Advanced Hemodynamic Monitoring: Basics and New Horizons

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Preface

In 2019, we decided to prepare a book titled "Advanced Hemodynamic Monitoring: Basics and New Horizons." The idea of a new book in the field of hemodynamic monitoring, where several comprehensive manuals and guidelines have already been published during the last years, was inspired by the necessity to describe how to use advanced hemodynamic monitoring in perioperative and intensive care medicine for both specialists and residents in a practical, concise, and informative way. Thus, this book reflects the increasing knowledge that anesthesiologists and intensivists need to have when using modern hemodynamic monitoring in daily clinical practice.

The book chapters are written by internationally well-known experts for hemodynamic monitoring and management and cover physiological background; basic skills of invasive, minimally invasive, and noninvasive methods; algorithms and treatment strategies for goal-directed hemodynamic therapy in perioperative and intensive care medicine. All sections of this book use a learning-oriented style, have boxes with practical advices and keynotes, and are illustrated with tables and figures summarizing the main content. The book covers all currently available hemodynamic monitoring methods including pragmatic step-by-step instructions for their practical use as well as potential future directions and developments.

We believe that our book will help readers both discover the opportunities of monitoring to diagnose alterations in cardiovascular dynamics and individualize hemodynamic management. We would like to thank all the authors for their expertise, work, and contribution to the chapters. The editors are deeply grateful to Prof. Valery Likhvantsev for the review of our book during the preparation process.

Finally, we would acknowledge help and assistance of the editorial and production staff at Springer Company, especially Sasirekka Nijanthan, Project Coordinator, Vignesh Manohar, Project Manager, and Andrea Ridolfi, Editor.

We hope that you find this book interesting and useful for clinical practice.

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Introduction

Cardiovascular disorders are frequent in patients having surgery and in critically ill patients. Hemodynamic monitoring thus is a cornerstone of multimodal patient monitoring both in the operation room and in the intensive care unit (ICU). Continued technological developments now allow monitoring of various hemodynamic variables reflecting global cardiovascular dynamics and the microcirculation.

Modern anesthesia and intensive care medicine require an in-depth understanding of invasive and noninvasive hemodynamic monitoring methods. Thus, our book starts from the basic cardiovascular variables including systemic and pulmonary arterial pressures and central venous pressure. The physiological background and clinical measurement techniques of pressure monitoring are described in Chaps. 1–4.

Besides blood pressure, blood flow plays a pivotal role in organ perfusion. Cardiac output can be measured by numerous different methods including indicator dilution, pulse wave analysis, ultrasound, and bioimpedance (Chaps. 5–11).

Volumetric cardiac preload variables such as global end-diastolic volume and extravascular lung water reflecting pulmonary hydration are discussed in Chaps. 12–14.

Hemodynamic management also includes predicting and monitoring the cardiovascular response to fluid therapy. So-called dynamic variables of fluid responsiveness based on cardiorespiratory interactions as well as functional hemodynamic tests to predict fluid responsiveness are specified in Chaps. 15–17.

The cardiovascular system transports blood to meet the metabolic demands of tissues and cells. Most current technologies enable optimization of oxygen delivery, but not oxygen consumption. Therefore, metabolic and microcirculation monitoring (Chaps. 18–20) has the potential to allow a deeper understanding of the mechanisms of tissue dysoxia and to discover new therapeutic pathways.

Hemodynamic management (*i.e.,* the optimization of hemodynamic variables based on advanced hemodynamic monitoring) has the ultimate goal to improve the postoperative outcome of patient having surgery (Chaps. 21 and 22) and critically ill patients with life-threatening conditions, including different types of circulatory shock (Chaps. 23–27).

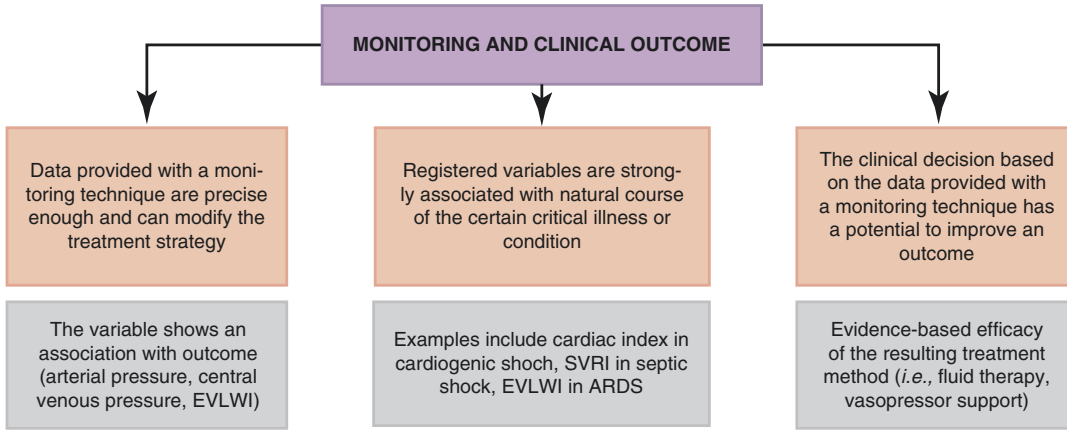

Fig. 1 The association between hemodynamic monitoring and clinical outcome. *EVLWI* extravascular lung water index, *SVRI* systemic vascular resistance index, *ARDS* acute respiratory distress syndrome

Innovative monitoring methods and approaches including new sensor technologies, close-loop hemodynamic management, and predictive analytics based on artificial intelligence and machine learning are discussed in Chaps. 27–29.

An ideal modern hemodynamic monitoring method would need to provide values of hemodynamic variables with high accuracy, precision, and response time; allow straightforward interpretation and identification of hemodynamic profiles; be operator independent; be associated with a low risk of complications; be cost-effective; and be able to trigger therapeutic interventions. Unfortunately, the ideal hemodynamic monitoring technique does not exist, but advanced hemodynamic monitoring enables individualized hemodynamic management that can eventually result in improved patient outcome (Fig. 1).

Contents

Part V Monitoring of Microcirculation

Part VI Hemodynamic Monitoring and Therapy in Perioperative Medicine

Part VIII Future of Hemodynamic Monitoring and Therapy

Part IX Conclusions

Part I

Measurement of Pressures

Pressure: Physiological Background

1

Konstantin M. Lebedinskii

Contents

The goal of this chapter is to underline the fundamental role of pressure and its gradients in relation to other variables, describing global circulation and local perfusion. Later chapters focus on systemic arterial, venous, and pulmonary blood pressure; thus, here we discuss only considerations that are common for all these parameters and their interactions.

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1.1 Basic Physics and Biomechanics

Pressure (P) is defined as the force (F) given at the area (S) of its action: $P = F/S$. *Hydrostatic pressure* is proportional to the fluid column height above the point of measurement h, fluid density ρ, and gravity acceleration g (9.8 $m \cdot s^{-2}$): $P = g \cdot \rho \cdot h$. Blaise Pascal's law (1647) postulates that any point of resting fluid pressure remains constant and distributes equally in all directions. The only limitation is continuity of homogenous fluid media—for example, in communicating vessels such as the vascular system [1]. Rising to the tissue or organ level, anatomical barriers can delimit compartments with different pressures, and therefore undergo the so-called *transmural pressure*. Thus, Pascal's law is not applicable to any heterogeneous structures—neither micro

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(from the cellular level to the tissue one) nor macro (thorax or abdominal viscera).

In hydrodynamics, *pressure difference* (ΔP) is a measure of flow driving energy. In electrodynamics *tension* (or *electric potential difference*) has the same meaning, "pumping" a current of charged particles through the circuit. This analogy is useful in understanding blood pressure physics and physiology.

Georg Ohm's law (1826) stated that for any part of a direct current circuit, current I is directly proportional to the tension U applied and inversely proportional to the resistance R: $I = U/R$. Initially derived from the description of heat conductivity, Ohm's law can also be applied to gas or liquid flows by changing current to flow Q and tension to pressure difference ΔP whereas hydrodynamic resistance R remains electric resistance equivalent. Vascular resistance is calculated as $R = \Delta P/Q$, using the difference between mean arterial and central venous pressures for systemic circulation and the difference between mean and occlusion pulmonary artery pressures for pulmonary circulation, although the denominator remains the same, *i.e.,* cardiac output. Thus, for the given pressure difference tissue blood flow rises proportionally to the local vascular resistance decrease [2], although widespread vasodilation requires compensation with cardiac output rising to prevent a systemic arterial pressure drop (for example, distributive shock) [3].

In the electric circuit, power consumption (W) can be expressed as $W = U{\cdot}I = I^2{\cdot}R$, the same equation is used for any pump power: $W = \Delta P{\cdot}Q$. Assuming $R = \Delta P/Q$ and therefore $\Delta P = Q{\cdot}R$, we get the same $W = Q^2{\cdot}R$. It means that for given U (or ΔP), W is more dependent upon I (*i.e., Q*) rather than R: for example, in the case of a short circuit, a drop in R leads to a rise in I producing a lot of heat ($I^2{\cdot}R{\cdot}t$, according to James Joule's law, 1841). In the circulation, overall power is primarily limited to the heart's ability to increase cardiac output. Thus, even despite a decrease in pressure, the drop in systemic R always leads to an increase in flow and power, excluding patients with the so-called "fixed cardiac output" (for example, severe aortic stenosis) [3].

1.2 Pressure Units

The pressure measurement unit in SI is Pascal (Pa), which is 1 N of orthogonal force distributed per 1 m^2 of surface. Numerous attempts to implement kPa in everyday medical practice have failed owing to decades of the habit of suing traditional units, originating from early measurement instrumentation. The mercury barometer invented by Evangelista Torricelli (1644), and later the water column manometer, were the most useful tools for measuring pressure, despite aneroid barometers, which have been known since 1844. Therefore, 1 mm of mercury column (1 mmHg = 133.322 Pa, sometimes called Torricelli, Torr) is much more common worldwide than Pa as a pressure unit for both hemodynamic and blood gas analysis measurements, whereas 1 cm of water column (1 cm H_2O = 98.0665 Pa) is still used in some cases for central venous pressure (CVP) and intra-abdominal pressure measurements. Its close approximation, 1 mbar = 100 Pa, is more useful in respiratory mechanics. Finally, since May 2019, further use of mmHg is officially not recommended [4].

1.3 Pressure Measurement

Measurement means *comparison* with another value. The most common measurement of pressure in medicine, *gauge pressure*, is measured in relation to current atmospheric pressure taken as zero level. *Absolute pressure* is measured in relation to a perfect vacuum: it is a sum of gauge pressure and actual atmospheric pressure. Speaking generally, *relative pressure* represents the difference between two pressure values. Although ΔP value is crucial for organ perfusion, during hemodynamic monitoring we never physically measure this variable directly but observe it as derived from calculations performed by the

monitor: for example, cerebral perfusion pressure is the difference between mean arterial and intracranial pressure [5].

Up till now, a transparent tube water manometer has been easily used to measure central venous or intra-abdominal pressure. Common non-invasive sphygmomanometers are useless for continuous pressure measurement and graphic representation. For these purposes electric pressure transducers, transforming pressure into analogous electric signal, were implemented in the 1970s. All of them are based on a flexible element, usually the diaphragm, undergoing certain transmural pressure—the difference between pressure to be measured and reference (zero) one. Deformation of the membrane leads to a change in sensor chain resistance, capacity or induces current by means of a ferromagnetic core movement within the coil [6]. Analog-to-digital conversion transformed all further data processing (filtration, amplification, recording, graphic representation, statistical analysis, automated interpretation, *etc.*) into digital format [7]. Monitors with modern disposable transducers usually provide accuracy of around ±1.5% of the scale [8].

According to Pascal's law, while measuring pressures inside communicating vessels, we always need to be sure that a proper zero level was chosen and reliably established. It seems physiological to place zero at the horizontal level, where exact pressure is applied [9]. Thus, central venous pressure is usually measured in relation to the right atrium level, intra-abdominal pressure—in the urinary bladder in a horizontal supine position in relation to the symphysis level, *etc.* For these relatively low pressures, including pulmonary artery pressures, both stable proper levelling and reliable transducer zeroing are essential for accurate measurement [10]. Arterial pressures, being much higher than venous or pulmonary bed values, are less sensitive to zero choice and maintenance; however, at the bedside it is convenient to place the bench with all the pressure sensors at the same level as the right atrium ("circulation zero level", in supine position—the lower margin of the *m. pectoralis major* at the armpit) [11, 12].

Practical Advice

Zero drift of the pressure transducer is the most frequent cause of significant deviations from real values of venous and pulmonary artery pressures, especially if the curve shape seen on the screen remains appropriate.

1.4 Pressure Curves and Values

Irrespective of the point and method of measurement, maximum arterial pressure (AP) during the cardiac cycle represents the systolic value (SAP), the nadir of the pressure oscillation represents the diastolic one (DAP), whereas the difference between the two is called pulse arterial pressure (APpulse; Fig. 1.1B; Table 1.1). Pulse arterial pressure is the physical quantity we feel as a pulse while palpating the artery (*pulse filling*).

Mean arterial pressure (MAP) can be defined as the average pressure value throughout the arterial pulse pressure cycle [15]. The graphic representation of the mean value on the arterial pressure plot is a horizontal line; the total area under the line and above the curve is exactly equal to the total area above the line and under the curve (Fig. 1.1A, B). A physical model of MAP can be presented as arterial pressure, totally damped by means of very long fluid-filled tubing between the artery and the pressure sensor: as the circuit remains closed but the long line eliminates fluctuations, the sensor measures mean pressure. Therefore, MAP is a constant pressure level, providing the large circuit with perfusion, equal to that provided by oscillating arterial pressure.

Both direct and oscillometric monitors do not calculate MAP from SAP and DAP but assess it directly *via* digital or analog procedures (see Chap. 2). Therefore, I have no idea why the myth about MAP calculation as a sum of DAP and one-third of APpulse [16] is so persistent. For a "normal" AP curve shape it often seems the case, but

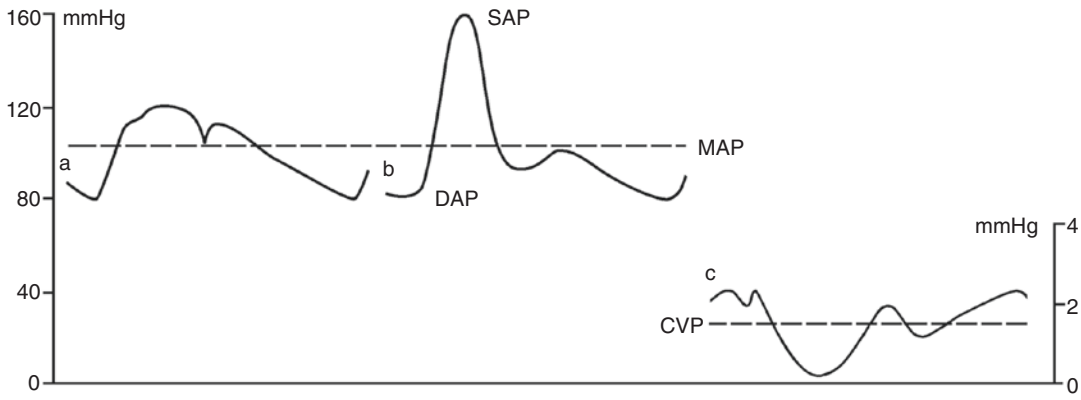

Fig. 1.1 Blood pressure curves in aortic root (a), arteria tibialis (b) and central vein (c). *SAP* systolic arterial pressure, *MAP* mean arterial pressure, *DAP* diastolic arterial pressure, *CVP* central venous pressure

Table 1.1 Normal ranges of different cardiovascular pressure values [13, 14]

Parameter, abbreviation	Measurement or calculation technique	Normal range, mmHg
Left atrium pressure	Direct (invasive) measurement	0–17
Left ventricle systolic pressure		100–140
Left ventricle diastolic pressure		3–12
SAP	Direct (invasive) or non-invasive measurement	115–139
DAP		75–89
MAP		70–105
APpulse	Calculation as difference SAP—DAP	40–60
Right atrium pressure	Direct measurement *via* Swan–Ganz catheter	0–7
Right ventricle systolic pressure		15–30
Right ventricle diastolic pressure		3–8
PAPsys		15–30
PAPdiast		4–15
PAPmean	Direct measurement *via* Swan–Ganz catheter; echocardiographic assessment based on tricuspid regurgitation	10–20
PAOP	Direct measurement *via* Swan–Ganz catheter	6–12
CVP	Direct measurement *via* central venous line	3–9

SAP systolic arterial pressure, *DAP* diastolic arterial pressure, *MAP* mean arterial pressure, *APpulse* pulse arterial pressure, *PAPsys* systolic pulmonary arterial pressure, *PAPdiast* diastolic pulmonary arterial pressure, *PAPmean* mean pulmonary artery pressure, *PAOP* pulmonary artery occlusion pressure, *CVP* central venous pressure

any changes in the wave pulse-to-period ratio result in evident errors (Fig. 1.1).

While moving from the aortic root to the peripheral arteries, pulse pressure rises owing to both an increase in SAP and a decrease in DAP (Fig. 1.2). An obvious explanation is that pulse wave spreads throughout the arterial branches, which are increasingly narrow and stiffer than the aorta [17]. In contrast to the rise in SAP, MAP remains almost unchanged within large arteries and then gradually decreases owing to a decline in both DAP and the dicrotic notch.

Despite its common description with a single mean value, CVP also oscillates because of multiple factors, including the "thoracic pump," the "muscle pump," and—even in the resting body on a breath hold!—the function of the heart chambers and valves (Fig. 1.1C). Although amplitudes of these oscillations with heart rate and breath rate frequencies are incomparable with an arterial pressure sweep, the venous pressure curve can also be analyzed.

The only part of the circulation where the heart rate cannot be directly seen from pressure and flow oscillations are the systemic capillaries. This does not mean, however, that the capillary non-pulsatile flow is steady: it oscillates owing to the vascular branching, nonlinear blood rheology, the passage of leucocytes, *etc.* [18]. The distal frontier of pulse flow oscillations can be seen at the bedside using a pulse oximeter, which analyzes pulsatile flow only, and therefore normally does not detect desaturation throughout the capillaries. However, nitrate infusion or a rare change

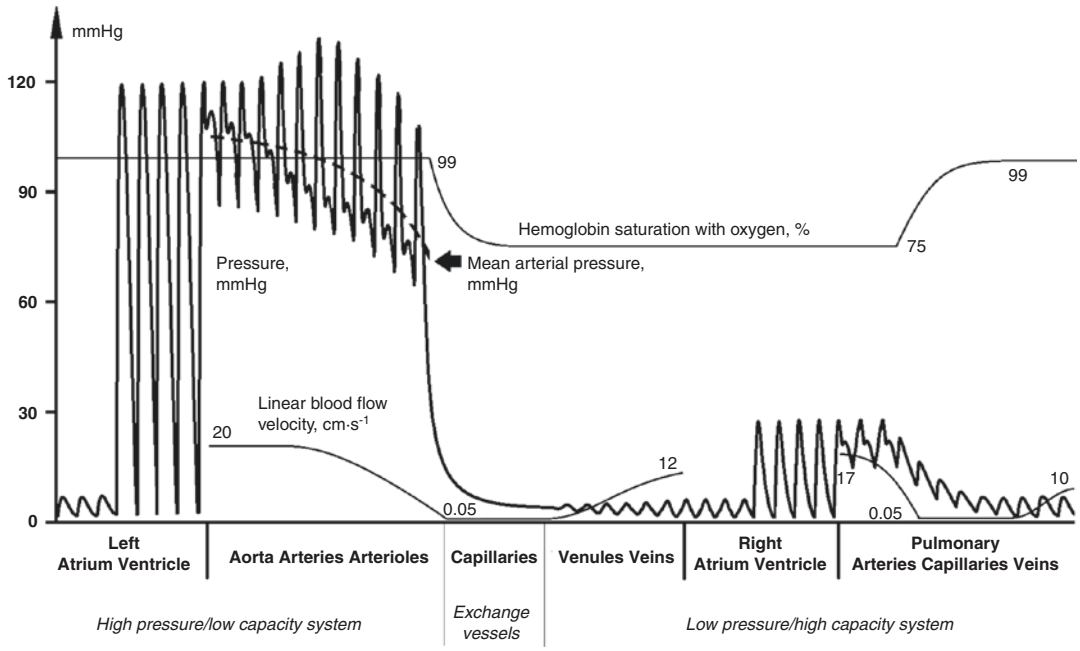

Fig. 1.2 Blood pressure, average flow velocity, and hemoglobin saturation with oxygen in consecutive segments of circulation

of finger (not forgetting infrared LED!) decrease SpO_2 despite normal SaO_2 as vasodilation expands the pulsatile flow to the capillary bed [19]. Contrary to popular belief [20], a pulse oximeter *does not measure arterial saturation with oxygen*—it measures *pulsatile flow saturation* regardless of anatomical location! In Romance languages the name of the device is most clear—for example, *saturomètre de pouls* in French.

1.5 Blood Pressure, Cardiac Output, and Tissue Perfusion

Why do we need arterial pressure of 120/80 mmHg while normal hydrostatic pressure at the entrance of the capillary bed is only around 25–35 mmHg?

The first reason is that, similar to plumbing, the circulation should provide sufficient flow regardless of the height of the fluid pipes. Although normal arterial pressure in a 6-m giraffe is around 240/120 mmHg, my height of only 1.83 m means that in an upright position my brain is 1830 mm H_2O (or 135 mmHg) above my heels. I will be happy to have an inverse interrelation, although my 120/80 mmHg is maintaining brain perfusion despite body position. As tetrapods are less familiar with essential hypertension, evolutionary physiologists consider the latter our redemption for the fall of *Homo erectus* [21].

The second reason can be explained by coming back to an analogy with electricity: why isn't 12 or 24 V sufficient for home electrical sockets whereas they are enough for the onboard network of a car? Obviously, it is because at home we have both low- (25 W) and high-power (5 kW) electrical devices with high resistance, and the latter can not be "perfused" with a low voltage! In the body, we also have vascular beds with architectonically high resistance for blood flow, regardless of vascular tone—such as the kidney, with its glomerular filter, the portal systems of the abdominal viscera, hypophysis, gonads, placenta, *etc.* [22]. This is the main reason for the "technological minimum" of arterial pressure, under which adequate perfusion of these regions becomes physically impossible, despite the rise in cardiac output. In a normotonic patient, we consider this lower limit of MAP as 65 mmHg [23].

Although "organs do need blood flow rather than pressure" (Adolf Jarisch Jr., 1929), a certain

pressure gradient remains necessary for sufficient perfusion because of vascular resistance. For different organs, this ΔP value may be presented as the difference between MAP and CVP (skin, fat, resting skeletal muscle), interstitial pressure (organs placed within rigid anatomical compartments—brain, kidney, working muscle), regional venous pressure (portal—for stomach and gut), or even the difference between two venous pressures (portocaval gradient for liver perfusion from the *v. portae*) [5, 24]. Pulmonary regional flow distribution depends upon the intra-alveolar and interstitial pressures and the position of the lungs in relation to the gravity vector, building four horizontal zones one above the other, as revealed by John B. West (1964) and Mike (J.M.B.) Hughes et al. (1968) (cited in Hall [25]).

Blood flow control *via* local vascular resistance is the basic mechanism of so-called *autoregulation*—the ability to keep the organ perfusion level optimally stable despite arterial pressure changes within certain limits. Beyond these limits blood flow becomes pressure dependent, provoking a risk of organ damage. Cerebral blood flow autoregulation, the best learned physiological model, involves myogenic, neurogenic, and local metabolic feedback loops [26], which seem to be impaired in hypertonic patients. The normal MAP range of cerebral perfusion autoregulation of between approximately 75 and 150 mmHg is shifted to the right and more or less narrowed in such subjects [27].

Last but not least, pressure is one of the main factors regulating tissue fluid exchange. According to the classic Ernest H. Starling theory (1896), persisting until the latest textbooks of physiology [25, 28, 29], hydrostatic pressure downslope throughout the capillaries transforms fluid filtration at the arteriolar end into its resorption at the venular pole of the capillary. However, recent revision of transcapillary fluid exchange based on glycocalyx role recognition, suddenly revealed that we do not have any direct evidence of fluid resorption in the capillaries [30, 31]. Therefore, not only 10% but the whole 100% of fluid, filtered in the capillaries, returns to the circulation *via* the lymphatic system [31].

1.6 Conclusion

Although the goal and obvious "gold standard" of hemodynamic stability is blood flow through each organ/tissue (milliliters per 100 g of tissue per minute), the inaccessibility of this value in clinical settings until now forced physicians to use gross substitutes, of which blood pressure became available first, whereas cardiac output did not become available until almost a century later. Their interaction is rather complex: although cardiac output is the cornerstone of global perfusion safety, it becomes futile when MAP is below the critical level. In turn, normal systemic pressure under low cardiac output is achievable only with extreme vasoconstriction, and thus certainly indicates organ hypoperfusion.

Keynotes

- Hydrostatic pressure follows Pascal's law and therefore depends upon body height above the level of measurement, whereas the pressure difference within the same vascular system describes flow energy.
- For an particular organ, the perfusion pressure gradient may depend upon not only systemic venous pressure but also interstitial pressure inside the rigid organ (tissue) capsule, whereas for the pulmonary bed it also depends upon the level in the height range of the lungs.
- A critical level of arterial pressure is determined by the organs, where vascular resistance is "structurally high" regardless of local or systemic vascular tone.
- Transducers, especially for central venous and pulmonary artery pressures, should be thoroughly zeroed at the level of the right atrium, calibrated, and perfectly fixed to avoid unintended zero drift.
- The difference between regional and systemic vasodilation is similar to that between regional and federal budgets. Regional vasodilation provides perfect local perfusion, whereas systemic vasodilation leads to a global hemodynamic default.

Conflict of Interest None.

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Systemic Arterial Pressure

2

Konstantin M. Lebedinskii and Yulia B. Mikhaleva

Contents

The goal of this chapter is to discuss the clinical aspects of systemic arterial blood pressure measurement, monitoring, and management in the operating room, emergency, and intensive care settings.

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2.1 Physiological Considerations

A review of the general blood pressure physiology is described in detail in Chap. 1. Here, we would like to highlight few points, namely those specific to systemic arterial pressure and important from a practical point of view.

The value of arterial blood pressure depends upon the point of measurement, and for some extent systolic arterial pressure (SAP) in large systemic arteries increases along the distance from the left ventricle, whereas diastolic arterial pressure (DAP) decreases slightly (Figs. 1.1 and 1.2; Chap. 1). Certainly, as blood still flows unidirectionally, mean arterial pressure (MAP) in the peripheral arteries is lower than in the aorta. However, why is pulse pressure (PP = SAP − DAP) in the *aa. radialis* or *tibialis* actually higher in

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comparison with the aortic root? The best example of the explanation is probably the so-called tsunami wave: in the open ocean one can see (sometimes, but sometimes one even cannot) a very long wave of only 1 m in height, but when coming into shallow water and narrowness it becomes 30 m high. Blood flow in the arterial part of vascular bed is an oscillatory process; therefore, wave dynamics is completely applicable to the explanation [1].

It was shown that PP is proportional to stroke volume (SV). In turn, the so-called pulse wave transit time (PWTT) between the peak of the R wave on ECG and the beginning of the local pulse wave is linked with local PP by linear function:

$$\mathrm{PP} = \mathrm{SV} / K = \alpha \times \mathrm{PWTT} + \beta, \qquad (2.1)$$

where K is the calibration coefficient for pulse wave contour analysis, α—experimental constant and β is calculated based on PP and α values [2]. Equation (2.1), giving the possibility of calculating SV from PP and PWTT, is a basis for the so-called estimated continuous cardiac output of non-invasive monitoring [3].

There is a common belief that DAP is determined mainly by systemic vascular resistance, whereas PP is an indicator of SV and, to a lesser extent, aortic compliance [4]. Although now we do have many reservations and exceptions (for example, abnormally low DAP in patients with sound aortic valve insufficiency, *etc.*), the abovementioned simple rule may be specifically applied to the dynamic evaluation. Speaking rigorously, all four pressure values are individual for each cardiac cycle and are related primarily to the fluctuations of SV. Under the condition of stable cardiac rhythm, this pressure variability can be used for preload assessment in mechanically ventilated patients (see Chap. 15).

As for any other physiological variables, interpretation of the systemic arterial pressure values is based with certain limits on normal range, and extremes of very low and very high values, requiring immediate intervention. This physiological scale for arterial pressure seems to be associated with organ/tissue perfusion autoregulation ranges, which means an ability to maintain stable blood flow (in milliliters per·100 g of tissue^{-1}·min^{-1}) despite changes in MAP level [5]. These autoregulation limits are known and can be applied not for single organ or tissue requirements but rather for most critical thresholds from the perfusion point of view. For the brain, normal autoregulation is preserved within the MAP range of approximately 50–150 mmHg whereas for the kidney it is between 75 and 170 mmHg [4]. However, in chronic hypertensive patients, these limits of flow pressure independence drift to the right (Fig. 2.1), and in a clinical setting MAP <65 mmHg persisting for 10 min is already associated with increased risk for ischemic stroke [6]. Therefore, the so-called "critical level" of systemic arterial pressure, which can be defined as MAP (or sometimes SAP) value, below which the perfusion of an organ (first of all, the kidney with its "structurally high" vascular resistance) becomes inadequate, seems to be individual and depends mainly upon the usual systemic arterial pressure level for an individual patient [7]. Whether such subcritical hypotension will lead to the ischemic organ damage or remain at the level of a critical incident depends primarily upon its extent and the time of exposure. In the retrospective study of 5127 patients, acute kidney injury (AKI) was associated with MAP <60 mmHg for 11–20 min, whereas 10 min of MAP <55 mmHg were sufficient for the same effect within 2 days of non-cardiac surgery [8]. Another study confirmed exactly the same for AKI risk thresholds for the population younger

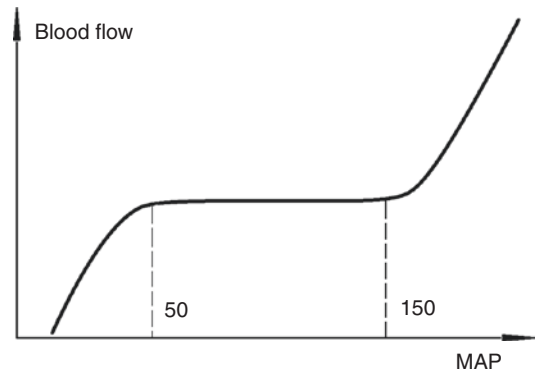

Fig. 2.1 Blood flow autoregulation phenomenon. *MAP* mean arterial pressure

than 60 years old [9]. A clear inverse relationship between hypotension depth and dangerous time exposure was also shown for ischemic stroke: in a cohort of 7457 patients who underwent cardiac surgery with cardiopulmonary bypass, a 10-min episode of MAP between 55 and 64 mmHg was associated with a 13% increased risk, whereas the same period of MAP below 55 mmHg led to a 16% increased risk of stroke [6].

Finally, systemic arterial pressure values are used for systemic vascular resistance (SVR) calculation as the main numerator constituent of the $\Delta P/Q$ fraction. Although for monitoring purposes, vascular resistance is a calculated parameter derived from pressure and flow values, in circulation biomechanics, flow and pressure are, *vice versa*, determined by the interrelation between cardiac contractility and vascular resistance—both total and regional [10]. At the same time, from an informatics point of view, a calculated figure of SVR does not give us any additional independent data besides that given by the difference in driving pressure and the cardiac output. For example, if cardiac output is close to the upper reference limit whereas MAP is closer to the lower one, the SVR could appear to be below the lower reference limit, but… do we have any reason to consider it abnormal?

2.2 Evolution of Measurement Methods

Although William Harvey (1578–1657), who discovered the circulation, used "tight and weak bandages" to compress arteries and veins separately, it was British priest, Rev. Stephen Hales (1677–1761), who measured blood pressure in the living creature for the first time: in 1727, he inserted a short brass cannula connected by a glass pipe into the carotid artery of a dying old mare. In 1876, Austro-Hungarian physician Samuel Siegfried Karl Ritter von Basch (1837–1905) invented a blood pressure gauge, based on gradual radial artery compression with a rubber bulb at the bottom of a mercury column barometer.

In 1896, Roman pediatrician Scipione Riva-Rocci used a common bike tire camera (of only 5 cm in width) with the same barometer to determine systolic pressure at the moment of pulse disappearance. In 1901, German physiologist Friedrich Daniel von Recklinghausen recognized significant overestimation of blood pressure because of too narrow cuffs and changed the standard width to 13 cm [11]. Nikolay S. Korotkoff (1874–1920), a surgeon from the military medical academy in St. Petersburg, while preparing his doctoral thesis, used a sphygmomanometer with Riva-Rocci's cuff to stop the flow into arteriovenous aneurisms, which he confirmed by auscultation. The possibility of using turbulent flow noises for bloodless determination of both SAP and DAP values, which was suddenly discovered in 1905, was immediately developed by the famous internist Mikhail V. Yanovskii (1854–1927) and his school.

In 1931, F.D. von Recklinghausen invented the so-called oscillatory method based on cuff pressure oscillations amplitude changes during gradual pressure release; now, it is used most widely as an NIBP monitoring technique. Between 1947 and 1949, Lysle H. Peterson, Robert D. Dripps, Kenneth F. Eather, and George C. Risman from Philadelphia published several papers on direct arterial pressure measurement *via* a plastic intravascular catheter. Between 1967 and 1973, Czech physiologist Jan Peňáz proposed and patented the first principle of continuous non-invasive arterial pressure monitoring—the so-called vascular unloading (or volume clamp) technique.

As for blood pressure registration during surgery, it was the famous Harvey W. Cushing (1869–1939) who introduced in 1895 anesthesia records ("ether chart") with temperature, heart, and respiratory rates; in 1901, on visiting the Ospedale di San Matteo (Padua), where Riva-Rocci's sphygmomanometer had already become standard, he added blood pressure to the chart [12].

2.3 Oscillatory Method

This technology, known as common NIBP (non-invasive blood pressure) monitoring, is most useful all over the world and has already been included in all the anesthesia safety standards for several decades. It is based on registration and analysis of pressure oscillations in the pneumatic

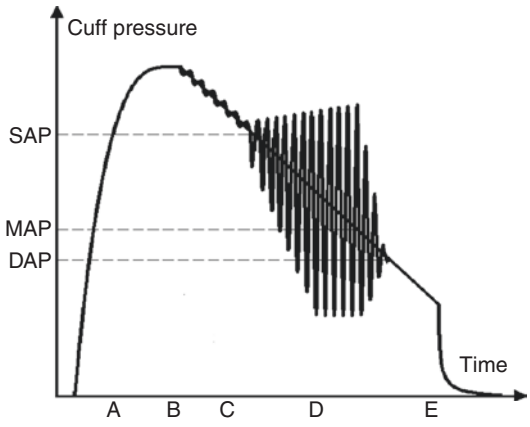

Fig. 2.2 Principle of oscillatory method of arterial pressure measurement (see text for abbreviations and designations). *DAP* diastolic arterial pressure, *MAP* mean arterial pressure, *SAP* systolic arterial pressure

cuff placed around the extremity segment as the pressure in the cuff gradually decreases. The principle of measurement is illustrated in Fig. 2.2.

During the first phase A, a compressor (or pneumatic valve) increases the pressure in the cuff above the expected level of SAP. During phase B, pressure stabilizes, then the release valve opens and the cuff pressure begins to deflate at a rate of around 2 mmHg·s^{-1} (phase C). A pressure sensor registers weak oscillations from the very beginning because until the cuff pressure exceeds SAP, the artery "pokes" into the cuff from above. When the cuff pressure drops to the level of SAP, the pulse wave penetrates under the cuff and thus the contact spot between the cuff and the artery rises rapidly, increasing the amplitude of pressure oscillations (phase D). Mean cuff pressure, which can be obtained by the damping of mechanical or digital oscillations, reflects SAP at the moment of the beginning of the amplitude rise. When the amplitude reaches its maximal value, the mean cuff pressure reflects MAP and, finally, the moment of oscillation disappearance gives a value of DAP. During the final phase E, the pressure drops to zero.

Despite their similarity at first sight, the physical difference between Korotkoff's method and the oscillatory technique is related to the frequency range of audible sounds (>20 Hz) and the heart rate (≈1–2 Hz) respectively. Thus, although providing the anesthesiologist with free time and hands, the oscillatory method is less protected from noise: in the case of any doubts or monitor faults we immediately return to "manual" (or, to be more precise, binaural) measurement. When the problem persists, DAP monitoring is indicated if possible.

Error sources and possible adverse events of "cuff technologies" are presented in Table 2.1. The most important technical rules to avoid errors and artifacts are (1) proper cuff size (its width should be 20–40% of the limb circumference), (2) proper cuff placement (the inlet of pneumatic tubing should be directly over the most palpable artery), and (3) proper pressure relief rate (around 2 mmHg per second) [4].

Practical Advice

To avoid inadvertent tourniquet ischemia, place the pulse oximeter sensor to the finger of the arm with the NIBP cuff. It also gives you the possibility of checking systolic arterial pressure value, at the same time looking at the current figures of decreasing cuff pressure and the plethysmography curve on the monitor screen.

2.4 Invasive Arterial Pressure Monitoring

Direct pressure measurement is the obvious "gold standard", as its accuracy and precision depend only upon the properties of the measuring system, consisting of intra-arterial catheter, pressure sensor (transducer), digital monitor, pressurized flushing bag, stopcock, and connecting tubing.

As invasive pressure monitoring presumes arterial cannulation, its indications consist of two parts: (1) indications for direct pressure monitoring and (2) indications for frequent arterial blood sampling [13]. The first list includes existing or expected hemodynamic disturbances (shock, resistance to initial therapy, huge volume losses and their replacement, intracranial surgery, severe

Table 2.1 Sources of errors and adverse events of non-invasive arterial pressure measurement and monitoring [17]

Cause of error, artifact or adverse event	Error direction, result	Preventive measures
1. Cuff is too narrow (<20% of the limb circumference)	Value overestimation	If a commonly used cuff is wrapped with tension or a large overlap, change the segment of the limb (forearm, thigh) or take a cuff of a different width
2. Cuff is too wide (>40% of the limb circumference)	Value underestimation	
3. Cuff pressure relief is too quick (>3 mmHg·s^{-1})	Value underestimation	Maintain the optimal cuff pressure release rate, not allowing it to be exceeded
4. Rigid tissue under the cuff (edema, shivering)	Value overestimation	Change the cuff placement, treat shivering, measure "manually"
5. Pressure is very low (SAP <60–70 mmHg)	Oscillatory method overestimates values	Find and treat the cause, turn to direct (invasive) monitoring, if possible
6. Pressure is very high (SAP >180–200 mmHg)	Oscillatory method underestimates values	
7. Shivering	Automatic measurement errors	Shivering prevention and treatment, "manual" pressure measurement (see point 4)
8. The inlet of the pneumatic tubing into the cuff is located far from the projection of the artery onto the skin	Oscillatory measurement impossibility	Place pneumatic tubing inlet exactly over the artery
9. The surgeon's belly or the assistant's buttocks lie on the cuff	Inability to measure or gross bidirectional errors	Think over the cuff placement in advance or… admonish colleagues throughout the surgery!
10. Compressor cycling in continuous mode due to measurement errors	Limb ischemia, compartment syndrome, thrombophlebitis, *n. ulnaris* paresthesia	Listen to the sounds of the compressor and manually interrupt measurements if necessary
11. Failure of the cuff pressure relief valve or accidental activation of static mode		Place the pulse oximeter sensor on the same limb as the cuff

SAP systolic arterial pressure

trauma, sound cardiovascular disorders or cardiac arrest, controlled hypotension or hypothermia), cardiac and/or major vascular surgery, and the inability to measure arterial pressure non-invasively (morbid obesity). The second group of indications includes clinical situations, when we need to monitor real-time blood gases, acid-base state, electrolytes or glucose levels, and blood coagulation.

As for the contraindications, all the absolute ones relate only to the site of catheterization—local skin and vascular lesions, collateral blood supply failure, *etc.,* while all the systemic states and diseases, making catheterization more risky, can be interpreted as only relative contraindications as the necessity for arterial cannulation is often absolute [14].

