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). Reg Anesth Pain Med 35:64–101

Hudcova J, McNicol E, Quah C, Lau J, Carr DB (2006) Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. Cochrane Database Syst Rev:CD003348

Hudson RJ, Thomson IR, Henderson BT, Singh K, Harding G, Peterson DJ (2002) Validation of fentanyl pharmacokinetics in patients undergoing coronary artery bypass grafting. Can J Anaesth 49:388–392

Huffmyer J, Tashjian J, Raphael J, Jaeger JM (2012) Management of the patient for transcatheter aortic valve implantation in the perioperative period. Semin Cardiothorac Vasc Anesth 16:25–40

Hughes MM, Atayee RS, Best BM, Pesce AJ (2012) Observations on the metabolism of morphine to hydromorphone in pain patients. J Anal Toxicol 36:250–256

Hutchinson MR, Northcutt AL, Hiranita T, Wang X, Lewis SS, Thomas J, van Steeg K, Kopajtic TA, Loram LC, Sfregola C, Galer E, Miles NE, Bland ST, Amat J, Rozeske RR, Maslanik T, Chapman TR, Strand KA, Fleshner M, Bachtell RK, Somogyi AA, Yin H, Katz JL, Rice KC, Maier SF, Watkins LR (2012) Opioid activation of toll-like receptor 4 contributes to drug reinforcement. J Neurosci 32:11187–11200

Ing Lorenzini K, Daali Y, Dayer P, Desmeules J (2012) Pharmacokinetic-pharmacodynamic modelling of opioids in healthy human volunteers.A minireview. Basic Clin Pharmacol Toxicol 110:219–226

International Pain Summit of the International Association for the Study of Pain (2011) Declaration of Montreal: declaration that access to pain management is a fundamental human right. J Pain Palliat Care Pharmacother 25:29–31

Ishihara M, Ikesue H, Matsunaga H, Suemaru K, Kitaichi K, Suetsugu K, Oishi R, Sendo T, Araki H, Itoh Y (2012) A multi-institutional study analyzing effect of prophylactic medication for prevention of opioid-induced gastrointestinal dysfunction. Clin J Pain 28:373–381

Ishii Y, Iida N, Miyauchi Y, Mackenzie PI, Yamada H (2012) Inhibition of morphine glucuronidation in the liver microsomes of rats and humans by monoterpenoid alcohols. Biol Pharm Bull 35:1811–1817

Jacobsohn E, Lee TW, Amadeo RJ, Syslak PH, Debrouwere RG, Bell D, Klock PA, Tymkew H, Avidan M (2005) Low-dose intrathecal morphine does not delay early extubation after cardiac surgery. Can J Anaesth 52:848–857

James MF (2009) Magnesium: an emerging drug in anaesthesia. Br J Anaesth 103:465–467

Jayr C (1998) Repercussion of postoperative pain, benefits attending to treatment. Ann Fr Anesth Reanim 17:540–554

Jeleazcov C, Saari TI, Ihmsen H, Schuttler J, Fechner J (2012) Changes in total and unbound concentrations of sufentanil during target controlled infusion for cardiac surgery with cardiopulmonary bypass. Br J Anaesth 109:698–706

Jonjev Z, Selestiansky J, Redzek A, Radovanovic N (2000) Myocardial revascularization with skeletonized left mammary artery. Med Pregl 53:174–179

Jungquist CR, Karan S, Perlis ML (2011) Risk factors for opioid-induced excessive respiratory depression. Pain Manag Nurs 12:180–187

Jurna I (2003) Serturner and morphine–a historical vignette. Schmerz 17:280–283

Kalso E, Mennander S, Tasmuth T, Nilsson E (2001) Chronic post-sternotomy pain. Acta Anaesthesiol Scand 45:935–939

Kapila A, Glass PS, Jacobs JR, Muir KT, Hermann DJ, Shiraishi M, Howell S, Smith RL (1995) Measured context-sensitive half-times of remifentanil and alfentanil. Anesthesiology 83:968–975

Kapoor S (2012) Opioid/naloxone prolonged release combinations for opioid induced constipation. World J Gastroenterol 18:3921–3922

Karagoz HY, Sonmez B, Bakkaloglu B, Kurtoglu M, Erdinc M, Turkeli A, Bayazit K (2000) Coronary artery bypass grafting in the conscious patient without endotracheal general anesthesia. Ann Thorac Surg 70:91–96

Katz J, Seltzer Z (2009) Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother 9:723–744

Kehlet H, Dahl JB (1993) The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg 77:1048–1056

Khan M, Fraser A (2012) Cox-2 inhibitors and the risk of cardiovascular thrombotic events. Ir Med J 105:119–121

Kiani S, Poston R (2011) Is endoscopic harvesting bad for saphenous vein graft patency in coronary surgery? Curr Opin Cardiol 26:518–522

Klockgether-Radke AP (2002) F. W. Serturner and the discovery of morphine. 200 years of pain therapy with opioids. Anasthesiol Intensivmed Notfallmed Schmerzther 37:244–249

Kocabas S, Yedicocuklu D, Yuksel E, Uysallar E, Askar F (2008) Infiltration of the sternotomy wound and the mediastinal tube sites with 0.25% levobupivacaine as adjunctive treatment for postoperative pain after cardiac surgery. Eur J Anaesthesiol 25:842–849

Koukis I, Argiriou M, Dimakopoulou A, Panagiotakopoulos V, Theakos N, Charitos C (2008) Use of continuous subcutaneous anesthetic infusion in cardiac surgical patients after median sternotomy. J Cardiothorac Surg 3:2

Kwok YH, Hutchinson MR, Gentgall MG, Rolan PE (2012) Increased responsiveness of peripheral blood mononuclear cells to in vitro TLR 2, 4 and 7 ligand stimulation in chronic pain patients. PLoS One 7:e44232

Lahtinen P, Kokki H, Hendolin H, Hakala T, Hynynen M (2002) Propacetamol as adjunctive treatment for postoperative pain after cardiac surgery. Anesth Analg 95:813–819, table of contents

Lahtinen P, Kokki H, Hakala T, Hynynen M (2004) S(+)-ketamine as an analgesic adjunct reduces opioid consumption after cardiac surgery. Anesth Analg 99:1295–1301; table of contents

Lahtinen P, Kokki H, Hynynen M (2006) Pain after cardiac surgery: a prospective cohort study of 1-year incidence and intensity. Anesthesiology 105:794–800

Lahtinen P, Kokki H, Hynynen M (2008) Remifentanil infusion does not induce opioid tolerance after cardiac surgery. J Cardiothorac Vasc Anesth 22:225–229

Langford RM, Mehta V (2006) Selective cyclooxygenase inhibition: its role in pain and anaesthesia. Biomed Pharmacother 60:323–328

Laorden ML, Ferenczi S, Pinter-Kubler B, Gonzalez-Martin LL, Lasheras MC, Kovacs KJ, Milanes MV, Nunez C (2012) Hypothalamic orexin–a neurons are involved in the response of the brain stress system to morphine withdrawal. PLoS One 7:e36871

Leal EN, Ribeiro JL, Oliveira MM, Roquette J (2005) Psychosocial aspects associated with pain perception in individuals undergoing coronary surgery. Rev Port Cardiol 24:1221–1231

Ledowski T, Stein J, Albus S, MacDonald B (2011) The influence of age and sex on the relationship between heart rate variability, haemodynamic variables and subjective measures of acute post-operative pain. Eur J Anaesthesiol 28:433–437

Ledowski T, Reimer M, Chavez V, Kapoor V, Wenk M (2012) Effects of acute postoperative pain on catecholamine plasma levels, hemodynamic parameters, and cardiac autonomic control. Pain 153:759–764

Lee GA (2008) Patients reported health-related quality of life five years post coronary artery bypass graft surgery–a methodological study. Eur J Cardiovasc Nurs 7:67–72

Lee W, Yan YY, Jensen MP, Shun SC, Lin YK, Tsai TP, Lai YH (2010) Predictors and patterns of chronic pain three months after cardiac surgery in Taiwan. Pain Med 11:1849–1858

Lena P, Balarac N, Lena D, De La Chapelle A, Arnulf JJ, Mihoubi A, Tapia M, Bonnet F (2008) Fast-track anesthesia with remifentanil and spinal analgesia for cardiac surgery: the effect on pain control and quality of recovery. J Cardiothorac Vasc Anesth 22:536–542

Leung K (2004a) [6-O-methyl-11C]Diprenorphine

Leung K (2004b) (20R)-4,5-alpha-Epoxy-17-methyl-3-hydroxy-6-[11C]methoxy-alpha,17-dimethyl-alpha- (2-phenylethyl)-6,14-ethenomorphinan-7-methanol

Lewis SS, Loram LC, Hutchinson MR, Li CM, Zhang Y, Maier SF, Huang Y, Rice KC, Watkins LR (2012) (+)-naloxone, an opioid-inactive toll-like receptor 4 signaling inhibitor, reverses multiple models of chronic neuropathic pain in rats. J Pain 13:498–506

Lima Canadas PP, Canas AC, Orradre Romeo JL, Rubio Martinez CI, Lopez Almodovar LF, Calleja HM (2005) Endothelium histological integrity after skeletonized dissection of the left internal mammary artery with ultrasonic scalpel. Interact Cardiovasc Thorac Surg 4:160–162

Lin Y, He B, Chen J, Wang Z (2012) Can dexmedetomidine be a safe and efficacious sedative agent in post-cardiac surgery patients: a meta-analysis? Crit Care 16:R169

Lippe PM, Brock C, David J, Crossno R, Gitlow S (2010) The First National Pain Medicine Summit–final summary report. Pain Med 11:1447–1468

Liu SS, Wu CL (2007) Effect of postoperative analgesia on major postoperative complications: a systematic update of the evidence. Anesth Analg 104:689–702

Liu SS, Block BM, Wu CL (2004) Effects of perioperative central neuraxial analgesia on outcome after coronary artery bypass surgery: a meta-analysis. Anesthesiology 101:153–161

Loboz KK, Shenfield GM (2005) Drug combinations and impaired renal function – the 'triple whammy'. Br J Clin Pharmacol 59:239–243

Lotsch J (2005) Pharmacokinetic-pharmacodynamic modeling of opioids. J Pain Symptom Manage 29:S90–S103

Macintyre PE, Loadsman JA, Scott DA (2011) Opioids, ventilation and acute pain management. Anaesth Intensive Care 39:545–558

Mansouri M, Bageri K, Noormohammadi E, Mirmohammadsadegi M, Mirdehgan A, Ahangaran AG (2011) Randomized controlled trial of bilateral intrapleural block in cardiac surgery. Asian Cardiovasc Thorac Ann 19:133–138

Mathews ET, Abrams LD (1980) Intrathecal morphine in open heart surgery. Lancet 2:543

Mathews TJ, Churchhouse AM, Housden T, Dunning J (2012) Does adding ketamine to morphine patient-controlled analgesia safely improve post-thoracotomy pain? Interact Cardiovasc Thorac Surg 14:194–199

Maund E, McDaid C, Rice S, Wright K, Jenkins B, Woolacott N (2011) Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review. Br J Anaesth 106:292–297

May G, Bartram T (2007) Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. The use of intrapleural anaesthetic to reduce the pain of chest drain insertion. Emerg Med J 24:300–301

Mazzeffi M, Khelemsky Y (2011) Poststernotomy pain: a clinical review. J Cardiothorac Vasc Anesth 25:1163–1178

McCormack PL (2011) Celecoxib: a review of its use for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. Drugs 71:2457–2489

McDaid C, Maund E, Rice S, Wright K, Jenkins B, Woolacott N (2010) Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) for the reduction of morphine-related side effects after major surgery: a systematic review. Health Technol Assess 14:1–153, iii–iv

McDonald SB, Jacobsohn E, Kopacz DJ, Desphande S, Helman JD, Salinas F, Hall RA (2005) Parasternal block and local anesthetic infiltration with levobupivacaine after cardiac surgery with desflurane: the effect on postoperative pain, pulmonary function, and tracheal extubation times. Anesth Analg 100:25–32

Meehan DA, McRae ME, Rourke DA, Eisenring C, Imperial FA (1995) Analgesic administration, pain intensity, and patient satisfaction in cardiac surgical patients. Am J Crit Care 4: 435–442

Meylan N, Elia N, Lysakowski C, Tramer MR (2009) Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials. Br J Anaesth 102:156–167

Michelet P, Guervilly C, Helaine A, Avaro JP, Blayac D, Gaillat F, Dantin T, Thomas P, Kerbaul F (2007) Adding ketamine to morphine for patient-controlled analgesia after thoracic surgery: influence on morphine consumption, respiratory function, and nocturnal desaturation. Br J Anaesth 99:396–403

Milgrom LB, Brooks JA, Qi R, Bunnell K, Wuestfeld S, Beckman D (2004) Pain levels experienced with activities after cardiac surgery. Am J Crit Care 13:116–125

Moen V (2010) Scandinavian guidelines for neuraxial block and disturbed haemostasis: replacing wishful thinking with evidence based caution. Acta Anaesthesiol Scand 54:6–8

Moore SM (1995) A comparison of women's and men's symptoms during home recovery after coronary artery bypass surgery. Heart Lung 24:495–501

Moore RA, Straube S, Paine J, Derry S, McQuay HJ (2011) Minimum efficacy criteria for comparisons between treatments using individual patient meta-analysis of acute pain trials: examples of etoricoxib, paracetamol, ibuprofen, and ibuprofen/paracetamol combinations after third molar extraction. Pain 152:982–989

Mota FA, Marcolan JF, Pereira MH, Milanez AM, Dallan LA, Diccini S (2010) Comparison study of two different patient-controlled anesthesia regiments after cardiac surgery. Rev Bras Cir Cardiovasc 25:38–44

Muehling BM, Ortlieb L, Oberhuber A, Orend KH (2011) Fast track management reduces the systemic inflammatory response and organ failure following elective infrarenal aortic aneurysm repair. Interact Cardiovasc Thorac Surg 12:784–788

Mueller XM, Tinguely F, Tevaearai HT, Revelly JP, Chiolero R, von Segesser LK (2000a) Pain location, distribution, and intensity after cardiac surgery. Chest 118:391–396

Mueller XM, Tinguely F, Tevaearai HT, Revelly JP, Chiolero R, von Segesser LK (2000b) Pain pattern and left internal mammary artery grafting. Ann Thorac Surg 70:2045–2049

Mugabure Bujedo B (2012) A clinical approach to neuraxial morphine for the treatment of postoperative pain. Pain Res Treat 2012:612145

Munir MA, Enany N, Zhang JM (2007) Nonopioid analgesics. Anesthesiol Clin 25:761–774, vi

Murphy EJ (2005) Acute pain management pharmacology for the patient with concurrent renal or hepatic disease. Anaesth Intensive Care 33:311–322

Na ES, Morris MJ, Johnson AK (2012) Opioid mechanisms that mediate the palatability of and appetite for salt in sodium replete and deficient states. Physiol Behav 106:164–170

Nikoda VV, Petrov RO, Sandrikov VA, Chizhov AI (1994) Effects of opioid analgesics on pulmonary ventilation and metabolism in patients with acute postoperative pain. Anesteziol Reanimatol 4:28–29

Nishimori M, Low JH, Zheng H, Ballantyne JC (2012) Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. Cochrane Database Syst Rev 7, CD005059

Oderda G (2012) Challenges in the management of acute postsurgical pain. Pharmacotherapy 32:6S–11S

Ogus H, Selimoglu O, Basaran M, Ozcelebi C, Ugurlucan M, Sayin OA, Kafali E, Ogus TN (2007) Effects of intrapleural analgesia on pulmonary function and postoperative pain in patients with chronic obstructive pulmonary disease undergoing coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 21:816–819

Olofsen E, Boom M, Nieuwenhuijs D, Sarton E, Teppema L, Aarts L, Dahan A (2010a) Modeling the non-steady state respiratory effects of remifentanil in awake and propofol-sedated healthy volunteers. Anesthesiology 112:1382–1395

Olofsen E, Mooren R, van Dorp E, Aarts L, Smith T, den Hartigh J, Dahan A, Sarton E (2010b) Arterial and venous pharmacokinetics of morphine-6-glucuronide and impact of sample site on pharmacodynamic parameter estimates. Anesth Analg 111:626–632

Ong CK, Lirk P, Tan CH, Seymour RA (2007) An evidence-based update on nonsteroidal anti-inflammatory drugs. Clin Med Res 5:19–34

Papadopoulos N, Hacibaramoglu M, Kati C, Muller D, Floter J, Moritz A (2013) Chronic poststernotomy pain after cardiac surgery: correlation of computed tomography findings on sternal healing with postoperative chest pain. Thorac Cardiovasc Surg 61(3):202–208

Parlow JL, Steele RG, O'Reilly D (2005) Low dose intrathecal morphine facilitates early extubation after cardiac surgery: results of a retrospective continuous quality improvement audit. Can J Anaesth 52:94–99

Parry M, Watt-Watson J, Hodnett E, Tranmer J, Dennis CL, Brooks D (2010) Pain experiences of men and women after coronary artery bypass graft surgery. J Cardiovasc Nurs 25:E9–E15

Peivandi AA, Weigang E, Kayhan N, Hakami L, Ister D, Denk K, Conzelmann LO, Vahl CF (2009) Reevaluation of two techniques of harvesting the skeletonized internal mammary artery. Thorac Cardiovasc Surg 57:214–216

Peters ML, Sommer M, de Rijke JM, Kessels F, Heineman E, Patijn J, Marcus MA, Vlaeyen JW, van Kleef M (2007) Somatic and psychologic predictors of long-term unfavorable outcome after surgical intervention. Ann Surg 245:487–494

Pettersson PH, Jakobsson J, Owall A (2005) Intravenous acetaminophen reduced the use of opioids compared with oral administration after coronary artery bypass grafting. J Cardiothorac Vasc Anesth 19:306–309

Phillips RS, Cleary DR, Nalwalk JW, Arttamangkul S, Hough LB, Heinricher MM (2012) Pain-facilitating medullary neurons contribute to opioid-induced respiratory depression. J Neurophysiol 108(9):2393–2404

Polanco MJ, Alguacil LF, Gonzalez-Martin C (2012) Pro-apoptotic properties of morphine in neuroblastoma x glioma NG108-15 hybrid cells: modulation by yohimbine. J Appl Toxicol

Popping DM, Elia N, Marret E, Remy C, Tramer MR (2008a) Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. Arch Surg 143:990–999, discussion 1000

Popping DM, Zahn PK, Van Aken HK, Dasch B, Boche R, Pogatzki-Zahn EM (2008b) Effectiveness and safety of postoperative pain management: a survey of 18 925 consecutive patients between 1998 and 2006 (2nd revision): a database analysis of prospectively raised data. Br J Anaesth 101:832–840

Rachinger-Adam B, Conzen P, Azad SC (2011) Pharmacology of peripheral opioid receptors. Curr Opin Anaesthesiol 24:408–413

Rainsford KD (2007) Anti-inflammatory drugs in the 21st century. Subcell Biochem 42:3–27

Rawal N (2012) Epidural technique for postoperative pain: gold standard no more? Reg Anesth Pain Med 37:310–317

Richardson J, Lonnqvist PA, Naja Z (2011) Bilateral thoracic paravertebral block: potential and practice. Br J Anaesth 106:164–171

Romeyke T, Stummer H (2012) Clinical pathways as instruments for risk and cost management in hospitals – a discussion paper. Glob J Health Sci 4:50–59

Royse CF (2009) High thoracic epidural anaesthesia for cardiac surgery. Curr Opin Anaesthesiol 22:84–87

Rubens FD, Boodhwani M (2009) Skeletonization of the internal thoracic artery for coronary artery bypass grafting. Curr Opin Cardiol 24:559–566

Saadat H, Ziai SA, Ghanemnia M, Namazi MH, Safi M, Vakili H, Dabbagh A, Gholami O (2012) Opium addiction increases interleukin 1 receptor antagonist (IL-1Ra) in the coronary artery disease patients. PLoS One 7:e44939

Sacerdote P, Franchi S, Panerai AE (2012) Non-analgesic effects of opioids: mechanisms and potential clinical relevance of opioid-induced immunodepression. Curr Pharm Des 18(37):6034–6042

Scarci M, Joshi A, Attia R (2010) In patients undergoing thoracic surgery is paravertebral block as effective as epidural analgesia for pain management? Interact Cardiovasc Thorac Surg 10:92–96

Schachner T, Bonatti J, Balogh D, Margreiter J, Mair P, Laufer G, Putz G (2003) Aortic valve replacement in the conscious patient under regional anesthesia without endotracheal intubation. J Thorac Cardiovasc Surg 125:1526–1527

Schwann NM, Chaney MA (2003) No pain, much gain? J Thorac Cardiovasc Surg 126:1261–1264
Scott LJ, Perry CM (2005) Remifentanil: a review of its use during the induction and maintenance of general anaesthesia. Drugs 65:1793–1823
Servin F (2003) Remifentanil; from pharmacological properties to clinical practice. Adv Exp Med Biol 523:245–260
Servin FS (2008) Update on pharmacology of hypnotic drugs. Curr Opin Anaesthesiol 21:473–477
Servin FS, Billard V (2008) Remifentanil and other opioids. Handb Exp Pharmacol:283–311
Shekar K, Roberts JA, Mullany DV, Corley A, Fisquet S, Bull TN, Barnett AG, Fraser JF (2012) Increased sedation requirements in patients receiving extracorporeal membrane oxygenation for respiratory and cardiorespiratory failure. Anaesth Intensive Care 40:648–655
Shi WD, Wang WW, Cui XG, Pan P, Zhang B, Li WZ (2012) Preventive and therapeutic effects of penehyclidine hydrochloride on morphine-induced increased bladder pressure, urinary bladder sphincter pressure and histological damage in rabbits. Chin Med J (Engl) 125:1141–1146
Simpson T, Lee ER, Cameron C (1996) Patients' perceptions of environmental factors that disturb sleep after cardiac surgery. Am J Crit Care 5:173–181
Smith TH, Grider JR, Dewey WL, Akbarali HI (2012) Morphine decreases enteric neuron excitability via inhibition of sodium channels. PLoS One 7:e45251
Staahl C, Olesen AE, Andresen T, Arendt-Nielsen L, Drewes AM (2009) Assessing analgesic actions of opioids by experimental pain models in healthy volunteers – an updated review. Br J Clin Pharmacol 68:149–168
Stoelting RK (1989) Intrathecal morphine–an underused combination for postoperative pain management. Anesth Analg 68:707–709
Stritesky M, Semrad M, Kunstyr J, Hajek T, Demes R, Tosovsky J (2004) On-pump cardiac surgery in a conscious patient using a thoracic epidural anesthesia–an ultra fast track method. Bratisl Lek Listy 105:51–55
Sultan P, Gutierrez MC, Carvalho B (2011) Neuraxial morphine and respiratory depression: finding the right balance. Drugs 71:1807–1819
Suzuki M (2009) Role of N-methyl-D-aspartate receptor antagonists in postoperative pain management. Curr Opin Anaesthesiol 22:618–622
Svircevic V, Nierich AP, Moons KG, Diephuis JC, Ennema JJ, Brandon Bravo Bruinsma GJ, Kalkman CJ, van Dijk D (2011a) Thoracic epidural anesthesia for cardiac surgery: a randomized trial. Anesthesiology 114:262–270
Svircevic V, van Dijk D, Nierich AP, Passier MP, Kalkman CJ, van der Heijden GJ, Bax L (2011b) Meta-analysis of thoracic epidural anesthesia versus general anesthesia for cardiac surgery. Anesthesiology 114:271–282
Swartjes M, Mooren RA, Waxman AR, Arout C, Van De Wetering K, Den Hartigh J, Beijnen JH, Kest B, Dahan A (2012) Morphine induces hyperalgesia without involvement of mu-opioid receptor or morphine-3-glucuronide. Mol Med 18:1320–1326
Tack J, Corsetti M (2012) Prucalopride: evaluation of the pharmacokinetics, pharmacodynamics, efficacy and safety in the treatment of chronic constipation. Expert Opin Drug Metab Toxicol 8:1327–1335
Tenenbaum J (1999) The epidemiology of nonsteroidal anti-inflammatory drugs. Can J Gastroenterol 13:119–122
Tennyson C, Young CP, Scarci M (2010) Is it safe to perform endoscopic vein harvest? Interact Cardiovasc Thorac Surg 10:625–629
Thavaneswaran P, Rudkin GE, Cooter RD, Moyes DG, Perera CL, Maddern GJ (2010) Brief reports: paravertebral block for anesthesia: a systematic review. Anesth Analg 110: 1740–1744
Toda A, Watanabe G, Matsumoto I, Tomita S, Yamaguchi S, Ohtake H (2013) Monitoring brain oxygen saturation during awake off-pump coronary artery bypass. Asian Cardiovasc Thorac Ann 21:14–21
Torigoe K, Nakahara K, Rahmadi M, Yoshizawa K, Horiuchi H, Hirayama S, Imai S, Kuzumaki N, Itoh T, Yamashita A, Shakunaga K, Yamasaki M, Nagase H, Matoba M, Suzuki T, Narita M

(2012) Usefulness of olanzapine as an adjunct to opioid treatment and for the treatment of neuropathic pain. Anesthesiology 116:159–169
Tsai HE, Liu LF, Dusting GJ, Weng WT, Chen SC, Kung ML, Tee R, Liu GS, Tai MH (2012) Pro-opiomelanocortin gene delivery suppresses the growth of established Lewis lung carcinoma through a melanocortin-1 receptor-independent pathway. J Gene Med 14:44–53
Tzortzopoulou A, McNicol ED, Cepeda MS, Francia MB, Farhat T, Schumann R (2011) Single dose intravenous propacetamol or intravenous paracetamol for postoperative pain. Cochrane Database Syst Rev:CD007126
Ucak A, Onan B, Sen H, Selcuk I, Turan A, Yilmaz AT (2011) The effects of gabapentin on acute and chronic postoperative pain after coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 25:824–829
Urell C, Westerdahl E, Hedenstrom H, Janson C, Emtner M (2012) Lung function before and two days after open-heart surgery. Crit Care Res Pract 2012:291628
Usichenko TI, Rottenbacher I, Kohlmann T, Julich A, Lange J, Mustea A, Engel G, Wendt M (2013) Implementation of the quality management system improves postoperative pain treatment: a prospective pre-/post-interventional questionnaire study. Br J Anaesth 110(1):87–95
Vadivelu N, Mitra S, Hines RL (2011) Peripheral opioid receptor agonists for analgesia: a comprehensive review. J Opioid Manag 7:55–68
Valdez-Morales E, Guerrero-Alba R, Ochoa-Cortes F, Benson J, Spreadbury I, Hurlbut D, Miranda-Morales M, Lomax AE, Vanner S (2013) Release of endogenous opioids during a chronic IBD model suppresses the excitability of colonic DRG neurons. Neurogastroenterol Motil 25(1):39–46
van Gulik L, Janssen LI, Ahlers SJ, Bruins P, Driessen AH, van Boven WJ, van Dongen EP, Knibbe CA (2011) Risk factors for chronic thoracic pain after cardiac surgery via sternotomy. Eur J Cardiothorac Surg 40:1309–1313
van Ojik AL, Jansen PA, Brouwers JR, van Roon EN (2012) Treatment of chronic pain in older people: evidence-based choice of strong-acting opioids. Drugs Aging 29:615–625
Visser LE, Graatsma HH, Stricker BH (2002) Contraindicated NSAIDs are frequently prescribed to elderly patients with peptic ulcer disease. Br J Clin Pharmacol 53:183–188
Waldhoer M, Bartlett SE, Whistler JL (2004) Opioid receptors. Annu Rev Biochem 73:953–990
Walker SM, Yaksh TL (2012) Review article: neuraxial analgesia in neonates and infants: a review of clinical and preclinical strategies for the development of safety and efficacy data. Anesth Analg 115:638–662
Watanabe G, Tomita S, Yamaguchi S, Yashiki N (2011) Awake coronary artery bypass grafting under thoracic epidural anesthesia: great impact on off-pump coronary revascularization and fast-track recovery. Eur J Cardiothorac Surg 40:788–793
White PF (2008) Multimodal analgesia: its role in preventing postoperative pain. Curr Opin Investig Drugs 9:76–82
White JM, Irvine RJ (1999) Mechanisms of fatal opioid overdose. Addiction 94:961–972
White PF, Rawal S, Latham P, Markowitz S, Issioui T, Chi L, Dellaria S, Shi C, Morse L, Ing C (2003) Use of a continuous local anesthetic infusion for pain management after median sternotomy. Anesthesiology 99:918–923
Wipke-Tevis DD, Stotts NA (1998) Effect of dressings on saphenous vein harvest incision pain, distress and cosmetic result. Prog Cardiovasc Nurs 13:3–13
Wolf AR (2012a) Effects of regional analgesia on stress responses to pediatric surgery. Paediatr Anaesth 22:19–24
Wolf AR (2012b) Paediatric cardiac anaesthesia: balancing risk and outcome. Br J Anaesth 109:12–15
Wu SY, Dun SL, Wright MT, Chang JK, Dun NJ (1999) Endomorphin-like immunoreactivity in the rat dorsal horn and inhibition of substantia gelatinosa neurons in vitro. Neuroscience 89:317–321
Yamanaka T, Sadikot RT (2013) Opioid effect on lungs. Respirology 18(2):255–262

# Postoperative Considerations of Cardiopulmonary Bypass in Adult Cardiac Surgery

12

Mahnoosh Foroughi

## Contents



**Abstract**

Development of the cardiopulmonary bypass (CPB) technology in the second half of the twentieth century was one of the most important medical events and was responsible of cardiac surgery basis and provided the condition to operate on a completely motionless, bloodless heart. It fulfills the role of the heart (and

M. Foroughi, MD
Cardiovascular Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
e-mail: mahnoosh.foroughi@gmail.com, m_foroughi@sbmu.ac.ir

A. Dabbagh et al. (eds.), *Postoperative Critical Care for Cardiac Surgical Patients*,
DOI 10.1007/978-3-642-40418-4_12, 

lungs) by preserving the systemic circulation. Since the first initial machine, evolution from cross-sectional technique till to minimal extracorporeal circulation continues. From there CPB has been the main part of heart surgery. As improved knowledge in pathophysiology of cardiopulmonary machine effects, efforts led to make new extracorporeal technology. Although it simplifies cardiac surgery, CPB by itself induces a systemic inflammatory response syndrome, mostly due to blood contact with artificial surfaces. It causes activation of coagulation, fibrinolytic cascade, complement, leukocyte, upregulation of proinflammatory cytokines, and production of oxygen free radicals and alters nitric oxide metabolism. Nearly all organs can be affected by these changes. The first section describes the parts of cardiopulmonary machine. The issues of most organs involvement during CPB are addressed in the second section.

## 12.1 Cardiopulmonary Bypass Circuit Structure

### 12.1.1 History

In spite of other fields of surgery, cardiac surgery was suspended for centuries due to lack of knowledge and technology. What was the cause of this slow and delayed evolution?

The lack of its requirements:

1. Inability to preserve systemic circulation independent to heart contraction
2. Need to preserve adequate systemic anticoagulation that could be reversed at the end of the operation
3. Need a method to exchange and correct blood gases during the operation, independent to lung function

The introduction of the heart–lung machine in 1953 and development of cardiopulmonary bypass allowed the surgical treatment of intracardiac diseases possible and become a standard part of cardiac operation; its development has a prolonged evolution way from concept of extracorporeal circulation (Le Gallois in 1812) to the Theodor Billroth opinion in 1881 “No surgeon who wished to preserve the respect of his colleagues would ever attempt to suture a wound of the heart,” to the first heart surgery using CPB by John Gibbon in 1953, significant refinement since then till to the present trend of minimal extracorporeal circulation. Pump structure: the cardiopulmonary bypass machine is equipment that provides mechanical circulatory support of the heart and lungs. The machine consists of pumps, membrane oxygenator, venous and arterial cannula, polyvinyl chloride (or silicone tubing), reservoir cardiotomy, and heat exchanger. This section discusses in brief the ingredients of cardiopulmonary bypass system for better understanding for postoperative care of cardiac surgery patients considering the related different viewpoints regarding the issue (Galletti 1993; Evora et al. 1995; Moen et al. 1996; Nolan et al. 1997; Stammers 1997; Shigeta et al. 1999; Edmunds 2002; Paparella et al. 2002; Litwak 2003; McLaughlin and Dunning 2003; Raymond et al. 2003; Chew 2004; Teoh et al. 2004; Thanikachalam et al. 2004; Daly et al. 2005; Raja and Dreyfus 2005; Salzberg et al.

2005; Boodhwani et al. 2006; Martens et al. 2006; Skinner et al. 2006; Apostolakis and Akinosoglou 2008; Campos and Paniagua 2008; Hirleman and Larson 2008; Spiess 2008; Boodhwani et al. 2009; Halkos and Puskas 2009; Vohra et al. 2009; Apostolakis et al. 2010; Sellke et al. 2010; Sobel 2010; Buffolo et al. 2011; Chauhan and Subin 2011; El-Essawi et al. 2011; Krane et al. 2011; Weisse 2011; Beckmann et al. 2012; Hausenloy et al. 2012; Papadopoulos et al. 2013).

### 12.1.2 Blood Circuit

In normal condition, blood enters the heart in the right atrium and passes through the right ventricle. From there the blood leaves the heart into the lungs where carbon dioxide is extracted from the blood and substituted by oxygen. Then the blood is sent back into the left atrium, enters into the left ventricle, and injected into the aorta where it transfers to the systemic circulation. The cardiopulmonary bypass acts nearly the same performance outside of the body. At the beginning of the operation, CPB tubing is primed by crystalloid solution. Colloid solutions, mannitol, sodium bicarbonate, heparin, and sometimes blood are prime additives. Venous line removes blood by means of gravity or siphonage from right side of the heart and returned it in oxygenated form to the systemic circulation via arterial line by pump. Pump acts like a ventricle. There is two type of pump: roller and centrifugal.

#### 12.1.2.1 Roller Pump

This pump consists of two rollers placed on the ends of a rotating arm, opposite to each other. It has occlusive nature. The rollers rotate and engage the tubing which is then compressed against the pump's housing, propelling blood ahead and forward flow is induced (Fig. 12.1). The flow rate is determined by the diameter of the tubing and the rotation rate of the rollers. It is not dependent to preload and afterload. The flow rate of 2–2.4 L/m$^2$/min is sufficient for adequate systemic perfusion, with consideration of patient's temperature. Optimal perfusion targets remain to be in controversy, but it is recommended to preserve mean arterial pressure 50–70 mmHg, CVP<5 mmHg, hematocrit more than 20 %, and mixed venous saturation >65 % during CPB.

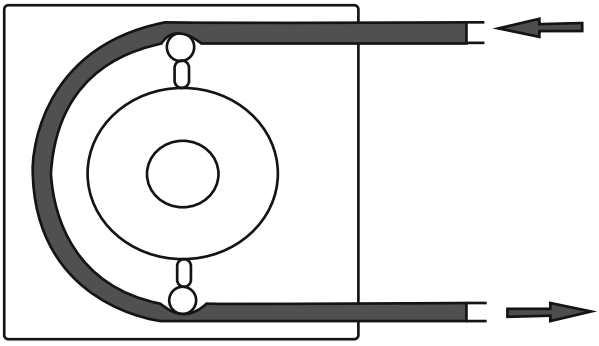


**Fig. 12.1** Roller pump

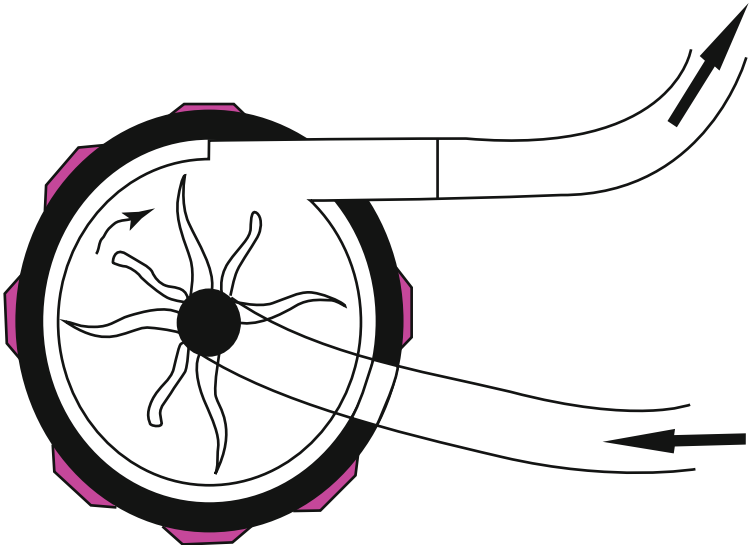


**Fig. 12.2** Centrifugal pump

#### 12.1.2.2 Centrifugal Pump

In plastic housing, a complex of plastic cones coupled magnetically to an electric motor. They rotate rapidly; by creating a pressure gradient between the inlet and outlet of the pump, kinetic energy is transferred to blood and resulting forward blood flow (Fig. 12.2). In spite of roller pump, centrifugal pump is non-occlusive; therefore flow rate is dependent to preload and afterload too.

### 12.1.3 Cardiotomy

A filtered reservoir collects blood drained from the venous circulation. It is for storage, defoaming, and filtration before added directly to arterial circuit. Other fluid such as blood products and medication may also be added.

Reservoir designs include open or closed systems. The open system (hard shell) has graduated lines that shows amount of blood volume in the container. The design is open to atmosphere, allowing blood interface with atmospheric gases possible. In the closed system, the soft pliable bag eliminates the air–blood interface. Volume is measured by weight or by change in radius of the container.

### 12.1.4 Membrane Oxygenator

A flat sheet of hollow fibers imitates the pulmonary capillary function, by interposing a thin membrane between blood and gases, and creates gas–blood interface gas without blood passing. Gas flows through the hollow fiber and blood flow is around

the fiber. In spite of carbon dioxide, oxygen is not diffusible in plasma well, so the blood is spread very thin to facilitate the transfer of oxygen by increased gradient pressure.

### 12.1.5 Anticoagulation

Unfractionated heparin is used to achieve adequate systemic anticoagulation, by measuring activated clotting time (ACT) ≥400 s. It remains the absolute choice of anticoagulant in cardiac surgery. Heparin is obtained from lung beef and or porcine intestinal mucosa. It isn't an anticoagulant itself but could potentiate the antithrombin III (AT), a potent endogenous anticoagulant of body.

Heparin is given in the bolus dose of 2.5–4 mg/kg to aim an ACT of 400–480 s, before aortic and venous cannulation. Additional heparin is repeated to maintain ACT above 400 s during CPB, for adequate anticoagulation state.

An inadequate response to heparin (heparin resistance) may be seen in patients with long preoperative heparin use; this condition is corrected by FFP or recombinant AT administration.

At the end of operation, after CPB weaning it is reversed by protamine (isolated from fish sperm) to establish normal hemostasis condition after surgery. There are some ways to determine the protamine dose: protamine titration, fixed dose of protamine (in the ratio of 1.2–1.5 mg for 100 unit of heparin previously administered), ACT/heparin dose response curve, and heparin concentration. Protamine has mild anticoagulant effect too and inhibits platelet-induced aggregation. Although it has short half-life, but care should be taken not to infuse protamine too fast as it can induce systemic hypotension due to systemic vasodilation and pulmonary vasoconstriction.

Heparin rebound, a state of recurrent anticoagulant activity of heparin after adequate protamine administration, contributes in postoperative bleeding. Because not all of heparin is bounded to protamine, some of it binds to other plasma proteins and vascular cells, reappearance in circulation gradually.

### 12.1.6 Cannulation

Arterial and venous cannulation sites are influenced by the planned operation. In routine valve and coronary surgeries, the ascending aorta and right atrium are selected. Alternative sites of arterial cannulation are the femoral artery, axillary artery, and left ventricular apex. Cannulation site for venous access can be the inferior and superior vena cava, femoral vein, and internal jugular vein. Cannula is made from clear polyvinyl chloride, the oxygenator casing and connections are from polycarbonate.

### 12.1.7 Cardioplegia

A blood-free and motionless operative field is obtained by potassium-based cardioplegic solution that causes diastolic electromechanical arrest. In addition to stop

electrical and consequently mechanical activation, preserving myocardial function and attenuating ischemic–reperfusion injury are other main goals of it. Cardioplegic solution can be categorized according to the type of solution (crystalloid vs. bloody), temperature (cold vs. warm), infusion type (antegrade into aortic root vs. retrograde through coronary sinus), and infusion interval (continuous vs. intermittent).

### 12.1.8 Heat Exchanger

The heat exchanger is used in combination with the oxygenator. This device is typically placed just before the oxygenator, because it helps to prevent bubble forming in the blood too. Heat exchanger controls the body temperature by heating or cooling blood passing through the circuit, at the beginning and end of CPB, respectively. In heat exchanger, the blood and water lines are separated by a metallic barrier. As the water temperature is changed, the blood temperature which enters the body circulation and the tissue temperature change. There is a consensus on protective effect of hypothermia for organ function during ischemic period. Hypothermia reduces oxygen consumption and metabolic rate. Even mild hypothermic condition can increase brain tolerance against ischemic injury. Although it is associated with side effects such as induced coagulopathy and leftward shift of oxygen–hemoglobin dissociation curve. Acid–base balance is affected by hypothermia, too. Depending on the type of operation, the patient's temperature may be kept normothermic to less than 20 °C. Monitoring the blood temperature during the operation and the speed and temperature of rewarming is mandatory. Rewarming too great or too quickly may affect important problems. Hyperthermia during rewarming period is known to intensify ischemic damages especially in the brain and kidney.

### 12.1.9 Arterial Filter

Inclusion of arterial filter in CPB circuit is used to reduce microembolic events. It holds air bubble, particles of platelet aggregation, and thrombus during CPB.

### 12.1.10 Minimized Extracorporeal Circulation

Minimized extracorporeal circulation (MECC) is an alternative to conventional CPB. It consists of a membrane oxygenator, centrifugal pump, and arterial filter. It includes short heparin-coated circuit, less prime volume, and no cardiotomy suction and venous reservoir, thus the blood–air interface is limited, while conventional CPB circuit is an open circuit because of free contact of blood–air. The shed blood is washed through cell-saving device before return to arterial line. It seems that these differences lead to attenuate the adverse effect of conventional CPB: less inflammatory response, reduced hemodilution (and therefore less need to blood transfusion), and less changes in hemostasis system; some studies showed cardiac

surgery with MECC is associated with less postoperative neurologic deficit, less need for blood transfusion, and less postoperative bleeding.

### 12.1.11 Ultrafiltration

Ultrafiltration removes water and low molecular weight materials from blood to a filtrate part under hydrostatic pressure through hollow-fiber semipermeable membrane. Ultrafiltration is used during cardiac surgery to reduce total body water, attenuate hemodilution during pump and need to transfusion, and remove inflammatory mediators. Hemodilution is inevitable at the beginning of CPB. There is a mixture of patients' blood with prime content of CPB tube at the beginning of CPB, inducing acute hemodilution. Although hemodilution decreases blood viscosity and facilitates tissue perfusion in hypothermic setting, studies have shown that intraoperative hematocrit less than 23 % is associated with interstitial edema (decreased oncotic pressure) in vital organs and increased mortality; it decreases blood transfusion requirement. There are two main types of ultrafiltration. Conventional ultrafiltration is done only during CPB, and modified ultrafiltration is performed after CPB weaning to concentrate plasma volume.

## 12.2 Cardiopulmonary Bypass-Related Complications

### 12.2.1 Inflammation

Cardiopulmonary bypass and blood contact with synthetic surface of CPB circuit can promote whole-body systemic inflammatory response that plays a role in multiorgan failure. Continuous exposure of heparinized blood to foreign surfaces in the perfusion circuit and nonendothelial cells in the wound provoke complement anaphylatoxins, adhesion molecules, proinflammatory cytokines, vasoactive substances, coagulation, and fibrinolytic activation. In addition, ischemic–reperfusion injury (due to aortic clamp and declamping), endotoxemia (due to splanchnic hypoperfusion), hypothermia, surgical trauma, blood loss, and transfusion may contribute in activation of inflammatory cascade. Leukocyte activation, especially neutrophil, is responsible to initiate the release of inflammatory mediators that have negative impact in all organs. The severity of this exaggerated response can range from being barely clinically detectable to respiratory failure, coagulopathy, and multiorgan dysfunction. There are suggested strategies to attenuate inflammatory response, though there is not a consensus regarding their clinical outcome and benefits; these include heparin-coated circuit, corticosteroids, hemofiltration, leukocyte depletion, minimized extracorporeal circulation, aprotinin, complement inhibitors, free radical scavengers, and antioxidants (Miller and Levy 1997; Paparella et al. 2002; El Kebir et al. 2005; Raja and Dreyfus 2005; Patel and Ghatak 2008; Warren et al. 2009a, b; Rimmele et al. 2010; Augoustides 2012; Dieleman et al. 2012; Hausenloy et al. 2012).

### 12.2.2 CPB and Hematologic Effect

All blood elements get impression during CPB due to activation of haemostatic–inflammatory system. Pump time duration and the influence of biomaterial substances in surface area of CPB have the most effect on the severity of humoral and cellular activation. In coagulation system, reduction in platelet count and function, consumption of coagulation factors and increased activity in fibrinolytic field occur. Blood contact with artificial surfaces of CPB circuit makes intrinsic coagulation pathway activation. Extrinsic coagulation pathway is activated in pericardial blood, which is usually aspirated and returned to pump circulation. In addition to mechanical trauma to red blood cell, mixture of blood with priming solution brings to a dilutional anemia in the beginning of CPB. There are strategies to decrease this response: heparin coating of CPB circuit, corticosteroids, leukocyte filter, and ultrafiltration (Chung et al. 1996).

### 12.2.3 CPB and Kidney

Prevalence of acute kidney injury (AKI) after cardiac surgery has been reported between 1 and 30 %, according to definitions used for AKI, as there is no consensus in definition. It is associated with significant short- and long-term mortality. After cardiac surgery, only minimal changes of serum creatinine as small as 0.3 mg/dL predict prognosis in this setting, even it remains in normal range too; so attention to preventable causes, early detection, and treatment are among the valuable issues for prevention of AKI after cardiac surgery (Ronco et al. 2002; Boldt et al. 2003; Lassnigg et al. 2004; Karkouti et al. 2005; Mitter et al. 2010; Moriyama et al. 2010; Park et al. 2010b; Mariscalco et al. 2011; Weir et al. 2011; Ko et al. 2012; Kohagura and Ohya 2012; Sviglerova et al. 2012; Tolpin et al. 2012).

The most important causes of AKI during CPB (which overlap and interact at the cellular level):

1. Hemodynamic insults (perioperative reduction of cardiac output and resultant decreased renal perfusion).
2. Inflammatory factors (contact activation of blood components).
3. Embolic events (both gaseous and particulate).
4. Preexisting kidney dysfunction.
5. Nephrotoxic agents (medications and intravenous contrast); in addition, type of operation has an effect on AKI. Among adult cardiac surgeries, coronary artery bypass graft (CABG) has the lowest incidence of AKI, while the combination of CABG and valve surgery is the highest risk factor.

CPB per se is responsible for renal injury duo to non-pulsatile flow. Other factors that are related to CPB include duration of CPB time and cross-clamp time, hemolysis, and hemodilution.

1. *Time duration of CPB and cross-clamp:* The consequences of prolonged CPB are extension of hypoperfusion time and release of more inflammatory mediators, as it is directly correlated to CPB duration and disturb tubular renal function.

2. *Hemolysis:* Hemolysis is the result of prolonged CBP time, cardiotomy suction, occlusive roller pump, blood exposure to artificial surface, and shear forces.
3. *Hemodilution:* Because of need to priming in CBP tubes, hemodilution is inevitable; it is suggested that hemodilution improves regional blood flow (by reduction of blood viscosity) in the setting of hypothermia and hypoperfusion; although it was thought that improvement in regional blood flow compensates the risk of acute anemia (loss of $O_2$-carrying capacity of blood), recent studies expressed that intraoperative hematocrit $\leq$21 % is an independent risk factor for postoperative AKI.

During operation modifiable factors that reduce the risk of AKI are prevention of excessive hemodilution, shorter duration of CPB, optimal glucose control, and use of $NaHCO_3$. In practice kidney function is assessed by measuring serum creatinine, but it has limitations. Rise in serum creatinine indicates the reduction of glomerular filtration rate and occurs slowly in several days after proved injury. So it is an unreliable and insensitive indicator during early stages of kidney injury. Multiple studies have suggested that NGAL (neutrophil gelatinase-associated lipocalin) is a sensitive biomarker that shows tubular cell damage as early as 2 h after the event. It can be used as a reliable marker to diagnosis of acute kidney injury in post-cardiac surgery (Ronco et al. 2002; Boldt et al. 2003; Lassnigg et al. 2004; Karkouti et al. 2005; Mitter et al. 2010; Moriyama et al. 2010; Park et al. 2010a, b; Mariscalco et al. 2011; Weir et al. 2011; Bayrak et al. 2012; Ko et al. 2012; Kohagura and Ohya 2012; Levi et al. 2012; Sviglerova et al. 2012; Tolpin et al. 2012; Vellinga et al. 2012; Yap and Lee 2012).

### 12.2.4 CPB and Lung

Pulmonary dysfunction and prolonged ventilation after cardiac surgery are important causes of morbidity. It occurs due to combined effects of anesthesia, surgical trauma, and CPB. Causative factors of pulmonary impairment function during cardiac surgery are:

1. Pulmonary ischemia
2. Reperfusion injury
3. Surgical trauma
4. Hypothermia
5. Blood loss and blood contact with artificial surfaces of CPB circuit

Lack or reduced blood flow through the lungs during surgery increases the damage of other factors. As the lung perfusion is limited to bronchial arterial system during aortic cross-clamp period. The clinical pattern of this injury has a range from subclinical functional changes to ARDS, due to lung edema, atelectasis, increased alveolar–arterial oxygen gradient, abnormal gas exchange, increased intrapulmonary shunting, and decreased lung compliance. Studies showed that neutrophil accumulation in lung during CPB, its activation, release of chemical mediators, and proteolytic enzymes are in charge of lung injury. In addition to inflammation response, volume overload during CPB plays an important role in accumulation of

interstitial fluid in lung too. It was shown that prolonged CPB time, aortic valve surgery, and combined valve/CABG procedures are independent factors of postoperative respiratory failure. There are some therapeutic intervention to prevent or treat pulmonary dysfunction, such as corticosteroid administration, leukocyte depletion, heparin-coated circuit, hemofiltration, maintaining pulmonary ventilation during CPB, maintaining pulmonary perfusion during CPB, pump time reduction, and use of minimized CPB (Carvalho et al. 2008; Filsoufi et al. 2008; Goebel et al. 2008; Suzuki 2010).