Choice of the artery for cannulation is usually based on technical convenience, as (1) the limb segment with the catheter should be easily immobilized and (2) all the pieces and especially connections of the hydraulic part of the monitoring system should be completely visible for the personnel at any moment [15]. Invisible system disconnection under the blanket for even 5 min could be fatal. Thus, the radial artery in the most popular choice, whereas the femoral artery is also often used, despite its proximity to the sources of infective media [16].

Practical Advice

To avoid unnoticed disconnection, all the parts and connections of the direct arterial line—from catheter entry under the skin to the pressurized flushing bag—should be permanently visible by the personnel.

Each exact monitoring system is characterized by its individual natural frequency f_c and damping coefficient ζ. Because during monitoring the liquid column in the measuring system undergoes forced fluctuations under the influence of pressure fluctuations in the artery, when f_c is equal or multiple of heart rate, a resonance becomes possible with an increase in the amplitude of fluctuations and, accordingly, an overestimation of the systolic blood pressure and an underestimation of the diastolic blood pressure. As for the damping coefficient ζ, its values range from 0 (the system does not dampen oscillations at all) to 1 (the system totally dampens oscillations and thus shows a horizontal line of MAP level). When ζ is too low, the system can magnify the amplitude of oscillations as heart rate (HR) increases, whereas too high a ζ value leads to a "rounded" curve with compressed amplitude. To avoid all these phenomena f_c should be not less than 10 Hz, optimally—between 10 and 20 Hz, whereas optimal ζ seems to be around 0.4–0.6 [13].

Standard check-up procedure for pressure monitoring system is known as "pop-test" and illustrated in Fig. 2.3. To provide the test, based on a single high pressure impulse from the flushing bag, one should give a short high-pressure surge with quick closure of the flushing stopcock.

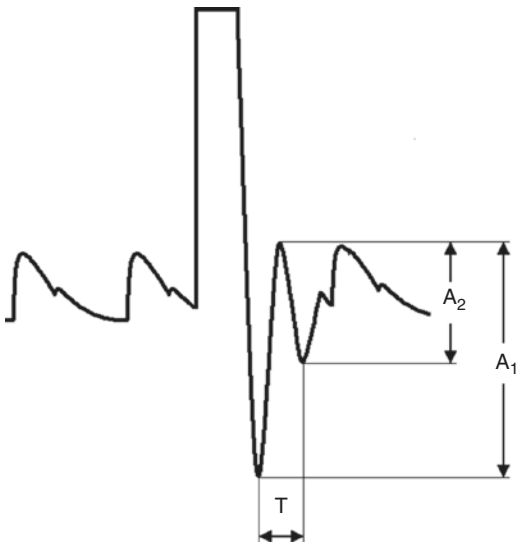

Fig. 2.3 "Pop-test" of direct arterial pressure monitoring system. A_1 and A_2 adjacent curve shoulders

This leads to several damped free pressure oscillations in the measuring system, giving the possibility of determining its vibrational properties. Avoiding rather complex calculations, we may conclude that period T should be 0.1–0.05 s, whereas optimal damping between adjacent curve shoulders (A_1/A_2) is 4–10 times. In an optimally damped system the number of free oscillations until arterial pressure curve indication restores is usually 2–3. In the real world, the vast majority of pressure monitoring systems are underdamped and have relatively low natural frequency (such as the system in Fig. 2.3); therefore the main goal is to avoid further natural frequency drop, leading to resonance as HR rises [17].

Catheters with proximal (*i.e.,* intra-arterial) pressure sensor at the tip (solid-state pressure catheters), although more expensive, are deprived of all the above-mentioned problems with natural frequency and damping intensity. The use of proximal pressure sensors, however, is mainly limited within experimental practice [18].

Possible causes of errors, artifacts, and adverse events while using a direct arterial line are summarized in Table 2.2.

Practical Advice

Do not remove the NIBP cuff when direct systemic arterial pressure monitoring is initiated.

It could help you to avoid too hasty activity, reflecting the highly volatile figures of "direct" arterial pressure [19].

2.5 Vascular Unloading (Volume Clamp) Technique

This principle provides the unique possibility of monitoring systemic arterial pressure, both continuously and non-invasively (Finapres, Finometer, Portapres, Cardiapres, and other similar devices for "continuous non-invasive arterial pressure"—CNAP). The main idea is to keep arterial wall permanently unloaded (*i.e.,* under zero transmural pressure) by means of a pneu-

Table 2.2 Sources of errors, artifacts, and adverse events of invasive (direct) arterial pressure monitoring [17]

Cause of error, artifact or adverse event	Error direction, result	Preventive measures
1. Catheter is too thick	Artery wall injury	Correct choice of elements for assembling the measurement system; refusal to use "improvised means" for this purpose
2. Catheter is too thin	Low f_c and high ζ	
3. Connecting tubing is too long		
4. Connecting tubing is too compliant		
5. Connecting tubing is too short	Low ζ	
6. Air bubbles in the system	Low f_c and high ζ	Regular efficient system flushing
7. Partial catheter occlusion with thrombus		
8. Complete catheter occlusion with thrombus	Display pressure curve interruption	
9. Catheter kinking or breaking	Low f_c and high ζ	Immobilization of the limb segment, catheter and the initial segment of the connecting tubing; effective sedation for severe motor restlessness
10. Plucking the catheter into the artery wall	Sudden blood pressure curve disappearance without patient's condition changes	
11. Pressure sensor "zero drift"	Incorrect indication of blood pressure values while maintaining the proper shape of the pressure curve	Regular sensor zeroing at the level of the patient's right atrium (in supine position—the level of the lower edge of the pectoralis major muscle in the armpit)
12. Pressure sensor dislocation in relation to the right atrium level		
13. Catheter tip whipping in the artery lumen, usually with a large difference in their calibers	Unusual shape of the curve—artifacts with the HR frequency; may resemble low ζ	Slightly pulling the catheter out of the artery while evaluating the curve, and then re-fixing the catheter
14. System disconnection or huge leakage	Sudden blood pressure figures drop, curve shape distortion, massive blood loss	Careful coupling of all the system elements, exclusion of joints without threads. The whole system should be completely visible any moment
15. Shivering, chills	"Sawtooth curve"	Cause identification and treatment
16. Distal arterial approach (radial, femoral or even more distal)	Overestimation of blood pressure figures compared with those in the aorta	Know and correct or choose a more central approach (axillary or brachial)
17. Sharp vasodilation on rewarming after CPB	Underestimation of blood pressure value in the radial artery	Know and correct, impossible to prevent
18. Balloon work in intra-aortic counterpulsation	HR overestimation due to counting IABP peaks	Correction of the HR figure based on the IABP operation multiplicity
19. Tissue tension and compression of the subclavian artery on the side of the mammary artery harvesting for CABG	Falling figures and curve shape distortion in the arteries of ipsilateral arm	Contralateral arm artery choice or, for bilateral harvesting, femoral artery catheterization
20. Artery injury due to its puncture and catheterization	Thrombosis, bleeding, hematoma	Careful step-by-step execution of all the technique precautions
21. Artery injury as the system is used	Thrombosis, hematoma	See points 8, 9
22. Thromboemboli or air bubbles pumping from the catheter into the distal vascular bed	Limb ischemia	Careful hermetic assembly of the monitoring system, its regular effective flushing. If there are clear signs of a thrombosis, do not flush the system with high pressure, but immediately remove the catheter
23. Retrograde pumping of thromboemboli or air bubbles into the aorta	Embolism in the systemic circulation	

f_c monitoring system natural frequency, ζ monitoring system damping coefficient, *HR* heart rate, *CPB* cardiopulmonary bypass, *IABP* intra-aortic balloon pump, *CABG* coronary artery bypass grafting

matic cuff on a palm finger. Keeping stable zero transmural pressure is possible only when cuff pressure precisely follows arterial blood pressure, which, in turn, is provided by a digital tracing servocontroller, a driving cuff pressure control valve with closed loop feedback by the finger photoplethysmography curve. Therefore, the cuff pressure curve becomes an exact copy of the arterial blood pressure curve [20, 21].

Main limitations of the method are dependent upon baseline vascular tone (ambient temperature, emotions, exercise), cuff placement thoroughness, better measurement of MAP and DAP in comparison with SAP, *etc.* [22]. The devices based on this principle have shown acceptable accuracy both in adults [23] and in children [24] and are well-known in cardiology and sports medicine; however, their use in anesthesiology, emergency, and critical care is not common.

2.6 Monitoring-Based Arterial Pressure Management

As has been well-known for many years, in contrast to alarm monitoring (for example, pulse oximetry), no method of numerical monitoring itself—without a clear uniform protocol of tactical decision making—could improve clinical outcomes [25].

What is the optimal blood pressure level? The answer evidently depends upon the patient, diagnosis, and multiple clinical features, including some special techniques, related to the surgery. There is no doubt, however, that an abnormal level of systemic arterial pressure is associated with unfavorable outcomes and, moreover, protocol-guided arterial pressure management improves outcomes [26]. Evidence- and common sense-based statements concerning systemic arterial pressure monitoring and management cited from the European Society of Intensive Care Medicine task force "Consensus on circulatory shock and hemodynamic monitoring" (2014) [7] and a brief fundamental review "Blood pressure targets in perioperative care" (2018, [26]) are summarized in Table 2.3. The main principle is personalization of optimal and acceptable systemic arterial pressure levels based on its individual baseline values.

When talking about induced controlled hypotension, especially desirable among ENT, orthopedic, and esthetic surgeons, it is very important to remember that all the considerations concerning acceptable arterial pressure limits are valid for these special settings also. Certainly, we do not now use the best traditional approaches such as cardiac output decrease with procainamide [27] or high spinal block [28], understanding that MAP but not cardiac output influences blood loss during surgery [29]. The situation has changed since the British confidential enquiry NCEPOD 1970–1982, when "controlled hypotension" was claimed to be the fourth main cause of anesthetic death and major neurological deficit [30]. However, the best modern definition of controlled hypotension, adjusted to the individual blood pressure level, is MAP decrease by 30% of the baseline values [31]—compare it with the limits marked in Table 2.3. In other words, controlled hypotension is a brilliant method, but only for patients who can survive it.

The authors of this chapter use a simple postural technique of induced hypotension, *i.e.,* head tilt for facial plastic surgery (the so-called SMAS lifting) under sevoflurane/dexmedetomidine anesthesia. It has the obvious advantages of fast and easy reversibility, the lack of an additional pharmacological burden, and thus never becomes uncontrolled [32, 33].

Almost the same words should be written about induced hypertension, which is used for some indications in neurological intensive care [34, 35] and for a final surgical hemostasis check-up. Although the latter technique is actually effective in diminishing postoperative blood loss and serious bleeding occurrence in thyroid surgery [36], its use should be approached extremely carefully and always requires both proper patient selection and reliable arterial pressure monitoring.

Table 2.3 Statements concerning systemic arterial pressure in anesthesiology and intensive care

Statement/recommendation	GRADE level of recommendation; quality of evidence	Type of statement, [reference]
In noncardiac surgery patients, maintain systemic arterial pressure at 90–110% of baseline values	Level 1; QoE moderate (B)	Provisional consideration [26]
In noncardiac surgery patients, if baseline is low (SAP <90 mmHg, DAP <50 mmHg), maintain 100–120% of baseline values	Level 2; QoE moderate (B)	Provisional consideration [26]
In noncardiac surgery patients, if baseline is high (130≤ SAP <160 mmHg, DAP ≥80 mmHg), maintain 80–110% of baseline values	Level 2; QoE low (C)	Provisional consideration [26]
In noncardiac surgery patients, if there is a high risk of organ ischemia or a high risk of pressure-related bleeding, maintain the upper or lower allowable ranges respectively (see above)	Level 2; QoE low (C)	Provisional consideration [26]
For cardiac surgery during CPB, maintain perfusion pressure (MAP equivalent) at 70–100 mmHg	Level 1; QoE moderate (B)	Provisional consideration [26]
For cardiac surgery during CPB, adjust perfusion pressure within the allowable range based on patient's baseline (see above)	Level 2; QoE low (C)	Provisional consideration [26]
We recommend frequent measurement of heart rate, blood pressure, body temperature, and physical examination variables (including signs of hypoperfusion, urine output and mental status) in patients with a history and clinical findings suggestive of shock	Ungraded	Best practice [7]
We recommend that the presence of arterial hypotension (defined as systolic pressure of <90 mmHg, or MAP of <65 mmHg, or decrease of ≥40 mmHg from baseline), although commonly present, should not be required to define shock	Level 1; QoE moderate (B)	Recommendation [7]
We recommend arterial and central venous catheter insertion in shock not responsive to initial therapy and/or requiring vasopressor infusion	Ungraded	Best practice [7]
We recommend individualizing the target blood pressure during shock resuscitation	Level 1; QoE moderate (B)	Recommendation [7]
We recommend initially targeting a MAP of ≥65 mmHg	Level 1; QoE low (C)	Recommendation [7]
We suggest tolerating a lower level of blood pressure in patients with uncontrolled bleeding (*i.e.,* in patients with trauma) without severe head injury	Level 2; QoE low (C)	Recommendation [7]
We suggest a higher MAP in septic patients with a history of hypertension and in patients that show clinical improvement with higher blood pressure	Level 2; QoE moderate (B)	Recommendation [7]

CPB cardiopulmonary bypass, *DAP* diastolic arterial pressure, *MAP* mean arterial pressure; *SAP* systolic arterial pressure

2.7 Conclusion

Although from physical point of view, it is probably the simplest and oldest approach to hemodynamic monitoring, systemic arterial pressure measurement remains its absolutely essential component. Including the whole spectrum of methods from Korotkoff's sound auscultation to the most sophisticated vascular unloading technique, we cover all possible kinds of clinical situations where blood pressure has a well-proven association with outcomes, while being rather volatile and easily controlled. Its effective and safe monitoring requires a good understanding of general blood pressure mechanics and physiology, knowledge of the principles of different techniques, details and pitfalls, and—for the invasive direct method—even certain manual skills. The current strategy of blood pressure management utilizes data of real-time monitoring and is focused on personalized choice of optimal and allowable ranges based on patient's individual baseline blood pressure values.

Keynotes

- Systemic arterial blood pressure, after more than a century, remains one of the most important life signs and easily available circulation monitoring variables. Its significance is supported by both physiological and clinical considerations, including the blood flow autoregulation concept and a well-proven influence on outcomes.
- Despite its "technical" character and availability in comparison with heart performance, the systemic arterial pressure level itself could be a trigger for immediate intervention: so-called subcritical hypotension (usually mean arterial pressure below 65 mmHg) means that regardless of the level of cardiac output, organs with "structurally high" local vascular resistance could get time-dependent irreversible ischemic injury.
- Non-invasive systemic arterial pressure monitoring is now available in both discrete and continuous versions, which are almost equally accurate enough to be used in various clinical settings. However, in anesthesiology, emergency medicine, and critical care the need for continuous arterial pressure monitoring is usually met by an invasive direct approach.
- Direct pressure monitoring *via* intra-arterial catheter is a recognized gold standard for accuracy, precision, and practical convenience, providing the additional possibility of frequent arterial blood sampling. Indications for arterial cannulation are often imperative; therefore, absolute contraindications exist only for certain artery approaches but not for the procedure itself.
- The modern concept of systemic arterial pressure monitoring and management includes switching to invasive mode in case of any doubts and sound artifacts, and taking into consideration patient's baseline arterial pressure level while targeting optimal and allowable figures of the parameter.

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Central Venous Pressure

3

Aleksey A. Smetkin and Vsevolod V. Kuzkov

Contents

3.1 Summary

Central venous pressure (CVP) reflects the pressure in the major veins, namely, vena cava *superior* and *inferior*. From the physiological point of view, the central venous pressure is a product of the complex interplay between potential heart performance and venous return; therefore, the response of CVP to the similar hemodynamic interventions can be opposite in different ICU patients. Historically, CVP was often used for the assessment of hemodynamics, volume status, and fluid responsiveness. However, over the last decades, multiple studies have demonstrated the absence of correlation of both absolute values and changes in CVP with end-diastolic left ventricle volume and cardiac output. Not surprisingly, CVP is unable to predict changes in cardiac output in response to fluid challenge. Nowadays, a certain "renaissance" of CVP seems to be possible since new studies show that increased baseline values and/or fast increment of this parameter are associated with progression to acute kidney injury, multiple organ failure, splanchnic congestion, and death. Thus, the therapy aiming to decrease CVP may improve organ function and clinical outcome. Obviously, there are many

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questions to be addressed concerning CVP in critically ill patients before the decision on when and how to use this hemodynamic parameter.

3.2 Introduction

The blood enters the heart chambers under certain force known as "filling pressure." In the case of the right atrium, the filling pressure is called the central venous pressure (CVP); to be more precise, CVP approximates the end-diastolic pressure in the right atrium. Monitoring of this parameter is widely available as central venous access is one of the routine invasive procedures performed in the majority of ICU patients.

A typical point of the CVP measurement is a proximal part of the vena cava *superior* near the junction with the right atrium where the tip of the central venous catheter is placed. As a rule, the geometric center of the right atrium should be taken as the baseline level for the CVP measurement. Pressure transducer is zeroed to atmospheric pressure at the "point of the right atrium" which can be easily determined by lowering the perpendicular of about 5-cm long (for an adult) from the front surface of the chest starting from the level of the sternum angle to the point of junction of the sternum and second rib [1]. In practice, the "phlebostatic point" is located at the intersection of the middle axillary line with the fifth rib or fourth intercostal space. It is easy to identify, but measurements will only be possible in a horizontal position. The values measured in the projection of the "phlebostatic point" exceed those at the level of the "point of the right atrium" approximately by 3 mmHg [2].

3.3 Morphology of the Central Venous Pressure Curve

The shape of the CVP curve has some distinct similarities with one of the systemic (arterial) blood pressure. According to the classic representation, five segments can be distinguished in the curve, three of those are peaks (waves *a*, *c*, and *v*) and two are descents (waves *x* and *y*) (Fig. 3.1). It is generally accepted that *c*, *x*, and *v* are of systolic origin, while wave *a* and descent *y* are diastolic. The most noticeable element of the CVP curve is wave *a*, which reflects the contraction of the right atrium that occurs after the completion of cardiac diastole. In approximate, wave *a* corresponds to the P wave on the electrocardiogram. With the beginning of the right atrium relaxation, wave *a* fades out and is interrupted by a small dicrotic *c* wave that is associated with isovolumetric contraction of the right ventricle and "prolapse" of the closed tricuspid valve toward the atrium.

If measured in a more distal section of the venous bed, for example, in the superior bulb of the internal jugular vein, wave *c* may be associated with the pulsation transmitted from the internal carotid artery ("carotid wave") [3]. Wave *c* corresponds to the onset of ventricular systole and, in part, to the period of early ejection. Atrial pressure continues to decline throughout the ventricle systole, turning into a descent, or cut *x*. At the end of the ventricle systole, a second rise in CVP is observed with the wave *v* associated with venous filling of the atrium during diastole, The wave *v* approximately corresponds to the T wave on ECG and is followed by a further decrease in the pressure curve with the formation of descent *y*, associated with the decline of the right atrium pressure during the ejection of blood into the ventricle (diastolic collapse) and the opening of the tricuspid valve. In some cases, plateau *h* can be recorded, persisting from the middle to the end of the diastole [3].

The most important argument in favor of analyzing the shape of the CVP curve is the possibility of early recognition of arrhythmias [4].

3.4 Determinants of the Central Venous Pressure

The resulting value of CVP is a product of the interplay of two key factors: the function of "venous return" characterizing the blood backflow to the right heart and the function of the heart (cardiac output and contractility) (Fig. 3.2) [5].

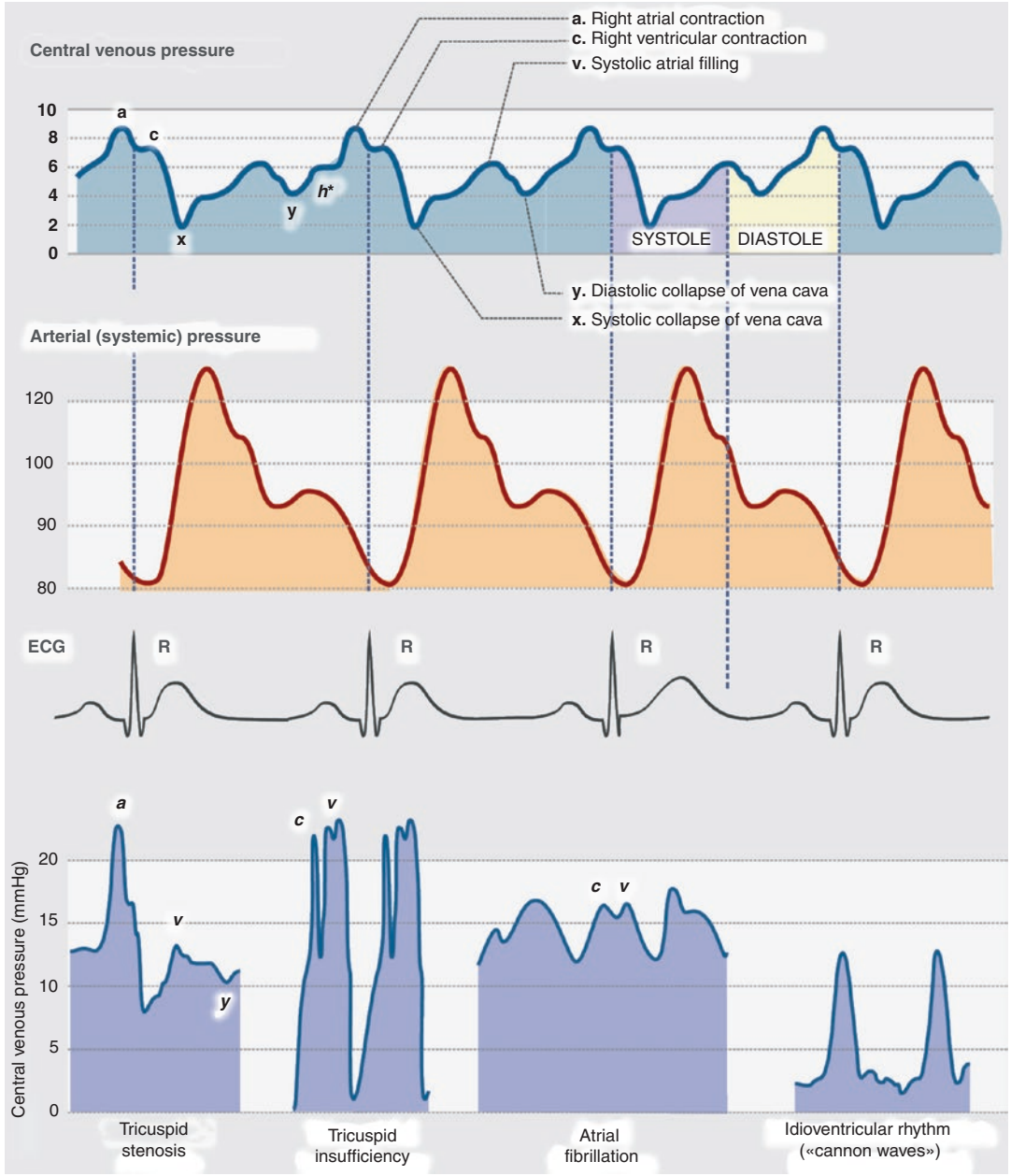

Fig. 3.1 Normal shape and elements of the central venous pressure curve (upper panel) and its changes under certain clinical conditions (lower panel)

The central venous pressure is largely dependent on the tone (resulting compliance) of the venous reservoir. It is considered that CVP is determined by the correspondence between the volume of blood and the capacity of the venous vascular bed, the condition of the main veins and heart valves (to a greater extent, the tricuspid valve), as well as the compliance of the right ventricle and pulmonary artery pressure [6]. These numerous factors significantly impede the straightforward clinical interpretation of the baseline value and changes in CVP.

According to the Guyton's model of circulation, there are three main determinants of cardiac

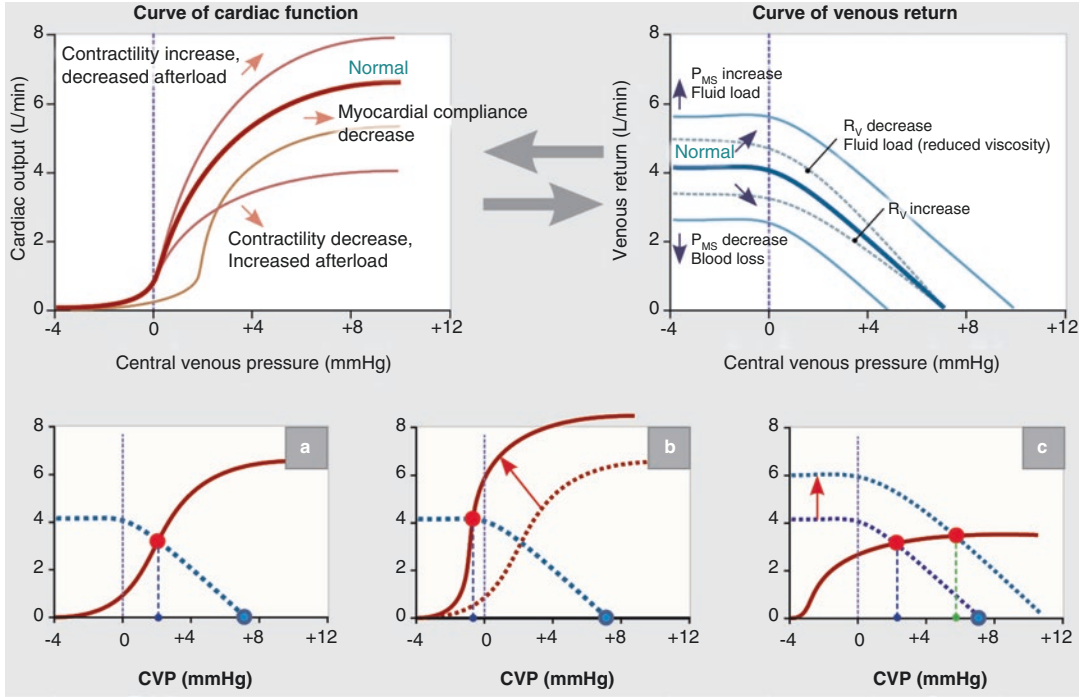

Fig. 3.2 A model of interplay between the venous return and the heart function (contractility). (**a**) An intersection of cardiac function and venous return curves gives resulting values of cardiac output (CO), venous return, and CVP. (**b**) Maximal venous return in low (negative) CVP ("waterfall" phenomenon) at the vertical position when the increase in contractility does not result in further CO increase. (**c**) Venous return curve crosses the plateau of the cardiac function curve; therefore, the augmentation of venous return does not result in further increase in CO. Please note that in accordance with the simultaneous position shift of the curves, the resulting CVP values can both increase and decrease depending on the personalized response to similar intervention (*i.e.,* fluid load, vasopressors). *CVP* central venous pressure, *CO* cardiac output, P_{MS} mean circulatory filling pressure, R_V resistance to the venous return

output—the pumping function of the heart, peripheral resistance to blood flow, and the volume of the circulatory system. Since venous return is equivalent to cardiac output, an increase in the latter can be achieved by increasing the mean systemic pressure and lowering the resistance to venous return or CVP. This is confirmed by the observations of an increase in cardiac output and a simultaneous decrease in CVP during moderate physical activity (Fig. 3.2) [7].

3.5 Interpretation of the Central Venous Pressure

The central venous pressure reflects the ability of the heart to "pump" an inflowing volume of blood and characterizes the filling pressure of the right ventricle. In this term, clinicians often use CVP as an indirect indicator of ventricular preload and intravascular volume.

Under the conditions of normal heart function and adequate intravascular volume, when patient is standing up or in the sitting position, CVP is usually below zero (atmospheric pressure). This can be explained by the "suction" function of the ventricles during diastole [8]. This effect must be considered during surgical interventions performed in the upright position (neurosurgery) due to the risk of air embolism.

Moreover, in most cases, CVP transducer is "calibrated" against relatively constant atmospheric pressure, not taking into account the changes in airway pressure [9]. However, in assessing CVP, one should consider the phase, type, and other characteristics of respiration. During spontaneous inspiration, a decrease in CVP (following a decrease in intrapleural

pressure) and an increase in blood flow into the heart (preload) can be observed because of the "suction" action of the chest. In contrast, inspiration during mechanical ventilation is accompanied by an increase in CVP and, in addition, results in a certain decrease in the volume of the heart due to the restriction of blood flow. In the routine clinical practice, CVP is usually evaluated at the end of expiration that provides the most accurate assessment of transmural pressure. The intrapleural pressure gradually returns to zero (atmospheric pressure) by the end of the passive spontaneous expiration or when the patient is disconnected from the mechanical ventilation and the transmural pressure matches CVP most closely.

Under pathological conditions, the role of CVP is not limited by indicating changes of the intravascular volume only (Fig. 3.3). For example, in the case of increased cardiac output (distributive shock, hyperdynamic state), we can observe reduced CVP despite normo- or hypervolemia. On the contrary, the increased values of CVP can be registered both in true volume overload and in normovolemia when the patient has severe heart dysfunction or pulmonary hypertension (*e.g.,* pulmonary embolism). The dynamic changes in myocardial compliance (*e.g.,* due to the use of various beta-adrenergic drugs) can further complicate these interactions.

3.6 The Current Place of the Central Venous Pressure in Clinical Practice

The mean value of CVP and its dynamic changes have been used for decades as indirect markers of the blood volume inflowing to the heart and, therefore, of ventricle preload. The physiological basis for the use of CVP as a guide for fluid therapy was first introduced in the 1950s by Hughes and Magovern in patients who underwent thoracotomy [10]. Later, the clinical value of CVP as a marker of preload has become a subject of constructive criticism [11, 12]. However, the question about the optimal ventricle preload indicator—volume or pressure—remains unresolved. Since the right and left parts of the heart are functionally combined, when the right ventricle reaches its functional plateau, the ejection of the left ventricle also becomes limited. The recognition of this phenomenon has led to the statement "Success of the left ventricle is impossible without the success of the right ventricle." On this basis, Magder advocates the view that it is unacceptable to use PAOP and the size of the left ventricle to optimize preload [9]. It should be recognized that the left ventricle can eject only the volume of blood that the right one delivers, and, *vice versa*, the right ventricle can dispose only the volume that the left one is able to accept.

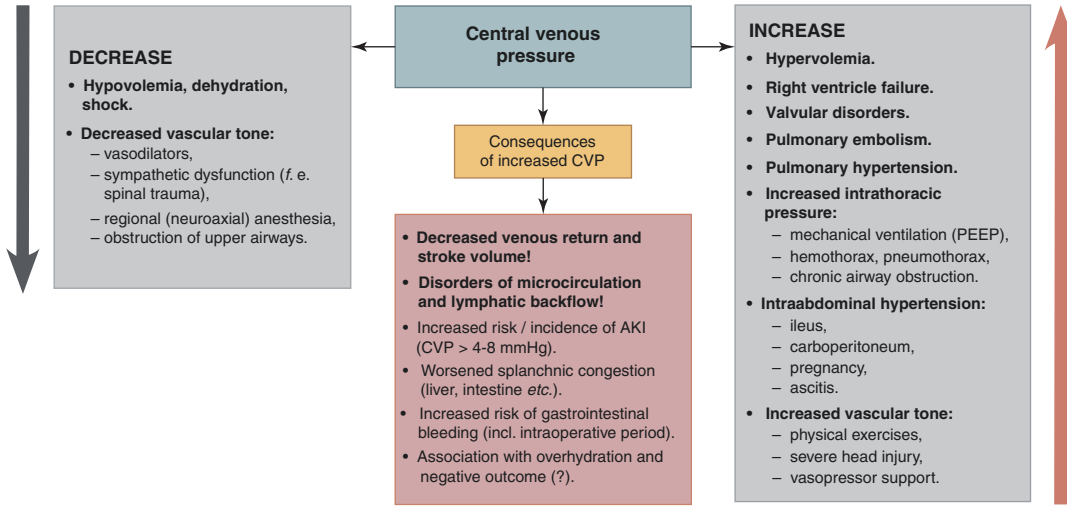

Fig. 3.3 The factors resulting in the changes of the central venous pressure (CVP) and the risks of increased CVP

A number of studies and recent systematic reviews have demonstrated that using the absolute values of CVP to predict fluid responsiveness is unreliable in most critically ill patients [12, 13]. Notably, the prognostic value of CVP regarding the preload of the left ventricle becomes completely unacceptable in patients with intraabdominal hypertension or increased airway pressure (*e.g.,* in COPD). At the same time, the question "How to treat a patient with shock and normal CVP, or, conversely, a stable patient with a low value of this parameter?" remains unresolved [14].

Practical Advice

The central venous pressure is an unreliable predictor of fluid responsiveness. Therefore, the use of CVP for this purpose should be discontinued.

3.7 Risks of Increased Central Venous Pressure and Further Perspectives

Recent studies have shown that liberal (or "aggressive") infusion therapy in critically ill leading to a rise in CVP above 8–12 mmHg is accompanied by increased risk and incidence of acute kidney injury, multiple organ dysfunction, and death [15–18]. As reported, a rise in CVP by 1 mmHg results in an increase of the risk of AKI by almost 2% [19]. It has also been demonstrated that an increase in CVP ≥12 mmHg in patients with sepsis is associated with profound microcirculation disorders [20]. Of note, the *Surviving Sepsis Campaign* no longer targets a central venous pressure of 8–12 mmHg as a goal of fluid resuscitation [21]. Recently, Xing et al. demonstrated the advantages of early renal replacement therapy aiming to reduce CVP in regard to the recovery of renal function in patients with sepsis-induced acute kidney injury [22]. Moreover, fluid de-escalation strategy in patients with ARDS leading to a decrease in CVP was associated with fewer days of mechanical ventilation [23]. Recent meta-analysis demonstrated that the application of different strategies (Trendelenburg position, nitroglycerine, furosemide, fentanyl, control of infusion rate, and clamping the intrahepatic vena cava) aiming at controlled low CVP (or even targeted "zero" CVP) in liver resection significantly reduces blood loss and requirement in blood transfusion [24].

Practical Advice

The central venous pressure has a potential to be considered as one from the parameters of safety of fluid therapy. During fluid load, the physician should be aware of the multiple risks of CVP exceeding 12 mmHg.

Nevertheless, the "optimal" CVP value has not been established yet. It should be personalized and kept as low as possible [25]. In addition, the visual analysis of the CVP curve is still useful in cardiac surgery and may give information about the tricuspid and mitral valve function, the hemodynamic effects of rhythm disturbances, and the presence of constrictive pericarditis and pericardial tamponade [26]. Thus, some authors advocate further studies aiming to evaluate the potential benefits of CVP monitoring [27].

3.8 Conclusion

The measurement of CVP requires knowledge of the methodology and cardiovascular physiology, while the analysis of the wave contour of CVP can help to detect cardiac disturbances. Obviously, CVP cannot be recommended for further use as a reliable predictor of fluid responsiveness. However, monitoring of changes in CVP has a potential to provide important information on the safety of fluid therapy and to detect the risk of acute kidney injury and microcirculatory distress. The future studies should address the association of CVP with overhydration and peripheral tissue edema and answer the question about possible role of this parameter in the personalized algorithms for de-escalation of fluid therapy.

Keynotes

- The central venous pressure (CVP) is a static parameter reflecting preload and function of the right ventricle only; thus, in many clinical situations, CVP does not correlate with the work of the left heart.
- The central venous pressure is unreliable as a predictor of fluid responsiveness.
- In critically ill patients, increased CVP is associated with development of organ dysfunction, especially acute kidney injury and splanchnic congestion.
- In certain clinical scenarios, therapy guided to decrease the elevated values of CVP might attenuate organ dysfunction and has a potential to improve outcome.

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Pulmonary Pressures

4

Daniel De Backer

Contents

There is a long-time interest for measuring pulmonary pressures. Already in the early 1900s, physicians attempted to insert catheters into the pulmonary circulation to measure pulmonary pressures [1]. Cournand first introduced in the early 1950s the use of pulmonary artery catheterization [1], but it is only with the introduction of the balloon-tipped pulmonary artery catheter (PAC), also named Swan-Ganz catheter [2], that the measurement of pulmonary artery pressures became popular in cardiovascular medicine and in the intensive care unit.

Pulmonary pressures include the pulmonary artery pressure (PAP) and the pulmonary artery occlusion pressure (PAOP). Beyond the interest of measuring these variables in specific conditions, it is important to understand the physiological role of these variables in cardiovascular and pulmonary medicine. Even if PAC is less used nowadays than at the end of the last century [3], the interest for its measured variables, including PAP and PAOP, remain [4]. Interestingly, several hemodynamic tools may serve as alternative to PAC, providing measurements of PAP and PAOP [5].

It is therefore important to understand the physiology of pulmonary pressures, their determinants, and their potential use in cardiovascular medicine and critical care.

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4.1 Physiological Considerations

The PAP is the back pressure of the right ventricle, and is therefore an important determinant of its afterload. The right ventricle difficulty affords an acute increase in PAP, which results from right ventricular dysfunction. Accordingly, the estimation of PAP is important at bedside. PAP can be increased in various conditions, including pulmonary embolism, ARDS, chronic pulmonary, and cardiac diseases.

While systolic, diastolic, and mean PAP can be measured, the mean PAP (PAPmean) is used to define pulmonary hypertension and best reflects the afterload of the right ventricle. The normal PAPmean is around 15 mmHg, but values higher than 20 mmHg define pulmonary hypertension [6]. In acute settings, the right ventricle becomes dysfunctional for values above 35 mmHg.

PAOP reflects the left atrial pressure, which is an important physiologic variable. First, the left atrial pressure is a reflection of the left ventricular preload, and hence an important contributor of cardiac output. Second, an elevated left atrial pressure is observed in left heart diseases. Finally, it is the back pressure of pulmonary bed, and thus may contribute to pulmonary hypertension.

An elevated PAOP contributes to pulmonary edema and is a key determinant of capillary leak, together with vascular permeability. Importantly, the hydrostatic pressure at the capillary level is the true capillary pressure, not PAOP or the left atrial pressure (the measurement of true capillary pressure will be discussed below).

The use of PAOP as left ventricular preload has been criticized. Indeed, as any other "static" measurement of preload, PAOP does not reliably predict fluid responsiveness. Nevertheless, extreme values keep some value to predict fluid responsiveness [7]. More importantly, PAOP can be used as a gauge of the benefit/risk ratio: low values of PAOP are associated with minimal risk during fluid administration while high values are associated with high risk of pulmonary edema, even if fluids increase cardiac output. Accordingly, many physicians use PAOP as a safety measure during fluid challenge [8].

4.2 Measurements

4.2.1 Invasive Measurement with Pulmonary Artery Catheter

The systolic, diastolic, and mean PAP are measured from the distal end of the pulmonary artery catheter (also called Swan-Ganz catheter [2]). The principle of PAOP measurement is that flow carries the inflated balloon into a distal branch of the pulmonary artery, occluding blood flow distal to the point where the catheter with the inflated balloon wedges. The PAOP is the pressure measured from the distal end of the catheter with its balloon inflated.

Even though misnamed as PAwedge, PAOP is not identical to PAwedge pressure. PAwedge is the pressure obtained when the catheter is wedged without inflating its balloon, corresponding to a more distal branch of pulmonary artery than that obtained with the balloon inflated for PAOP measurement. PAOP also differs from the PA capillary pressure which corresponds to the hydrostatic pressure at the level of pulmonary capillaries and is obtained using a specific calculation algorithm.

PAOP reflects the pressure at the level of relatively large segments of the pulmonary artery bed; hence, this pressure mostly represents the pressure in the large pulmonary veins, and hence the left atrial pressure. PAwedge occludes smaller vessels, closer to capillaries, and hence is closer, but not equivalent, to the capillary pressure.

The true capillary pressure cannot be measured but can be calculated by several ways. The easiest is the computation by the Gaar equation [9]:

$$\text{Pulmonary capillary pressure} = \text{PAOP} + 0.4 \times (\text{PAPmean} - \text{PAOP}).$$

This formula, obtained in experimental conditions using an isolated perfused lung model, is valid only when resistances are normally distributed in the pulmonary arterial and venous tree, which is not true in disease states. Alternatively, the capillary pressure can be calculated from the

decay of the PA curve during balloon inflation [10, 11].