### 12.2.5 CPB and CNS

Neurologic abnormalities such as stroke (prolonged or permanent deficit) and postoperative cognitive dysfunction are relatively common problems despite improvement in anesthetic and surgical techniques. They are important and disturbing complications after cardiac surgery. The independent predictors of postoperative stroke are:

1. Peripheral vascular disease
2. Diabetes mellitus
3. History of cerebrovascular disease
4. High transfusion requirement
5. Urgent operation
6. Left main coronary disease
7. Carotid bruits

CPB-related mechanisms include:

1. Macro- or microemboli (gas, atheromatous plaque, inorganic, and biologic debris from open cardiac procedures)
2. Systemic inflammatory response
3. Perioperative hypoperfusion
4. Extensive aortic calcification
5. Prolonged CPB time
6. Hemorrhage
7. Cerebral hyperthermia

The majority of strokes are due to embolic event, and watershed component is seen in few patients; the most atheromatous embolic event happens during manipulation of atherosclerotic aorta (cannulation, cross-clamp, and declamping), and its consequences are crack or rupture of atherosclerotic plaque leading to debris release, cerebral embolization, and ischemic brain injury. Aortic clamping in the presence of exophytic plaque is contraindicated, and elimination of CPB is recommended in this condition. It is suggested that epiaortic ultrasonography be used to identify atheromatous plaque and help to select the suitable site for aortic cannulation in the diseased ascending aorta. It is more sensitive than digital palpation and transesophageal echocardiography and gives information about the entire length of the ascending aortic wall; it can affect the rate of stroke whenever operative strategies are changed. Prevention of microemboli is accomplished by the use of a membrane oxygenator,

the prevention of air entering the circuit, and the use of a microfilter that will effectively trap microemboli and prevent from reentering the blood stream and preventing the manipulation of diseased aorta. Prolonged period of hypoperfusion is a predisposing factor of ischemic events especially in old, diabetic, and hypertensive patients who have impaired autoregulatory mechanism in cerebral circulation; maintaining high perfusion pressure is recommended in these patients during CPB. Cerebral oximetry monitor can be used to assess cerebral perfusion during cardiac surgery. Decrease and increase in temperature of brain (during cooling and rewarming period) happens more quickly than other parts of the body because of the well-perfused state. Rapid rewarming at the end of CPB can lead to cerebral hyperthermia and exacerbated neurologic dysfunction. During complex aortic arch surgery, neurologic complication is associated less in antegrade cerebral perfusion (through right axillary artery cannulation) than retrograde cerebral perfusion and deep hypothermic circulatory arrest; in these patients femoral artery cannulation has the risk of retrograde cerebral embolization and worse neurologic outcome. Those who experience stroke during 24 h of CPB had adverse outcome in contrast to late presentation, although the majority of strokes happen after initial normal neurologic recovery of CPB, delayed stroke. Cognitive disorder such as a decrease in baseline performance is more frequent than neurologic deficit by the same mechanisms. Mild hypothermia is recommended for the reduction of postoperative cognitive disorder (Hogue et al. 1999, 2007, 2008a, b; Puskas et al. 2000; Salazar et al. 2001; Ascione et al. 2002; Bucerius et al. 2003; Bergman et al. 2004; Carrascal et al. 2005; Zingone et al. 2006; Biancari et al. 2007; Nathan et al. 2007; Campos and Paniagua 2008; Gottesman et al. 2008; Grogan et al. 2008; Lisle et al. 2008; Tully et al. 2008; Grigore et al. 2009; Slater et al. 2009; Coburn et al. 2010; Lombard and Mathew 2010; Rudolph et al. 2010; Hedberg et al. 2011; El Zayat et al. 2012; Messerotti Benvenuti et al. 2012a, b; Misfeld et al. 2012; Sanders and Grocott 2012; Sun et al. 2012; Bartels et al. 2013; Bruggemans 2013; Reinsfelt et al. 2013).

### 12.2.6 Off-Pump Coronary Artery Bypass

In an attempt to decrease the deleterious effects of CPB, off-pump coronary artery bypass (OPCAB) was renewed and suggested as a viable less invasive option from the mid-1990s. During CPB, activation of physiologic mechanisms (due to blood contact with artificial surfaces of bypass circuit, surgical trauma, and ischemic–reperfusion injury) is the cause of systemic inflammatory response, associated with postoperative organ dysfunction. This response is significantly less in OPCAB operations. Activation of coagulation and fibrinolytic cascade does not happen with the same severity in OPCAB patients. There is less blood loss and transfusion requirement in OPCAB operations. Better preservation of renal function is seen in OPCAB patients by prevention of renal hypoperfusion and non-pulsatile flow in CPB state. Even in patients with chronic kidney disease, OPCAB operation is associated with less hospital mortality and incident renal replacement therapy. There is better myocardial function and rapid recovery in OPCAB by avoidance of aortic

cross-clamp and global myocardial ischemia. OPCAB patients with preexisting pulmonary diseases have better postoperative clinical course. There are no significant differences of neurologic complication (stroke and cognitive dysfunction) between the two types as that may be related to partial aortic clamp use for proximal anastomoses. The concern about OPCAB was incomplete revascularization, suboptimal anastomoses and their patency, hemodynamic instability during operation, and that it is time consuming as it is technically demanding and needs a steep learning curve. Although debate continues, studies show in experienced hands the outcome parameters are comparable and as effective and safe as on-pump surgery. It is not recommended for small, intramyocardial coronary arteries, hemodynamically unstable patients, and moderate aortic or mitral regurgitation. On-pump beating heart surgery is recommended in chronic hemodialysis patients and when coronary surgery is indicated in acute coronary syndrome. Decompression of ventricles by CPB reduces myocardial oxygen consumption, while OPCAB surgery prevents global myocardial ischemia by absence of aortic cross-clamp (Allen et al. 1986; Cooley 2000; Osaka et al. 2001; Ascione et al. 2003; Black et al. 2004; van Dijk et al. 2007; Raja and Dreyfus 2008; Atluri et al. 2009; Apostolakis et al. 2010; Rimmele et al. 2010; Serrano et al. 2010; Puskas et al. 2011; Moller et al. 2012).

## References

Allen BS, Rosenkranz ER, Buckberg GD, Vinten-Johansen J, Okamoto F, Leaf J (1986) High oxygen requirements of dyskinetic cardiac muscle. J Thorac Cardiovasc Surg 92:543–552

Apostolakis E, Akinosoglou K (2008) The methodologies of hypothermic circulatory arrest and of antegrade and retrograde cerebral perfusion for aortic arch surgery. Ann Thorac Cardiovasc Surg 14:138–148

Apostolakis EE, Koletsis EN, Baikoussis NG, Siminelakis SN, Papadopoulos GS (2010) Strategies to prevent intraoperative lung injury during cardiopulmonary bypass. J Cardiothorac Surg 5:1

Ascione R, Reeves BC, Chamberlain MH, Ghosh AK, Lim KH, Angelini GD (2002) Predictors of stroke in the modern era of coronary artery bypass grafting: a case control study. Ann Thorac Surg 74:474–480

Ascione R, Caputo M, Angelini GD (2003) Off-pump coronary artery bypass grafting: not a flash in the pan. Ann Thorac Surg 75:306–313

Atluri P, Kozin ED, Hiesinger W, Woo YJ (2009) Off-pump, minimally invasive and robotic coronary revascularization yield improved outcomes over traditional on-pump CABG. Int J Med Robot 5:1–12

Augoustides JG (2012) The inflammatory response to cardiac surgery with cardiopulmonary bypass: should steroid prophylaxis be routine? J Cardiothorac Vasc Anesth 26:952–958

Bartels K, McDonagh DL, Newman MF, Mathew JP (2013) Neurocognitive outcomes after cardiac surgery. Curr Opin Anaesthesiol 26:91–97

Bayrak S, Yurekli I, Gokalp O, Kiray M, Bademci MS, Ozcem B, Besir Y, Yilik L, Kestelli M, Gurbuz A (2012) Assessment of protective effects of methylprednisolone and pheniramine maleate on reperfusion injury in kidney after distant organ ischemia: a rat model. Ann Vasc Surg 26:559–565

Beckmann S, Lynn P, Miller S, Harris R, Dimarco R, Ross J (2012) Evaluation of coagulation factors and platelet function from an off-line modified ultrafiltration technique for post-cardiopulmonary bypass circuit blood recovery. Perfusion 28:214–222

Bergman P, Hadjinikolaou L, Dellgren G, van der Linden J (2004) A policy to reduce stroke in patients with extensive atherosclerosis of the ascending aorta undergoing coronary surgery. Interact Cardiovasc Thorac Surg 3:28–32

Biancari F, Mosorin M, Rasinaho E, Lahtinen J, Heikkinen J, Niemela E, Anttila V, Lepojarvi M, Juvonen T (2007) Postoperative stroke after off-pump versus on-pump coronary artery bypass surgery. J Thorac Cardiovasc Surg 133:169–173

Black EA, Ghosh S, Sin K, Spyt T, Pillai R (2004) Off-pump coronary artery bypass surgery. Asian Cardiovasc Thorac Ann 12:379–386

Boldt J, Brenner T, Lehmann A, Suttner SW, Kumle B, Isgro F (2003) Is kidney function altered by the duration of cardiopulmonary bypass? Ann Thorac Surg 75:906–912

Boodhwani M, Williams K, Babaev A, Gill G, Saleem N, Rubens FD (2006) Ultrafiltration reduces blood transfusions following cardiac surgery: a meta-analysis. Eur J Cardiothorac Surg 30:892–897

Boodhwani M, Rubens FD, Wozny D, Nathan HJ (2009) Effects of mild hypothermia and rewarming on renal function after coronary artery bypass grafting. Ann Thorac Surg 87:489–495

Bruggemans EF (2013) Cognitive dysfunction after cardiac surgery: pathophysiological mechanisms and preventive strategies. Neth Heart J 21:70–73

Bucerius J, Gummert JF, Borger MA, Walther T, Doll N, Onnasch JF, Metz S, Falk V, Mohr FW (2003) Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients. Ann Thorac Surg 75:472–478

Buffolo E, Lima RC, Salerno TA (2011) Myocardial revascularization without cardiopulmonary bypass: historical background and thirty-year experience. Rev Bras Cir Cardiovasc 26:III–VII

Campos JM, Paniagua P (2008) Hypothermia during cardiac surgery. Best Pract Res Clin Anaesthesiol 22:695–709

Carrascal Y, Casquero E, Gualis J, Di Stefano S, Florez S, Fulquet E, Echevarria JR, Fiz L (2005) Cognitive decline after cardiac surgery: proposal for easy measurement with a new test. Interact Cardiovasc Thorac Surg 4:216–221

Carvalho EM, Gabriel EA, Salerno TA (2008) Pulmonary protection during cardiac surgery: systematic literature review. Asian Cardiovasc Thorac Ann 16:503–507

Chauhan S, Subin S (2011) Extracorporeal membrane oxygenation, an anesthesiologist's perspective: physiology and principles. Part 1. Ann Card Anaesth 14:218–229

Chew MS (2004) Does modified ultrafiltration reduce the systemic inflammatory response to cardiac surgery with cardiopulmonary bypass? Perfusion 19(Suppl 1):S57–S60

Chung JH, Gikakis N, Rao AK, Drake TA, Colman RW, Edmunds LH Jr (1996) Pericardial blood activates the extrinsic coagulation pathway during clinical cardiopulmonary bypass. Circulation 93:2014–2018

Coburn M, Fahlenkamp A, Zoremba N, Schaelte G (2010) Postoperative cognitive dysfunction: incidence and prophylaxis. Anaesthesist 59:177–184; quiz 185

Cooley DA (2000) Con: beating-heart surgery for coronary revascularization: is it the most important development since the introduction of the heart-lung machine? Ann Thorac Surg 70:1779–1781

Daly RC, Dearani JA, McGregor CG, Mullany CJ, Orszulak TA, Puga FJ, Schaff HV, Sundt TM III, Zehr KJ (2005) Fifty years of open heart surgery at the Mayo Clinic. Mayo Clin Proc 80:636–640

Dieleman JM, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, Schepp RM, Boer C, Moons KG, van Herwerden LA, Tijssen JG, Numan SC, Kalkman CJ, van Dijk D (2012) Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. JAMA 308:1761–1767

Edmunds LH Jr (2002) The evolution of cardiopulmonary bypass: lessons to be learned. Perfusion 17:243–251

El Kebir D, Hubert B, Taha R, Troncy E, Wang T, Gauvin D, Gangal M, Blaise G (2005) Effects of inhaled nitric oxide on inflammation and apoptosis after cardiopulmonary bypass. Chest 128:2910–2917

El-Essawi A, Hajek T, Skorpil J, Boning A, Sabol F, Ostrovsky Y, Hausmann H, Harringer W (2011) Are minimized perfusion circuits the better heart lung machines? Final results of a prospective randomized multicentre study. Perfusion 26:470–478

El Zayat H, Puskas JD, Hwang S, Thourani VH, Lattouf OM, Kilgo P, Halkos ME (2012) Avoiding the clamp during off-pump coronary artery bypass reduces cerebral embolic events: results of a prospective randomized trial. Interact Cardiovasc Thorac Surg 14:12–16

Evora PR, Pearson PJ, Schaff HV (1995) Protamine induces endothelium-dependent vasodilatation of the pulmonary artery. Ann Thorac Surg 60:405–410

Filsoufi F, Rahmanian PB, Castillo JG, Chikwe J, Adams DH (2008) Predictors and early and late outcomes of respiratory failure in contemporary cardiac surgery. Chest 133:713–721

Galletti PM (1993) Cardiopulmonary bypass: a historical perspective. Artif Organs 17:675–686

Goebel U, Siepe M, Mecklenburg A, Doenst T, Beyersdorf F, Loop T, Schlensak C (2008) Reduced pulmonary inflammatory response during cardiopulmonary bypass: effects of combined pulmonary perfusion and carbon monoxide inhalation. Eur J Cardiothorac Surg 34:1165–1172

Gottesman RF, McKhann GM, Hogue CW (2008) Neurological complications of cardiac surgery. Semin Neurol 28:703–715

Grigore AM, Murray CF, Ramakrishna H, Djaiani G (2009) A core review of temperature regimens and neuroprotection during cardiopulmonary bypass: does rewarming rate matter? Anesth Analg 109:1741–1751

Grogan K, Stearns J, Hogue CW (2008) Brain protection in cardiac surgery. Anesthesiol Clin 26:521–538

Halkos ME, Puskas JD (2009) Off-pump versus on-pump coronary artery bypass grafting. Surg Clin North Am 89:913–922, ix

Hausenloy DJ, Boston-Griffiths E, Yellon DM (2012) Cardioprotection during cardiac surgery. Cardiovasc Res 94:253–265

Hedberg M, Boivie P, Engstrom KG (2011) Early and delayed stroke after coronary surgery – an analysis of risk factors and the impact on short- and long-term survival. Eur J Cardiothorac Surg 40:379–387

Hirleman E, Larson DF (2008) Cardiopulmonary bypass and edema: physiology and pathophysiology. Perfusion 23:311–322

Hogue CW Jr, Murphy SF, Schechtman KB, Davila-Roman VG (1999) Risk factors for early or delayed stroke after cardiac surgery. Circulation 100:642–647

Hogue CW Jr, Freedland K, Hershey T, Fucetola R, Nassief A, Barzilai B, Thomas B, Birge S, Dixon D, Schechtman KB, Davila-Roman VG (2007) Neurocognitive outcomes are not improved by 17beta-estradiol in postmenopausal women undergoing cardiac surgery. Stroke 38:2048–2054

Hogue CW, Fucetola R, Hershey T, Freedland K, Davila-Roman VG, Goate AM, Thompson RE (2008a) Risk factors for neurocognitive dysfunction after cardiac surgery in postmenopausal women. Ann Thorac Surg 86:511–516

Hogue CW Jr, Fucetola R, Hershey T, Nassief A, Birge S, Davila-Roman VG, Barzilai B, Thomas B, Schechtman KB, Freedland K (2008b) The role of postoperative neurocognitive dysfunction on quality of life for postmenopausal women 6 months after cardiac surgery. Anesth Analg 107:21–28

Karkouti K, Beattie WS, Wijeysundera DN, Rao V, Chan C, Dattilo KM, Djaiani G, Ivanov J, Karski J, David TE (2005) Hemodilution during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery. J Thorac Cardiovasc Surg 129:391–400

Ko B, Garcia S, Mithani S, Tholakanahalli V, Adabag S (2012) Risk of acute kidney injury in patients who undergo coronary angiography and cardiac surgery in close succession. Eur Heart J 33:2065–2070

Kohagura K, Ohya Y (2012) Early detection and prediction by biomarkers of acute kidney injury after cardiac surgery. Circ J 76:53–54

Krane M, Voss B, Hiebinger A, Deutsch MA, Wottke M, Hapfelmeier A, Badiu CC, Bauernschmitt R, Lange R (2011) Twenty years of cardiac surgery in patients aged 80 years and older: risks and benefits. Ann Thorac Surg 91:506–513

Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Druml W, Bauer P, Hiesmayr M (2004) Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. J Am Soc Nephrol 15:1597–1605

Levi TM, Rocha MS, Almeida DN, Martins RT, Silva MG, Santana NC, Sanjuan IT, Cruz CM (2012) Furosemide is associated with acute kidney injury in critically ill patients. Braz J Med Biol Res 45:827–833

Lisle TC, Barrett KM, Gazoni LM, Swenson BR, Scott CD, Kazemi A, Kern JA, Peeler BB, Kron IL, Johnston KC (2008) Timing of stroke after cardiopulmonary bypass determines mortality. Ann Thorac Surg 85:1556–1562; discussion 1562–1553

Litwak RS (2003) Historical vignettes concerning cardiopulmonary bypass without homologous blood and perfusion hypothermia. Perfusion 18:201–206

Lombard FW, Mathew JP (2010) Neurocognitive dysfunction following cardiac surgery. Semin Cardiothorac Vasc Anesth 14:102–110

Mariscalco G, Lorusso R, Dominici C, Renzulli A, Sala A (2011) Acute kidney injury: a relevant complication after cardiac surgery. Ann Thorac Surg 92:1539–1547

Martens TP, Argenziano M, Oz MC (2006) New technology for surgical coronary revascularization. Circulation 114:606–614

McLaughlin KE, Dunning J (2003) In patients post cardiac surgery do high doses of protamine cause increased bleeding? Interact Cardiovasc Thorac Surg 2:424–426

Messerotti Benvenuti S, Zanatta P, Longo C, Mazzarolo AP, Palomba D (2012a) Preoperative cerebral hypoperfusion in the left, not in the right, hemisphere is associated with cognitive decline after cardiac surgery. Psychosom Med 74:73–80

Messerotti Benvenuti S, Zanatta P, Valfre C, Polesel E, Palomba D (2012b) Preliminary evidence for reduced preoperative cerebral blood flow velocity as a risk factor for cognitive decline three months after cardiac surgery: an extension study. Perfusion 27:486–492

Miller BE, Levy JH (1997) The inflammatory response to cardiopulmonary bypass. J Cardiothorac Vasc Anesth 11:355–366

Misfeld M, Leontyev S, Borger MA, Gindensperger O, Lehmann S, Legare JF, Mohr FW (2012) What is the best strategy for brain protection in patients undergoing aortic arch surgery? A single center experience of 636 patients. Ann Thorac Surg 93:1502–1508

Mitter N, Shah A, Yuh D, Dodd OJ, Thompson RE, Cameron D, Hogue CW (2010) Renal injury is associated with operative mortality after cardiac surgery for women and men. J Thorac Cardiovasc Surg 140:1367–1373

Moen O, Fosse E, Dregelid E, Brockmeier V, Andersson C, Hogasen K, Venge P, Mollnes TE, Kierulf P (1996) Centrifugal pump and heparin coating improves cardiopulmonary bypass biocompatibility. Ann Thorac Surg 62:1134–1140

Moller CH, Penninga L, Wetterslev J, Steinbruchel DA, Gluud C (2012) Off-pump versus on-pump coronary artery bypass grafting for ischaemic heart disease. Cochrane Database Syst Rev 3:CD007224

Moriyama MT, Tanaka T, Morita N, Ishii T, Chikazawa I, Suga K, Miyazawa K, Suzuki K (2010) Renal protective effects of erythropoietin on ischemic reperfusion injury. Cell Transplant 19:713–721

Nathan HJ, Rodriguez R, Wozny D, Dupuis JY, Rubens FD, Bryson GL, Wells G (2007) Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: five-year follow-up of a randomized trial. J Thorac Cardiovasc Surg 133:1206–1211

Nolan SP, Zacour R, Dammann JF (1997) Reflections on the evolution of cardiopulmonary bypass. Ann Thorac Surg 64:1540–1543

Osaka S, Ohsawa H, Miyazawa M, Honda J (2001) Off-pump Coronary Artery Bypass Grafting in patients on chronic hemodialysis. J Card Surg 16:302–309

Papadopoulos N, Bakhtiary F, Grun V, Weber C, Strasser C, Moritz A (2013) The effect of normovolemic modified ultrafiltration on inflammatory mediators, endotoxins, terminal complement complexes and clinical outcome in high-risk cardiac surgery patients. Perfusion 28: 306–314

Paparella D, Yau TM, Young E (2002) Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. Eur J Cardiothorac Surg 21:232–244

Park SW, Chen SW, Kim M, Brown KM, D'Agati VD, Lee HT (2010a) Protection against acute kidney injury via A(1) adenosine receptor-mediated Akt activation reduces liver injury after liver ischemia and reperfusion in mice. J Pharmacol Exp Ther 333:736–747

Park SW, Chen SW, Kim M, D'Agati VD, Lee HT (2010b) Selective intrarenal human A1 adenosine receptor overexpression reduces acute liver and kidney injury after hepatic ischemia reperfusion in mice. Lab Invest 90:476–495

Patel JA, Ghatak SB (2008) Pexelizumab and its role in the treatment of myocardial infarction and in coronary artery bypass graft surgery: a review. Recent Pat Cardiovasc Drug Discov 3:145–152

Puskas JD, Winston AD, Wright CE, Gott JP, Brown WM III, Craver JM, Jones EL, Guyton RA, Weintraub WS (2000) Stroke after coronary artery operation: incidence, correlates, outcome, and cost. Ann Thorac Surg 69:1053–1056

Puskas JD, Williams WH, O'Donnell R, Patterson RE, Sigman SR, Smith AS, Baio KT, Kilgo PD, Guyton RA (2011) Off-pump and on-pump coronary artery bypass grafting are associated with similar graft patency, myocardial ischemia, and freedom from reintervention: long-term follow-up of a randomized trial. Ann Thorac Surg 91:1836–1842; discussion 1842–1833

Raja SG, Dreyfus GD (2005) Modulation of systemic inflammatory response after cardiac surgery. Asian Cardiovasc Thorac Ann 13:382–395

Raja SG, Dreyfus GD (2008) Current status of off-pump coronary artery bypass surgery. Asian Cardiovasc Thorac Ann 16:164–178

Raymond PD, Ray MJ, Callen SN, Marsh NA (2003) Heparin monitoring during cardiac surgery. Part 2: Calculating the overestimation of heparin by the activated clotting time. Perfusion 18:277–281

Reinsfelt B, Westerlind A, Blennow K, Zetterberg H, Ricksten SE (2013) Open-heart surgery increases cerebrospinal fluid levels of Alzheimer-associated amyloid beta. Acta Anaesthesiol Scand 57:82–88

Rimmele T, Venkataraman R, Madden NJ, Elder MM, Wei LM, Pellegrini RV, Kellum JA (2010) Comparison of inflammatory response during on-pump and off-pump coronary artery bypass surgery. Int J Artif Organs 33:131–138

Ronco C, Bellomo R, Kellum JA (2002) Continuous renal replacement therapy: opinions and evidence. Adv Ren Replace Ther 9:229–244

Rudolph JL, Schreiber KA, Culley DJ, McGlinchey RE, Crosby G, Levitsky S, Marcantonio ER (2010) Measurement of post-operative cognitive dysfunction after cardiac surgery: a systematic review. Acta Anaesthesiol Scand 54:663–677

Salazar JD, Wityk RJ, Grega MA, Borowicz LM, Doty JR, Petrofski JA, Baumgartner WA (2001) Stroke after cardiac surgery: short- and long-term outcomes. Ann Thorac Surg 72:1195–1201; discussion 1201–1192

Salzberg SP, Adams DH, Filsoufi F (2005) Coronary artery surgery: conventional coronary artery bypass grafting versus off-pump coronary artery bypass grafting. Curr Opin Cardiol 20:509–516

Sanders RD, Grocott HP (2012) Perioperative stroke: time to redefine the impact of age? Stroke 43:3–5

Sellke FW, Chu LM, Cohn WE (2010) Current state of surgical myocardial revascularization. Circ J 74:1031–1037

Serrano CV Jr, Souza JA, Lopes NH, Fernandes JL, Nicolau JC, Blotta MH, Ramires JA, Hueb WA (2010) Reduced expression of systemic proinflammatory and myocardial biomarkers after off-pump versus on-pump coronary artery bypass surgery: a prospective randomized study. J Crit Care 25:305–312

Shigeta O, Kojima H, Hiramatsu Y, Jikuya T, Terada Y, Atsumi N, Sakakibara Y, Nagasawa T, Mitsui T (1999) Low-dose protamine based on heparin-protamine titration method reduces platelet dysfunction after cardiopulmonary bypass. J Thorac Cardiovasc Surg 118:354–360

Skinner SC, Hirschl RB, Bartlett RH (2006) Extracorporeal life support. Semin Pediatr Surg 15:242–250

Slater JP, Guarino T, Stack J, Vinod K, Bustami RT, Brown JM III, Rodriguez AL, Magovern CJ, Zaubler T, Freundlich K, Parr GV (2009) Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. Ann Thorac Surg 87:36–44; discussion 44–35

Sobel BE (2010) A perspective on the development of coronary revascularization. Coron Artery Dis 21:199–203

Spiess BD (2008) Treating heparin resistance with antithrombin or fresh frozen plasma. Ann Thorac Surg 85:2153–2160

Stammers AH (1997) Historical aspects of cardiopulmonary bypass: from antiquity to acceptance. J Cardiothorac Vasc Anesth 11:266–274

Sun X, Lindsay J, Monsein LH, Hill PC, Corso PJ (2012) Silent brain injury after cardiac surgery: a review: cognitive dysfunction and magnetic resonance imaging diffusion-weighted imaging findings. J Am Coll Cardiol 60:791–797

Suzuki T (2010) Additional lung-protective perfusion techniques during cardiopulmonary bypass. Ann Thorac Cardiovasc Surg 16:150–155

Sviglerova J, Kuncova J, Nalos L, Holas J, Tonar Z, Rajdl D, Stengl M (2012) Cardiac remodeling in rats with renal failure shows interventricular differences. Exp Biol Med (Maywood) 237:1056–1067

Teoh KH, Young E, Blackall MH, Roberts RS, Hirsh J (2004) Can extra protamine eliminate heparin rebound following cardiopulmonary bypass surgery? J Thorac Cardiovasc Surg 128:211–219

Thanikachalam M, Lombardi P, Tehrani HY, Katariya K, Salerno TA (2004) The history and development of direct coronary surgery without cardiopulmonary bypass. J Card Surg 19:516–519

Tolpin DA, Collard CD, Lee VV, Virani SS, Allison PM, Elayda MA, Pan W (2012) Subclinical changes in serum creatinine and mortality after coronary artery bypass grafting. J Thorac Cardiovasc Surg 143:682–688.e1

Tully PJ, Baker RA, Kneebone AC, Knight JL (2008) Neuropsychologic and quality-of-life outcomes after coronary artery bypass surgery with and without cardiopulmonary bypass: a prospective randomized trial. J Cardiothorac Vasc Anesth 22:515–521

van Dijk D, Spoor M, Hijman R, Nathoe HM, Borst C, Jansen EW, Grobbee DE, de Jaegere PP, Kalkman CJ (2007) Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. JAMA 297:701–708

Vellinga S, Verbrugghe W, De Paep R, Verpooten GA, Janssen van Doorn K (2012) Identification of modifiable risk factors for acute kidney injury after cardiac surgery. Neth J Med 70:450–454

Vohra HA, Whistance R, Modi A, Ohri SK (2009) The inflammatory response to miniaturised extracorporeal circulation: a review of the literature. Mediators Inflamm 2009:707042

Warren OJ, Smith AJ, Alexiou C, Rogers PL, Jawad N, Vincent C, Darzi AW, Athanasiou T (2009a) The inflammatory response to cardiopulmonary bypass: Part 1. Mechanisms of pathogenesis. J Cardiothorac Vasc Anesth 23:223–231

Warren OJ, Watret AL, de Wit KL, Alexiou C, Vincent C, Darzi AW, Athanasiou T (2009b) The inflammatory response to cardiopulmonary bypass: Part 2. Anti-inflammatory therapeutic strategies. J Cardiothorac Vasc Anesth 23:384–393

Weir MR, Aronson S, Avery EG, Pollack CV Jr (2011) Acute kidney injury following cardiac surgery: role of perioperative blood pressure control. Am J Nephrol 33:438–452

Weisse AB (2011) Cardiac surgery: a century of progress. Tex Heart Inst J 38:486–490

Yap SC, Lee HT (2012) Adenosine and protection from acute kidney injury. Curr Opin Nephrol Hypertens 21:24–32

Zingone B, Rauber E, Gatti G, Pappalardo A, Benussi B, Dreas L, Lattuada L (2006) The impact of epiaortic ultrasonographic scanning on the risk of perioperative stroke. Eur J Cardiothorac Surg 29:720–728

# Fluid Management and Electrolyte Balance

# 13

Felice Eugenio Agrò, Marialuisa Vennari, and Maria Benedetto

## Contents



F.E. Agrò, MD (✉) • M. Vennari, MD • M. Benedetto, MD
Anesthesia, Department of Intensive Care and Pain Management,
Campus Bio-Medico of Rome, Via A. Del Portillo, 200 00128 Rome, Italy
e-mail: f.agro@unicampus.it; m.vennari@unicampus.it; m.benedetto@unicampus.it

A. Dabbagh et al. (eds.), *Postoperative Critical Care for Cardiac Surgical Patients*,
DOI 10.1007/978-3-642-40418-4_13, 

**Abstract**

Cardiac surgery is responsible for profound modification in body water distribution, electrolyte plasma concentration, and acid–base balance. Maintaining fluid, electrolyte, and acid–base balance it must be taken into account the alterations due to anaesthesia, the effects of cardiac surgery together with patient's comorbidities and physiological response to the surgical stress. However the ideal approach to perioperative fluid management in cardiac surgery is still debated. The debate involves the kind of fluid to use (crystalloids vs colloids, colloid vs colloid, balanced vs unbalance solutions) and the amount of fluid to administer (liberal vs restrictive). The goal-directed therapy seems to be the best choice to guide the quantity of fluid infused, potentially impacting on outcomes. Electrolytes are always modified after cardiac surgery. With respect to the past, the benefit of their administration (in particular calcium) has been discussed in literature. In this chapter, the basis of fluid and electrolyte management in cardiac surgery patient is explained, through understanding physiology and pathophysiology.

## 13.1 Introduction

In 1865, Claude Bernard firstly referred to human body as a "milieu interieur," provided of its own homeostasis (Bernard 1865). The homeostasis is the prerequisite of the performance of any physiological function, and it is founded on three main systems, electrolyte system, acid–base system, and osmolar system, that are strictly interconnected. Any change in one of them is responsible of modification of both the remainders. In the "milieu interieur," they are responsible for body water distribution and movements of fluids and molecules. Maintaining or restore the homeostasis of the "milieu interieur" acting on the three systems is the final goal of any clinical treatment, in particular, in the perioperative setting of cardiac surgery. In this case, the maintenance of fluid, ionic, osmolar, and acid–base balance is the sum of complex clinical evaluations and actions, taking into account the kind of surgery, the alterations due to anesthesia, the effects of cardiopulmonary bypass, patient's comorbidities and his own response to surgical stress (Fanzca 2012). In clinical practice, there is still much uncertainty that should be in part overcome through an adequate knowledge of human physiology.

### 13.1.1 Physiology of Body Fluids

The human body is divided into two main compartments: the intracellular space (ICS) and the extracellular space (ECS). The ECS is divided into three additional compartments: the intravascular space (IVS, plasma), the interstitial space (ISS), and the transcellular space (TCS). These compartments contain the total amount of body water and are surrounded by a semipermeable membrane through which fluids pass from one space to another (Agrò and Vennari 2013a) (Fig. 13.1).

Body water accounts for approximately 60 % of body weight; it is mainly distributed in the ECS and ICS. The ICS contains nearly 55 % of total body water and the ECS approximately 45 % (about 15 L in a normal adult). Among the three compartments, the IVS accounts for about 15 % of ECS water, the ISS for nearly 45 %, and the TCS for about 40 % (Agrò and Vennari 2013a) (Fig. 13.2).

The TCS is a functional compartment represented by the amount of fluid and electrolytes continually exchanged (in and out) by cells with the ISS and by the IVS with the ISS (Agrò and Vennari 2013a). Other fluids composing the ECS are secretions, ocular fluid, and cerebrospinal fluid (Agrò and Vennari 2013a; Chappell et al. 2008).

Fluid and electrolyte balance is both an external balance between the body and its environment and an internal balance between the ECS and ICS and between the IVS and ISS. This balance is based on specific chemical and physical properties of body fluids, such as ionic composition, pH, protein content, osmotic pressure, osmolarity, and colloid osmotic pressure (Agrò and Vennari 2013a) (Table 13.1).

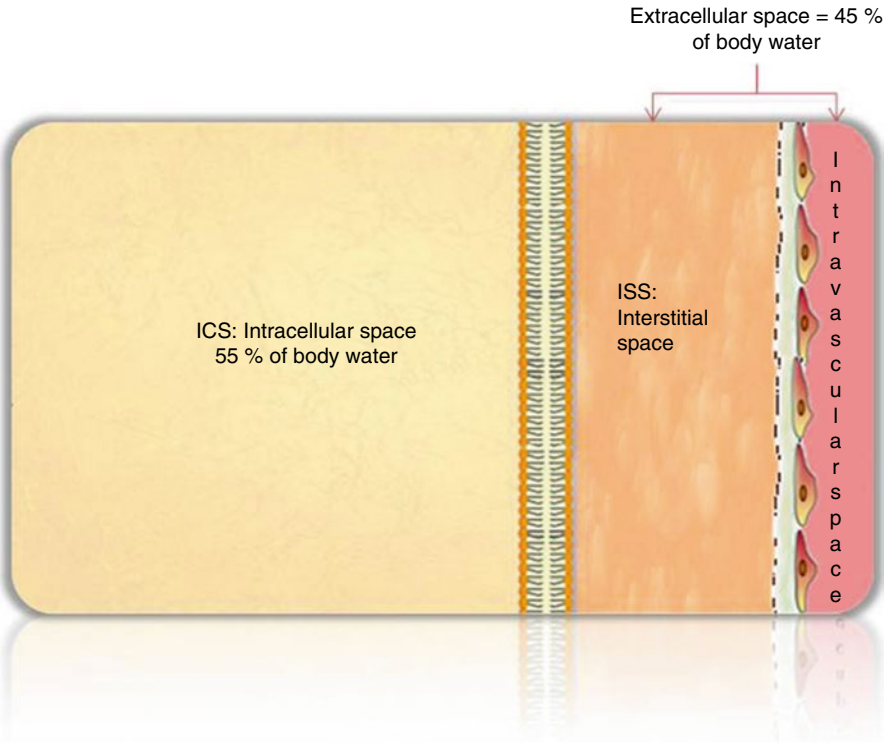



**Fig. 13.1** Body compartment representation (From Agrò and Vennari 2013a, pp. 1–26)

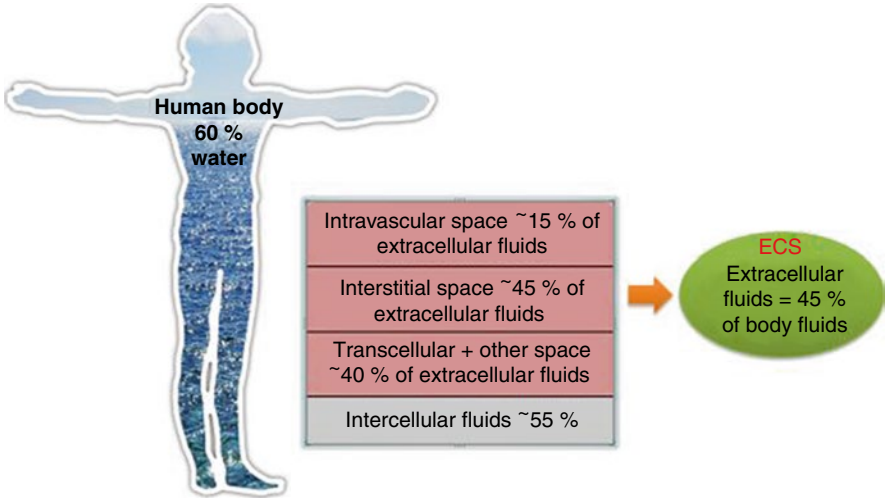



**Fig. 13.2** Body water distribution (From Agrò and Vennari 2013a, pp. 1–26)

**Table 13.1** Main properties of body fluids

| Properties | Plasma | Interstitial fluid | Intracellular fluid |
|---|---|---|---|
| Colloid osmotic pressure (mmHg) | 25 | 4 | – |
| Osmolality (mOsmol/kg) | 280 | 280 | 280 |
| pH | 7.4 | 7.4 | 7.2 |
| $Na^+$ (mEqlL) | 142 | 143 | 10 |
| $K^+$ (mEqlL) | 4 | 4 | 155 |
| $Cl^-$ (mEqlL) | 103 | 115 | 8 |
| $Ca^{2+}$ (mEqlL) | 2.5 | 1.3 | <0.001 |

From Agrò and Vennari (2013a, pp. 1–26)

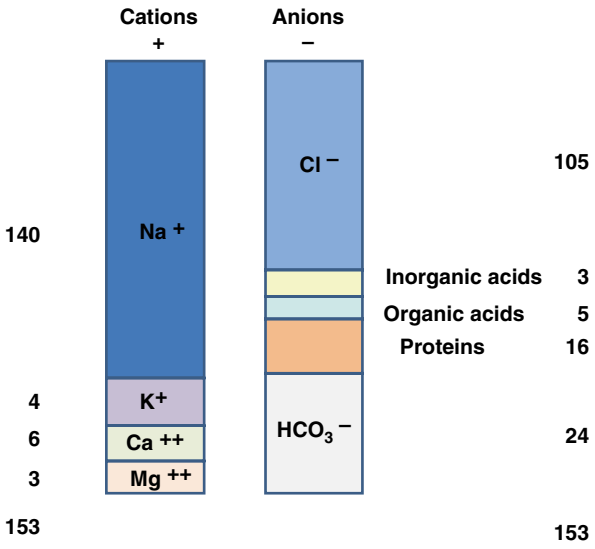



**Fig. 13.3** Gamble gram. Electric neutrality principle: the sum of plasmatic cations is equivalent to the sum of plasmatic anions

## 13.1.2 Ionic Balance

Ionic balance is based on the principle of the "electric neutrality": the sum of cations must be the same of the sum of anions. In other words, the net sum of the electric charge in the body fluids is zero. Ionic composition of ICS and ECS are different and further differences exist in the ECS between the IVS and the ISS (Table 13.1).

In clinical practice, the only value directly measurable is the plasma concentration of each ion is the only value directly measurable. Generally, this value is considered as a reference to evaluate the presence of electrolyte alterations. The relationship between the ionic plasmatic composition and the neutrality principle is expressed by the Gamble gram (Fig. 13.3). Examining the Gamble gram is immediately evident that the sum of cations ($Na^+$ + $K^+$ + $Ca^{++}$ + $Mg^{++}$ + others) is 154 mEq/L and is the same of anions ($Cl^-$ + bicarbonate + proteins + phosphates + sulfates + organic acids). $Na^+$ and $K^+$ represent 94 % of all IVS cations, while $Cl^-$ and

bicarbonate represent 84 % of all anions. $Na^+$, $K^+$, $Ca^{++}$, and $Mg^{++}$ are generally measured through laboratory exams, while bicarbonate is only calculated by using the Henderson–Hasselbalch equation, when arterial blood sample is performed (Gamble 1947) (see Chap. 15).

#### 13.1.2.1 Sodium

Sodium is the most highly represented cation in the ECS, and it has a key hemodynamic role: it is the main determinant of ECS volume, contributes to renin–angiotensin–aldosterone system activation, and regulates ADH secretion. Sodium concentration determines body fluid osmolarity. Changes in sodium plasma level are responsible for modification in fluid movement across the body space, determining ICS and ECS volume variation. The normal sodium concentration in plasma and the ISS is about 142 mEq/L, and it is higher than the ICS concentration (10 mEq/L) (Agrò and Vennari 2013a; Miller 2009).

#### 13.1.2.2 Potassium

Potassium is the main cation of the ICS. It plays a central role in determining the resting cell membrane potential, especially for excitable cells such as myocytes. Therefore, it influences the transmission of impulses along the cardiac pacemakers (potentially predisposing to arrhythmias) and the contraction of myocardial cells. It is also involved in a variety of metabolic processes, including energy production and the synthesis of nucleic acids and proteins. The normal potassium concentration in plasma is about 4.5 mEq/L (Agrò and Vennari 2013a; Miller 2009).

#### 13.1.2.3 Calcium

Several extra- and intracellular activities are regulated by calcium action. Calcium is involved in endocrine, exocrine, and neurocrine secretion; coagulation activation; muscle contraction (it has a great inotropic effect); potential membrane depolarization; cell growth; enzymatic regulation; and in the metabolism of other electrolytes (especially potassium and magnesium). The normal calcium plasma concentration is 2–2.6 mEq/L. Calcium may circulate in the plasma bound to albumin and free from proteins. Free calcium may be ionized (physiologically active) or nonionized (chelated with inorganic anions such as sulfate, citrate, and phosphate). The amounts of the three forms are altered by many factors, such as pH, plasma protein levels (hypoalbuminemia reduces total calcium, but not free fraction), and percentage of anions associated with ionized calcium (blood products contain citrate) (Agrò and Vennari 2013a; Miller 2009).

#### 13.1.2.4 Magnesium

Magnesium is the physiological antagonist of calcium. It plays a crucial role in neuromuscular stimulation and modulation of excitable cells activity (membrane stabilizing activity); it also acts as a cofactor of several enzymes involved in the metabolism of three major categories of nutrients: carbohydrates, lipids, and proteins. The normal plasma concentration is about 0.85–1.25 mEq/L (Agrò and Vennari 2013a; Miller 2009).

#### 13.1.2.5 Chloride

Chloride is the most important anion of the ECS. Together with sodium, it determines the ECS volume. It is also responsible for the resting potential of the membrane and action potential, acid–base balance, and plasma osmotic pressure. The normal plasma chloride concentration is 97–107 mEq/L (Agrò and Vennari 2013a; Miller 2009).

#### 13.1.2.6 Bicarbonate

Bicarbonate is the main buffer system of the blood. It plays a crucial role in maintaining acid–base balance. Two-thirds of the $CO_2$ in the human body is metabolized as bicarbonate, through the action of carbonic anhydrase. The equilibrium between $CO_2$ and bicarbonate leads to the elimination of volatile acid. The bicarbonate buffer system is described by the following equilibrium reaction (Agrò and Vennari 2013a):

$$CO_2 + H_2O \longleftrightarrow H_2CO_3 \longleftrightarrow HCO_3^- + H^+$$

When there is an increased concentration of $H^+$, the system reacts by shifting the reaction equilibrium to the left (towards the production of $CO_2$), while when the concentration of $H^+$ is reduced, the system moves to the right, resulting in the production of $H^+$. The bicarbonate buffer system works "in concert" with several organs (see Chap. 15). Bicarbonate has a normal plasma concentration of about 24 mmol/L (Agrò and Vennari 2013a).

### 13.1.3 Osmolar Balance

Chemical properties of ICS and ECS are very different (Table 13.1). According to their $Na^+$ and glucose concentration, ICS is sweet, while ECS is salty. Despite such difference, the principle of iso-osmolarity is crucial for body balance: ICS osmolarity and ECS osmolarity must be the same. Osmotic pressure (μ) is the force exerted by the sum of osmotically active particles ($Na^+$ and other electrolytes) that do not freely pass through semipermeable membranes (Agrò and Vennari 2013a). According to osmotic pressure difference among the compartments, water freely passes form ICS to ECS, and vice versa, in order to achieve the equilibrium (Agrò and Vennari 2013a) (Fig. 13.4). In particular, water shifts from the body compartment with lower osmotic pressure to that with higher osmotic pressure. The osmotic pressure gradient between the two compartments is described as tonicity (Agrò and Vennari 2013a; Voet et al. 2001).

The osmotic pressure of the plasma osmotic pressure is $288 \pm 5$ mOsm/L, and it can be calculated by measuring the plasma concentrations of Na, glucose, and urea.

$$\text{Plasma osmotic pressure} = 2 \times \left[ Na^+ \right] (\text{mmol/L}) + \text{urea}/2{,}8 (\text{mg/dL}) + \text{glucose}/18 (\text{mg/dL})$$

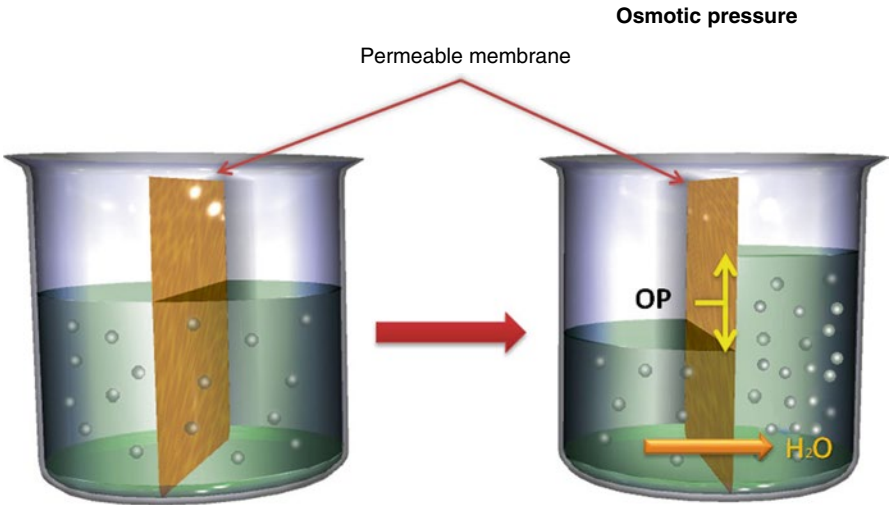



**Fig. 13.4** Osmotic pressure. According to osmotic pressure, water diffusion will take place from low to high electrolytic concentration (From Agrò and Vennari 2013a, pp. 1–26)

The difference between measured osmolarity and calculated osmolarity is called the osmolar gap. A high osmolar gap suggests either the presence of an exogenous compound (e.g., ethanol) whose identity should be sought or the elevation of endogenous constituents that may not have been measured (e.g., proteins, ketoacids, lipids) (Hendry 1961).

The main determinant of plasma osmolarity is $Na^+$. Sodium salts are responsible for the 95 % of the whole plasma osmotic pressure. Since osmotic pressure determines water tendency to move in or out of the cell, the $Na^+$ concentration is the main determinant of the relative volumes and hydration of the ICS and ECS (Voet et al. 2001). When the ECS osmotic pressure increases (i.e., hypernatremia), water immediately passes from ICS to ECS to restore osmotic equilibrium, leading to a reduction in ICS volume and an increase in ECS volume, while the opposite movement develops when ECS osmotic pressure is reduced (i.e., hyponatremia), with an increase in ICS volume and a reduction in ECS volume (Agrò and Vennari 2013a). Sodium and water movements are further related by the mechanism of regulation of osmolarity and volemia. They are hormonal systems such as ADH, renin–angiotensin–aldosterone (RAA) system, ANP, BNP, and the thirst. Although with different thresholds of sensibility (i.e., ADH is more sensible to osmolarity, while RAA system to volemia), they are all enrolled both in case of osmolarity and volemia alterations (Agrò and Vennari 2013a). Being the sole organ able to divide water movement from $Na^+$ movement, the kidney is the main target of the regulatory systems. When an increase in plasmatic osmotic pressure develops, ADH and the thirst promote water reabsorption and intake, while when plasmatic osmotic pressure reduces, the reduction in water intake and its increased kidney excretion restore normo-osmolarity (Agrò and Vennari 2013a) (Fig. 13.5).

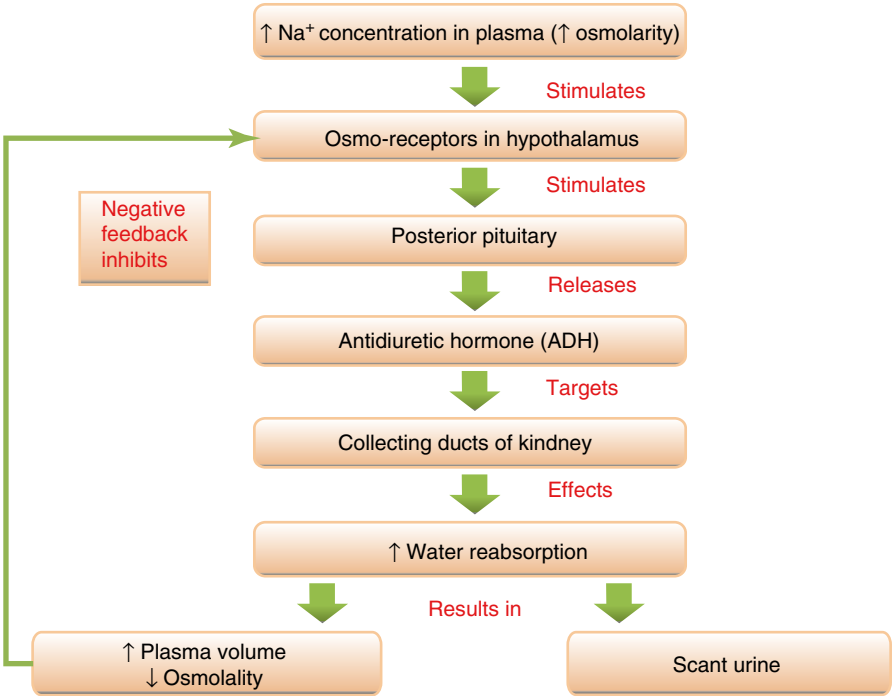



**Fig. 13.5** Mechanism of ADH secretion: when fluid volume decreases plasma sodium concentration and plasmatic osmolarity increases, leading to hypothalamic osmoreceptor stimulation. The hypothalamus will then stimulate the posterior pituitary gland that releases antidiuretic hormone. ADH will make renal distal tubules able to reabsorb water into the IVS in order to maintain homeostasis of fluid balance. ADH secretion is more sensible to plasmatic osmolarity than circulating blood (From Agrò and Vennari 2013b, pp. 71–92)

The RAA system is manly enrolled in sodium and water renal reabsorption, when hypovolemia develops. In case of hypervolemia, the ANP and the RAA system inhibition lead to excretion of sodium and water overload (Agrò and Vennari 2013a) (Fig. 13.6).