Practical Advice
PAOP is not identical to pulmonary capillary pressure, the true hydrostatic force contributing to pulmonary edema. Pulmonary capillary pressure is difficult to measure in clinical practice; accordingly PAOP is the best estimate of the force leading to pulmonary edema.

As the heart is in the chest, measurements of pulmonary pressures are influenced by pleural pressure. To minimize the influence of pleural pressure, the tip of the pulmonary artery catheter should be positioned in the West zone III, where PAP is higher than pulmonary venous pressure, itself higher than the alveolar pressure. Malposition of the catheter in West zone I or II is suggested when respiratory variations in PAOP are larger than respiratory variations in PAP [12]. Measurements should always be obtained at end-expiration.

Practical Advice
Pulmonary pressures should always be measured at end-expiration.

It is possible to estimate pulmonary artery transmural pressures during mechanical ventilation. The transmission index is computed as a ratio of PAOP during different phases of breathing to driving pressure: (PAOP end-inspiration – PAOP end-expiration)/(plateau pressure – PEEP).

Transmural PAOP is computed according to following formula: PAOP end-expiration – (transmission index × PEEP) [13]. For the other pressures, the same formula can be used.

Practical Advice
Transmural PAOP reflects the pressure contributing to pulmonary edema and left ventricular preload.

4.2.2 Noninvasive Measurement (Echocardiography)

Except with echocardiography, there is no other means to determine pulmonary artery pressure at bedside. In addition, the reliability of pulmonary artery pressure with echocardiography has been challenged [14, 15], but these studies were not performed in critically ill patients. In addition, the measurements were often not obtained the same day with the two techniques.

Systolic PAP is measured from the maximal velocity of tricuspid regurgitation, which estimates the systolic transvalvular gradient. Systolic PAP is computed using the simplified Bernoulli equation as 4 × (tricuspid regurgitant jet peak velocity)^2 + right atrial pressure (RAP).

Mean and diastolic PAP can be estimated from protodiastolic and telediastolic velocities of pulmonary valve regurgitant flow, respectively, using the same formula as above. This measurement cannot always be obtained in critically ill patients.

In addition, pulmonary hypertension is suggested by a decrease in pulmonary artery acceleration time < 90 ms or by a biphasic pulmonary flow. While a quantitative measurement cannot be obtained, this measurement is helpful to detect pulmonary hypertension when other measurements cannot be easily obtained.

PAOP can be estimated by different indices. The most accurate and easier to obtain in most conditions is the mitral inflow maximal early velocity (E) divided by mitral annulus maximal early velocity (Ea). This E/Ea ratio shows a good relation with invasive PAOP in critically ill patients [16, 17]. Nevertheless, the limits of agreement are too broad for precise numerical estimation so that this measurement is usually used as a semiquantitative assessment (PAOP low/intermediate/high) or for following the individual response to an intervention [18].

Practical Advice
Several echocardiographic indices can be used to estimate PAP and PAOP. Even though less precise than the invasive mea-

surements, echocardiography also allows to identify the consequences of pulmonary hypertension on the right ventricle and the source of the elevated PAOP.

Practical Advice
When pulmonary hypertension is identified, measuring the gradient between PAP diastolic and PAOP is helpful to discriminate precapillary and postcapillary pulmonary hypertension.

4.3 Pulmonary Artery Pressure in Practice

The measurement of pulmonary artery pressure is useful for several purposes: identification of the cause of right ventricular dysfunction, evaluation of the impact of therapeutic interventions, prognostic value in respiratory and cardiovascular patients, *etc*.

When PAH is identified, it is important to understand whether it is due to an increased left atrial pressure (postcapillary PAH) or caused by an increase in the resistance of pulmonary artery vessels (precapillary PAH). To differentiate both, it is useful to compute the gradient between PAPdiastolic and PAOP. A gradient below 3 mmHg indicates postcapillary PAH, while a gradient higher than 5 mmHg indicates precapillary PAH.

When right ventricular dysfunction is identified, the measurement of PAP is useful to orient into its causative mechanism: primary right ventricular cardiac dysfunction (right ventricular infarction of tricuspid disease) is associated with low or normal PAP while right ventricular failure due to an increased afterload (obstructive shock) is associated with an increase in PAP (Fig. 4.1). In addition, the severity of PAH helps to discriminate between an acute mechanism, in which PAPmean is seldom higher than 45 mmHg, and chronic ones, in which very high PAPmean levels can be observed.

Practical Advice
Measuring pulmonary pressures is helpful to understand the cause of right ventricular dysfunction.

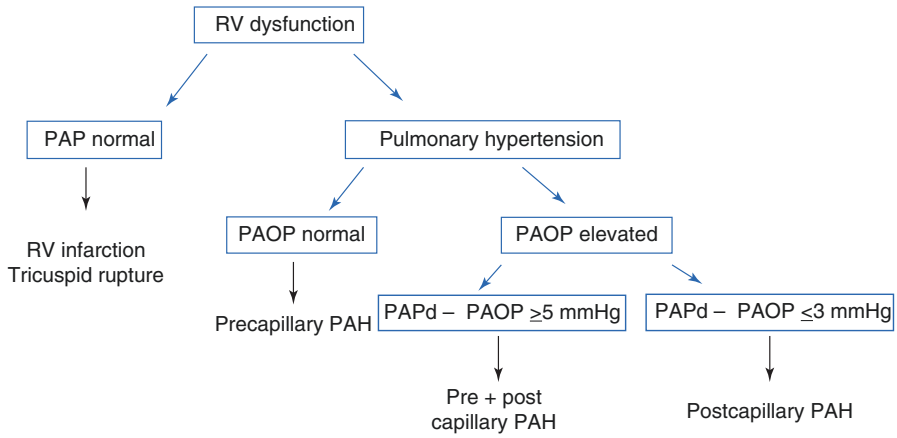

Fig. 4.1 Usefulness of pulmonary arterial pressure measurement for the interpretation of right ventricular dysfunction. *RV* right ventricle, *PAH* pulmonary hypertension, *PAP* pulmonary artery pressure, *PAPd* diastolic pulmonary artery pressure, *PAOP* pulmonary artery occlusion pressure

The measurement of PAP is also useful to assess the impact of various interventions (*i.e.,* inhaled nitric oxide), helping to find the optimal dose of the agent.

Finally, monitoring PAP is particularly useful in the postoperative management of patients at risk to develop right heart failure during interventions such as heart transplantation, implantation of left ventricular assist device, or cure of mitral stenosis.

4.4 Pulmonary Artery Occlusion Pressure in Practice

PAOP can be used for several purposes: evaluation of volume status, evaluation of left ventricular cardiac function, and identification of hydrostatic pulmonary edema.

The evaluation of volume status is not straightforward. The measured PAOP is the result of volume status and systolic/diastolic properties of the left ventricle, the latter potentially influenced by right ventricular function due to ventricular interaction and pericardial constraints. And the measured value is influenced by pleural/pericardial pressure.

Practical Advice
PAOP reflects the balance between volume status and left heart function.

Given the complexity and multiplicity of the interactions, a low PAOP is associated with low volume status and excellent cardiac function. An elevated PAOP is associated with either severe hypervolemia, impaired cardiac function, or elevated pleural/pericardial pressure. Additional evaluation, usually with echocardiography, is useful to discriminate between these three factors. Finally, a normal PAOP can represent normovolemia in a patient with normal cardiac function, hypovolemia in a patient with impaired cardiac function, or hypervolemia in a patient with excellent cardiac function. Again, echocardiography may help to differentiate between these possibilities.

The usefulness of PAOP to guide fluid administration has been much debated [19]. Acceptably, the prediction of fluid responsiveness is relatively poor with PAOP, as with any other static measurements (filling pressures and cardiac volumes), as each patient is characterized by its own Starling relationship. Accordingly, only very low values predict fluid responsiveness, and very high values predict the absence of response to fluids.

PAOP can nevertheless be still useful for fluid management. In patients with impaired cardiac function, PAOP better predicts fluid responsiveness than cardiac volumes [20]. More importantly, PAOP can be used as a safety value. An increase in cardiac output is very unlikely in a patient with high PAOP, but also administration of fluids is very unsafe. Given the exponential relationship between PAOP and the left ventricular volume, the administration of fluids in patients with elevated PAOP will sharply raise it further, potentially leading to pulmonary edema. In these conditions, PAOP is often used as a safety value, prompting to stop fluid administration when a predefined PAOP value is reached [8].

Practical Advice
PAOP is a poor predictor of fluid responsiveness. However, PAOP is helpful for guiding fluid resuscitation, establishing the benefit/risk profile before fluid administration and serving as a safety variable during fluid administration.

Finally, PAOP is often used to identify hydrostatic pulmonary edema in the presence of lung infiltrates. PAOP differentiates between ARDS and hydrostatic edema, with PAOP values >18 mmHg identifying a significant contribution of hydrostatic edema [21]. It can also be used to identify weaning-associated pulmonary edema [22, 23]. Nevertheless, there are two important limitations for the interpretation of PAOP as a cause of hydrostatic pulmonary edema. First,

PAOP measurements are affected by pleural pressure, and the critical determinant of hydrostatic pulmonary edema is transmural PAOP and not intravascular PAOP. Second, lung edema occurs at a lower PAOP value in the context of increased permeability [9] and may develop at higher values in the context of chronically elevated left atrial pressure. Accordingly, the contribution of hydrostatic pressure to pulmonary edema is progressively increased rather than sharply increasing just above 18 mmHg.

Practical Advice
PAOP is helpful to discriminate hydrostatic from nonhydrostatic pulmonary edema.

4.5 Conclusions

The measurements of pulmonary artery pressures, including PAOP, are important for patient management. Even though these are less frequently measured than at the end of last century, understanding the physiology of pulmonary pressures, PAOP, and right and left ventricular functions is crucial.

Keynotes
- Pulmonary artery pressure is a key determinant of the right ventricular afterload.
- The evaluation of the right ventricular function should take into account PAP measurements.
- When pulmonary hypertension is diagnosed, PAOP should be measured to differentiate pre- and postcapillary hypertension.
- PAOP cannot predict fluid responsiveness. It is nevertheless useful for the guidance of fluid administration (safety limit).
- PAOP is useful to identify the hydrostatic component of pulmonary edema.

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Part II

Measurement of Cardiac Output

Cardiac Output: Physiological Background

5

Konstantin M. Lebedinskii, Andrey I. Lenkin, and Alexei E. Karelov

Contents

The goal of this chapter is to discuss the definition, physiological role, and main determinants of cardiac output (CO) among the other variables characterizing systemic circulation. Principles, techniques, and details of CO measurement and monitoring are described in Chaps. 6–11.

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5.1 Definition and Limitations

Since in the circuit of mammalian blood circulation all four heart chambers are connected in a consequential chain, "cardiac output" does not mean total heart performance, but flow within the whole closed system. Normally, in the absence of significant transverse shunts (*i.e.,* septal defects or patent arterial duct), left ventricle performance per minute (but not stroke volumes beat-by-beat) is exactly equal to that of the right one. Proceeding

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with this ideal model, CO can be defined as flow (volume given at time, $L \cdot min^{-1}$), running through consequently connected systemic and pulmonary circles of circulation. In the real world, however, some part of ventricular output can return to the atrium during systole because of atrioventricular valve failure, to the ventricle during diastole owing to aortic or pulmonary trunk valve leak, or another part can flow between systemic and pulmonary circulation *via* a septal defect or arterial duct, *etc.* [1]. Therefore, global overall flow sometimes becomes futile; moreover, it often neither exists nor can be measured with any of the numerous methods developed since 1870 [2]. We can accurately measure left ventricle stroke volume (SV) or flow *via* the aortic root, right heart, and pulmonary artery, but none of these three different values gives an accurate picture of body perfusion.

Practical Advice

Although pulmonary artery thermodilution remains the "clinical gold standard" for almost half a century, we should remember that various CO monitoring technologies not only give different figures but measure different values, each with its own normal range.

Within the frames of fashionable "physiological nihilism" mainstream [3] from these facts there may be the illusion that CO is not a reliable criterion for hemodynamic adequacy. A proper conclusion is that to interpret CO values correctly you have to know (1) the exact place (cross-section of systemic or pulmonary circulation) where it was measured, and (2) the technical principle and details of the measurement technology used, including normal range results.

Practical Advice

A mystery of any monitoring technology is that the sicker the patient, the worse we are equipped, the less time we have, *i.e.,* the more we need the most reliable clinical data; the worse the method works, the more erroneous its results are. Knowledge of all the limitations and sources of errors is absolutely necessary for the safe use of any monitoring method.

Despite common belief that CO can be calculated as a product of SV and heart rate (HR) [4], the variability of SV values, especially in the case of hypovolemia [5] or arrhythmias [6], makes such a calculation futile: the results can be different three times at the same moment. Only the summation of all the SV values during a minute is always correct by definition:

$$CO = \sum_{i=1}^{HR} \left(SV_i \right) \tag{5.1}$$

It is especially important when the measurement method, namely SV (such as echocardiography, electric impedance or reactance cardiography, pulse wave contour analysis), whereas methods measuring flow regardless of SV (Fick's principle, indicator dilution, including thermodilution and "ultrasound dilution," partial CO_2 rebreathing) extrapolate flow values to a 60-s period and therefore are insensitive to SV variability [7].

5.2 Clinical Significance

Although the ultimate goal of circulation is to provide optimal blood flow to organs and tissues (milliliters per 100 g of tissue per minute) [8], until this moment modern medicine regardless of the level of equipment does not have a reliable bedside monitor of tissue perfusion [9]. Thus, for many decades CO as the total sum of all the regional flows as a gross substitute for each exact one remains the most desirable value of the whole spectrum of hemodynamic monitoring data [10]. Actually, primary or secondary low CO syndrome plays a leading role in the mechanisms of cardiogenic, hypovolemic, and obstructive

shock—all the kinds of shock except for the "warm" distributive one [11]. Therefore, normal CO is considered to be one of the most relevant cornerstones of the everyday clinical cliché of "hemodynamic stability" [12]—although "stable" does not always mean "good": low CO is sometimes extremely stable (*i.e.,* difficult to correct) until the moment of death. Certainly, we should conclude that an adequate CO level is an absolutely necessary (but not sufficient!) condition of adequate circulation [13].

Despite endless debates concerning the choice of methods for CO assessment, focused on the unresolvable dilemma "accurate or non-invasive?" [14], recent studies have shown the ability of CO monitoring (including semi-invasive and non-invasive modalities) to improve outcomes in both intensive care and high-risk surgery [15, 16]—under a single essential condition: as no monitor can influence outcome *per se*, a strict goal-directed protocol should govern all the links between the monitoring data and clinical decisions [17].

The core position of CO among other circulation variables was underlined by the results of the PiCClin study (2016), where underestimation >20% of the true CO value appeared to be the most frequent error (54%) in clinical hemodynamic assessment before transpulmonary thermodilution measurement [18]. Surprisingly, shares of this mistake were similar among residents (52.7%) and consultants (55.6%), a humiliating clinical experience as the basis of empiric medical practice.

Furthermore, the well-known fact that true CO values cannot be derived from easily available hemodynamic variables—heart rate, systolic or pulse arterial blood pressure, *etc.* [19]—means that now we do not have a reliable alternative to CO measurement.

Practical Advice

Measurement remains the only possible way of determining CO accurately. Despite their attractivity, CO calculations based on estimations are unreliable, demonstrating that the greater bias the more severe the patient is.

5.3 Cardiac Output Dimension

The physical dimension of CO is flow (blood volume given at the time of its passage through the ventricles, $L \cdot min^{-1}$). However, this form of expression is difficult to normalize as the values are dependent upon age and body size. Although Adolf Fick proposed the first principle of CO measurement in 1870, routinely available monitoring has become possible a century later with the invention of the thermodilution Swan–Ganz balloon catheter [20]. Step-by-step, in 1897–1953 George N. Stewart, Valdemar Henriques, and William F. Hamilton made real breakthroughs, implementing the indicator dilution method [21]. For the first time it allowed CO to be measured in clinical settings with an acceptable accuracy. The first problem appeared was a very wide range of CO values in healthy volunteers, making it difficult to define limits of physiological range, even given at body weight ($mL \cdot min^{-1} \cdot kg^{-1}$).

In 1929, Arthur Grollman, developing another technique—indicator gas dilution with inhaled acetylene—tried to reduce CO values to the body surface area (m^2), available since 1916 owing to the formular by D. DuBois and E.F. DuBois. This parameter, called initially Grollman index, and then cardiac index (CI, $L \cdot min^{-1} \cdot m^{-2}$), appeared to be rather stable and normalized within the limits of approximately 2.5 and 3.5 $L \cdot min^{-1} \cdot m^{-2}$ [22].

This dimension can be mathematically further reduced as follows:

$$\left[L \cdot min^{-1} \cdot m^{-2} \right] = L^3 \cdot t^{-1} \cdot L^{-2} = L \cdot t^{-1}, \quad (5.2)$$

where L means length and t—time. Thus, surprisingly "normalized" CO dimension is linear velocity, which coincides with V.M. Khaiutin and L.L. Schick's hypothesis (1967) that the final goal of circulatory control is keeping the stable linear velocity of capillary blood flow, providing a proper structure of flow with a clear plasma layer close to the endothelium [23]. This dynamic flow structure is the basis of the so-called Fåhreus-Lindquist phenomenon (1931)—a decrease in blood viscosity at the diameter of the vessels decreases up to figures comparable with red blood cell diameter [24].

5.4 Physiological Scale of Cardiac Output

For steady state the normal CI range is approximately 2.5–3.5 L·min^{-1}·m^{-2}. Circulation with CI <2.5 L·min^{-1}·m^{-2} is called hypodynamic (shock, heart failure), whereas figures above 4.0 characterize hyperdynamic circulation (fever, sepsis, hyperthyreosis, *etc.*). Sound landmarks include 1.5 L·min^{-1}·m^{-2} for severe shock, 2.0 for a decision threshold of mechanical circulatory support, whereas 2.5 L·min^{-1}·m^{-2} often marks a "safety limit" for shock patients [25, 26]. However, despite decades of using routine CO monitoring, so far we do not know particular normal or even optimal CI values for some common states with altered metabolism—for example, critical illness or general anesthesia for major surgery [27]. Moreover, extensive literature is devoted to a comparison of different CO monitoring methods: as already mentioned above, the fact that they are not interchangeable concerning exact figures is now generally accepted [28, 29]. As any other monitoring data, CO should never be treated itself—apart from another criterion of perfusion adequacy such as dynamic observation, lactate level, and mixed venous oxygen saturation [30, 31]. Finally, "the more the better" approach to CO management, advocated since the late 1970s by William Shoemaker's team as a supranormal oxygen delivery concept, is now rejected as "an oversimplification of a complex phenomenon" (J.-L. Vincent [32]).

5.5 The Place of Cardiac Output Among Other Hemodynamic Variables

Interrelations of the main hemodynamic variables are shown on the block scheme (Fig. 5.1). The role of blood for circulation and perfusion may be described with only two parameters—volume and rheological properties. Vessels can be divided into capacitive (systemic veins and the whole pulmonary circulation) and resistive (systemic arteries and arterioles). The proportion between blood volume and vascular capacity, or to be more precise, the ability of this proportion to fill ventricles during diastole, determines volemic status and, thus, venous return as a main heart preload factor. Interrelation between arterial tone and blood rheology forms hydrodynamic resistance of vessels as a main afterload determinant.

Moving down to the myocardium properties, end-diastolic volume (EDV) seems to be a dynamic equilibrium between diastolic ventricular elastance (E, or, *vice versa*, compliance $C = 1/E$) and volemia, when diastole is not too short for this balance to be reached [33]. Symmetrically, end-systolic volume (ESV) can be presented as a dynamic balance point between ventricular contractility and afterload. Stroke volume is the difference between the two, which can be expressed in symbolic form by the equation:

$$\mathrm{SV} = \mathrm{EDV} - \mathrm{ESV} \sim \frac{\text{Venous return}}{\text{Elastance}} - \frac{\text{Vascular resistance}}{\text{Contractility}} \tag{5.3}$$

where EDV and ESV are directly proportional to the numerators and inversely proportional to the denominators of both fractions respectively. Equation (5.3) summarizes the options for SV control, including both widely (posture, volemic infusion, diuretics, exfusion, vasoactive agents, inotropes, β-blockers, *etc.*) and rarely used (elastance/compliance) ones [34].

The influence of cardiac rhythm is more complex. Although profound bradycardia obviously leads to low CO, tachycardia may also result in drop in CO because of the so-called "short diastole" associated with an insufficient time for ventricular filling. The limits of the hemodynamically effective rhythm of ventricular contractions are usually considered to be

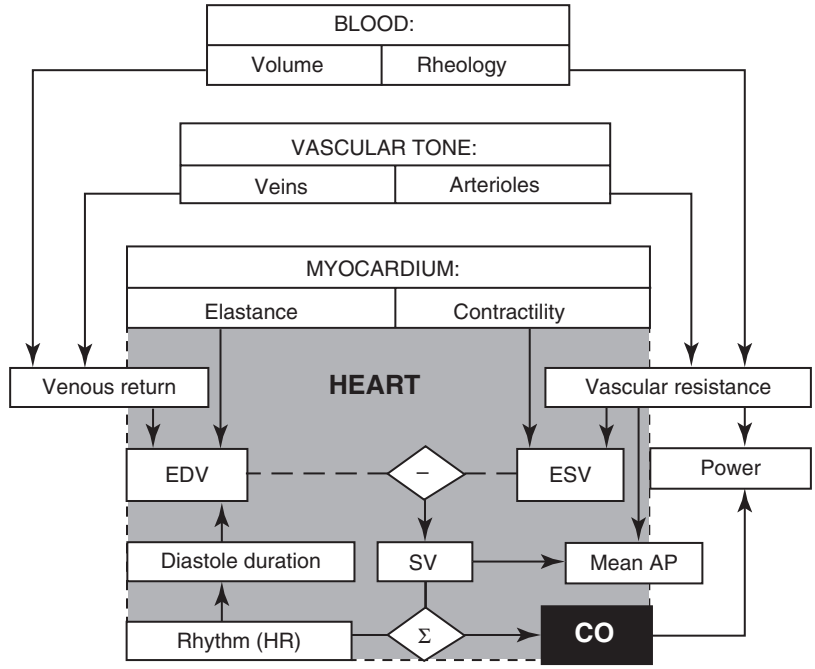

Fig. 5.1 Interrelation between the main terms and variables of systemic circulation. *AP* arterial pressure, *CO* cardiac output, *EDV* end-diastolic volume, *ESV* end-systolic volume, *HR* heart rate, *SV* stroke volume

40–160 min^{-1}, but can be significantly expanded in well-trained individuals [35]. Finally, the synchronized function of the atria and ventricles contributes approximately 15–20% into each SV because of the so-called overcharging ventricles with blood [36].

Stroke volume and systemic vascular resistance (SVR) are the main factors defining mean arterial pressure (MAP), which becomes individual for each cardiac cycle as SV variability rises [37], whereas the power consumption (W) of the ventricles is a product of pump performance (*i.e.,* CO) and pressure gradient (ΔP): $W = CO \cdot \Delta P$ (see Chap. 1). The latter is presented as the difference between mean arterial (output) and atrial (input) pressures. Neglecting the left heart input and central venous pressures, power can be presented as:

$$W = CO \cdot MAP = CO \cdot CO \cdot SVR = CO^2 \cdot SVR \quad (5.4)$$

Although Fig. 5.1 ignores many physiological variables and links—autonomous reflex pathways, arterial impedance, cardiopulmonary interactions, *etc.* [38]—it reflects principal terms and conceptual links and interrelations.

5.6 Cardiac Cycle and Interaction of Cardiac Output Determinants

In 1917, Hermann Straub presented the cardiac contraction cycle with closed loop in V–P orthogonal coordinates (Fig. 5.2a), showing many variables on the same plot: end-diastolic, end-systolic, and stroke volumes, systolic and diastolic arterial and end-diastolic left-ventricle pressures. The physiological meaning of loop elements [4] is described in Table 5.1. Loop changes can easily illustrate the influence of the main determinants of SV [39].

A preload rise (Fig. 5.2b) leads to an increase in SV because the EDV rise prevails over the ESV increase. From 1-2-3-4, the left ventricle (LV) loop moves to the right and becomes wider (5-6-7-8) with a significant rise in ejection fraction (EF) and stroke work. Systolic arterial pressure (SAP) increases, in contrast to the relatively unchanged diastolic arterial pressure (DAP). The afterload rise (Fig. 5.2c) at the first moment increases both SAP and DAP, with a decrease in SV due to an increase in ESV, but without changes in EDV or end-diastolic pressure (EDP;

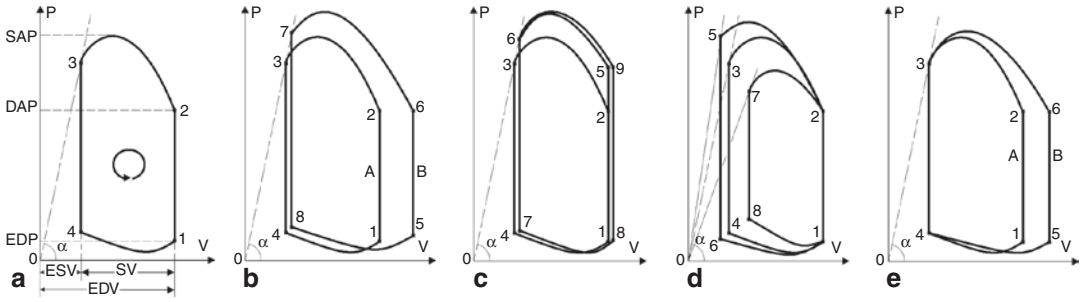

Fig. 5.2 Cardiac cycle: left ventricle volume–pressure closed loop diagram (**a**). Influence of various factors on the cardiac cycle and stroke volume (**b**–**e**). *DAP* diastolic arterial pressure, *EDP* end-diastolic pressure, *EDV* end-diastolic volume, *ESV* end-systolic volume, *SAP* systolic arterial pressure, *SV* stroke volume

Table 5.1 Physiological meanings of the left ventricle volume–pressure loop elements (Fig. 5.2) [4]

Loop element	Physiological meaning
Point 1	LV contraction beginning; mitral valve closure. EDV reflects preload as a pre-contractive cardiac myofibril length
Segments 1–2	Isometric (V = const) LV contraction; *dP/dt* reflects contractility (systolic elasticity) of the ventricle, isolated from both pre- and afterload influences
Point 2	Aortic valves opening; LV ejection beginning. Reflects afterload as maximal cardiac myofibril tension
Segments 2–3	LV ejection
Maximal pressure	Systolic left ventricle pressure ≈ systolic aortic pressure; transition between fast and slow ejection phases
Point 3	Aortic valves closure; LV ejection finish. Reflects contractility as LV wall tension at the moment of reaching ESV and ESP. Marked with dicrotic notch at the arterial pressure curve
Segments 3–4	Isometric (V = const) LV relaxation
Point 4	Mitral valve opening; beginning of LV diastolic filling
Segment 4–1	LV diastolic filling—passive and active (with atrial contraction)
Minimal pressure	The moment of the beginning of left atrium systole
Angle α (3-0-V axis)	Arctg(ESP/ESV) is the geometric LV contractility index
Angle 1-0-V axis	Arctg(EDP/EDV) is geometric LV diastolic elasticity (or compliance) index
1-2-3-4 loop area	LV stroke work
SV/EDV	LV ejection fraction

AP arterial pressure, *EDV* end-diastolic volume, *ESP* end-systolic pressure, *ESV* end-systolic volume, *LV* left ventricle, *HR* heart rate, *SV* stroke volume

1-5-6-7 loop). Then, however, a proportional rise of EDV occurs, and SV returns to the baseline (6-7-8-9 loop). Contractility changes (Fig. 5.2d) move only the left part of the loop with SAP, EF, and loop area changes, but without changes in the EDV, EDP, and DAP. In contrast, a decrease in elasticity (Fig. 5.2e) shifts only the right part of the loop: EDV, SAP, EF, and the loop area rise without changes in ESV, EDP, and DAP.

In the real world, however, the response of CO to afterload changes depends upon the preload level, and, *vice versa*, the preload shift may lead to different reactions in patients with different baseline afterload [40]. In 1969, C. Herndon and K. Sagawa described the 3D CO response surface (Fig. 5.3) of a healthy experimental dog heart–lung complex to the preload (mean right atrial pressure, MRAP) and afterload (MAP) shifts [41]. The most important fact is that within the

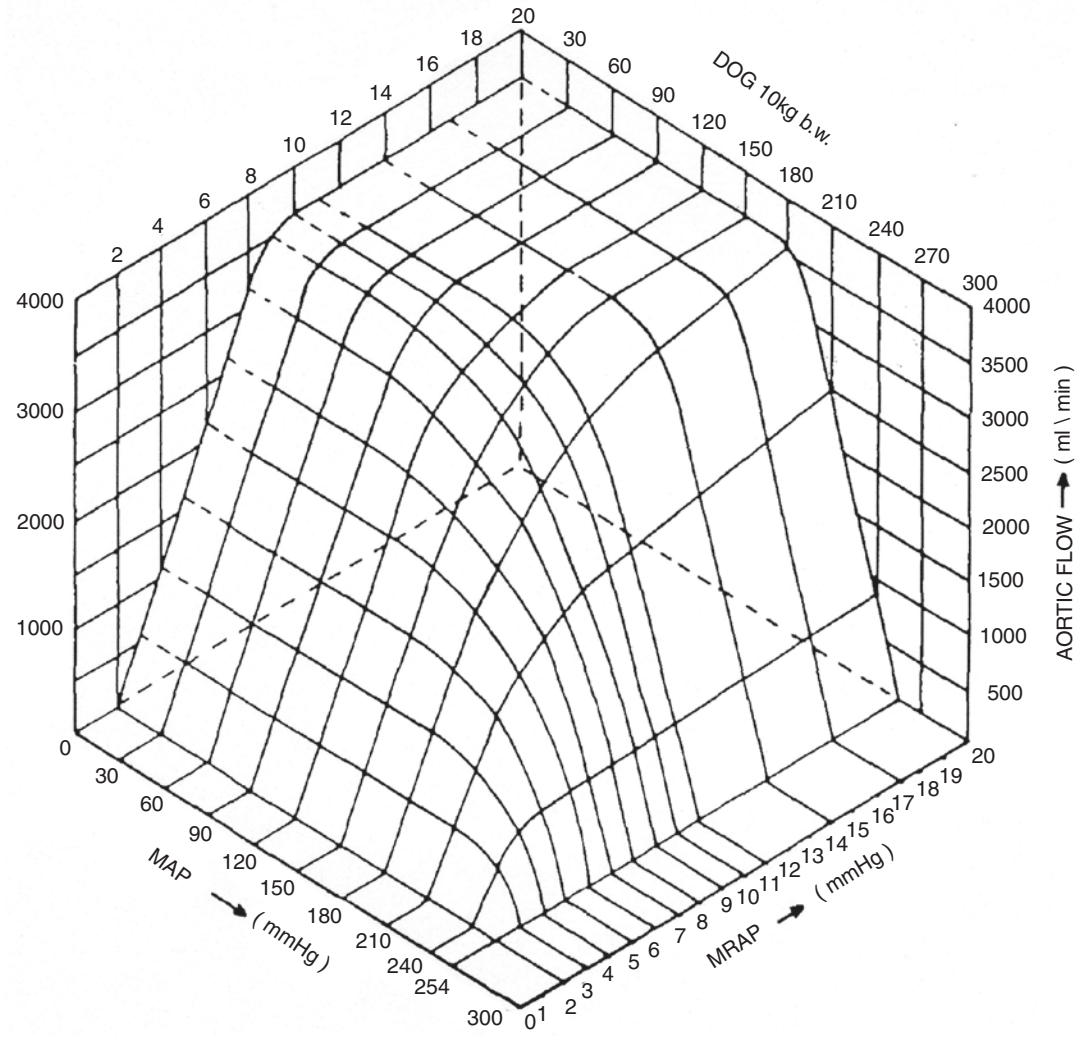

Fig. 5.3 Cardiac output surface in mean right atrial pressure—mean arterial pressure orthogonal coordinates (experimental dog heart–lungs complex [41]). *MAP* mean arterial pressure, *MRAP* mean right atrial pressure

whole range of physiological values, CO easily responds to preload (Frank–Starling curves family along the MRAP axis), whereas a depressive response to afterload increase appears only at high levels of MAP—above 120 mmHg. As physiologists say, CO is invariant in relation to the aortic pressure, whereas preload is the most potent physiological inotrope [42]. At the same time, the amplitude of CO response in both cases depends upon the level of the "second variable"—afterload for preload response and *vice versa*.

Practical Advice

A decision concerning preload or afterload change (volume load or diuretics, vasopressors or vasodilators, *etc.*) requires not only the 2D picture to be taken into account: the same infusion can result in a CO rise in patients with low or normal afterload, whereas a patient with high SVR may respond with a drop in CO; the response to vasodilators or pressors also depends upon volemic status, *etc.*

Table 5.2 *European Society of Intensive Care Medicine* statements on cardiac output measurement in the "Consensus on circulatory shock and hemodynamic monitoring" (2014, [45])

Statement/recommendation	GRADE level of recommendation; quality of evidence	Type of statement
We do not recommend routine measurement of cardiac output for patients with shock responding to the initial therapy	Level 1; QoE low (C)	Recommendation
We recommend measurements of cardiac output and stroke volume to evaluate the response to fluids or inotropes in patients who are not responding to initial therapy	Level 1; QoE low (C)	Recommendation
We suggest sequential evaluation of hemodynamic status during shock	Level 1; QoE low (C)	Recommendation
We suggest that inotropic agents should be added when the altered cardiac function is accompanied by a low or inadequate cardiac output, and signs of tissue hypoperfusion persist after preload optimization	Level 2; QoE low (C)	Recommendation
We recommend not giving inotropes for isolated impaired cardiac function	Level 1; QoE moderate (B)	Recommendation

5.7 Energy Cost of Cardiac Output

As mentioned above, ventricular power consumption (W) is defined by its performance (output) and provision of pressure gradient. At first sight, namely, these two variables should be main determinants of myocardial oxygen consumption (MVO_2). For arterial blood pressure it is partially true, but in contrast to W, MVO_2 is almost independent of CO itself: surprisingly, its best correlate is the area under the LV pressure curve during the ejection period, called "tension–time index" (TTI) in the classic paper by S.J. Sarnoff, E. Braunwald, and G.H. Welch (1958) [43]. This concept seems to be the initial point of our permanent perioperative struggle against hypertension and tachycardia, supported over the past few decades by Giora Landesberg's concept of nonthrombotic perioperative acute myocardial infarction due to so-called demand ischemia [44].

5.8 Conclusion

Cardiac output is one of the principal parameters of circulation and, therefore is amongst the main objects of hemodynamic monitoring. While measuring CO, one should know exactly what physical quantity was measured—ventricular SV, flow *via* the aortic root or the right heart and pulmonary artery, *etc*. Many different factors affect the performance of the heart ventricles—from relatively simple ones, such as diastolic filling pressures or systemic vascular resistance, to rather complex ones, such as cardiac rhythm. From a practical point of view, we do need to imagine clearly not 2D (such as the Frank–Starling curve) or even 3D pictures (such as Herndon and Sagava's plot) but actually multidimensional dependencies. For example, a catecholamine given at the same dosage can simultaneously influence contractility, afterload, ventricular compliance, and cardiac rhythm. The main statements concerning CO monitoring from the 2014 *European Society of Intensive Care Medicine* "Consensus on circulatory shock and hemodynamic monitoring" [45] are summarized in Table 5.2. As for any other monitoring modalities, physiological interpretation, or, sometimes, even the simplest question: "What is good and what is bad regarding CO in this exact clinical circumstance?" is the core problem of CO monitoring.

Keynotes

- Although being a "gross substitute" of exact organ (tissue) perfusion values, cardiac output is one of the most important hemodynamic variables, indicating a wide spectrum of syndromes—from

shock to malignant hyperthermia, and being a necessary (but not sufficient!) condition of global circulation adequacy.

- Cardiac output can be neither estimated properly from a physician's clinical experience, irrespective of qualification level, nor calculated from more available data such as blood pressure and heart rate; the only reliable source of the cardiac output value is direct measurement.
- Cardiac index, expressed in $L \cdot min^{-1} \cdot m^{-2}$, is the most comparable and normalized characteristic of cardiac output with a normal range of approximately 2.5–3.5 $L \cdot min^{-1} \cdot m^{-2}$.
- Cardiac output monitoring is now routinely available with numerous technologies that are not interchangeable regarding exact figures and normal ranges. Bedside use of any monitoring method requires knowledge of its limitations and sources of errors; sometimes only dynamic assessment or additional laboratory data give a reliable picture of systemic perfusion adequacy.
- Ventricle preload, afterload, diastolic elasticity, contractility, and rhythm are the main determinants of cardiac output, the influences of which are mutually dependent and often unavailable for selective control and even measurement. Therefore, therapeutic intervention for low cardiac output syndrome should be planned, taking into consideration all of these multidimensional interactions.

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Pulmonary Artery Thermodilution

6

Amelie Zitzmann, Daniel A. Reuter, and Benjamin Löser

Contents

6.1 Pulmonary Artery Catheter and Pulmonary Artery Thermodilution

A pulmonary artery catheter (PAC), also known as Swan-Ganz catheter, named after the American cardiologists Swan and Ganz, who introduced it into clinical practice in 1970 [1], provides the clinician with right-sided pressures and related parameters as well as mixed venous saturation. It is a useful monitoring device in situations, in which the knowledge of cardiac output (CO), pulmonary artery pressure

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(PAP), pulmonary artery occlusion pressure (PAOP), and oxygenation parameters is needed. It is the only device offering the possibility to assess and monitor right ventricular function and corresponding PAP continuously [2]. To date, cardiac output measurement using pulmonary artery thermodilution (PATD) is still considered the gold standard for bedside CO monitoring.

6.2 Background of Pulmonary Artery Thermodilution

In a structurally normal heart (without any intracardiac recirculation or shunting), blood flow through the right ventricular outflow tract (RVOT) is equal to a time-averaged CO of the left ventricle, commonly referred to as *the cardiac output*. Techniques to measure this blood flow are based on measuring the dilution of a known quantity of an indicator substance by the passing blood flow. The method most commonly used in clinical practice is thermodilution, which was first described by Branthwaite and Bradley in 1968 [3].

For PATD and CO monitoring using a PAC, a defined bolus of cool fluid is injected through a lumen at the central venous site. While the fluid bolus is then carried with the bloodstream through the right heart and into the pulmonary arteries, it mixes with the blood and is therefore diluted. Thus, the bolus gets warmer, whereas the blood temperature drops. This drop in temperature is recorded with a thermistor close to the tip of the catheter. With this blood temperature curve over time, the specific heat capacity and specific gravity of both blood and injectate as well as the volume of the injectate, the blood flow through RVOT and hence CO can be determined using the Stewart-Hamilton equation.

In addition to this bolus method, continuous cardiac output measurement is possible using modified catheters equipped with thermal filaments. These thermal elements generate heat pulses that are used for thermodilution similar to the cold bolus principle.

6.3 Derived and Calculated Hemodynamic Variables

PATD does not only provide the clinician with CO; additional variables can be derived or calculated from the measured parameters (Table 6.1).

6.3.1 Vascular Resistances

Physiologically, resistances are altered for circulatory regulation and for demand-based distribution of the blood into certain organs. Only the right heart catheterization enables the clinician to determine both systemic and pulmonary vascular resistances. In clinical practice, *systemic vascular resistance* (SVR) can help to differentiate between the various forms of shock, especially between hypotension with vasoconstriction or vasodilatation. Therefore, SVR can be a tool to guide therapy with vasopressors and/or inotropes.

Pulmonary vascular resistance (PVR) is the ratio of transpulmonary pressure gradient to pulmonary blood flow. Despite numerous attempts to quantify PAP and vascular resistance with less invasive means such as echocardiography or computed tomography imaging, none of them has proven accurate enough. Thus, right heart catheterization remains the method of choice to determine those parameters [4].

PVR itself or indexed to body surface area (BSA) as pulmonary vascular resistance index (PVRI) is used for diagnosis and guidance of treatment of pulmonary hypertension, for assessment of suitability for closure of atrial and ventricular septal defects [5], and for candidacy for cardiac transplantation [6]. In intensive care settings, PVR(I) commonly serves as a surrogate for right ventricular afterload, therefore guiding vasopressor and inotropic therapy of right ventricular dysfunction and failure [7].