### 13.1.4 Fluid Movement Through Capillary Membranes

Fluid movements across capillary membrane are regulated by physical forces and specific properties of the semipermeable membranes (Agrò and Vennari 2013a).

Accordingly, electrolyte and protein concentrations, as well as osmotic properties, play a crucial role, as expressed in the Starling equation:

$$Jv = K_f \left( [P_c - P_i) \quad \sigma [\delta_c - \delta_i] \right)$$

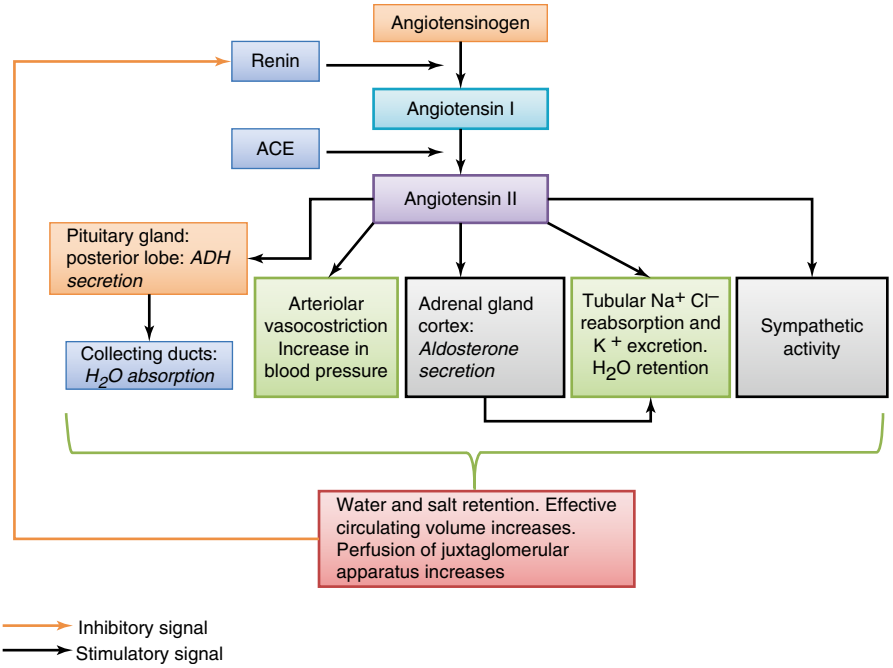



**Fig. 13.6** Renin–angiotensin–aldosterone system: hypovolemia reduces perfusion of juxtaglomerular apparatus, with renin release. Circulating renin converts angiotensinogen to angiotensin I; subsequently ACE (angiotensin-converting enzyme) acts on angiotensin I converting it to angiotensin II. This hormone increases NSS activity, increases reabsorption of Na and water by kidneys directly and through aldosterone action, and determines vasoconstriction and ADH secretion (From Agrò and Vennari 2013b, pp. 71–92)

According to this equation, water flow depends on six variables:

1. Capillary hydrostatic pressure ($P_c$)
2. Interstitial hydrostatic pressure ($P_i$)
3. Capillary oncotic pressure ($\delta_c$)
4. Interstitial oncotic pressure ($\delta_i$)
5. Filtration coefficient ($K_f$)
6. Diffusion coefficient ($\sigma$)

The equation states that the net filtration ($Jv$) is proportional to the net driving force ($[P_c - P_i] - \sigma\ [\delta_c - \delta_i]$). If this value is positive, water leaves the IVS (filtration). If it is negative, water enters or remains in the IVS (absorption) (Fig. 13.7). A modification of only one of the forces involved in the Starling equation may alter fluid movement across body compartment (Agrò and Vennari 2013a).

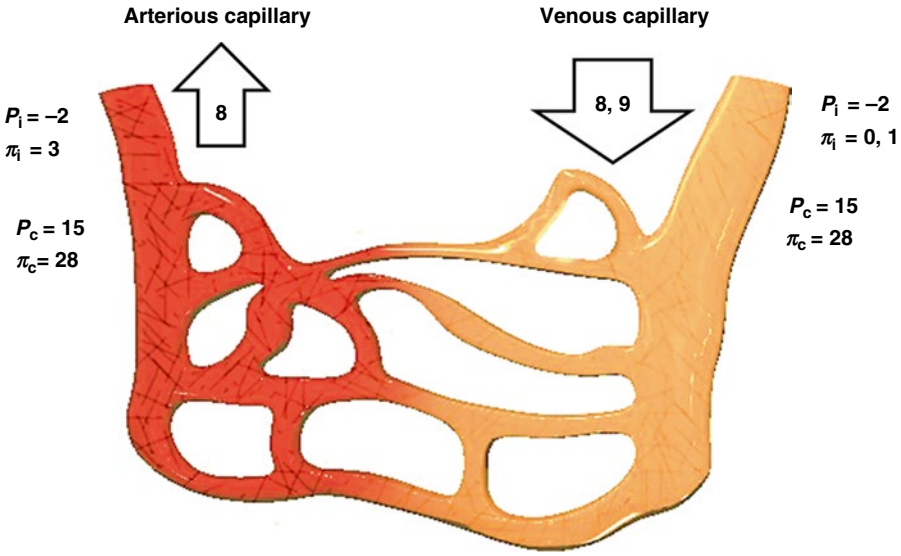



**Fig. 13.7** Starling forces. On the arterial side of capillary vessels, forces putting out water overcome those putting in. On the venous side is the contrary (Modified from Agrò and Vennari2013a, pp. 1–26)

## 13.2 Basis of Fluid and Electrolyte Pathophysiology in the Postoperative ICU Setting of Cardiac Surgery

### 13.2.1 Alterations in Water Distribution

Adequate fluid replacement in cardiac patients is fundamental to the successful of surgery. In patients undergoing cardiac surgery, a correct fluid management maintains an adequate circulatory volume and a proper electrolyte and acid–base balance, avoiding arrhythmic (i.e., atrial fibrillation), hemodynamic (i.e., hypotension, pulmonary edema), and other complications (Agrò et al. 2013a).

Hypovolemia is a frequent occurrence among cardiac surgical patients. Fluid imbalance may be due to an absolute volume deficit or to a relative volume deficit and may be associated to concurrent electrolyte and acid–base problems (Agrò et al. 2013a).

Absolute volume deficits can be due to hemorrhage (i.e., coagulation and platelet impairment, surgical complications) or to severe dehydration issues (i.e., diuresis induced by mannitol often used during cardiopulmonary bypass), while relative volume deficits can be due to vasodilatation caused by sedation, systemic inflammatory response syndrome (SIRS) due to surgical stress and cardiopulmonary

bypass (CPB), and by rewarming (Tommasino et al. 1988). In this case, there is a shift of fluid from IVS to ISS. Hypovolemia develops in absence of obvious fluid loss, leading to a reduction in cardiac index (CI), tissue perfusion, and $O_2$ delivery ($DO_2$) with a high risk of organ failure, potentially fatal (Agrò et al. 2013a).

Another cause of concern is the risk of fluid overload, which may precipitate or worsen the cardiac function (especially in patients with impaired ventricular contractility or compliance), leading to acute pulmonary edema and/or cardiogenic shock. These events may complicate patient management, requiring the use of inotropes and other cardiovascular active drugs. Moreover, a fluid overload may lead to interstitial edema, compression of microvasculature, and an increased oxygen diffusion distance, compromising $DO_2$ and $O_2$ diffusion to tissues (Fanzca 2012). Finally, aggressive perioperative fluid administration may cause hemodilution, with an increased need for blood products (Vretzakis et al. 2011).

In order to avoid both hypovolemia and fluid overload, stabilization of the cardiovascular system through a rational fluid therapy should take into account the type of surgery and the mechanism of fluid movement among body compartments (Stephens and Mythen 2003; Adams 2007).

According to Starling equation, ISS volume is generally maintained by lymphatic drainage. Any flux of fluid into the ISS increases its hydrostatic pressure and decreases its oncotic pressure, limiting the development of interstitial edema. In literature many works demonstrated that the Starling equation does not fully explain the movement between IVS and ISS across the endothelial membrane (Fanzca 2012; Adams 2007; Hu and Weinbaum 1999; Hu et al. 2000; Levick 2004). The deviation from theory is due to a meshwork of membrane bound, negatively charged glycoproteins and proteoglycans, called endothelial glycocalyx.

The endothelial glycocalyx is a dynamic structure continuously degraded and resynthesized. It is composed by proteins produced by endothelial cells or entrapped from the plasma. Glycocalyx is a barrier for larger molecules and probably is mainly responsible for the oncotic gradient across IVS and ISS (Fanzca 2012). Moreover, it prevents the endothelial adhesion of inflammatory cells, reducing the consequence of the increase of endothelial permeability. In fact, a damage of the glycocalyx leads to the passage of larger molecules form the IVS into the ISS, reducing the IVS–ISS oncotic gradient and increasing the ISS fluid volume with tissue edema. Various conditions associated to cardiac surgery may potentially destroy glycocalyx: hemodilution, ischemia and reperfusion damage, and inflammation (Fanzca 2012).

Hemodilution may cause the dissolution of bound plasma protein into the flowing blood and the loss of glycocalyx (Pries et al. 1998; Rehm et al. 2001). The effect may be due to ANP increased levels in cardiac surgery and to fluid overload (Fanzca 2012; Bruegger et al. 2005).

In patients undergoing cardiopulmonary bypass, plasma level of glycocalyx component (heparin sulfate and syndecam-1) was significantly increased with respect to preoperative levels, demonstrating a dangerous effect of ischemia on glycocalyx (Fanzca 2012; Rehm et al. 2007).

In a coronary artery animal model, the loss of glycocalyx due to ischemia leads to an increased permeability to water, albumin, and hydroxyethyl starches (Rehm et al. 2004).

Van den Berg et al. (2003) demonstrated in a rat model the correlation between the presence of myocardial edema and the absence of endothelial glycocalyx. Interstitial edema may be detrimental for cardiac cells resulting in impairment of function (Fanzca 2012; Dongaonkar et al. 2010).

### 13.2.2 Electrolyte Modifications

Strictly related to fluid management is the management of electrolyte and acid–base balance. Electrolyte alterations are frequent in the postoperative period after cardiac surgery. Polderman and Girbes (2004) compared sodium, potassium, calcium, magnesium, and phosphate levels at the admission to ICU of patient undergone CABG vs. patients undergone other major surgeries. Although all patients received electrolyte intraoperative supplementation, they found a higher percentage (88 % vs. 20 %) of patients with deficit of one or more electrolytes in the first group rather than in the second. These alterations may be due to increased kidney elimination, especially in the case of furosemide and mannitol use, and intracellular shift caused by alteration of ISS, IVS, and ICS equilibrium caused by CPB, extracorporeal circulation, and stress response (SIRS) (Fanzca 2012).

## 13.3 Clinical Management of Fluid-Therapy

The ideal approach to perioperative fluid management is still debated in cardiac surgery patients. In clinical practice, it may be very difficult: practitioners have to take into account surgical-related factors, such as kind of procedure and duration, CPB duration, SIRS, patient-related factors, such as cardiac disease, presence of reduced ventricular function and its postoperative modification, need for pharmacologic or mechanical assistance, comorbidities (renal and pulmonary dysfunctions are frequent among cardiac surgery patients), and possible complications.

The clinical and literary debate involves different specialists (anesthesiologists, intensivists, and surgeons) and concerns the establishment of the ideal fluid management in terms of kind and amount of fluid to administer.

### 13.3.1 Which Kind of Fluid?

The choice of the fluid to administer should be guided by the properties of the targeted body space (IVS, ISS, whole body water) (Agrò and Benedetto 2013).

Different solutions are available: crystalloids, colloids, and other fluids, such as dextrose solutions, mannitol solutions, and other concentrated solutions. Each one has its specific indications and side effects (Nuevo et al. 2013).

Historically, the debate about fluid management was developed around the dispute of crystalloids vs colloids. In its course, the medical literature has largely demonstrated the difference in the pharmacokinetics and pharmacodynamics of these two classes of plasma substitutes. Consequently, crystalloids should no longer be considered as an alternative to colloids, and vice versa. Instead, crystalloids and colloids must be considered as two faces of the same coin and their use as part of an integrative fluid management (Agrò and Vennari 2013b).

Recently, the historical debate of crystalloid vs colloid has enlarged to include colloid/colloid discussion. Nonetheless, the physical and chemical properties of various colloids determine the different therapeutic and adverse effects. Thus, any debate about intravenous volume replacement with colloids should consider the potential side effects, involving endothelial integrity, coagulation, platelet function, and organ function (e.g., the kidneys), and not only the effect of the chosen fluid on hemodynamics (Agrò et al. 2013a).

The electrolyte composition of the fluid (crystalloid or colloid) is another source of controversy. The debate on balanced, plasma-adapted solutions started in the 1970s, when their features were first described. A new definition was proposed in 2000 in "Avoiding Iatrogenic Hyperchloremic Acidosis: Call for a New Crystalloid Fluid," published in *Anesthesiology*, which referred to the classic need of "a solution containing sodium bicarbonate" because it was clear that "…the predominate physiologic deficit is metabolic acidosis…" (Dorje et al. 2000). Subsequent developments were summarized in 2003 by Reid et al. (2003), who highlighted that scientists and clinicians must inevitably reach a compromise in their long-standing attempts to find the ideal physiological solution.

### 13.3.2 Physical and Chemical Properties

Depending on their physical and chemical properties, IV solutions may be classified as balanced or unbalanced; plasma adapted or non-plasma adapted; and isotonic, hypertonic, or hypotonic (Agrò and Benedetto 2013).

A balanced, plasma-adapted solution has a composition closer to plasma. It contains sodium, chloride, potassium, magnesium, and calcium in similar concentrations than plasma and contains metabolizable anions, and it is isotonic respect to plasma (same osmolarity). Except for the risk of fluid overload, the infusion of this solution reduces the incidence of side effects related to fluid management, such as metabolic acidosis, electrolytic imbalances, and cellular tone alterations (Agrò and Benedetto 2013).

The infusion of hypotonic or hypertonic solutions will change plasma osmolarity, resulting in a modification of body water distribution. In particular, a hypotonic solution reduces plasma osmotic pressure, since water will move from the ECS to the ICS (Agrò and Benedetto 2013; Williams et al. 1999). Cellular edema and lysis (i.e., hemolysis) may occur (Fig. 13.8). Larger volumes of hypotonic solutions have

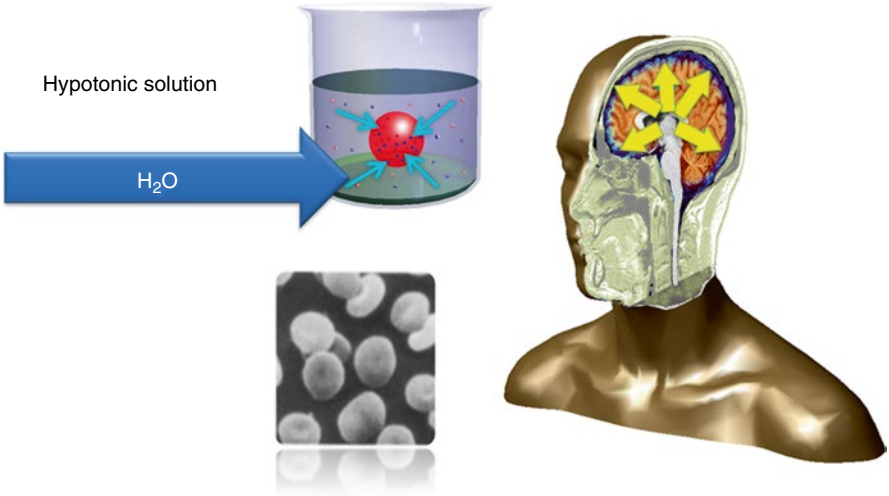



**Fig. 13.8** Cellular and cerebral edema caused by hypotonic solutions (Agrò and Benedetto 2013, pp. 27–36)

been known to produce a transient increase in intracranial pressure (ICP), due to cerebral edema (Agrò and Benedetto 2013; Tommasino et al. 1988). The magnitude of this increase can be predicted by the reduction of plasma osmolality (Agrò and Benedetto 2013; Schell et al. 1996). Patients with an osmolality below 240 mOsmol/kg will fall into a coma, with a mortality rate of 50 % (Agrò and Benedetto 2013; Arieff et al. 1976). Consequently, the infusion of large amount of hypotonic solutions should be avoided, except specific cases (Agrò and Benedetto 2013).

On the other side, hypertonic solutions increase plasma osmotic pressure, moving water from the ICS to the ECS, causing cellular dehydration and, potentially, apoptosis (Agrò and Benedetto 2013) (Fig. 13.9). Many clinical settings may increase plasma osmotic pressure, with a very high mortality (Agrò and Benedetto 2013). Hypovolemic shock triggers hyperglycemia with hyperosmolarity, through the release of epinephrine or through an increase in lactate blood levels (Agrò and Benedetto 2013; Boyd and Mansberger 1968; Järhult 1973; Kenney et al. 1983). It has been shown that in ICU patients, non-survivors had a higher plasma osmolarity than survivors (Agrò and Benedetto 2013; Holtfreter et al. 2006). Moreover, hypertonicity has been shown to make solutions more acidifying. The administration of hypertonic solution reduces strong ion difference (SID) through dilution caused by water movement from ICS to ECS (Makoff et al. 1970) (see Chap. 15).

## 13.4 Crystalloids

Crystalloids are low molecular weight salts, dissolved in water. After the infusion, water and salt pass across the body compartment according to physiology (Nuevo et al. 2013).

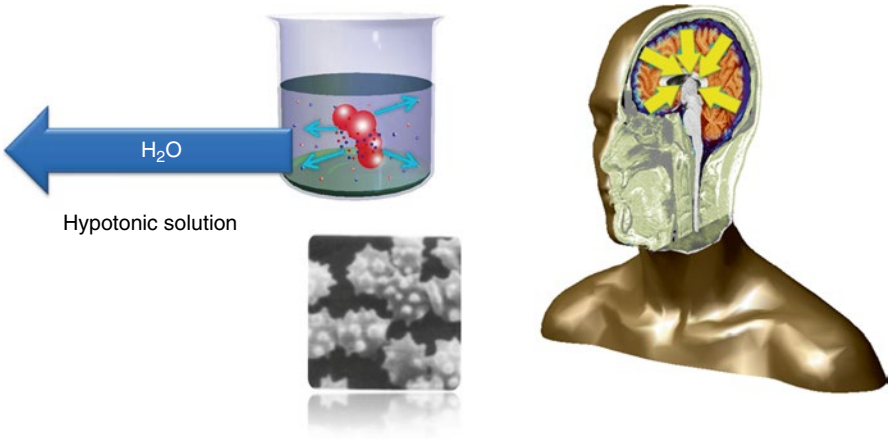



**Fig. 13.9** Hypertonic solutions cause cellular dehydration, leading to apoptosis (From Agrò and Benedetto 2013, pp. 27–36)

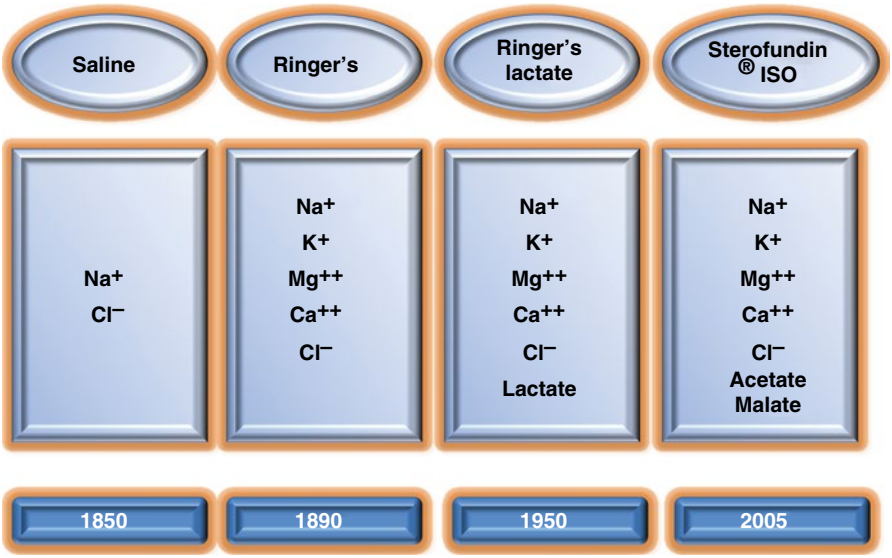



**Fig. 13.10** Crystalloid generations (Modified from Nuevo et al. 2013, pp. 37–46)

### 13.4.1 Classification

Based on their tonicity, crystalloids are classified as hypotonic, isotonic, or hypertonic. There are different generations of crystalloids on the market (Nuevo et al. 2013) (Fig. 13.10). Many studies have focused on producing more balanced and plasma-adapted crystalloids in order to reduce side effect of their use. So far, the rational use of crystalloids remains a clinical problem (Nuevo et al. 2013).

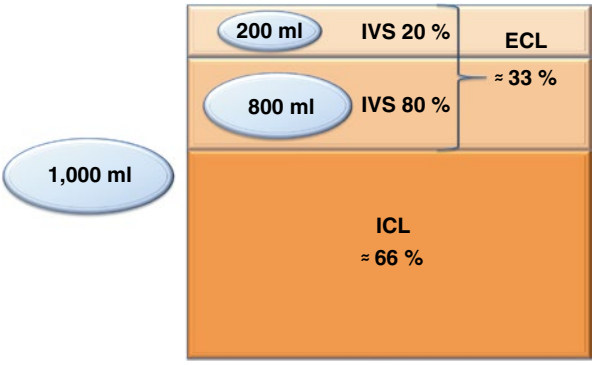



**Fig. 13.11** Representation of isotonic crystalloid distribution. *IVS* intravascular space, *ISS* interstitial space, *ECS* extracellular space (Modified from Nuevo et al. 2013, pp. 37–46)

### 13.4.2 Pharmacokinetics: Distribution and Duration of Action

An isotonic crystalloid is distributed in the IVS (20 %) but mostly in the ISS (80 %). Accordingly, the efficiency of these solutions to expand the plasma volume is only 20 %; the remainder is sequestered in the ISS (Agrò and Benedetto 2013; Reid et al. 2003; Lamke and Liljedahl 1976; Grathwohl et al. 1996; Greenfield et al. 1989; Hauser et al. 1980; Hahn et al. 1997; Takil et al. 2002) (Fig. 13.11). Olsson et al. (2004) found that approximately 30 % of infused crystalloids remain within the IVS for only 30 min. Crystalloids have a short-term volume effect due to their rapid movement from the IVS into the ISS (Nuevo et al. 2013). Thus, the use of crystalloids to replace severe volume deficits, following massive blood or rapid fluid loss, is not effective to restore fluid balance and blood pressure (Drummond and Petrovitch 2005; McIlroy and Kharasch 2003). Attaining the targeted goal of adequate blood pressure requires massive, repetitive infusions, causing the dilution of osmotically active component of plasma and a reduction in plasma oncotic pressure causing further interstitial edema and electrolyte imbalances (Fanzca 2012).

### 13.4.3 Properties of the Main Crystalloids

The main properties of the most widely used crystalloids are described in Table 13.2 (Nuevo et al. 2013).

### 13.4.4 Normal Saline Solution

The standard 0.9 % NaCl solution is also known as a normal or physiological saline solution. It contains only sodium and chloride, at the same high concentration ($Na^+ = Cl^- = 154$ mmol/L) (Nuevo et al. 2013). Consequently, its administration may cause metabolic acidosis and sodium overload. Sodium overload promotes interstitial edema, particularly in the face of the endocrine response to cardiac surgery, the

**Table 13.2** Main properties of crystalloids

| Electrolyte or parameter | Plasma | 0,9 % NaCl | Ringer lactate | Ringer acetate | Sterofundin® |
|---|---|---|---|---|---|
| Colloid osmotic press. (mmHg) | 25 | – | – | – | – |
| Osmolality (mOsm/kg) | 287 | 308 | 277 | 256 | 291 |
| Sodium (mEq/L) | 142 | 154 | 131 | 130 | 145 |
| Potassium (mEq/L) | 4.5 | – | 5,4 | 5 | 4 |
| Magnesium (mEq/L) | 1.25 | – | – | 1 | 1 |
| Chloride (mEq/L) | 103 | 154 | 112 | 112 | 127 |
| Calcium (mEq/L) | 2.5 | – | 1.8 | 1 | 2.5 |
| Bicarbonate (mEq/L) | 24 | – | – | – | – |
| Lactate (mEq/L) | 1 | – | 28 | – | – |
| Acetate/malate(mEq/L) | – | – | – | 27/– | 24–5 |
| SID (mEq/L) | 38–42 | 0 | 26 | 26 | 29 |

Modified from Nuevo et al. (2013, pp. 37–46)

cortisol- and aldosterone-induced sodium retention (Fanzca 2012). This mechanism may be further worsening in patients with kidney dysfunction or postoperative cardiac impairment (Nuevo et al. 2013). Finally, normal saline solution is slightly hypertonic (osm 308 mOsm/kg), potentially providing the tipical complications of hypertonic solutions including a high acidifying power (Nuevo et al. 2013). As a result, normal saline solution is not actually normal, because it is neither isotonic, nor balanced, nor plasma adapted (Nuevo et al. 2013).

### 13.4.5 Ringer Lactate and Ringer Acetate

Ringer solutions are second-generation crystalloids. Compared to saline solutions, they have less sodium (130 mmol/L) and less chloride (112 mmol/L). They also contain potassium, calcium, magnesium (Ringer acetate), and metabolizable ions: lactate (Ringer lactate) and acetate (Ringer acetate) (Nuevo et al. 2013).

Ringer lactate may interfere with lactate monitoring and may precipitate or aggravate a lactic acidosis, especially in critical cardiac patients (see Chap. 15). Therefore, Ringer acetate is generally preferred (Nuevo et al. 2013). Both Ringer solutions are more plasma adapted than normal saline, but are nonetheless unbalanced (Nuevo et al. 2013).

### 13.4.6 Latest-Generation Crystalloids

The ionic composition of the latest-generation crystalloids is very close to plasma. They have a lower chloride content than normal saline and have metabolizable

anions (acetate, malate). For this reason they differ from Ringer solutions that contain only acetate or malate as metabolizable anions (Nuevo et al. 2013). As a result, these are isotonic, balanced, and plasma-adapted solutions that reduce the risk of cellular osmotic damage (particularly cerebral), of chloride and sodium excess, and dilution acidosis, with a decreased influence on lactate monitoring, lactic acidosis, and base excess (BE) (Nuevo et al. 2013, see Chap. 15).

### 13.4.7 Potential Risks and Side Effects

#### 13.4.7.1 Water Distribution Modification

Over the past decades, clinicians have routinely restored fluid in the IVS with crystalloids. However, due to the rapid interstitial fluid shifts and the great distribution volume of crystalloids, large doses must be administered. This in turn causes fluid overload, particularly interstitial edema and potential pulmonary edema (they may be deleterious for cardiac surgery patients), as well as metabolic acidosis (Nuevo et al. 2013). Finally, a crystalloid volume-replacement strategy may alter the plasma albumin concentration. Large-volume infusions of crystalloids can lead to albumin hemodilution effects and cause a reduction in colloid oncotic pressure (COP), yet reduced by extracorporeal circulation diluting effects (Fanzca 2012; Nuevo et al. 2013). The reduction of COP alters Starling forces: fluids move from the IVS to ISS and remain in the ISS. The result is interstitial edema up to "compartmental syndrome," and thus albumin leakage (a vicious circle is established!) with a little improvement of hemodynamics (IVS fluid has not been restored because the infused volume shifts in ISS) (Nuevo et al. 2013; Cervera and Moss 1974). In critically ill patients, a reduction in COP is associated with a mortality rate of approximately 50 % (Nuevo et al. 2013; Morissette et al. 1975; Rackow et al. 1977).

#### 13.4.7.2 Electrolyte Modifications

A large amount of crystalloids infusion may cause hyperchloremia (especially using older generation crystalloid) that alters kidney perfusion leading to sodium and chloride retention. Chloride retention brings to hyperchloremic acidosis further invalidating glomerular filtration rate, while sodium overload causes water retention (Nuevo et al. 2013). The result is a fluid overload that may precipitate the hemodynamic status of the patient, especially in the first hours after the surgery, with a weight gain that may increase mortality (Nuevo et al. 2013; Zander 2009).

#### 13.4.7.3 Clotting Disorders

It is common knowledge that crystalloid administration is an economical means of volume replacement, with an apparently lower risk of clotting disorders (Nuevo et al. 2013). However, in two studies Ruttmann et al. (2001, 2002) and Ng et al. (2002) have shown that in vivo dilution with crystalloids resulted in a significant potentiation of coagulation, due to a decreased concentration of antithrombin III. The resultant hypercoagulability is unrelated to the type of crystalloid. It is also associated with an increased risk of perioperative deep vein thrombosis (Nuevo et al. 2013).

### 13.4.8 Hypertonic Crystalloids

Hypertonic crystalloid solutions (HCS) contain higher sodium concentrations, ranging from 3 to 7.5 % (Nuevo et al. 2013). According to their high osmolarity, they have a greater expanding volume effect with respect to isotonic crystalloid. HCS may improve the cardiovascular system (especially after CPB-related changes in body fluid compartments due to a capillary permeability) with only a smaller infused volume than isotonic crystalloids (4 mL/kg). However, HCS have a transient volume effect (Nuevo et al. 2013).

Jarvela et al. (2001) studied patient fluid management after CABG surgery. They found that 30 min after the infusion 7.5 % hypertonic saline determined a higher volume expansion with respect to HES 6 %/120/0.7, but lower after 70 and 110 min. HES volume expansion persists for all the observation time, while 7.5 % hypertonic saline volume expansion was shorter. EVS expansion was greater and faster with HCS than with 0,9 % saline solution.

The hemodynamic effects of HCS can be due to the following mechanisms (Nuevo et al. 2013):

- Direct myocardial, positive inotropic effect
- Direct vasodilator effect (both the systemic and the pulmonary circulation)
- Reduced venous capacitance
- Fluid shift into the IVS from ISS

Initially, there was enthusiasm in the use of HCS for patients in refractory hypovolemic shock states; At the beginning there was great enthusiasm in the use of HCS, especially in refractory hypovolemic shock states. However they may have life-threatening side effects (Nuevo et al. 2013).

After their infusion, there is a rapid shift of water from EVS into the IVS, without a reduction in COP (McIlroy and Kharasch 2003). An adequate volume status of both the ICS and ECS spaces is necessary to obtain this effect; so that, the prolonged usage of HCS crystalloid is not recommended (Maningas and Bellamy 1986; McIlroy and Kharasch 2003). Both Wade et al. (1997) and Bunn et al. (2002) reported, in their meta-analyses, no significant improvement in outcome in critical patients by using HCS. They hypothesized that the combined used of HCS and colloids would be superior to isotonic fluid resuscitation (Agrò and Vennari 2013b). HCS infusion may be indicated in case of hyposmolarity with hyponatremia (see subsequent paragraphs).

## 13.5 Colloids

Colloids are high molecular weight molecules that do not dissolve completely in water, nor do they pass freely through the capillary membrane. According to their molecular size, structure, and vessel permeability, colloids determine the oncotic pressure (Agrò et al. 2013b).

### 13.5.1 Classification

Many colloids have been studied. They include natural colloids (human albumin, HA) and synthetic colloids (dextrans, gelatins, hydroxyethyl starches), differing in

**Table 13.3** Properties of some colloid

| Electrolyte or parameter | Plasma | Venofundin® 6 % | Gelofusine® 4 % | Tetraspan® 6 % |
|---|---|---|---|---|
| Colloid osmotic press. (mmHg) | 25 | 37.8 | 33.3 | 37.8 |
| Osmolality (mOsm/Kg) | 287 | 308 | 274 | 296 |
| Colloid molecule | Albumin | HES 130/0.42 | MFGel | HES 130/0.42 |
| Sodium (mEq/L) | 142 | 154 | 154 | 140 |
| Potassium (mEq/L) | 4.5 | – | – | 4 |
| Magnesium (mEq/L) | 1.25 | – | – | 1 |
| Calcium (mEq/L) | 2.5 | – | – | 2.5 |
| Chloride (mEq/L) | 103 | 154 | 120 | 118 |
| Bicarbonate (mEq/L) | 25 | – | – | – |
| Acetate/malate (mEq/L) | – | – | – | 24/5 |

From Agrò et al. (2013b, pp. 47–70)

their physicochemical properties, pharmacokinetics, clinical effects, and safety. Colloids also can be classified according to their electrolyte composition and tonicity. Consequently, there are balanced and unbalanced colloids, plasma-adapted and non-plasma-adapted colloids, and isotonic and hypertonic colloids (Agrò et al. 2013b).

### 13.5.2 Physiological Properties of the Main Colloids

The table below describes the main properties of some colloids used in clinical practice (Agrò et al. 2013b) (Table 13.3).

### 13.5.3 Pharmacokinetics: Distribution and Duration of Action

The IVS volume expansion after the infusion of a colloid depends on the oncotic pressure and the molecular weight (MW), and the higher the oncotic pressure and the higher the MW, the greater the initial volume increase in the intravascular space (IVS) after the infusion. The duration of IVS volume expansion is influenced by MW and organ elimination (mainly kidneys). Thus, different colloids have different durations of volume effects (Agrò et al. 2013b; Mitra and Khandelwal 2009).

Isotonic and iso-oncotic colloids have a lower volume-replacing power, in contrast to hypertonic and hyperoncotic colloids. Based on previous evidence (Agrò et al. 2013b; Nadler et al. 1962), McIlroy and Kharasch (2003) found that an isotonic colloid is distributed only within the IVS. The efficiency of this kind of solution to expand plasma volume is thus 100 % with respect to the infused volume (Agrò et al. 2013b) (Fig. 13.12). However, iso-oncotic, isosmotic colloids rapidly leave the vascular tree, through extravasation or metabolism, especially during certain conditions, such as systemic inflammation, sepsis, capillary leak syndrome, and third-space syndrome, reducing the effective expansion of IVS volume (Chappell et al. 2008; Agrò et al. 2013b; Roberts and Bratton 1998).

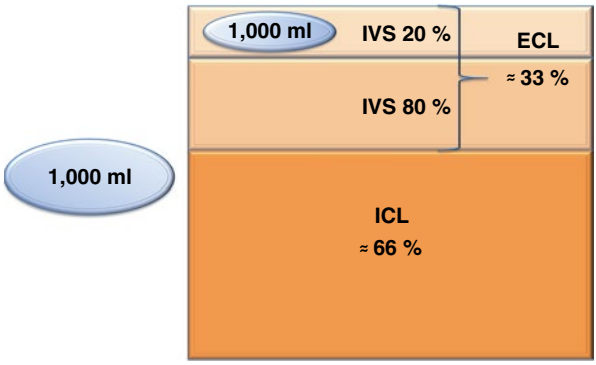



**Fig. 13.12** Isotonic colloid distribution. *IVS* intravascular space, *ECS* extracellular space, *EVS* extravascular space, *ICS* intracellular space (From Agrò et al. 2013b, pp. 47–70)

## 13.6 Natural Colloids: Albumin (HA)

For many years, HA was considered the gold standard in hypovolemia treatment. HA is composed of 585 amino acids with a molecular mass of 69,000 Da. It is the main plasma protein (50–60 %), accounting for 80 % of normal oncotic pressure. Furthermore, HA contributes to the formation of a normal anion gap and acid–base balance while being a charged protein (Agrò et al. 2013b).

### 13.6.1 Composition and Concentration

Current HA solutions consist of 96 % albumin, with the remaining 4 % being globulins. Different concentrations of HA are commercially available: 20 and 25 % HA (hyperoncotic), 5 % HA (iso-oncotic), and 4 % HA (hyponcotic) (Agrò et al. 2013b).

### 13.6.2 Pharmacokinetics: Distribution, Elimination, and Duration of Action

A 5 % HA solution can be reasonably considered for volume replacement, leading to an 80 % initial volume expansion, whereas HA 25 % leads to a 200–400 % volume increase within 30 min. The volume effect lasts for 16–24 h (Agrò et al. 2013b; Mitra and Khandelwal 2009). The decrease in the plasma HA concentration is firstly due to passage from the IVS to the EVS through the transporter albondin (transcapillary exchange) and secondly to the fractional degradation rate (Agrò et al. 2013b; Dubois and Vincent 2007).

### 13.6.3 Clinical Use

There is an extensive literature about the use of HA as the treatment for acute hypovolemia, especially in cardiac surgery. In this class of patients, it has been

historically considered the best volume-replacement solution. Additional applications are sepsis, systemic inflammatory response syndrome, and capillary leakage syndromes (Agrò et al. 2013b).

Based on the results of the SAFE study Investigators et al. (2011), HA has been mainly used to treat low plasma protein levels, especially in Austrian and German hospitals. The rationale is to prevent fluid extravasation by increasing the IVS COP in patients at high risk of hypoalbuminemia (Agrò et al. 2013b). Low serum albumin (<2 g/dL) was shown to be a marker of poor outcome, with a mortality of approximately 100 % (Agrò et al. 2013b; Fleck et al. 1985; Marik 1993; Margarson and Soni 1998; Rubin et al. 1997).

HA is not exclusively retained in the IVS: rather, 10 % of the administered dose leaves the IVS within 2 h. It is therefore likely to leak into the ISS, potentially aggravating interstitial edema and hypoalbuminemia, without clinical benefits, especially in patients with increased vessel permeability (cardiac surgery, cardiopulmonary bypass stress response, glycocalyx damages) (Agrò et al. 2013b).

A meta-analysis by Russell et al. (2004) showed HA use yields good results with respect to platelet count as well as a positive influence on oncotic pressure and postoperative weight gain in cardiac surgery patients, with respect to crystalloids.

HA rational use is guided by absolute and relative indications. The administration of HA is indicated in acute conditions requiring plasma expansion and in chronic conditions characterized by low albumin plasma levels (Vincent et al. 2003). There is widespread consensus in the literature and in clinic regarding absolute indications. Relative indications refer to settings in which HA is indicated when other specific criteria are satisfied (Agrò et al. 2013b).

The cardiac surgery is a relative indication to HA use. Particularly in hypoalbuminemic cardiac surgery patients, even if the clinical benefits are not yet clear (Agrò et al. 2013b). Another relative indication that may be present in cardiac surgery patients is hemorrhagic shock (Agrò et al. 2013b).

HA dose can be calculated as follows (Agrò et al. 2013b):

$$\text{Dose}(\text{g}) = \left[\text{targeted albuminemia}(2.5\,\text{g/dL}) - \text{real albuminemia}(\text{g/dL})\right] \times \text{plasmatic volume}(0.8 \times \text{body weight in kg})$$

Albumin is routinely administered, albeit improperly, in post-cardiac surgery ICU patients in case of (Agrò et al. 2013b):

- Hypoalbuminemia in the absence of peripheral edema or acute hypotension
- Malnutrition and malabsorption
- Wound healing
- Nonhemorrhagic shock
- Diuretic-responsive ascites
- Hemodialysis
- Ischemic stroke.

HA use in the cardiac surgery patient is expensive and the clinical advantages achievable do not seem to justify its cost (Agrò et al. 2013b).

### 13.6.4 Potential Risks and Side Effects

Several lines of evidence explain why HA supplementation may worsen the ICU patient condition (Agrò et al. 2013b). In fact, after rapid volume replacement, cardiac failure may occur, causing or worsening pulmonary edema, especially in capillary leak syndrome (Agrò et al. 2013b; Kaminski and Williams 1990). Furthermore, HA may impact coagulation and hemostasis by enhancing antithrombin III activity and inhibiting platelet function (Agrò et al. 2013b; Rajnish et al. 2004). Tobias et al. (1998) found that albumin may also lead to hypocoagulability. Dietrich et al. (1990) showed an in vitro increase in bleeding time, which may increase blood loss in postsurgical patients. Finally, albumin administration may impair the efficiency of endothelial cell adhesion. The importance of this effect is uncertain, since increased plasma levels of endothelial adhesion molecules may be markers of mortality (Agrò et al. 2013b; Kaminski and Williams 1990).

In acute renal failure, HA may accumulate after its massive administration (Agrò et al. 2013b; Kaminski and Williams 1990).

HA is generally well tolerated, but immediate allergic reactions are possible, consisting in fever, nausea, vomiting, pruritus, hypotension, and even cardiorespiratory collapse (Agrò et al. 2013b).

## 13.7 Synthetic Colloids

Synthetic or artificial colloids (dextrans, gelatins, hydroxyethyl starches) are produced from biological, nonhuman molecules. Their assessment criteria include (Agrò et al. 2013b) (Table 13.4):

- Concentration
- Initial volume effect
- Duration of the volume effect
- Side effects

**Table 13.4** Comparison between therapeutic and side effects of artificial colloids

| | Volemic effect | | Side effect | | |
|---|---|---|---|---|---|
| Colloid | Efficacy | Duration | AKI | Coag. | Anaph. |
| Dextrans | +++ | +++ | $+++_{(40)}$ | $+++_{(70)}$ | ++ |
| Gelatins | + | + | + | + | +++ |
| HES high MMW | +++ | +++ | ++ | +++ | + |
| HES low MMW | +++ | ++ | + | ++ | + |

From Agrò et al. (2013b, pp. 47–70)
+ mild, ++ moderate, +++ high, *MMW* mean molecular weight

## 13.8 Dextrans

Dextrans are glucose polymers of different sizes, derived from *Leuconostoc mesenteroides*, a bacterium originally isolated from contaminated sugar beets (Agrò et al. 2013b).

Dextrans are mainly used in the USA, as they are no longer available in European countries. The most widely used dextran solutions are dextran 40 (a 10 % solution with 40,000 mean MW) and dextran 70 (a 6 % solution with 70,000 mean MW) (Agrò et al. 2013b) (Table 13.5).

### 13.8.1 Pharmacokinetics: Distribution, Elimination, and Duration of Action

Dextrans are endowed with a high COP, due to their high water-binding capacity. After the infusion, dextrans lead to a 100–150 % increase in the volume of the IVS (Agrò et al. 2013b; Mitra and Khandelwal 2009). They are mainly eliminated by the kidney, while only a small fraction transiently passes into the ISS or is eliminated by the gastrointestinal tract. In particular, smaller molecules (14,000–18,000 kDa) are excreted by the kidneys within 15 min, whereas larger molecules are excreted after several days. At 12 h from administration, 60 % of dextran 40 and 30 % of dextran 70 has already been eliminated (Agrò et al. 2013b; Mitra and Khandelwal 2009; Arthurson et al. 1964; Atik 1967).

### 13.8.2 Clinical Use

Dextran solutions may be suitable in post-cardiac surgery ICU patients because they have positive effects on circulation. In fact, they have been shown to adequately restore and maintain hemodynamic in case of shock and to ameliorate tissue perfusion and microcirculation. At the same degree of hemodilution, rheological effects are mainly correlated with the use dextran 40 rather than with any other plasma substitute. Moreover, dextran protects against ischemia–reperfusion injury by reducing the harmful interactions between activated leukocytes and the microvascular endothelium (Agrò et al. 2013b).

**Table 13.5** Main properties of dextrans

| Characteristics of dextran solutions | 6 % Dextran 70 | 10 % Dextran 40 |
|---|---|---|
| Mean molecular weight (Dalton) | 70,000 | 40,000 |
| Volume efficacy (%) | 100 | 175–(200) |
| Volume effect (hours) | 5 | 3–4 |
| Maximum daily dose (g/kg) | 1.5 | 1.5 |

From Agrò et al. (2013b, pp. 47–70)

### 13.8.3 Potential Risks and Side Effects

Despite evidence on improvement of macro- and microcirculation after infusion, dextrans are no longer used because of their side effects (Agrò et al. 2013b).

Dextrans administration may lead to anaphylactoid reactions more frequently and more severely than other colloids. This is due to the massive production of vasoactive mediators triggered by anti-dextran antibodies. These reactions may be prevented by pretreatment of the solution with 20 mL of hapten (dextran 1,000) few minutes before infusion (Agrò et al. 2013b; Allhoff and Lenhart 1993).

Another possible side effect is renal dysfunction and AKI, through the production of hyperviscous urines leading to swelling and vacuolization of tubular cells and tubular plugging. This is especially true in patients with advanced age, hemodynamic alterations, preexisting renal disease, and dehydration (Agrò et al. 2013b; Mitra and Khandelwal 2009; Baron 2000; Moran and Kapsner 1987).

Finally, dextrans may alter platelet function, decrease factor VIII levels, and increase fibrinolysis, with significant bleeding disorders, especially after the administration of high doses (Agrò et al. 2013b; Mitra and Khandelwal 2009; Barron et al. 2004). These side effects resulted in maximum daily dose recommendation of approximately 1.5 L (Feng et al. 2006).

Currently, dextrans have a very limited use in the clinical practice, especially in ICU patients who present many risk factors for the development of dextran side effects (Agrò et al. 2013b).

## 13.9 Gelatins

Gelatins are polydispersed peptides derived from bovine collagen. Three types of gelatins are currently available: cross-linked or oxypolygelatins (e.g., Gelofundiol), urea-cross-linked gelatins (e.g., Haemagel), and succinylated or modified fluid gelatins (e.g., Gelofusine) (Table 13.6). Their average MW is 30–35,000 Da, and they are based on unbalanced, hypotonic solutions. In particular, polygelines are dispersed in a 3.5 % polyelectrolyte solution generally containing $Na^+$ 145 mEq/L, $K^+$ 5.1 mEq/L, $Ca^{2+}$ 6.25 mEq/L, and $Cl^-$ 145 mEq/L. Thus, they may increase serum calcium,

**Table 13.6** Main properties of gelatins

| Characteristics of gelatin solutions | Succinylated gelatins | Cross-linked gelatins | Urea-cross-linked gelatins |
|---|---|---|---|
| Concentration (%) | 4.0 | 5.5 | 3.5 |
| Mean molecular weight (Dalton) | 30,000 | 30,000 | 35,000 |
| Volume efficacy (%) | 80 | 80 | 80 |
| Volume effect in hours | 1–3 | 1–3 | 1–3 |
| Osmolarity (mOsm/L) | 274 | 296 | 301 |

From Agrò et al. (2013b, pp. 47–70)

in particular after large-volume infusions. Succinylated gelatins are dispersed in a 4 % polyelectrolyte solution generally containing $Na^+$ 154 mEq/L, $K^+$ 0.4 mEq/L, $Ca^{2+}$ 0.4 mEq/L, and $Cl^-$120 mEq/L (effective SID = 34). Their low chloride content reduces the risk of hyperchloremic acidosis and may be helpful in patients with acid–base alterations (see Chap. 15). They are compatible with blood transfusions because of their low calcium content (Agrò et al. 2013b; Mitra and Khandelwal 2009).

### 13.9.1 Pharmacokinetics: Distribution, Elimination, and Duration of Effect

Gelatins have similar IVS volume-expanding power and a half-life of about 2.5 h. After 24 h post-administration, 13 % remains in the IVS, 16 % has passed into the ISS, 71 % is rapidly cleared by the kidneys, and a small amount has been cleaved by proteases in the reticuloendothelial system (RES). Notably, the volume expansion is lower than the infused volume (about 70–80 %). Gelatins have the shortest duration of effect than any other colloids. Therefore, repeated infusions are required and allowed by their rapid elimination, as there are no dose limitations, in contrast to other colloids (Agrò et al. 2013b; Mitra and Khandelwal 2009; Barron et al. 2004).

### 13.9.2 Potential Risks and Side Effects

In ICU patients and in patients with severe hemorrhagic shock, who need large intravascular volume replacement, gelatin solutions are still widely adopted because of the lack of accumulation in the reticuloendothelial system (RES), the unlimited dose, and the absence of significant side effects on kidney function. Conversely, they are the second most frequent cause of anaphylactic shock in cardiac surgery patients, following antibiotics (Agrò et al. 2013b; Barron et al. 2004).

Historically, gelatins have been considered safer than other colloid with respect to bleeding. However, recently, there has been evidence of platelet dysfunction and clotting disorders (Agrò et al. 2013b). In a study comparing the effects of progressive hemodilution with gelatins, saline, hydroxyethyl starches, and albumin on blood coagulation, significant changes in the thromboelastogram were found after the infusion of gelatin solutions (Adamson 2008). Nonetheless, in clinical practice, they seem to impair fibrin polymerization less than the "modern" medium molecular weight starches (Agrò et al. 2013b).

## 13.10 Hydroxyethyl Starches

Hydroxyethyl starches (HES) are modified natural polysaccharides derived from amylopectin, a highly branched starch similar to glycogen, derived from maize or potatoes. Polymerized D-glucose units are connected by 1–4 linkages with one 1–6 branching linkage every 20 glucose units. Natural starches cannot be used in clinical

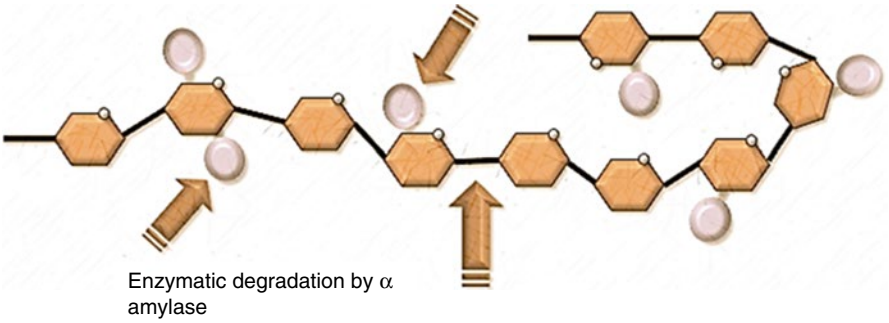



**Fig. 13.13** Effect of **α**-amylases on natural starches (From Agrò et al. 2013b, pp. 47–70)

routine since they are rapidly hydrolyzed by circulating α-amylases (Fig. 13.13). HES are obtained by replacing the hydroxyl groups of natural starches with hydroxyethyl groups at the C2, C3, and C6 carbon positions of anhydroglucose residues. A greater solubility and less amylase degradation are obtained, especially for hydroxyethyl groups at the C2 position (Agrò et al. 2013b; Mitra and Khandelwal 2009).

### 13.10.1 Classification

The first HES was produced in the 1970s in the USA. Since then, further generations have been produced. HES are designated by a series of numeric parameters (e.g., HES 10 % 200/0.5/5) reflecting their pharmacokinetics. The first number relates to the solution concentration, the second represents the mean MW (MMW), the third is the molar substitution rate (MSR), and the fourth is the C2:C6 ratio. Thus, HES may be classified according to (Agrò et al. 2013b):

- Concentration (3 %, 6 %, 10 %)
- MMW (low molecular weight, 70 kDa; medium molecular weight, 130–270 kDa; high molecular weight, >450 kDa)
- MSR (low MS, 0.4–0.5; high MS, 0.62–0.7)
- C2:C6 ratio

The volume-expansion power of HES is firstly influenced by concentration. HES at 6 % concentration are iso-oncotic and have a 100 % volume-expanding power (1 L of fluid infused = 1 L of plasma volume expansion). HES at 10 % concentration are hyperoncotic and have a volume-expanding power >100 % (1 L of fluid infused = >1 L of plasma volume expansion) (Agrò et al. 2013b; Mitra and Khandelwal 2009; Dubois and Vincent 2007).

HES are polydispersed solutions made up of different-sized molecules. Particles with a low MW (45–70 kDa) have a rapid enzymatic degradation and a fast renal excretion, because their size is under the renal threshold. Particles with high MW (>70 kDa) have a longer half-life, according to both their size and their rate of enzymatic degradation. The combined effect of the particles with different metabolism

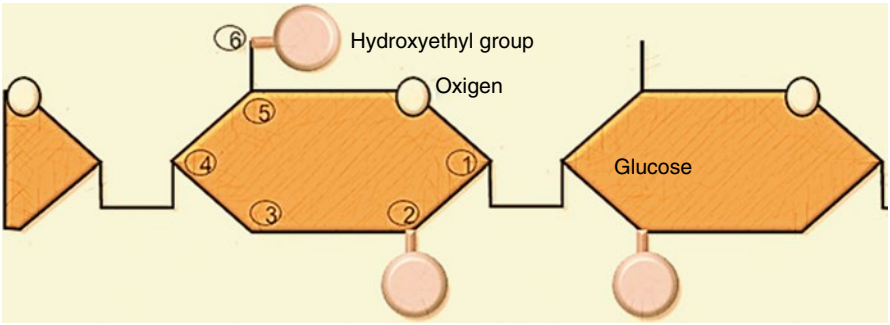



**Fig. 13.14** Representation of the C2:C6 ratio (From Agrò et al. 2013b, pp. 47–70)

influences duration of volemic effect after HES infusion (Agrò et al. 2013b; Barron et al. 2004).

The MSR is the rate of the total number of hydroxyethyl groups to the total number of glucose units. The MSR impacts human α-amylase degradation and thus the breakdown of the starch: the higher the MSR, the slower the degradation, the longer the volume effect, and the higher the incidence of side effects (Agrò et al. 2013b; Mitra and Khandelwal 2009; Barron et al. 2004).

The quotient of the total number of hydroxyethyl groups on carbon atom 2 and the total number of hydroxyethyl groups on carbon atom 6 yields the C2:C6 ratio (Fig. 13.14). For example, a C2:C6 ratio of 9 to 1 means that substitution with hydroxyethyl groups at position C2 is nine times higher than at position C6 (Agrò et al. 2013b; Barron et al. 2004). The C2 hydroxyethyl group hinders the action of α-amylase, delaying HES degradation and increasing the volume-expanding power. A higher C2:C6 ratio means lower α-amylase degradation, with a longer and greater volume effect (Agrò et al. 2013b; Mitra and Khandelwal 2009; Barron et al. 2004).

HES can also be classified according to the electrolyte features of the carrier solution, yielding balanced or unbalanced, plasma-adapted, and non-plasma-adapted HES solutions (Agrò et al. 2013b).

Three successive generations of HES have been commercialized (Agrò et al. 2013b) (Table 13.7):

- First generation: MW > 450 kDa, MS > 0.7, and high C2:C6 ratio
- Second generation: lower MW (200 kDa), MS (0.5), and lower C2:C6 ratio
- Third generation: MW = 130 kDa, MS < 0.5, and lower C2:C6 ratio

Thus, HES widely differ with respect to the extent and duration of their volume-expansion power and their side effects (Agrò et al. 2013b).

### 13.10.2 Pharmacokinetics: Distribution, Elimination, and Duration of Action

The water-binding capacity of HES varies between 20 and 30 mL/g (Agrò et al. 2013b; Mitra and Khandelwal 2009). As previously described, smaller

**Table 13.7** Comparison between HES generation properties

| Concentration | Origin | Solvent | Mean molecular weight (MMW) | Molar substitution rate (MSR) | C2:C6 ratio |
|---|---|---|---|---|---|
| 3 % (hyponcotic) | Potato-derived HES | Unbalanced | Low = 70 KD | Low = <0.5 | 9:1 |
| 6 % (normoncotic) | Waxy maize-derived HES | Balanced | Medium 130–370 KD | Medium = 0.5 | 6:1 |
| 10 % (hyperoncotic) | – | – | High > 450 KD | High = >0.5 | 4:1 |

From Agrò et al. (2013b, pp. 47–70)

**Table 13.8** Properties of different HES

| Properties | HES 70/0.5 | HES 130/0.4 | HES 200/0.5 | HES 200/0.5 | HES 200/0.62 | HES 400/0.7 |
|---|---|---|---|---|---|---|
| Concentration (%) | 6 | 6 | 6 | 10 | 6 | 6 |
| Mean molecular weight (KD) | 70 | 130 | 200 | 200 | 200 | 450 |
| Volume effect in hours | 1–2 | 2–3 | 3–4 | 3–4 | 5–6 | 5–6 |
| Volume efficacy (%) | 100 | 100 | 100 | 130 | 100 | 100 |
| Molar substitution rate | 0.5 | 0.4 | 0.5 | 0.5 | 0.62 | 0.7 |
| C2:C6 ratio | 4:1 | 9:1 | 6:1 | 6:1 | 9:1 | 4.6:1 |

From Agrò et al. (2013b, pp. 47–70)

molecules are rapidly excreted by the kidney (up to 50 % of the administered dose within 24 h), whereas larger molecules are retained for longer amounts of time. The oncotic effect of HES is due solely to the number of particles, and not their size. While renal elimination of the small molecules reduces the oncotic power, this is compensated by the enzymatic degradation of the large molecules. Consequently, the expanding power of HES is greater than that of other synthetic colloids, particularly gelatins (Agrò et al. 2013b). The duration of the volume effect equals the time interval of HES retention in the vascular bed, usually 8–12 h. A minor amount of the small molecules passes into the ISS, for later redistribution and elimination. Another fraction is trapped by RES, which slowly breaks down the starch (tissue storage) (Agrò et al. 2013b; Mitra and Khandelwal 2009). Thus, HES can be detected for several days after their infusion (Solanke et al. 1971).

As mentioned, there are potato- and maize-derived HES. They have the same oncotic power and plasma-expanding effects, even if the former have a more rapid elimination due to their lower amylopectin content (about 80 %) (Agrò et al. 2013b; Lehmann et al. 2007).

In the subsequent HES generations, MMW, MSR, and the C2:C6 ratio have been modified to allow α-amylase degradation, to reduce the retention of residual fractions, and to prolong the volume effect, with less accumulation and side effects (Agrò et al. 2013b; Mitra and Khandelwal 2009) (Table 13.8).

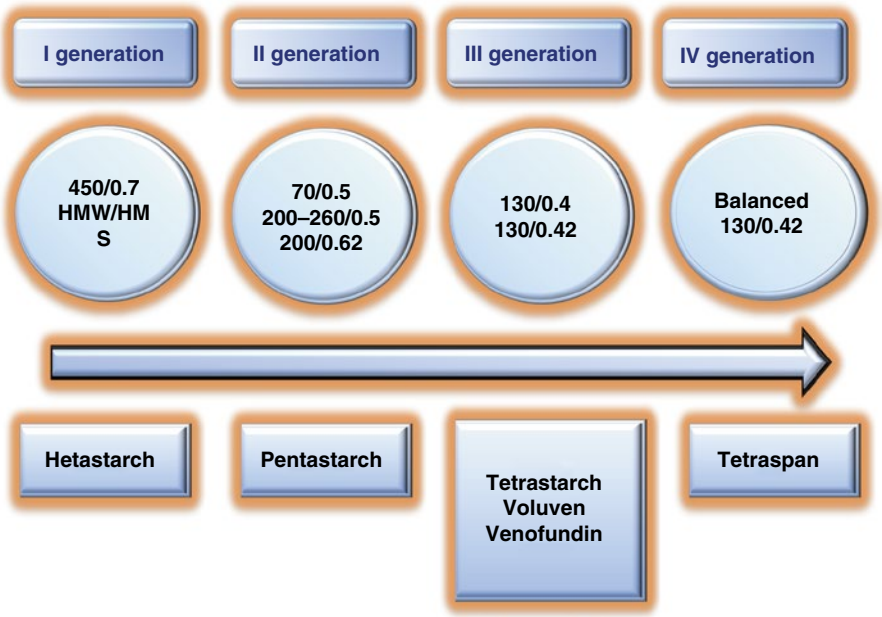



**Fig. 13.15** The four HES generations (From Agrò et al. 2013b, pp. 47–70)

HES molecules had generally dispersed in unbalanced, non-plasma-adapted solutions (first, second, and third generations). The first balanced HES solution (Hextend) had high MMW (550 kDa) and MS (0.7). However, it resulted in tissue storage, impaired coagulation, and platelet dysfunction. Consequently, the fourth-generation HES have a lower MMW and MSR and are dissolved in balanced solutions (Agrò et al. 2013b) (Fig. 13.15). At the state of the art, newest-generation HES, such as 6 % HES 130/0.42, have the best clinical profile. It is available in two different carrier solutions: 0.9 % saline solution (Venofundin) and a solution very similar to plasma (Tetraspan) (Agrò et al. 2013b).

### 13.10.3 Clinical Use

In Until now HES have been widely used to correct hypovolemia in cardiac surgery patients. The rational of HES use in the postoperative setting of cardiac surgery has been founded on the evidence of HES improvement on the macro- and microcirculation their effects are determined by the high hemodilutional power in combination with a specific action on red cells, platelets, plasma viscosity, and endothelium. A lower blood viscosity means a reduced vascular resistances, increased venous return, and improved CI. This ameliorates tissue perfusion and oxygenation, with fewer infectious complications, especially in ICU patients (Agrò et al. 2013a).

The first- and second-generation HES demonstrated good hemodynamic effects, but were the cause of important side effects involving renal function, coagulation, platelets, and tissue storage and frequently causing pruritus (Agrò et al. 2013a).

HES with a lower MMW and a lower MSR (third and fourth generations) have been shown until now safer in terms of kidney injury, even at higher doses than older HES generation. In fact, HES 6 % 130/0.4 may confer protection in ischemic/toxic renal injury, at least compared to HES 6 % 200/0.5. This is an important highlight considering that acute renal failure is a frequent complication in cardiac surgery patients, especially after CPB (Agrò et al. 2013a).

Third-generation HES result in improved tissue oxygenation in patients undergoing major abdominal surgery. In particular, patients treated with HES in 0.9 % NaCl experienced greater dilution and hyperchloremic acidosis than patients treated with HES in balanced solutions (Agrò et al. 2013b; Wilkes et al. 2001).

The preservation of endothelial function and the maintenance of endothelial integrity using HES 6 %/130/0.4 was also reported. HES solutions with a narrow range of MMW were shown to be effective in reducing capillary edema in an animal model. Furthermore, an improvement in tissue oxygenation secondary to HES infusion has been demonstrated. One explanation for these results is a direct effect of HES on inflammation (e.g., via a reduction in NF-κB release) (Agrò et al. 2013a; Dieterich et al. 2006; Traumer et al. 1992; Tian et al. 2004).

These observations point to potential beneficial effects of HES in reducing systemic stress and the inflammatory response due to surgery and CPB, which may cause glycocalyx damage and capillary leak syndrome, with interstitial and pulmonary edema, increased $VO_2$, and reduced $DO_2$ and $O_2$ tissue diffusion. Thus, modern HES preparations can be expected to reduce cardiovascular changes that may alter or precipitate disturbances in the hemodynamic and metabolic equilibrium of cardiac surgery patients. Larger studies are needed to confirm HES anti-inflammatory effects on cardiac surgery outcomes (Fanzca 2012; Agrò et al. 2013a, b).

### 13.10.4 Potential Risks and Side Effects

The use of HES is nowadays an important matter of debate, due to their side effectcs. This is particularly true in cardiac surgical patients. In particular, these patients are at increased risk to develop bleeding, renal failure, and alteration of colloids' volume effect. The development of one of this feature may affect their survival (Fanzca 2012; Agrò et al. 2013b).

#### 13.10.4.1 Coagulation and Platelet Function

One concern regarding HES use in cardiac surgery is their association with coagulation and platelet disturbances and, consequently, a greater bleeding risk with an increased transfusional need. There is broad debate about whether HES coagulation and platelet effects have an actual clinical impact (Agrò et al. 2013a).

Observed decreases in von Willebrand factor, fibrinogen levels, and thrombin generation presumably alter the coagulation time, clot formation time, and

maximum clot firmness, as shown on intrinsic thromboelastography (Agrò et al. 2013b). Previous reports in the literature showed a severe increase in the bleeding risk with high MMW and MSR HES (i.e., Heptastich, MW 450 kDa; MSR, 0.7). This is due to a von Willebrand-like syndrome, with decreased factor VIII activity and reduced levels of von Willebrand factor antigen and factor VIII-related ristocetin cofactor. HES also impair fibrin polymerization, although HES with a medium MMW and a low MS probably do not strongly affect the coagulation system (Agrò et al. 2013b; DeJonge and Levi 2001; Sanfelippo et al. 1987; Treib et al. 1999; Madjdpour et al. 2005).

The effect of HES on platelet function during cardiac surgery is an additional concern of HES use.

HES with a high MMW, high MSR, and high C2:C6 ratio (e.g., HES 450/0.7 or HES 200/0.62) alter platelet function to a greater extent than HES with a lower MMW and a lower MSR, as mentioned above for coagulation (Agrò et al. 2013b; Kozek-Langenecker 2005; Strauss et al. 2002; Haynes et al. 2004). Franz et al. (2001) studied the effects of IV infusion of saline solution and four HES preparations with different MWW and MSR on platelet function. HES 450/0.7, HES 200/0.6, and HES 70/0.5 prolonged platelet function analyzer (PFA)-100 closure times. All of the tested HES preparations reduced platelet GP IIb/IIIa expression. By contrast, the newest-generation HES seem to have reduced negative effects on platelets (Agrò et al. 2013b). Stogermuller et al. (2000) reported that expression of platelet GP IIb/IIIa was reduced after the infusion of unbalanced HES 200. However, according to in vitro studies, GP IIb/IIIa expression increases with high MMW, high MSR HES in a balanced solution. This unexpected result was obtained with a solvent containing calcium chloride dehydrate (2.5 mmol/L) (Agrò et al. 2013b; Stögermüller et al. 2000). HES in balanced plasma-adapted solutions was shown to have fewer effects on platelets. Many reports confirmed the importance of the solvent in determining potential adverse effects of HES solutions (Agrò et al. 2013b; Franz et al. 2001). Gallandat et al. (2000) found that in cardiac surgery patients, new-generation HES increase von Willebrand factor levels to a greater extent than HES 200/0.5, resulting in a reduction of bleeding risk and transfusional need. Similar results were found in patients undergoing orthopedic surgery and major surgery (Agrò et al. 2013b).

However, negative effects of modern HES preparations on coagulation and platelets have also been reported. For example, Scharbert et al. (2004) found an impairment of platelet function by HES 130 similar to that of HES 200 in patients with chronic back pain undergoing epidural anesthesia. Nevertheless, HES 130 produced a not clinically significant platelet alteration. Similar results were reported for minor elective surgery (Agrò et al. 2013b). Finally, in a recent meta-analysis, the use of third- vs second-generation HES was not related to clinical (and statistically significant) differences in patients with blood loss after surgery (Agrò et al. 2013b; Raja et al. 2011).

#### 13.10.4.2 Kidney Dysfunction

Another clinical concern about HES use is the risk of kidney failure. All colloids can induce kidney injury. The anatomic feature of HES-induced renal damage is an

*osmotic nephrosis-like lesion*. In fact, histological studies conducted after HES infusion revealed a reversible swelling of renal tubular cells due to the reabsorption of colloidal molecules. The most likely mechanism of renal dysfunction is a tubular obstruction caused by hyperoncotic urine formation with the storage of colloidal molecules filtered by the glomeruli. This mechanism is further impaired by a condition of dehydration. Another suggested mechanism is an increase in plasma oncotic pressure, with secondary renal macromolecules accumulation. Adequate hydration using crystalloids may prevent this injury (Agrò et al. 2013b).

The proposed risk factors for HES-related kidney dysfunction are age (older patients have a higher risk), hypovolemia, previous kidney alterations (chronic or acute injury due to other causes), and others comorbidities (such as diabetes and other conditions causing direct or indirect renal alterations). Other risk factors are the type of HES administered (higher MMW and MS) and the total amount infused per Kg of body weight. Some studies showed an increased incidence of kidney dysfunction in patients treated with high MMW and high MS HES (Agrò et al. 2013b).

Clinical evidences of the renal effects of HES use are not uniform, and there is still intense debate in the literature as to whether there is truly a critical creatinine level for HES administration. In a retrospective study on transplanted kidneys from brain-dead donors, Legendre et al. (1993) found an 80 % rate of renal injury after the infusion of HES 200. However, these anatomic alterations did not cause adverse effects in kidney transplant recipients (Agrò et al. 2013b). A similar study found that the use of 6 % HES 200/0.62 caused renal dysfunction after transplantation (Cittanova et al. 1996). In a prospective multicenter study, patients with sepsis or septic shock were treated with HES 200/0.62 or gelatins (Schortgen et al. 2001). In the HES group, 42 % of the patients developed acute renal failure, while in the gelatin group only 23 % of the patients showed kidney alterations. Neither the need for renal replacement therapy nor mortality was significantly different between the two groups (Agrò et al. 2013b). In two meta-analyses HES was related to a higher significant risk of renal damage and dysfunction (Wiedermann 2008; Davidson 2006). On the other hand, large doses (>2 L) of HES solution with low MMW and low MSR have been safely used (Agrò et al. 2013b). Moreover, in a large observational study, ICU patients receiving HES (type not specified) had the same incidence of acute renal dysfunction and similar renal failure scores than patients receiving other plasma substitutes (Sakr et al. 2007).

In the recent literature, the administration of the newest-generation HES was suggested to reduce the risk of short-term and long-term renal injury (Agrò et al. 2013b; Mitra and Khandelwal 2009). In a study on brain-dead kidney donors, Blasco et al. (2008) compared HES 130/0.4 and HES 200/0.62. At 1 month and 1 year post-administration, they found better effects on renal function (lower serum creatinine) with HES 130/0.4 than with HES 200/0.62 (Feng et al. 2006).

The use of fourth-generation HES seems to cause much less harm than older-generation HES, even in patients with previous renal impairment. The infusion of 500 mL of HES 6 %/130/0.4 did not cause any kidney damage in volunteers showing mild-to-severe renal dysfunction (Agrò et al. 2013b; Jungheinrich et al. 2002).

In a review comprising 34 studies (2,607 patients), HES was compared with other fluids. The results evidenced an increased risk of acute renal dysfunction with HES, especially in patients with sepsis (Agrò et al. 2013b; Dart et al. 2010).

According to the recent literature, the newest-generation HES seems to be the better colloidal solutions with respect to kidney oncotic damage while assuring an adequate volume replacement. However, the influence of HES on kidney function remains controversial, and large studies are still needed to evaluate the incidence of acute kidney injury with HES in patients without sepsis, directly applying the RIFLE criteria, by precisely measuring the GFR and urine output together with creatinine and neutrophil gelatinase-associated lipocalin (NGAL) (Fanzca 2012; Agrò et al. 2013b).

#### 13.10.4.3 Anaphylaxis

All colloidal plasma substitutes can cause anaphylactic/anaphylactoid reactions due to specific or nonspecific histamine release. In a trial comprising approximately 20,000 patients, Laxenaire et al. (1994) found a decreased incidence of anaphylaxis with HES compared to other colloids. Histamine release seems to be induced by the starch itself; thus, it is unlikely that recent modifications of the MMW, MS, or C2:C6 ratio are the cause of the increased anaphylactic power (Agrò et al. 2013b).

#### 13.10.4.4 Storing and Itching

HES are stored in either the reticuloendothelial or mononuclear phagocyte system, depending on their chemical features, without causing phagocyte dysfunction. High MMW HES have an elevated rate of storage, especially after prolonged or repetitive administrations. By contrast, in animal studies, the newest-generation HES were found to cause less storage, even after multiple uses (Agrò et al. 2013b). One day after the infusion of HES 130/0.4, the percentage remaining in the plasma is approximately 2 %, rather than the 8 % after the infusion of HES 200/0.5 (Agrò et al. 2013b). Moreover, in a prospective crossover study on healthy volunteers, HES 130/0.42 showed minimal accumulation after repeated administration, whereas HES 200/0.5 was stored in significant amounts (Agrò et al. 2013b; Waitzinger et al. 2003).

Itching reportedly occurs after prolonged administration of large amounts of HES, especially the older-generation ones. In some cases, pruritus has been reported after a single large HES dose (≥2 L). Itching induced by HES has a late onset (weeks or even months after their administration) and long lasting. It is due to storage of the material in small peripheral nerves (Agrò et al. 2013b). In a prospective multicenter study, 500 patients were observed 3–9 weeks postoperatively; no differences were found in terms of itching between patients treated with HES and control patients (Agrò et al. 2013b; Metze et al. 1997).

## 13.11 Hypertonic Colloid Solutions

In a recent study, the hemodynamic effects of hypertonic colloids (7,2 % HES, HC) was compared with ringer, after CABG (Sirvinskas et al. 2007). At 15 min from the infusion, they were shown to significantly increase CI with a lower infused volume. Systemic and pulmonary resistances were lower in the HC group at short (15 min), intermediate (60 min), and longer time (180 min) after the infusion. HC and crystalloid groups did not differ in mean blood loss.

The use of 7,5 % HES was shown to have a positive effect on hemodynamics with reduced fluid requirements and few effect on postoperative bleeding after CABG (Habicher et al. 2011).

## 13.12 Comparison Between Crystalloids and Colloids

The previous paragraphs evidenced the crucial need to restore IVS volume in the cardiac surgery patients.

Theoretically, we expect greater advantages in blood volume expansion with isotonic colloids than with isotonic crystalloids (Agrò and Vennari 2013b) (Fig. 13.16).

Crystalloids are mainly distributed in the ISS, with less effectiveness in maintaining plasma volume, because they do not contain oncotic particles (Agrò and Vennari 2013b). Their duration of action is short, with larger volume needed for a specific target volume expansion (Hendry 1961; Rackow et al. 1983). Their infusion dilutes plasma proteins, thus reducing the COP. Consequently, there is a diffusion of fluids from the IVS to the ISS. This fluid shift increases when vascular permeability is altered, increasing interstitial edema. A relationship between the administration of high fluid volumes and increased mortality has been reported in cardiac surgery patients (Agrò et al. 2013a; Pradeep et al. 2010).

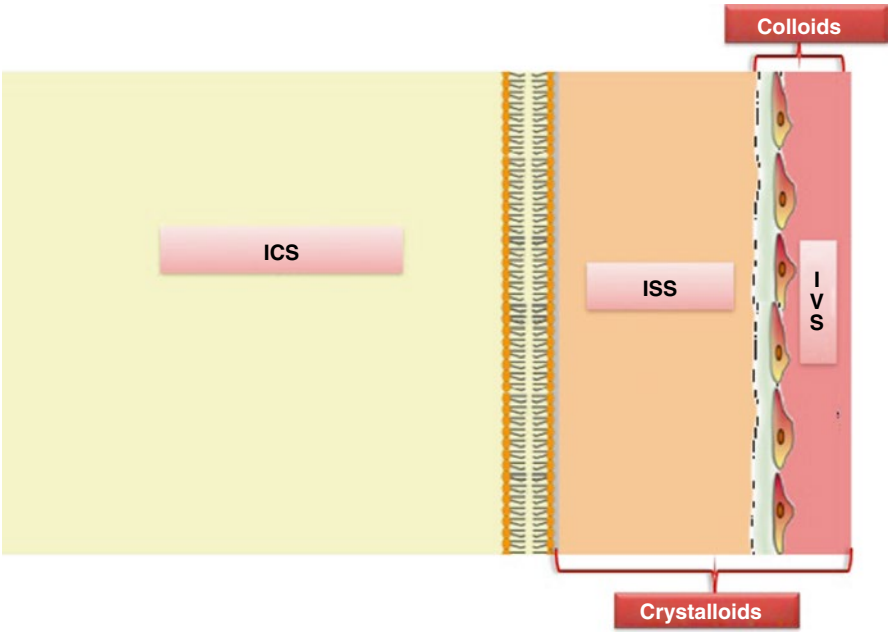



**Fig. 13.16** Comparison between colloids and crystalloids distribution (Modified from Agrò and Vennari 2013b, pp. 71–92)

According to the literature, the use of crystalloids for volume stabilization in patients with circulatory shock is related to a higher risk of altered lung function because of pulmonary edema (fluid overload, referred to as "Da Nang lung" based on the large number of cases in the Vietnam war) (Agrò et al. 2013a; Olsson et al. 2004; Stein et al. 1975). In particular, the use of crystalloids seems to be less appropriate in patients with reduced myocardial function. Animal studies on acute normovolemic hemodilution with Ringer's lactate vs HES demonstrated that the HES group presented a significative increase in CI. Moreover, the microscopic study of the left ventricular wall revealed the destruction of myofilaments and mucosal gastric pH was significantly reduced (index of hypoperfusion) in the Ringer's lactate group (Otsuki et al. 2007). Cardiopulmonary bypass with crystalloids has also been associated with postoperative myocardial edema and cerebral dysfunction with respect to colloids (Lasks et al. 1977; Iriz et al. 2005). On the other hand, Ringers solutions were found to not increase water pulmonary volume with respect to dextran 70, after CABG procedures, with no difference on $PO_2/FiO_2$ (Karanko et al. 1987). Similar results were found in a more recent study comparing 0.9 % saline, 4 % gelatin, 6 % HES 200/0.5, and 5 % albumin in a sample of major vascular surgery: no differences were found in $PaO_2/FIO_2$ ratio and in pulmonary leak index among the groups (Verheij et al. 2006a).

Colloids are distributed in the IVS, with a larger increase in plasma volume because they contain oncotic particles. They have a longer duration of action, with smaller volumes needed for a specific target volume expansion than crystalloids (Agrò et al. 2013a; Verheij et al. 2006b; Ernest et al. 2001). If endothelial permeability is intact, colloids are retained in the IVS, with a subsequent increase of the plasma oncotic pressure and the diffusion of fluids from the ISS to the IVS (Agrò and Vennari 2013b) (Fig. 13.16). Colloids have a "contest volume effect": in hypovolemic patients, they have a volume effect >90 % of the volume infused; in normovolemic patients, two-thirds of the infused volume shifts to the ISS within minutes (Chappell et al. 2008). Consequently, they should be used only in hypovolemia, even when there is capillary membrane damage. In fact, in this case, hypovolemia is connected to the shift into the ISS of protein-rich fluids, with a plasma COP reduction. Colloids that are able to increase COP are needed: their use may reduce ISS overload (Chappell et al. 2008; Agrò and Vennari 2013b).

In 2006, Verheij et al. (2006b) showed that volume expansion and CI were significantly higher after colloid infusion than after the administration of crystalloids, following cardiac surgery. He found colloids were approximately five times as efficient in expanding the IVS volume with respect to saline 0.9 %. Ley et al. (1990) compared fluid replacement with crystalloids or colloids in patients undergoing coronary artery bypass or valve substitution. Patients treated with HES showed a reduced length of ICU stay than patients treated with normal saline solution. In addition, they required fewer fluid infusions after surgery and showed better hemodynamic performance than the crystalloid group (Agrò et al. 2013a).

Despite this evidence, colloids have been associated with coagulopathy and platelet dysfunction, predisposing cardiac surgery patients to postoperative bleeding (in particular when high MW molecules and CPB are involved) and to

**Table 13.9** Comparison between crystalloid and colloid effects

| Crystalloids | Colloids |
|---|---|
| Facilitate fluid overload | Less time in intensive care |
| Lower and short time volemic effect | Less fluids after surgery |
| Pulmonary edema | Better hemodynamic performance |
| Less indicate in patients with reduced myocardial function | Anaphylactic reactions |
| Hemodilution | Coagulopathy |
| Suggested for continuous loss | Suggested for temporary loss |

anaphylaxis (especially gelatins) may cause tubular damage with renal dysfunction (Agrò et al. 2013a; Mahmood et al. 2009).

At the state of the art, crystalloids are suggested for continuous losses (*perspiratio insensibilis* and urinary output), while colloids are suggested for temporary losses (IVS loss, such as due to hemorrhage) (Agrò et al. 2013a; Agrò and Vennari 2013b). A comparison between crystalloid and colloid effect is presented in the table below (Table 13.9).

## 13.13 Comparison Between HES and Other Colloids

In literature, there is a large production concerning the use of colloids in cardiac patient, their hemodynamic, and side effects (Agrò et al. 2013a).

Verheij et al. (2006a) found no significant difference in hemodynamic state and COP registration after the infusion of 6 % HES 450/0.7, 5 % HA, or 6 % dextran. For the same solutions, Jones et al. (2004) demonstrated no significant differences in hemodynamic power. On the other hand, Niemi et al. (2008) found that CI and $DO_2$ increase immediately after the infusion (at ICU arrival) of 6 % HES 130/0.4, whereas over a more long term (2 and 18 h after ICU arrival) the increase of CI was comparable in HES and 4 % HA groups. This finding might be related to a greater plasma-expanding effect of HES compared to HA, due to a higher in vivo molecular weight (Treib et al. 1999). This hypothesis is supported by a higher hemodilution instantly after HES infusion. Moreover, the positive immediate effect of HES on CI may be due to HES capacity of blunt the CPB-induced inflammatory process and endothelial activation. The effect of HES on $DO_2$ seems to be higher with respect to hemodilution due to HES expanding effect (Niemi et al. 2008; Feng et al. 2006). According to this study, HA seems to have a delayed hemodynamic effect with respect to HES solutions after cardiac surgery leading to a reduced $DO_2$ and a higher incidence of metabolic acidosis (BE more negative) (Agrò et al. 2013a; Niemi et al. 2008).

In 2006, Palumbo et al. (2006) found that after the infusion of crystalloids, CVP does not significantly change and that CI significantly increases after the infusion of 6 % HES 130/0.4, but not after the infusion of 20 % HA. In addition, Van der Linden et al. (2004) showed that the quantity of colloids necessary to maintain target values of CI, $SvO_2$, and diuresis did not significantly change between 6 % HES 200/0.5 and

3.5 % urea-linked gelatin during and after cardiac surgery. COP and rescue colloid administration were similar too.

Another issue is the hemodynamic effects of the different HES, depending on their metabolism. The enzymatic degradation of HES has two opposing effects on volemic expansion: a reduction in volume expansion, because it improves renal excretion, and an increase in hemodynamic power, by increasing the number of active osmotic particles (Agrò and Vennari 2013b). Most studies report similar hemodynamic effects between HES with higher MMW and MSR and HEs with lower MMW and MSR (Agrò and Vennari 2013b; Gandhi et al. 2007; Ickx et al. 2003). However, according to a report on a small sample population (20 patients) plasma volume expansion induced by an HES with low MMW and MSR (HES 130/0.4) is longer lasting than that achieved with the infusion of an HES with high MMW and MSR (HES 670/0.75) (Agrò and Vennari 2013b; James et al. 2004).

The effect of a solution on coagulation per volume infused is an important factor to consider in choosing the solution to administer.

There is some evidence that HES affects coagulation to a greater extent than gelatins in cardiac surgery (Agrò et al. 2013a; Niemi et al. 2006). Specifically, there is greater blood loss and an increased need for blood products in patients treated with HES 200/0.5 (Agrò et al. 2013a; Van der Linden et al. 2004). In contrast, the high-dose administration of newer HES (6 % HES 130/0.4) was comparable to gelatin with regard to blood loss (Van der Linden et al. 2005; Ooi et al. 2009). Although the difference among HES has been confirmed by a study in noncardiac surgery patient in which high MW HES showed more negative effect on coagulation than low MW HES (Brunkhorst et al. 2008), in a study on CABG patients, the maximum dose (50 mL/kg) of 6 % HES 130/0.4 showed the same effect on coagulation and blood requirement with respect to 33 mL/kg of 6 % HES 200/0.5 (Habicher et al. 2011).

The rational for HA use in cardiac surgery patients is the minimal effect on coagulation (Agrò et al. 2013a). A recent study demonstrated a reduction in postoperative transfusion requirement in patient undergone off-pump CABG and treated with 1 L of HA respect with those treated with 1 L of first-generation HES (Hecth-Dolkin et al. 2009). HA was shown to have lower effect on coagulation at thromboelastometry rather than 4 % succinylated gelatin or 6 % HES 200/0.5 after cardiac surgery. Absolute drainage loss and transfusion requirements were not significantly different between the groups (Niemi et al. 2006). The same study group confirmed the increased coagulation impairment after the infusion of 15 mL/kg of either 6 % HES 200/0.5 or 6 % HES 130/0.4 with respect to 4 % albumin at 15 mL/kg. Although, drain blood loss and transfusion requirements did not differ between the groups over the study period (Habicher et al. 2011; Niemi et al. 2006).

Literature suggests that newer-generation HES and gelatins have few and comparable effects on coagulation, risk of postoperative bleeding, and transfusion requirement. In particular, HES are safe when infused at submaximum doses. HA shows reduced effects at thromboelastometry, which does not correlate with an effective clinical benefit (bleeding and transfusion requirement) (Habicher et al. 2011). Moreover, there are several studies demonstrating the lack of effect of HA on patient outcome in the critically ill (Agrò et al. 2013a). These evidences and the

costs of HA have determined a reduction of its use in the management of cardiac surgery patients.

Since HES was introduced to the market, there is ongoing debate on their renal effects. At the state of the art, there is still a debate about colloids' effects on renal function (Habicher et al. 2011). In an isolated renal perfusion model in which tubular damage occurs, HES were shown to impair kidney function (Agrò et al. 2013a; Hüter et al. 2009). However, different results emerged from studies on the latest-generation HES: compared to gelatins, third- and fourth-generation HES exhibit positive effects on both the inflammatory response and endothelial integrity, with reduced renal effects and a decrease in the total volume of colloid required (Agrò et al. 2013a).

Gelatins cause greater kidney damage than HES, when compared to third- and fourth-generation HES (Agrò et al. 2013a). Allison and colleagues (1999) studied the influence of gelatin and HES 6 % 200/0.5 on the renal excretion of albumin. Excretion was significantly higher in the gelatin group, consistent with a better integrity of vascular membranes in the HES-treated patients. In a study on aortic aneurysm surgery patients, 6 % HES of 200/0.62 or HES 130/0.4 and 4 % gelatin were compared with respect to renal effects (Mahmood et al. 2007). HES were shown to improve renal function and reduced renal injury compared with gelatins. In another study on septic patients, HES 200/0.6 with a maximum dose of 33 mL/kg HES (cumulative dose of 80 mL/kg) and 3 % gelatin with no dose limitation were compared. HES correlated to a significantly higher rate of AKI; however, no increase in renal replacement therapy was shown (Schortgen et al. 2001). Further similar studies found a negative effect of HES administration on renal function. The need for replacement therapy, correlated to cumulative dose, which was often exceeded (Sirvinskas et al. 2007; Ickx et al. 2003).

On the other side, other studies relieved no renal effect using HES in patients who underwent kidney transplantations or with preexisting renal damage (Deman et al. 1999; Jumgheinrich et al. 2002).

On the base of evidence, it is not possible to recommend the use of modern HES in cardiac surgery patients with respect to renal effect (Drt et al. 2010). However, newest-generation HES seems to be safer with respect to renal dysfunction, and there are no studies demonstrating a severe renal effect after the use, especially when limiting dose is respected (Agrò et al. 2013a; Habicher et al. 2011).

In a recent prospective, randomized, single-blinded, controlled study, HES 6 % 130/0.4 at a maximum dose of 30 mL/kg/day is safe with regard to blood loss, transfusion requirements, and renal function in patient undergone CABG procedures. They suggested the use of HES 6 % 130/0.4 instead of gelatins (Ooi et al. 2009).

Recent literature questioned the clinical role of HES for fluid resuscitation in critically ill patients (1) and found an increased risk of death and need of renal replacement therapy (RRT) respect with crystalloids, up to 90 days from administration.

According to these evidences HES use has been "black boxed" in USA, Australia and New Zeeland and it has been precautionary withdrawn in Italy and in whole Europe, until the regulatory authorities make a definitive decision. It is mandatory to seriously consider the new findings about HES and at the same time be cautious until the

definitive decision about that will be taken. In any case, at the state of the art, the dilemma about the ideal solution still remain unsolved and new scenarios should be opened.

## Suggested References

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care John A et Al. (NEJM 2012)

Colloids versus crystalloids for fluid resuscitation in critically ill patients (Review) Perel P, Roberts I, Ker K Cochrane Database Syst Rev. 2013 Feb

JAMA. 2013 Feb 20;309(7):678-88. doi: 10.1001/jama.2013.430. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis

## 13.14 Comparison Between Balanced and Unbalanced Solutions

When evaluating the effects of different volume-replacement strategies, the electrolytic composition has to be taken into account. Hyperchloremia caused by neither non-balanced nor non-plasma-adapted solutions can alter kidney sensitivity to vasoconstrictors, leading to increased vascular tone and a reduction in glomerular filtration. Balanced and plasma-adapted solutions avoid hyperchloremia, with a lower risk of kidney injury, even in cardiac surgery patients, as well as a reduced bleeding risk and inflammatory response (Agrò et al. 2013a).

Furthermore, there is growing evidence that the use of balanced solutions reduces the need for blood products because of the improved coagulation status (Agrò et al. 2013a; Roche et al. 2002; Martin et al. 2002). Finally, balanced plasma-adapted solutions better maintain acid–base balance, alterations of which may worsen the hemodynamic status of cardiac patients (Agrò et al. 2013a; Base et al. 2011) (see Chap. 15).

## 13.15 How Much Fluid?

The second main concern of the debate on fluid management is "how much to fill" the patient. In fact, although there are many evidences about the benefits of fluid administration in restoring and maintaining an adequate IVS volume, the risk to develop congestive heart failure with interstitial edema, respiration complication, and wound healing delay remains in the case of excessive fluid administration (Agrò et al. 2013a; Agrò and Vennari 2013b). Moreover, in daily practice, practitioners have to face with the lack of consensus guidelines and the limited equipment for hemodynamic monitoring. As a consequence, it is not surprising that the need for rescue therapy in shock patient, congestive heart failure, and prolonged mechanical ventilation is yet too frequent both in operating room than in ICU (Habicher et al. 2011).

In a 50-year ongoing debate, literature proposed many strategies for perioperative fluid management in cardiac surgery patient (Agrò et al. 2013a; Agrò and Vennari 2013b).

### 13.15.1 Liberal vs. Restricted Approach

Historically, there have been two main approaches to fluid management: liberal and restrictive. Studies used different references to establish the nature (liberal or restrictive) of fluid administration. As a consequence, literature may appear contradictory.

Considering a normal water assumption of 25–35 mL/Kg, a patient with no particular fluid loss should be treated with 1,75–2,75 L/die (Powell-Tuck et al. 2008). According to this basal requirement, a fluid strategy may be considered (Varadhan and Lobo 2010):

- Liberal, when more of 2,75 L/die of fluid is administered
- Restrictive when less of 1,75 L7Die is administered

In the liberal approach, fluid replacement has been funded on the estimation of preoperative loss due to fasting, intraoperative loss due to perspiration insensibilis, urine output and bleeding, and anticipated postoperative loss due to fluid shifting in the third space (Fanzca 2012; Shires et al. 1961). According to this approach, the surgical patient is hypovolemic before the start of the procedure because of fasting and intestinal cleaning preparation (when necessary); the perspiratio has a great increase when the continuity of skin is interrupted by the surgical procedure; the third-space shifting is the natural response to surgical stress, an effective ECS (Jenkins et al. 1975; Campbell et al. 1990; Holte and Kehlet 2002). Finally, the kidney is able to eliminate any fluid overload (Watenpaugh et al. 1992). As a consequence, a preoperative fluid load is needed and should consist of about 20 ml/kg/h IV fluids (Chappell et al. 2008; Campbell et al. 1990; Maharaj et al. 2005) as the administration of about 20 mL/Kg/h of IV fluids (Bamboat and Bordeianou 2009).

Although the use of a liberal approach was supported by some studies demonstrating an improvement of tissue perfusion and oxygenation and the reduction of inflammatory response and of organ failure risk (Maharaj et al. 2005; Arkilic et al. 2003; Mythen and Webb 1995; Holte et al. 2004; Lobo et al. 2010; Hiltebrand et al. 2007), it has been related with a fluid overload potentially impacting on patient outcomes (Nisanevich et al. 2005; Lobo et al. 2002). A mathematical model demonstrated that using a liberal approach causes a massive retention of fluid in the stressed tissues, especially when infusion overcomes 10 mL/kg/h, with reduced or no impact on IVS volume (Tatara and Tashiro 2007). Moreover, in a normal organism the surgical stress increases the capacity of fluid overload elimination, but not in a proportional way to the administration. As a consequence, if administration is excessive, fluids will accumulate (Holte et al. 2007a).

Lowell et al. found that at ICU admission, 40 % of surgery patients presented an increase of total body water of 10 % or more (Lowell et al. 1990). This fluid overload may need days to be eliminated, determining a body weight gain. The gain is

mainly due to interstitial edema responsible for heart failure; pulmonary edema and ARDS; increased abdominal pressure, with possible development of compartmental syndrome; tissue hypoperfusion and hypoxia, slowing down wound healing and increasing risk of dehiscence; ileus; and MOF (Reid et al. 2003; Bamboat and Bordeianou 2009; Lobo et al. 2001; Balogh et al. 2003; Shandall et al. 1985; Sheridan et al. 1987; Lobo 2004). Finally, fluid and sodium overload causes cellular membrane hyperpolarization, neurotransmitter metabolism alteration, and mitochondrial dysfunction (Wilkes et al. 2001; Petty and Ashbaugh 1971).

At the state of the art, it is not clear if a liberal fluid administration is the cause of the consequence of fluid shift in the third space. In animal models, the surgical damage (mechanical and inflammatory) has been shown as the first cause of fluid shift that is increased by abundant fluid administration (Chan et al. 1983). However, literature on major abdominal surgery demonstrated the liberal approach may augment the risk of complication development, increase hospital stay, and worsen outcomes (Varadhan and Lobo 2010; Nisanevich et al. 2005; Brandstrup 2006; Brandstrup et al. 2003).

Moreover, evidence demonstrated that Shire theory premises were not very correct. In fact, it has been shown that preoperative fasting does not produce a significative reduction in IVS volume (Jacob et al. 2008); basal perspiratio is 0,5 mL/Kg/h, and during surgery, it is no more than 1 mL/kg/h (Lamke et al. 1977); the stress response to surgery is responsible of an inappropriate increase of ADH and aldosterone levels, determining an overload of water and sodium; finally, a "primitive" third space does not exists (Chappell et al. 2008). These evidences suggest the use of a restrictive approach to fluid management, first proposed by Moore et al. (1955). Many studies demonstrated that a restrictive management (defined as a contained infusion respected liberal approach) reduces the risk of complications and hospital stay, favoring wound healing and postoperative recovery of organ function (especially abdominal) and lowering the incidence of cardiopulmonary events, with no cases of prerenal AKI (Chappell et al. 2008; Nisanevich et al. 2005; Lobo et al. 2002; Moyer 1950). On the other hand, when a real restrictive administration is realized (infusion <1,75 L/die), perioperative morbidity increased (Vermeulen et al. 2009; Holte et al. 2007b; MacKay et al. 2006). In fact, a restrictive management may cause hypovolemia with hypoperfusion and $DO_2$ reduction, increasing the risk of organ damage. Moreover, there is an increase viscosity of body fluids potentially leading to microcirculation alteration and microthrombosis, pulmonary mucus concentration with bronchial obstruction, and atelectasis development (Lobo and Allison 2005) (Fig. 13.17).

Despite scientific evidences, the discussion remains opened about the ideal fluid management in the cardiac surgery patient, because works are widely different, and no studies have been conducted on cardiac surgical population. For these reasons, the literature of the last two decades has emphasized a guided fluid management as an alternative to both restrictive and liberal approach (Habicher et al. 2011). It consists on the administration of fluids according to the evaluation of physiological parameters and hemodynamic variables. This approach is called goal-directed therapy (Agrò and Vennari 2013b).

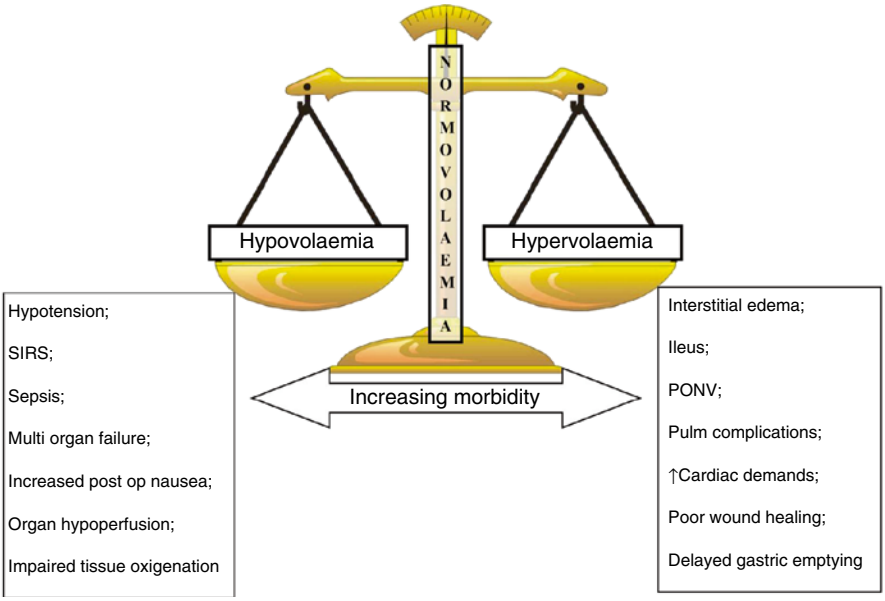



**Fig. 13.17** Liberal and restrictive approaches: consequences on morbidity

### 13.15.2 Goal-Directed Fluid Therapy

In cardiac surgery patient, a rational fluid administration is one of the main tools useful to optimize tissue perfusion (Habicher et al. 2011).

Goal-directed therapy (GDT) is a complex strategy for fluid infusions aimed at optimizing tissue perfusion and oxygenation. Through hemodynamic monitoring, GDT allows physicians to administer fluids and/or use others therapies, such as inotropic or vasoactive drugs, only to those patients who need them, in order to assure sufficient $DO_2$ to fulfill the metabolic requirement of the particular patient. With GDT, hemodynamic management is therefore personalized (Agrò and Vennari 2013b).

#### 13.15.2.1 Physiological Basis

Management of both critically ill and major surgery patients is mainly aimed at assuring adequate tissue perfusion and oxygenation. A continuous supply of oxygen is needed because it is indispensable for aerobic metabolism (Agrò and Vennari 2013b).

Physiologically adequate $DO_2$ is assured by cardiovascular and respiratory systems, and it corresponds to the quantity (in mL) of oxygen per minute carried to the tissues (Agrò and Vennari 2013b; Lees et al. 2009).

$DO_2$ is defined by the following equation (Agrò and Vennari 2013b):

$$DO_2\left(\text{mL}/\text{min}\right) = \text{cardiac output}\left(CO\right) \times \text{arterial oxygen content}\left(CaO_2\right) \qquad (13.1)$$

$DO_2$ physiologically corresponds to 900–1,100 mL/min or to 500–600 mL/min/$m^2$ if reported as body surface area ($DO_2I$) (Agrò and Vennari 2013b).

Considering the factors determining CO and $CaO_2$, Eq. 13.1 can be rewritten as (Agrò and Vennari 2013b):

$$DO_2\left(\text{mL}/\text{min}\right) = \left(\text{HR}\times\text{SV}\right)\ \left[\left(1{,}34\times\text{Hb}\times\text{SaO}_2\right)+\left(0.003\times\text{paO}_2\right)\right] \tag{13.2}$$

where:

- HR is the heart rate.
- SV is the stroke volume.
- 1.34 is the number of mL of oxygen carried by hemoglobin at 100 % saturation.
- Hb is the amount of hemoglobin in g/dL.
- $SaO_2$ is the arterial $O_2$ saturation in arterial blood.
- 0.003 is the solubility coefficient of oxygen.
- $PaO_2$ is the partial $O_2$ pressure of arterial blood.