Practical Advice

Particularly with poor contractile function, cardiac output is strongly dependent on afterload. Thus, when treating low cardiac output, information on afterload given by vascular resistances is important.

Table 6.1 Pulmonary artery thermodilution: calculated and derived parameters

Parameter	Description	Calculation [standard values]
Cardiac index (CI)	Cardiac output related to body surface area (BSA)	CI = CO/BSA [2.5–4.5 L/min/m^2]
Stroke volume (SV)	Volume of blood pumped into the systemic circulation by the left ventricle per heartbeat	SV = CO/HR [70–100 mL]
Stroke volume index (SVI)	SV referenced to BSA	SVI = SV/BSA [36–48 mL/m^2]
Systemic vascular resistance (SVR)	Determinant of left-ventricular afterload and often used as a surrogate	SVR = ((MAP-CVP)/CO) × 80 [800–1500 dyn × s/cm^5]
Systemic vascular resistance index (SVRI)	SVR related to BSA	SVRI = ((MAP-CVP)/(CO × BSA)) × 80 [1600–2500 dyn × s/cm^5/m^2]
Pulmonary vascular resistance (PVR)	Resistance that blood must overcome to pass into the pulmonary vasculature	PVR = ((PAPmean–PAOP)/CO) × 80 [90–150 dyn s/cm^5]
Pulmonary vascular resistance index (PVRI)	PVR related to BSA	PVRI = (PAPmean–PAOP)/CO × BSA) × 80 [160–270 dyn × s/cm^5/m^2]
Stroke work index (SWI)	Work done by each ventricle to eject the stroke volume in relation to BSA	LVSWI = SVI × (MAP–PAOP) × 0.0136 [45–80 g m/m^2] RVSWI = SVI × (PAPmean-CVP) × 0.0136 [5–10 g·m/m^2]
Right ventricular function index (RVFI)	Ratio of systolic pulmonary artery pressure to cardiac index	RVFI = PAPsys/CI [risk factor of mortality in pulmonary arterial hypertension if >35 mmHg/L/min/m^2]
Pulmonary arterial capacitance (C_{PA})	Quantifies stiffness of the pulmonary arteries	C_{PA} = SV/(PAPsys–PAPdias) [mL/mmHg; no standard values]

CO cardiac output, *CI* cardiac index, *BSA* body surface area, *SV* stroke volume, *HR* heart rate, *SVI* stroke volume index, *SVR* systemic vascular resistance, *SVRI* systemic vascular resistance index, *PVR* pulmonary vascular resistance, *PVRI* pulmonary vascular resistance index, *SWI* stroke work index, *LVSWI* left ventricular stroke work index, *RVSWI* right ventricular stroke work index, *RVFI* right ventricular function index, C_{PA} pulmonary arterial capacitance, *MAP* mean arterial pressure, *CVP* central venous pressure, *PAPsys/mean/dias* systolic/mean/diastolic pulmonary artery pressure, *PAOP* pulmonary artery occlusion pressure

6.3.2 Stroke Work Index

Stroke work can be used for the evaluation of contractility. For better interindividual comparability, stroke work is often indexed to body surface area, resulting in stroke work index (SWI). Stroke work calculation is done separately for each ventricle as pressure-volume-work, neglecting kinetic work. It represents the area bound by corresponding pressure-volume loops.

Left ventricular stroke work index (LVSWI) will decrease in the case of heart failure and usually increase in response to treatment with inotropes. However, LVSWI only represents the area within the pressure-volume loop, but not its position on the axes. Several factors can simultaneously influence the left ventricular performance. Changes in preload, ventricular compliance, and function can displace the pressure-volume-loops and the area between the slopes. Inferences about the cause of altered function cannot be made, and LVSWI as a single parameter should not be used to guide therapy. However, it can provide information on left ventricular systolic function, especially in cases where left ventricular ejection fraction does not reliably represent cardiac performance, *e.g.,* in cases with mitral regurgitation [8].

Also, preoperative LVSWI has been found to be a significant predictor of outcome after mitral valve surgery for functional regurgitation in non-ischemic dilated cardiomyopathy: lower preoperative values of LVSWI are associated with worse outcome [9].

During the cardiac cycle, the right ventricle pumps an equal stroke volume as the left ventricle, but at markedly lesser stroke work. A high *right ventricular stroke work index* (RVSWI) is

associated with worse kidney function in patients with heart failure with preserved ejection fraction [10]. In contrast, patients with low RVSWI show an increased risk for the need of a right ventricular assist device after left ventricular assist device implantation [11].

6.3.3 Right Ventricular Function Index (RVFI)

RVFI is a measure of load-adaptability, *i.e.,* it can be used to evaluate the extent to which (elevated) PAP is associated with right ventricular function. A right ventricle, which can increase its contractility and therefore preserve its stroke volume in response to an increased afterload, should stay well compensated—albeit at increased workload. In contrast, with right heart failure, a previously elevated PAP may decrease [12]. An increase in RVFI is then interpreted as a ventricular-vascular mismatch and is associated with poor survival in critically ill patients with severe pulmonary hypertension and in patients undergoing cardiac surgery [13, 14].

6.3.4 Capacitance

Capacitance quantifies the stiffness of the pulmonary arteries. Pulmonary arterial stiffness plays an important role in right ventricular remodeling and therefore might be a target for altering right ventricular failure. It can also predict survival independently from resistance in heart failure with reduced or preserved ejection fraction as well as in idiopathic pulmonary arterial hypertension [15–17].

6.4 Step-by-Step Approach for Clinical Practice

6.4.1 Step 1. Indication

In critically ill patients, a PAC should be used if a hemodynamic situation raises a specific question that remains unanswered by clinical examination or less invasive methods. Possible indications are listed in Table 6.2, contraindications (Table 6.3) need to be considered to avoid harm to patients. Figure 6.1 may be a helpful approach in decision-making. Monitoring and treatment of right ventricular dysfunction and pulmonary arterial hypertension remain the domain of the right heart catheterization and PATD [2].

Table 6.2 Indications for pulmonary artery catheters and thermodilution

Cardiogenic shock with • Right ventricular dysfunction/failure (*e.g.,* myocardial infarction) • Low cardiac output (CI < 1.2 L/min/m^2) • IABP-support
CO monitoring in patients with severe aortic or mitral wave regurgitation
In patients with specific questions, such as assessment of • Pulmonary arterial pressure • Pulmonary vascular resistance • Right ventricular pressure • Pulmonary artery occlusion pressure • Pulmonary shunt-volumes/fractions • Mixed venous oxygen saturation
For cardiac surgery in • Patients with severe left ventricular dysfunction • High-risk patients with complex procedures • Special procedures (*e.g.,* LVAD-implantation, cardiac transplantation)

CO cardiac output, *CI* cardiac index, *IABP* intra-aortic balloon pump, *LVAD* left ventricular assist device

Table 6.3 Absolute and relative contraindications for pulmonary artery catheters and thermodilution

Absolute	• Right-sided endocarditis • Thrombus/tumor in RA or RV • Mechanical tricuspid or pulmonary valve replacement • Inexperienced intensivist regarding to measurements and data interpretation
Relative	• Bioprosthetic tricuspid or pulmonary valve replacement • Transvenous pacemaker, especially <7 days since implantation • Left-bundle branch block • Severe aortic valve stenosis

RA Right atrium, *RV* Right ventricle

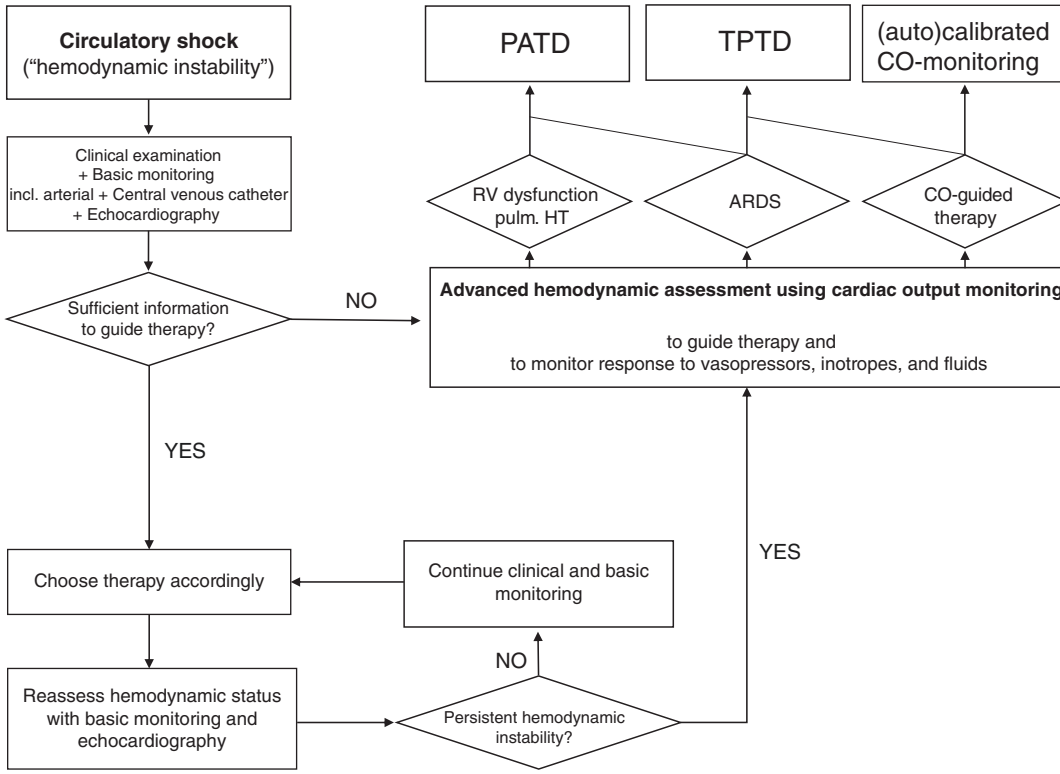

Fig. 6.1 Indications for thermodilution [29, 30]. *PATD* pulmonary artery thermodilution, *TPTD* transpulmonary thermodilution, *CO* cardiac output, *RV* right ventricular, pulm. *HT* pulmonary hypertension, *ARDS* acute respiratory distress syndrome, *CO* cardiac output

Practical Advice

Pulmonary artery catheterization and thermodilution should not routinely be used in patients with shock but should be considered in patients with refractory shock and in particular when right ventricular dysfunction is present or suspected.

6.4.2 Step 2. Preparation and Obtaining Pulmonary Artery Occlusion Pressure

To achieve high-quality and reliable results, the preparation is equally essential as the performance of the PATD itself. Therefore, check that all catheters are in place, connected to the monitor, zeroed to atmospheric pressure, and the specific waveforms (arterial, central venous, and pulmonary arterial) with reasonable values are displayed. A so-called flush-test can be useful to check for damping. At this stage, performing a pulmonary artery occlusion maneuver can help to verify the correct position of the PAC and determine PAOP (which is needed for later calculations) at the same time. For reliable calculation of PVR(I), the tip of the catheter needs to be located in West zone III, where pulmonary artery pressure and pulmonary venous pressure are greater than alveolar pressure, thus ensuring continuity in the fluid column between the left atrium and the catheter tip [18].

Practical Advice
When the tip of the PAC is in West zone III, PAOP should be lower than diastolic pulmonary artery pressure and should be altered less than 50% of changes in positive end-expiratory or plateau pressures during mechanical ventilation.

Make sure that the proximal and distal thermistors are connected to the monitor and that the proximal thermistor is connected to the central venous port of the PAC. After verifying the settings at the CO monitor (patient's data, set injectate type (commonly NaCl 0.9%), volume, and constants), prepare syringes with cooled solution respecting hygiene rules in order to avoid catheter-associated bloodstream infections. For the injectate volume, refer to the settings of the CO monitor. The colder and the larger the volume, the better the signal-to-noise ratio [19]. The highest reproducibility of CO measurements in critically ill patients was demonstrated with 10-mL iced injectate, which also reflects the common clinical practice.

6.4.3 Step 3. Performing Pulmonary Artery Thermodilution

Due to a short indicator transit time from the injection site at the right atrium to the thermistor at the pulmonary artery, a single PATD measurement is usually shorter than a respiratory cycle. The right ventricular output may vary due to cyclic changes in venous return and right ventricular afterload during both spontaneous breathing and mechanical ventilation. Thus, for performing PATD, certain aspects on the timing of the injections need to be considered: performing PATD at the same moment of the respiratory cycle should create reproducible values for subsequent comparison. On the other hand, measurements performed in that manner might still not represent the mean CO or even the relative phasic changes in the flow; therefore, pseudorandomized injections at different positions at the respiratory cycle could better reflect the current CO and better enable comparison [20].

In order to reduce errors and to average results, a series of injections should be performed. Clear recommendations on the number can not be given, but it seems that three injections, although clinically mostly performed, are insufficient with regard to accuracy and reproducibility [21, 22]. Injections need to be done as fast and smoothly as possible. The results of the individual measurements should be within a 10% range. Reject aberrant measurements (outside the 10% range) and the sets with highest and lowest results. If necessary, repeat PATD.

6.4.4 Step 4. Calculation and Interpretation of Hemodynamic Variables

Analysis and interpretation should always take the patient's context and the current clinical situation into account. In contemporary CO monitors, calculations are performed automatically. With attention to typical reasons for erroneous results in PATD (Table 6.3), use all available findings to guide therapy. Consider preexisting clinical conditions and diseases as well as medication and functional or laboratory monitoring of organs that are most likely affected by cardiac dysfunction (*i.e.,* the brain, kidneys, liver, and gut).

Therapy goals should be defined and aimed at individually for every patient. Choose the therapy in accordance to pharmacology and physiology with the help of corresponding guidelines [23].

6.5 Risks and Limitations of Pulmonary Artery Thermodilution

As a result of the SUPPORT trial [24, 25], a high number of intensivists is reluctant to use the PAC in monitoring critically ill patients, most likely due to persistent doubts about its safety and its efficacy in guiding beneficial therapy. In addition, the PAC faces competition from supposedly

less invasive hemodynamic monitoring devices such as transpulmonary thermodilution, pulse contour analysis, and echocardiography.

Like any other device, the PAC and therefore PATD have risks that need to be considered (Table 6.4). However, careful operation of the catheter will reduce them to a minimum. The PAC-specific risks (0.3% severe complications, 0.1% attributable mortality) have been reported to be lower as the risks associated with transesophageal echocardiography.

Specific conditions can lead to erroneous results (Table 6.5), but even with correctly determined variables, misinterpretation with potential consecutive inappropriate therapies is a well-known phenomenon [26].

For the so-called continuous CO monitoring PAC, it must be taken into account that it cannot be used for CO surveillance in rapidly changing hemodynamic situations. They have a certain delay in displaying CO (3–12 min) as the CO is averaged over several cardiac cycles [27].

Table 6.4 Adverse events associated with pulmonary artery catheters and thermodilution

During catheter insertion/access	• Arterial puncture • Pneumothorax • Air embolism • Nerve damage/neuropathy • Arrhythmias from minor dysrhythmias to VT or VF, RBBB • Pulmonary artery rupture • Damage of valves (tricuspid, pulmonary)
With catheter long-term use	• Pulmonary artery rupture • Pulmonary infarction • Catheter-associated bloodstream infections • Valvular or endocardial vegetations • Thrombus formation (vascular, mural)

VT ventricular tachycardia, *VF* ventricular fibrillation, *RBBB* right bundle branch block

6.6 Conclusion

PATD still is the gold standard for CO measurement. The proper use requires a profound theoretical and clinical knowledge, not only about patients' pre-existing conditions but also about the limitations, pitfalls, and difficulties in interpreting measurement results. For the experienced user, PAC/PATD provides a comprehensive view of the hemodynamic situation, which can help optimize global oxygen balance.

Table 6.5 Sources of measurement errors and variability [28]

Overestimation of CO	Inconsistent changes in CO	Underestimation of CO
Loss of indicator (injectate volume or temperature) • Prior to injection (volume too small) • During injection (dissipation through intravascular catheter portions, catheter dead space) • After injection (conductive rewarming, diversion of indicator from normal itinerary, especially in right-to-left intracardiac shunts)	• Significant tricuspid regurgitation • Irregular respiratory pattern • Concurrent IV infusions • Exogenous cooling/warming • Extrasystolia • Uneven injection technique • Prolonged injection time • Transient lowering of heart rate during cold indicator injection	• Left-to-right intracardiac shunts • Hypoxic pulmonary vasoconstriction at the part of the pulmonary artery tree where the PAC resides, *e.g.,* due to pneumothorax, pneumonia

CO cardiac output; *IV* intravenous, *PAC* pulmonary artery catheter

Keynotes

- Pulmonary artery thermodilution (PATD) is a valuable tool to determine cardiac output and derived parameters in critically ill patients.
- Right ventricular failure and associated and contributing diseases in the critical care setting are the domain of PATD. In addition, derived parameters can help in decision-making in interventional or surgical therapy of cardiac conditions.
- The complexity of parameters needs careful and skilled interpretation in the context of the individual patient.

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Transpulmonary Thermodilution

7

Evgenia V. Fot and Vsevolod V. Kuzkov

Contents

7.1 Introduction

The optimal management of the critically ill patients demands precise and continuous monitoring of multiple clinical parameters. Over the past decades, the transpulmonary thermodilution technique (TPTD) has gained a wide application in the ICU settings and partially replaced pulmonary artery catheter (PAC) in the area of advanced hemodynamic monitoring. This technique integrates a variety of static and dynamic hemodynamic parameters. The knowledge of TPTD variables and of those obtained with the pulse contour analysis after calibration by thermodilution can help in the decision-making process in shock, ARDS, severe trauma, burn injuries, and high-risk surgical procedures. The TPTD is less invasive compared to PAC and provides relevant information regarding cardiac output, preload, systolic function, and lung edema.

7.2 Methodology

The TPTD requires a central venous access and a specific thermistor-tipped arterial catheter, which is usually inserted into the femoral artery. During thermodilution, a known volume of a cold indicator, typically 0.9% saline, is injected into the vena cava *superior* or the right atrium, mixing with the blood flow in the right heart, pulmonary circulation, left heart, and aorta. An arterial thermistor-tipped catheter records the changes in circulating blood temperature and generates a thermodilution curve. The cardiac output (CO) can be calculated

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from the area under thermodilution curve using the Stewart-Hamilton equation:

$$CO = K \times V_{inj} \times \left(T_b - T_i\right) / \int \Delta T_b \times dt$$

where K is the correction constant, V_{inj} is the injectate volume, T_b is the blood temperature, T_i is the injectate temperature, and $\int \Delta T_b \times dt$ is the integral of the temperature change over time (reflecting area under thermodilution curve).

The measurement of CO by TPTD serves as a calibration value for the calculation of CO derived from the arterial pulse contour waveform, which allows continuous (beat-to-beat) CO monitoring. The methodology of transpulmonary thermodilution measurements is described in detail in Table 7.1 and Fig. 7.1.

In addition to CO, several volumetric variables including global end-diastolic volume

Table 7.1 Calculation of the selected transpulmonary thermodilution-derived hemodynamic variables

Variable	Calculation
Intrathoracic thermal volume (ITTV)	CO × MTt
Pulmonary thermal volume (PTV)	CO × DSt
Global end-diastolic volume (GEDV)	ITTV–PTV
Intrathoracic blood volume (ITBV)	1.25 × GEDV [1]
Stroke volume (SV)	CO/HR
Global ejection fraction (GEF)	(4 × SV)/GEDV
Cardiac function index (CFI)	CO/GEDV
Cardiac power index (CPI)	MAP × CO
Extravascular lung water (EVLW)	ITTV–ITBV
Pulmonary blood volume (PVB)	ITBV–GEDV
Pulmonary vascular permeability index (PVPI)	EVLW/PBV

CO cardiac output, *MTt* mean transit time, *DSt* downslope time, *HR* heart rate, *ITTV* intrathoracic thermal volume, *PTV* pulmonary thermal volume, *GEDV* global end-diastolic volume, *EVLW* extravascular lung water, *PVPI* pulmonary vascular permeability index, *PBV* pulmonary blood volume, *ITBV* intrathoracic blood volume, *MAP* mean arterial pressure

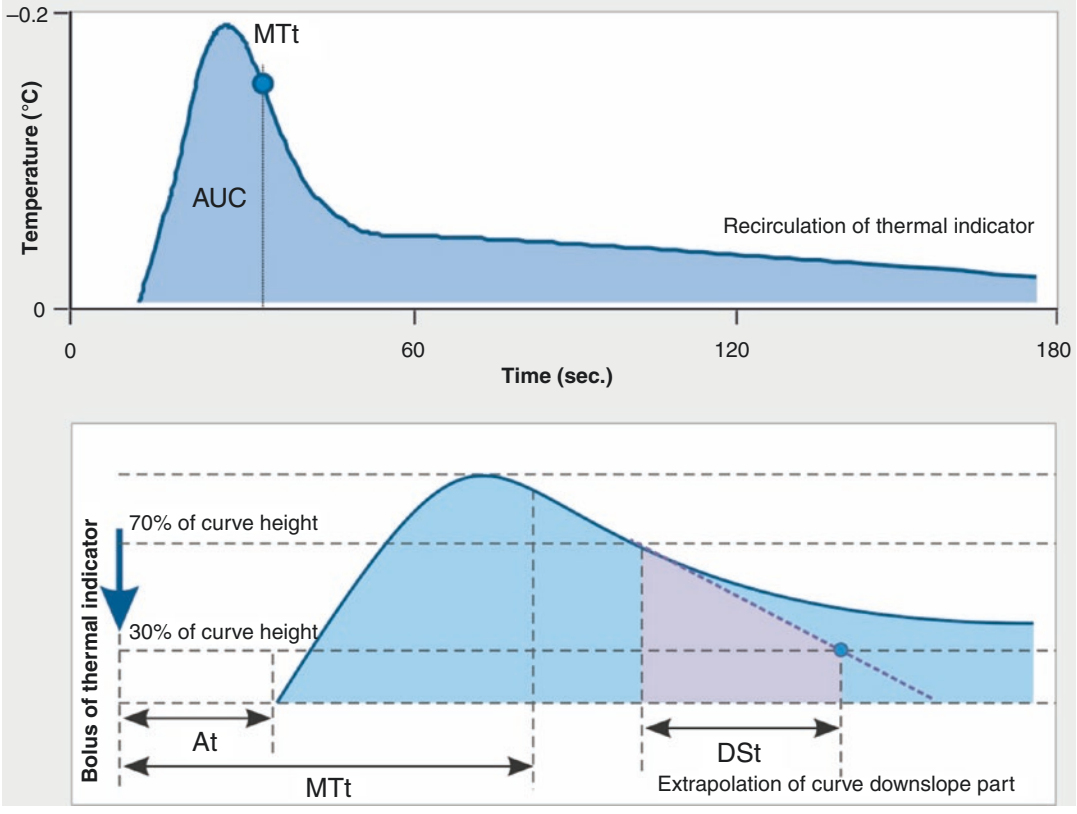

Fig. 7.1 The transpulmonary thermodilution curve and mathematical analysis. The mean transit time (*MTt*) is the mean time required for the indicator to reach the detection point at the tip of the arterial catheter (mostly positioned in the femoral artery) and the downslope time (*DSt*) is the exponential decline time of the thermodilution curve. *At* appearance time, *AUC* area under curve

(GEDV) and extravascular lung water (EVLW) can be readily measured and calculated from the mean and downslope times of cold indicator (see Chaps. 12–14). The values of several TPTD-derived variables are indexed for body weight or surface area, while recent models of monitoring systems use predicted body weight (PBW) and predicted body surface area (BSA) for the personalized volumetric management.

Today, two TPTD devices are commercially available: the PiCCO system (PULSION Medical Systems, Feldkirchen, Germany), now integrated into the PulsioFlex platform (Getinge, Gothenburg, Sweden), and the VolumeView™ system, which is incorporated in the EV1000 platform (Edwards Life Sciences, Irvine, USA) [2]. In addition, Philips, Dräger, Mindray, Nihon Kohden and GE have modules allowing to use the PiCCO arterial catheter and central venous catheter injectate device with their monitoring systems. Figure 7.2 demonstrates the schematic view of the system for TPTD.

Several important steps should be followed for the correct bedside application of TPTD. These steps are also shown at electronic supplementary material (courtesy of Drs. Evgenia V. Fot and Dmitry A. Svirsky, Department of Anesthesiology and Intensive Care Medicine, Northern State Medical University, Arkhangelsk, Russian Federation):

- Check and input correctly the biometric parameters (weight, height, gender).
- Perform a visual assessment of the arterial waveform, and perform a rapid flush test by ejecting a small volume of thermal indicator into the arterial catheter. The square waveform generated after the test has been suggested as a suitable method for determining the adequate dynamic response characteristics of the monitoring system.
- Place the pressure transducer at the phlebostatic axis (at the level of the right atrium), and zero the system against the ambient pressure.
- Measure and enter the central venous pressure for the calculation of the systemic vascular resistance.
- Prepare the correct solution for bolus injection. It is recommended to use 0.9% normal saline with a volume of 0.2 mL/kg (maximum

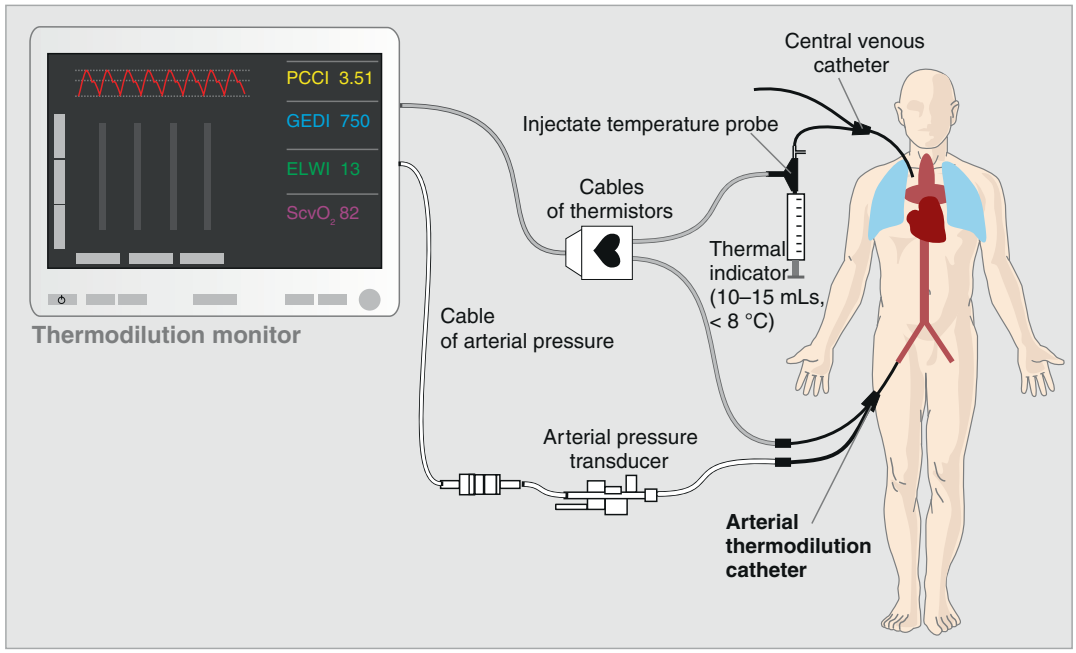

Fig. 7.2 The schematic presentation of the transpulmonary thermodilution

20 mL)—usually 15 mL for adult patient. It is important to inject the exact amount that was pre-set on the monitor. For the correct measurement of EVLW, the injectate temperature should be less than 8 °C [3].

- Injection should be performed in the most distal lumen of the central venous catheter, and the connection should be as close to the patient as possible. A fast and steady injection is recommended at a speed of >2.5 mL/s. The whole bolus hence should be injected for less than 6 s for a 15 mL [4].
- Perform the assessment of the TPTD curve. A typical TPTD curve has a flat portion, which reflects the transit time of the cold injectate from the injection site to thermistor, followed by a rise and fall in $\Delta T°$ with an exponential decrease, ending by a plateau due to physiological recirculation of the indicator.
- A series of at least three cold boluses is needed to obtain an adequate precision of the measurements [2]. A single measured value of CO should not deviate by more than 15% from the mean value. The same is true for GEDVI and EVLWI.

The most common conditions and sources of the erroneous measurements leading to the incorrect results of TPTD are listed in Table 7.2.

The specific limitations of the TPTD should be recognized. If cardiac index is severely decreased (typically, below 1.5–2.0 L/min/m^2), particularly, in combination with a relatively low heart rate, TPTD may not provide any reliable results because of prolonged thermodilution curve. Another limitation of TPTD for measuring CO is that it performs only intermittent measurements. The continuous "beat-to-beat" pulse contour analysis provides real-time monitoring of CO, although calibration must be performed every 6–8 h during the steady state or every time, when CO is needed for interpreting the

Table 7.2 Common conditions and errors influencing on variables obtained with transpulmonary thermodilution

Source of error	Comments
Incorrect technique of injection	An interrupted injection can cause the thermodilution curve to be bifid with over- or underestimation of the volumetric indices If the femoral vein is used for injection, all TPTD values like CO, GEDVI, and EVLWI are increased, due to the longer transit time of the indicator and the augmented volume participating in thermodilution. The femoral arterial catheter should not be inserted on the same side as the femoral vein catheter [5] The room temperature of injectate leads to a systematic overestimation of CO, GEDVI, and EVLWI [3]
Shunts	Shunts influence the shape of the thermodilution curve. The TPTD can be a simple tool to diagnose and monitor the right-to-left intracardiac shunting in ARDS patients [6]. A left-to-right shunt is characterized by an early recirculation of the cold indicator responsible for a premature flattening of the descending portion of the curve, resulting in an increased mean transit time (up to 25%) and increased downslope time (up to 50%) and hence affecting EVLWI [7]
Effect of CRRT	Continuous renal replacement therapy has no major clinical impact with a small decrease in CO and GEDVI and a small increase in EVLWI [8]. The effects may be more pronounced if CO is low and the blood flow over the circuit is high [9]
Effect of ECMO	Marked increases in GEDVI and EVLWI after the onset of ECMO. CO and hemodynamic parameters not derived from TPTD are not affected by the extracorporeal circuit [10]. In other opinion, ECMO can be considered as a contraindication to TPTD [2]
Valvular disorders and heart function	Regurgitation of the thermodilution injectate can prolong the transit time of the indicator or interfere with the thermodilution curve. The long and flat running of the thermodilution curve may result in an overestimation in the GEDVI and EVLWI. Mitral regurgitation gives a consistent increase in the volumetric parameters, while aortic stenosis gives an inconsistent increase
Pleural effusion	The pleural effusion of large volume leads to an overestimation of EVLWI, because the cold indicator also diffuses in the pleural liquid [11]. Most recent data have questioned the serious influence of pleural effusion on the accuracy of TPTD [12]

Table 7.2 (continued)

Source of error	Comments
Pneumonectomy	The correct calculation of the CO and GEDVI is possible in patients after pneumonectomy. The underestimation of the EVLWI is dependent on the amount of lung resection, whereas the trend of the EVLWI remains accurate [13]
Pulmonary embolism	The GEDVI will be overestimated, while the EVLWI will be underestimated [14]. In the case of pulmonary embolism complicated with an opening of *patent foramen ovale* and transient right-to-left shunting, the "camel"-like thermodilution curve can be observed
Aortic aneurism	In patients with an aortic aneurysm and a femoral arterial catheter, GEDVI and ITBVI are overestimated due to the volume of the aneurysm; thus axillary, brachial, or a long radial catheter might be recommended [15]
Ventilator settings	The theoretical effects of PEEP on the measurement of EVLW by TPTD are contradictory [2]. The PEEP increase can directly result in the increase of EVLWI due to the blockade of lymphatic flow [16]. One-lung ventilation can affect estimation of EVLWI [17]

TPTD transpulmonary thermodilution, *CO* cardiac output, *GEDVI* global end-diastolic volume index, *EVLWI* extravascular lung water index, *ARDS* acute respiratory distress syndrome, *PEEP* positive end-expiratory pressure, *ECMO* extracorporeal membrane oxygenation, *CRRT* continuous renal replacement therapy

hemodynamic changes [18]. A specific limitation of GEDV is that it does not distinguish between left and right cardiac preloads. In practice, in the case of the right ventricular dilation, GEDVI is increased, while the left ventricular preload is normal [19, 20]. In patients with septic shock, GEDV increases along with fluid administration but remains constant during dobutamine administration despite increased CO [21]. It has been suspected that mathematical coupling exists between GEDV and CO since both variables are derived from the same thermodilution curve.

The TPTD is contraindicated in the case of femoral vascular prostheses (with the radial or axillar arteries as possible alternatives for the femoral insertion site) and, plausibly, extracorporeal membrane oxygenation [2, 22]. Since TPTD needs catheterization of the artery and central vein, the procedure requires evaluation of the coagulation profile including platelet count, fibrinogen, international normalized ratio, and activated partial thromboplastin time. As has been shown in a multicenter trial, TPTD can be accompanied by minor problems such as oozing after insertion (3.3%) or the removal of the catheter (3.5%), small local hematomas after insertion (4.5%) and after the removal (1.2%) of the catheter, site inflammation (2%), catheter-related infection (0.78%), ischemia (0.4%), pulse loss (0.4%), or femoral artery thrombosis (0.2%) [23]. However, the use of TPTD catheters did not increase the risk of complications when compared with the commonly used short peripheral arterial catheters or PAC [23]. Thus, the risk of possible complications of TPTD should be weighed against the severity of the patient condition and possible benefits. Therefore, TPTD is justified, first of all, for high-risk surgical or critically ill patients [24] and recommended by the European Society of Intensive Care Medicine as a part of the current standard for managing shock and ARDS [25].

7.3 Conclusions

The TPTD is an advanced monitoring technique providing complex view into the hemodynamic profile of the patient at the bedside. Being less invasive compared with pulmonary arterial catheter, TPTD is safe in the overwhelming majority of cases if take into account the indications and contraindications for the procedure. In addition to the assessment of cardiac output, TPTD provides a wide spectrum of clinically relevant hemodynamic parameters characterizing preload, contractility, fluid status, and vascular permeability. However, before using TPTD, the clinician should be aware of the fact that none of the monitoring systems are able to improve patient outcome unless coupled with an appropriate treatment algorithm utilizing the evidence-based interventions and personalized patient care.

Keynotes

- Transpulmonary thermodilution is an invasive technique of bedside volumetric hemodynamic monitoring providing valuable information regarding cardiac output, global contractility, preload status, lung edema, and vascular permeability.
- The strict and thorough adherence to the technical requirements is of paramount importance to provide clinically plausible and reproducible measurements.
- Specific conditions, clinical scenarios, and technical errors may result in either overestimation or underestimation of TPTD-derived parameters.
- Further studies of "patient-specific" values of the parameters obtained by TPTD and algorithms of personalized management are warranted.

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Pulse Wave Analysis

8

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8.1 Introduction: Pulse Wave Analysis from a General Hemodynamic Measurement Viewpoint

Among the most important physiological roles of the cardiovascular system is the transport of oxygen molecules into the tissues. Cardiac output (CO) is a major and also the most variable determinant of this delivery and is sometimes called "the sixth" vital function. The need for precise monitoring of cardiac output in critically ill/high-risk surgical patients dates back to the past century. The gold standard of CO monitoring was established with the introduction of the pulmonary artery catheter (PAC) in clinical practice during the 1970s. Unfortunately, PAC use is accompanied by multiple complications because of its invasiveness and its use has diminished over the years. Moreover, several new systems for less invasive cardiac output monitoring have been developed. Pulse wave analysis systems are considered as "minimally" invasive methods. They are used either in a "calibrated" manner together with another (often more invasive) technique (thermodilution) or as a single technological solution without calibration. These (true "minimally invasive") methods require only a conventional arterial line to acquire an input signal. This minimal invasiveness plays a major role in the risk-benefit profile of the hemodynamic treatment in the individual patient. Advanced hemodynamic monitoring is recommended to optimize cardiovascular status in high-risk surgery [1] and critically ill patients [2]. However, for example, in major abdominal surgery, the general risk of a poor outcome is less than 5%, although the reported incidence of PAC-associated complications is in fact higher [3]; thus, it is more feasible to use a less-invasive technique of cardiac output monitoring.

8.2 Basic Technology Consideration

The idea that from an arterial pulse wave signal one could obtain flow variables is not new. The original works of Otto Frank in late nineteenth century paved the way for mathematical models to do so. However, without sophisticated computer technology, their bedside use was illusory. The stroke volume (SV; and subsequently multiplying heart rate [HR] by CO) is acquired continuously beat-to-beat (or by averaging a few beats within a very short time window). This acquisition is not a direct measurement of stroke volume, but mathematical estimation only. This fact is crucial to understanding the limits of the method. The input signal of each device is gained from the arterial pressure waveform. Stroke volume is a variable of volume; thus, there must be a conversion of pressure to volume measurement, which is not straightforward from a mathematical point of view. Obtaining flow from pressure needs precise knowledge of the pressure–volume relationship in the arterial vessel tree, especially in large arteries. This was the issue of the Windkessel model (air chamber/elastic reservoir) originating in 1899 with Frank [4].

Unlike Frank's Windkessel, current models use a complex relation of three or more elements. These models describe pressure–flow relations in the arterial system throughout three main parameters—peripheral resistance (systemic vascular resistance, SVR), total arterial compliance (Ca), and aortic characteristic impedance (Za). Briefly, Za is the ratio of pressure to flow in central arteries. It is determined mechanically by the strain forces of the arterial wall against the propagation of the pressure wave along with the vascular system. The Ca is defined as the blood volume and intraluminal pressure relationship. It depends on the elastic properties of the arterial wall. These conversion factors (Ca, Za, or others) are difficult to measure directly; therefore, they are usually somehow estimated to calculate flow from pressure. Models not based on the Windkessel model have been developed nowadays, but the idea of conversion of pressure to flow using mathematical calculation and assumed conversion constants describing properties of the cardiovascular system underlies all of them.

8.3 Calibrated Systems

Nowadays, several PWA systems are available on the market. Based on the method of acquisition of conversion factors, they are divided

into calibrated and uncalibrated. Calibrated devices gain the conversion constants using an intermittent technique of CO assessment (such as thermodilution), which is integrated into the system. This makes these monitors more invasive but less prone to erroneous measurement.

Two systems are calibrated using transpulmonary thermodilution: the PiCCO system (Getinge, Gothenburg, Sweden) and VolumeView system (Edwards Lifesciences, Irvine, CA, USA). After injection of cold saline bolus into the central vein, CO is calculated from the thermodilution curve recorded in the central artery. Another device—LiDCOplus (LiDCO, London, UK) is calibrated using the lithium dilution technique. After injection of a small amount of lithium chloride into central vein (but a peripheral catheter may be used as well), a lithium dilution curve is detected in any artery.

During the calibration, the dedicated constants (basically, variables describing actual properties of the vascular tree) are established, enabling further continuous assessment of SV/CO based on similar PWA algorithm to the uncalibrated counterparts. The calibration interval is between 3 and 6 h regardless of the dilution technique. Abrupt changes in the properties of the cardiovascular system occurring between calibrations may severely decrease the monitor's accuracy; in particular, systemic resistance plays a major role. Therefore, recalibration should be performed after major manipulations with vasopressor and inotropic drugs.

8.4 Uncalibrated Systems

In the uncalibrated group, four devices/systems categorized as minimally invasive are available—the FloTrac system incorporated into the EV1000 or Hemosphere devices (Edwards LifeSciences, Irvine, CA, USA), the ProAQT system of the PulsioFlex monitor (Pulsion, Maquet Getinge Group, Gothenburg, Sweden), PulseCO™ algorithm integrated into several LiDCO monitors (LiDCO, London, UK), and finally the pressure recording analytical method (PRAM) by MostCare (Vytech health, Padova, Italy; Table 8.1).

Uncalibrated PWA devices are connected either to the standard arterial line or they take a continuous pressure signal from whichever patient monitoring system. There is an ongoing debate whether different arteries could be used interchangeably. Physiologically, there are differences in arterial curve shape regarding the distance from the heart. Moreover, in some pathological conditions (such as sepsis or high-dose vasopressor therapy), the arterial pressure in central and peripheral arteries can differ significantly. These factors interfere with PWA accuracy; thus, one must comply with each manufacturer's recommendations. Sometimes, the arterial catheter location needs to be identified in the PWA device settings.