Thus, oxygen delivery can be improved by modifying:

- SV, by using inotropic or vasoactive drugs (post-load) and fluid administration (preload)
- Hb, by the transfusion of red cells
- $SaO_2$ and $paO_2$, by $O_2$ therapy and in some cases by mechanical ventilation (Agrò and Vennari 2013b)

Oxygen demand consumption ($VO_2$) is the quantity (in mL) of oxygen consumed by the tissue per minute. It depends on the metabolic state and it is increased by surgical stress and critical conditions. $VO_2$ may be described by the following relationship (Agrò and Vennari 2013b):

$$\begin{aligned}VO_2\left(\text{mL}/\text{min}\right) = {}& \text{caridac output}\left(\text{CO}\right)\times[\text{arterial}\,O_2\text{content}\left(CaO_2\right)\\ & -\text{venous}\,O_2\text{content}\left(CvO_2\right)\end{aligned} \tag{13.3}$$

Equation 13.3 can be rewritten as (Agrò and Vennari 2013b):

$$\begin{aligned}VO_2\left(\text{mL}/\text{min}\right) = {}& (\text{FC}\times\text{SV})\times[(1{,}34\times\text{Hb}\times\text{SaO}_2)\\ & +(0.003\times\text{paO}_2)-(1.34\times\text{Hb}\times\text{SvO}_2)+\left(0.003\times\text{pvO}_2\right)]\end{aligned} \tag{13.4}$$

where:

- CO and $CaO_2$ are described by the same factor as in Eq. 13.2.
- $SvO_2$ is the saturation of mixed venous blood.
- $PvO_2$ is the partial $O_2$ pressure in mixed venous blood (Agrò and Vennari 2013b).

$VO_2$ is about 200–300 mL/min (110–160 mL/min/$m^2$ if reported as body surface area) at basal metabolism (Roberts and Bratton 1998). Under stress conditions it may increase four- to sixfold.

$O_2$ extraction ($O_2ER$) is the fraction of $DO_2$ released to the tissues per minute (Agrò and Vennari 2013b). It is a tissue oxygenation index, expressed as:

$$O_2\text{ER} = \frac{VO_2}{DO_2} \tag{13.5}$$

Under basal conditions, the ratio is 0.25, but it can increase in order to assure $VO_2$. In fact, normally, $VO_2$ is maintained despite wide-ranging $DO_2$ values, through an increase of $O_2ER$. Below a critical value of $DO_2$ (critical $DO_2$), $O_2ER$ can no longer increase, and $VO_2$ becomes flow dependent (Agrò and Vennari 2013b). Tissue hypoxia appears and anaerobic metabolism starts. The tissue hypoxia causes unbalance between ATP production and ATP demand. A reduction in cAMP and cGMP levels activates the endothelium, reducing its barrier function and causing the release of pro-inflammatory cytokines, leading to capillary leak syndrome. Disruption of the endothelial barrier exposes the blood to procoagulant factors and leukocyte adhesion molecules. Leukocytes and complement are activated, leading to a systemic inflammation with organ hypoperfusion and failure (multiorgan failure). The detection and prevention of tissue hypoxia is therefore crucial, especially in cardiac surgery patient (Agrò and Vennari 2013b; Lamke et al. 1977).

A rational approach to fluid therapy (GDT) is the most readily available and simplest tool to assure adequate $DO_2$. Some patients have reduced compensatory mechanisms when $VO_2$ increases, because of comorbidities (cardiovascular or pulmonary diseases), and thus have a higher probability of reaching the critical $DO_2$ under stress conditions, such as surgery. Cardiac surgery patients are high-risk patients who are likely to benefit from a GDT approach (Agrò and Vennari 2013b).

#### 13.15.2.2 Hemodynamic Variables in GDT

The rational approach to fluid administration in GDT is based on the prediction of fluid responsiveness. Fluid-responder patients are those who, according to Starling's law, will benefit from fluid loading in terms of hemodynamic stability and $DO_2$ (Agrò and Vennari 2013b). It has been shown that if fluid responsiveness is not assessed, only 40–72 % of critically ill patients respond to fluid therapy with a significant increase in stroke volume (Michard and Teboul 2002). It is immediately evident that fluid responsiveness is not evaluable on the bases of the sole clinic (Grebe et al. 2006). In fact, clinical parameters change later than the effect volume. This should bring to a tardive treatment of hypovolemia, potentially fatal for cardiac surgery patients (Grebe et al. 2006; Grocott et al. 2005).

Defined hemodynamic variables are necessary to evaluate volume status and to test fluid responsiveness. These can be divided into static and dynamic. Static variables indicate hemodynamic status at a specific time, for the preload value at that time. An example of static variable is the value of CI obtained in a single thermodilution. Dynamic variables indicate hemodynamic changes in response to a periodic variation in preload. Static indexes are comparable to a picture, while dynamic ones to a movie. Dynamic variables are better indicators of fluid responsiveness than static ones (Agrò and Vennari 2013b; Lees et al. 2009).

Historically, filling pressures (CVP, MAP, and PCWP) were used to guide intravascular volume therapy. In cardio-surgical ICU, CVP is the most used (87 % of intensivists), followed by MAP (84 %) and PCWP (30 %) (Kastrup et al. 2007). Many studies have shown that CVP does not adequately reflect preload and fails to predict fluid responsiveness (Agrò and Vennari 2013b; Kastrup et al. 2007; Cavallaro et al. 2008; Marik et al. 2008). In one study, PCWP was found to adequately predict fluid responsiveness in 19 patients who underwent CABG (Bennett-Guerrero et al. 2002). Other studies found a significant CVP and PCWP increase after a fluid

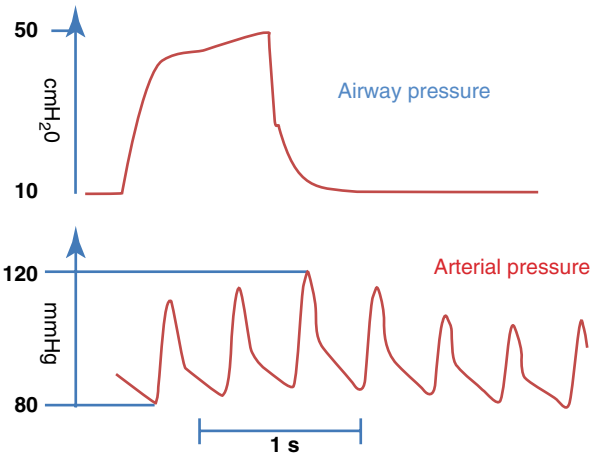



**Fig. 13.18** PPV and intrathoracic pressure. In the inspiratory phase of mechanical ventilation, the intrathoracic pressure increases, reducing preload and consequently increasing PPV. In expiration, intrathoracic pressure decreases, increasing preload and consequently reducing reduction in PPV (Agrò and Vennari 2013b, pp. 71–92)

challenge, but they did not correlate to an increase in SV (Wiesenack et al. 2001; Brock et al. 2002). Moreover, pressure parameters are altered by intra-abdominal pressure variation, modification of cardiac compliance, pulmonary resistance, and cardiac pathologies (Marik et al. 2008). As a result, they are not very reliable and useful in cardiac surgery patients who present at least one of these conditions (Habicher et al. 2011; Wittkowski et al. 2009; Michard et al. 2003; Hofer et al. 2005a; Reuter et al. 2002a, b; Sakka et al. 2009; Breukers et al. 2009a, b; Goedje et al. 2000).

Pulse wave analysis allows the assessment of other functional hemodynamic parameters, such as stroke volume variation (SVV), pulse pressure variation (PPV), and continuous CI (Agrò and Vennari 2013b). Intermittent transpulmonary thermodilution can be used to calibrate pulse wave analysis, enhancing the reliability of CI measurements, according to the monitoring system applied (Agrò and Vennari 2013b).

Pulse pressure is defined as the difference between systolic and diastolic pressure for each heartbeat (Roberts and Bratton 1998). PPV corresponds to the variation in pulse pressure at different heartbeats induced by variations of the intrathoracic pressure due to mechanical ventilation (Agrò and Vennari 2013b) (Fig. 13.18). A PPV cutoff value of 12 % has been shown to be useful to identify responder patient (PPV >12 %) and nonresponder patients (PPV <12 %) (Auler et al. 2008). In a study on CABG patients comparing PEEP and fluid infusion effects on hemodynamics, PPV was found to be the best predictor of fluid responsiveness with respect to PCWP and other variables (Bendjelid et al. 2004). PPV use in guiding volume therapy has been demonstrated, suggesting a possible improvement in outcome after high-risk surgery (Lopes et al. 2007).

SVV is based on cyclic changes in the SV due to intrathoracic pressure during mechanical ventilation (Agrò and Vennari 2013b) (Fig. 13.19).

$$\mathrm{SVV} = \left(\mathrm{SV\,max} - \mathrm{SV\,min}\right) / \mathrm{SV\,mean}$$

It is conceptually similar to PPV, but more precise and reliable (Agrò and Vennari 2013b). SVV has been found to consistently predict fluid responsiveness, with

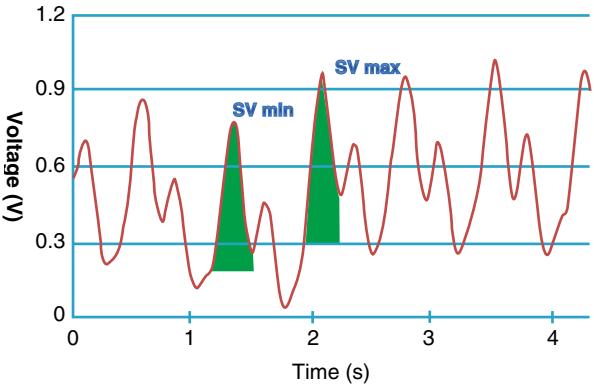



**Fig. 13.19** Pulse wave analysis and SVV: the area under the curve corresponds to the SV. Knowing the HR, CI may be calculated continuously (Agrò and Vennari 2013b, pp. 71–92)

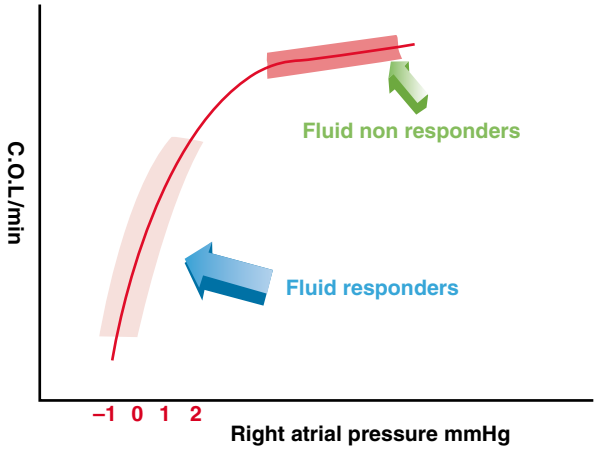



**Fig. 13.20** Fluid responsiveness and Frank–Starling law (From Agrò and Vennari 2013b, pp. 71–92)

threshold values of 11–13 % (Agrò and Vennari 2013b; Marik et al. 2009; Benes et al. 2010). SVV may indicate the actual position on the Frank–Starling curve. When the heart operates on the ascending limb of the Frank–Starling curve, the intrathoracic pressure induces large changes in preload and SV (SVV >13 %), indicating a preserved preload reserve and an improvement after fluid administration (fluid responders). By contrast, at the plateau of the Frank–Starling curve, small changes in SV are observed (SVV <13 %), representing a lower preload reserve and a minimal or no improvement after fluid administration (fluid nonresponders) (Fig. 13.20). In this case, inotropes may be required (Agrò and Vennari 2013b). In a study on 20 patients who underwent cardiac surgery, SVV modification correlated to CI changes (Reuter et al. 2002b).

However, there are some limitations that may exclude a valid use of SVV (Agrò and Vennari 2013b):

- Right ventricular failure
- Arrhythmias
- Spontaneous breathing
- Ratio heart rate/respiratory rate <3.6
- Low tidal volume (<8 mL/kg)

In fact, Reuter et al. (2003) demonstrated that tidal volume may affect reliability of SVV value in cardiac surgery patients. In a similar population, SVV was found to be reduced by high blood pressure value and increased by high airway pressure, without effective change in volemic status (Habicher et al. 2011).

Both high PPV and SVV are indicators of hypovolemia, indicate fluid responsiveness, and correlate to the CI increase after fluid challenge administration (Habicher et al. 2011; Wiesenack et al. 2003; Hofer et al. 2005b). This evidence was confirmed in a study on off-pump CABG patients, in which both SVV and PPV strongly correlated to CI improvement after a fluid challenge, with respect to filling pressure (Habicher et al. 2011; Belloni et al. 2008). As a consequence, dynamic parameters such as PPV and SVV are able to adequately distinguish fluid-responder and fluid-nonresponder patients and are suitable to guide fluid management in the perioperative period of cardiac surgery, with respect to filling pressure (Habicher et al. 2011; Brock et al. 2002).

GEDV (global end-diastolic volume) is a volumetric parameter easily obtainable through transpulmonary thermodilution. It may index to body surface (GDVI) (Wittkowski et al. 2009). It has been showed as a better marker of cardiac preload than CVP (Agrò and Vennari 2013b). This evidence was confirmed by a study where GEDVI was compared to PAC pressure through echocardiography: it correlated with ventricular preload (Hofer et al. 2005a). However, it is a static parameter that does not allow the evaluation of cardiac responsiveness to fluid loading (Agrò and Vennari 2013b).

ITBV (intrathoracic blood volume) is another volumetric index of preload (ITBVI). In cardiac surgery patients with hypovolemia, ITBV has been shown to significantly correlate to SV increase after a fluid challenge, with respect to CVP and PCWP (Habicher et al. 2011; Brock et al. 2002). These results are confirmed by many studies on cardiac surgery patients (Habicher et al. 2011; Wiesenack et al. 2001; Reuter et al. 2002a, b). Moreover, in another study on cardiac surgery patients, a filling pressure-guided management was compared to a management based on ITBVI, CI, MAP, HR, and $ScvO_2$ use. The first group showed a longer ICU and hospital stay, with respect to the second group (Smetkin et al. 2009).

In the case of left ventricular failure or acute lung injury, the EVLW (extravascular lung water, index of lung edema) can be used. EVLW is an independent predictor of survival (Agrò and Vennari 2013b). In GDT, the use of EVLW accelerates the resolution of lung edema, whether due to increased vascular permeability or to an increase in hydrostatic pressure (Agrò and Vennari 2013b).

In cardiac surgery patients, the use of a goal-directed protocol (GEDV > 800 mL/$m^2$, EVLW = 10–12 mL/kg) resulted in an enhanced postoperative outcome (Agrò and Vennari 2013b; Goepfer et al. 2007).

Left ventricular end-diastolic area (LVEDA) is the most popular echocardiographic parameter (measured with transesophageal probe) used to assess preload, very easy to measure, and reliable with respect to other sophisticated parameters.

Literature evidenced LVEDA is a valid parameter to guide fluid management in cardiac surgery patients and to evaluate fluid responsiveness (LVDA increase in fluid responder after the challenge) (Habicher et al. 2011; Cheung et al. 1994; Tousignant et al. 2000). LVEDA correlates with SVV and ITBV (Buhre et al. 2001). In patients who underwent cardiac surgery, LVEDA showed a better predictive

capacity to fluid responsiveness than filling pressure (Wiesenack et al. 2005). As a consequence, its use is suitable in this kind of patients (Habicher et al. 2011).

Literature has showed that volumetric parameters are superior to conventional filling pressures to assess cardiac preload and might prove helpful in guiding fluid therapy in cardiac surgical patients (Habicher et al. 2011).

#### 13.15.2.3 Monitoring Systems in GDT

The use of GDT requires hemodynamic assessment and monitoring. The ideal system should be simple, non- or hardly invasive, safe, and precise, allowing immediate therapeutic intervention. Unfortunately, this system has not yet been invented. Many systems have been proposed for hemodynamic assessment, especially recently (Agrò and Vennari 2013b). All these systems have to be compared to the Swan–Ganz or pulmonary artery catheter (PAC), which remains the gold standard, despite its limits. In fact, many clinical trials showed that PAC is not suitable for GDT in the routine perioperative setting (Agrò and Vennari 2013b). Its use is further discouraged by the invasiveness of the procedure, which exposes patients to complications. In addition, PAC cannot be used without adequate training and experience. Finally, its performance mainly refers to filling pressure values (PVC, PCWP), which have been found to be not so effective in clinical practice. Consequently, its fame in the literature and in clinics has decreased over the years (Agrò and Vennari 2013b). Moreover, less invasive systems with similar precision have been introduced. Modern technologies provide filling volume values that are more reliable as preload and fluid responsiveness indexes (Agrò and Vennari 2013b; Lees et al. 2009). Current and less invasive flow monitoring techniques include Doppler technologies or arterial pressure waveform analysis.

The esophageal Doppler (ED) allows measurement such as LVEDA and the blood velocity at the level of the descending aorta. The flow time in the descending aorta corrected for HR (FTc normally 330–360 ms) corresponds to the SV. According to the chosen probe, the correspondence is obtained through a monogram calculated from comparative studies performed with a PAC or through the measurement of the vessel cross section. At lower velocities, hypovolemia should be suspected. FTc correlates with LVEDA (Agrò and Vennari 2013b; DiCorte et al. 2000). ED requires shorter operator training than other systems and does not require calibration, but it is difficult to use in awake patients and in prolonged monitoring; finally, its results may be operator dependent. GDT using ED was shown to improve patient outcomes (Agrò and Vennari 2013b). Chytra et al. (2007) have shown that the optimization of fluid management using ED in trauma patients reduces blood lactate levels, the incidence of infections, and the duration of ICU and hospital stay. A meta-analysis showed that patients undergoing major abdominal surgery, who received ED-oriented GDT, had a reduction in complications, requirement of inotropes, ICU admissions, and hospital stay, with a rapid organ function recovery (Agrò and Vennari 2013b; Abbas and Hill 2008).

New monitoring devices, assessing dynamic and volumetric parameters, are PICCO system and PiCCO2 Pulsion Medical Systems, Munich, Germany; FloTrac, Edwards Life Systems; and LiDCOrapid, LiDCO, London, UK.

These devices use transpulmonary thermodilution and/or pulse wave analysis. When the methodologies are used in combination, the validity of pulse pressure

analysis depends on periodic recalibration through thermodilution (Agrò and Vennari 2013b; Marik et al. 2011; Reuter et al. 2010). These systems require invasive arterial lines and a central venous catheter, but they are less invasive than PAC.

The Picco system needs a modified arterial catheter with a temperature and pressure sensor. It must be positioned in a central artery through femoral, brachial, axillary, or radial access (Habicher et al. 2011). The Picco system lets a continuous monitoring of SV, SVV, and CI, while it yields static parameters such as the GEDV/GEDVI, ITBV/ITBVI, and EVLW through thermodilution methodology (Michard et al. 2003). The Picco system uses a single-indicator thermodilution. It has been shown as reliable in many studies on cardiac and noncardiac patients, although it determines a slight overestimation of haemodynamic paramteters (Habicher et al. 2011). SVV evaluated by the Picco plus system (an evolution of Picco) adequately indicates fluid-responder patients in various clinical settings (Agrò and Vennari 2013b).

Another system based on pulse wave analysis is the FloTrac/Vigileo system. It uses Langewouters' algorithm to perform the wave analysis and does not require thermodilution for calibration. Consequently, it can be used only with a normal invasive arterial line connected to the FloTrac sensor (Agrò and Vennari 2013b). A study on 40 patients undergoing cardiac surgery compared the SVV measured with FloTrac/Vigileo and the PiCCO plus and found no significant difference in the prediction of fluid responsiveness (Agrò and Vennari 2013b; Hofer et al. 2008). In high-risk patients undergoing major abdominal surgery, Benes et al. found that intraoperative fluid optimization through the Vigileo/FloTrac system decreased the incidence of postoperative complications, reducing hospitalization time (Agrò and Vennari 2013b; Benes et al. 2010). The Vigileo/FloTrac system may be used with the Presep catheter (Edwards Life Science, Irvine, CA). It is a central catheter that allows $S_CVO_2$ continuous monitoring. The limits of Vigileo involve the validity of the wave pressure analysis and SVV values only in mechanically ventilated patients (Agrò and Vennari 2013b).

A new, noninvasive monitor for the measurement of continuous CI is the Nexfin HD (Bmeye) monitor. It measures CI continuously completely noninvasively by an inflatable finger cuff. The Nexfin HD using volume clamp technology continuously measures finger blood pressure and converts the value into a blood pressure wave of the brachial artery. The truly noninvasive nature of the Nexfin HD allows the measurement of CI and can be used in awake, not mechanically ventilated patients (Agrò and Vennari 2013b).

#### 13.15.2.4 Clinical Impact in Cardiac Surgery Patients

GDT has been demonstrated to reduce length of ICU stay, ameliorating outcomes (Habicher et al. 2011). Since 1988, many studies on different monitoring systems have demonstrated GDT benefits in noncardiac major surgery patients, maintaining a $DO_2 \geq 600$ mL/min/m$^2$ (Agrò and Vennari 2013b; Habicher et al. 2011; Shoemaker et al. 1988; Pearse et al. 2005a, b; Giglio et al. 2009).

Considering a cardiac surgery population, only one study using PAC demonstrated that an $S_VO_2$-oriented management may improve morbidity and hospital stay length (Habicher et al. 2011; Polonen et al. 2000).

In a more recent study on 30 cardiac surgery patients, monitored with floTrac in order to optimize CI, SVV, and $DO_2$, there was no significant improvement on outcome respect to standard management, probably due to the small sample (Habicher et al. 2011; Kapoor et al. 2008).

The ICU use of esophageal Doppler flowmetry (aimed at maintaining a stroke index above 35 mL/m$^2$) has been found to reduce the length of hospital stay in cardiac surgery patients (Habicher et al. 2011; McKendry et al. 2004). Moreover, comparing 40 cardiac surgery patients treated with a GEDVI, ITBVI, CI, and MAP-guided algorithm, with a historic sample treated with standard approach, the GDT group presented a shorter duration of mechanical ventilation and a reduced need for intensive therapies and catecholamines (Habicher et al. 2011; Goepfert et al. 2007). In a similar study conducted in off-pump coronary artery bypass patients, it was shown that GDT determined an increased use of dobutamine and colloids, correlating with a reduction of the length ICU and hospital stay (Habicher et al. 2011; Smetkin et al. 2009).

Although more studies are needed, the present evidences suggest GDT as a useful clinical tool to improve cardiac surgery fluid management during ICU stay, favorable impacting on outcomes (Habicher et al. 2011).

## 13.16 Electrolyte Management

### 13.16.1 Sodium

In the cardiac surgery patient, sodium overload is the most common alteration due to fluid administration and to the surgical stress response (increased level of aldosterone and cortisol). In this case, it is accompanied by hypervolemia and fluid overload, with interstitial edema (Fanzca 2012). Hypernatremia may be also due to a loss of hypotonic fluids. Renal losses may be caused by furosemide use, osmotic diuresis (severe hyperglycemia, uremia, mannitol overdose), preexisting renal diseases, and the development of ATN (polyuric phase). In these cases, sodium losses are associated to water losses, with a reduction of IVS fluid and the presence of sign and symptoms of hypovolemia (Agrò and Vennari 2013a). Less frequently, hypernatremia may be due to a loss of free body water (hypernatremia due to sodium concentration). In this case, EVS volume is preserved. The most frequent cause of normovolemic hypernatremia is the lack of an adequate restore of perspiratio insensibilis, especially when it is increased (i.e., patients with fever) (Agrò and Vennari 2013a). A possible flow chart for hypernatremia diagnosis is presented below (Fig. 13.21).

Thirst is one of the first symptoms of hypernatremia, observable in awake patients. Other symptoms are lethargy, reduction of consciousness up to coma and convulsions, peripheral edema, myoclonus, ascites and/or pleural effusion, tremor and/or rigidity, and increased reflexes (Agrò and Vennari 2013a). If hypernatremia develops slowly, it is well tolerated because the brain is able to regulate its own volume in response to ECS fluid and osmolarity changes. Acute and severe

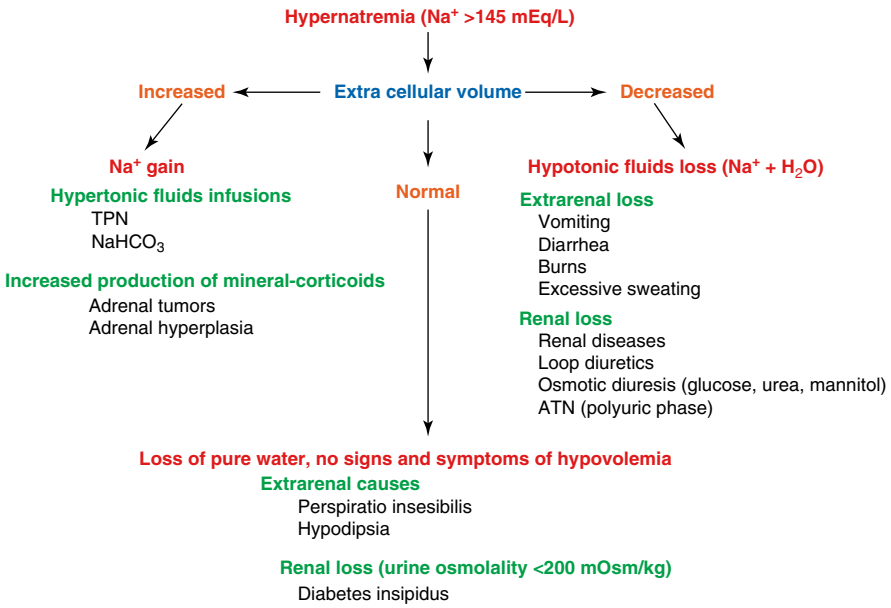



**Fig. 13.21** Flowchart for hypernatremia diagnosis

hypernatremia may lead to a shift of water from the ICS, causing brain shrinkage and tearing of the meningeal vessels, with the risk of intracranial hemorrhage, especially when patients have started therapy with LMWH (Agrò and Vennari 2013a; Miller 2009).

Hypernatremia management is based on normal osmolarity and volume restoration. It includes the administration of hypotonic crystalloids or dextrose solutions. The rate of correction depends on the symptoms and the development of hypernatremia (acute, subacute, or chronic). Chronic hypernatremia needs more care in the treatment. In fact the brain has yet developed compensation mechanism, and a too rapid correction may lead to cerebral edema (Agrò and Vennari 2013a).

As a general rule, it is reasonable to have an initial sodium target of 145 mEq/L, with a rate of correction of plasmatic [Na+], not greater than 1–0,5 mEq/h (Agrò and Vennari 2013a).

A useful formula to establish the rate of infusion for an adequate corrected is reported:

$$\frac{0,5\,\text{mEq/h}}{\left(\text{infused}\left[\text{Na}\right]-\text{measured}\left[\text{Na}\right]\right)\text{in mEq/L/total body water}}\times 1,000 = \text{mL/h}$$

where

- 0,5 mEq/L is the recommendable rate of [Na+] correction
- Infused [Na] is the concentration of sodium in the solution chosen for the correction

- Measured [Na] is the sodium plasma concentration of the patient
- Body water is calculated as

$$\text{Total body water} = \left(\text{correction factor} \times \text{body weight in Kg}\right) + 1$$

Correction factor:

- 0,6 men and children
- 0,5 women
- 0,5 old men
- 0,45 old women

In the postoperative period, many cardiac surgery patients may present a reduction of sodium plasma levels, due to a shift of water from ICS to IVS rather than a reduction in total body sodium content. The shift is caused by hyperglycemia (diluting hyponatremia) triggered by the surgical stress response, the reduction in insulin production and insulin resistance, and by an overload in the bypass pump prime (Fanzca 2012; Kutschen et al. 1985). A similar mechanism may be triggered by mannitol overdose. In these cases, hyponatremia is accompanied by hypertonicity (plasma osmolarity >300 mosm/L) (Agrò and Vennari 2013a).

Other causes responsible for hyponatremia in the ICU cardiac surgery patient are associated to a reduction of plasma osmolarity (true hyponatremia). In this case, IVS volume may be normal, increased, or reduced (Agrò and Vennari 2013a).

Advanced heart failure, severe hypovolemia, and hepatic complications with ascites alter ADH release and the kidneys' capacity to dilute urines, leading to hyponatremia with IVS volume reduction and interstitial edema development.

The use of diuretics (especially if inappropriate), and the development of SIADH due to cerebral complications or prolonged mechanical ventilation, may cause normo-hypervolemic hyponatremia without edema.

Hyponatremia with hypovolemia may be due to cerebral salt wasting (cerebral complications), hypokalemia, renal losses, and extrarenal losses. The most frequent cause of renal losses in the cardiac surgery patient is diuretics use and the development of ATN. Possible extrarenal losses are PONV, gastric suction, and diarrhea (i.e., related to enteral nutrition in long-stay patient). In the critical patient, frequent causes of hypovolemic hyponatremia are third-space syndromes.

Hyponatremia symptoms depend on the severity of the sodium deficit. Clinical features are weakness, nausea, vomiting, modification of consciousness (agitation, confusion, coma, and seizures), visual alteration, cramps, and myoclonus. When the sodium level falls below 123 mEq/L, cerebral edema occurs. At a sodium concentration of 100 mEq/L, cardiac symptoms develop. In diluting hyponatremia, an increase in IVS volume can lead to pulmonary edema, hypertension, and heart failure (Agrò and Vennari 2013a).

Sodium levels alteration are related to an increased risk of postoperative delirium, especially in patients with preexisting hyponatremia (Fitzsimons and Agnihotri 2007).

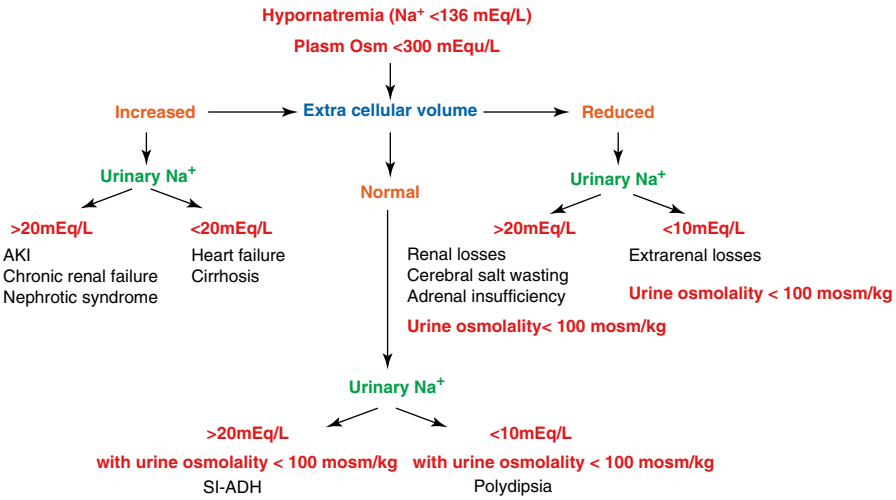



**Fig. 13.22** Flow chart for hyponatremia diagnosis

A possible flow chart for hyponatremia diagnosis is showed in the flow chart below (Fig. 13.22).

The first-line treatment of hyponatremia is the elimination of the underlying cause. The second-line treatment is correction of the sodium deficit, generally through intravenous sodium administration (0,9 % saline solution or other hypertonic saline solutions). The dose of sodium required to correct hyponatremia may be calculated using the following formula (Agrò and Vennari 2013a):

$$\text{Sodium deficit}\left(\text{mEq}\right) = \left(130\,\text{mEq} - \text{measured serum Na mEq}\right) \times \text{Total body water}$$

The rate of infusion of the chosen fluid may be calculated according to the same formula explained for hypernatremia. A recommendable initial [Na] target is 125–130 mEq/L. A slow rate (maximum rate = 0.5 mEq/L/h) of correction is always indicated, because rapid correction can cause central pontine myelinolysis, especially in the case of chronic hyponatremia. For this reason, it is suggested to use a velocity rate correspondent to the half of the obtained value. In case of hypervolemia, it may be preferred to utilize water restriction and a diuretic, such as furosemide (Agrò and Vennari 2013a).

A possible flow chart for hyponatremia management is showed below (Fig. 13.23).

## 13.16.2 Potassium

Maintaining adequate potassium levels is crucial for bypass pump separation and to prevent postoperative dysrhythmias. In the perioperative setting, many factors may

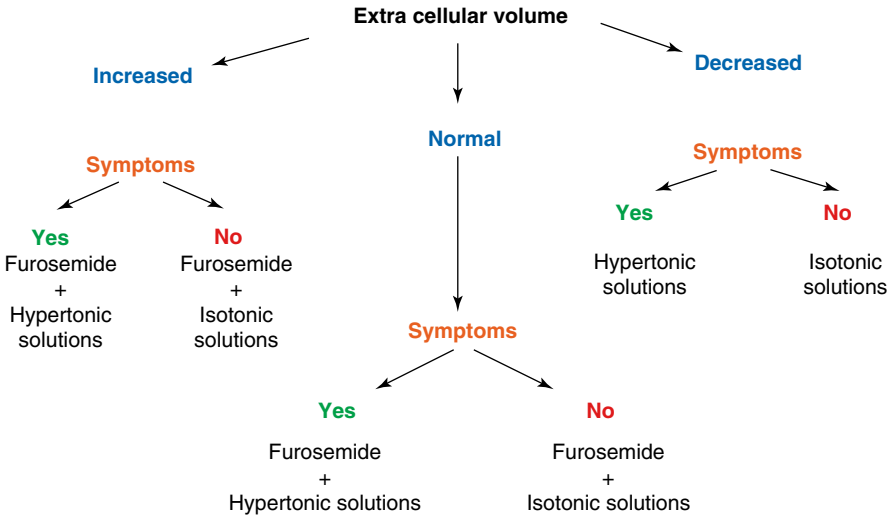



**Fig. 13.23** Flow chart for hyponatremia management

affect potassium plasma levels in different directions. Generally, factors determining a reduction of potassium levels are predominant; as a consequence, potassium loss must be adequately prevented and managed (Fanzca 2012).

Hyperkalemia may be the consequence of an increase in total potassium body stores or of a shift of potassium from the ICS to the ECS (Agrò and Vennari 2013a).

In the cardiac surgery patient, an increase in [$K^+$] is commonly due to ICS shift caused by academia, hypoinsulinemia, and hemolysis and to potassium IV load due to cardioplegia (Fanzca 2012).

In the case of postoperative ATN, hyperkalemia often reflects a reduced renal excretion of potassium due to reduced tubular secretion, rather than a reduced glomerular filtration. Adrenal dysfunction (due to disease or drugs), with reduced aldosterone production, can lead to potassium retention (Agrò and Vennari 2013a). Muscular weakness, up to paralysis, is one of the main manifestations of hyperkalemia. Cardiac signs are increased automaticity and repolarization of the myocardium, leading to ECG alterations and arrhythmias. Mild hyperkalemia may appear with T waves and a prolonged PR interval; severe hyperkalemia may cause a wide QRS complex, asystole, or ventricular fibrillation (Agrò and Vennari 2013a).

The management of hyperkalemia includes heart protection and facilitating in ICS redistribution of potassium. Rapid-effect therapies are the administration of calcium gluconate, insulin with glucose (considering patients' glycemia), and correction of acidemia through bicarbonate administration or hyperventilation. In acute and severe cases (often associated to AKI and development of postoperative complication such as sepsis), CRRT may be indicated considering other electrolytes and acid–base status. Additional therapies are resin exchange, diuretics, aldosterone agonists, and β-adrenergic agonists. They act in a long term and their use is suitable

in long-stay ICU patients who have developed a chronic condition responsible of hyperkalemia (Agrò and Vennari 2013a).

Cardiac surgery patients often present hypokalemia, which may be caused by an absolute deficiency of total body potassium stores or by an abnormal shift of potassium from the ECS to the ICS (despite normal total potassium) (Agrò and Vennari 2013a).

In the perioperative setting, a reduction in potassium level is due to augmented catecholamine production with increased skeletal uptake; diuresis caused by hypothermia, furosemide, and mannitol use during CPB; and increased cortisol and aldosterone levels due to surgical stress. Other causes may be gastrointestinal loss or renal losses due to diuretic or the development of acute renal damage. Hypokalemia is always associated to metabolic alkalosis (see acid–base paragraph) (Fanzca 2012; Agrò and Vennari 2013a).

Hypokalemia signs and symptoms depend on the potassium level. Arrhythmias (frequently, atrial fibrillation and premature ventricular beat) and other electrocardiographic abnormalities (sagging of the ST segment, T-wave depression, and U-wave elevation) appear at potassium concentrations <3 mEq/L (Agrò and Vennari 2013a).

The rate of potassium administration (generally potassium chloride) must be adjusted considering the distribution within the ECS. The administration rate is limited to 0.5–1.0 mEq/kg/h (Agrò and Vennari 2013a).

### 13.16.3 Calcium

Hypocalcemia is frequent during the intraoperative period. Hypocalcemia refers to free ionized calcium levels in the plasma. It develops when calcium concentrations are low but plasma protein levels are normal. As a consequence, it is necessary to know if the calcium values measured is the total plasma value (in this case, it should be adjusted for albumin value) or the ionized fraction (Agrò and Vennari 2013a).

In cardiac surgery patients, hypocalcemia is generally limited, and it is caused by citrate use, hemodilution, increase of albumin binding fraction, and hypomagnesemia. In these cases, hypocalcemia is treated in order to normalize calcium level and to uptake its effects on myocardium (protection and inotropism) and vessels (vasopressor) (Fanzca 2012). In the ICU setting, the most frequent cause of hypocalcemia is hypoalbuminemia. Other causes are the development of postoperative renal dysfunctions, hyperventilation, blood transfusion (citrate chelation), and septic complications (the pathogenesis of the mechanisms correlating sepsis and hypocalcemia is not fully understood) (Fanzca 2012).

The main clinical manifestations of hypocalcemia are due to the increased cardiac and neuromuscular excitability and to the reduced contractile force of cardiac and vascular smooth muscles. Tetanic syndrome, a result of increased neuromuscular excitability, is characterized by numbness (especially around the mouth, lips, and tongue) and muscle spasms, particularly in the hands, feet, and face (characteristic are Chvostek and Trousseau signs). Regarding the cardiovascular alterations,

hypocalcemia causes prolongation of the PQ interval, which predisposes patients to the onset of severe ventricular arrhythmias. Hypocalcemia may also lead to hypotension.

Nervous symptoms are due to the impaired mental status (Agrò and Vennari 2013a).

The treatment of hypocalcemia should be causal but should also be aimed at quickly increasing the serum calcium concentration. It may be corrected by administering 10 % calcium chloride (1.36 mEq/mL) or calcium gluconate (0.45 mEq/mL) (Agrò and Vennari 2013a). The role of calcium administration has been discussed in literature. In particular, there is concern about the exacerbation of ischemia–reperfusion damage. In fact, in ischemic cells, there are high calcium levels due to the impairment of ATP–calcium pump and to a reverse activity of $Na^{+}$–$Ca^{2+}$ pump. Finally, calcium transport is impaired by the oxidative stress. Intracellular hypercalcemia leads to mitochondrial dysfunction and cellular death. Calcium administration may further increase calcium flux into cardiac cells, accelerating this process (Fanzca 2012). In patients undergoing to CABG, (Fanzca 2012) found a transient improvement (<10 min) in systolic function, associated to a diastolic dysfunction (reduced myocardial compliance), when calcium was administered early after bypass separation. However, in a subsequent study the reduction of diastolic function after CABG was not related to calcium administration (Fanzca 2012; Ekery et al. 2003). Moreover, calcium has been shown to reduce adrenalin effect in the postoperative period and in animal studies to increase the negative inotropic effect of protamine (Fanzca 2012; Zaloga et al. 1990; David et al. 2001). Evidence suggests that the use of calcium at the time or before the reperfusion has benefit which cannot be obtained using other agents, although implying potentially adverse effect (Fanzca 2012).

Hypercalcemia is less frequent in the immediate postoperative period of cardiac surgery. It is generally related to an overtreatment of hypocalcemia, while in the long-stay ICU patient it may be due to the development of renal dysfunction or increased bone reabsorption (immobilization) (Agrò and Vennari 2013a).

Main symptoms of hypercalcemia may be remembered using the rhyme: “groans (constipation), moans (psychic moans, e.g., fatigue, lethargy, depression), bones (bone pain, especially in hyperparathyroidism), stones (kidney stones), and psychiatric overtones (including depression and confusion).” Other symptoms are anorexia, fatigue, vomiting, and nausea. ECG alterations, such as a short QT interval or widened T wave, are suggestive of hypocalcemia. Symptoms are common at high calcium concentration (>3 mEq/L). Severe hypocalcemia (>4 mEql/L) is a medical emergency. It may lead to coma and cardiac arrest (Agrò and Vennari 2013a).

Hypercalcemia management involves increased diuresis and plasma dilution. Accordingly, diuretics and saline solutions are used, because sodium reduces calcium reabsorption by the kidneys. In patients with a chronic cause or status leading to hypocalcemia, other possible treatments are calcitonin, bisphosphonate, and glucocorticoids. In all patients, rapid mobilization and physiotherapy after the surgery is fundamental to maintain bone balance (Agrò and Vennari 2013a).

### 13.16.4 Magnesium

Hypomagnesemia is frequent in the postoperative period after cardiac surgery. It may be triggered by hyperaldosteronism (heart failure, stress response), by calcium alteration (hypercalcemia), and by the use of drugs such as diuretics or adrenergic drugs (Agrò and Vennari 2013a). The effects of magnesium deficits are neuromuscular excitability disorders (related to the concurrent development of hypercalcemia), such as involuntary contraction of the facial muscles, cramps, tetany, and arrhythmias, or other symptoms mainly related to metabolism, such as morning fatigue. Hypomagnesemia may lead to hypertension, coronary vasoconstriction, and arrhythmias (Fanzca 2012; Kimura et al. 1989; Booth et al. 2003). It may also be characterized by an alteration of consciousness, as demonstrated by confusion, hallucinations, and epilepsy.

Magnesium supplementation has been demonstrated to reduce the reperfusion injury, by blocking calcium ingress in myocardial cells and acting as a free radical scavenger (Fanzca 2012; Garcia et al. 1998). In fact, in animal studies, magnesium use has been related with a reduction of infarct size. The timing of administration appears to be very important: no effects have been found when administration is realized early after the reperfusion (Fanzca 2012; Ravn et al. 1999; Herzog et al. 1995). Literature also demonstrated that after CABG, magnesium supplementation reduces the risk of postoperative arrhythmias, improves the short-term neurological function, and may have a significant opioid-sparing effect (Fanzca 2012; England et al. 1992; Miller et al. 2005).

Magnesium inhibits platelet function with a prolongation of bleeding time at 24 h after cardiac surgery. However, a correlation of this effect with an increase of postoperative blood losses is not clear (Fanzca 2012; Gries et al. 1999). On the other side, a recent study demonstrated reduced postoperative bleeding and transfusional need after CABG, in patient receiving magnesium (Fanzca 2012; Dabbagh et al. 2010).

Hypermagnesemia is less frequent in cardiac surgery patient. The most common and probable cause is kidney failure. Hemolysis, hypocalcemia, adrenal insufficiency, diabetic ketoacidosis, lithium intoxication, and hyperparathyroidism are other predisposing conditions. Hypermagnesemia is characterized by weakness, hypocalcemia, nausea and vomiting, hypotension, breathing symptoms, and arrhythmias up to asystole (Agrò and Vennari 2013a).

In severe cases, the first line in hypomagnesemia management is the administration of calcium gluconate, since calcium is the natural antagonist of magnesium. Subsequently, according to renal function, diuretics or dialysis is needed (Agrò and Vennari 2013a).

**Conclusion**

A perfect fluid management for perioperative treatment of cardiac surgery patient is still lacking. One of the first goals is to contain the IVS losses to a minimum using the cell savage technique and reducing the need for colloids (with their side effect!) (Fanzca 2012).

Preload assessment and $DO_2$ optimization by assessing fluid responsiveness represent the main goal in cardiac surgery patients. The best approach is using GDT to measure preload and to restore it in patients with reduced circulating volume (fluid responders) while using a continuous infusion of fluid to compensate urinary loss and perspiration, being mindful of glycocalyx alterations caused by cardiac surgery and that may generate tissue edema (Fanzca 2012; Becker et al. 2010).

Colloids are needed when a fast hemodynamic improvement is necessary (Agrò and Vennari 2013b). The volume effect of colloids depends on the IVS volume and hydration state of the patient. Giving fluids, not before but when hypovolemia occurs, seems to be more rational because the volume effects of colloids are more effective (Chappell et al. 2008; Roberts and Bratton 1998). Treating relative hypovolemia with colloids in patients undergoing surgery or in the critically ill who need sedation ignores the indirect vasodilator effect of anesthetic drugs. Thus, when vascular tone is restored, a relative hypervolemia can occur, potentially causing postoperative pulmonary edema (Roberts and Bratton 1998).

Crystalloids are needed to compensate urinary and perspiration losses, avoiding overload (Agrò and Vennari 2013b).

Possible future strategies could be aimed to protect and rapidly restore the endothelial glycocalyx (Fanzca 2012).

## References

Abbas SM, Hill AG (2008) Systematic review of the literature for the use of oesophageal Doppler monitor for fluid replacement in major abdominal surgery. Anaesthesia 63:44–51

Adams HA (2007) Volumen und Flüssigkeitsersatz – Physiologie, Pharmakologie und klinischer Einsatz. Anästh Intensivmed 48:448–460

Adamson JW (2008) New blood, old blood, or no blood? N Engl J Med 358:1295–1296

Agrò FE, Benedetto M (2013) Properties and composition of plasma substitutes. In: Agrò FE (ed) Body fluid management – from physiology to therapy, 1st edn. Springer, Milan

Agrò FE, Vennari M (2013a) Physiology of body fluid compartments and body fluid movements. In: Agrò FE (ed) Body fluid management – from physiology to therapy, 1st edn. Springer, Milan

Agrò FE, Vennari M (2013b) Clinical treatment: the right fluid in the right quantity. In: Agrò FE (ed) Body fluid management – from physiology to therapy, 1st edn. Springer, Milan

Agrò FE, Fries D, Vennari M (2013a) Cardiac surgery. In: Agrò FE (ed) Body fluid management – from physiology to therapy, 1st edn. Springer, Milan

Agrò FE, Fries D, Benedetto M (2013b) How to maintain and restore the balance: colloids. In: Agrò FE (ed) Body fluid management – from physiology to therapy, 1st edn. Springer, Milan

Allhoff T, Lenhart FP (1993) Severe dextran-induced anaphylactic/anaphylactoid reaction in spite of hapten prophylaxis. Infusionsther Transfusionsmed 20:301–306

Allison KP, Gosling P, Jones S et al (1999) Randomized trial of hydroxyethyl starch versus gelatin for trauma resuscitation. J Trauma 47:1114–1121

Arieff AI, Llach F, Massry SG (1976) Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes. Medicine 55:121–129

Arkilic CF, Taguchi A, Sharma N et al (2003) Supplemental perioperative fluid administration increases tissue oxygen pressure. Surgery 133:49–55
Arthurson G, Granath K, Thoren L et al (1964) The renal excretion of LMW dextran. Acta Clin Scand 127:543–551
Atik M (1967) Dextran-40 and dextran-70, a review. Arch Surg 94:664–667
Auler JOJ, Galas F, Hajjar L et al (2008) Online monitoring of pulse pressure variation to guide fluid therapy after cardiac surgery. Anesth Analg 106:1201–1206
Balogh Z, McKinley BA, Cocanour CS et al (2003) Supranormal trauma resuscitation causes more cases of abdominal compartment syndrome. Arch Surg 138:633–642
Bamboat ZM, Bordeianou L (2009) Perioperative fluid management. Clin Colon Rectal Surg 22(1):28–33
Baron JF (2000) Adverse effects of colloids on renal function. In: Vincent JL (ed) Yearbook of intensive care and emergency medicine, 1st edn. Springer, Berlin
Barron ME, Wilkes MM, Navickis RJ (2004) A systematic review of the comparative safety of colloids. Arch Surg 139:552–563
Base EM, Standl T, Lassnigg A et al (2011) Efficacy and safety of hydroxyethyl starch 6 % 130/0.4 in a balanced electrolyte solution (Volulyte) during cardiac surgery. J Cardiothorac Vasc Anesth 25(3):407–414
Becker B, Chappel D, Bruegger D et al (2010) Therapeutic strategies targeting the endothelial glycocalyx: acute deficit but great potential. Cardiovasc Res 87:300–310
Belloni L, Pisano A, Natale A et al (2008) Assessment of fluid responsiveness parameters for off-pump coronary artery bypass surgery: a comparison among LiDCO, transesophageal echocardiography, and pulmonary artery catheter. J Cardiothorac Vasc Anesth 22:243–248
Bendjelid K, Suter PM, Romand JA (2004) The respiratory change in preejection period: a new method to predict fluid responsiveness. J Appl Physiol 96:337–342
Benes J, Cytra I, Altmann P et al (2010) Intraoperative fluid optimization using stroke volume variation in high risk surgical patients: result of prospective randomized study. Crit Care 14:R118
Bennett-Guerrero E, Kahn RA, Moskowitz DM et al (2002) Comparison of arterial systolic pressure variation with other clinical parameters to predict the response to fluid challenges during cardiac surgery. Mt Sinai J Med 69:96–100
Bernard C (1865) Introdution à l'étude de la médecine expérimentale. Paris. Éditions Garnier-Flammarion, 1966, 318 pp. Collection: Texte intégral. Texte originalement publié en 1865
Blasco V, Leone M, Antonini F et al (2008) Comparison of the novel hydroxyethyl starch 130/0.4 and hydroxyethyl starch 200/0.6 in brain-dead donor resuscitation on renal function after transplantation. Br J Anaesth 100:504–508
Bojar RM (2005) Early postoperative care. In: Bojar RM (ed) Manual of perioperative care in adult cardiac surgery, 4th edn. Blackwell Publishing Inc., Malden
Booth J, Philips-Bute B, McCants C et al (2003) Low serum magnesium level predicts major adverse cardiac events after coronary artery bypass graft surgery. Am Heart J 145:1108–1113
Boyd DR, Mansberger AR Jr (1968) Serum water and osmolal changes in hemorrhagic shock: an experimental and clinical study. Am Surg 34:744–749
Brandstrup B (2006) Fluid therapy for the surgical patient. Best Pract Res Clin Anaesthesiol 20:265–283
Brandstrup B, Tønnesen H, Beier-Holgersen R et al (2003) Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. Ann Surg 238:641–648
Breukers RM, de Wilde RBP, van den Berg PCM et al (2009a) Assessing fluid responses after coronary surgery: role of mathematical coupling of global end-diastolic volume to cardiac output measured by transpulmonary thermodilution. Eur J Anaesthesiol 26:954–960
Breukers RM, Trof RJ, de Wilde RBP et al (2009b) Relative value of pressures and volumes in assessing fluid responsiveness after valvular and coronary artery surgery. Eur J Cardiothorac Surg 35:62–68
Brock H, Gabriel C, Bibl D et al (2002) Monitoring intravascular volumes for postoperative volume therapy. Eur J Anaesthesiol 19:288–294

Bruegger D, Jacob M, Rehm M et al (2005) Atrial natriuretic peptide induces shedding of endothelial glycocalyx in coronary vascular bed of guinea pig hearts. Am J Physiol Heart Circ Physiol 289:H1993–H1999

Brunkhorst FM, Engel C, Bloos F et al (2008) Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 358:125–139

Buhre W, Buhre K, Kazmaier S et al (2001) Assessment of cardiac preload by indicator dilution and transoesophageal echocardiography. Eur J Anaesthesiol 18:662–667

Bunn F, Roberts I, Tasker R, Akpa E (2002) Hypertonic versus isotonic crystalloid for fluid resuscitation in critically ill patients (Cochrane Review). Cochrane Database Syst Rev. 2004;(3): CD002045

Campbell IT, Baxter JN, Tweedie IE et al (1990) IV fluids during surgery. Br J Anaesth 65:726–729

Carl M, Alms A, Braun J et al (2000) Die intensivmedizinische Versorgung herzchirurgischer Patienten: Hämodynamisches Monitoring und Herz-Kreislauf-Therapie S3-Leitlinie der Deutschen Gesellschaft für Thorax-, Herz- und Gefäbchirurgie (DGTHG) und der Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI). Thorac Cardiovasc Surg 55:130–148

Cavallaro F, Sandroni C, Antonelli M (2008) Functional hemodynamic monitoring and dynamic indices of fluid responsiveness. Minerva Anestesiol 74:123–135

Cervera AL, Moss G (1974) Crystalloid distribution following haemorrhage and haemodilution: mathematical model and prediction of optimum volumes for equilibration at normovolemia. J Trauma 14:506–520

Chan ST, Kapadia CR, Johnson AW et al (1983) Extracellular fluid volume expansion and third space sequestration at the site of small bowel anastomoses. Br J Surg 70:36–39

Chappell D, Jacob M, Hofmann-Kiefer K et al (2008) A rational approach to perioperative fluid management. Anesthesiology 109:723–740

Cheung AT, Savino JS, Weiss SJ et al (1994) Echocardiographic and hemodynamic indexes of left ventricular preload in patients with normal and abnormal ventricular function. Anesthesiology 81:376–387

Chytra I, Pradl R, Bosman R et al (2007) Esophageal Doppler-guided fluid management decreases blood lactate levels in multiple-trauma patients: a randomized controlled trial. Crit Care 11(1):R24

Cittanova ML, LeBlanc I, Legendre C et al (1996) Effects of hydroxyethyl starch in braindead kidney donors on renal function in kidney-transplant recipients. Lancet 348:1620–1622

Dabbagh A, Rajaei S, Shamsolhrar M (2010) The effect of intravenous magnesium sulfate on acute postoperative bleeding in elective coronary artery bypass surgery. J Perianesth Nurs 25:290–295

Dart AB, Mutter TC, Ruth CA et al (2010) Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database Syst Rev 20(1), CD007594

David J, Vivien B, Lecarpentier Y et al (2001) Extracellular calcium modulates the effects of protamine on rat myocardium. Anesth Analg 92:817–823

Davidson IJ (2006) Renal impact of fluid management with colloids: a comparative review. Eur J Anaesthesiol 23:721–738

DeJonge E, Levi M (2001) Effects of different plasma substitutes on blood coagulation: a comparative review. Crit Care Med 29:1261–1267

Deman A, Peeters P, Sennesael J (1999) Hydroxyethyl starch does not impair immediate renal function in kidney transplant recipient. A retrospective, multicenter analysis. Nephrol Dial Transplant 14:1517–1520

DiCorte CJ, Latham P, Greilich PE et al (2000) Esophageal Doppler monitor determinations of cardiac output and preload during cardiac operations. Ann Thorac Surg 69:1782–1786

Dieterich HJ, Weissmuller T, Rosenberger P et al (2006) Effect of hydroxyethyl starch on vascular leak syndrome and neutrophil accumulation during hypoxia. Crit Care Med 34:1775–1782

Dietrich G, Orth D, Haupt W et al (1990) Primary hemostasis in hemodilution-infusion solutions. Infusionstherapie 17:214–216

Dongaonkar R, Stweart R, Geisller H, Laine G (2010) Myocardial microvascular permeability, interstitial oedema, and compromised cardiac function. Cardiovasc Res 87:331–339

Dorje P, Adhikary G, Tempe DK (2000) Avoiding iatrogenic hyperchloremic acidosis: call for a new crystalloid fluid. Anesthesiology 92:625–626
Drt A, Mutter T, Ruth C et al (2010) Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database Syst Rev 1, CD007594
Drummond JC, Petrovitch CT (2005) Intraoperative blood salvage: fluid replacement calculation. Anesth Analg 100:645–649
Dubois MJ, Vincent JL (2007) Colloid fluids. In: Hahn RG, Prough DS, Svensen CH (eds) Perioperative fluid therapy, 1st edn. Wiley, New York
Ekery D, Davidoff R, Orlandi Q et al (2003) Imaging and diagnostic testing: dysfunction after coronary artery bypass grafting: a frequent finding of clinical significance not influenced by intravenous calcium. Am Heart J 145:896–902
England M, Gordon G, Salem M et al (1992) Magnesium administration and dysrhythmias after cardiac surgery. A placebo controlled double-blind randomized trial. JAMA 268: 2395–2402
Ernest D, Belzberg AS, Dodek PM (2001) Distribution of normal saline and 5 % albumin infusions in cardiac surgical patients. Crit Care Med 29:2299–2302
Fanzca RY (2012) Perioperative fluid and electrolyte management in cardiac surgery: a review. J Extra Corpor Technol 44:20–26
Feng X, Yan W, Liu X et al (2006) Effects of hydroxyethyl starch 130/0.4 on pulmonary capillary leakage and cytokines production and nF-kappaB activation in ClP-induced sepsis in rats. J Surg Res 135:129–136
Fitzsimons M, Agnihotri A (2007) Hyponatremia and cardiopulmonary bypass. J Cardiothorac Vasc Anesth 86:1883–1887
Fleck A, Raines G, Hawker F et al (1985) Increased vascular permeability. Major cause of hypoalbuminaemia in disease and injury. Lancet 1:781–783
Franz A, Bräunlich P, Gamsjäger T et al (2001) The effects of hydroxyethyl starches of varying molecular weights on platelet function. Anesth Analg 92:1402–1407
Gallandat Huet RCG, Siemons AW, Baus D et al (2000) A novel hydroxyethyl starch (VoluvenR) for effective perioperative plasma volume substitution in cardiac surgery. Can J Anaesth 47:1207–1215
Gamble J (1947) Chemical anatomy, physiology and pathology of extracellular fluid. Harvard University Press, Cambridge
Gandhi SD, Weiskopf RB, Jungheinrich C et al (2007) Volume replacement therapy during major orthopedic surgery using Voluven® (hydroxyethyl starch 130/0.4) or hetastarch. Anesthesiology 106:1120–1127
Garcia L, Dejong S, Martin S et al (1998) Magnesium reduces free radicals in an in vivo coronary occlusion reperfusion model. J Am Coll Cardiol 32:536–539
Giglio MT, Marucci M, Testini M et al (2009) Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials. Br J Anaesth 103:637–646
Goedje O, Seebauer T, Peyerl M et al (2000) Hemodynamic monitoring by double-indicator dilution technique in patients after orthotopic heart transplantation. Chest 118:775–781
Goepfer MS, Reuter DA, Akyiol D et al (2007) Goal-directed fluid management reduces vasopressor and catecholamine use in cardiac surgery patients. Intensive Care Med 33:96–103
Goepfert MSG, Reuter DA, Akyol D et al (2007) Goal-directed fluid management reduces vasopressor and catecholamine use in cardiac surgery patients. Intensive Care Med 33: 96–103
Grathwohl KW, Bruns BJ, LeBrun CJ et al (1996) Does haemodilution exist? Effects of saline infusion on hematologic parameters in euvolemic subjects. South Med 89:51–55
Grebe D, Sander M, von Heymann C et al (2006) Fluid therapy—pathophysiological principles as well as intra- and perioperative monitoring. Anasthesiol Intensivmed Notfallmed Schmerzther 41:392–398
Greenfield RH, Bessen HA, Henneman PL (1989) Effect of crystalloid infusion on hematocrit and intravascular volume in healthy, no bleeding subjects. Ann Emerg Med 18:51–55

Gries A, Bode C, Gross S et al (1999) The effect of intravenously administered magnesium on platelet function in patient after cardiac surgery. Anesth Anal 88:1231–1239
Grocott MP, Mythen MG, Gan TJ (2005) Perioperative fluid management and clinical outcomes in adults. Anesth Analg 100:1093–1106
Habicher M, Perrino AJ, Spies CD et al (2011) Contemporary fluid management in cardiac anesthesia. J Cardiothorac Vasc Anesth 25(6):1141–1153
Hahn RG, Drobin D, Ståhle L (1997) Volume kinetics of Ringer's solution in female volunteers. Br J Anaesth 78:144–148
Hauser CJ, Shoemaker WC, Turpin I et al (1980) Oxygen transport responses to colloids and crystalloids in critically ill surgical patients. Surg Obstet 150:811–816
Haynes GH, Havidich JE, Payne KJ (2004) Why the food and drug administration changed the warning label for hetastarch. Anesthesiology 101:560–561
Hecth-Dolkin M, Barkan H, Tahara A et al (2009) Hetastarch increases the risk of bleeding complications in patients after off-pump coronary bypass surgery. J Thorac Cardiovasc Surg 138:703–711
Hendry EB (1961) Osmolarity of human serum and of chemical solutions of biological importance. Clin Chem 7:156–164
Herzog W, Schlossberg M, MacMurdy K et al (1995) Timing of magnesium therapy affects experimental infarct size. Circulation 92:2622–2626
Hiltebrand LB, Pestel G, Hager H et al (2007) Perioperative fluid management: comparison of high, medium and low fluid volume on tissue oxygen pressure in the small bowel and colon. Eur J Anaesthesiol 24:927–933
Hofer CK, Furrer L, Matter-Ensner S et al (2005a) Volumetric preload measurement by thermodilution: a comparison with transoesophageal echocardiography. Br J Anaesth 94:748–755
Hofer CK, Müller SM, Furrer L et al (2005b) Stroke volume and pulse pressure variation for prediction of fluid responsiveness in patients undergoing off-pump coronary artery bypass grafting. Chest 128:848–854
Hofer CK, Senn A, Weibel L et al (2008) Assessment of stroke volume variation for prediction of fluid responsiveness using the modified FloTrac™ and PiCCOplus™ system. Crit Care 12:R82
Holte K, Kehlet H (2002) Compensatory fluid administration for preoperative dehydration: does it improve outcome? Acta Anaesthesiol Scand 46:1089–1093
Holte K, Klarskov B, Christensen DS et al (2004) Liberal versus restrictive fluid administration to improve recovery after laparoscopic cholecystectomy: a randomized doubleblind study. Ann Surg 240:892–899
Holte K, Hahn RG, Ravn L et al (2007a) Influence of a "liberal" versus "restrictive" intraoperative fluid administration on elimination of a postoperative fluid load. Anesthesiology 106: 75–79
Holte K, Foss NB, Andersen J et al (2007b) Liberal or restrictive fluid administration in fasttrack colonic surgery: a randomized, double-blind study. Br J Anaesth 99:500–508
Holtfreter B, Bandt C, Kuhn SO et al (2006) Serum osmolality and outcome in intensive care unit patients. Acta Anaesthesiol Scand 50:970–977
Hu X, Weinbaum S (1999) A new view of Starling's hypothesis at the micro-structural level. Microvasc Res 58(3):281–304
Hu X, Adamson RH, Liu B, Curry FE, Weinbaum S (2000) Starling forces that oppose filtration after tissue oncotic pressure is increased. Am J Physiol Heart Circ Physiol 279(4):H1724–H1736
Hüter L, Simon TP, Weinmann L et al (2009) Hydroxyethyl starch impairs renal function and induces interstitial proliferation, macrophage infiltration and tubular damage in an isolated renal perfusion model. Crit Care 13:R23
Ickx BE, Bepperling F, Melot C et al (2003) Plasma substitution effects of a new hydroxyethyl starch HES 130/0.4 compared with HES 200/0.5 during and after extended acute normovolaemic haemodilution. Br J Anaesth 91:196–202
Iriz E, Kolbakir F, Akar H et al (2005) Comparison of hydroxyethyl starch and ringer as prime solution regarding S-100beta protein levels and informative cognitive tests in cerebral injury. Ann Thorac Surg 79:666–671

Jacob M, Chappel D, Conzen P et al (2008) Blood volume is normal after overnight fasting. Acta Anaesthesiol Scand 52:522–529
James MF, Latoo MY, Mythen MG et al (2004) Plasma volume changes associated with two hydroxyethyl starch colloids following acute hypovolaemia in volunteers. Anaesthesia 59:738–742
Järhult J (1973) Osmotic fluid transfer from tissue to blood during hemorrhagic hypotension. Acta Physiol Scand 89:213–226
Jarvela K, Koskinen M, Kaukinen S et al (2001) Effects of hypertonic saline (7.5 %) on extracellular fluid volumes compared with normal saline (0.9 %) and 6 % hydroxyethyl starch after aortocoronary bypass graft surgery. J Cardiothorac Vasc Anesth 15:210–215
Jenkins MT, Giesecke AH, Johnson ER (1975) The postoperative patient and his fluid and electrolyte requirements. Br J Anaesth 47:143–150
Jones SB, Whitten CW, Monk TG (2004) Influence of crystalloid and colloid replacement solutions on hemodynamic variables during acute normovolemic hemodilution. J Clin Anesth 16:11–17
Jumgheinrich C, Scharpf R, Wargenau M et al (2002) The pharmacokinetics and tolerability of an intravenous infusion the new hydroxyethyl starch 130/04 (6 % 500 ml) in mild to severe renal impairment. Anaesth Analg 95:544–551
Jungheinrich C, Scharpf R, Wargenau M et al (2002) The pharmacokinetics and tolerability of an intravenous infusion of the new hydroxyethyl starch 130/0.4 (6 %, 500 mL) in mild-to-severe renal impairment. Anesth Analg 95:544–551
Kaminski MV, Williams SD (1990) Review of the rapid normalization of serum albumin with modified total parenteral nutrition solutions. Crit Care Med 18:327–335
Kapoor PM, Kakani M, Chowdhury U et al (2008) Early goal-directed therapy in moderate to high-risk cardiac surgery patients. Ann Card Anaesth 11:27–34
Karanko MS, Klossner JA, Laaksonen VO (1987) Restoration of volume by crystalloid versus colloid after coronary artery bypass: hemodynamics, lung water, oxygenation, and outcome. Crit Care Med 15:559–566
Kastrup M, Markewitz A, Spies C et al (2007) Current practice of hemodynamic monitoring and vasopressor and inotropic therapy in post-operative cardiac surgery patients in Germany: results from a postal survey. Acta Anaesthesiol Scand 51:347–358
Kenney PR, Allen-Rowlands CF, Gann DS (1983) Glucose and osmolality as predictors of injury severity. J Trauma 23:712–719
Kimura T, Yasue H, Sukaino N et al (1989) Effects of magnesium on isolated human coronary arteries. After CABG it has been shown as a predictor of major cardiac events. Circulation 79:118–124
Kozek-Langenecker SA (2005) Effects of hydroxyethyl starch solutions on hemostasis. Anesthesiology 103:654–660
Kutschen F, Galletti P, Hahn C et al (1985) Alterations of insulin and glucose metabolism during cardiopulmonary bypass under normothermia. J Thorac Cardiovasc Surgery 89:97–106
Lamke LO, Liljedahl SO (1976) Plasma volume changes after infusion of various plasma expanders. Resuscitation 5:93–102
Lamke LO, Nilsson G, Reithner H (1977) Water loss by evaporation from the abdominal cavity during surgery. Acta Chir Scand 143:279–284
Lasks H, Standeven J, Balir O et al (1977) The effects of cardiopulmonary by-pass with crystalloid and colloid hemodilution on myocardial extravascular water. J Thorac Cardiovasc Surg 73:129–138
Laxenaire M, Charpentier C, Feldman L (1994) Reactions anaphylactoides aux subitutes colloidaux du plasma: incidence, facteurs de risque, mecanismes. Ann Fr Anest Reanimat 13:301–310
Lees N, Hamilton M, Rhodes A (2009) Clinical review: goal-directed therapy in high risk surgical patients. Crit Care 13:231. doi:10.1186/cc8039
Legendre C, Thervet E, Page B et al (1993) Hydroxyethyl starch and osmotic-nephrosis-like lesions in kidney transplantation. Lancet 342:248–249
Lehmann G, Marx G, Forster H (2007) Bioequivalence comparison between hydroxyethyl starch 130/0.42/6:1 and hydroxyethyl starch 130/0.4/9:1. Drugs R & D 8:229–240

Levick JR (2004) Revision of the Starling principle. New views of tissue fluid balance. J Physiol 557:704

Ley SJ, Miller K, Skov P et al (1990) Crystalloid versus colloid fluid therapy after cardiac surgery. Heart Lung 19:31–40

Lobo DN (2004) Sir David Cuthbertson medal lecture. Fluid, electrolytes and nutrition: physiological and clinical aspects. Proc Nutr Soc 63:453–466

Lobo DN, Allison SP (2005) Fluid, electrolyte and nutrient replacement. In: Burnand KG, Young AE, Lucas J et al (eds) The new aird's companion in surgical studies, 3rd edn. Churchill Livingstone, London

Lobo DN, Stanga Z, Simpson JAD et al (2001) Dilution and redistribution effects of rapid 2- litre infusions of 0.9 % (w/v) saline and 5 % (w/v) dextrose on haematological parameters and serum biochemistry in normal subjects: a double-blind crossover study. Clin Sci (Lond) 101:173–179

Lobo DN, Bostock KA, Neal KR et al (2002) Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. Lancet 359:1812–1818

Lobo DN, Stanga Z, Aloysius MM et al (2010) Effect of volume loading with 1 liter intravenous infusions of 0.9 % saline, 4 % succinylated gelatine (Gelofusine) and 6 % hydroxyethyl starch (Voluven) on blood volume and endocrine responses: a randomized, threeway crossover study in healthy volunteers. Crit Care Med 38:464–470

Lopes MR, Oliveira MA, Pereira VO (2007) Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery: a pilot randomized controlled trial. Crit Care 11:R100

Lowell JA, Schifferdecker C, Driscoll DF et al (1990) Postoperative fluid overload: not a benign problem. Crit Care Med 18:728–733

MacKay G, Fearon K, McConnachie A et al (2006) Randomized clinical trial of the effect of postoperative intravenous fluid restriction on recovery after elective colorectal surgery. Br J Surg 93:1469–1474

Madjdpour C, Dettori N, Frascarolo P et al (2005) Molecular weight of hydroxyethyl starch: is there an effect on blood coagulation and pharmacokinetics? Br J Anaesth 94:569–576

Maharaj CH, Kallam SR, Malik A et al (2005) Preoperative intravenous fluid therapy decreases postoperative nausea and pain in high risk patients. Anesth Analg 100:675–682

Mahmood A, Gosling P, Vohra RK (2007) Randomized clinical trial comparing the effects on renal function of hydroxyethyl starch or gelatin during aortic aneurysm surgery. Br J Surg 94:427–433

Mahmood A, Gosling P, Barclay R et al (2009) Splanchnic microcirculation protection by hydroxyethyl starches during abdominal aortic aneurysm surgery. Eur J Vasc Endovasc Surg 37:319–325

Makoff DL, da Silva JA, Rosenbaum BJ et al (1970) Hypertonic expansion: acid-base and electrolyte changes. Am J Physiol 218:1201–1207

Maningas PA, Bellamy RF (1986) Hypertonic sodium chloride solutions for the prehospital management of traumatic hemorrhagic shock: a possible improvement in the standard of care? Ann Emerg Med 15:1411–1414

Margarson MP, Soni N (1998) Serum albumin: touchstone or totem? Anaesthesia 53:789–803

Marik PE (1993) The treatment of hypoalbuminemia in the critically ill patient. Heart Lung 22:166–170

Marik PE, Baram M, Vahid B (2008) Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. Chest 134:172–178

Marik PE, Cavallazzi R, Vasu T et al (2009) Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review. Crit Care Med 37:2642–2647

Marik PE, Cecconi M, Hofer CF (2011) Cardiac output monitoring: an integrative perspective. Crit Care 15:214

Martin G, Bennett-Guerrero E, Wakeling H et al (2002) A prospective, randomized comparison of thromboelastographic coagulation profile in patients receiving lactated Ringer's solution, 6 % hetastarch in a balanced-saline vehicle, or 6 % hydroxyethyl starch in saline during major surgery. J Cardiothorac Vasc Anesth 16:441–446
McIlroy DR, Kharasch ED (2003) Acute intravascular volume expansion with rapidly administered crystalloid or colloid in the setting of moderate hypovolemia. Anesth Analg 96(6):1572–1577
McKendry M, McGloin H, Saberi D et al (2004) Randomised controlled trial assessing the impact of a nurse delivered, flow monitored protocol for optimisation of circulatory status after cardiac surgery. BMJ 329:258
Metze D, Reimann S, Szepfalusi Z et al (1997) Persistent pruritus after hydroxyethyl starch infusion therapy: a result of long-term storage in cutaneous nerves. Br J Dermatol 136:553–559
Michard F, Teboul J-L (2002) Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest 121:2000–2008
Michard F, Alaya S, Zarka V et al (2003) Global end-diastolic volume as an indicator of cardiac preload in patients with septic shock. Chest 124:1900–1908
Mille S, Crystal E, Garfinkle K et al (2005) Effects of magnesium in atrial fibrillation after cardiac surgery: a meta analysis. Heart 91:618–623
Miller RD (2009) Miller's anesthesia, 7th edn. Churchill Livingstone, New York
Mitra S, Khandelwal P (2009) Are all colloids same? How to select the right colloid? Indian J Anaesth 53(5):592
Moore FD, Steenburg RW, Ball MR et al (1955) Studies in surgical endocrinology. The urinary excretion of 17-hydroxycorticoids, and associated metabolic changes, in cases of soft tissue trauma of varying severity and in bone trauma. Ann Surg 141:145–174
Moran M, Kapsner C (1987) Acute renal failure associated with elevated plasma oncotic pressure. N Engl J Med 317:150–153
Morissette M, Weil MH, Shubin H (1975) Reduction in colloid osmotic pressure associated with fatal progression of cardiopulmonary failure. Crit Care Med 3:115–117
Moyer CA (1950) Acute temporary changes in renal function associated with major surgical procedures. Surgery 27:198–207
Mythen MG, Webb AR (1995) Preoperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. Arch Surg 130(4):423–429
Nadler SB, Hidalgo JU, Bloch T (1962) Prediction of blood volume in normal human adults. Surgery 51:224–232
Ng KFJ, Lam CCK, Chan IC (2002) In vivo effect of haemodilution with saline on coagulation: a randomized controlled tril. Br J Anaesth 88:475–480
Niemi TT, Suojaranta-Ylinen RT, Kukkonen SI et al (2006) Gelatin and hydroxyethyl starch, but not albumin, impair hemostasis after cardiac surgery. Anesth Analg 102:998–1006
Niemi T, Schramko A, Kuitunen A et al (2008) Haemodynamics and acid-base equilibrium after cardiac surgery: comparison of rapidly degradable hydroxyethyl starch solutions and albumin. Scand J Surg 97:259–265
Nisanevich V, Felsenstein I, Almogy G et al (2005) Effect of intraoperative fluid management on outcome after intraabdominal surgery. Anesthesiology 103:25–32
Nuevo FR, Vennari M, Agrò FE (2013) How to maintain and restore fluid balance: crystalloids. In: Agrò FE (ed) Body fluid management – from physiology to therapy, 1st edn. Springer, Milan
Olsson J, Svensén CH, Hahn RG (2004) The volume kinetics of acetated Ringer's solution during laparoscopic cholecystectomy. Anesth Analg 99:1854–1860
Ooi JS, Ramzisham AR, Zamrin MD (2009) Is 6 % hydroxyethyl starch 130/0.4 safe in coronary artery bypass graft surgery? Asian Cardiovasc Thorac Ann 17:368–372
Otsuki D, Fantoni D, Margarido C et al (2007) Hydroxyethyl starch is superior to ringer as a replacement fluid in pig model of acute normovolemic haemodilution. Br J Anaesth 98:29–37
Palumbo D, Servillo G, D'Amato L et al (2006) The effects of hydroxyethyl starch solution in critically ill patients. Minerva Anestesiol 72:655–664

Pearse R, Dawson D, Fawcett J et al (2005a) Changes in central venous saturation after major surgery, and association with outcome. Crit Care 9:R694–R699
Pearse R, Dawson D, Fawcett J et al (2005b) Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. Crit Care 9:R687–R693
Petty TL, Ashbaugh DG (1971) The adult respiratory distress syndrome. Clinical features, factors influencing prognosis and principles of management. Chest 60(3):233–239
Polderman K, Girbes R (2004) Severe electrolyte disorders following cardiac surgery. A prospective controlled observational study. Crit Care 8:459.66
Polonen P, Ruokonen E, Hippelainen M et al (2000) A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. Anesth Analg 90:1052–1059
Powell-Tuck J, Gosling P, Lobo DN et al (2008) British consensus guidelines on intravenous fluid therapy for adult surgical patients. GIFTASUP. Crit Care Med 2008;36:1323–1329. Available from http://www.bapen.org.uk/pdfs/bapen_pubs/giftasup.pdf. Accessed 1 Apr 2010
Pradeep A, Rajagopalam S, Kolli HK et al (2010) High volumes of intravenous fluid during cardiac surgery are associated with increased mortality. HSR Proc Intensive Care Cardiovasc Anesth 2:287–296
Pries AR, Secomb TW, Sperandi M, Gaehtgens P (1998) Blood flow resistance during hemodilution. Effect of plasma composition. Cardiovasc Res 37:225–235
Rackow E, Fein AI, Leppo J (1977) Colloid osmotic pressure as a prognostic indicator of pulmonary oedema and mortality in the critically ill. Chest 72:709–713
Rackow EC, Falk JL, Fein IA et al (1983) Fluid resuscitation in circulatory shock: a comparison of the cardio-respiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. Crit Care Med 11:839–850
Raja SG, Akhtar S, Shahbaz Y et al (2011) In cardiac surgery patients does Voluven® impair coagulation less than other colloids? Interact Cardiovasc Thorac Surg 12:1022–1027
Rajnish KJ et al (2004) Albumin: an overview of its place in current clinical practice. Indian J Anaesth 53:592–607
Ravn H, Moeldrup U, Brookes C et al (1999) Intravenous magnesium reduces infarct size after ischemia/reperfusion injury combined with a thrombogenic lesion in the left anterior descending artery. Arterioscler Thromb Vasc Biol 19:569–574
Rehm M, Haller M, Orth V et al (2001) Changes in blood volume and hematocrit during acute preoperative volume loading with 5 % albumin or 6 % hetastarch solutions in patients before radical hysterectomy. Anesthesiology 95:849–856
Rehm M, Zahler S, Lotsc M et al (2004) Endothelial glycocalyx as an additional barrier determining extravasation of 6 % hydroxyethyl starch or 5 % albumin solutions in the coronary vascular bed. Anesthesiology 100:1211–1223
Rehm R, Bruegger D, Christ F et al (2007) Shedding of the endothelial glycocalyx in patients undergoing major vascular surgery with global and regional ischemia. Circulation 116:1896–1906
Reid F, Lobo DN, Williams RN et al (2003) (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. Clin Sci 104:17–24
Reuter DA, Felbinger TW, Moerstedt K et al (2002a) Intrathoracic blood volume index measured by thermodilution for preload monitoring after cardiac surgery. J Cardiothorac Vasc Anesth 16:191–195
Reuter DA, Felbinger TW, Kilger E et al (2002b) Optimizing fluid therapy in mechanically ventilated patients after cardiac surgery by on-line monitoring of left ventricular stroke volume variations. Comparison with aortic systolic pressure variations. Br J Anaesth 88:124–126
Reuter DA, Bayerlein J, Goepfert MS et al (2003) Influence of tidal volume on left ventricular stroke volume variation measured by pulse contour analysis in mechanically ventilated patients. Intensive Care Med 29:476–480
Reuter DA, Huang C, Edrich T et al (2010) Cardiac output monitoring using indicator dilution techniques: basic, limits and perspectives. Anesth Analg 110:799–811
Roberts JS, Bratton SL (1998) Colloid volume expanders. Problems, pitfalls and possibilities. Drugs 55(5):621–630

Roche AM, James MF, Grocott MP et al (2002) Coagulation effects of in vitro serial haemodilution with a balanced electrolyte hetastarch solution compared with a saline-based hetastarch solution and lactated Ringer's solution. Anaesthesia 57:950–955

Rubin H, Carlson S, DeMeo M et al (1997) Randomized, double-blind study of intravenous human albumin in hypoalbuminemic patients receiving total parenteral nutrition. Crit Care Med 25:249–252

Russell JA, Navickis RJ, Wilkes MM (2004) Albumin versus crystalloid for pump priming in cardiac surgery: meta-analysis of controlled trials. J Cardiothorac Vasc Anesth 18:429–437

Ruttmann TG, James MFM, Lombard EM et al (2001) Haemodilution-induced enhancement of coagulation is attenuated in vitro by restoring antithrombin III to predilution concentration. Anaesth Intensive Care 29:489–493

Ruttmann TG, James MFM, Finlayson J et al (2002) Effects on coagulation of intravenous crystalloid or colloid in patients undergoing peripheral vascular surgery. Br J Anaesth 89:226–230

SAFE Study Investigators, Finfer S, McEvoy S et al (2011) Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. Intensive Care Med 37(1):86–96

Sakka SG, Becher L, Kozieras J et al (2009) Effects of changes in blood pressure and airway pressures on parameters of fluid responsiveness. Eur J Anaesthesiol 26:322–327

Sakr Y, Payen D, Reinhart K et al (2007) Effects of hydroxyethyl starch administration on renal function in critically ill patients. Br J Anaesth 98:216–224

Sanfelippo MJ, Suberviola PD, Geimer NF (1987) Development of a von Willebrand-like syndrome after prolonged use of hydroxyethyl starch. Am J Clin Pathol 88:653–655

Scharbert G, Deusch E, Kress HG et al (2004) Inhibition of platelet function by hydroxyethyl starch solutions in chronic pain patients undergoing peridural anesthesia. Anesth Analg 99:823–827

Schell RM, Applegate RL, Cole DJ (1996) Salt, starch, and water on the brain. J Neurosurg Anesthesiol 18:179–182

Schortgen F, Lacherade JC, Bruneel F et al (2001) Effects of hydroxyethyl starch and gelatin on renal function in severe sepsis: a multicenter randomized study. Lancet 357:911–916

Shandall A, Lowndes R, Young HL (1985) Colonic anastomotic healing and oxygen tension. Br J Surg 72:606–609

Sheridan WG, Lowndes RH, Young HL (1987) Tissue oxygen tension as a predictor of colonic anastomotic healing. Dis Colon Rectum 30:867–871

Shires T, Williams J, Borwn F (1961) Acute change in extracellular fluids associated with major surgical procedures. Ann Surg 154:803–810

Shoemaker WC, Appel PL, Kram HB et al (1988) Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 94:1176–1186

Sirvinskas E, Sneider E, Svagzdiene M et al (2007) Hypertonic hydroxyethyl starch solution for hypovolaemia correction following heart surgery. Perfusion 22:121–127

Smetkin AA, Kirov MY, Kuzkov VV et al (2009) Single transpulmonary thermodilution and continuous monitoring of central venous oxygen saturation during off-pump coronary surgery. Acta Anaesthesiol Scand 53:505–514

Solanke TF, Khwaja MS, Kadomemu EL (1971) Plasma volume studies with four different plasma volume expanders. J Surg Res 11:140–143

Stein L, Berand J, Morisette M (1975) Pulmonary edema during volume infusion. Circulation 52:483–489

Stephens R, Mythen M (2003) Optimizing intraoperative fluid therapy. Curr Opin Anaesthesiol 16:385–392

Stögermüller B, Stark J, Willschke H et al (2000) The effect of hydroxyethyl starch 200 kD on platelet function. Anesth Analg 91:823–827

Strauss RG, Pennell BJ, Stump DC (2002) A randomized, blinded trial comparing the hemostatic effects of pentastarch versus hetastarch. Transfusion 42:27–36

Takil A, Eti Z, Irmak P et al (2002) Early postoperative respiratory acidosis after large intravascular volume infusion of lactated Ringer's solution during major spine surgery. Anesth Analg 95:294–298

Tatara T, Tashiro C (2007) Quantitative analysis of fluid balance during abdominal surgery. Anesth Analg 104:347–354
Tian J, Lin X, Guan R et al (2004) The effects of hydroxyethyl starch on lung capillary permeability in endotoxic rats and possible mechanisms. Anesth Analg 98:768–774
Tobias MD, Wambold D, Pilla MA et al (1998) Differential effects of serial hemodilution with hydroxyethyl starch, albumin, and 0.9 % saline on whole blood coagulation. J Clin Anesth 8:366–371
Tommasino C, Moore S, Todd MM (1988) Cerebral effects of isovolemic hemodilution with crystalloid or colloid solutions. Crit Care Med 16:862–868
Tousignant CP, Walsh F, Mazer CD (2000) The use of transesophageal echocardiography for preload assessment in critically ill patients. Anesth Analg 90:351–355
Traumer LD, Brazeal BA, Schmitz M et al (1992) Pentafraction reduces the lung lymph response after endotoxin administration in the ovine model. Circ Shock 36:93–96
Treib J, Baron JF, Grauer MT et al (1999) An international view of hydroxyethyl starches. Intensive Care Med 25:258–268
Van den Berg B, Vink H, Spaan J (2003) The endothelial glycocalyx protects against myocardial edema. Circ Res 92:592–594
Van der Linden PJ, De Hert SG, Daper A et al (2004) 3.5 % urea-linked gelatin is as effective as 6 % HES 200/0.5 for volume management min cardiac surgery patients. Can J Anaesth 51:236–241
Van der Linden PJ, De Hert SG, Deraedt D et al (2005) Hydroxyethyl starch 130/0.4 versus modified fluid gelatin for volume expansion in cardiac surgery patients: the effects on perioperative bleeding and transfusion needs. Anesth Analg 101:629–634
Varadhan KK, Lobo DN (2010) A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right. Proc Nutr Soc 69:488–498
Verheij J, van Lingen A, Raijmakers PGHM et al (2006a) Effect of fluid loading with saline or colloids on pulmonary permeability, oedema and lung injury score after cardiac and major vascular surgery. Br J Anaesth 96:21–30
Verheij J, van Lingen A, Beishuizen A et al (2006b) Cardiac response is greater for colloid than saline fluid loading after cardiac or vascular surgery. Intensive Care Med 32:1030–1038
Vermeulen H, Hofland J, Legemate DA et al (2009) Intravenous fluid restriction after major abdominal surgery: a randomized blinded clinical trial. Trials 10:50
Vincent JL, Dubois MJ, Navickis RJ et al (2003) Hypoalbuminemia in acute illness: is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials. Ann Surg 237:319–334
Voet D, Voet JG, Pratt CW (2001) Fundamentals of biochemistry. Wiley, New York
Vretzakis G, Kleitsaki A, Aretha D, Karanikolas M (2011) Management of intraoperative fluid balance and blood conservation techniques in adult cardiac surgery. Heart Surg Forum 14:E28–E39
Wade CE, Kramer GC, Grady JJ, Fabian TC, Younes RN (1997) Efficacy of hypertonic 7.5 % saline and 6 % dextran-70 in treating trauma: a meta-analysis of controlled clinical studies. Surgery 122:609–616
Waitzinger J, Bepperling F, Pabst G et al (2003) Hydroxyethyl starch (HES) [130/0.4], a new HES specification: pharmacokinetics and safety after multiple infusions of 10 % solution in healthy volunteers. Drugs R & D 4:149–157
Watenpaugh DE, Yancy CW, Buckey JC et al (1992) Role of atrial natriuretic peptide in systemic responses to acute isotonic volume expansion. J Appl Physiol 73:1218–1226
Wiedermann CJ (2008) Systematic review of randomized clinical trials on the use of hydroxyethyl starch for fluid management in sepsis. BMC Emerg Med 8:1
Wiesenack C, Prasser C, Keyl C et al (2001) Assessment of intrathoracic blood volume as an indicator of cardiac preload: single transpulmonary thermodilution technique versus assessment of

pressure preload parameters derived from a pulmonary artery catheter. J Cardiothorac Vasc Anesth 15:584–588

Wiesenack C, Prasser C, Rodig G et al (2003) Stroke volume variation as an indicator of fluid responsiveness using pulse contour analysis in mechanically ventilated patients. Anesth Analg 96:1254–1257

Wiesenack C, Fiegl C, Keyser A et al (2005) Continuously assessed right ventricular end diastolic volume as a marker of cardiac preload and fluid responsiveness in mechanically ventilated cardiac surgical patients. Crit Care 9:R226–R233

Wilkes NJ, Woolf R, Mutch M et al (2001) The effect of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. Anesth Analg 93:811–816

Williams EL, Hildebrand KL, McCormick SA et al (1999) The effect of intravenous lactated Ringer's solution versus 0.9 % sodium chloride solution on serum osmolality in human volunteers. Anesth Analg 88:999–1003

Wittkowski U, Spies C, Sander M et al (2009) Haemodynamic monitoring in the perioperative phase. Available systems, practical application and clinical data. Anaesthesist 58:764–778–780–766

Zaloga G, Strikland R, Butterworth J et al (1990) Calcium attenuates epinephrine's betaadrenergic effects in postoperative surgery patients. Circulation 81:196–200

Zander R (2009) Fluid management. Bibliomed, Medizinische Verlagsgesellschaft mbH, Melsungen

# Acid–Base Balance and Blood Gas Analysis

# 14

Felice Eugenio Agrò, Marialuisa Vennari, and Maria Benedetto

## Contents



F.E. Agrò, MD (✉) • M. Vennari, MD • M. Benedetto, MD
Anesthesia, Department of Intensive Care and Pain Management,
Campus Bio-Medico of Rome, Via A. Del Portillo, 200 00128 Rome, Italy
e-mail: f.agro@unicampus.it; m.vennari@unicampus.it; m.benedetto@unicampus.it

A. Dabbagh et al. (eds.), *Postoperative Critical Care for Cardiac Surgical Patients*,
DOI 10.1007/978-3-642-40418-4_14, © Springer-Verlag Berlin Heidelberg 2014

**Abstract**

Cardiac surgery patients may present many alterations of acid–base balance due to cardiac pathology, comorbidities, type and duration of surgery, and CPB. Acid–base status evaluation through Arterious Blood Gas (ABG) is the base for an adequate perioperative treatment. ABG interpretation needs more useful tools than those proposed by the Henderson–Hasselbach approach, such as anion gap, standard base excess, and strong ions difference, in order to identify the underlying acid–base disorders. In this chapter the physiology and pathophysiology of acid–base balance in cardiac patients and their consequence on perioperative management are described; an overview on ABG interpretation and its relation with diagnostic hypothesis and therapeutic management are presented.

## 14.1 Introduction

"The most significant and the most conspicuous property of blood is the extraordinary ability to neutralize large amounts of acids or bases without losing its neutral reaction" (Henderson 1908).

Acid–base balance represents a complex system through which the body maintains a neutral pH (7.38–7.42) in order to prevent protein degradation and alteration of all biochemical reactions leading to death. In the human body there are many acids produced by proteic, glicidic, and lipidic metabolisms. Every day the energetic systems generate 15,000–20,000 mEq of $CO_2$. Moreover a normal diet determines the formation of 50–100 mEq of $H^+$. As a consequence our body has to fight against acidity. Although a conspicuous production of acids, normally free $H^+$ plasma concentration is very low (0.00004 mEq/L) and pH homeostasis is guaranteed. The body has three systems opposing acid and base concentration blood variation: blood buffer systems, lungs, and kidneys, with different time of action (Agro and Vennari 2013; Kellum and Weber 2009) (Table 14.1).

Blood buffer systems have an immediate action time. They are present in a total amount lower than produced acids (2,400 mEq/L). This difference entails the need for a continuous renovation of buffer systems.

The most important blood buffer is the $HCO_3^-/H_2CO_3$ system (see Chap. 13). Its main role is imputable to three factors: it represents the 65 % of whole buffer power of our body, it has an ubiquitarious distribution (interstitial space (ISS), intracellular space (ICS), plasma, red cells, bones), and it has a pathway of elimination and a pathway of renovation (Rose 1995).

Other buffer systems are hemoglobin, plasma proteins, and phosphate systems.

Hemoglobin lies the $H^+$ (carbaminohemoglobin) formed by the diffusion of $CO_2$ from plasma into erythrocytes (formation and dissociation of $H_2CO_3$ for combination with $H_2O$), while bicarbonate returns in the plasma (Rose 1995).

**Table 14.1** Body compensatory system and time of action

| Homeostatic system | Action time |
|---|---|
| Blood buffer systems | Immediate (fraction of second) |
| Lung (ventilation regulation) | 1–15 min |
| Kidney (alkaline or acid urine elimination) | Hours–days |

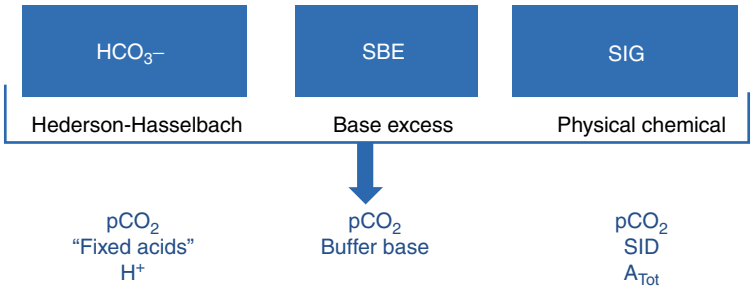



**Fig. 14.1** The three possible approaches to acid–base balance system description. Some factors (i.e., $pCO_2$) are considered by all the approach (Modified from Agro and Vennari (2013, pp. 1–26))

Other plasma proteins present as anion may buffer $H^+$ excess, exchanging $Ca^{2+}$ with $H^+$: the aminic group $NH_2^-$ lies $H^+$, becoming $NH_3$ and releasing $Ca^{2+}$ (acidosis increases free $Ca^{2+}$) (Rose 1995). Phosphate ions act as a buffer system in a similar way as bicarbonate, but they are present in very low concentration in the extracellular space (ECS) with respect to bicarbonate, while are very important in maintaining ICS pH (Rose 1995):

$$H_2PO_4^- \leftrightarrow H^+ + HPO_4^{2-} \leftrightarrow N_2HPO_4.$$

The kidneys and lungs eliminate acids or bases in excess, permitting a regeneration of blood buffer systems. When the primitive cause of an acid–base alteration is respiratory, a metabolic compensation develops (see Chap. 14): the kidney eliminates excess $H^+$ and nonvolatile acids, regenerating bicarbonate through their production (from amino acid metabolism) and their increased reabsorption from proximal tubules (acid urine excretion) or increasing bicarbonate elimination and $H^+$ reabsorption (alkaline urine excretion). When the primitive alteration is metabolic, a respiratory compensation develops hyperventilation leads to $CO_2$ elimination when metabolic acidosis occurs, while hypoventilation generates $CO_2$ retention when metabolic alkalosis develops. The lung acts in some minutes, while the kidney in some hours (8–12 h) (Agro and Vennari 2013; Rose 1995).

There are three approaches to interpreting acid–base balance physiology. They use distinct variables derived from a set of master equations that can be transferred from one approach to the other two (Agro and Vennari 2013; Kellum 2000) (Fig. 14.1).

## 14.2 The Descriptive Approach

The traditional descriptive approach is based on arterial pH, $pCO_2$, and bicarbonate measurements. This approach originated at the end of the nineteenth century, when Henderson revisited the Law of Mass Action from an acid–base equilibrium perspective (Agro and Vennari 2013; Kellum 2005a). The result was

$$[H^+] = Ka \bullet [HA] / [A^-].$$

where $[H^+]$ is the hydrogen ion concentration in solution, HA is a weak acid, $A^-$ a strong base, and Ka is the dissociation constant of the acid. Henderson's equation revealed that when $[HA] = [A^-]$, $[H^+]$ does not change as a result of small variations in the amount of acid or base in the solution (Agro and Vennari 2013).

For the $H_2CO_3/HCO_3^-$ system, the relation is

$$[H^+] = Ka \bullet [H_2CO_3] / HCO_3^-.$$

Considering that $H_2CO_3$ is $CO_2$ dissolved in water, the relation may be rewritten:

$$[H^+] = Ka \bullet [pCO_2] / HCO_3^-.$$

In 1917, K.A. Hasselbalch applied Henderson's equation to the main physiological buffer system ($CO_2/HCO_3^-$) using logarithms, giving rise to the Henderson–Hasselbalch equation (Agro and Vennari 2013; Kellum 2005b):

$$pH = pKa + \log ([HCO_3^-] / [pCO_2])$$

The $pCO_2$ value describes the respiratory contribution ($CO_2$ elimination/retention) to acid–base imbalances, while the metabolic contribution (acid overproduction, accumulation, reduced metabolism) is described by the bicarbonate concentration in the blood. When $pCO_2$ is increased, $H^+$ production increases and a respiratory acidosis develops, while when $pCO_2$ is reduced $H^+$ production reduces, leading to a respiratory alkalosis. When bicarbonate is reduced, free $H^+$ increases and a metabolic acidosis develops, while when bicarbonate increases, free $H^+$ is reduced, causing metabolic alkalosis (see Chap. 13).

Since the 1940s, researchers have recognized the limitations of this approach to acid–base physiology: blood bicarbonate concentration is useful in determining the type of acid–base abnormality, but it is not able to quantify the amount of acid or base excess–deficit in the plasma, unless $pCO_2$ is held constant. This observation promoted more researches, in order to quantify the metabolic component (Agro and Vennari 2013; Kellum 2005a).

## 14.3 The Semiquantitative Approach

In 1957, K.E. Jörgensen and P. Astrup developed a tool to calculate bicarbonate concentration, in which fully oxygenated whole blood was equilibrated with a $pCO_2$ of 40 mmHg at 37 °C. This measurement was called standard bicarbonate. However, subsequent studies determined the role of the other plasma buffer systems (albumin, hemoglobin, and phosphates), which were not considered using either the bicarbonate concentration or the standard bicarbonate method (Agro and Vennari 2013; Astrup et al. 1960).

In 1948, Singer and Hastings defined the sum of the nonvolatile weak acid as the "buffers" and bicarbonates as the "buffer base" (Agro and Vennari 2013; Siggaard-Andersen 1962). This led to several revisions of the method to calculate changes

in the buffer base, including the base excess (BE) methodology (Agro and Vennari 2013; Kellum 2005a, b; Astrup et al. 1960; Siggaard-Andersen 1962; Grogono et al. 1976; Severinghaus 1976).

BE is the quantity of metabolic acidosis or alkalosis, defined as how much base or acid should be added to an in vitro whole blood sample to reach a pH of 7.40, while the $pCO_2$ is maintained at 40 mmHg. The most widely used formula for calculating BE is the equation of Van Slyke (Agro and Vennari 2013; Kellum 2005a; Siggaard-Andersen 1977; Wooten 1999; Brackett et al. 1965):

$$BE = (HCO_3^- - 24.4 + [2.3 \times Hb + 7.7] \times [pH - 7.4]) \times (1 - 0.023 \times Hb)$$

where $HCO_3$ and hemoglobin (Hb) are expressed in mmol/L.

Subsequently the standard base excess (SBE) was developed (Siggaard-Andersen and Fogh-Andersen 1995). SBE is the BE corrected for the buffer effect of hemoglobin (assuming a mean extracellular hemoglobin concentration of 50 g/L), and it better quantifies the acid–base status in vivo with respect to BE (Agro and Vennari 2013; Brackett et al. 1965; Prys-Roberts et al. 1966):

$$SBE = 0.93 \times \{[HCO_3^-] + 14.84 \times (pH - 7.4) - 24.4\}.$$

## 14.4 The Quantitative Approach

Another approach to acid–base pathophysiology is the calculation of the anion gap (AG), which is the difference in the main measured plasma anion and cation concentrations (Fanzca 2012; Astrup et al. 1960):

$$[(Na^+ + K^+) - (Cl^- + HCO_3^-)] = 8 - 16 \text{ mEq/L}.$$

The AG corresponds to the difference between nonmeasured anions and cations:

$$[(Ca^{2+} + Mg^{2+}) - (PO_4^{3-} + SO_4^{2-} + \text{organic anions} + \text{proteins})].$$

Generally, AG values indicate a variation in the concentration of organic acids (lactic acidosis, ketoacidosis). In fact, when their levels increase, the produced $H^+$ consumes bicarbonate, increasing AG values, while the organic anions maintain electric neutrality of the plasma (Agro and Vennari 2013). A possible limit of the AG is the wide variability in both plasma albumin concentrations and renal function with respect to phosphate storage, especially in critically ill patients (Agro and Vennari 2013; Kellum 2005a).

In the 1980s, P. Stewart introduced a new approach finalized to identify dependent and independent variables enrolled in $H^+$ concentration determination (pH) (Agro and Vennari 2013). This approach was based on (Agro and Vennari 2013; Kellum 2005a):

- The Law of Mass Conservation
- The electric neutrality
- Water dissociation constant

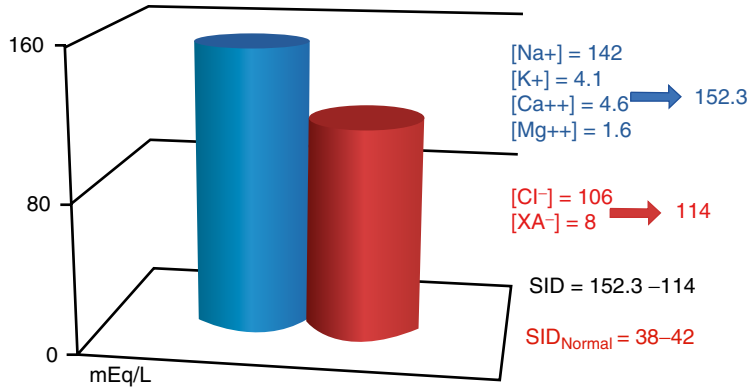



**Fig. 14.2** SID representation. *SID* strong ion difference, *XA*$^-$ dissociated organic acids (Modified from Agro and Vennari (2013, pp. 1–26))

Stewart's approach considers three independent variables (Agro and Vennari 2013; Kellum 2005a):

- The strong ion difference (SID)
- Total weak acid concentration (Atot)
- $pCO_2$

The relationship between SID, $pCO_2$, and Atot is the only determinant of pH, as well as of $[HCO_3^-]$, which are dependent variables (Morgan 2005).