Unlike calibrated devices, uncalibrated systems use advanced internal nomograms based on various demographic data and/or autocalibration by the properties of the curve itself to allow for pressure–flow conversion. Specific constructors'

Table 8.1 Overview of the pulse wave analysis methods

Name	Manufacturer	Technical background	External calibration
FloTrac IQ (Vigileo, EV 1000, Hemosphere)	Edwards LifeSciences, Irvine, CA, USA	Analysis of arterial pressure curve shape	No
ProAQT® (PulsioFlex, PiCCO2)	Maquet Getinge group, Gothenburg, Sweden	Pulse contour analysis	External CO input
PulseCO™ (LiDCOrapid, LiDCOplus, LiDCO unity)	LiDCO, London, UK	Pulse power analysis	External CO input
PRAM™ (MostCare)	Vytech health, Padova, Italy	Pressure analytical method	No

CO cardiac output

solutions are proprietary. Pulse wave analysis allows not only estimation of CO and SV, but also some more advanced dynamic variables, such as stroke volume variation, pulse pressure variation, *dP*/*dt*max, and others. Moreover, some of these devices enable external calibration by manual input of actual CO values derived from whichever technology. This makes some of the PWA algorithms more robust and allows more precise CO estimation.

8.5 Measurement Preconditions

A continuous arterial pressure curve of sufficient quality is crucial for the PWA. The signal must avoid over- and underdamping. Over- and underdamped lines indicate that the dynamic response of the system might not be suitable for analysis. This situation seems to be common in critical care units (up to 30% of cases) [5]. Unfortunately, the automatic detection of arterial wave quality is not incorporated into most PWA devices; it depends on operators' visual inspection. Checking the signal quality should be done regularly by the rapid flush test. After termination of the square line from the rapid flush, the pulse waveform should return after one to three oscillations. No visible oscillation indicates overdamping; on the contrary, more than three oscillations detect underdamping. Correct damping allows systems to recognize the dicrotic notch, which is crucial for identifying systolic and diastolic portions of the arterial curve.

Practical Advice

Thorough assessment of the quality of the pressure curve and optimal damping using the fast flush test must be performed regularly to obtain reliable SV/CO estimation by PWA.

8.6 Specific Technology Consideration

8.6.1 The FloTrac System

Edwards Lifesciences Inc. (Irvine, CA USA) has marketed FloTrac IQ (previous version named "FloTrac") since 2005. The FloTrac transducer is directly connected to a standard (radial or femoral) arterial catheter and may be used with several monitoring platforms of the same manufacturer—Vigileo (nowadays retracted), EV1000, and the brand new Hemosphere. The system does not allow external calibration and is based on mathematical/statistical analysis of the shape of the arterial pressure curve. The basic principle can be described by the relationship between pulse pressure (PP) and SV. Pulse pressure is represented by standard deviation (σ_{AP}) of the measured data points (Fig. 8.1). The frequency of acquiring these data points is at present 100 Hz; standard deviation is calculated in a 20-s window. Using σ_{AP} instead of PP eliminates the influence of the reflected pressure wave from the distal part of the arterial tree, making it usable in different arterial locations. σ_{AP} is multiplied by the χ (khi) factor, which represents a polynomial function of arterial wall physical characteristics (actually, arterial compliance), heart rate, mean arterial pressure (MAP), and waveform details (coefficients of kurtosis and skewness). Arterial compliance is estimated using Langevouter's equation, based on a large database of subjects, and depends on gender, age, height, and weight. All these variables must be entered manually before measurement starts. The in-depth waveform analysis processing is kept secret. The χ factor is re-calculated every 20 s; in fact, this corresponds to "autocalibration". The fourth generation of software has an expanded internal database and improved SV tracking with elimination of abnormal beats (due to arrhythmia).

$$APCO = PR \cdot (\sigma_{AP} \cdot \chi)$$

$\chi \approx$ HR, σ_{AP}, BSA, MAP, C(P), μ_{3ap} – skewness, μ_{4ap} – kurtosis

Fig. 8.1 The FloTrac equation and HemoSphere device. *APCO* arterial pressure cardiac output, *PR* pulse rate, σ_{AP} standard deviation of arterial pressure, χ khi factor, *HR* heart rate, *MAP* mean arterial pressure, *BSA* body surface area, *C(P)* aortic compliance estimation. Image courtesy and copyright of Edwards Lifesciences Corporation

Practical Advice

The FloTrac IQ is minimally invasive with precautions linked only to arterial puncture complications. It provides continuous CO monitoring as well as some more advanced hemodynamic parameters. Its accuracy might be unsatisfactory in patients with severe vasoplegia, arrhythmias, and aortic valve diseases—factors that modify the arterial waveform, especially its compliance. The model is calibrated for subjects within the weight range from 40 to 150 kg.

8.6.2 ProAQT® Algorithm

The ProAQT® technology is based on pulse contour analysis and is the same as for continuous CO tracking (during intervals between thermodilution calibration measurements) with a PiCCO device and the uncalibrated version of the PulsioFlex monitor; both manufactured by Pulsion (Maquet Getinge Group, Gothenburg, Sweden). For initiation of the measurement, two possibilities can be chosen—the first is to manually enter CO values from the reference method (thermodilution, echocardiography, *etc.*), the second is autocalibration, which is an estimation of CO based on a database of patients' characteristics. This autocalibration can be reassessed whenever by the user.

The sampling of waveform has a frequency of 250 Hz. It works only with the systolic part of the curve (to the dicrotic notch in other words; Fig. 8.2). It has an internal calibration factor (k), which corresponds to the arterial impedance. After autocalibration, trends in CO are assessed by pulse contour analysis. The shape of the arterial curve is reflected by dP/dt integration into the systolic portion of the curve. The idea is that through continuous measurement, any change in systolic area under curve corresponds to a change in CO. Systemic vascular resistance is derived from mean arterial pressure and CO validated by calibration, and serves to increase the accuracy of the method as well as the k factor.

Practical Advice

The ProAQT® largely depends on a high-quality arterial curve. Because of dependency on arterial vascular tone estimation (k factor), any significant fluctuation of afterload might lead to inaccurate values. Cardiac arrhythmias possess similar limits to other PWA devices. Unlike others, the device enables external calibration using any technology.

$$nCO = k.\ HR\ .\ \int_{systole}\left[\frac{P(t)}{SVR} + C(p)\ .\ \frac{dP}{dt}\right]\ .\ dt$$

Fig. 8.2 The PiCCO/ProAQT equation and PulsioFlex device. *nCO* nominal cardiac output, *k* calibration factor, *HR* heart rate, *P(t)/SVR* area under the pressure curve, *C(p)* compliance, *dP/dt* shape of the curve. Image courtesy and copyright of Pulsion Medical Systems SE—Getinge group

8.6.3 PulseCO™

The PulseCO™ algorithm is included into LiDCO devices (LiDCO, London, UK)—namely LiDCO Rapid, LiDCO Unity, and calibrated LiDCO Plus. Uncalibrated devices are connected to the patient through a standard arterial line as with previous systems, but do not need any special transducer. Besides, a non-invasive continuous pressure curve obtained by CNAP™ technology may be used. Moreover, it can cooperate with standard monitors of vital signs *via* analog output. Calibration is allowed by imputing CO from the reference method. The PulseCO™ technology background is so-called pulse power analysis based on the law of conservation of energy and mass. The arterial curve over time is transformed to the volume over time curve (Fig. 8.3). It does not rely on the shape of the arterial pressure curve. The algorithm incorporates population nomograms, which calculate aortic volume from demographic data (such as age, gender, height, *etc.*), the "cal" element in the equation. The stroke volume value is further adjusted from pressure by an exponential function containing the value of arterial blood pressure and an estimation of aortic compliance (internal autocorrelation). Data are gained beat-to-beat.

Practical Advice

Unlike pulse contour analysis devices, pulse power analysis might be more robust, with a lower quality signal. As it does not rely on the morphology of the curve, reflecting the pressure wave from the periphery is not an issue; thus, it can be used in every arterial location almost interchangeably. Contraindications are conditions related to anatomical cardiac abnormalities that can compromise the accuracy of the PulseCO™, such as aortic valve regurgitation and intra-aortic balloon pump.

8.6.4 Pressure Recording Analytical Method

The MostCare (Vytech health, Padova, Italy) system is based on the PRAM algorithm. It determines the arterial impedance from perturbations of the arterial pressure waveform. It does not use any internal population-based nomograms. The system does not require a special transducer or any external calibration. The impedance estimation is based on a small radial

$$\Delta V = cal \times \Delta P \times SO \times e^{-k \times p}$$

Fig. 8.3 The PulseCO equation and LiDCO device. Simplified pressure—volume change transformation of the PulseCO. Image courtesy and copyright of LiDCO

expansion of the vessel in response to pressure variations ("perturbation" or "points of instability") characterized by modification of velocity and acceleration in the relationship to the previous and the next point. These points are mainly caused by backward traveling waves from the distal periphery. In other words, analysis depends on the morphology of the arterial wave. It records data with a sampling frequency of 1000 Hz and calculates impedance with every heartbeat, which allows a higher degree of precision. Further calculation of CO uses the area under the systolic part of the curve divided by an impedance value (Fig. 8.4). Unlike other devices, MostCare offers a large panel of hemodynamic variables, including dicrotic pressure, arterial elastance, *etc*. However, most of these variables have not been thoughtfully studied yet and their real clinical impact remains questionable so far.

Practical Advice

MostCare is less invasive and does not rely on population nomograms. Nevertheless, the limits are predominantly caused by dependency on extremely high-quality arterial pressure signal. Possible inaccuracy might be observed in vascular diseases (such as atherosclerosis).

8.7 Precision, Trending Ability, Validation

The limits of acceptable accuracy (ability to give the true value) of CO monitoring devices was historically set up by Critchley and Critchley [6], who showed that the limits of agreement of absolute CO values between PWA and a reference method (PAC, *etc.*) are supposed to be within 30%. Precision (the ability of the device to give reproducible results) and trending (the ability to follow changes) are both important for correct assessment of CO change over time. Clinically, precision and trending are actually more important than absolute CO values (accuracy). Uncalibrated systems have been extensively studied regarding these aspects. Currently, based on their demonstrated clinical utility, we accept a certain limit of inaccuracy.

The FloTrac algorithm has been validated more extensively than the others. Slagt et al. in a meta-analysis [7] concluded that the accuracy of the monitor under normo- or hypodynamic conditions is sufficient, as well as trending ability. Moreover, detecting rapid changes in SV and thus trending in stroke volume variation (SVV) has been shown to be satisfactory in comparison with the PiCCO device [8]. The clinical algorithms with this parameter have been validated in several studies, especially in perioperative care [9, 10]. The third generation software was considered reliable even in cardiac and septic

$$SV = \frac{Asys}{Z(t)}$$

Fig. 8.4 The PRAM equation and MostCare Up device. *Asys* area under the systolic curve, *Z(t)* system impedance. Image courtesy and copyright of VYGON

patients, although with a percentage error of 29% [11]. However, FloTrac has been demonstrated to be unreliable under certain pathological circumstances, for instance, in patients with low SVR [12], high-dose vasopressor therapy [13], and during liver transplantation and cardiac surgery. According to the manufacturer, the accuracy and trending ability were claimed to improve in each software version. However, the validation studies of the current (fourth) generation could not show sufficient accuracy in a state of low SVR or low CO common in critical care.

Regarding the ProAQT™ algorithm, there are some concerns over calibration frequency necessary. The uncalibrated algorithm is based on the calibrated PiCCO pulse contour, which is known to be prone to increasing inaccuracy over time and under changing resistance conditions. For perioperative care, which is rarely longer than 4 h and mostly associated with preload changes, clinical use is advocated. Indeed, the PulsioFlex monitor was successfully employed in a multicenter perioperative optimization study [14].

The PulseCO™-derived preload responsiveness parameters (SVV, pulse pressure variation [PPV], and systolic pressure variation) have been shown to be accurate predictors of fluid responsiveness in postoperative ICU patients receiving sedation and mechanical ventilation [15]. However, Davies et al. [16] compared LiDCOrapid with esophageal Doppler in high-risk surgery with the conclusion that only SVV had any clinical utility without any meaningful agreement in CO values.

The PRAM monitor has very few validation studies [17]. In CABG patients, Giomarelli [18] has shown that PRAM is accurate for real-time CO estimation during surgery. On the contrary, the results in septic patients were unsatisfactory [19]. In another study, Donati et al. [20] compared PRAM, PiCCO, and PAC in a medical–surgical ICU with a percentage error below the 30% threshold.

8.8 Pulse Wave Analysis in Clinical Practice

Nowadays it is recommended to use advanced perioperative hemodynamic monitoring in high-risk surgery patients owing to the potential of lowering morbidity and mortality [1]. The PWA devices with acceptable accuracy and trending are beneficial in this situation when low invasiveness is a clear advantage. Moreover, the derived parameters such as SVV and PPV are extremely useful in these conditions. Pulse wave analysis is also useful in post-anesthesia care units. Unfortunately, PWA should not be used during

procedures when arterial tone is profoundly affected—such as in liver transplantation surgery or sepsis. In cardiac surgery, because of extensive manipulation of all three CO domains, using PWA devices is generally inappropriate, with the need for more invasive methods.

In critical care, CO monitoring should be used when a shock of known origin leads to hemodynamic instability, which persists after initial therapy. According to recent guidelines [21], uncalibrated PWA devices are not supposed to be used in these settings. Calibrated PWA coupled with dilution methods (thermal or lithium) are particularly designed for this purpose. Moreover, such devices can focus on advanced fluid management through markers of fluid overload (extravascular lung water and pulmonary vascular permeability index).

Practical Advice

Uncalibrated PWA monitors offer clinically useful assessment of trends in hemodynamic variables during the perioperative period. Improvements in graphical interfaces and use of alternative variables (stroke volume variation, *etc.*) further help in the functional assessment of temporary changes and therapeutic effects. In case of doubt regarding validity of measured values some of these devices enable external calibration using thermodilution or echocardiography.

For complex cases, and especially in the ICU, calibrated technologies should be used.

8.9 Conclusions

Pulse wave analysis technology is a cornerstone of today's advanced perioperative hemodynamic management with the potential to decrease complications and improve outcomes. Several different technologies are marketed; thus, it is crucial to be familiar with those chosen in a particular setting as they might differ in performance under heterogenous conditions. Increasing accuracy and new hemodynamic variables are expected in the future.

Keynotes

- PWA devices estimate cardiac output from the arterial pressure curve signal using sophisticated computer technology.
- A continuous arterial pressure curve of sufficient quality is obligatory.
- Nowadays, four different devices are marketed.
- Uncalibrated PWA monitors offer clinically useful assessment of trends in hemodynamic variables during the perioperative period.
- For complex cases (especially in the ICU) calibrated technologies should be used.

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Doppler Techniques

9

Lester A. H. Critchley, Li Huang, and Jie Zhang

Contents

9.1 Basic Principles

The Doppler method of measuring blood flow is based on generating high-frequency sound waves, or ultrasound, that are passed through the body and used to detect the flow of the red blood cells in the blood vessels such as the aorta. Unlike conventional ultrasound which images the underlying tissues by sending out pulses of ultrasound and detecting returning waves as they bounce off tissue interfaces at different distances from an ultrasound probe, the Doppler detects the shift in ultrasound frequency caused by movement. The faster the movement, the greater the frequency shift which is plotted on a vertical axis against time along a horizontal axis to produce a velocity profile. Positive frequency shifts arise from flow toward and negative shifts from flow away from the probe.

The probe contains a crystal that oscillates at a high frequency (*i.e.,* 2–4 MHz) when an alternating current is passed through it, the piezo-electric

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effect, and this generates an ultrasound beam. The same, or second, crystal produces an electric current when caused to vibrate by the reflected ultrasound waves. The crystal can be used as either a transmitter or a receiver. The resulting electrical signal is amplified to produce a Doppler velocity profile that represents the blood flow in the vessel. By measuring the area under the curve during one heartbeat cycle, a variable is derived known as the velocity time interval (VTI) or stroke distance (SD).

To measure stroke volume, one also needs to know (1) the cross-sectional area (CSA) of the vessel which is multiplied by the VTI. Multiplying by the heart rate gives cardiac output. The CSA is either measured by echocardiography or estimated from the subjects' age and height using an algorithm. If the direction of the ultrasound beam is at an angle (θ) to the direction of blood flow, the Doppler shift, and thus VTI, is reduced. The extent of attenuation is proportional to the cosine of θ; where in line with the direction of flow (*i.e.,* parallel), there is no attenuation (×1.0), but at right angles to the flow (*i.e.,* perpendicular), there is no detected Doppler shift (×0.0). A deviation (θ) from the line of flow of up to 25° produces an attenuation of <×0.9 or less than 10%.

Doppler ultrasound is considered to be safe. The heating effect on the insonated tissue is minimal. However, the insertion of an esophageal probe could potentially cause the patient mechanical harm, and the probe should be tested for electrical safety.

9.2 Methods in Clinical Use

Pulsed systems: Most echocardiographs also perform Doppler measurements. A region of interest is found using ultrasound imaging, and then the Doppler signal from the region is displayed. Often colors are used to display blood velocity. The diameter of the vessel, and thus the CSA, can also be measured. The most commonly used technique uses the apical window and measures flow exiting the left ventricle.

Continuous wave Doppler: This requires a probe with both transmitting and receiving crystals working simultaneously. Two methods are currently used clinically:

1. Transthoracic Doppler which uses either (a) the suprasternal route to measure from the aortic valve (AV) outflow and (b) the precordial route *via* the left third or fourth rib space to measure from the pulmonary valve (PV). The only available device that performs these measurements is the UltraSound Cardiac Output Monitor or USCOM (USCOM Ltd., Sydney, Australia). Its use is intermittent because a handheld probe is used that does not maintain itself in a focused position.
2. Esophageal Doppler which uses a flexible probe that passes through the nose or mouth and down the esophagus to lie beside the descending aorta in the lower thorax. It is the only truly continuous method because the probe remains in a focused position. The principle device currently being sold is the CardioQ (Deltex Medical Ltd., Chichester, UK). It uses a disposable probe. A reusable esophageal Doppler probe system is available, the Waki-To (Atys Medical, Soucieu en Jarrest, France). Arrow International produced a reusable probe system called the HemoSonic 100, but this was discontinued in 2006.

Measurements can also be made by placing a transducer directly on the aorta, pulmonary artery, or other vessel. Such measurements can only be made in special circumstances such as open-heart surgery or animal research. Directly placed probes provide more accurate readings. Strictly speaking these are not Doppler measurements as the current standard, Transonic probes, uses ultrasound transit time to detect blood flow. Previously electromagnetic flow probes were used.

9.3 The USCOM

The USCOM 1A was launched in 2003 and since then its design has not changed significantly. It is a robust, lightweight (6.5 kg), portable standalone unit with batteries and plug in handheld probe (Fig. 9.1). It produces both a visual and

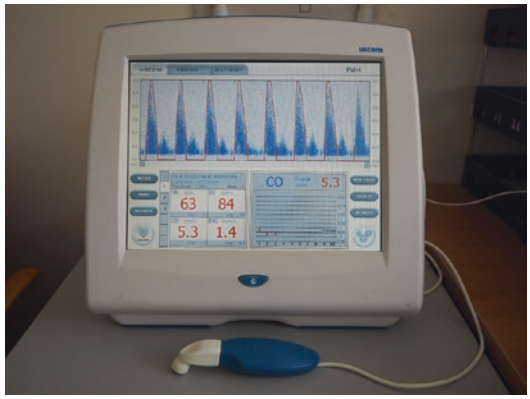

Fig. 9.1 USCOM monitor and handheld probe. The screen shows velocity profiles outlined by flow trace software. Beneath are four selected parameters and trend plot

audible Doppler signal. It has a touch screen display which provides three screen views including (1) waveforms, (2) trends, and (3) patient reports. Measurements are made on the screen by outlining the captured velocity profile, which is done either automatically by flow tracking software or by hand using a touch point function. By inputting the measured variables such as blood pressure, oxygen saturation, and hemoglobin level a number of other circulatory parameters are generated which facilitate the use of decision charts. The USCOM can be used to measure the flow from either the aortic or pulmonary outflow tracts. During anesthesia the suprasternal approach (AV) is preferred, while the precordial approach (PV) is used in more ambulatory situations.

9.4 Velocity Profile Acquisition

Aortic measurement: The USCOM in AV mode uses a 2.2-MHz handheld probe which is applied on the patient's suprasternal notch. The transmitter/receiver surface is circular and makes a right angle with the handle. The direction of the beam is aimed toward the root of the heart and aortic outlet. The beam is focused to obtain the maximal resolution Doppler signal either visually or by listening to the audible sound. Focusing involves rotating the probe head in both the (1) anterior-posterior and (2) right-to-left lateral directions. Once focused the probe is held in position until a series of velocity profiles are saved on the screen. One screen sweep takes 7.5 s. Cardiac output and other parameters are calculated in real-time. The probe and software are designed to provide optimum readings (Table 9.1). However, in some patients, the velocity profile is suboptimal and provides unreliable data (Table 9.2: USCOM 1–6). The velocity profile can be score for its quality and reliability [1, 2].

Table 9.1 Factors that improve performance

1.	The USCOM uses a divergent beam (*i.e.,* cone shaped), so its area of capture is larger than a conventional ultrasound imaging beam. The CardioQ probe is sited in close proximity to the descending aorta within the thorax
2.	Flow detection is continuous as two Doppler crystals, transmitter and receiver, are used
3.	Both the USCOM and CardioQ use the peak flow signal to outline and perform calculations. When using the USCOM, the peak signal comes from the narrowest point in the aortic outflow track proximal to the valve where flow rate is greatest. Because the flow is pulsatile and originates from the left ventricle, the laminar flow does not form, and all the red blood cells move at the same velocity. Beyond the outflow the thoracic aorta distends which slows the flow rate
4.	The USCOM relies on the beam being parallel to aortic outflow. Having a divergent beam helps in this respect. Furthermore, misalignments of up to 25° cause only minor attenuations of the Doppler signal (*i.e.,* ×0.9 or <10%)
5.	Training to ensure proper focusing of the beam and correct recognition of aortic or pulmonary blood flow plus well-designed software that allows a good operator to device coordination help to guarantee good signal acquisition

Pulmonary artery measurement: The USCOM in PV mode uses the same 2.2-MHz handheld probe. The third or fourth left intercostal space beside the sternum is insonated. The flow in the pulmonary artery is away from the probe, giving an inverted velocity profile. It helps to have the patient in a left lateral position (Table 9.2: USCOM 2, 7). Focusing the probe is similar to the suprasternal approach and is better tolerated. The PV and AV readings should be similar, which is a useful check for correct signal acquisition.

Table 9.2 Common problems encountered when using continuous wave Doppler devices

	Site	USCOM
1	AV	In some patients it can be difficult to insert the probe far enough into the sternal notch and the beam is block by the sternal bone
2	AV	When probe placement and signal detection proves to be difficult, it can be quite uncomfortable and painful for the patient. Even when anesthetized the patient may be stimulated which leads to higher-than-resting readings. Heart rate increases provide a good guide to probe causing stimulation
3	AV PV	There are many flow signals that arising within the thorax, the largest being from the aortic outflow. Unfamiliarity with the technique can lead to the wrong signal being selected and the device underreading
4	AV	Calcification of the aorta can prevent sufficient beam energy reaching the aortic outflow and a greatly attenuated Doppler signal results. This is commonly encountered in elderly patients [5]
5	AV	Age-related tortuosity of the aortic arch can also effect signal detection [6]
6	AV	In high cardiac output states such as sepsis or anemia, the USCOM can overread because spikes in the velocity profile occur that are caused by turbulence. The flow-tracking function is particularly susceptible, and re-outlining the flow profile using touch point can help
7	PV	In some patients it can be difficult to insonate the pulmonary artery because the highly echogenic lung edge obstructs the beams passage, and this can be made worse when the lungs are hyperinflated by positive pressure ventilation
		CardioQ
1	OES	The esophageal probe is uncomfortable restricting its use to anesthetized, sedated, and unconscious patients. Furthermore, the patient needs to have a normal esophagus, and the presence of oro−/nasogastric tubes and devices may block the probe's beam
2	OES	A recognizable Doppler flow profile is not always detected, and this is probably due to air or esophageal spasm. There may also be a morphological reason resulting in the esophagus not lying adjacent to the descending aorta. If available, reviewing a thoracic CT scan can help to identify a reason
3	OES	The probe can pick up signals from the pulmonary or celiac vessels if wrongly positioned. The Deltex medical website provides good information on the correct signal identification
4	OES	The aorta becomes wider and longer with aging, and this effects the angle made by the ultrasound beam with the aorta. Unfolding of the aorta can be seen on the chest radiograph. Small movements in the insertion depth can cause significant changes in the size of the velocity profile due to changes in the insonation angle [7]
5	OES	The aorta becomes wider with age, and the rate of flow within the aorta becomes less for the same cardiac output. The CardioQ adjusts for this aging effect when calibrated. However, conditions such as hypertension can cause the aorta to age faster than predicted by the algorithm

Calibration: The USCOM measures flow (VTI) and cross-sectional area (CSA) of the vessel has to be derived from a height-based algorithm [3]. The algorithm is only accurate up to 16% (95% confidence limits) which contributes to the reported percentage error (PE) in Bland-Altman style comparative studies.

9.5 Esophageal Doppler

Development of esophageal Doppler by Deltex Medical, formerly Doptek, dates from the late 1980s [4]. The CardioQ is a portable bedside monitor that attaches to a disposable esophageal probe. Over the years there have been a number of soft and hardware modifications, and it now accommodates other hemodynamic monitoring modalities. Early prototypes had an additional external transthoracic probe, the SupraQ. Today the system supports pulse pressure using the Liljestrand–Zander algorithm and impedance cardiography in their ODM+ and TrueVue models. It displays the Doppler velocity profile in real time which is outlined to measure cardiac output. Trends are also displayed. Data can be downloaded. Operation is by knobs and buttons (Fig. 9.2).

The Waki-To is made by a French company, Atys Medical, that produces a range of clinical ultrasound devices. It has a reusable esophageal probe with higher-quality crystals than dispos-

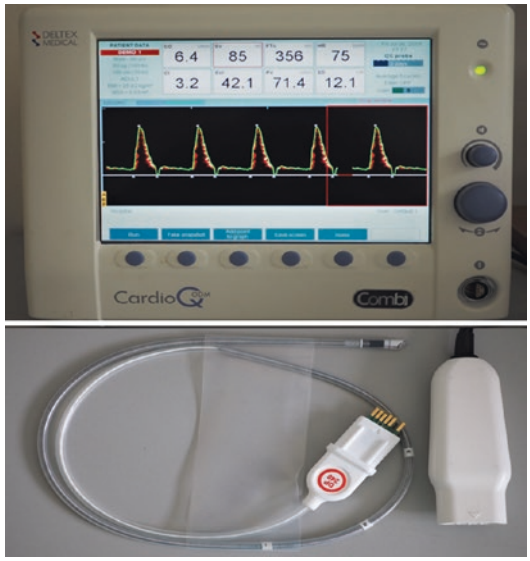

Fig. 9.2 CardioQ and esophageal probe. COMBI research model. The screen shows outlined flow profiles with measured parameters displayed above which is controlled by knobs and buttons. Beneath flow profile an arterial pressure trace can be displayed. Probe has sealed tip with two transducers at 45°, flexible wire stalk with depth markers and plug connector with computer memory chip

able probes. The display and velocity profile analysis function are similar to the CardioQ.

The CardioQ probe has a flexible wire stalk that facilitates insertion and positioning with markers to indicate insertion depth. The tip has two ultrasound crystals (4 MHz), transmitter and receiver, that are set at a 45-degree angle. The tip is sealed and tested for electrical safety (Fig. 9.2). A memory chip records calibration data, time and date. Probes range between 6-h and 10-day use. They are sterile packed and designed for single use.

The probe is inserted to 35–45 cm so that the tip lies about the level of the sixth thoracic vertebrae behind the heart. It is focused by rotation and adjusting depth. Both visual and audible signals can be used. An acceptable visual flow profile has a well-formed crescent shape with no diastolic extension. However, the alignment of the probe's beam can move and refocusing is required. A nose clip can be used to maintain insertion depth. Flow profile morphology can be used to diagnose different hemodynamic states.

Calibration: The CardioQ is calibrated using an internal algorithm based on the height derived from population data. Age is needed because the descending aorta widens with age and loss of elasticity (Table 9.2: CardioQ 4, 5). Accuracy relies on the descending aorta and esophagus lying parallel and the split ratio (*i.e.,* 0.3:0.7) between the aortic blood flow to the upper body (*i.e.,* subclavian and jugular arteries) and lower body remaining constant. It is worth noting that a significant proportion (*i.e.,* 25–30%) of the descending aorta's blood flow occurs during diastole due to elastic recoil, and the proportion varies with changes in afterload.

9.6 Readings

In addition to stroke volume and cardiac output, the USCOM measures stroke volume variation (SVV) and an inotropy index (ION). The CardioQ measures Flow Time corrected (FTc) to a 60-s period, which is used like SVV to drive goal-directed fluid therapy.

9.7 Clinical Utility and Reliability

The USCOM is sold worldwide. It has a wide range of reported applications including hemodynamic evaluation of athletes in training, medical patients, emergency room assessment and resuscitation, intraoperative fluid management, critical care, and pediatric/neonatal use. Over 500 papers have been published on its reliability and clinical utility. The vast majority of validation studies have been Bland-Altman style comparisons with other methods. A meta-analysis of data from these studies has found the USCOM to be no more precise than other methods with a PE of 43% [8]. Errors that arise from its method of calibration and faults with operator technique rather than the lack of soundness of the Doppler method may account for the high PE [9].

The USCOMs ability to track changes in cardiac output has been under researched, presumably because of the difficulties in performing suitable studies, especially in the clinical setting.

The authors of this chapter performed a number of studies published between 2013 and 2016 that concluded that (1) with cross checking and (2) attention to detail Doppler methods can provide reliable trend data in the clinical setting [10, 11] and (3) that the shifts in calibration found with other methods are less common [12, 13].

The CardioQ is also sold worldwide. Its main clinical application has been to guide fluid therapy by optimizing the Frank–Starling curve. Boluses of intravenous fluid (*i.e.,* 200 mL over 5 min) are recommended, and an increase in stroke volume of greater than 10% shows fluid responsiveness which initiates further boluses. An alternative test is to raise the legs. In 2011, NICE (National Institute for Health and Care Excellence, UK) recommended using the CardioQ as part of an ERAS (Enhanced Recovery After Surgery) program, notably bowel surgery. More recent publications that support using the CardioQ during surgery include the FEDORA trial [14].

9.8 Obstacles to Clinical Acceptance

Doppler techniques that monitor cardiac output have been available for over 20 years, yet they have never been fully accepted into clinical practice. Possible reasons include (1) a lack of development and marketing, (2) poor financial model, (3) high operator dependency, (4) does not work in every patient, and (5) a lack of familiarity with using Doppler data by clinicians (Table 9.3).

Practical Advice

- Continuous wave (CW) Doppler is an underused hemodynamic monitoring modality.
- Two Doppler modalities are used: (1) Transthoracic (USCOM) and (2) Doppler (CardioQ & Waki-To).
- One has to gain proficiency in the uses of these CW Doppler techniques to obtain reliable data.

Table 9.3 Reasons for the lack of acceptance of the continuous wave Doppler monitoring

1.	Currently marketed Doppler flow devices are produced by small independent companies that lack the finance to develop fully the potential of their product
2.	The USCOM has minimal running costs to support suppliers financially, whereas the CardioQ requires a costly single-use disposable probe which limits clinical use. Neither is a good financial model
3.	Using Doppler devices to measure cardiac output reliably is highly operator dependent. Both the USCOM and CardioQ have learning curves of 10–20 examinations before they can be used with any confidence. Furthermore, performing measurements is time-consuming and distracts the clinician from other important tasks
4.	Currently available systems fail to provide an acceptable Doppler signal, and thus reliable readings, in a significant proportion of patients, especially the elderly
5.	Cardiac output and associated parameters are not regularly used today and hospital doctors lack training in their use. Furthermore, the development of bedside echocardiography has eclipsed the need for routine cardiac output monitoring. Thus, there is little incentive to use Doppler monitoring except by a few enthusiasts

- In some patients an inadequate Doppler flow profile is obtained and the data is unreliable. The user needs to be able to recognize such cases. Aging is the main cause of calcification, enlargement, and tortuosity of the aorta.
- Single readings may be inaccurate because of inherent calibration errors. However, when Doppler is used to assess changes in stroke volume and cardiac output in response to treatment (*i.e.,* trending), the data is much more reliable.
- Using readings from several monitoring sources improves user ability to determine the true value of cardiac output.

Keynotes

- Continuous wave Doppler is underused technique.
- Both transthoracic and esophageal modes are used.
- Measurements are highly operator dependent.
- Reliability is affected by age-related changes to the aorta.
- More reliable when used to monitor trends.

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Hemodynamic Focused Echocardiography

10

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Contents

Abbreviations

4C	Four-chamber view
AS	Aortic stenosis
AV	Aortic valve
CO	Cardiac output
DO_2	Oxygen delivery
FAST	Focused Assessment with Sonography in Trauma

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HFpEF	Heart failure with preserved ejection fraction
IAS	Interatrial septum
ICU	Intensive care unit
IVC	Inferior vena cava
LA	Left atrium
LV	Left ventricle
LVEDD	End-diastolic left ventricular diameter
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
ME	Midesophageal
PLAX	Parasternal long axis
PPV	Pulse pressure variation
PSAX	Parasternal short axis
RV	Right ventricle
S4C	Subcostal four-chamber view
SAX	Short axis
SIVC	Subcostal view of the inferior vena cava
SIVC-DI	SIVC-distensibility index
SV	Stroke volume
SVC	Superior vena cava
SVC-CI	SVC collapse index
TAPSE	Tricuspid annular plane systolic excursion
TEE	Transesophageal echocardiography
TGSAX	Transgastric short axis
TTE	Transthoracic echocardiography
VTI	Velocity time integral

10.1 Introduction

Adequate oxygen delivery (DO_2) is critical for the maintenance of physiological homeostasis and organ function and is significantly dependent upon cardiac stroke volume (SV). The determinants of SV are pre- and afterload, intrinsic contractility, heart rate/rhythm, and valve function. A critically reduced DO_2 due to a compromised SV in the perioperative setting can worsen outcome especially in high-risk patients with preexisting cardiovascular risk factors [1–3].

In this context, hemodynamic focused echocardiography provides a real-time pathophysiologically oriented approach, which allows guiding cardiovascular therapy [4–12]. It has been shown that the use of an echocardiography-based hemodynamic optimization protocol improved outcomes among septic patients in an the intensive care unit (ICU) setting [13–15]. In hemodynamically unstable patients unresponsive to initial treatment, there exists a class I indication for performing a timely echocardiographic examination in order to accurately assess and implement interventions aimed at maintaining hemodynamic stability [12, 16–19]. In order to adequately interpret and evaluate echocardiographic findings, however, a standardized curricular training and continuously available supervision is inevitable [20, 21]. In addition, "focused examiners" have the responsibility to *seek expert help* whenever needed.

In this chapter, a practical six-step approach toward a perioperative echocardiographic-based hemodynamic optimization is presented. It should be noted that the proposed algorithm may be used "as needed" in the case of hemodynamic instability or "as a predefined monitoring tool" within a goal-directed treatment strategy with monitoring intervals appropriately addressing the patient's hemodynamic risk. It may also be beneficial to be able to compare perioperative echocardiographic findings with a preoperative baseline exam. Nevertheless, it is of importance that echocardiographic findings must always be interpreted in the context of the clinical situation along with the patients' medical background. For instance, fluid substitution will be indicated in a trauma patient with low blood pressure, overall small heart chambers and a small inferior vena cava on echocardiography.

10.2 Imaging Views

The following views should be used within a hemodynamic focused transthoracic (TTE) or transesophageal (TEE) echocardiography:

10.2.1 Transthoracic Echocardiography: Parasternal Long and Short Axis, Apical or Subcostal Four-Chamber View with Subcostal View of the Inferior Vena Cava

In order to obtain a parasternal long-axis (PLAX) view (Fig. 10.1), the cardiac ultrasound probe needs to be placed on the thorax in the left parasternal position, with the marker pointing toward the right shoulder. An optimal view should be gained *via* carefully moving the probe between the intercostal spaces (ICS), starting from the second ICS to the fifth ICS. Once the most optimal view has been obtained, the following structures should be apparent in the PLAX: the right ventricular outflow tract, the interventricular septum with the upper aortic wall, the aortic valve, the left atrium, the mitral valve, the left ventricle without the cardiac apex, and the posterior wall of the left ventricle. With the PLAX view, a global assessment of major cardiac structures, as well as volume status, myocardial morphology, and valve status can be assessed. Next, the parasternal short-axis (PSAX) view (Fig. 10.2) can be obtained by simply rotating the probe clockwise 90°, so that the marker on the probe is in the direction of the left shoulder.

Once the optimal view has been obtained, the following structures should become apparent: the cross-shaped left ventricle with the anterior, inferior, septal, and lateral wall segments. Adjacent

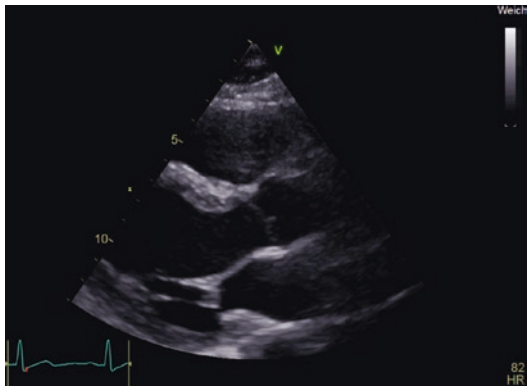

Fig. 10.1 Parasternal long-axis view

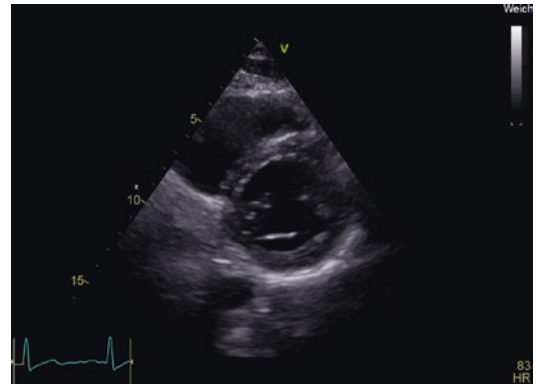

Fig. 10.2 Parasternal short-axis view

to this is the crescent-shaped right ventricle. The cardiac apex, the cross-shaped aortic, and mitral valves, as well as the anterolateral and posteromedial papillary muscles, can be obtained *via* angulating the probe from cranial to caudal. Additionally, the pulmonary valve, the main pulmonary artery trunk, its associated branches, and the right and left pulmonary arteries can be visualized at the level of the aortic valve, normally seen on the right-hand side of the monitor. On the opposite side of the monitor, additional cardiac structures such as the aortic valve, right atrium, tricuspid valve, and right ventricle can be visualized.

The next view which should be acquired is the apical four-chamber (4C) view (Fig. 10.3), which is best visualized by probe placement in the fifth ICS, between the medioclavicular and posterior axillary line, while the probe marker is pointing to the direction of the left shoulder.

Similarly to the PLAX view, the 4C view requires the movement of the probe between the ICS in order to obtain the best examination window.

Upon obtainment of the 4C view, both the atria and ventricles, along with the tricuspid and mitral valves become apparent. In the middle of the sonographic window, the interventricular septum should be present. In order to prevent the underestimation of left ventricular, as well as the overestimation of the right ventricular dimensions, the lowest ICS 4C view should be used. This prevents the so-called "foreshortening."

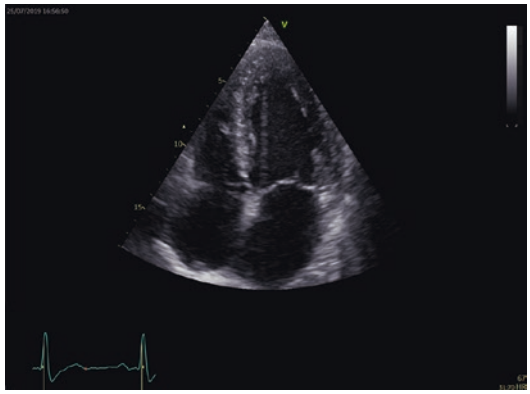

Fig. 10.3 Apical four-chamber view

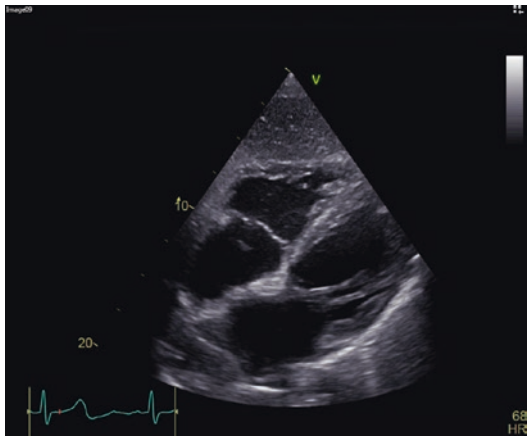

Fig. 10.4 Subcostal four-chamber view

Additionally, the 4C view allows for the visualization of the left ventricular wall, which includes the inferior septal wall, and the anterior-lateral wall on the opposite side. Furthermore, a five-chamber (5C) view, which includes the left ventricular outflow tract and aortic valve, can be observed *via* probe angulation cranially. To round out the TTE, a final view should be obtained, aptly termed the subcostal four-chamber (S4C) view (Fig. 10.4). This is performed by placing the probe inferior to the xiphoid process, with the marker pointing to the patients' left side.

In this view, a four-chamber view along with the tricuspid and mitral valves is seen. The last structure which needs to be obtained for a comprehensive hemodynamic is the inferior vena cava (IVC) (Fig. 10.5), which can be visualized

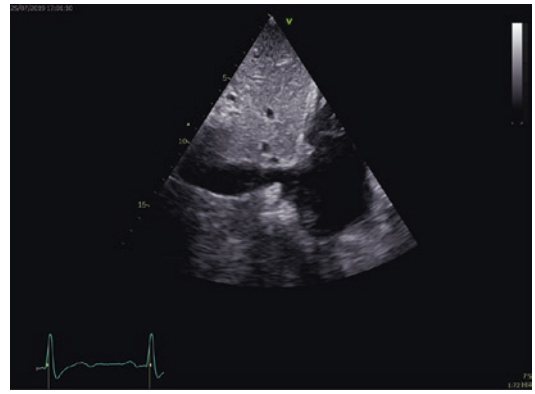

Fig. 10.5 Subcostal view of the inferior vena cava

by rotating the marker toward the head of the patient. This step-by-step method rounds out the TTE assessment.

Practical Advice
In the PLAX view, the highest intercostal view that yields a sufficient image should be used, whereas in the 4C view, the lowest intercostal space as lateral as possible should be used to prevent foreshortening.

10.2.2 Transesophageal Echocardiography: Midesophageal Four-Chamber view, Midesophageal View of the Superior Vena Cava, Transgastric Short Axis View [22]

The first step is passing the probe through the upper esophageal sphincter until the first image of the left atrium is obtained. Usually, this occurs upon a 30-cm depth from the dental arch. Upon obtaining the view of the left atrium, the probe is described as being in the transesophageal position. From this position, the midesophageal four-chamber (ME4C) view (Fig. 10.6) can be obtained. By rotating the image, the left ventricular axis and the apex should become apparent in the sectional image. Similar to the 4C view of the TTE, the foreshortening of the left ventricle

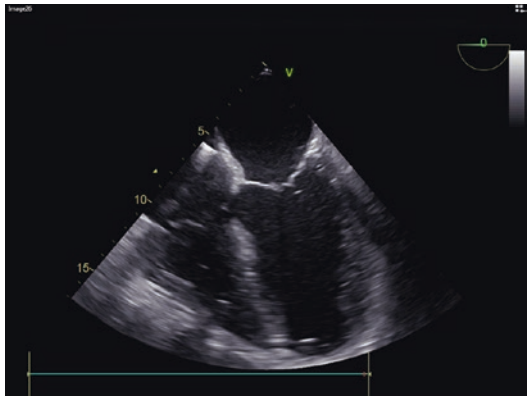

Fig. 10.6 Midesophageal four-chamber view

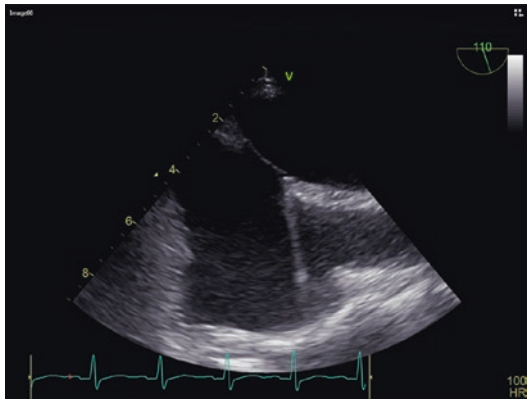

Fig. 10.7 Bicaval view

should be kept in mind. The annulus diameter of both atrioventricular valves should be acquired, while attempting to maximize the views of these valves in order to assess valve function and morphology. This can be achieved by retroflecting the probe and rotating the probe by 0–20°.

The next structures to be visualized are the right ventricle and the tricuspid valve, which should be directly in the center of the monitor. This is done by tilting the probe to the right. In order to obtain the optimal views of the great caval veins entering into the right atrium, interatrial septum, and the fossa ovalis area, the probe should be rotated 100°, thereby acquiring the bicaval view (Fig. 10.7) and the midesophageal view of the SVC.

By increasing the depth of the probe approximately 40–45 cm from the dental arch, with the probe in the "0" position of flexion and rotation

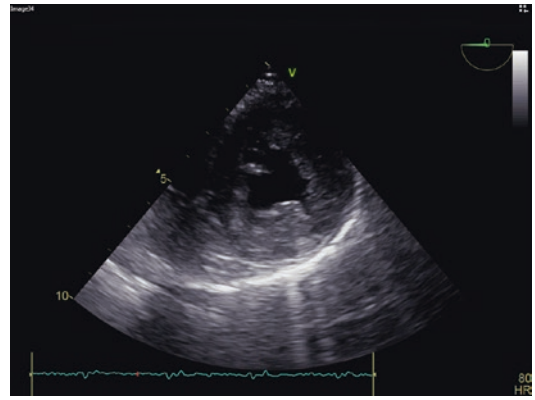

Fig. 10.8 Transgastric short-axis view

without applying force, the image is momentarily lost. Upon this loss of image, the probe should be placed in the anteflexion position and retracted until the cross-sections of the left and right ventricles are observable. The probe should then be rotated until the cross-sections of both papillary muscles are obtained and the entire symmetric left ventricle is acquired. Thereby the transgastric short-axis (TGSAX) view (Fig. 10.8) is obtained. This is an excellent position to assess the left ventricle at the midpapillary level as well as wall motion of all coronary regions. Also, this view can be reliably utilized to assess cardiac volume status and contractility.

Practical Advice
If the insertion of the TEE probe is difficult, the performance of an Esmarch (jaw thrust) maneuver as well as the usage of a laryngoscope can be helpful.

10.3 Hemodynamic Assessment

The next section details a step-by-step algorithmic approach for rapid hemodynamic assessment in order to optimize SV function in the high-risk surgical patient. All steps encompass the TTE and TEE approach.

The additional use of (color) Doppler modalities may allow for semiqualitative evaluation of

the heart valves [23]. Though TTE is noninvasive and may be the method of choice, TEE may offer better image quality, particularly in patients with morbid obesity or on mechanical ventilation [24]. Nevertheless, image acquisition will be impossible in some patients at all as well as in most patients in prone position.

10.4 Step 1: Cardiac Filling Impairment

The first step is to rule out cardiac filling impairment due to pericardial effusion or tamponade requiring immediate evacuation. Not only in the cardiac surgery setting but also due to trauma or due to chronic disease, a relevant accumulation of fluid in the pericardium can occur [25–28]. Echocardiographic signs of hemodynamically relevant pericardial effusions may include the existence of pericardial effusion with consecutive hypovolemia of all heart chambers, collapse of the right cardiac chambers, and/or dilatation of IVC. When using a TTE, the S4C view should be used, while for TEE, the ME4C should be used initially.

10.5 Step 2: Volume Status

The second step is to estimate the volume status of the patient, as both hypo- and hypervolemia can reduce SV and thus DO_2. The four-chamber (4C) views and the short-axis (SAX) views at the level of the papillary muscles are suitable for obtaining a quick overview.

Although resting diameters for cardiac chambers are gender and body surface area specific [29], the size of the left ventricle (LV) and the right ventricle (RV) should be measured. An end-diastolic left ventricular diameter (LVEDD) of 35–55 mm may reflect normal LV, and a basal RV diameter of ≤41 mm may reflect normal RV size. Qualitatively, hemodynamic-relevant hypovolemia may provoke a "kissing papillary muscle" sign: the opposite myocardial walls of the corresponding ventricle come in contact with one another during systole. Nevertheless, a preoperative dilated LV (*e.g.,* LVEDD 65 mm) due to a reduced global systolic function may be interpreted as "hypovolemic" if the LVEDD is within normal range (*e.g.,* LVEDD 50 mm).

Practical Advice

A pronounced concentric hypertrophy as evidenced by a myocardial wall thickness of >14 mm (*i.e.,* due to severe aortic stenosis) must be excluded prior to the diagnosis of hypovolemia [30]!

The assessment of the interatrial septum (IAS) in the four-chamber (4C, ME4C) views can be used for qualitative estimation of atrial filling pressures. A hypermobile IAS is commonly observed during global hypovolemia. A sole increase in left atrial filling pressure will shift the IAS permanently convex to the right, whereas increased right atrial filling pressure shifts the IAS permanently convex to the left atrium in combination with the left cardiac hypovolemia [31]. Global hypervolemia may be identified with all heart chambers appearing "overfilled" or "stretched" and a in the middle-fixated IAS [32, 33].

Volume responsiveness can be estimated by interrogating the IVC *via* TTE or the SVC *via* TEE. The IVC diameter may be used to estimate the right atrial filling pressure [34]. In awake and spontaneously breathing patients, the normal diameter for the IVC is <21 mm [35]. During mechanical inspiration, venous return is reduced due to the increased intrathoracic pressure and the IVC distends ("IVC-distensibility index, DI") [36]. Thus, the more pronounced intravascular hypovolemia is present, the greater the IVC will distend [37]. An IVC-DI of >18% in controlled ventilated septic patients may indicate a positive volume response resulting in an increased cardiac output (CO) after fluid resuscitation [38–42]. In patients with preserved spontaneous respiration, the patient is asked to inspire deeply once and expire passively afterward, while the variation in IVC diameter is recorded [43]. An IVC diameter

Table 10.1 Qualitative echocardiographic evaluation of volume status/fluid responsiveness

Status	Respiratory modulation	Interpretation	Fluid response
IVC/SVC dilated (*i.e.*, round in shape, stretched, visual aspect of overfilling)	No variation	Filling pressure ⇧	Negative ("stop signal" for further fluid administration)[a]
IVC/SVC small/collapsed	Pronounced variation	Filling pressure ⇩	Positive
IVC/SVC intermediate	Passive leg raising (PLR) and/or fluid challenge (FC) If stroke volume increases with unchanged systemic resistance, fluid substitution is clinically indicated		

[a]In the context of chronic cardiovascular disease, a positive volume responsiveness may occasionally be given despite a dilated vena cava without respiratory oscillation. Further evaluation may be done by means of PLR/FC

variability of ≥48% represents a positive volume response. The same is also possible with TEE using the SVC collapse index (SVC-CI) [44]. In contrast, the SVC will be compressed during mechanical inspiration due to its intrathoracic position: SVC collapse index (SVC-CI) [44]. A SVC-CI of >36% measured with TEE indicates a positive volume response. Nonetheless, like many other methods, these easy-to-determine quantitative variables are subject to individual cut-off variations (*e.g.,* IVC-DI "gray zone" 8–30%) [42, 45–48]. Therefore, in extension to quantitative determinations, the approach shown in Table 10.1 may be helpful in deciphering the measurements taken from the IVC/SVC [49–51].

However, from a clinical point of view, one has to differentiate between (a) "relative" hypovolemia (*i.e.,* all heart chambers appeared to be "normally" filled; however, additional fluid substitution may cause an increase in SV—"volume responsiveness"), (b) "global" hypovolemia (*i.e.,* all heart chambers are reduced in size due to a significant reduction in the total circulating blood volume—additional fluid substitution will lead to an increase in SV), and (c) "partial" hypovolemia (*i.e.,* LV hypovolemia in the case of RV failure—fluid substitution will mostly not be effective in increasing left ventricular SV because of the incapability of the RV).

10.6 Step 3: Right Ventricle Function

A restricted RV function is associated with increased perioperative mortality [52–54]. Additionally, sufficient LV function depends on sufficient preload provided by the RV [55]. The RV thus may be assessed prior to LV assessment [56].

This is achieved by measuring RV diameter (Step 2) as well as the volume/diameter relation between the right and left ventricles, the "RV/LV index" (≤0.6). A RV/LV index of ≥1.0 indicates a severe RV dilatation [57]. Hypertrophy of the free right ventricular wall (>5 mm) may indicate a chronic disease process [58]. The thickness of the right ventricular wall is best measured from the subcostal at the level of the anterior tricuspid valve tip or alternatively in the PLAX [34].

RV contractility is assessed in the four-chamber views. With a normal RV function, the free RV wall should move inward [34]. The systolic movement of the lateral tricuspid valve annulus toward the apex (tricuspid annular plane systolic excursion, TAPSE) (Fig. 10.9) can be used as a quantitative measurement. A TAPSE of ≥17 mm indicates a normal systolic RV function [34]. Hemodynamically relevant RV dysfunction may be suspected if the RV appears dilated with impaired systolic function. In addition, RV overloading can displace the interventricular septum toward the LV ("paradoxical septum shift") (D-sign) (Fig. 10.10), thereby further restricting cardiac function.

Practical Advice

The acuity of a right ventricular dysfunction can be differentiated based on the diameter of the right ventricular wall. A hypertrophy of the free right ventricular wall (>5 mm) indicates a chronic disease process, whereas a normal right ventricular wall and signs of right ventricular dysfunction propose an acute pathology.

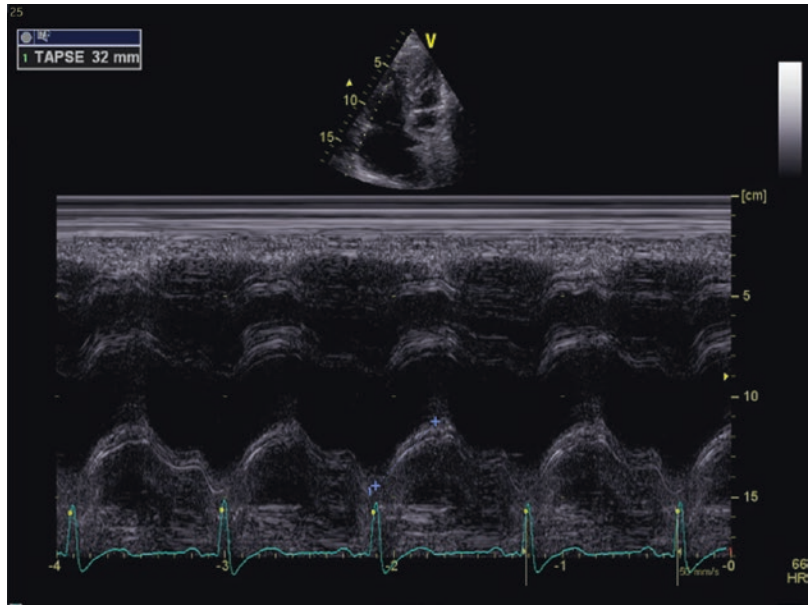

Fig. 10.9 Tricuspid annular plane systolic excursion

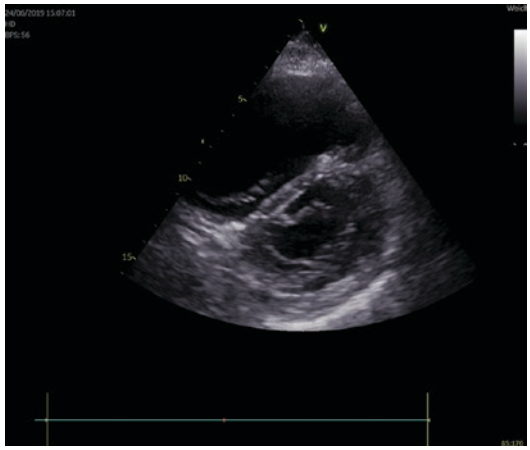

Fig. 10.10 Paradoxical septum shift in the right ventricular dysfunction seen in the parasternal short-axis view

10.7 Step 4: Left Ventricle Function

LV should be assessed in an analogous manner to the RV (see also Steps 2 and 3). The left ventricular ejection fraction (LVEF) is determined to quantify global systolic function. For normal clinical concerns, however, a qualitative assessment of the LVEF ("eyeballing") may be sufficient [59]. PSAX or TGSAX as well as four-chamber (4C or ME4C) views allow for a quick orientation [60].

Hemodynamic-relevant systolic LV dysfunction may be excluded if the LV appears nondilated with normal systolic function (LVEF >50%). However, isolated diastolic LV dysfunction (heart failure with preserved ejection fraction, HFpEF) may be present [61]. If diastolic dysfunction is suspected, an expert consultation should be made in order to guide further diagnostics and therapy [62]. However, a hypertrophied LV with normal systolic function in conjunction with a pronounced dilation of the left atrium (LA) may be related to HFpEF in a breathless patient with/without signs of pulmonary edema [63].

Finally, regional wall motion abnormalities—hypokinesia, akinesia, or dyskinesia [64]—may hint at specific cause such as myocardial infarction or takotsubo syndrome, which require a specific diagnostic testing (*e.g.,* electrocardiogram, cardiac enzymes, coronary angiography) and treatment.

Practical Advice
If the LV appears nondilated with normal systolic function, hemodynamic-relevant systolic LV dysfunction can be excluded. However, if the patient shows clinical signs of heart failure and echocardiography reveals a hypertrophied LV and a pronounced dilation of the LA, HFpEF should be considered.

10.8 Step 5: Valve Function

The visual and thus qualitative evaluation of valves in the hemodynamic focused examination is used to assess valve opening and closure as well as to recognize morphological abnormalities. Thin leaflets with a normal opening/closing and without turbulent flow in the color Doppler determined in ≥2 cross-sectional views may exclude hemodynamic-relevant valve dysfunction. Hemodynamic-relevant stenosis may be suspected in the case of a thickened or calcified valve with a restricted opening resulting in antegrade flow accelerations/turbulences in the color Doppler. On the other hand, hemodynamic-relevant regurgitation might be suspected if a visible coaptation defect and/or an exaggerated leaflet motion during valve closing in conjunction with a wide, turbulent, backward color jet ("vena contracta") (Fig. 10.11) is observed [23]. In suspicion of a hemodynamically relevant valve abnormality, a comprehensive evaluation should be performed immediately by a certified examiner [65–67].

Practical Advice
Thin leaflets with normal opening and closing and without turbulent color flow exclude hemodynamic-relevant valve dysfunction.

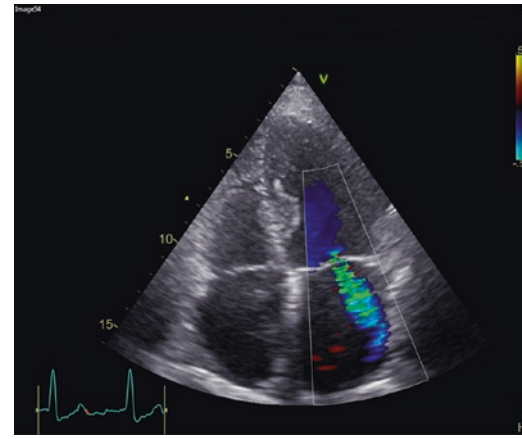

Fig. 10.11 Turbulent backward color jet in mitral valve insufficiency seen in the apical four-chamber view

10.9 Step 6: Cardiac Output Estimation

Transthoracic and transesophageal echocardiography are capable of estimating cardiac output, although discontinuously, using continuous-wave (cw) Doppler across the left ventricular outflow tract (LVOT)/aortic valve (AV) measuring the velocity time integral (VTI) [68]. A VTI of 18–22 cm indicates a normal stroke volume, whereas a VTI of <18 cm suspects decreased stroke volume and >22 cm an increased one [69]. Prior to this, a relevant aortic stenosis must be excluded. However, echocardiography may not be interchangeable with other cardiac output monitoring [70]. Thus, a continuous hemodynamic monitoring should be implemented in hemodynamic unstable patients to assess the therapeutic success after initial echocardiographic evaluation [71, 72].

Practical Advice
A VTI of 18–22 cm indicates normal, a VTI of <18 cm decreased, and >22 cm increased stroke volume.

10.10 Conclusion

Hemodynamic focused echocardiography as a rapid bedside diagnostic method can examine signs of filling impairment, volume status and volume responsiveness, right and left ventricular function, and heart valve function as well as estimate cardiac output. Using a stepwise approach, high-risk patients within the perioperative setting can be assessed in the case of hemodynamic instability to rapidly pinpoint pathophysiological causes. The summary of all echocardiographic findings, including clinical symptoms and patient history, allows a differentiated assessment of the patient's cardiovascular function and can thus help to guide a (patho)physiologically orientated and individualized hemodynamic therapy in order to optimize and maintain stroke volume.

Keynotes

- Hemodynamic focused echocardiography allows to examine the signs of cardiac filling impairment, cardiac preload, myocardial contractility, and cardiac heart valve function.
- Echocardiographic signs of filling impairment are pericardial effusion with hypovolemia of all heart chambers, collapse of right cardiac chambers, and/or dilatation of the inferior vena cava.
- Volume status/responsiveness can be assessed by examining a potential kissing papillary muscle sign and the positioning and movement of the interatrial septum as well as the diameter and respiratory variation of the superior and inferior vena cava.
- The right ventricle is assessed by examining the volume/diameter relation between the right and left ventricles, the diameter of the right ventricular wall, the movement of the right ventricular free wall, and the lateral tricuspid valve annulus toward the apex as well as the position and movement of the interventricular septum.
- A qualitative assessment of the left ventricular ejection fraction with eyeballing may be equivalent to a quantitative one for normal clinical concerns in the context of a hemodynamically focused examination.
- Thin leaflets with a normal opening/closing and without turbulent flow in color Doppler exclude hemodynamically relevant valve dysfunction.
- A velocity time integral, measured with continuous-wave Doppler across the left ventricular outflow tract/aortic valve, of 18–22 cm indicates normal, whereas a VTI of <18 cm a decreased and >22 cm an increased stroke volume. Prior to this, aortic stenosis must be excluded.

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Bioimpedance and Bioreactance

11

Arthur Pavot, Jean–Louis Teboul,
and Xavier Monnet

Contents

11.1 Introduction

Electrical bioimpedance and bioreactance are two techniques for measuring cardiac output (CO) that can be used for hemodynamic monitoring. They are both based on the principle that during the cardiac cycle, changes in intrathoracic volume, and more particularly in the volume of the aorta induced by systolic ejection, lead to changes in electrical conductivity and impedance of the thorax. Quantifying these changes over the course of a cardiac cycle makes it possible to estimate stroke volume (SV) and hence CO. Bioreactance can be viewed as a technological improvement over bioimpedance.

In this chapter, we will summarize the mode of operation of these two techniques, detail the clinical studies which evaluated their reliability, list their limitations, and conclude their potential indications.

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11.2 Bioimpedance

11.2.1 Operating Mode

In 1950, Nyboer described the relationship between SV and the changes of the electrical impedance of the thorax during the cardiac cycle [1]. The use of bioimpedance in cardiovascular monitoring started in the mid-1960s, when the continuous measurement of CO was described for the first time in aerospace medicine [2].

The basic principle of the technique is that the cardiac cycle induces changes in the electrical impedance of the aorta, with simultaneous changes in the amplitude and phase of an electrical current applied through the thorax. These changes in thoracic electrical impedance are proportional to changes in the volume of the thoracic aorta and then to SV.

In practice, the system requires that a high-frequency electrical current is applied at a fixed amplitude across the thorax by electrodes located on the skin on the neck and at the lower part of the thorax (thoracic bioimpedance) or around the cuff of an intubation probe (endotracheal bioimpedance). Adjacent electrodes detect the beat-to-beat variations of voltage of the outward current (Fig. 11.1) [3].

The impedance of an electric current is defined by the ratio between voltage and current intensities. At baseline, basal impedance is closely related to the thoracic total fluid content. During cardiac ejection, blood flow through the aorta increases the total volume of iron in the thorax, inducing a decrease in its impedance. A basic hypothesis to derive CO from bioimpedance is that changes in impedance during the cardiac cycle are related to changes in the aortic volume and not in the volume of the cardiac chambers. This is likely true since the heart chambers are electrically isolated by the myocardial wall and since the volume of the atria and the other thoracic vessels is relatively constant [3].

Stroke volume (SV) is obtained from the product of the ventricular ejection time (VET) and the slope of the initial change of the aortic volume obtained from the first derivative of the impedance signal (dZ/dt_{max}). Since these changes only indicate relative changes of CO, a calibration factor (CF) is necessary to derive absolute values, based on an initial cohort of patients [3]:

$$SV = VET \times dZ / dt_{max} \times CF$$

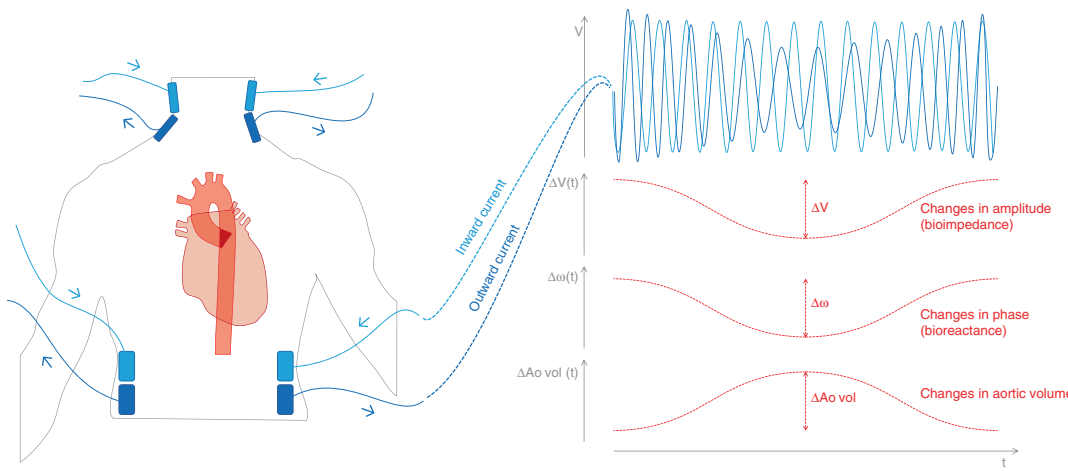

Fig. 11.1 Schematic functioning of thoracic electrical bioimpedance and bioreactance. At each heartbeat, the change in amplitude (ΔV, measured for bioimpedance) and in phase ($\Delta\omega$, measured for bioreactance) of the outward current compared to the inward current applied through the thorax by skin electrodes are used to estimate the increase in aortic volume (ΔAo vol), and thus stroke volume (partially adapted from [3], with permission)

Cardiac output is estimated from SV, and a moving average of the beat-to-beat values of CO is calculated over a period that depends upon the constructor.

Thoracic bioimpedance is used in many commercial devices: NCCOM (Bomed Medical, Irvine, CA, USA), BioZ (Cardiodynamics, San Diego, CA, USA), NICCOMO (MEDIS, Limenau, Germany), ICON (Osypka Cardiotronic, Berlin, Germany), ICG (Philips Medical Systems, Andover, MA, USA), NICOMON (Larsen and Toubro Ltd., Mumbai, India), the CSM3000 (Cheers Sails Medical, Shenzhen, China), and PHYSIOFLOW (Manatec Biomedical, Paris, France). The NICaS system (NI Medical, Petah-Tikva, Israel) uses the same principles but applied to the whole body [3]. The ECOM device (ECOM; ConMed, Utica, NY, USA) is the only one using endotracheal bioimpedance [4].

11.2.2 Advantages and Limitations

The main advantage of thoracic bioimpedance, which simply derives CO from electrodes pasted on the skin, is that it is one of the least invasive techniques for the continuous monitoring of CO. The devices are affordable and simple to use. Also, the bioimpedance measurement of CO is continuous and, provided that the period over which SV is automatically averaged is not too long, it is able to detect its short-time changes.

Nevertheless, thoracic bioimpedance suffers from several limitations. First, it is considerably affected by electrical noise, created by movements of the patient and surrounding electrical devices such as the ventilator or electrocautery [5]. It is to circumvent these limitations that endotracheal bioimpedance has been developed [4].

Second, many situations prevent the validation of assumptions on which the operation of the technique is based. Stroke volume must be associated with aortic deformation during systole. When it is not the case (aortic dissection or prosthesis), the effectiveness of bioimpedance is drastically reduced [3]. Other much more common conditions, such as obesity, low hematocrit, high blood pressure, or dehydration, may also limit or alter the principles on which the CO estimation is based [3].

11.2.3 Validation

Dozens of validation studies investigated the reliability of the measurement of CO through bioimpedance in a large variety of settings, from ambulatory patients at home to the intensive care unit (ICU) and the operating room. Results are equivocal [6–9]. Interestingly, the most positive studies were conducted outside from the ICU setting, perhaps because the latter increases the risk of electrical interference caused by the number of electrical devices surrounding the patient [3]. Confirming previous ones [8, 9], the most recent meta-analysis included 13 studies in adults (620 patients) and 11 studies in pediatrics (603 patients) evaluating thoracic bioimpedance [6]. The percentage error was 48% in adults and 42% in children, while values below 30% are usually judged as clinically acceptable [10]. Endotracheal bioimpedance has been less evaluated, but the available results are not better [4]. Overall, these results explain that bioimpedance is consensually not considered as reliable enough, at least in ICU patients [3, 5, 6, 11].

11.3 Bioreactance

11.3.1 Operating Mode

As described above, traditional bioimpedance uses the modulation of amplitude to estimate SV. With thoracic bioreactance, the hypotheses supporting the estimation of SV are the same, but the signal which is used for this purpose is the modulation of phase rather than of amplitude (Fig. 11.1). The advantage of the frequency modulation over the amplitude modulation, as for

radiobroadcasting, is that the signal-to-noise ratio is largely increased. In theory, this may circumvent many limitations of bioimpedance.

The NICOM (Starling SV in its new version) is the only available bioreactance device. It has been developed by Cheetah Medical (Centre St, MA), which has now joined Baxter International Inc.

11.3.2 Validation

Compared to bioimpedance, most recent bioreactance has been more scarcely investigated. The percentage error compared to the reference method ranged from 26% [12] to 145% [13] in these studies. As for bioimpedance, the worst results were obtained in studies conducted in the ICU [13, 14].

A limitation of the former NICOM device was that it averaged CO on a rather long time period and it refreshed the value displayed on the device screen every 30 s only. The new Starling SV device has been modified to shorten the latency to CO changes. In spite of a limited ability to measure absolute values of CO, the Starling SV was shown to reliably detect its changes during a passive leg-raising test, whose effects of CO occur within less than a minute [15].

A randomized trial included patients with sepsis admitted at the emergency room and distributed them between usual care and hemodynamic evaluation with the passive leg-raising test monitored by the bioreactance device. Although there was no difference in survival between groups, patients monitored with bioreactance demonstrated lower net fluid balance and reductions in the risk of renal and respiratory failure [16].

Practical Advice
Bioreactance essentially provides a continuous measurement of cardiac output. The last version allows the assessment of quite rapid changes, like during a passive leg-raising test, for instance.

11.3.3 Indications

To determine the potential indications for bioreactance, two elements must be taken into account. The first is that, as we have seen, the reliability of the system appears to be better outside the ICU than inside. The second element is that the system provides only CO as exploitable hemodynamic information. Therefore, like other non- or minimally invasive hemodynamic monitoring systems (esophageal Doppler, uncalibrated pulse contour analysis, volume clamp), this system is mainly intended for the perioperative context in the operating room. Its ease of implementation and ease of use make it a good candidate for prehospital monitoring or in the emergency medicine department, if continuous cardiovascular monitoring is deemed necessary.

Practical Advice
Bioreactance is better indicated in the operating room than in the intensive care unit.

However, it should not be used in ICUs. In the most severe patients, we should instead turn to the pulmonary arterial catheter or transpulmonary thermodilution, which are more reliable systems and which provide a large amount of hemodynamic information, even if they are more invasive and more expensive [11, 17].

11.4 Conclusion

Bioimpedance and bioreactance base their estimation of CO on the changes in impedance and reactance, respectively, of an electric current applied through the thorax during the cardiac cycle. Bioreactance should be seen as an improvement in bioimpedance, notably having a better signal/noise ratio.

Systems validation studies have shown variable results, more favorable with bioreactance, but possibly poorer in the ICU setting than in other ones. These systems are indicated in the

context of the operating theater, the prehospital medicine or the emergency department, but not in the ICU, where more reliable and informative systems are indicated.

Keynotes

- Bioreactance and bioimpedance are techniques that estimate cardiac output and are totally noninvasive.
- Bioreactance likely has a higher signal-to-noise ratio than bioimpedance. It is likely less sensitive to electrical interferences.
- Bioreactance and bioimpedance only provide cardiac output and the variables that can be inferred from it, like the peripheral arterial resistance.
- Bioreactance is likely less reliable in critically ill patients than in the operating room. The last version of the commercially available device is more reactive to rapid changes in cardiac output.

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Part III

Monitoring of Volumetric Parameters

Volumetric Parameters: A Physiological Background

12

Vsevolod V. Kuzkov

Contents

12.1 Introduction

As has been stated in Chaps. 3 and 4, the diagnostic and prognostic values of filling pressures (central venous and pulmonary arterial occlusion pressures) are limited by presenting only one part of the "static" parameters of preload [1, 2]. Another part of preload, the volumetric variables, deals with quantification of volume of all the heart chambers, great vessels, and pulmonary vascular bed, as well as the extravascular compartment of the lungs [1, 3, 4]. Thus, the direct quantification of the volumetric parameters using transpulmonary thermodilution in parallel with assessment of fluid responsiveness has opened up new opportunities for the personalization of hemodynamic therapy in different categories of the critically ill [3, 5].

One of the key volumetric parameters is the *global end-diastolic volume index* (GEDVI), also referred as a current clinical "gold standard" of bedside invasive preload assessment (Chap. 13). The discrete evaluation of the end-diastolic volumes of the right- and left-sided heart chambers, as well as the ejection fractions, is also technically possible, but highly invasive as it requires both systemic and pulmonary arterial catheters and is mainly limited to the clinical research activity for invasive cardiology and organ transplantation [6–8]. The combination of the GEDVI and other variables can be helpful in assessment of heart contractility ("inotropism"). Therefore, a

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range of derived parameters based on the methodology of single transpulmonary thermodilution (Chap. 7) are of interest, including the *global ejection fraction* (GEF) and the *cardiac function index* (CFI).

The increased vascular permeability is a complex and multifactorial pathophysiological phenomenon that cannot currently be measured directly at the bedside [9, 10]. Indeed, all attempts to normalize the preload can be ineffective and even dangerous when the fluids leave the vascular bed and leak into the interstitial space. Thus, the interpretation of volumetric parameters and a safe clinical decision would be incomplete without information about the severity of pulmonary edema and capillary leak [1]. The volumetric monitoring gives us a clinical clue to the indirect assessment of these processes by means of the *extravascular lung water index* (EVLWI) and the *pulmonary vascular permeability index* (PVPI; Chap. 14).

Practical Advice

"Classic" volumetric monitoring includes the global end-diastolic volume index, the extravascular lung water index, and the global ejection fraction/cardiac function index. These parameters characterize preload, lung fluid balance, and heart contractility respectively.

Unfortunately, in many complex clinical scenarios, attempts to increase the circulating blood volume with fluid therapy do not result in a steady increase in cardiac output and oxygen delivery as fluids readily extravasate [10, 11]. Thus, in these situations the hemodynamic stabilization can eventually be achieved only at the price of progressing tissue edema, worsening organ function, and developing complications (Fig. 12.1). As these complications are the key features of the distributive shock (Chap. 25), monitoring the GEDVI, EVLWI, and PVPI in the critically ill reflects the dynamic fluid balance between the intra- and extravascular compartments [12–14].

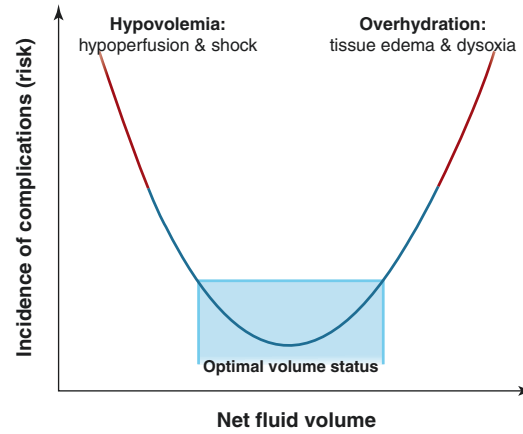

Fig. 12.1 Incidence of complications: dangers of hypovolemia and overhydration

Considered together, the volumetric variables can characterize both the efficacy and safety of the preload optimization, the response of cardiac contractility and the contribution of the "fluid sink" of the vascular bed, making volumetric monitoring an attractive approach for the bedside personalization of hemodynamic status. The normal clinical values of the volumetric parameters are presented in Table 12.1.

Of note, the *static volumetric* and the *dynamic fluid responsiveness parameters* are not interchangeable and have different practical applications [15, 16]. Dynamic parameters are often evaluated together with functional tests to predict the short-term response of cardiac output to fluid load; however, the fluid responsiveness cannot guarantee that an instantly increased preload will be associated with steady, prolonged and, last but not least, physiologically beneficial, hemodynamic changes (Chaps. 15–17).

The clinical area of application of volumetric monitoring includes many critical care and perioperative scenarios. The most promising indications are different subsets of circulatory shock associated with cardiovascular comorbidities and respiratory failure, as well as the perioperative period of high-risk and complicated interventions such as complex cardiothoracic surgery and organ transplantation (Table 12.2).

Table 12.1 The normal values and ranges of hemodynamic and volumetric variables[a]

Variable	Ranges
Flow	
Cardiac output, L/min	5.0–7.0
Cardiac index, L/min/m^2	3.0–5.0
Pulse contour cardiac index, L/min/m^2	3.0–5.0
Cardiac preload	
Global end-diastolic volume index, mL/m^2	680–800
Intrathoracic blood volume index, mL/m^2	850–1000
Central venous pressure, mmHg	5–7
Volume responsiveness	
Stroke volume variation, %	≤10
Pulse pressure variation, %	≤10
Afterload	
Systemic vascular resistance index, dyn × s × cm^{-5}/m^2	1700–2400
Cardiac contractility	
Cardiac function index, L/min	4.5–6.5
Global ejection fraction, %	25–35
Index of left ventricular contractility (dPmax), mmHg/s	1200–2000
Cardiac power index, W/m^2	0.5–0.7
Pulmonary edema	
Extravascular lung water index, mL/kg PBW	3–7
Pulmonary vascular permeability index	1–3

PBW predicted body weight
[a]The volumetric parameters discussed are presented in bold

Table 12.2 The areas for clinical application of volumetric hemodynamic monitoring

Critical care settings	Perioperative settings
• Sepsis and septic shock [2, 17, 18] • Nonseptic distributive shock [11] • Pulmonary edema [17, 19] • Cardiogenic shock and severe heart failure [20] • Severe acute respiratory distress syndrome [17, 21] • Severe burns [22] • Severe subarachnoid hemorrhage [23] • Severe necrotizing pancreatitis [24] • Overhydration [11]	• Complex cardiac surgery [25, 26] • Thoracic surgery (lung transplantation) [27, 28] • Complex neurosurgery [29] • Liver transplantation [30, 31]

Practical Advice

Personalized approach to "normal" values of the global end-diastolic volume index may be considered in some subsets of ICU patients, including "permissive hypovolemia" (GEDVI 500–650 mL/m^2) for those with severe global permeability syndrome and "permissive hypervolemia" (GEDVI 800–950 mL/m^2) for those with severe systolic heart failure.