SID is the difference in the total amount of strong (totally dissociated) anions and cations:

$$SID = ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-] + [A^-] + [SO_4^{2-}])$$ (Fig. 14.2).

Considering water electric neutrality and water constant dissociation, it is possible to demonstrate two fundamental principles (Mercieri and Mercieri 2006):

1. SID is the independent variable influencing $H^+$ and $OH^-$ concentrations.
2. SID may vary only adding or reducing strong ions.

As a consequence, $H^+$ or $OH^-$ variations are index of a primary SID modification, and the primum movens of acid–base alteration is the variation of strong ions concentration. If strong anions increase with respect to strong cations, SID will be negative and $H^+$ are increased with respect to $OH^-$: $H^+$ concentration is the same of the opposite of SID value (electro neutrality principle); while $OH^-$ are inversely related to the opposite of SID value (Mercieri and Mercieri 2006):

$$[H^+] = -[SID]$$

$$[OH^-] = -K'w / [SID].$$

On the other hand, if strong cations prevail on strong anions, SID is positive. In this case $OH^-$ are higher than $H^+$ and $OH^-$ are the same of SID value (electro neutrality principle), while $H^+$ are inversely related to SID (Mercieri and Mercieri 2006):

$$[OH^-] = [SID]$$

$$[OH^-] = -K'w / [SID].$$

SID is physiologically positive (38–42 mEq/L). To preserve electric neutrality it must be balanced by a corresponding excess of negative charges, represented by a dissociated weak acid such as $HCO_3^-$, proteins (especially albumin), phosphate, and minimal concentrations of $CO_3^{2-}$ and $OH^-$. Generally, proteins, phosphate, and other nonvolatile acids are indicated as $A^-$ (Kellum 2005a; Mercieri and Mercieri 2006; Kellum et al. 1995).

As a consequence (Mercieri and Mercieri 2006):

$$SID = \text{bicarbonate} + A^-.$$

The SID value obtained with this formula is called effective SID (eSID) vs the apparent SID (aSID), obtained by the calculus of the sum of strong anions and strong cations. When there is a difference between aSID and eSID, a strong, non-measured anion is present (i.e., lactate, ketoacids), and it is causing a consumption of buffer systems (bicarbonate and $A^-$), with a reduction of eSID (Mercieri and Mercieri 2006).

The balance between aSID and eSID is defined as SID gap (SIG) and is an index for strong anions that are not measurable ($XA^-$) (Fencl et al. 2000):

$$SIG = XA^- = aSID - eSID = 6 - 10 \text{ mEq / L}.$$

In body fluid compartments there are varying concentrations of nonvolatile weak acids. In plasma they are represented by inorganic phosphate and albumin. The same applies to ISS, although total concentrations here are very small. In red cells the predominant source is hemoglobin (Morgan 2005).

The undissociated form of weak acids (HA) is neutral; the dissociated form ($A^-$) is negative. Their concentrations reflect the Law of Mass Conservation

$$([Atot] = [A^-] + [HA])$$

and the dissociation equilibrium

$$([H^+] * [A^-] = Ka * [HA]).$$

As a consequence $A^-$, HA, and $H^+$ may vary with pH, but Atot remains the same and is the independent variable influencing other parameters (Mercieri and Mercieri 2006).

When $CO_2$ is present in water solution, it originates four kinds of molecules: dissolved $CO_2$, $H_2CO^3$, $HCO_3^-$, and $CO_3^{2-}$. These species are involved in a chemical reaction in our body resulting in effects on acid–base balance (Mercieri and Mercieri 2006).

Adding $CO_2$ to solutions (body fluids) containing strong ions and weak acids, Stewart needed six equations to describe acid–base balance modification (Table 14.2).

Knowing the independent variables ($pCO_2$, SID, Atot), the system may be solved for the remaining unknown variables ($[A^-]$, $[HCO_3^-]$, $[OH^-]$, $[CO_3^{2-}]$, [HA], and [H+]) (Morgan 2005).

**Table 14.2** The six equations of Stewart's approach

| Physical and chemical law | Equation |
|---|---|
| Water constant dissociation | $[H^+] \times [OH^-] = K'w$ |
| Weak acid constant dissociation | $[H^+] \times [A^-] = Ka \times HA$ |
| Mass conservation law | $[HA] + [A^-] = A_{tot}$ |
| Acid carbonic constant dissociation | $[H^+] \times [HCO_3^-] = Kc \times pCO_2$ |
| Bicarbonate constant dissociation | $[H^+] \times [CO_3^{2-}] = Kc \times [HCO_3^-]$ |
| Electric neutrality | $SID + [H^+] - [H^+] - [HCO_3^-] - [CO_3^{2-}] - [A^-] - [OH^-] = 0$ |

Resolving the system for pH ($-\log [H^+]$), a resultant is a simplified equation that may be written as (Mercieri and Mercieri 2006)

$$pH = pK1 + \log \{SID + -[ATOT / (1 + 10p^{Ka-pH})]\} / pCO_2.$$

When $SID = HCO_3^-$ and $Atot = 0$, the equation becomes the same of Henderson–Hasselbalch (Mercieri and Mercieri 2006):

$$pH = pK1 + \log [HCO_3^-] / pCO_2.$$

## 14.5 Relation Among Fluid, Electrolyte, and Acid–Base Balance

In the 13th chapter and in the previous paragraphs, it has been evidenced that body homeostasis is mainly based on three principles (Fig. 14.3):

- The electric neutrality principle (ionic)
- The iso-osmolarity principle (osmolar)
- The neutrality principle (acid–base)

These three principles are strictly interconnected as is immediately evident from Stewart's approach to acid–base balance.

Hydro-electrolytic and acid–base balances are related by bicarbonate: it is present in the Gamble gram and in the Henderson–Hasselbalch equation. Variation of bicarbonate plasma levels may affect the electric neutrality and the neutrality principles. Hydrogen ions are also present in Gamble ionogram and in the Henderson–Hasselbalch equation.

Osmolar and hydro-electrolytic balances are mainly connected by sodium, present in Gamble gram and osmolarity equation, where sodium concentration is multiplied for two. As a consequence, little sodium variation may have great influences on osmolarity. Generally sodium is contained in the plasma as salts such as $NaHCO_3$ or NaCl.

If bicarbonates are reduced other anions have to increases in order to maintain electric neutrality. Chloride and bicarbonates are strictly related and their sum must be constant in any moment: if one of them increases, the other reduces and vice

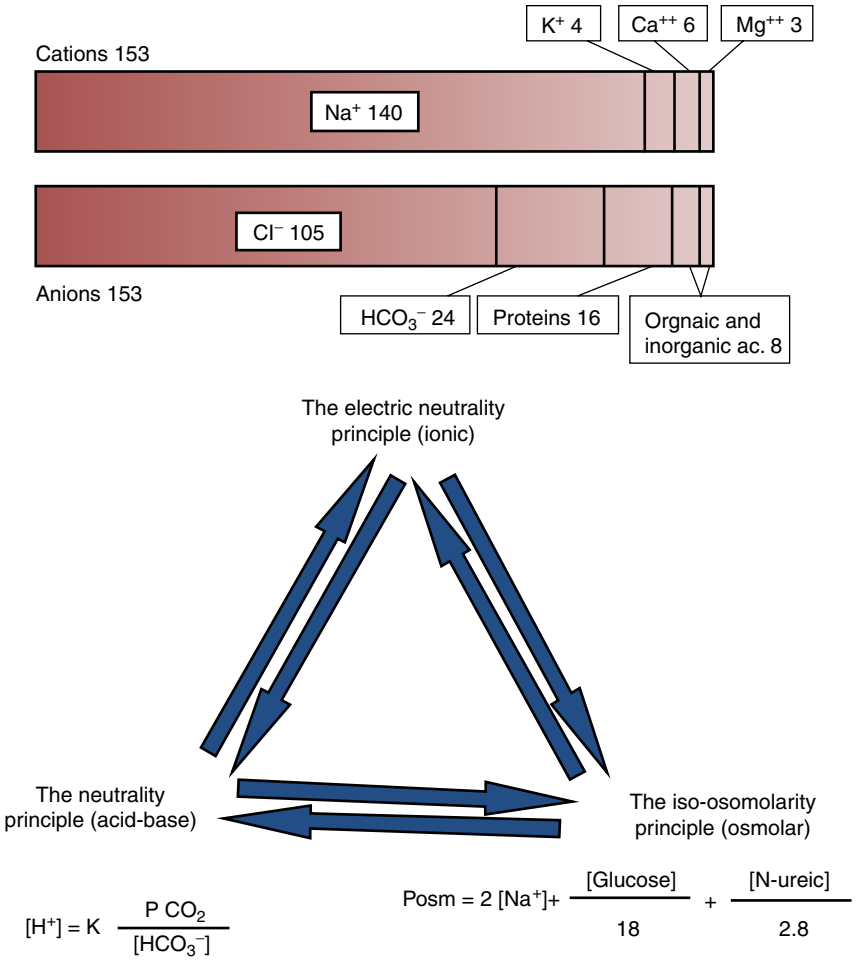



**Fig. 14.3** Relation among the ionic, acid–base, and osmolar balances

versa, in a rate of 1:1. In order to maintain electric neutrality, when both chloride and bicarbonates are reduced, other anions concentration should be increased (see Gamble gram and AG) (Sgambato and Prozzo 2003; Vulterini et al. 1992).

Finally, all acid–base interventions, including fluid administration, act through SID (electrolyte, osmolarity) or Atot or in combination (Morgan 2005; Sgambato and Prozzo 2003).

The clinical consequences of the relations between the three systems are presented in some examples:

1. In case of diarrhea, bicarbonate will be reduced. To respect electric neutrality principle, a hypobicarbonatemia causes hyperchloremia. It is also responsible of a variation in Henderson–Hasselbalch equation with an increase of hydrogen ion concentration and the development of metabolic acidosis.

2. In case of vomitus, there is a loss of HCl. In order to respect electric neutrality, chloride reduction is replaced by bicarbonate increase. The loss of hydogenions and the reduction of bicarbonate increase will determine a metabolic alkalosis (accompanied by hypochloremia). In case of prolonged vomitus, to restore fluid and chloride deficit fluid are administered. The restoration of chloride levels determines a reduction of bicarbonate and, consequently, a correction of alkalosis.
3. Bicarbonate is present in the plasma as sodium salt. As a consequence, any variation in bicarbonate levels will modify sodium and osmolar balance and vice versa. For example, when bicarbonate ($NaHCO_3$) is administered to correct a severe metabolic acidosis, osmolarity increases potentially developing hypervolemia. Moreover, sodium overload determines a reduction of other cations ($K^+$ or $Ca^{2+}$).

## 14.6 Basis of Pathophysiology of Acid–Base Balance in the Postoperative ICU Setting of Cardiac Surgery

Maintaining acid–base balance during and after cardiac surgery is essential for the success of the surgery, especially for procedures requiring prolonged bypass time. As an example, cardiac surgery patients are at high risk for developing arrhythmias: the presence of a neutral pH is necessary to obtain a response to pharmacological and electric treatments. At the same time acid–base status is considered as an index of adequate perfusion of tissue (i.e., lactate increase, adequate renal compensation) and may modify blood flux distribution. Moreover pH and $pCO_2$ variation may influence Hb-curve dissociation reducing Hb saturation (acidosis, $pCO_2$ increases) or reducing Hb capacity to transfer $O_2$ to tissue (alkalosis, $pCO_2$ decreases) (Agrò et al. 2013). Literature demonstrated in experimental and clinical studies the influence of pH on vascular tone resulting in possible blood flux redistribution and blood pressure alteration (Celotto et al. 2008). Both modification of ECS pH (pHe) and ICS pH (pHi) may cause these alterations through many proposed mechanisms: neurotransmitter release, prostanoids, purines, smooth cell hyperpolarization, NO, and changes in intracellular calcium concentration (Franco-Cereceda et al. 1993; Aalkjaer and Poston 1996; Ishizaka and Kuo 1996). Moreover, acid–base balance alterations have been related to modification of endothelium activity, with different effects according to the type of considered vessel (Celotto et al. 2008).

On the other hand, cardiac surgery is responsible for profound alteration in acid–base system. The mechanism at the base of this modification is different, causing an impact on acid–base balance in opposite directions (Dobell et al. 1960; Beecher and Murphy 1950; Gibbon et al. 1950; Puyau et al. 1962). Some of these mechanisms depend on the type of oxygenator and the type of blood flow during the CPB and CPB duration, the kind and the duration of postoperative mechanical ventilation, hypotension in the postoperative setting (need for inotropes and/or vasoactive drugs, bleeding), kind of fluid used for priming and for liquid management (balanced vs unbalanced), temperature modifications (hypothermia reduces buffer system dissociation, determining a "natural alkaline shift," while $CO_2$ becomes more soluble and

$pCO_2$ is decreased), and hemolysis (Fanzca 2012; Ito et al. 1957; Coffin and Ankeney 1960; Litwin et al. 1959; Kirklin et al. 1956).

The more frequent alteration of acid–base equilibrium in cardiac patients is metabolic acidosis (Fanzca 2012). It is thought to be due to preexisting respiratory alkalosis, increased lactate levels, hypoxia, and hypoperfusion (Dobell et al. 1960; Beecher and Murphy 1950; Gibbon et al. 1950; Puyau et al. 1962; Ito et al. 1957). Acidosis induces systemic vasodilatation (included coronary) and pulmonary vasoconstriction (Fanzca 2012). Although vasodilatation may have positive effect, such as an increase in coronary blood flow, its consequence may be detrimental in patients presenting a cardiac dysfunction after the surgery (Celotto et al. 2008; Clancy and Gonzalez 1975; Ely et al. 1982). Moreover, acidosis reduces the responsiveness to catecholamines, decreasing pharmacological effectiveness of the treatment of postoperative hemodynamic instability and further precipitating patients' conditions. Pulmonary vasoconstriction may increase pulmonary resistance and decompensate the hemodynamic and respiratory status of cardiac surgery patients (Celotto et al. 2008).

## 14.7 Fluid and Electrolyte Management Consequences on Acid–Base Balance

The previous chapter evidenced the relation among fluid administration and modification of acid–base status, according to fluid properties. Moreover, Stewart's approach underlined the role of electrolyte in maintaining or modifying acid–base balance. As a consequence, the debate on SID of infused solution has adjunct to literature discussion.

### 14.7.1 Hyperchloremic Acidosis

When establishing fluid therapy, both acid–base and electrolyte iatrogenic disorders must be avoided. Generally, metabolic acidosis with hyperchloremia is the most frequently induced alteration (Agro and Benedetto 2013). Many available solutions do not contain Atot (anions), leading to a dilution of ECS Atot and, consequently, to a metabolic alkalosis. However, this effect is commonly overwhelmed by the increase of the SID with the infusion, contributing to acidosis development (Morgan 2005). Clinical studies have revealed that chloride excess causes a specific splanchnic and renal vasoconstriction, interferes with cellular exchanges, and reduces the glomerular filtration rate (GFR), leading to sodium and water retention (Agro and Benedetto 2013; Quilley et al. 1993; Wilcox 1983). Hyperchloremia is generally associated with metabolic acidosis and may cause a further reduction in GFR (Agro and Benedetto 2013; Wilcox 1983). It has been shown that balanced and plasma-adapted solutions help to avoid hyperchloremic acidosis, while assuring the same volume effect as unbalanced solutions and potentially reducing morbidity and mortality (Agro and Benedetto 2013; Zander 2006).

### 14.7.2 Dilution Acidosis

Currently available solutions used throughout the world do not contain the physiological buffer base bicarbonate because it cannot be incorporated into polyelectrolyte solutions, since carbonate precipitation would occur (Agro and Benedetto 2013). For this reason, any fluid infusion may cause "dilution" acidosis, i.e., a dilution of the $HCO_3^-$ concentration, while the $CO_2$ partial pressure (buffer acid) remains constant (Agro and Benedetto 2013; Shires and Holman 1948; Asano et al. 1966). In the recent literature, the classic view of dilution acidosis has been reviewed. In fact, according to Stewart's approach, bicarbonate is a dependent variable, while the SID of the infused solution is the determinant of acid–base effects. When SID of used fluid is zero, such as saline solutions with $[Cl^-] = [Na^+]$, dextrose, mannitol, or water, the administration of large volume leads to a reduction (dilution) of SID, causing metabolic acidosis, independently from plasma $[Cl^-]$ variations (Makoff et al. 1970; Miller and Waters 1997; Storey 1999; Figge et al. 1998). Metabolic acidosis may have catastrophic consequences, especially in patients with preexisting acidosis (i.e., patient with reduced CI and hypoperfusion) (Agro and Benedetto 2013).

### 14.7.3 SID

In order to avoid iatrogenic alteration of acid–base balance, an infused solution should reduce SID (acidifying power) in a minimal rate, necessary to counteract the Atot dilution alkalosis. As a consequence, the concept of balanced solution should be extended considering SID and, particularly, the need for a SID lower than plasma, but higher than zero (Morgan 2005). The ideal SID value is 24 mEq/L. It means that 24 mEq/L of the strong anion $Cl^-$ should be replaced by other anions, such as metabolizable anions (Morgan 2005; Morgan et al. 2004).

### 14.7.4 Metabolizable Anions and Base Excess

To compensate the absence of bicarbonate, initially $OH^-$, $HCO_3^-$, and $CO_3^{2-}$ were adjuncted in vitro as components of IV fluids. It was immediately evident they rapidly equilibrate with $CO_2$ (Morgan 2005). To overcome this problem, metabolizable anions were used. Metabolizable anions are organic anions that may be converted to $HCO_3^-$ by tissues. The main metabolizable anions are gluconate, malate, lactate, citrate, and acetate. In IV fluid, the most frequently used metabolizable ions are acetate, malate, and lactate (Agro and Benedetto 2013).

Acetate and malate are contained in plasma in very low concentrations. They may be metabolizable in all tissues, especially in muscles, liver, and heart (Agro and Benedetto 2013; Lundquist 1962). Acetate is an early-onset (within 15 min) alkalinizing anion, while malate has a slower action (Agro and Benedetto 2013; Mudge et al. 1949; Knowles et al. 1974; Akanji et al. 1989).

The most commonly used metabolizable anion is lactate, which is normally produced in the human body. In fact, lactate is the main product of anaerobic

glycolysis. It is metabolizable only by the liver (Agro and Benedetto 2013). However, the use of lactate has been the cause of debate in clinical practice and in the literature, especially with respect to patients with preexisting lactic acidosis. This condition is a manifestation of disproportionate tissue lactate formation, with respect to hepatic lactate metabolism (Agro and Benedetto 2013; Johnson et al. 1969; Levraut et al. 1998). Lactate levels are major criteria in the routine evaluation of critically ill patients; indeed, changes in lactate concentration can provide an early and objective evaluation of patient responsiveness to therapy (Agro and Benedetto 2013; Abramson et al. 1993; Bakker et al. 1996; Cowan et al. 1984; Falk et al. 1985; Friedman et al. 1995; Henning et al. 1982; McNelis et al. 2001; Vincent et al. 1983; Rivers et al. 2001). Furthermore, plasma lactate levels in the first 24–48 h have a high predictive power for mortality in patients with various forms of shock, including cardiac, hemorrhagic, and septic shock (Agro and Benedetto 2013). In these situations, the administration of lactate-containing fluids may exacerbate the already existing lactic acidosis and interfere with lactate monitoring for diagnostic purpose (Agro and Benedetto 2013; Levraut et al. 1998; Weil and Afifi 1970). According to these evidences, common sense suggests that in ICU patients any use of lactate-containing solutions should be avoided (Agro and Benedetto 2013).

Another indicator of acidosis is base excess (BE). Since 1990, clinical trials have demonstrated that evaluating BE at the time of admission of critically ill patients is indeed the best prognostic indicator for mortality, complication rate, and transfusion needs (Agro and Benedetto 2013). Persistent base excess disorders above or below 4 mmol/L differ with respect to mortality rates: 9 and 50 %, respectively (Agro and Benedetto 2013; Kincaid et al. 1998).

Balanced, plasma-adapted solutions reduce the risk of acidosis and BE alterations (Agro and Benedetto 2013).

### 14.7.5 Crystalloids and Acid–Base Status

The composition of widely used crystalloids is discussed in the 13th chapter (see Table 13.3).

Normal saline solution is a solution with SID = 0, and literature has extensively demonstrated that it causes metabolic acidosis, especially after large amount of infusion during normovolemic hemodilution or for cardiopulmonary bypass (Morgan 2005; Morgan et al. 2004; Beers 2006; Scheingraber et al. 1999; McFarlane and Lee 1994; Prough and Bidani 1999; Rehm et al. 2000; Hayhoe et al. 1999; Liskaser et al. 2000; Himpe et al. 2003). In addition to renal effects (discussed in chapter 14th), metabolic acidosis inhibits cardiac contractility, adrenoceptor function, and coagulation (Fanzca 2012).

Considering a stable and normal plasma lactate concentration of 2 mEq/L, Ringer lactate and Ringer acetate SID is 27 mEq/L. As a consequence, they are slightly alkalinizing solutions, reducing metabolic acidosis risk, typical of first-generation crystalloids (Morgan 2005; Reid et al. 2003; Traverso et al. 1986; Waters et al. 2001).

Both Ringer solutions are more plasma-adapted than normal saline but are nonetheless unbalanced.

Last generation crystalloids are isotonic, balanced, and plasma-adapted solutions that reduce the risk of chloride excess and dilution acidosis, with a decreased influence on lactate monitoring, lactic acidosis, and base excess (BE). They have a SID higher than zero but lower than plasma (SID ~ 29 mEq/L) and, like Ringers solutions, have an alkalinizing power (Morgan 2005).

### 14.7.6 Colloids and Acid–Base Status

As for crystalloids, SID value of each colloid is an important feature to consider before the administration. The possible effects of their SID is reduced by two factors: the lower amount infused with respect to crystalloids and their possible contribution to Atot (the colloidal molecules may be weak acid) (Finfer et al. 2004; Liskaser and Story 1999). As a consequence, Atot dilution alkalosis is reduced, as long as colloidal molecules persist in the extravascular space (Morgan 2005). However, after the infusion, weak acid colloids with SID > 0, such as albumin (HA) and gelatins, presented a tendency to induce metabolic acidosis similar to 0.9 % saline solution and other colloids with SID = 0 (Morgan 2005).

Currently available HA solutions are prepared as NaCl solutions (SID =0), which can lead to metabolic acidosis and hyperchloremia and interfere with sodium and water excretion, thus impairing renal function, especially in hypovolemic shock patients. In acute renal failure, HA may accumulate after its massive administration (Morgan 2005).

Succinylated gelatins are dispersed in a 4 % polyelectrolyte solution generally containing $Na^+$ 154 mEq/L, $K^+$ 0.4 mEq/L, $Ca^{2+}$ 0.4 mEq/L, and $Cl^-$120 mEq/L (effective SID = 34). Their low chloride content reduces the risk of hyperchloremic acidosis and may be helpful in patients with acid–base alterations.

Recent balanced HES presented SID closer to the ideal value (24 mmEq/L). They have been demonstrated to reduce the risk of iatrogenic metabolic acidosis and potentially improve gastric mucosal blood flow, with a possible impact on endotoxemia survival (Wilkes et al. 2001; Kellum 2002). In a prospective, randomized, double-blind study of cardiac surgery patients, a balanced HES 130/0.4 preparation was compared to an unbalanced HES 130/0.4: while the hemodynamic status did not differ between the two groups, the base excess was significantly less negative in the balanced than in the unbalanced HES group (Base et al. 2011).

## 14.8 Maintaining Acid–Base Balance

### 14.8.1 Arterial Blood Gas Analysis Interpretation

The evaluation of seriated arterial blood gases analysis (ABG) appears as indispensable to guide the postoperative management of the cardiac surgery patients and to

permit a precocious diagnosis of tissue hypoperfusion and $DO_2$ modification. In fact, ABG gives direct information about the main determinant of $DO_2$ ($pO_2$, $SpO_2$, and Hb) and indirect information about CI, tissue perfusion, and oxygenation (lactic acidosis, hypoxic acidosis). Moreover it allows the identification of ionic, osmolar, and acid–base alterations. Acid–base alteration are often cause of matter in clinical practice, they should be unrecognized and have catastrophic impact on patients.

According to acid–base perspective, ABG interpretation may use one of the approach previously presented (Henderson-Hasselbalch, BE, AG, or Stewart's approach) or more of one of them, in order to better understand the contemporary ionic and osmolar alterations and the cause of acid–base disturbance.

Examining ABG it is important to take into account that pH, $pCO_2$, and $pO_2$ are measured while $HCO_3^-$ and BE values are calculated.

To evaluate the acid–base state of the patient, the first value to consider is pH.

A pH <7.38 indicates acidemia; a pH >7.42 indicates alkalemia. According to the presence of buffer and compensatory systems, pH may be normal, but the other parameters may be changed indicating alkalosis or acidosis. This situation is the more frequent in the clinical practice and requires a profound knowing of physiology and of the meaning of the different parameters obtainable with ABG.

In clinical practice, it is useful to only consider $pCO_2$ and bicarbonates values. This use should be disapproved in order to avoid disagreeable mistake. In fact an increased $pCO_2$ (>40 mmHg) may suggest a respiratory acidosis or the compensation for a metabolic alkalosis, while a reduced $pCO_2$ (<40 mmHg) may indicate a respiratory alkalosis or the compensation for a metabolic acidosis. At the same time a reduced $HCO_3^-$ (<24 mEq/L) may suggest a metabolic acidosis or the compensation for a respiratory alkalosis, while an increased $HCO_3^-$ (>24 mEq/L) may indicate a metabolic alkalosis or the compensation for respiratory acidosis (Fig. 14.4).

Acid–base disorders of different origin may be contemporarily present (i.e., a metabolic acidosis due to hypoperfusion with a respiratory alkalosis due to hyperventilation). To better understand the number, the nature, and the gravity of the acid–base disturbance, other factors may be considered. The time of development of the observed alteration may be helpful. If an alteration appears few hours ago, it is improbable that bicarbonate variation may represent a renal compensation, but it is more probable that it represents an underlying metabolic disturbance.

The evaluation of Boston rules, BE, AG, and SID may be more useful to solve the "ABG enigma."

An eight-step approach to ABG acid–base status interpretation:

1. pH (acidosis or alkalosis?)
2. $pCO_2$ (same or opposite direction with respect to pH?)
3. $HCO_3^-$ (same or opposite direction with respect to pH?)
4. Compensation (Boston rules)
5. AG
6. Delta gap (if AG increased)
7. SID–SBE
8. Electrolytes

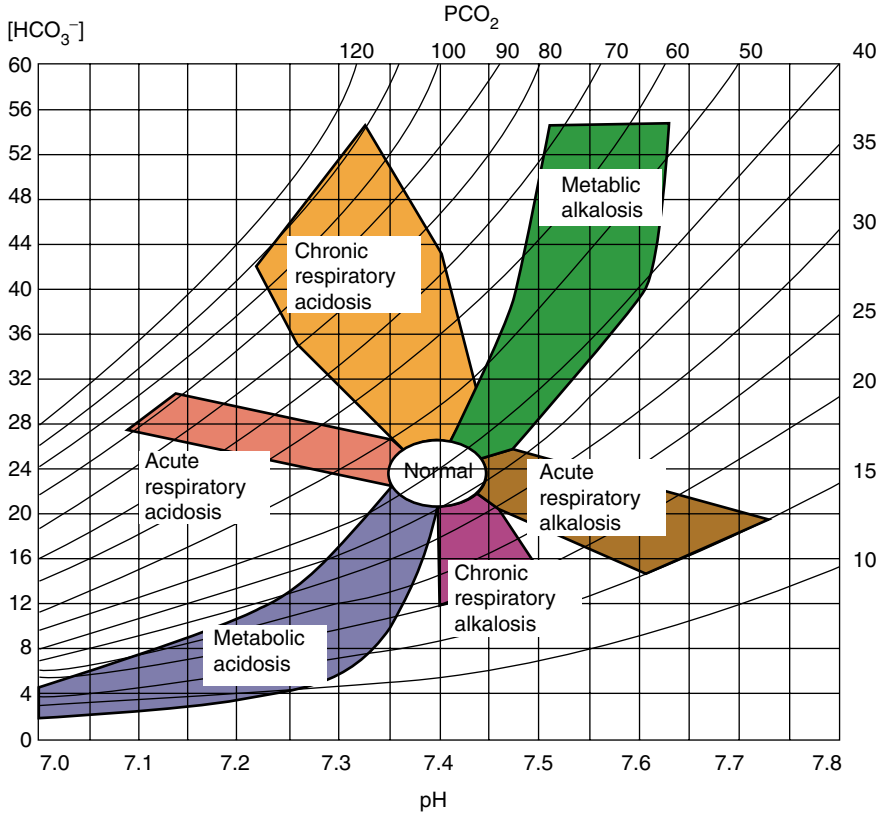



**Fig. 14.4** A Graphic tool to rapidly identify acid–base patient disorders knowing pH, $[HCO_3^-]$, and $pCO_2$

### 14.8.2 Boston Rules

Boston rules are mathematic relation between bicarbonate and $pCO_2$ values, based on the observation of patients with note and compensate (normal pH) acid–base alterations.

In case of metabolic acidosis, $pCO_2$ should reduce by 1,5 mmHg for each 1 mEq/L of $HCO_3^-$ reduction. If $pCO_2$ is lower with respect to the expected value, there is a contemporary respiratory alkalosis; if it is higher there is a contemporary respiratory acidosis (Beers 2006).

In case of metabolic alkalosis, $pCO_2$ should increase by 0,7 mmHg for each 1 mEq/L of $HCO_3^-$ increasing. If $pCO_2$ is lower with respect to the expected value, there is a contemporary respiratory alkalosis; if it is higher there is a contemporary respiratory acidosis (Beers 2006).

**Table 14.3** Bicarbonate and $pCO_2$ variation according to Boston rules

| pH | Disorder | $HCO_3$ | $PCO_2$ | Compensation evaluation | Comment |
|---|---|---|---|---|---|
| ≤7.38 acidosis | Metabolic | ≤24 mEq/L | ↓ 1.5 mmHg for each 1 mEq/L of $HCO_3$ ↓ | $pCO_2$ value higher | Respiratory acidosis |
| | | | | $pCO_2$ value lower | Respiratory alkalosis |
| | Respiratory | ↑ 1 mEq/L (acute), ↑ 4 mEq/L(chronic) for each 10 mmHg of $pCO_2$ ↑ | ≥40 mmHg | $HCO_3$ value higher | Metabolic alkalosis |
| | | | | $HCO_3$ value lower | No time for compensation or metabolic acidosis |
| ≥7.42 alkalosis | Metabolic | ≥24 mEq/L | ↑0.7 mmHg for each 1 mEq/L of $HCO_3$↑ | $pCO_2$ value higher | Respiratory acidosis |
| | | | | $pCO_2$ value lower | Respiratory alkalosis |
| | Respiratory | ↓ 1 mEq/L (acute), ↓ 4 mEq/L (chronic) for each 10 mmHg of $pCO_2$ ↓ | ≤40 mmHg | $HCO_3$ value higher | No time for compensation or metabolic alkalosis |
| | | | | $HCO_3$ value lower | Metabolic acidosis |

In case of acute respiratory acidosis, $HCO_3^-$ should increase by 1 mEq/L for each 10 mmHg of $pCO_2$ increasing; in case of chronic acidosis, the increase should be 4 mEq/L. If the bicarbonate is lower with respect to the expected value, there has been no enough time for the development of compensation, or there is a contemporary metabolic acidosis; while if it is higher there is an underlying metabolic alkalosis (Beers 2006).

In case of acute respiratory alkalosis, bicarbonate should reduce by 1 mmEq/L for each 10 mmHg of $pCO_2$ decreasing; while in case chronic respiratory alkalosis, the reduction should be 5 mmEq/L. If bicarbonate is lower with respect to the expected value, there is a contemporary metabolic acidosis; while if it is higher there is a contemporary metabolic alkalosis or little time to develop compensation (Beers 2006) (Table 14.3).

### 14.8.3 Base Excess and Standard Base Excess

A positive BE (>+2) suggests an alkalosis (metabolic), while a negative BE (<−2) suggests an acidosis (metabolic).

SBE is a practical tool to replace SID at bedside (Morgan et al. 2000; Schlichtig et al. 1998a; Schlichtig et al. 1998b). Normally it ranges in −3/+3 mEq/L and it represents the change in SID value needed to restore acid–base balance. If SBE<−3

there is a metabolic acidosis (SID increased); while if SBE>+3 there is a metabolic alkalosis (Vulterini et al. 1992). In case of acidosis, SBE corresponds to the theoretical $NaHCO_3$ dose (in mmol/L) per liter of ECS water, which is needed to normalize acid–base balance; while in case of alkalosis it corresponds to the theoretical dose of HCl (Fanzca 2012).

### 14.8.4 Anion Gap

An increased AG (>16 mEq/L) indicates a metabolic acidosis due to the presence of nonmeasurable acids such as the organic lactate acid (ABG also reports lactate values) or other inorganic acids (i.e., phosphate retention in kidney dysfunctions) (Beers 2006).

A normal AG may indicate a metabolic acidosis due to $HCO_3^-$ reduction (i.e., dilution acidosis, renal lost such as postoperative NTA) or to increased $Cl^-$ (fluid infused, hyperchloremia). According to the electro neutrality principle, the AG remains stable because $HCO_3^-$ variations are compensated by $Cl^-$, and vice versa: metabolic acidosis with normal AG is always hyperchloremic.

In order to complete the evaluation of patient's acid–base asset, it is important to consider the rate between the difference of patient AG with respect to the normal AG (AG gap) and the difference of normal bicarbonate with respect to the patient's bicarbonate (bicarbonate gap). This ratio is defined as delta gap and it may suggest the presence of more than one acid–base disturbance (Beers 2006):

$$\begin{aligned}\text{Delta gap} &= (\text{Measured AG} - \text{Normal AG}) / (\text{Normal } HCO_3^- - \text{Measured } HCO_3^-) \\ &= (\text{Measured AG} - 12) / (24 - \text{measured } HCO_3^-) \\ &= \Delta \text{ AG} / \Delta \, HCO_3^-.\end{aligned}$$

If the only alteration is metabolic acidosis with AG, the delta gap value should be 1, reflecting the buffering of nonmeasurable acids. If the delta gap value is <1, bicarbonate reduction is due to the presence of other acids rather than nonmeasurable acids: there is another cause of metabolic acidosis with normal AG and hyperchloremia should be present. When the delta gap value is >1, the reduction of bicarbonate is contrasted by a factor leading to their increase: there is a contemporary metabolic acidosis (Beers 2006).

Referring to AG, it is fundamental to establish the plasma levels of proteins (especially albumin), nonmeasured cation ($Ca^{2+}$ and $Mg^{2+}$) and measured cation (especially $Na^+$) levels, the presence of renal dysfunction with possible increased uremia, and the lipidic asset.

In fact, AG may be increased by hyperalbuminemia (rare in ICU patients) and uremia (increased anions) or by hypocalcemia and hypomagnesemia (reduced cations); while it may be reduced by hypoalbuminemia (frequent in ICU post-bypass patient) or by hypermagnesemia and hypercalcemia (increased cations). Finally AG may result negative (artifact) in case of severe hypernatremia or hyperlipidemia.

### 14.8.5 Stewart's Approach and SID

According to Stewart's approach ($[SID]+[H^+]=[HCO_3^-]+[A^-]+[CO_3^{2-}]+[OH^-]$), acid–base alterations are due to modification of independent variables. As a consequence, respiratory unbalance is caused by $pCO_2$ modification, while metabolic alteration is imputable to SID and/or Atot modification.

SID decreases in metabolic acidosis and increases in metabolic alkalosis (Fanzca 2012; Kellum 2005a). In fact, a reduction of SID value (strong anions > strong cations; SID <38 mEq/L) leads to $H^+$ increase in order to maintain electric neutrality. SID reductions may be due to an increase of organic acids such as lactate or ketones, a loss of cations (i.e., diarrhea), an alteration of $Cl^-$excretion by the kidney (i.e., development of postoperative AKI), $Cl^-$overload (unbalanced solution use), or intoxication (i.e., salicylates). Another cause of SID reduction in postoperative ICU patients may be phosphate retention ($H^+$ will increases to compensate) caused by renal dysfunction, especially in patients with chronic renal diseases (Fanzca 2012; Morgan 2005).

The reduction of SID ($H^+$ increase) will be compensated by homeostatic alkalinizing reactions:

- Kidney increases $Cl^-$excretion (strong anions reduce, SID increases, and $H^+$ reduce).
- Association of weak acid such as phosphate and proteins with formation of HA until 3–4 mEq/L (in severe cases).
- Hyperventilation: $pCO_2$ decreases by 1,2 mmHg for each 10 mEq/L of SID reduction.

On the other hand, an increase of SID value (strong cations > strong anions; SID >42 mEq/L) causes alkalosis leading to $H^+$ reduction in order to respect electric neutrality. SID increases may be due to loss of anions (vomitus, diuretics) or cation administration (i.e., transfusions, excess of unbalanced IV fluids). Generally the more frequent cause is hypochloremia. In cardiac surgery ICU patients, SID increase may be due to hypoalbuminemia leading to reduction of Atot (Fanzca 2012; Morgan 2005).

The increase of SID ($H^+$ reduction) will be compensated by homeostatic acidifying reactions:

- Kidney retains $Cl^-$ (strong anions increases, SID reduces, and $H^+$ increases).
- $Na^+$ shift into cell (strong cations reduce, SID reduces, and $H^+$ increases).
- Dissociation of weak acid with formation of $A^-$ and $H^+$.
- Hypoventilation: $pCO_2$ increases by 0.7 mmHg for each 10 mEq/L of SID increase.

The value of Atot depends primarily by plasmatic proteins and in minimal part by other weak acids. An increase of its value is caused by an increase in plasma proteins or phosphate levels. An increase of Atot has the same effect of a decrease in SID: it causes metabolic acidosis. By contrast, hypoalbuminemia causes metabolic alkalosis, as SID increases (Fanzca 2012; Morgan 2005).

In case of respiratory acidosis, the increase of $H^+$ is compensated by an increase of SID (determining $H^+$ decrease) due to a reduction of $Cl^-$. In acute cases the shift

**Table 14.4** Metabolic disorders according to Stewart's approach

| | | |
|---|---|---|
| Metabolic acidosis | ↓SID and ↓SIG<br>RTA, TPN, normosaline, anion exchange resins, diarrhea, and loss of pancreatic secretions | ↓SID and ↑SIG<br>Ketoacidosis, lactic acidosis, salicylate, methanol |
| Metabolic alkalosis | ↑ SID<br>Loss of $Cl^-$: vomitus, gastric drainage, diuretics, post-hypercapnia, villous adenoma with diarrhea, mineralocorticoid excess, Cushing, Liddle, Bartter, liquorice<br>Sodium excess: Ringer, TPN, transfusions | ↓$A_{tot}$<br>Hypoalbuminemia (nephrotic syndrome, cirrhosis) |

of $Cl^-$ in the red cells is the most rapid mechanism of compensation and $Cl^-$ reduces by 1 mEq/L for each increase of 10 mmHg of $pCO_2$ value. In chronic cases $Cl^-$is eliminated by the kidney and its reduction is 3–4 mEq/L for each 10 mmHg of $pCO_2$ increase. These modifications are accompanied by $HCO_3^-$ increase (Henderson 1908; Morgan 2005; NC et al. 1969).

In case of respiratory alkalosis the $H^+$ reduction is compensated by SID reduction (determining $H^+$ increase) due to a reduced renal excretion of $Cl^-$ and in minimal part to lactate production for glycolysis activation in red cells and liver, caused by the movement of the dissociation curve of Hb (Table 14.4).

Stewart's approach evidences the role of renal regulation of $Cl^-$ in maintaining the acid–base homeostasis. As a consequence, it is crucial in postoperative cardiac surgery patients to maintain an adequate renal function and to avoid any factor causing renal dysfunction or precipitating preexisting alterations (Fanzca 2012; Morgan 2005).

Evidence confirmed the points suggested by Stewart's approach demonstrating genetic modification of $Cl^-$ membrane channel, and transporters are enrolled in the development of chronic acid–base alterations (i.e., Bartter Syndrome, renal tubular acidosis, Gitelman syndrome) (NC et al. 1969; Rodriguez-Soriano 2000; Choate et al. 2003; Bates et al. 1997; Shaer 2001).

## 14.9 Metabolic Acidosis

Metabolic acidosis is the most frequent acid–base alteration in cardiac surgery patients (and generally in all postsurgical patients) in the ICU setting. It may have many causes that should be contemporarily present (Fanzca 2012; Morgan 2005).

Hemodynamic instability (development of mechanical and arrhythmic postoperative complications, hemorrhage, impairment of cardiac function, vasodilatation, and capillary leakage due to postoperative SIRS) may cause tissue hypoperfusion with the manifestation of a lactic acidosis (Fanzca 2012; Morgan 2005; Beers 2006).

Lactic acidosis may be present in patients who develop hepatic damages, especially in patients with chronic hepatic disease in whom the surgery stress may induce liver insufficiency, or when a preexisting or acute cardiac failure may cause a hepatic dysfunction due to stasis (Fanzca 2012; Morgan 2005; Beers 2006).

Another cause may be due to the development of intestinal ischemia, especially in multi-district vasculopathic patients and in long-stay ICU patients (Fanzca 2012; Morgan 2005; Beers 2006).

In diabetic patients, a strict control of glycemia levels may cause ketoacidosis, which should be considered also in patients with anamnesis positive for alcoholism or prolonged fasting.

In ICU patients there often is a hyperchloremic acidosis caused by IV fluid infusion, especially when large amounts are needed and unbalanced or plasma-adapted solutions are used (Fanzca 2012; Morgan 2005; Beers 2006).

A severe and prolonged reduction of diuresis and the development of postoperative AKI (especially ATN) may also be the cause of metabolic acidosis due to altered $Cl^-$, bicarbonate excretion, and reduced lactate and other nonvolatile acid clearance, especially in patients with preexisting or precipitating renal dysfunction (Beers 2006).

In complicated, long-stay ICU patients, the need for enteral nutrition, gastric aspiration, and the development of gastrointestinal dysfunction such as diarrhea may be the other cause of metabolic acidosis with normal AG (Beers 2006).

As long as a mild metabolic acidosis develops, clinical manifestations are strictly related to the cause. When a severe acidosis appears (pH <7,2) or a mild acidosis rapidly develops, symptoms such as nausea, vomiting, and malaise may be observed in the awake patient. The clinical characteristic of metabolic acidosis is hyperpnea due to the respiratory compensation; other manifestations are due to lower pH and are caused by acidosis, cardiac effects (hypotension, shock, and arrhythmias), and cerebral effects (mental status impairment up to coma) (Beers 2006).

ABG values for metabolic acidosis are showed in the table below (Table 14.5).

According to the management of all acid–base alteration, the treatment of metabolic acidosis is to eliminate the underlying cause or causes. As a consequence, an adequate integration between ABG information, patient clinic, patient anamnesis, and therapy in course is fundamental.

**Table 14.5** Metabolic acidosis: ABG values

| Parameter | Variation |
|---|---|
| pH | ≤7.38 |
| $HCO_3^-$ | <24 mEq/L |
| $pCO_2$ | Reduced: 1.5 mmHg for each 1 mEq/L $HCO_3^-$ reduction |
| BE | <−2 mEq/L |
| AG | >16 mEq/L: lactic acidosis<br>Normal: hyperchloremic acidosis |
| Delta gap | <1: two causes of metabolic acidosis |
| SID | <38 mEq/L<br>If SIG >10 mEq/L: lactic acidosis<br>If SIG <6 mEq/L: hyperchloremic acidosis |
| Lactate | >4 mEq/L: lactic acidosis |
| Electrolyte | Hyperkalemia ($H^+/K^+$ exchange) or hypokalemia ($K^+$ depletion) |

The use of IV bicarbonate is generally indicated when acidemia (especially severe acidemia) is developing. Sodium bicarbonate use may be more useful in some cases and even deleterious in some others.

When acidemia is the consequence of a loss of bicarbonate or to inorganic acids (AG normal, $Cl^-$ increased, $HCO_3^-$ reduced), the use of IV bicarbonate is considered appropriate to restore plasma levels. When acidemia is due to organic nonmeasurable acids (more frequently lactic acidosis), the use of bicarbonate is controversial: it may be helpful to avoid deleterious consequence of acidity (i.e., protein denaturation), but this may cause other deleterious mechanism (Fanzca 2012; Morgan 2005; Beers 2006).

Bicarbonate reacts with $H^+$ producing $H_2CO_3$ and finally $CO_2$ that is eliminated through the lungs. In patients under mechanical ventilation (MV), clinicians may modify ventilator parameters in order to optimize the clearance of $pCO_2$. Spontaneous breathing patients and in those with pulmonary complication (i.e., postoperative pneumonia, pleural effusion in case of cardiac insufficiency, pulmonary edema), it may be more difficult to increase $VCO_2$ even using invasive and noninvasive ventilation. As a consequence $pCO_2$ retentions with respiratory acidosis may develop, aggravating the patient's status. The overproduction of $CO_2$ may aggravate intracellular acidosis because the infused bicarbonate does not pass across the cellular membrane, while the obtained $CO_2$ freely pass. It reacts with endocellular water finally producing $H^+$ (Fanzca 2012; Morgan 2005; Beers 2006).

In case of lactic acidosis, if liver metabolism is preserved, lactate is metabolized to bicarbonate. Adding more exogenous bicarbonate may induce metabolic alkalosis responsible of a shift of Hb-saturation curve, reducing the releasing of $O_2$ to tissue. This may be deleterious when lactic acidosis is the consequence of a hypoxia or a hypoperfusion, causing organ impairment (first of all cardiac). Bicarbonate may also reduce portal flux and the efficiency of hepatic lactate clearance (Fanzca 2012; Morgan 2005; Beers 2006).

Sodium bicarbonate administration may depress cardiac function, worsening the hemodynamic status of postoperative ICU patient, especially when there has just been a cardiac failure.

Along with bicarbonate, sodium is administered too, the development of hypernatremia and hyperosmolarity is possible, especially when large amount of sodium bicarbonate are used (Fanzca 2012; Morgan 2005; Beers 2006). Finally the administration of exogenous bicarbonate reduces free ionized $Ca^{2+}$ and $K^+$ levels that may be deleterious in patients with hypokalemic acidosis (generally due to renal loss of salts) (Fanzca 2012; Morgan 2005; Beers 2006).

In mechanically ventilated patients hyperventilation may be used without bicarbonate administration in order to compensate metabolic acidosis. The consequence is the induction of a respiratory alkalosis that may reduce the hepatic clearance of lactate with a reduction of portal flux, potentially generating liver hypoxia and increase of lactate production (Fanzca 2012; Morgan 2005; Beers 2006).

In case of postoperative AKI, the use of CRRT should be precociously considered (Fanzca 2012; Morgan 2005; Beers 2006).

Bicarbonate is generally used when pH <7.2, bicarbonate is <12 mEq/L, and hyperkalemia develops with difficulties to control its value with other treatments (when acidosis is symptomatic or when the patient is waiting for CRRT) (Fanzca 2012; Morgan 2005; Beers 2006).

Sodium bicarbonate amount (bicarbonate deficit) may be calculated according to bicarbonate value (Beers 2006):

$$HCO_3^- \text{ deficit} = 0.4 \text{ body weight} \times (\text{goal } HCO_3^- - \text{measured } HCO_3^-$$

or BE (Beers 2006):

$$HCO_3 - \text{deficit} = BE \ (\text{mEq/L}) \times \text{body weight} / 4.$$

## 14.10 Metabolic Alkalosis

Metabolic alkalosis is less frequent with respect to metabolic acidosis in cardiac surgery patients. Generally it is due to a predominance of bicarbonate levels caused by retention, acid loss (renal and gastrointestinal), intracellular $H^+$ shift, and/or alkali administration (Beers 2006).

In an ICU setting metabolic alkalosis is generally caused by acid losses and may be due to secondary hyperaldosteronism caused by hypovolemia, heart failure, renal artery stenosis (polivasculopatic patients), cirrhosis (patients with hepatic diseases), or renal impairment; HCl and KCl losses may be due to PONV (especially when high dose of opioids are needed) or to gastric suction. Hypokalemia and hypomagnesemia are other causes of metabolic alkalosis because $K^+$ and $Mg^+$ renal reabsorption is realized through $H^+$ exchange (Fanzca 2012; Morgan 2005; Beers 2006). However, the most frequent cause of metabolic alkalosis in postoperative ICU patients is the use of diuretics (especially furosemide in continuous infusion). Furosemide may lead to metabolic alkalosis through a different mechanism: hyperaldosteronism due to hypovolemia, $Cl^-$ losses, and hypokalemia (Fanzca 2012; Morgan 2005; Beers 2006).

Other causes of metabolic alkalosis are due to bicarbonate retention overload, such as post-hypercapnic persistent elevation of bicarbonate, generally associated to $K^+$, $Cl^-$, and volume depletion; lactate or ketoacidosis conversion to bicarbonate (augmented after bicarbonate administration for acidosis); and $NaHCO_3$ loading (Fanzca 2012; Morgan 2005; Beers 2006).

A cause of metabolic alkalosis may be the administration of some kind of antibiotics such as carbapenicillin, penicillin, and ticarcillin. This should be considered in ICU patients with a prolonged therapy with them (generally complicated, long-stay patients) or with a recent story of protracted use of them (Fanzca 2012; Morgan 2005; Beers 2006).