12.2 Transpulmonary Thermodilution and Volumetric Parameters

Transpulmonary thermodilution (TPTD) for volumetric hemodynamic assessment is currently recommended for advanced monitoring in severe shock [3, 5, 32] and can be achieved in several commercially available systems of complex hemodynamic monitoring [33, 34].

The invasive quantification of volumetric hemodynamic parameters, characterizing heart filling and vascular permeability, is based on the dilution of a thermal indicator, injected into the systemic circulation.

The methodology of TPTD is described in detail in Chap. 7. In brief, the thermal indicator "keeps warm" (or loses the "negative heat") depending on multiple intrinsic factors (blood flow velocity, time of heat exchange, and tissue heat capacity) when passing by and mixing with blood of the heart chambers, limited portions of the great vessels (vena cava and aorta), and the pulmonary vascular bed [33]. The process of this thermal exchange depends on both the physical volume of distribution and the thermal capacity/conductivity of the pulmonary tissue, therefore allowing the quantification of the EVLWI. The physiology and mathematical background for the calculation of the volumetric parameters are depicted in Fig. 12.2.

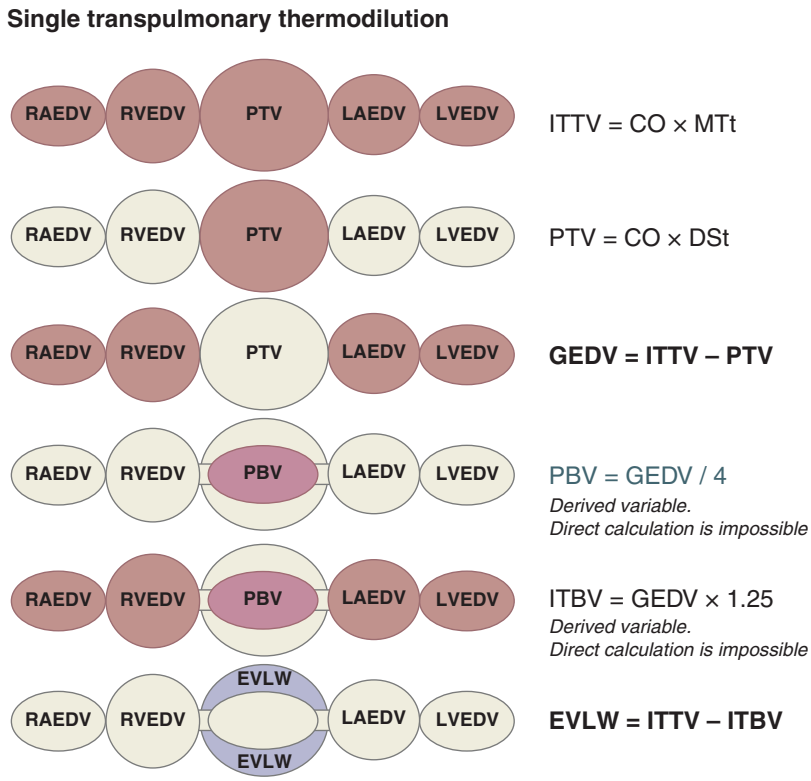

Fig. 12.2 Physiological layout and calculation of the volumetric parameters using single transpulmonary thermodilution. *EDV* end-diastolic volume, *RA* right atrium, *RV* right ventricle, *LA* left atrium, *LV* left ventricle, *MTt* mean transit time of the thermal indicator, *DSt* down-slope time of the thermodilution curve, *CO* cardiac output, *ITTV* intrathoracic thermal volume, *PTV* pulmonary thermal volume, *GEDV* global end-diastolic volume, *PBV* pulmonary blood volume, *ITBV* intrathoracic blood volume, *EVLW* extravascular lung water

12.3 Volumetric Parameters of Preload

12.3.1 Global End-Diastolic Volume Index

As has been stated already, the preload assessment with central venous and pulmonary artery occlusion pressures is limited by changing myocardial compliance, positive pressure mechanical ventilation, and, in some cases, valvular disturbances. The dynamic parameters and functional tests do predict instant heart response to the rapid increase in preload but cannot help us to assess the real-time kinetics of the fluid being administered. In addition, the use of functional parameters is restricted in overhydrated ICU patients and in the late phase of distributive shock. Therefore, according to the current phasic paradigm of shock management, the GEDVI can be one of the most promising variables for preload quantification.

Practical Advice

Among current volumetric parameters, the global end-diastolic volume index measured using single transpulmonary thermodilution represents a clinical "gold standard" for bedside preload assessment in the critically ill.

There are many reasons why the GEDVI is the most accurate preload marker. Of note, the GEDVI is the summarized value of the maximal volumes of all four heart chambers indexed to the calculated body surface area. Thus, the GEDVI is more accurate for preload assessment than central venous pressure (CVP), pulmonary artery occlusion pressure, the right ventricular end-diastolic volume, and the left ventricular end-diastolic area [35, 36]. In contrast to CVP, the GEDVI accurately quantifies the preload in septic shock and severe ARDS [17, 37]. The accu-

racy of this parameter has also been confirmed in children and neonates [38, 39]. In many cases, the GEDVI has been used as a reference parameter for echocardiographic variables [36, 40]. This parameter is plausible during normovolemia, moderate hypovolemia, pulmonary hypertension and inotropic support [41, 42]. Moreover, the GEDVI accurately characterizes preload in both controlled mechanical ventilation and spontaneous breathing. However, aortic aneurism and prominent dilatation of the left atrium can result in a falsely increased GEDVI. The plausibility of GEDVI interpretation can also be limited in severe heart failure [42, 43]. The interplay between the GEDVI and another important volumetric parameter, the EVLWI, during fluid resuscitation is of utmost clinical interest in many categories of ICU patients [44, 45]. The methodology of measurement and the clinical application of the GEDVI are discussed in detail in Chaps. 7 and 13 respectively.

12.3.2 Global Ejection Fraction

The GEF is another important volumetric variable allowing an assessment of the heart performance, particularly systolic function, in terms of its work (stroke volume) and preload. The calculation of the GEF using TPTD is based on the following formula: (4 × SV)/GEDV; thus, the normal value of GEF (25–35%; Table 12.1) differs from the echocardiographic ejection fraction. Most frequently, the decrease in GEF can result from the dilatation of the heart chambers, leading to increased GEDV. This parameter is a valuable key to revealing heart failure, whereas isolated right heart failure, pulmonary hypertension, and increased right heart afterload are known limitations decreasing the clinical plausibility of its measurement [46, 47]. In the case of systolic heart failure, both the GEF and the CFI (see below) are declining [46]. Nakwan et al. has shown that both the CFI and the GEF obtained using transpulmonary thermodilution are associated with the left ventricle ejection fraction measured using echocardiography in septic shock [48], whereas the GEF correlates closely with the results of transesophageal echocardiography in acute myocardial ischemia [49]. However, when assessment of cardiac output is unaffected by differences in ventricular size and outflow obstruction, the GEDVI, GEF, and CFI do not reflect the largely increased heart volumes and markedly impaired left ventricular function in dilated cardiomyopathy [50].

12.3.3 Cardiac Function Index

The CFI is a ratio of the cardiac index and the intrathoracic blood volume index (Fig. 12.2) and independently characterizes heart contractility under the current preload settings [51–53]. With normal values within the range 4.6–6.5 min^{-1}, this parameter is sensitive to the inotropic support and the position of the Frank–Starling curve [49]. It has also been proposed that assessment of cardiac function by the CFI using the transpulmonary thermodilution technique is a plausible alternative to the pulmonary catheter, and a low CFI identifies cardiac dysfunction in both acute heart failure and sepsis [54].

12.4 Other Volumetric Parameters

12.4.1 Extravascular Lung Water Index

The extravascular lung water index is a volumetric parameter quantifying pulmonary edema [3, 12, 14]. This parameter and the use of EVLW as a target for therapy are described in more detail in Chaps. 7, 14, and 26.

The close interplay between cardiac output and volumetric parameters can be integrated into clinical decision trees for the management of critically ill patients; the example of such an algorithm is presented in Fig. 12.3. The typical changes in volumetric hemodynamic parameters in the common critical care scenarios are presented in Table 12.3.

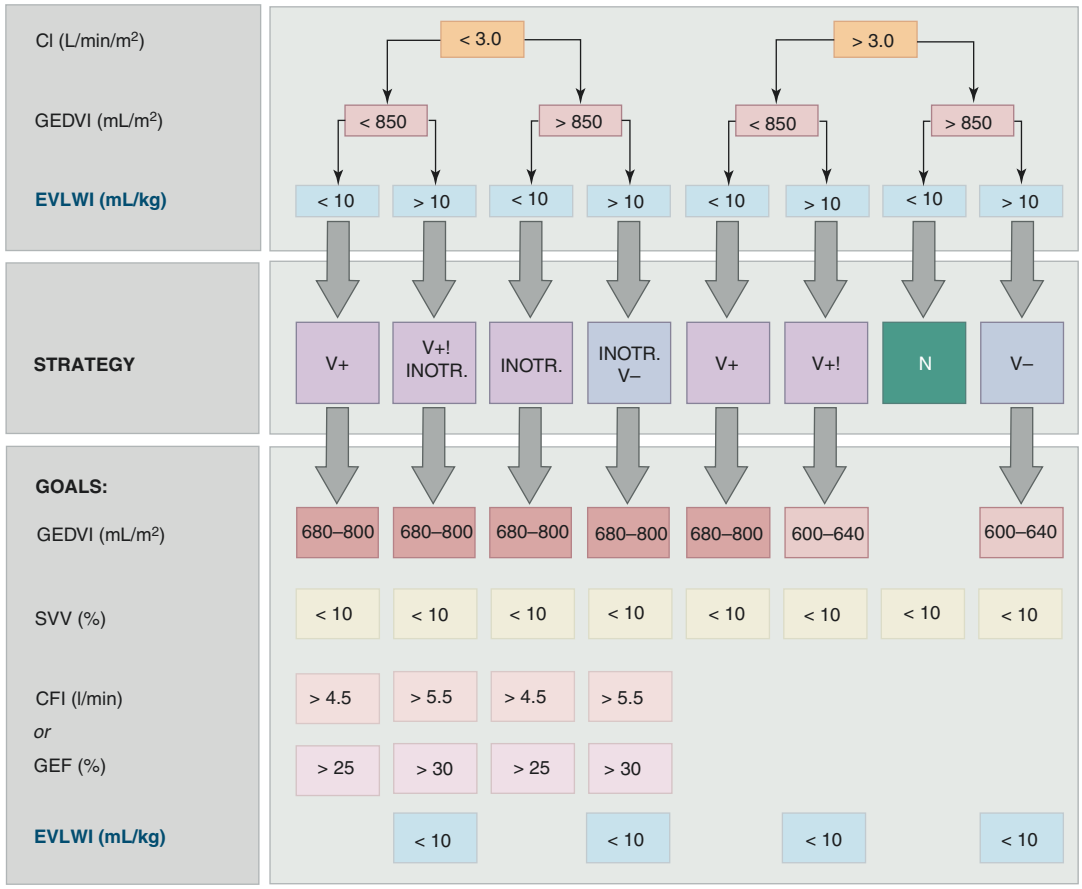

Fig. 12.3 A clinical decision tree for the personalization of hemodynamic management based on the volumetric parameters. *CI* cardiac index, *GEDVI* global end-diastolic volume index, *EVLWI* extravascular lung water index, *SVV* stroke volume variation, *CFI* cardiac function index, *GEF* global ejection fraction, *V+* fluid bolus (volume load), *V+!* titrated fluid (volume with caution!), *INOTR* inotropes, *V–*dehydration, *N* normal state

Table 12.3 The changes in volumetric parameters in the selected critical care scenarios

Condition	Etiology	Change in volumetric parameters
Severe hypovolemia (hemorrhagic shock)	Hemorrhage, severe burns, decreased preload in high intrapleural pressure, pneumothorax	Low GEDVI (usually <600 mL/m²), relatively low EVLWI (4–7 mL/kg), low CO, low CFI, low GEF. Increase in GEDVI leads to a rise in CO without the obvious risk of early EVLW accumulation
Overhydration	Volume overload, acute kidney injury, lymphatic blockade (sepsis, PEEP), ARDS	Normal to increased GEDVI. Increased EVLWI (usually above 10 mL/kg). No fluid responsiveness observed
Severe heart failure, cardiogenic shock	Structural changes leading to decreased myocardial contractility	Normal to increased GEDVI and "gray zone" EVLWI (7–10 mL/kg). In severe pulmonary edema, the EVLWI readily decreases after diuretics or positive pressure ventilation. Markedly decreased CO (below 1.8–2.0 L/min), decreased GEF (below 20%) and CFI

Table 12.3 (continued)

Condition	Etiology	Change in volumetric parameters
Pulmonary edema/ARDS	Direct and indirect causes of ARDS (pneumonia, sepsis, shock, pancreatitis, *etc.*)	Increased EVLWI (usually above 10 mL/kg) and PVPI (usually above 2.5–3.0). Low-to normal GEDVI during the early phase. Despite fluid responsiveness, attempts to increase the GEDVI by giving fluids lead to a rise in the EVLWI, therefore posing the question of a "permissive" hypovolemia
Distributive shock	Mostly sepsis	Increased EVLWI (sometimes even without ARDS criteria), normal-to-increased CO (hyperdynamic state), varying GEDVI (usually decreased during a capillary leak). Normal GEF and CFI do not exclude diastolic heart dysfunction

CO cardiac output, *GEDVI* global end-diastolic volume index, *EVLWI* extravascular lung water index, *PVPI* pulmonary vascular permeability index, *CFI* cardiac function index, *GEF* global ejection fraction, *PEEP* positive end-expiratory pressure, *ARDS* acute respiratory distress syndrome

12.5 Conclusion

Today, invasive volumetric monitoring is used in a variety of life-threatening critical care scenarios. The applicability and reproducibility of measurements for a wide range of hemodynamically unstable conditions are the key advantages of this technique. The accuracy of volumetric parameters for the quantification of preload, myocardial contractility, and pulmonary edema has been proven by numerous experimental and clinical studies. Because in critical care medicine volumetric monitoring co-exists with less-invasive ultrasound methods, we believe that both approaches will progress side-by-side. However, in contrast to echocardiography, transpulmonary thermodilution is less operator dependent and gives an all-in-one hemodynamic "bundle," facilitating a clinical decision. Thus, integration of personalized algorithms guided by volumetric parameters into the management of severe shock and acute respiratory distress syndrome would open up new horizons for the improvement of clinical outcomes and warrants further studies.

Keynotes

- The key target of volumetric monitoring is an accurate and versatile assessment of preload, heart function, and lung fluid balance.
- Volumetric monitoring can significantly improve our understanding of the kinetics of fluids used for resuscitation in the most severely ill ICU patients.
- In clinical practice, volumetric monitoring is interrelated with the real-time measurement of stroke volume and prediction of fluid responsiveness.
- The optimization of preload under the tight control of extravascular lung water may improve the safety of the phase management of shock and facilitate the personalization of hemodynamic therapy.
- Further studies are needed to investigate treatment protocols based on volumetric parameters.

Conflict of Interest None.

Funding None.

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Global End-Diastolic Volume

13

Samir G. Sakka

Contents

13.1 Introduction

The assessment of cardiac preload and fluid responsiveness remains a major and ongoing challenging task in the management of critically ill patients. While intravascular pressures, *e.g.,* central venous (CVP) and pulmonary artery occlusion pressure (PAOP), have been clinically commonly used in this field for several decades, experimental and clinical studies revealed their limitations as markers of cardiac preload [1]. As alternative, volumetric variables instead of pressure variables have been established and clinically evaluated over the last years. One of these volumetric hemodynamic variables is the global end-diastolic volume (GEDV) which can be obtained clinically by the transpulmonary thermodilution technique.

Up to date, no scientific evidence for a positive impact on the outcome for a specific monitoring technique or a single hemodynamic variable-guided treatment exists; however, recommendations are available applying GEDVI (GEDV index, as divided by body surface area) for the assessment of cardiac preload in critically ill patients [2]. General aspects on how to guide fluid treatment and assess cardiac preload in critically ill patients are provided in part in Table 13.1.

According to a relatively current survey, GEDVI is used in the clinical decision-making process by about 70% of Swiss intensivists when applying the transpulmonary thermodilution technique [3]. In the following chapter, physiological considerations, potential limitations, and

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Table 13.1 Summary of the consensus statements of the task force of the ESICM (European Society of Intensive Care Medicine)

Statement/recommendation	GRADE level of recommendation; quality of evidence	Type of statement
Optimal fluid management does improve patient outcome; hypovolemia and hypervolemia are harmful	Ungraded	Statement of fact
We recommend assessing the volume status and volume responsiveness	Ungraded	Best practice
We recommend that commonly used preload measures (such as CVP or PAOP or end-diastolic area or global end-diastolic volume) alone should not be used to guide fluid resuscitation	Level 1; QoE moderate (B)	Recommendation
We recommend not to target any absolute value of ventricular filling pressure or volume	Level 1; QoE moderate (B)	Recommendation
We recommend that fluid resuscitation should be guided by more than one single hemodynamic variable	Ungraded	Best practice
We recommend using dynamic over static variables to predict fluid responsiveness, when applicable	Level 1; QoE moderate (B)	Recommendation

GRADE Grading of Recommendations Assessment, Development and Evaluation system of evidence review. *QoE* quality of evidence, *CVP* central venous pressure, *PAOP* pulmonary artery occlusion pressure
Modified from [2]

clinical data with respect to the measurement and clinical implementation of GEDV and goal-directed management will be presented.

13.2 Physiological Considerations

The GEDV which is defined as the sum of the end-diastolic volumes of all heart chambers is derived by an advanced analysis of the transpulmonary thermodilution curve. Experimental and clinical data showed a nearly proportional relation between the GEDV and the intrathoracic blood volume (ITBV) which can be derived from the double (*i.e.,* thermo-dye) dilution technique [4, 5]. Due to the factor 1.25 found in humans [5], GEDV and ITBV may be used interchangeably. Although it seems that GEDV is mathematically coupled with cardiac output, unequivocal impact could not be demonstrated in various studies [6–8].

In general, the relation between intravascular and extravascular fluid is of major relevance in the management of critically ill patients. Here, GEDV as an instrument to assess cardiac preload may be helpful as extravascular lung water is theoretically and as clinically shown to be related to GEDV [2, 9, 10]. As pointed out by Marik [9], there is an optimum point characterized by the best preload

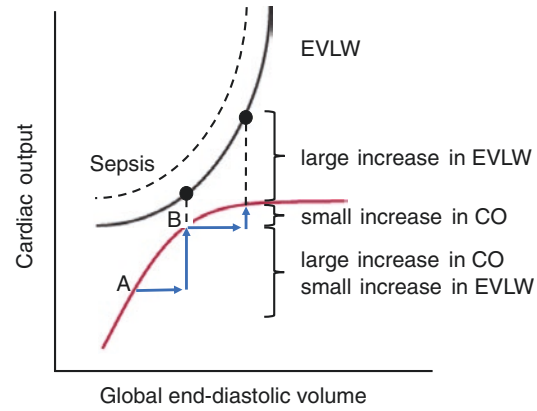

Fig. 13.1 Relation between cardiac preloads as assessed, for instance, by global end-diastolic blood volume and extravascular lung water. Reproduced with permission from [9]

conditions and lowest associated risk for the extravasation of fluid into the tissue (Fig. 13.1).

For clinical application, two commercially systems are currently available for the measurement of GEDV by the transpulmonary thermodilution technique. While the PiCCO® device (Pulsion, Maquet Getinge) assesses GEDV according to the Newman principle, the VolumeView® system (Edwards) assesses it from a different geometrical analysis of the thermodilu-

tion curve, which is based on the slopes of the up and down parts of the curve and a proprietary function [11]. Nevertheless, both systems have been demonstrated to be interchangeable [12].

As GEDV is assessed by bolus injection-based thermodilution, one aspect may be the reliability and accuracy of measurement of the cardiac output and GEDV [13]. In particular, the minimum number of single measurements that is needed to obtain GEDV reliably is of clinical interest. Monnet et al. [14] impressively showed that the injection of at least three boluses of cooled 0.9% saline is sufficient for an acceptable precision. Notably, Huber et al. demonstrated that the injection of room temperature 0.9% saline in comparison to a cooled solution results in a slight but significant overestimation of GEDVI. In this scenario, the percentage error values for GEDVI were found acceptable only in the case of "jugular" (*v. cava superior*) injection of the indicator [15].

In general, the injection site of the cold bolus is of clinically relevant impact [16–20]. As the transit time of the indicator is a major determinant for the measurement, the larger the distance between the injection and detection site results in higher values of GEDV. Thus, the measurement of GEDV *via* injection into the *v. cava superior* yields lower values when compared to the application of the bolus *via* a *v. femoralis* catheter [16]. As long as the position of the central venous and the arterial thermistor catheter remains unchanged, changes in GEDV even more than the absolute values should be used clinically. Irrespective of the two different commercially available systems [1, 21], this relation could be demonstrated by clinical data [15, 16]. Saugel et al. [16] summarized that femoral injection of the thermo-bolus provides precise data on GEDV with a high correlation, but an obvious significant bias related to the augmented injection volume. Femoral venous injection results in a significantly higher GEDV when compared to *v. cava superior* injection. After using a correction formula, GEDV (femoral) showed high predictive capabilities for GEDV (jugular) [17, 18].

Practical Advice

The injection and detection site are of particular clinical relevance, as especially GEDV is dependent upon the distance between, *e.g.,* absolute values are higher for femoral injection.

As of clinical relevance, GEDVI has been described by Wolf et al. to be dependent on gender and age [22]. Thus, when interpreting the absolute values of GEDVI, these factors need to be considered (Fig. 13.2).

In a large cohort, Eichhorn et al. [23] showed by analyzing data from 1925 patients from 64 studies that GEDVI values are heterogeneous, particularly in critically ill patients, and often exceed the proposed normal ranges derived from healthy individuals. For instance, GEDVI was significantly higher in nonsurgical patients with sepsis than in patients undergoing major surgery. In detail, the mean GEDVI was higher by 94 mL/m^2 when compared to 788 mL/m^2 in surgical patients. The authors recommended that these aspects should be considered when defining different therapeutic targets for different patient populations.

Huber et al. [24] found using data from 234 patients that GEDV was independently associated with higher age, male sex, height, and actual body weight. Interestingly, age and height were the most relevant parameters. In detail, each year in age and each cm in height were associated with an increase in GEDV by 9 and 15 mL, respectively.

Practical Advice

The absolute values of GEDV may be less clinically relevant and helpful in the decision-making during different maneuvers compared to its changes.

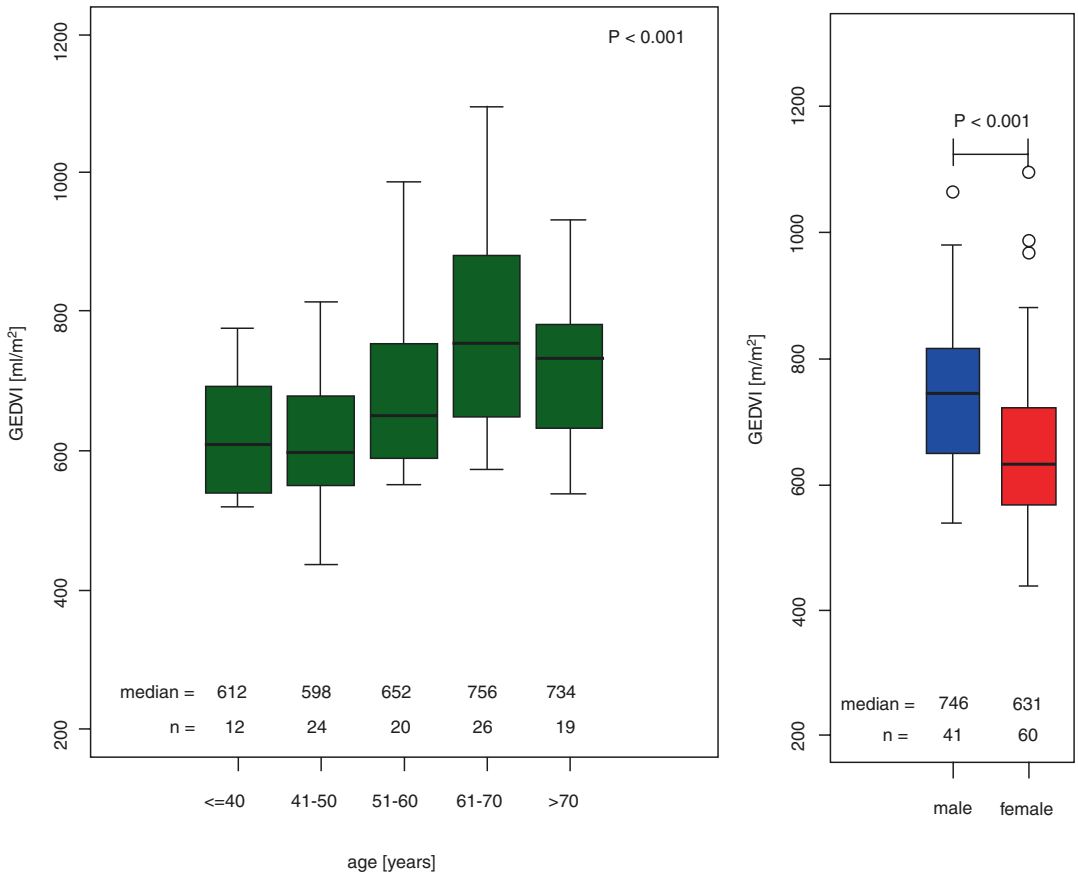

Fig. 13.2 Relation between age and gender and global end-diastolic blood volume index (GEDVI). Reproduced with permission from [22]

Table 13.2 Global ejection fraction ("ejection fraction") corrected volumetric target values. Critically ill: an unstable patient with clinical diminished preload [28]

Ejection fraction	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%
GEDVI target (normal)	1175	1050	950	850	775	700	625	575	525	475	435
GEDVI target (critically ill)	1450	1300	1150	1025	925	825	750	675	600	550	500

GEDVI global end-diastolic volume index, *normal* a stable patient

Independent from "physiological" variations, specific pathologies, *e.g.,* aortic aneurysms or cardiac enlargement, may particularly result in individually different reference values for GEDV. When larger intracardiac or intravascular cavities exist, individual Frank-Starling relation may be shifted to the right, indicating a larger GEDV required for optimal cardiac output [25, 26].

Consequently, Malbrain and colleagues analyzed the relation between the parameters obtained by the transpulmonary thermodilution technique. These authors found that after considering global ejection fraction (GEF), the correlation between the corrected GEDVI (cGEDVI) and cardiac index was better and statistically significant [27]. By using a normal GEF of approximately 0.30 in critically ill patients, they proposed a GEF-corrected cGEDVI = (GEDVI)/exp(2.74 × (0.3-GEF)) (Table 13.2) [28]. For instance, Brücken et al. [29] using the concept of cGEDVI described in patients with prone positioning that cGEDVI measurements are possibly

influenced by prone positioning. According to their conclusion, the differences in cGEDVI were found to be low and though statistically significant presumably of no clinical relevance. So far, large-scale prospective studies on the clinical impact of using cGEDVI in clinical routine are not available.

13.3 Potential Limitations

In general, different authors [30, 31] argued on the reliability of the absolute value of GEDV based on a comparison with data from biplane ventriculography or echocardiography in normal individuals and patients with sepsis. These authors reported that GEDV as derived from transpulmonary thermodilution is overestimated and concluded that only changes in GEDV after volume expansion or catecholamine administration are a pertinent indicator of cardiac preload and should be used cautiously.

Based on the underlying measurement principle, any loss of indicator is mandatorily associated with an error in the estimation of GEDV. As described in the case reports with relevant loss of indicator, *e.g.,* by bleeding or shunt phenomena, the determination of GEDV by transpulmonary thermodilution is erroneous [32].

In patients with a high blood flow *via* an extracorporeal circulation and thus relevant percentage loss of indicator (*e.g.,* ECMO), Herner et al. [33] reported a markedly enhanced GEDVI. These increases in GEDVI after the onset of ECMO were found to be even more pronounced for indicator injection *via v. femoralis* compared to *v. jugularis*.

Furthermore, one-lung ventilation may pose relevant impact on the measurement of GEDV. In an experimental model, Haas et al. [34] described that one-lung ventilation may have significant influence on the measurement of GEDVI. Nevertheless, as Trepte et al. [35] demonstrated by experimental data, the estimation of fluid responsiveness during one-lung ventilation is comparably reliable between GEDVI, SVV, and PPV, respectively.

13.4 Clinical Studies

Numerous studies are available having shown that both GEDV and ITBV are superior to cardiac filling pressures with respect to the estimation of cardiac preload in high-risk surgical patients, in patients with pancreatitis and subarachnoid hemorrhage, and critically ill patients in septic shock or burns [36–40].

Practical Advice
In patients undergoing mechanical ventilation, GEDV is considered superior to cardiac filling pressures for the assessment of cardiac preload and fluid responsiveness.

So far, most studies on GEDV in anesthesia and intensive care medicine were performed in mechanically ventilated patients. However, few data are available in spontaneous breathing. Animal experimental data [41] during normovolemia, blood removal, and re-transfusion plus over-infusion revealed that GEDV and the left ventricular end-diastolic area but not filling pressures (CVP or PAOP) accurately reflected the rapid changes in cardiac preload. In this study, only stroke volume variation and GEDV showed a significant correlation with fluid responsiveness [41].

Most studies were performed in adults; however, experimental and clinical data showed that GEDV is also a reliable marker of cardiac preload in children [42]. Cecchetti et al. [43] consistently described a significant correlation between GEDV and cardiac index or stroke volume index in different populations of children, *i.e.,* those with hemorrhagic and cardiogenic shocks. Noteworthy, the results in other subpopulations were less good. The authors speculated that the influence of non-preload-dependent mechanisms on cardiac output may be responsible for this finding [43].

Practical Advice
Not only in adults but also in children, GEDV is regarded as reliable instrument to assess cardiac preload.

de la Oliva et al. [44] provided the "normal" values for GEDVI in pediatric patients with cardiovascular dysfunction and dilated cardiomyopathy: a 1.33-fold normal GEDVI represented the upper limit of patent preload responsiveness, with the highest expected responsiveness being below 0.67-fold of the normal GEDVI. The maximum response of the Frank-Starling relationship and therefore the level of no additional preload reserve was found between 1.33- and 1.51-fold of the normal GEDVI. Above 1.51-fold of the normal GEDVI, preload responsiveness was found unlikely and the risk of pulmonary edema maximal.

However, when functional hemodynamic parameters (*e.g.,* pulse pressure variation or stroke volume variation) cannot be used for the direct assessment of fluid responsiveness, volumetric variables, such as GEDV or ITBV, or the end-diastolic area as obtained by echocardiography, may be regarded as superior. In special clinical circumstances, *e.g.,* open-chest scenarios, when dynamic preload parameters obviously come to their limitations, GEDV remains a reliable marker of cardiac preload. As shown by de Waal et al. [45], in patients with open-chest surgery, the specificity and sensitivity for estimating fluid responsiveness were significantly higher. The authors concluded that in comparison to volumetric variables static and dynamic preload indicators fail to predict fluid responsiveness under open-chest conditions. As shown clinically, GEDV enables to track the changes in cardiac preload in the postoperative period and spontaneous breathing and may be superior to CVP [46].

Noteworthy, GEDV enables to track the acute changes in cardiac afterload as induced, for instance, by vasopressor therapy, as GEDV rapidly increases with higher mean arterial pressure [47, 48]. As confirmed by echocardiography, GEDV reveals increased intracardiac volume without a significant change in cardiac output.

Several clinical studies emphasized that renal replacement therapy had no clinically relevant effect on the measurement of GEDVI in critically ill patients with maintained cardiac output [49–52]. Furthermore, the dialysis catheter tip position had no significantly different influence under these conditions. However, these findings may be different in higher extracorporeal flow conditions as mentioned above.

Practical Advice
In critically ill patients, with preserved and stable hemodynamics, renal replacement therapy ensures valid measurements of GEDV, and the interruption of the extracorporeal circuit is not required.

13.5 Global End-Diastolic Volume-Guided Therapy

Over the last years, several studies were performed in anesthesia and intensive care medicine, showing that goal-directed treatment based on GEDV as a marker of cardiac preload may have positive impact on the patients' outcome.

In patients undergoing elective cardiac surgery, Goepfert et al. [53] described in 2007 that GEDV-guided treatment is associated with better preserved hemodynamic stability and earlier fulfillment of the criteria for patients being fit for discharge. Although this study used a pre-implementation historical control group, the results were promising. A few years later, the same group published a prospective, randomized clinical study and found that early goal-directed hemodynamic therapy based on cardiac index, stroke volume variation, and optimized GEDVI (Fig. 13.3) was associated with lower complication rates and a shorter length of ICU stay after cardiac surgery [54].

In non-cardiac surgical patients, similar results are available. Current data suggest that with respect to complication rates during liver surgery or hemodynamic stability during peritonectomy

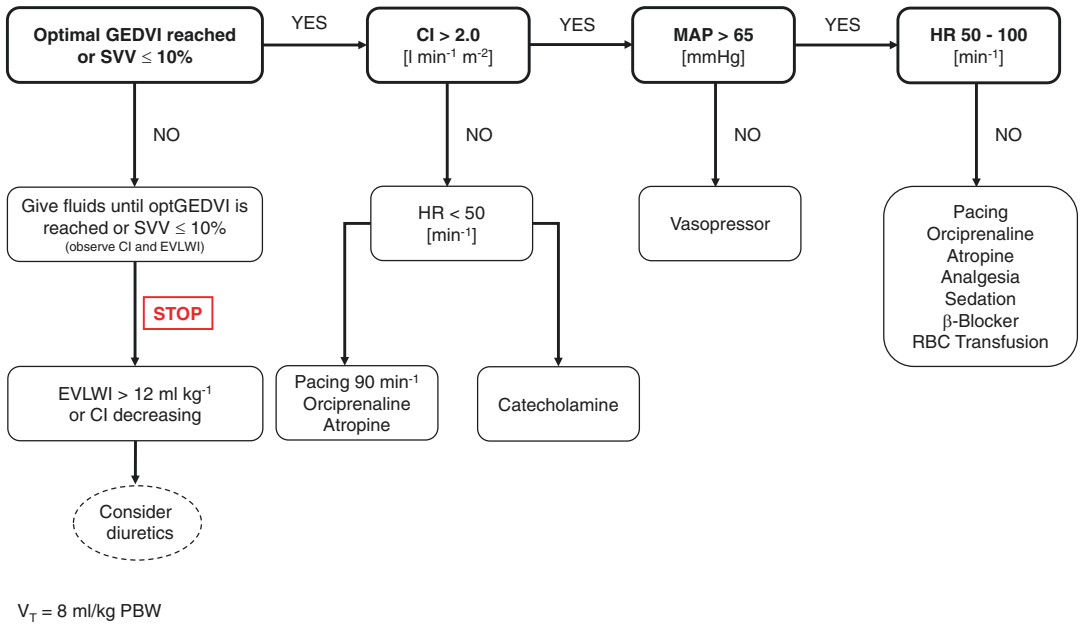

Fig. 13.3 Goal-directed hemodynamic treatment algorithm of the goal-directed therapy group. *GEDVI* global end-diastolic volume index (mL/m^2), *EVLWI* extravascular lung water index (mL/kg), *CI* cardiac index (L/min/m^2), *MAP* mean arterial pressure (mmHg), *HR* heart rate (bpm), *SVV* stroke volume variation, *PBW* predicted body weight. Reproduced with permission from [54]

with hyperthermic chemotherapy, GEDV-guided management may be of particular benefit [55, 56]. Own preliminary data in patients with peritonectomy and hyperthermic chemotherapy suggested that perioperative monitoring and treatment by an algorithm containing GEDV led to a lower SAPS score on ICU admission and enabled for earlier negative fluid balancing [57].

Practical Advice

In the perioperative setting, data available so far indicate that guiding intra- and postoperative fluid and vasoactive drug treatment is associated with higher hemodynamic stability, better preserved organ function, positive influence on fluid balances, and potential to shorten the length of ICU stay.

Furthermore, the data obtained in critically ill patients with burns indicate that GEDV may be helpful to avoid unnecessary fluid overload in patients [58]. Monitoring of GEDVI enables to identify cardiac preload conditions near to hypovolemia which, as long as no signs of organ hyperperfusion exist, should be tolerated and fluid administration avoided. In patients with subarachnoid hemorrhage, GEDVI-guided management was found to be associated with more pronounced hemodynamic stability and lower rate of cerebral vasospasms, a major determinant of neurological outcome in this population [59, 60]. However, the number of patients was too low to allow for general recommendations.

For patients with sepsis, Morisawa et al. [61] found no significant efficacy; early goal-directed therapy guided by GEDVI showed a trend of shorter length of stay in the intensive care unit and lower 3-day infusion balance than the CVP-guided group. The GEDVI monitoring did not appear to improve the ventilator-free days over a 28-day period. In 2015, Zhang et al. [62] reported in patients with sepsis or ARDS using ITBV for guidance no positive impact on outcome and improvement in fluid management when compared to

CVP-based strategy. However, when correcting for the severity of illness by APACHE scoring, patients having undergone extended hemodynamic monitoring were found to have a significantly lower mortality than that predicted by the score [63].

Adler et al. [64] reported by a retrospective analysis that therapy guided by volumetric (GEDVI) and arterial waveform-derived variables (PPV, SVV) can reduce the incidence of AKI in patients with cardiogenic shock after cardiac arrest treated with mild therapeutic hypothermia. Larger prospective randomized trials are required to confirm these results.

Practical Advice
In critically ill patients suffering from various diseases, GEDV-guided management may be associated with a positive impact on organ function. No evidence for the benefit with respect to outcome is available so far.

A recent systematic review by Scully et al. [65] identified nine trials which used dynamic parameters derived from transpulmonary thermodilution devices. Finally, six of them used primarily static parameters to guide fluid therapy. There was evidence for a significant reduction in positive fluid balance in four of the nine studies. The results suggest the benefit of transpulmonary thermodilution monitoring in the septic shock population indicating a reduced positive fluid balance when the devices are utilized for at least 72 h. Both dynamic and static parameters derived from transpulmonary thermodilution devices were found to lead to a reduction in positive fluid balance in septic shock patients compared to the measurements of CVP and early goal-directed therapy.

13.6 Conclusions

Global end-diastolic volume is a reliable marker of cardiac preload in critically ill patients undergoing mechanical ventilation. In particular scenarios, *e.g.*, open-chest conditions, GEDV should be especially considered and used for these purposes as dynamic parameters have limitations. Clinical data from patients undergoing elective cardiac and noncardiac surgery showed that goal-directed treatment using GEDV for preload assessment is associated with the potential to reduce vasoactive drugs, gain stable metabolic conditions, and shorten the length of stay on the intensive care unit. However, further prospective clinical trials are required to underline and differentiate the impact of GEDV-guided hemodynamic management of critically ill patients.

Keynotes
- Global-end diastolic blood volume (GEDV) as a static parameter derived from transpulmonary thermodilution is a reliable marker of cardiac preload in mechanically ventilated critically ill patients.
- The correction of GEDV by ejection fraction seems to be very helpful in the interpretation of absolute GEDV values.
- The absolute values of GEDV vary as explained by the underlying principle according to different injection and detection sites of the indicator.
- As GEDV has been reported to be higher than described by reference techniques, its trend may be helpful in guiding fluid and vasoactive drug strategy.
- Goal-directed treatment based on GEDV-containing algorithms has been found to be associated with higher hemodynamic stability, better preserved metabolism, and the potential to shorten the length of ICU stay in elective surgical patients.

Conflict of Interest Samir G. Sakka a member of the Medical Advisory Board of Pulsion, Maquet Getinge Group.

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Extravascular Lung Water

14

Takashi Tagami

Contents

14.1 Introduction

Pulmonary edema is one of the most common problems among critically ill patients with a profound effect on patient outcomes [1, 2]. Several publications have reported mortality reaching up to approximately 12% for cardiogenic [3] and 30% for non-cardiogenic pulmonary edema [1]. Thus, a better understanding and detailed evaluation of pulmonary edema is crucial for critical care management, especially fluid therapy. In this chapter, we will review the pathophysiology of pulmonary edema and the problems associated with it in clinical practice and describe several merits of evaluating pulmonary edema quantitatively using transpulmonary thermodilution-derived variables.