When a metabolic alkalosis persists during the time, it indicates an increased renal reabsorption of bicarbonates. The more frequent stimuli for bicarbonate reabsorption are hypovolemia (GFR reduction) and hypokalemia. In fact, in case of

**Table 14.6** Metabolic alkalosis: ABG values

| Parameter | Variation |
|---|---|
| PH | ≥7.42 |
| $HCO_3^-$ | >24 mEq/L |
| $pCO_2$ | -Increased: 0.7 mmHg for each 1 mEq/L of $HCO_3^-$ increasing |
| BE | >+2 mEq/L |
| AG | Normal |
| Delta gap | >1 contemporary metabolic acidosis and metabolic alkalosis |
| SID | >42 mEq/L |
| Lactate | Normal |
| Electrolyte | Hypokalemia, hypomagnesemia, hypocalcemia, hypochloremia |

hypovolemia, the kidney increases $Na^+$ (and water) reabsorption to restore IVS volume. Sodium is reabsorbed as NaCl or $NaHCO_3$. Maintaining IVS volume is more vital than correct alkalemia, as a consequence $NaHCO_3$ will be reabsorbed till IVS volume is restored. This mechanism is present only if hypovolemia is caused by acid fluid losses (vomitus, gastric suction, diuretics). Hypokalemia leads to a shift of $H^+$ from ECS to ICS, with stimulus (intracellular acidosis) to $H^+$ secretion and $HCO_3$ reabsorption in tubular cells. Frequently two or more causes of metabolic alkalosis may coexist: for example, the use of diuretic may cause hypovolemia and hypokalemia (Fanzca 2012; Morgan 2005; Beers 2006; Narins and Gardner 1981; Adrogue and Madias 1998; Worthley 2003).

As long as a mild metabolic alkalosis is present, the main clinical features are related to the underlying cause. Severe alkalosis causes the increase of $Ca^{2+}$ binding to proteins, leading to hypocalcemia with neuromuscular excitability, lethargy to coma, delirium, seizures, and tetanus. Alkalemia reduces the thresholds for arrhythmias and angina development (Fanzca 2012; Morgan 2005; Beers 2006).

ABG values for metabolic alkalosis are showed in the table (Table 14.6).

In some cases the $Cl^-$ urinary concentration may be used to distinguish metabolic alkalosis: $Cl^-$ responsive and not $Cl^-$responsive (Beers 2006).

Urinary $Cl^-$ <15 mEq/L metabolic alkalosis $Cl^-$ responsive:

- Vomitus, gastric suction
- Diuretics
- Post-hypercapnic

Urinary $Cl^-$ >20 mEq/L metabolic alkalosis not $Cl^-$ responsive:

- Hyperaldosteronism
- Hypokalemia

The treatment of metabolic alkalosis depends on the cause. Metabolic alkalosis involving $Cl^-$ losses responds to administration of fluid containing NaCl. Generally 0.9 % saline solution is used. In order to avoid other electrolytic disorders, the infusion of a balanced solution may be suggested. It is recommendable to start the infusion at a rate of 50–100 ml/h and to subsequently increase the rate, according to the estimated and measured losses (Fanzca 2012; Morgan 2005; Beers 2006).

When metabolic alkalosis is not $Cl^-$ responsive, the correction of $K^+$ and $Mg^{2+}$ levels is needed. According to Stewart's approach $K^+$ deficit should be replaced using KCl. In fact in case of hypokalemia, the deficit is mainly in the ICS: the administered $K^+$ moves into cells, while $Cl^-$ remains in ECS reducing SID (and SBE), with an acidifying effect (Fanzca 2012; Morgan 2005; Beers 2006).

The correction of volume, $Cl^-$, and/or $K^+$ depletion leads to $K^+/H^+$ exchange, restoring $H^+$ plasma levels and reducing $Na^+$ (and consequently $HCO_3^-$) reabsorption.

Patients with post-hypercapnic alkalosis or furosemide-induced alkalosis may be treated with acetazolamide that increases $HCO_3^-$ kidney excretion, with caution to $PO_4^-$ and $K^+$ kidney losses. Acetazolamide is also useful in case of secondary hyperaldosteronism, in which metabolic alkalosis is related to volume overload (Fanzca 2012; Morgan 2005; Beers 2006).

In case of severe alkalosis (pH >7,5), a rapid correction is needed. In this case HCl use may be indicated. HCl 0.1–0.2 normal may be safe used through a central line. The dose may be calculated as

$$\begin{aligned} HCO_3^- \text{ excess} &= 0.4 \text{ body weight (measured } HCO_3^- - \text{goal } HCO_3^-) \\ &= 0.4 \text{ body weight (measured } HCO_3^- - 24). \end{aligned}$$

An infusion rate of 0.1–0.2 mmol/Kg/h is recommended with frequent ABG sample needed.

CRRT may be indicated in severe cases, especially if a contemporary fluid overload is present (Fanzca 2012; Morgan 2005; Beers 2006).

## 14.11 Respiratory Acidosis

Respiratory acidosis is due to $CO_2$ accumulation caused by a reduced elimination or an increased production.

A reduction in $CO_2$ elimination is caused by hypoventilation. Frequent cause of hypoventilation in cardiac surgery in ICU settings may be caused by sedation effects (during weaning from MV and in the immediate post-extubation period), neuromuscular blocker effects (fast-track protocols or long-stay patients with protracted curarization), postoperative pain and the development of complications such as cerebral complications or abdominal complications (ascites, abdominal distension), cardiac failure with pulmonary edema or/and pleural effusion, pneumothorax (post-central line positioning or MV related); pneumonia (VAP), and atelectasis. Other causes of hypoventilation may be due to patient's comorbidity such as COPD, OSAS, and restrictive pulmonary diseases. These diseases may cause chronic acidosis that may be associated to acute causes (Fanzca 2012; Morgan 2005; Beers 2006).

Frequent causes of $CO_2$ overproduction may be hypovolemia, sepsis, and an inadequate artificial nutrition (long-stay patient) with an excess of calories. On the other hand malnutrition may cause muscular weakness (Fanzca 2012; Morgan 2005; Beers 2006).

**Table 14.7** Respiratory acidosis: ABG values

| Parameter | Variation |
|---|---|
| PH | ≤7.38 |
| $HCO_3^-$ | >24 mmEq/L<br>Acute acidosis: 1 mEq/L for each 10 mmHg of $CO_2$ increasing<br>Chronic acidosis: 4 mEq/L for each 10 mmHg of $CO_2$ increasing |
| $pCO_2$ | >45 mmHg |
| AG | Normal |
| SID | Normal |
| Lactate | Normal |
| Electrolyte | Hyperkalemia (H+/K+ exchange) |

Finally it is fundamental to remember the detrimental effect of a prolonged MV on respiratory muscles and its effects during MV weaning attempts and the role of oxygen administration resulting in hyperoxemia and subsequent hypoventilation (Fanzca 2012; Morgan 2005; Beers 2006).

Clinical presentation of respiratory acidosis depends on the gravity of the disturbance and the time of development. Typical manifestations of rapid and mild–severe acidosis are cerebral and they include headache, anxiety, confusion, lethargy, and coma. Mild or chronic acidosis is generally better tolerated and may be associated to sleep alterations, daytime sleepiness, and tremors. Other symptoms may be those of hypoxemia that frequently accompanies hypercapnia. Patients may also present dyspnea, bradypnea, and use of accessory respiratory muscles. Many clinical manifestations of respiratory acidosis are not observable in the sedated patient. Respiratory acidosis is associated with hyperkalemia potentially leading to arrhythmias (Fanzca 2012; Morgan 2005; Beers 2006).

ABG values for respiratory acidosis are showed in the table (Table 14.7).

In order to better understand the underlying cause of a respiratory acidosis, it should be useful to calculate the alveolar–arterial (A-a) $O_2$ gradient:

$$\text{A} - \text{a gradient} = \text{FiO}_2 - (\text{paO}_2 + 5/4\,\text{paCO}_2) = 10\ \text{mmHg}.$$

A normal gradient indicates an extrapulmonary cause, while an increase gradient indicates a pulmonary alteration (Beers 2006).

Treatment is based on the management of the underlying cause and the increase of alveolar ventilation. In particular, in the case of a chronic acidosis it is needed to remove or reduce precipitating factors such sedative or analgesic drugs, the adequate use of PS ventilation and PEEP for alveolar recruitment before the extubation, a praecox respiratory gymnastic and the preventive use of NIV. In patients who develop hypercapnia after extubation (with negative anamnesis), it is needed to immediately search for the cause and, when necessary, to use NIV before tracheal intubation. The goal is the achievement of a normal $pCO_2$, except for patients with chronic acidosis in which the goal is the hypercapnic status before decompensation. Moreover, in these cases clinicians should avoid a too rapid $pCO_2$ reduction resulting in a post-hypercapnic alkalosis (kidney is slower than lung) and in a rapid variation of cerebral pH that may cause seizures and death (Beers 2006).

## 14.12 Respiratory Alkalosis

Respiratory alkalosis is caused by an increase of alveolar ventilation. Many stimuli may lead to hyperventilation as a physiological response: hypoxemia, hypotension, severe anemia, and metabolic acidosis. These causes are often present in cardiac surgery patients in the ICU setting, especially in complicated cases (Fanzca 2012; Morgan 2005; Beers 2006).

Other causes leading to respiratory alkalosis are fever and sepsis, pain (insufficient analgesic administration), anxiety and agitation (postoperative delirium, central complication), COPD, and pulmonary embolism (Fanzca 2012; Morgan 2005; Beers 2006).

Finally the most frequent cause of respiratory alkalosis in ICU patients is iatrogenic: MV. It may be cause of pseudorespiratory alkalosis: in cases of hypoperfusion–hypoxemia, the underlying metabolic acidosis is masked by a $CO_2$ elimination over the normal rate and due to the mechanical control of alveolar ventilation. This alteration may be detected by studying the arterial–venous difference in $pCO_2$, pH, and the other ABG markers of metabolic acidosis such as AG and SID (Fanzca 2012; Morgan 2005; Beers 2006).

Clinical manifestations of respiratory alkalosis are related to the rapidity of development and to the gravity of hypocapnia. Tachypnea and/or dyspnea is often the only presentation. Other signs and symptoms are mainly cerebral and are due to the change in central cerebral flux and pH: headache, paresthesias, cramps, and syncope.

ABG values for respiratory alkalosis are showed in the table (Table 14.8).

Respiratory alkalosis is not life threatening and, as a consequence, no intervention is required to directly correct the pH. Treatment is based on the management of the underlying cause. It is important to recognize potentially severe causes, such as pulmonary embolism, and their immediate management. In ICU setting where patients are in VM, the first line of treatment is to reduce ventilation, excluding other possible causes of respiratory alkalosis (Fanzca 2012; Morgan 2005; Beers 2006).

**Table 14.8** Respiratory alkalosis: ABG values

| Parameter | Variation |
|---|---|
| PH | ≥7.42 |
| $HCO_3^-$ | <24 mEq/L<br>Acute alkalosis: 1 mmEq/L for each 10 mmHg of $CO_2$ decreasing<br>Chronic alkalosis: 4 mmEq/L for each 10 mmHg of $CO_2$ decreasing |
| $pCO_2$ | <35 mmHg |
| AG | Normal |
| SID | Normal |
| Lactate | Normal |
| Electrolyte | Hypokalemia and hypophosphatemia (K+ and $PO_4^-$ intracellular shift), hypocalcemia (increased protein binding), hyperchloremia (to compensate $HCO_3^-$ reduction) |

**Conclusion**

Critical care practitioners should consider the acid–base status of a patient before any therapeutic maneuver, especially in choosing the IV fluid to administer.

Literature discussed about the need for balanced pH solutions, especially in cardiac surgery patients. Although it is necessary to avoid solutions with very low or very high pH (especially for rapid infusion), the administration of solutions with different pH may have the same effect on the basis of their electrolytic composition, according to their SID (Fanzca 2012).

Older generation of IV fluids has a SID = 0 and reduce plasma SID, resulting in metabolic acidosis, while modern fluids present a SID higher than zero, but lower than plasma (26–29 mEq/L), resulting in a mild alkalinizing effect. In the recent literature the need for solution with a balanced SID (ideal value +24) has been evidenced. Although no commercially available solutions present the ideal SID value (Morgan 2005).

In a modern view, a balanced, plasma-adapted solution should have a qualitative and quantitative composition closer than plasma and contain metabolizable anions in order to have an SID closer as possible to +24 mEq/L.

## References

Aalkjaer C, Poston L (1996) Effects of pH on vascular tension: which are the important mechanisms? J Vasc Res 33:347–359

Abramson D, Scalea TM, Hitchcock R et al (1993) Lactate clearance and survival following injury. J Trauma 35:584–589

Adrogue HJ, Madias NE (1998) Medical progress: management of life-threatening acid–base disorders: second of two parts. N Engl J Med 338:107–111

Agro FE, Benedetto M (2013) Properties and composition of plasma substitutes. In: Agrò FE (ed) Body fluid management – from physiology to therapy, 1st edn. Springer, Milan

Agro FE, Vennari M (2013) Physiology of body fluid compartments and body fluid movements. In: Agrò FE (ed) Body fluid management – from physiology to therapy, 1st edn. Springer, Milan

Agrò FE, Fries D, Vennari M (2013) Cardiac surgery. In: Agrò FE (ed) Body fluid management – from physiology to therapy, 1st edn. Springer, Milan

Akanji AO, Bruce MA, Frayn KN (1989) Effect of acetate infusion on energy expenditure and substrate oxidation rates in non-diabetic and diabetic subjects. Eur J Clin Nutr 43:107–115

Asano S, Kato E, Yamauchi M et al (1966) The mechanism of the acidosis caused by infusion of saline solution. Lancet 267:1245–246

Astrup P, Jorgensen K, Siggaard-Andersen O (1960) Acid–base metabolism: new approach. Lancet 1:1035–1039

Bakker J, Gris P, Coffermils M et al (1996) Serial blood lactate levels can predict the development of multiple organ failure following septic shock. Am J Surg 224:97–102

Base EM, Standl T, Lassnigg A et al (2011) Efficacy and safety of hydroxyethyl starch 6% 130/0.4 in a balanced electrolyte solution (Volulyte) during cardiac surgery. J Cardiothorac Vasc Anesth 25(3):407–414

Bates CM, Baum M, Quigley R (1997) Cystic fibrosis presenting with hypokalemia and metabolic alkalosis in a previously healthy adolescent. J Am Soc Nephrol 8:352–355

Beecher HK, Murphy AJ (1950) Acidosis during thoracic surgery. J Thorac Surg 19:50

Beers MH (2006) Acid–base regulation and disorders. In: Beers MH (ed) The Merck manual XVIII, Whitehouse Station, NJ

Brackett NC, Cohen JJ, Schwartz WB (1965) Carbon dioxide titration curve of normal man. N Engl J Med 272:6–12
Celotto AC, Capellini VK, Baldo CF et al (2008) Effects of acid–base imbalance on vascular reactivity. Br J Med Biol Res 41(6):439–445
Choate KA, Kahle KT, Wilson FH et al (2003) WNK1, a kinase mutated in inherited hypertension with hyperkalemia, localized to diverse Cl transporting epithelia. Proc Natl Acad Sci U S A 100:663–668
Clancy RL, Gonzalez NC (1975) Effect of respiratory and metabolic acidosis on coronary vascular resistance. Proc Soc Exp Biol Med 148:307–311
Coffin LH, Ankeney JL (1960) The effect of extracorporeal circulation upon acid–base equilibrium in dogs. Arch Surg 80:447
Cowan BN, Burns HJ, Boyle P et al (1984) The relative prognostic value of lactate and haemodynamic measurements in early shock. Anaesthesia 39:750–755
Dobell ARC, Gutelius JR, Murphy DR (1960) Acidosis following respiratory alkalosis in thoracic operations with and without heart lung bypass. J Thorac Surg 39:312
Ely SW, Sawyer DC, Scott JB (1982) Local vasoactivity of oxygen and carbon dioxide in the right coronary circulation of the dog and pig. J Physiol 332:427–439
Falk JL, Rachow EC, Leavy J et al (1985) Delayed lactate clearance in patients surviving circulatory shock. Acute Care 11:212–215
Fanzca RY (2012) Perioperative fluid and electrolyte management in cardiac surgery: a review. J Extra Corpor Technol 44:20–26
Fencl V, Jabor A, Kazda A et al (2000) Diagnosis of metabolic acid–base disturbances in critically ill patients. Am J Respir Crit Care Med 162:2246–2251
Figge J, Jabor A, Kazda A et al (1998) Anion gap and hypoalbuminemia. Crit Care Med 26:1807–1810
Finfer S, Bellomo R, Boyce N et al (2004) A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 350:2247–2256
Franco-Cereceda A, Kallner G, Lundberg JM (1993) Capsazepine sensitive release of calcitonin gene-related peptide from Cfibre afferents in the guinea-pig heart by low pH and lactic acid. Eur J Pharmacol 238:311–316
Friedman C, Berlot G, Kahn RJ et al (1995) Combined measurement of blood lactate concentrations and gastric intramucosal pH in patients with severe sepsis. Crit Care Med 23:1184–1193
Gibbon JH, Allbritten FP, Stayman JW, Judd JM (1950) A clinical study of respiratory exchange during prolonged operations with an open thorax. Ann Surg 132:611
Grogono AW, Byles PH, Hawke W (1976) An in vivo representation of acid–base balance. Lancet 1:499–500
Hayhoe M, Bellomo R, Lin G et al (1999) The aetiology and pathogenesis of cardiopulmonary bypass-associated metabolic acidosis using polygeline pump prime. Intensive Care Med 25:680–685
Henderson LJ (1908) The theory of neutrality regulation in the animal organism. Am J Physiol 21:427
Henning RJ, Weil MH, Weiner F (1982) Blood lactate as a prognostic indicator of survival in patients with acute myocardial infarction. Circ Shock 9:307–315
Himpe D, Neels H, De Hert S et al (2003) Adding lactate to the prime solution during hypothermic cardiopulmonary bypass: a quantitative acid–base analysis. Br J Anaesth 90:440–445
Ishizaka H, Kuo L (1996) Acidosis-induced coronary arteriolar dilation is mediated by ATPsensitive potassium channels in vascular smooth muscle. Circ Res 78:50–57
Ito I, Faulkner WR, Kolff WJ (1957) Metabolic acidosis and its correction in patients undergoing open heart operation; experimental basis and clinical results. Cleve Clin Q 24:193
Johnson V, Bielanski E, Eiseman B (1969) Lactate metabolism during marginal liver perfusion. Arch Surg 99:75–79
Kellum JA (2000) Determinants of blood pH in health and disease. Crit Care 4:6–14
Kellum JA (2002) Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: improved short-term survival and acidbase balance with Hextend compared with saline. Crit Care Med 30:300–305

Kellum JA (2005a) Clinical review: reunification of acid–base physiology. Crit Care 9:500–507
Kellum JA (2005b) Making strong ion difference the euro for bedside acid–base analysis. Intensive Care Emerg Med 14:675–685
Kellum JA, Weber PAW (2009) Stewart's textbook of acid–base, 2nd edn. Lulu Enterprises, London
Kellum JA, Kramer DJ, Pinsky MR (1995) Strong ion gap: a methodology for exploring unexplained anions. J Crit Care 10:51–55
Kincaid EH, Miller PR, Meredith JW et al (1998) Elevated arterial base deficit in trauma patients: a marker of impaired oxygen utilisation. J Am Coll Surg 187:384–392
Kirklin JW, Donald DE, Harshbarger HG et al (1956) Studies in extra- corporeal circulation: applicability of Gibbon type pump-oxygenator to human intracardiac surgery-forty cases. Ann Surg 144:2
Knowles SE, Jarrett IG, Filsell OH et al (1974) Production and utilization of acetate in mammals. Biochem J 142:401–411
Levraut J, Ciebiera JP, Chave S et al (1998) Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. Am J Respir Crit Care Med 157:1021–1026
Liskaser F, Story DA (1999) The acid–base physiology of colloid solutions. Curr Opin Crit Care 5:440–442
Liskaser FJ, Bellomo R, Hayhoe M et al (2000) Role of pump prime in the etiology and pathogenesis of cardiopulmonary bypass-associated acidosis. Anesthesiology 93:1170–1173
Litwin MS, Panico FG, Rubini C et al (1959) Lacticacidemia in extracorporeal circulation. Ann Surg 149:188
Lundquist F (1962) Production and utilization of free acetate in man. Nature 193:579–580
Makoff DL, da Silva JA, Rosenbaum BJ et al (1970) Hypertonic expansion: acid–base and electrolyte changes. Am J Physiol 218:1201–1207
McFarlane C, Lee A (1994) A comparison of plasmalyte 148 and 0.9% saline for intraoperative fluid replacement. Anaesthesia 49:779–781
McNelis J, Marini CP, Jurkiewicz A et al (2001) Prolonged lactate clearance is associated with increased mortality in the surgical intensive care unit. Am J Surg 182:481–485
Mercieri A, Mercieri M (2006) L'approccio quantitativo di Stewart all'equilibrio acido-base. G Ital Nefrol 3:280–290
Miller LR, Waters JH (1997) Mechanism of hyperchloremic nonunion gap acidosis. Anesthesiology 87:1009–1010
Morgan TJ (2005) Clinical review: the meaning of acid–base abnormalities in the intensive care unit – effects of fluid administration. Crit Care 9:204–211
Morgan TJ, Clark C, Endre ZH (2000) The accuracy of base excess: an in vitro evaluation of the Van Slyke equation. Crit Care Med 28:2932–2936
Morgan TJ, Venkatesh B, Hall J (2004) Crystalloid strong ion difference determines metabolic acid–base change during acute normovolemic hemodilution. Intensive Care Med 30:1432–1437
Mudge GH, Manning JA, Gilman A (1949) Sodium acetate as a source of fixed base. Proc Soc Exp Biol Med 71:136–138
Narins RG, Gardner LB (1981) Simple acid–base disturbances. Med Clin North Am 65(321):360
NC B, Cohen JJ, Schwartz WB (1969) Carbon dioxide titration curve of normal man. N Engl J Med 272:6–12
Prough DS, Bidani A (1999) Hyperchloremic metabolic acidosis is a predictable consequence of intraoperative infusion of 0.9% saline. Anesthesiology 90:1247–1249
Prys-Roberts C, Kelman GR, Nunn JF (1966) Determinants of the in vivo carbon dioxide titration curve in anesthetized man. Br J Anesth 38:500–550
Puyau FA, Fowler REL, Novick R et al (1962) The acid–base vector of open-heart surgery. Circulation 26:902–912
Quilley CP, Lin YS, McGiff JC (1993) Chloride anion concentration as a determinant of renal vascular responsiveness to vasoconstrictor agents. Br J Pharmacol 108:106–108

Rehm M, Orth V, Scheingraber S et al (2000) Acid–base changes caused by 5% albumin versus 6% hydroxyethyl starch solution in patients undergoing acute normovolemic hemodilution: a randomized prospective study. Anesthesiology 93:1174–1183
Reid F, Lobo DN, Williams RN et al (2003) (Ab)normal saline and physiological Hartmann's solution: A randomized double-blind crossover study. Clin Sci 104:17–24
Rivers E, Nguyen B, Havstad S et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
Rodriguez-Soriano J (2000) New insight into the pathogenesis of renal tubular acidosis-from functional to molecular studies. Pediatr Nephrol 14:1121–1136
Rose DB (1995) Fisiologia clinica dell'equilibrio acido-base e dei disordini elettrolitici. McGraw-Hill Libri Italia, Milano
Scheingraber S, Rehm M, Sehmisch C, Finsterer U (1999) Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 90:1265–1270
Schlichtig R, Grogono AW, Severinghaus JW (1998a) Current status of acid–base quantitation in physiology and medicine. Anesthesiol Clin North Am 16:211–233
Schlichtig R, Grogono AW, Severinghaus JW (1998b) Human $PaCO_2$ and standard base excess compensation for acid–base imbalance. Crit Care Med 26:1173–1179
Severinghaus JW (1976) Acid–base balance nomogram–a Boston-Copenhagen détente. Anesthesiology 45:539–541
Sgambato F, Prozzo S (2003) Gap anionico: un ponte tra i due equilibri. Giorn Ital Med Int 2(1): 20–27
Shaer AJ (2001) Inherited primary renal tubular hypokalemic alkalosis: a review of gitelman and Bartter syndromes. Am J Med Sci 322:316–332
Shires GT, Holman J (1948) Dilution acidosis. Ann Intern Med 28:557–559
Siggaard-Andersen O (1962) The pH-log $PCO_2$ blood acid–base nomogram revised. Scand J Clin Lab Invest 14:598–604
Siggaard-Andersen O (1977) The Van Slyke equation. Scand J Clin Lab Invest 146:15–20
Siggaard-Andersen O, Fogh-Andersen N (1995) Base excess or buffer base (strong ion difference) as measure of a non-respiratory acid–base disturbance. Acta Anesth Scand 107:123–128
Storey DA (1999) Intravenous fluid administration and controversies in acid–base. Crit Care Resusc 1:151–156
Traverso LW, Lee WP, Langford MJ (1986) Fluid resuscitation after an otherwise fatal hemorrhage: 1. Crystalloids solutions. J Trauma 26:168–175
Vincent JL, DuFaye P, Beré J et al (1983) Serial lactate determinations during circulatory shock. Crit Care Med 11:449–451
Vulterini S, Colloca A, Chiappino MG, Bolignari P (1992) L'equilibrio acido-base ed il suo studio mediante il dosaggio degli elettroliti del sangue venoso. Ediz Instr. Laboratory, Milan
Waters JH, Gottleib A, Schoenwald P et al (2001) Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. Anesth Analg 93:817–822
Weil MH, Afifi AA (1970) Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). Circulation 41:989–1001
Wilcox CS (1983) Regulation of renal blood flow by plasma chloride. J Clin Invest 71:726–735
Wilkes NJ, Woolf R, Mutch M et al (2001) The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid–base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. Anesth Analg 93:811–816
Wooten EW (1999) Analytic calculation of physiological acid–base parameters in plasma. J Appl Physiol 86:326–334
Worthley LIG (2003) Acid–base balance and disorders. In: Bersten AD, Soni N (eds) Oh's intensive care manual, 5th edn. Butterworth Heinemann, Edinburgh
Zander R (2006) Infusion fluids: why should they be balanced solutions? Eur J Hosp Pharm Pract 12:60–62

# Risk and Outcome Assessments

# 15

Manuel Caceres

## Contents



**Abstract**

Over the last three decades, the assessment of risk and comparison of outcomes have evolved from the reporting of raw mortality and morbidity rates to the comparison of risk-adjusted results using a variety of complex statistical methods. Concurrently, various multi-institutional registries have emerged as a result of voluntary initiatives or mandatory requirements from state and nationwide regulations. Consequently, the reporting of outcomes, previously limited to single institutional data, has more currently focused on larger multi-institutional

M. Caceres, MD
Department of Thoracic Surgery,
Veterans Affairs Medical Center, Memphis, TN 38103, USA
e-mail: caceres_manuel@hotmail.com

A. Dabbagh et al. (eds.), *Postoperative Critical Care for Cardiac Surgical Patients*,
DOI 10.1007/978-3-642-40418-4_15, © Springer-Verlag Berlin Heidelberg 2014

registries suitable to develop risk models with sufficient predictive power. With the rapid evolution of organized medicine and the heightened attention to quality improvement, it is essential for the practitioner in the community to understand the basic concepts in the assessment of risks and comparison of outcomes.

The following chapter intends to present the foundation of risk-adjustment methodologies and to depict an outline of the most common databases currently used for research and quality improvement purposes.

## 15.1 Historical Background

The inception of quality improvement strategies in health care dates back to over 150 years ago with the efforts of Florence Nightingale, the founder of modern nursing, to determine the elements associated to improved outcomes. Florence Nightingale collected data, monitored patient outcomes, and implemented interventions that in less than 6 months significantly decreased the mortality events among injured soldiers during the Crimean war (Ellis 2008).

The assessment of outcomes in modern medicine has centered on the collection of patient-specific data through local and multi-institutional databases. Various institutions have developed local databases for over 30 years, and multi-institutional registries have significantly grown in size and complexity during the last decade.

In 1972, the Veterans Affairs Administration initiated the systematic collection of patient-specific data, highlighting the inception of multi-institutional databases. In 1986, the Health Care Financing Agency (HCFA), former Center for Medicare and Medicaid Services (CMS), released hospital-specific raw mortalities for coronary artery bypass grafting (CABG), raising widespread concern that the published rates did not account for the disparate case mix among institutions (Anderson 1994). These events served as a stimulus in the last two decades to create comprehensive multi-institutional registries to generate risk-adjusted models that could level the field in the comparison of outcomes.

## 15.2 Risk-Adjustment Methodology

### 15.2.1 Data Collection

Two broad categories of registries are commonly used in the assessment of surgical outcomes, clinical and administrative. Data managers with various levels of clinical background generally collect and enter patient-specific data into clinical databases, whereas administrative databases rely largely on the International Classification of Diseases (ICD) codes assigned by coding personnel without specific clinical background. Clinical databases can be voluntary (e.g., The Society of Thoracic Surgeons National Cardiac Database) or mandatory (e.g., The New York State Cardiac Registry), and administrative databases are generally mandatory according to state or national requirements.

Because of the inherent errors in data collection using ICD code information, the accuracy and detail is generally higher with clinical as compared to administrative databases. Missing information varies widely among databases, and various

imputation techniques are established for adjustment. Intra-variable and inter-variable safe checks are present in some databases (not available in administrative databases) to assure consistency of the data entered, e.g., a record positive for cardiogenic shock and labeled as an elective admission is inconsistent and will be rejected in databases with safe checks in place. Auditing is an additional measure to ensure data quality and is enforced in some databases.

### 15.2.2 Risk Modeling

While various methods are available to develop risk-adjusted models, multivariable logistic regression analysis has emerged as the preferred strategy. Multivariable logistic regression models a binary response variable (e.g., mortality (death = 0, alive = 1)) as a function of explanatory continuous or categorical variables, in which the natural logarithm of the odds of a specific event represents the response variable and a variety of continuous or categorical variables function as explanatory variables (Bewick et al. 2005).

Given the binary response event defined as "mortality" and "$p$" the probability of death, the odds of the event, i.e., mortality, is defined as follows:

$$\text{Odds}: p/(1-p)$$

A multivariable logistic regression model conforms to the following formula:

$$\text{Ln}\,[p/(1-p)] = A_0 + A_1 * X_1 + A_2 * X_2 + A_3 * X_3 \ldots A_n * X_n$$

In which $A_0$ is a constant, $n$ is the number of explanatory variables, $A_n$ are the coefficients of determination, and $X_n$ are the explanatory variables in the model. $X_n$ can be a categorical (entry values: 0 or 1) or a continuous variable (entry value: absolute value of the variable or any specific variable transformation).

The odds ratio (OR) for a specific variable after adjusting for every other variable in the model, i.e., the increased mortality risk for each unit increase of the explanatory variable $X_n$, is defined as

$$\text{OR}\left[\text{CI}, p-\text{value}\right] = e^{A_n}$$

The CI (confidence interval) and the $p$-value determine the significance of the OR, namely, if the $p$-value shows statistical significance, a variation in the explanatory variable will have an effect in the response variable, provided the remaining variables remain constant.

### 15.2.3 Variable Selection

The variables entered in a risk model are commonly selected according to clinical principles; however, the number of variables selected has to be balanced to maximize the predictive power of the model. Too few variables can limit the predictive power by ignoring the effect of relevant unmeasured variables. Likewise, an

excessive number of variables can create random error or noise, also called over-fitting, which prevents a model from being reproducible. The rule of ten in logistic regression suggests that the absolute number of the outcome event variable should be at least ten times the number of variables initially considered in a model, i.e., with 100 mortality events in a study sample, the model should not consider more than ten explanatory variables to avoid over-fitting (Peduzzi et al. 1996). Thus, although many institutional studies present risk-adjusted results, the majority lacks the necessary power to meet this requirement, and registry data is often necessary to obtain accurate ORs; this is particularly true in low-frequency outcome variables, such as operative mortality in cardiac surgery.

### 15.2.4 Risk Model Assessment

There are generally three steps in the assessment of the accuracy of a risk model. First, the model is tested for its performance across the spectrum of predicted probability of the outcome variable, also called calibration or goodness of fit. Furthermore, the sensitivity of the model to discriminate between positive or negative outcome events is measured, also called discrimination. Finally, the model undergoes "validation" by testing the goodness of fit and discrimination in a dataset comparable to the one used to create the model.

#### 15.2.4.1 Goodness of Fit

The calibration or goodness of fit of a model is most commonly measured by the Hosmer–Lemeshow test, by which the study population is divided into ten equal-sized groups arranged from the lowest to the highest predicted probability of the outcome event. The observed and expected values for each of the two outcomes (e.g., death or survival) are entered in a contingency table, and the test statistic is used to determine whether there is a significant difference between the observed and expected values within each decile (Table 15.1). A $p$-value of >0.05 is generally accepted to indicate that the observed frequencies are similar to those predicted by the model, thus reflecting an adequate goodness of fit (Hosmer and Lemeshow 2000).

#### 15.2.4.2 Model Discrimination

The model discrimination determines the ability to distinguish between both outcome events, e.g., survival or death. The model discrimination is calculated with the area under the receiver-operating-characteristic (ROC) curve and is measured by the c-statistic, which ranges from "0" to "1." The ROC curve is plotted based on the true-positive and false-positive rates of the prediction of the outcome event, through multiple iterations of the model performance in the entire study population (Fig. 15.1). In this manner, a c-statistic of 0.5 has no discriminatory value because an event predicted as positive will be equally possible to be a true-positive or a false-positive event; thus, providing a predictive power not greater than random chance. A c-statistic of 0.7–0.9 is usually reported in most models with adequate predicted power (Bewick et al. 2004).

**Table 15.1** Hosmer–Lemeshow contingency table

| Decile group | Total events | Outcome event = 0 | | Outcome event = 1 | |
|---|---|---|---|---|---|
| | | Observed events | Expected events | Observed events | Expected events |
| 1 | 100 | 95 | 92.1 | 5 | 7.9 |
| 2 | 100 | 93 | 90.3 | 7 | 9.7 |
| 3 | 100 | 93 | 93.1 | 7 | 6.9 |
| 4 | 100 | 91 | 92.5 | 9 | 7.5 |
| 5 | 100 | 90 | 88.3 | 10 | 11.7 |
| 6 | 100 | 89 | 87.8 | 11 | 12.2 |
| 7 | 100 | 87 | 90.3 | 13 | 9.7 |
| 8 | 100 | 85 | 81.6 | 15 | 18.4 |
| 9 | 100 | 84 | 83.2 | 16 | 16.8 |
| 10 | 100 | 82 | 84.1 | 18 | 15.9 |

The Hosmer–Lemeshow test statistic determines if there is a significant difference between the observed and expected values in the contingency table

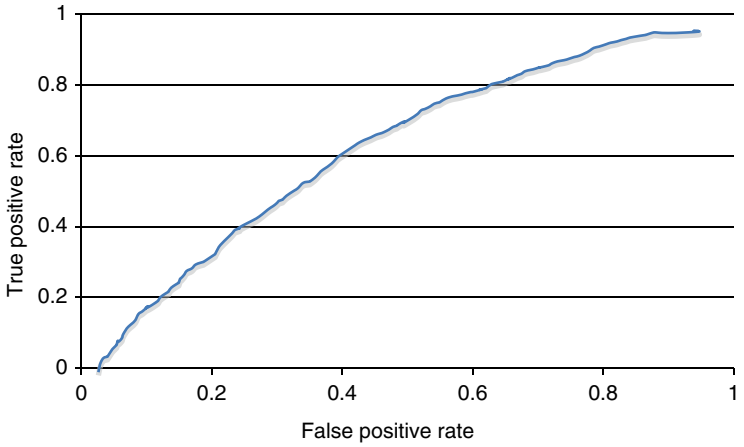



**Fig. 15.1** Receiver-operating-characteristic curve. The c-statistic [range (0.0–1.0)] is calculated as the area under the receiver-operating-characteristic curve

### 15.2.4.3 Model Validation

It is preferable to validate the goodness of fit and discrimination in a different dataset than the one used to create the model. The original dataset can be partitioned into a training set (sample used to develop the model) and a testing set (sample used to validate the model). These categories are not required to be of the same size, but each one must be representative of the entire dataset. The validation process is conducted by applying the risk model into the testing set and recalculating the goodness of fit ($p$-value) and discrimination (c-statistic) (Bewick et al. 2005).

### 15.2.5 Methods for Risk-Adjusted Comparison of Outcomes

In order to determine areas in which to implement quality improvement measures, risk-adjusted methods are necessary in the comparison of institution-specific or surgeon-specific outcomes. The following are common indexes used for these comparisons:

#### 15.2.5.1 Observed-to-Expected (O/E) Ratio

The observed and expected rates of an outcome event are calculated for a study population. The expected rate is calculated by averaging the predicted risk of the outcome event in each patient. A random effects variable may also be entered in the model to adjust for the random variation among institutions. The O/E ratio for a specific provider is compared to the O/E ratio of the entire population, which should be in very close proximity to the neutral value of 1.0. A significant difference in this comparison reflects a deviation of the outcome event for a particular provider.

#### 15.2.5.2 Risk-Adjusted Rates

A comparison of outcomes can also be presented by comparing the risk-adjusted rates of the outcome event (e.g., risk-adjusted mortality):

Risk-adjusted rate = [observed rate/expected rate] * Observed rate of the event in the entire population.

While this value does not represent an actual rate of the event, it uses the collective rate of the outcome event as a reference to compare the observed rates among providers.

## 15.3 Cardiac Surgery Registries

During the last decade there has been a considerable increase in the number of scientific publications originating from multi-institutional registries. The following is a brief description of the most commonly used databases in the study of cardiac surgery outcomes:

### 15.3.1 Administrative Databases

#### 15.3.1.1 The Medicare Provider Analysis and Review (MEDPAR) Database

The MEDPAR registry is an administrative claims database composed of records from claims made by Medicare beneficiaries. Each record corresponds to a hospital admission, and the data entered originates from the Uniform billing-92 (UB-92) discharge summary found in all hospital charts. The primary diagnosis, comorbidities, and procedures from each record are identified using ICD codes. The data in this database corresponds to Medicare beneficiaries from Medicare-certified hospitals; thus, it only represents patients older than 65 years using Medicare benefits (Welke et al. 2007).

#### 15.3.1.2 California Discharge Database

The State of California requires for every nonfederal hospital to provide discharge information of all hospital admissions in a biannual basis, representing a reporting rate of 100 % since it is a mandatory requirement. Diagnosis, comorbidities, and procedures are identified through ICD codes. Unlike other administrative databases, the California discharge database discriminates between primary and secondary diagnoses and identifies the procedure dates, thus allowing the inclusion of timing of specific interventions as one of the components of the risk models (Weiss et al. 2008).

#### 15.3.1.3 Nationwide Inpatient Sample (NIS)

The NIS originated in 1988 and is a non-mandatory database of hospital inpatient stays, developed as part of the Healthcare Cost and Utilization Project. The NIS is the largest all-payer inpatient care database and contains records of hospital admissions for about 20 % of nonfederal hospitals in the United States, covering 45 states. The NIS contains clinical and resource use information in a typical discharge abstract, with safeguards to protect the privacy of patients, physicians, and hospitals, and it can be weighted to project national estimates. Researchers and policymakers use the NIS to identify, track, and analyze national trends in health-care utilization, access, charges, quality, and outcomes. The NIS also includes charge information for all patients regardless of payer, including Medicare, Medicaid, private insurance, and the uninsured.

As of 2002, the NIS contains elements for adjustment of the severity of illness, and beginning in 2005, Diagnosis and Procedure Groups Files were established with software tools to facilitate the use of ICD-9 diagnostic and procedure codes. In 2009 the NIS included a Hospital Weights file to describe hospital structural characteristics and the provision of outpatient services. The NIS data is available for purchase to all participants contingent upon a signed agreement to use the data for research purposes only and to make no attempt to identify the individuals in the database (http://www.hcup-us.ahrq.gov/nisoverview.jsp).

### 15.3.2 Clinical Databases

#### 15.3.2.1 New York State Cardiac Registry

Because of disparate outcomes seen across institutions in New York State and the release of poorly adjusted institution-specific cardiac surgery outcomes by the HCFA, the New York State Department of Health decided to create a patient-specific clinical database, a mandatory registry for all cardiac programs in New York State. In 1990, the first risk-adjusted institutional mortality rates were reported, and as a result of a subsequent lawsuit, the Department of Health was forced to release surgeon-specific mortality rates as of 1992. Risk-adjusted mortality rates and outlier status are published for cardiac programs in an annual basis, and surgeon-specific results are presented on a rolling 3-year basis to accumulate meaningful data. Auditing of the New York State database is regularly conducted and involves the inspection of risk factor coding by utilization review agents from the Department of Health and the review of medical records by the Cardiac Services Program staff (Hannan et al. 2012).

A multiple logistic regression model is developed to calculate the expected mortality as a function of patient-specific risk factors. The institutional and provider-specific risk-adjusted mortality rates are calculated by multiplying the statewide mortality rate by the ratio of the observed-to-expected mortality rate ratios for a specific institution or provider. The 95 % confidence intervals are constructed to identify outliers in performance above and below the statewide mortality rate (Hannan et al. 2012).

#### 15.3.2.2 Northern New England Cardiovascular Disease Study Group

The Northern New England Cardiovascular Disease Study Group is a voluntary regional consortium that comprises six institutions in the northeast. Data is prospectively entered, and risk-adjusted outcomes are compared among institutions by using multivariable logistic regression models. This registry was initially created as a quality improvement initiative and determined that the difference in outcomes was not solely related to differences in the case mix of patients, but it may have resulted from differences in unmeasured quality of care variables among institutions. This registry has been used to explore quality improvement strategies by regular feedback of outcomes to the institutions, round-robin visits, and analysis of cause-specific mortality (O'Connor et al. 1991).

#### 15.3.2.3 Veterans Administration Database

Starting in 1987, the Veterans Administration Cardiac Surgery Programs were required to complete a datasheet including pre-, intra- and postoperative data. Since then, the Veterans Administration Cardiac Database was established as a mandatory clinical registry with data entered by independent nursing personnel and submitted in a biannual basis. Risk adjustment for operative mortality and morbidity is conducted through multivariable logistic regression, and O/E ratios are reported to each participating institution to prompt program review and institute measures for quality improvement. This database has the restriction of including only veterans and, thus, is limited primarily to elderly men (Grover et al. 2001).

#### 15.3.2.4 The Society of Thoracic Surgeons (STS) National Cardiac Database

Likewise to the New York State Department of Health, in 1987 the STS implemented a voluntary clinical database following the reporting of misleading raw mortality rates by the HCFA. The participation in the STS cardiac database has progressively increased and currently covers about 90 % of the cardiac surgery programs in the United States, representing the largest repository of clinical data in cardiac surgery. Designated data managers at an institutional level are responsible for the data entry, and intra- and inter-variable software-generated safe checks are established to ensure consistency across data fields. Missing data has been reduced to a minimum with less than 1 % in the majority of fields. The Duke Clinical Research Institute conducts a thorough data analysis and, through multivariable logistic regression, periodically creates risk models of operative mortality and standardized postoperative complications for CABG, mitral valve, and aortic valve surgery (Grover et al. 2001; Caceres et al. 2010).

## 15.4 Cardiac Surgery Risk Calculators

In an era of increasing emphasis on the quality of medical care, benchmarking of cardiac surgical outcomes is essential to allow proper risk-adjusted comparisons. Cardiac surgery risk calculators represent the cornerstone in the prediction of surgical outcomes, allowing for the comparison of observed-to-expected rates and risk-adjusted event rates. Furthermore, risk calculators are useful tools for proper patient selection and informed patient consent. Multiple risk calculators in cardiac surgery have been developed, but only two systems have been thoroughly validated:

### 15.4.1 The STS Cardiac Surgery Risk Calculator

The STS database has served as the source of patient data to develop the STS cardiac surgery risk calculators. Although initially intended for CABG, iterations have been created for aortic, mitral, or tricuspid valve surgery. Risk models are developed through multivariable logistic regression, and predicted risks are calculated for specific outcome variables. Initial calculators focused on operative mortality, but in 2003 specific risk calculators were developed for nine endpoints: operative mortality, permanent stroke, renal failure, prolonged ventilation, deep sternal wound infection, major morbidity or mortality, prolonged postoperative length of stay (> 14 days), and short postoperative length of stay (Shroyer et al. 2003). Definitions for each endpoint and the variables used for the calculations have been previously described by the STS (Shahian et al. 2009). The risk calculators for specific outcomes can be accessed at http://riskcalc.sts.org/STSWebRiskCalc273/.

### 15.4.2 The European System for Cardiac Operative Risk Evaluation (EuroSCORE)

The EuroSCORE was developed in 1999 from nearly 20,000 patients and 128 European centers as a simplified tool to calculate the operative mortality risk in cardiac surgery. The initial version was developed as an additive system with scores for each risk factor derived from coefficients obtained in a multivariable regression model (Roques et al. 1999). The total score was calculated as the sum of the scores of 17 participating variables, and it was correlated to a specific predicted mortality risk. In 2003 a second iteration was developed, the logistic EuroSCORE, as a multivariable logistic regression formula; similar to the additive system, coefficients were determined for each participating variable, and the categorical or continuous values of each variable were entered in a logistic regression formula that calculated the predicted mortality risk as described under 2.2 (Michel et al. 2003). The additive system seemed to underestimate the outcomes in high-risk patients (EuroSCORE >6) and the logistic EuroSCORE was developed to bridge this gap in the calculations. A third iteration was developed in 2011, the EuroSCORE II, as a logistic regression formula similar to the logistic EuroSCORE, with several modifications to the participating variables (http://www.euroscore.org/calc.html).

Unlike the STS risk calculator, the EuroSCORE does not include calculations for morbidity endpoints and does not provide separate risk models for each type of cardiac surgical procedure; however, it adjusts for the number of surgical interventions, e.g., CABG with mitral valve surgery counts as two procedures, CABG with mitral and tricuspid valve surgery counts as three procedures. The EuroSCORE risk calculator can be accessed at http://www.euroscore.org/

## 15.5 Limitations of Current Databases

Clinical databases have been successful in presenting early outcomes following cardiac surgery; however, longitudinal follow-up including midterm or long-term outcomes has been limited. At present, only early outcome data is available in clinical databases, while administrative databases, although with lower data accuracy, have the potential to retrieve long-term data through payer claims records. The difficulty to assign patient identifiers that could serve as relational links among databases has prevented the integration of early- and long-term outcome data. Likewise, the difficulty in merging clinical databases from different specialties has restricted the assessment of cardiac care outcomes to either surgical or medical modalities of treatment. An attempt to bridge this gap is in effect by standardizing the data definitions between the American College of Cardiology and the Society of Thoracic Surgeons databases.

## 15.6 Summary

The last two decades have witnessed the origin and expansion of a variety of multi-institutional registries, essential tools in the assessment of outcomes and the implementation of quality improvement initiatives. The analysis of risk-adjusted results has been useful in identifying institutions with outlier results and implementing specific strategies to address gaps in the quality of care. The data analysis of early outcomes in cardiac surgery has been satisfactory through clinical databases, but there are still limitations in assessing the continuity of cardiac care, necessary in the modeling of mid- and long-term outcomes. In the current landscape of scrutiny by consumers and payer organizations, quality improvement remains at the forefront agenda of organized medicine; thus, proper risk adjustment through reliable regional and nationwide registries is essential for the accurate assessment of the quality of cardiac care.

## References

Anderson RP (1994) First publications from the Society of Thoracic Surgeons National Database. Ann Thorac Surg 57:6–7

Bewick V, Cheek L, Ball J (2004) Statistics review 13: receiver operating characteristic curves. Crit Care 8:508–512

Bewick V, Cheek L, Ball J (2005) Statistics review 14: logistic regression. Crit Care 9:112–118

Caceres M, Braud RL, Garrett HE Jr (2010) A short history of the Society of Thoracic Surgeons national cardiac database: perceptions of a practicing surgeon. Ann Thorac Surg 89:332–339

Ellis H (2008) Florence Nightingale: creator of modern nursing and public health pioneer. J Perioper Pract 18:404–406

Grover FL, Shroyer AL, Hammermeister K, Edwards FH, Ferguson TB Jr, Dziuban SW Jr, Cleveland JC Jr, Clark RE, McDonald G (2001) A decade's experience with quality improvement in cardiac surgery using the Veterans Affairs and Society of Thoracic Surgeons national databases. Ann Surg 234:464–472

Hannan EL, Cozzens K, King SB III, Walford G, Shah NR (2012) The New York State cardiac registries: history, contributions, limitations, and lessons for future efforts to assess and publicly report healthcare outcomes. J Am Coll Cardiol 59:2309–2316

Hosmer DW, Lemeshow S (2000) Applied logistic regression, 2nd edn. Wiley, New York

Michel P, Roques F, Nashef SA, EuroSCORE Project Group (2003) Logistic or additive EuroSCORE for high-risk patients? Eur J Cardiothorac Surg 23:684–687

O'Connor GT, Plume SK, Olmstead EM, Coffin LH, Morton JR, Maloney CT, Nowicki ER, Tryzelaar JF, Hernandez F, Adrian L et al (1991) A regional prospective study of in-hospital mortality associated with coronary artery bypass grafting. The Northern New England Cardiovascular Disease Study Group. JAMA 266:803–809

Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR (1996) A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 49:1373–1379

Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, Cortina J, David M, Faichney A, Gabrielle F, Gams E, Harjula A, Jones MT, Pintor PP, Salamon R, Thulin L (1999) Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg 15:816–822

Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand S-LT, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP (2009) The Society of Thoracic Surgeons 2008 cardiac surgery risk models: Part 1. Coronary artery bypass grafting surgery. Ann Thorac Surg 88:2–22

Shroyer LW, Coombs LP, Peterson ED, Eiken MC, Delong ER, Chen AY, Ferguson TB, Grover FL (2003) The Society of Thoracic Surgeons: 30-day operative mortality and morbidity risk models. Ann Thorac Surg 75:1856–1864

Weiss ES, Chang DD, Joyce DL, Nwakanma LU, Yuh DD (2008) Optimal timing of coronary artery bypass after acute myocardial infarction: a review of California discharge data. J Thorac Cardiovasc Surg 135:503–511

Welke KF, Peterson ED, Vaughan-Sarrazin MS, O'Brien SM, Rosenthal GE, Shook GJ, Dokholyan RS, Haan CK, Ferguson TB Jr (2007) Comparison of cardiac surgery volumes and mortality rates between the Society of Thoracic Surgeons and Medicare databases from 1993 through 2001. Ann Thorac Surg 84:1538–1546

# Index



A. Dabbagh et al. (eds.), *Postoperative Critical Care for Cardiac Surgical Patients*,
DOI 10.1007/978-3-642-40418-4, © Springer-Verlag Berlin Heidelberg 2014