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14.2 What Is Pulmonary Edema?

A pair of human lungs contain about 700 million alveoli [4]. Although alveoli are microscopically small, their overall superficial area is approximately 100 m^2. Each alveolus consists of an epithelial layer, interstitium, and capillaries. The gaseous exchange of oxygen and carbon dioxide occurs between the inhaled air and the bloodstream in normal lungs (Fig. 14.1). The space outside the capillaries is known as the extravascular lung space with the fluid inside known as the extravascular lung water (EVLW).

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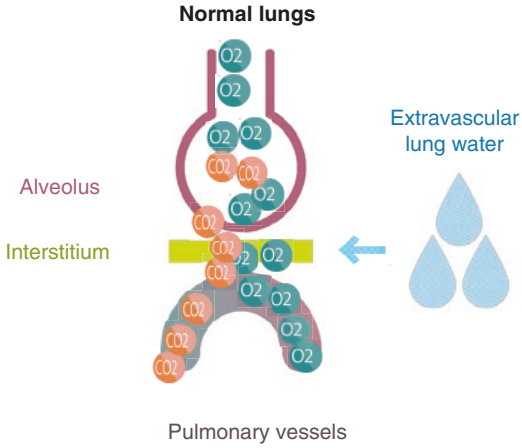

Fig. 14.1 The lungs with normal extravascular lung water amount. The lungs consist of alveoli, interstitium, and capillaries. The gaseous exchange of oxygen and carbon dioxide occurs without delay between inhaled air and the bloodstream

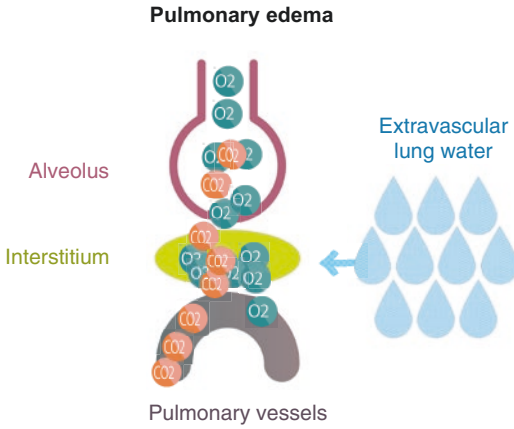

Fig. 14.2 The lungs in pulmonary edema with increased extravascular lung water amount. Pulmonary edema is accumulation of excess EVLW in the lungs. This EVLW accumulation impairs respiratory gas exchange, resulting in respiratory distress

Pulmonary edema is the accumulation of excess EVLW in the lungs [4] which impairs respiratory gas exchange, resulting in respiratory distress (Fig. 14.2) [5]. This pathological condition of the edema develops mainly by two mechanisms, an increase in the pulmonary capillary hydrostatic pressure (hydrostatic or cardiogenic pulmonary edema) and an increase in pulmonary capillary permeability (acute respiratory distress syndrome (ARDS)) [2]. An increase in the pulmonary capillary hydrostatic pressure is the main precursor of cardiogenic pulmonary edema. The elevated vascular pressure is usually accompanied by an increase in blood volume in the pulmonary vessels (*e.g.,* fluid overload, untreated renal failure, or congestive heart failure). However, leaky lungs secondary to inflammatory mediators result in an increase in pulmonary capillary permeability, which is a representative type of non-cardiogenic pulmonary edema, including ARDS.

14.3 Evaluation of Pulmonary Edema

The question that arises is how can we evaluate the degree of pulmonary edema (*i.e.,* EVLW amount) and differentiate cardiogenic from non-cardiogenic pulmonary edema in clinical practice?

The severity of pulmonary edema is evaluated by subjective methods (*e.g.,* patient history, the presence of rales during physical examination, and chest X-ray findings) [2]. However, the interpretation of these methods is often limited due to subjectivity causing interobserver error, even among experts [6]. Several studies suggested only a moderate correlation between chest radiographic findings and EVLW amount [7, 8].

In addition, it is clinically difficult to discriminate between the edema caused by increased hydrostatic pressure in the course of cardiac disease, or by increased permeability associated with ARDS [2]. The latest Berlin definition of ARDS [9] basically consists of four main components: (1) acute onset, (2) chest radiography findings, (3) arterial blood gas results (PaO_2/FiO_2 ratio), and (4) the absence of cardiogenic pulmonary edema. Thus, the presence of cardiogenic pulmonary edema while diagnosing ARDS should be ruled out. The Berlin definition [10] panel agreed, in their conceptual model, of ARDS being a type of acute, diffuse, inflammatory lung injury leading to an increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue. Despite being the hallmarks of ARDS, none of the suggested criteria evalu-

ated the increase in pulmonary vascular permeability and increased EVLW.

In a supplemental publication of the Berlin definition [10], expert panels (the ARDS Definition Task Force) presented typical examples of 12 chest radiographs, categorized into three groups, namely, consistent with, inconsistent with, and equivocal for ARDS. However, the interpretation of chest radiography is complicated and lacks objectivity. Sjoding et al. [8] recently reported clinicians showing only moderate interobserver agreement when diagnosing ARDS in patients with hypoxic respiratory failure under the Berlin criteria. The results were driven primarily by the low reliability of the interpretation of chest images [8]. This conclusion was supported by a recent multicenter prospective study of the inter-rater agreement, where 286 intensivists independently reviewed the same 12 chest radiographs developed by the panels, pre- and post-training. In the study, when the Berlin radiographic definition was used, radiographic diagnostic accuracy and inter-rater agreement were found to be poor and were not significantly improved by the training set of chest radiographs developed by the ARDS Definition Task Force [7].

Therefore, without any objective methods, the precise investigation of pulmonary edema regarding its existence, severity, and the nature of the disease (cardiogenic versus non-cardiogenic) is difficult.

14.4 Transpulmonary Thermodilution-Derived Extravascular Lung Water and Pulmonary Vascular Permeability

The last two decades have witnessed the evolution of the transpulmonary thermodilution technique for measuring EVLW and pulmonary vascular permeability index (PVPI). The details of the transpulmonary thermodilution technique were described elsewhere (Chap. 7).

The transpulmonary thermodilution-derived variables EVLW and PVPI are sensitive, specific, and conceptual markers for evaluating pulmonary edema [11–18]. The accuracy of the EVLW measurement was first validated against the gold standard gravimetric measurement in animal models [19]. The thermodilution measurement of EVLW values showed high accuracy in the normal lungs, cardiogenic pulmonary edema, and ARDS models. In a human autopsy study, a definite correlation was observed between EVLW and post-mortem lung weight from a wide range of normal and injured lungs [11]. More recently, Venkateswaran et al. [20] reported a close correlation of the EVLW with gravimetric measurements of lung water in human brain-dead donors. The most reliable pathophysiological feature of ARDS is the development of diffuse alveolar damage (DAD) with increased permeability [4], which results in the accumulation of water in the lungs, and designated as EVLW. We validated this relationship between EVLW and DAD in a pathological study using nationwide autopsy database [16].

Several studies suggest a normal EVLW value of 7 mL/kg and not exceeding 10 mL/kg (indexed by predicted body weight). Our clinical-pathological study showed the mean EVLW values of approximately 7.3 ± 2.8 mL/kg to be the normal reference range for humans [11]. This value was supported by Eichhorn et al. in a meta-analysis of clinical studies where they found a mean EVLW of 7.3 mL/kg (95% confidence interval, 6.8–7.6) in patients undergoing elective surgery, without pulmonary edema [21]. More recently, Wolf et al. [22] obtained a similar result (8 mL/kg, interquartile range of 7–9) in 101 elective brain tumor surgery patients.

Practical Advice

The normal reference range of extravascular lung water index for human is approximately 7 ± 3 mL/kg.

In addition, Japanese nationwide autopsy data (n = 1688) indicated that an EVLW of >9.8 mL/kg represented the optimal discrimination threshold for a diagnosis of pulmonary edema from the normal

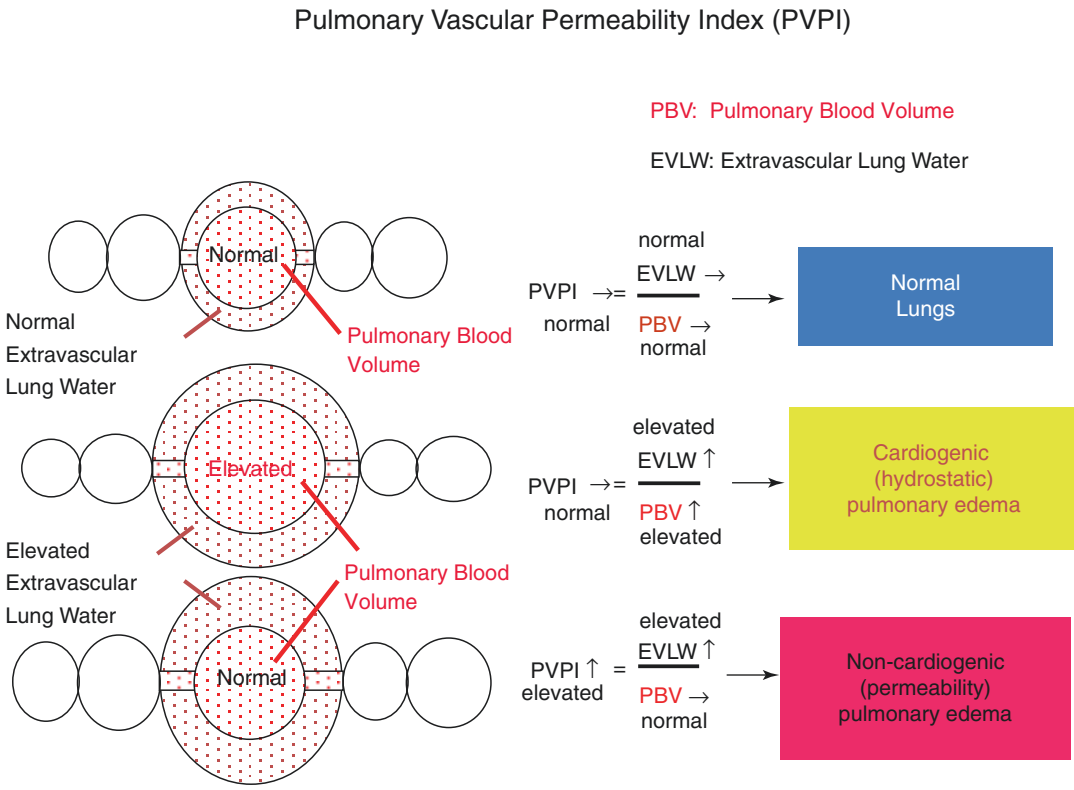

Fig. 14.3 Pulmonary vascular permeability index (PVPI)**.** PVPI is calculated as the ratio of extravascular lung water (EVLW) and pulmonary blood volume. For example, if the EVLW is elevated without a corresponding increase in PVPI, the patient has cardiogenic, pulmonary edema. In contrast, an increase in EVLW along with an increase in PVPI means that the patient has ARDS

lungs, and an EVLW level of 14.6 mL/kg represents a 99% positive predictive value [16]. Several experts have proposed the inclusion of EVLW >10 mL/kg as an ideal criterion in a future definition of ARDS [23, 24]. According to pathological [16] and clinical [25] studies, EVLW values above 10 mL/kg represent higher-than-normal EVLW, and 15 mL/kg is the cutoff for severe pulmonary edema. By assessing EVLW, we can objectively evaluate the initial severity of pulmonary edema and subsequent changes quantitatively, thereby monitoring the ongoing therapeutic strategy.

Practical Advice
Extravascular lung water index of >10 mL/kg is a reasonable criterion for pulmonary edema and >15 mL/kg for a high degree of severity.

PVPI allows the distinction between the pulmonary edemas [19, 26] and can be calculated from the relationship between EVLW and pulmonary blood volume (Fig. 14.3). If the EVLW is elevated without a corresponding increase in PVPI, the patient has cardiogenic pulmonary edema. However, an increase in EVLW along with an increase in PVPI corresponds to the patient having permeability pulmonary edema. Previous studies indicated the use of PVPI to differentiate cardiogenic and non-cardiogenic (ARDS) pulmonary edema [27, 28]. PVPI, along with EVLW, correlates with the level of a biological mediator which is related to the increased pulmonary vascular permeability and the accumulation of lung water [13, 29].

Monnet et al. [28] first showed the differentiation of hydrostatic pulmonary edema from permeability pulmonary edema, with a cutoff PVPI

value of 3. A large-scale, prospective multicenter study from Japan found almost the same results, with a PVPI cutoff value between 2.6 and 2.85 (specificity, 0.90 and 0.95, respectively) providing a definitive diagnosis of ARDS, and a value of <1.7 (specificity, 0.95) ruled out an ARDS diagnosis [27]. Another study evaluating patients with either normal cardiac function or chronic cardiac dysfunction found a PVPI of <3 in all studied patients [30]. Collectively, PVPI <2 may represent normal pulmonary permeability, and PVPI >3 indicates high permeability of the lungs.

Practical Advice

Pulmonary vascular permeability index >3 suggests increased vascular permeability. Pulmonary vascular permeability index <2 can rule out high vascular permeability.

Several clinical studies conducted with ARDS patients suggest the correlation of both EVLW and PVPI with the disease severity [31] and risk factors of mortality [15, 32]. The landmark study by Sakka et al. [31] showed the degree of initial EVLW on admission to the intensive care unit correlated with mortality, with a significant cut-off point of 14 mL/kg. The relationship between EVLW and prognosis was also clearly demonstrated in a systematic review of literature [32] and a recent large-scale study [15]. The results of our multicenter study suggested the decrease in EVLW during the first 48 h associated with a 28-day survival in ARDS [33]. Therefore, the initial absolute value of EVLW is useful for the diagnosis of ARDS, along with the subsequent changes in clinical practice [33].

14.5 Diagnostic Framework for Pulmonary Edema Using Extravascular Lung Water and Pulmonary Vascular Permeability Index

Accurate and objective diagnoses can be made for pulmonary edema using the following diagnostic framework by EVLW and PVPI (Fig. 14.4) [24]. For diagnosing the existence of pulmonary

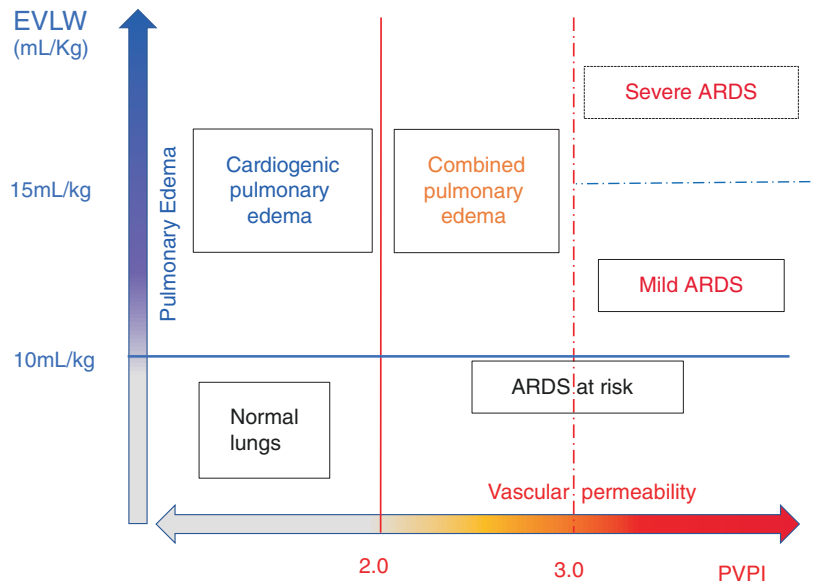

Fig. 14.4 Diagnostic framework for pulmonary edema. Pulmonary edema: extravascular lung water (EVLW) >10 mL/kg. Cardiogenic pulmonary edema: EVLW >10 mL/kg and pulmonary vascular permeability index (PVPI) <2.0. ARDS: EVLW >10 mL/kg and PVPI >3.0. Combined pulmonary edema (*e.g.,* cardiogenic pulmonary edema, reduced cardiac function or fluid overload, and permeability lung injury secondary to the generation of inflammatory mediators): EVLW >10 mL/kg and PVPI of 2.0–3.0. (Reproduced from [24] with permission)

edema, EVLW >10 mL/kg may be reasonable. EVLW >15 mL/kg indicates severe pulmonary edema. After quantitative diagnosis as pulmonary edema by EVLW >10 mL/kg, PVPI should be examined. PVPI <2 represents normal pulmonary permeability, suggesting cardiogenic pulmonary edema. PVPI >3 (with EVLW >10 mL/kg) represents permeability pulmonary edema or ARDS. PVPI >3 and EVLW >15 suggest severe ARDS. Even though the initial EVLW and PVPI are high and indicate a high probability of mortality, with the improvement in values over time (especially during the first 48 h), there may be hope for a better outcome.

14.6 Conclusions

The transpulmonary thermodilution-derived variables EVLW and PVPI can quantitatively express its existence, severity, and the nature of pulmonary edema at the bedside. The accuracy is validated compared to the gold standard method, and the precision is clinically acceptable. EVLW >10 mL/kg is a reasonable criterion for inferring the existence of pulmonary edema and EVLW >15 mL/kg for a severe condition. PVPI <2 may represent normal pulmonary permeability, and PVPI >3 suggests leaky lungs. EVLW and PVPI may be better alternatives to define management algorithms for pulmonary edema patients.

Keynotes

- Extravascular lung water and pulmonary vascular permeability index can be measured by the transpulmonary thermodilution technique.
- Extravascular lung water index of >10 mL/kg is a reasonable criterion for pulmonary edema and extravascular lung water index of >15 mL/kg for a high degree of severity.
- In addition to extravascular lung water index of >10 mL/kg, pulmonary vascular permeability index of >3 suggests an increased vascular permeability (*i.e.,* ARDS), and pulmonary vascular permeability index <2 represents normal vascular permeability (*i.e.,* cardiogenic pulmonary edema).

Conflict of Interest Takashi Tagami is a member of the Medical Advisory Board of Pulsion/Gettinge.

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Part IV

Assessment of Fluid Responsiveness and Dynamic Tests

15 Fluid Responsiveness and Dynamic Tests: Physiological Background

Xavier Monnet and Jean–Louis Teboul

Contents

15.1 Introduction

Fluid administration is the first therapeutic measure in almost all forms of acute circulatory failure. It is, basically and physiologically, intended to increase the cardiac preload and, in response, cardiac output (CO) [1]. However, it appeared in the 1990s that this beneficial effect of volume expansion does not occur in many cases. Apart from cases of obvious deep hypovolemia, the response to fluid loading is only present in half of the cases for which it is carried out.

In this chapter, we will consider the effects that can be expected from fluid administration

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and the physiological reasons behind the lack of "fluid responsiveness" in some cases. We will describe the concept of predicting the response to volume expansion, and we will introduce the chapters devoted to the indices and tests that have been developed for that prediction.

15.2 What Are the Physiological Effects of Volume Expansion?

Fluid administration is often decided facing arterial hypotension. Basically, the effect of fluid infusion is to expand the intravascular volume, increase cardiac preload, venous return and CO, and eventually to improve oxygen delivery and restore adequate oxygen consumption. The increase in arterial blood pressure may accompany the increase in CO, but not systematically.

15.2.1 Systemic Venous Return Curve

Systemic venous return is the flow of blood flowing through the two *venae cavae*. The heart can only eject through the aorta what it has received through *venae cavae*, such that at equilibrium, CO is equal to systemic venous return. In the physiological model proposed by Guyton, systemic venous return depends, on the one hand, on resistance to systemic venous return and, on the other hand, on the pressure gradient which is established between upstream, the mean systemic pressure (Psm), and downstream, the right atrial pressure (RAP) [2]. The mean systemic pressure is the pressure in the cardiovascular system when the heart is stopped. At this time, at least before a vasodilation caused by tissue ischemia occurs, the arterial pressure drops and the RAP rises, both converging toward the Psm value. From this point of view, the physiological role of the cardiac pump is to maintain a pressure gradient between blood pressure and Psm and between the latter and RAP.

The mean systemic pressure reigns in the volume of venous blood that undergoes the stress of the venous walls, which is called "stressed blood volume" [2]. Beside it, there is an "unstressed blood volume," on which the walls of the veins, which are very compliant, do not exert pressure. This volume represents a physiological reserve on which the protective mechanisms can draw to cope with hypovolemia and shock. Indeed, one of the levers of the sympathetic system is to stimulate the alpha-receptors of the vein wall, inducing venoconstriction and recruiting a part of the unstressed blood volume to increase cardiac preload [3].

The relationship between systemic venous return on the ordinate and RAP on the abscissa shows that the more the downstream pressure—the RAP—increases, the more the venous return decreases (Fig. 15.1). At most, the venous return is zero (the venous return curve crosses the *x* axis) when the RAP is equal to the Psm [2].

When the intravascular volume increases during fluid infusion into the venous system, the stressed blood volume and the Psm increase. Since the resistance to venous return is not significantly changed in the same time, venous return, and then CO, should increase. Nevertheless, at this point and before going further in the hemodynamic effects of fluids, another physiological relationship must be considered.

15.2.2 Cardiac Function Curve

According to the Frank-Starling relationship, which links, not systemic venous return, but CO and cardiac preload (Fig. 15.1), the gradual increase in cardiac preload results in a large and then decreasing increase in CO. The initial and steep part of the curve denotes a state of "preload responsiveness" of CO, while the distal and flat parts correspond to a state of "preload unresponsiveness". The slope of the curve depends on the ventricular systolic function [3].

Since, at equilibrium, CO equals venous return, the systemic venous return and the Frank-Starling curve have the same *x* and *y* axes and can be superimposed (Fig. 15.1) [2]. At the intersection of both, an "equilibrium point" describes the interaction between all the variables for a given functioning state of the cardiovascular system.

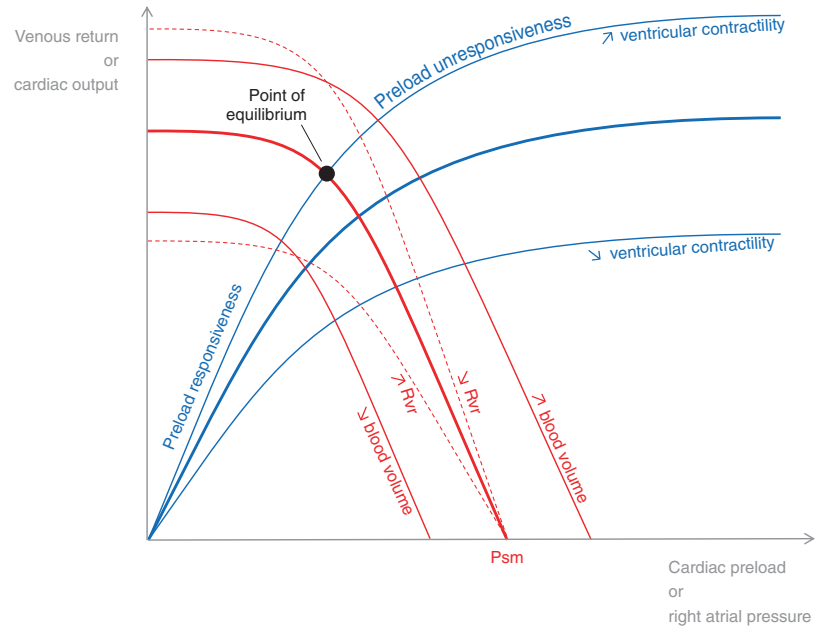

Fig. 15.1 The venous return and the Frank-Starling curves. The venous return curve is in red and the Frank-Starling curve in blue. *Psm* mean systemic pressure, *Rvr* resistance to venous return

15.3 Patients Do Not Constantly Respond to Volume Expansion

Volume expansion as a treatment for acute circulatory failure has been used for a very long time. However, during the 1980s, some studies that monitored not only blood pressure but also CO showed that the latter does not systematically increase with fluid infusion [4]. Some systematic reviews of these studies even showed that this only occurs in half of the cases where volume expansion is carried out [5].

The reasons for this lack of response to the filling are twofold. First, one can theoretically raise the possibility that the volume of fluid administered is too low relative to the volume of stressed blood volume. For example, a volume expansion of a few hundred milliliters administered to an adult patient with high venous vasodilation may have only an insensitive effect on cardiac preload. From this point of view, Aya et al. have shown that an infusion of at least 4 mL/kg of fluid is necessary for the Psm to increase significantly, at least above the smallest value that can be measured by the techniques available today [6].

Second, and this is the main reason, if both ventricles operate in a state of preload unresponsiveness, the increase in preload cannot lead to any significant increase in CO (Fig. 15.1) [3, 7]. Of note, preload responsiveness, also called preload dependence, is a physiological state. In patients, it disappears either because of an impairment of the contractility of the ventricles (lowering of the slope of the cardiac function curve, Fig. 15.1) or because the patients have already received a certain volume of fluid (displacement toward the right on the cardiac function curve, Fig. 15.1), or because of both causes combined.

In the case of preload unresponsiveness, volume expansion increases Psm. However, due to the lack of preload responsiveness, the increase in intraventricular volume does not lead to a significant increase in flow. By contrast, the intraventricular pressure increases, and, ultimately, the RAP increases backward in an amplitude identical to that of the Psm. Thus, the Psm-RAP gradient does not change, explaining why venous return and therefore CO do not change significantly (Fig. 15.2) [8].

In contrast, in the case of preload responsiveness, the increase in intraventricular volume following fluid infusion results in increased CO. The left intraventricular pressure increases a little or

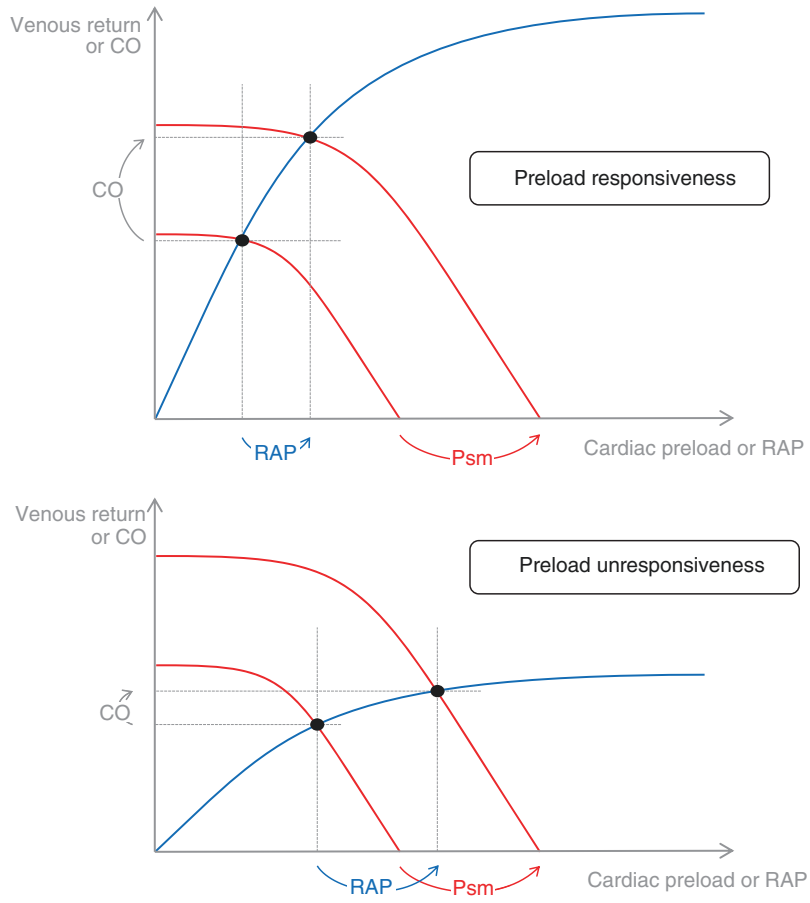

Fig. 15.2 The effects of volume expansion on the venous return curve and the Frank-Starling curve depending on the degree of preload responsiveness. The venous return curve is in red and the Frank-Starling curve in blue. *CO* cardiac output, *Psm* mean systemic pressure, *RAP* right atrial pressure, *Rvr* resistance to venous return

not. As a result, the same is true for RAP, so that the Psm-RAP pressure gradient increases. As the resistance to venous resistance is not significantly changed, venous return and, thus, CO increase (Fig. 15.2) [8].

15.4 How Does Volume Expansion Improve Tissue Oxygenation?

Oxygen delivery, which is the flow of oxygen that passes through the arteries, depends on CO and on arterial oxygen concentration. Then, volume expansion should increase oxygen delivery in the case of preload responsiveness [9]. However, this occurs only if hemodilution induced by the increase in the intravascular compartment does not overtake the increase in CO (Fig. 15.3) [9].

The increase in oxygen delivery may improve oxygen consumption provided that both are on the dependent part of their relationship, which means that oxygen consumption is reduced below oxygen requirements. This point is important, because it means that volume expansion should be performed only in the case of clinical signs of skin and organ hypoperfusion and/or in the case of tissue hypoxia, as evidenced by elevated lactate, elevated carbon dioxide pressure-derived indices, and low venous oxygen saturation [1]. In particular, it must always be kept in mind that preload responsiveness is a physiological condition, and its mere presence should not encourage the administration of fluid.

The improvement of circulatory failure after fluid infusion also depends on the integrity of the microcirculation, of the mitochondria, and of the organ function (Fig. 15.3) [1].

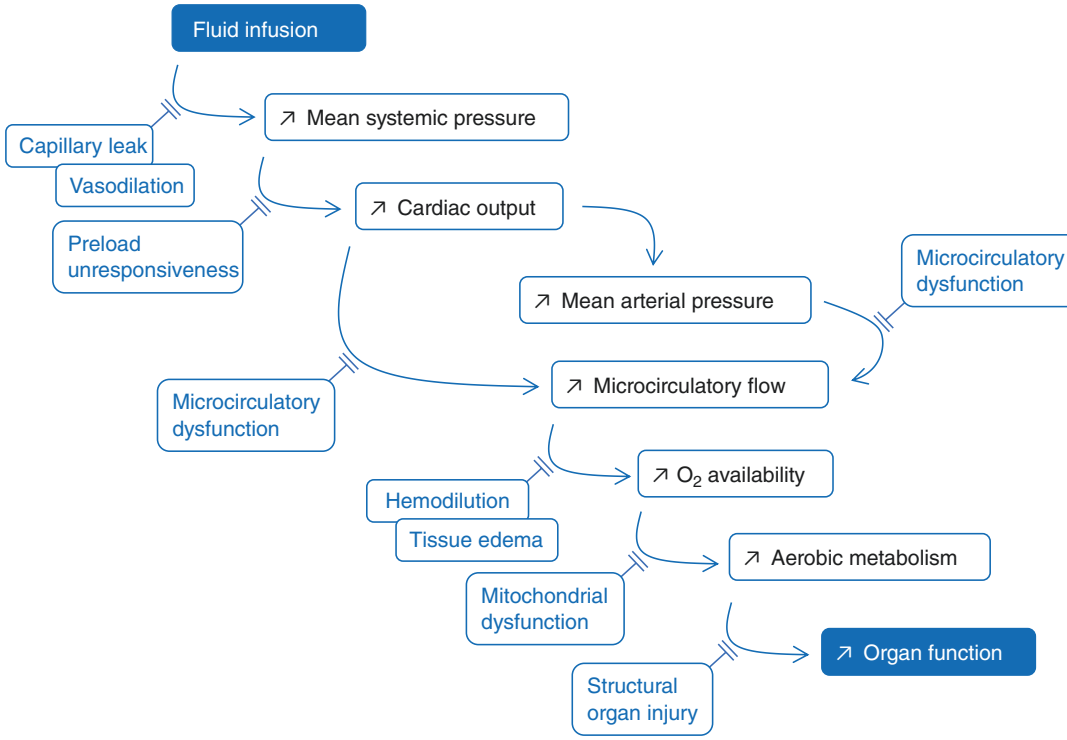

Fig. 15.3 Schematic pathway through which fluid administration leads to organ function improvement and the issues that may interrupt it. Reproduced from [1]

Practical Advice
Even if it induces a significant increase in cardiac output, fluid administration does not always improve tissue oxygenation. The benefit of fluid boluses on tissue oxygenation should be precisely assessed.

15.5 Fluids Are Toxic!

In cases in which fluid infusion does not result in hemodynamic benefit, it can only exert harmful effects. However, at the same time as the inconsistency of fluid responsiveness was evidenced, the toxicity of the fluids became increasingly obvious. Increased cardiac preload, elevated intravascular hydrostatic pressure, and enlarged extracellular compartment are responsible for various deleterious effects [10].

The extravasation of fluid causes peripheral and generalized edema, which is not only of cosmetic concern. It may indeed result in organ edema and visceral swelling, reducing the perfusion pressure gradient from the arteries to the tissues. Venous hypertension also reduces the perfusion pressure gradient, and the elevated levels of central venous pressure (CVP) have been found to be associated with impaired renal function [11] and poor prognosis [12].

Hemodilution induced by the increase in intravascular volume should not be neglected, since it is of the order of 8% [9]. It induces a proportional decrease in arterial oxygen content and, therefore, in arterial oxygen delivery. Preexisting right heart failure, especially if it has developed acutely, is likely to be aggravated by the increased preload induced by vascular filling. Increasing the right ventricular end-diastolic volume might induce a displacement of the interventricular septum to the left in the incompressible space of the

pericardium. This induces a decrease in compliance of the left ventricle, which contributes to the decrease in CO.

Numerous clinical studies have shown that the fluid balance (fluid intake-output) is a factor which negatively influences outcome, independently of other factors of severity [10]. This has been demonstrated by clinical studies carried out on patients in several pathological conditions, including septic shock [13, 14], acute respiratory distress syndrome [15], and acute renal failure [16].

The risk of volume expansion is also linked to the risk of the administered substance itself. The renal risks associated with the administration of hydroxyethyl starches and their contraindication during septic shock are known [17]. Isotonic saline is likely to induce hyperchloremic acidosis, even if it only appears for very large-infused volumes [18].

Practical Advice

The increase in the cumulative fluid balance should be particularly avoided in patients with septic shock, acute respiratory distress syndrome, intra-abdominal hypertension, and acute kidney injury.

Of note, fluid balance does not only result from the fluids administered intermittently for performing volume expansion, facing low arterial pressure and CO. It also results from "maintenance" fluids, administered to cover the patient's daily basal requirements of water and electrolytes, and from "replacement" fluids, administered to correct the existing or developing deficits that cannot be compensated by oral intake [10]. This can be seen in situations where fluids are lost *via* drains or stomata, fistulas, fever, open wounds (including evaporation during surgery, severe burn injury, *etc.*), polyuria (salt wasting nephropathy or diabetes insipidus), and others [10]. Then, the reduction of the total cumulative fluid balance might be achieved not only by avoiding fluid administration at the resuscitation phase but also by removing fluids at the de-escalation phase [10].

15.6 Prediction of the Response to Volume Expansion

Fluids are not harmless treatments and should be viewed as drugs in their own right. Their effectiveness is inconsistent in many cases, and their side effects are not uncommon [10]. Thus, it seems logical to predict before starting their administration whether they will be effective. With this strategy of predicting the response to volume expansion, one takes the risk of fluid administration only if there is a reasonable percentage chance that it will actually increase CO.

At the same time, a sound fluid strategy should precisely assess the patient's risk of fluid loading. The risks of worsening acute respiratory distress syndrome, intra-abdominal hypertension, and right heart failure should also be taken into account [10].

There are, however, cases for which the increase in CO in response to vascular filling is very likely and where early detection of preload responsiveness is unnecessary. This is the case during obvious fluid losses, such as during severe extracellular dehydration or during hemorrhagic shock. This is also the case in the initial phase of septic shock, before any volume expansion. Venous vasodilation induces strong relative hypovolemia such that the response to volume expansion is certain. In these cases, the detection of preload responsiveness would be useless and could only delay the resolution of circulatory failure.

Practical Advice

Preload responsiveness is a normal condition. Fluid responsiveness should be assessed only if cardiac output is obviously too low, as indicated by low indices of tissue perfusion.

Testing preload responsiveness might be also useful at the de-escalation phase. Indeed, the risk at this phase is to remove too much fluid and to induce decreased CO and hypotension. Nevertheless, CO can only decrease as a response to fluid removal if both ventricles are preload dependent. Then, the absence of preload responsiveness at the stage of de-escalation indicates that it is safe to remove fluid [19].

Practical Advice
Detecting preload responsiveness might be useful at the de-escalation phase. In the case of preload unresponsiveness, the risk that fluid removal decreases cardiac output and arterial pressure is unlikely.

15.7 How to Detect Preload Responsiveness?

15.7.1 Static Indices

For years, fluid administration has been based on "static" cardiac preload indices. For example, low CVP would suggest fluid should be infused, while for high CVP values, it will be useless. Besides CVP, many other indicators of cardiac preload could be used as well: the pulmonary artery occlusion pressure measured with the pulmonary artery catheter, E-over-e' ratio in echocardiography, which only imprecisely estimates the previous one, the end-diastolic surface or volume of the left ventricle in echocardiography, the duration of the ejection flow in esophageal Doppler, and the global end-diastolic volume with transpulmonary thermodilution.

However, all these indices do not allow one to predict before administering it whether fluid will be effective or not. In addition to the measurement errors which may occur for these preload indices, they suffer from a physiological limitation. The observation of the Frank-Starling relationship clearly shows that since the slope of the Frank-Starling curve varies from one patient to another, the same given the level of preload can correspond to a state of preload unresponsiveness or of preload responsiveness (Fig. 15.1). As a matter of fact, numerous studies have shown that a given value of static preload indices, the most used being CVP, does not make it possible to predict the response to volume expansion, except perhaps for extreme values.

15.7.2 Dynamic Preload Responsiveness Detection

In contrast to this "static" method, the detection of preload responsiveness should be based on a "dynamic" approach. Its principle is to vary the cardiac preload (for dynamic *tests*), or to observe spontaneous variations in the cardiac preload (for dynamic *indices*), and to observe the effects induced on stroke volume, CO or their substitutes. The following chapters are devoted to these tests and indices. The superiority of this dynamic approach over the static approach is very clearly established today.

15.8 Conclusion

Volume expansion during circulatory failure can increase CO and, eventually, oxygen delivery, only in the case of preload responsiveness. Given the side effects of fluids in many situations, it appears as reasonable to test preload responsiveness before exposing patients to these dangerous drugs. For this purpose, a physiology-based approach should rely on the dynamic tests and indices, rather than the static indices of cardiac preload.

Keynotes
- Except in cases of obvious fluid losses or in cases of early septic shock before fluid administration, only half of the patients respond to fluid administration by a significant increase in cardiac output.

- The harmful effects of fluid overload are very well demonstrated.
- The fact that the response to fluid infusion is not constant and the fact that fluid accumulation is harmful both justify the prediction of fluid responsiveness before fluid infusion is started.
- The static indices of cardiac preload, such as central venous pressure for instance, do not allow one to predict fluid responsiveness.
- Dynamic indices or tests should rather be used for this purpose.
- Detecting preload responsiveness might be useful to lead fluid removal safely.

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Dynamic Indices

16

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Contents

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16.1 Introduction

The means to predict the response of cardiac output and stroke volume (SV) to volume expansion can be divided into indices, which can be observed directly, and tests, which require intervention. The indices assess the variability in SV that occurs in the event of preload dependence in patients on mechanical ventilation. In this chapter, we will detail the principles underlying these indices, their usefulness in practice, and their limitations. The tests are the subject of another chapter.

16.2 Respiratory Variations in Stroke Volume and Arterial Pulse Pressure

16.2.1 What Are the Phenomena Causing the Respiratory Variability of Stroke Volume?

These phenomena are linked to cardiopulmonary interactions: positive pressure ventilation is responsible for cyclic variations in loading conditions of the left and right ventricles. In brief, the principle is that the more the two ventricles are preload responsive, the more SV increases during insufflation and decreases during expiration [1, 2].

At insufflation, the intrathoracic pressure, which prevails in the pleural space, increases. This increase is transmitted to the right atrium, whose wall is thin and in direct contact with the pleura (Fig. 16.1). The increase in right atrial pressure (RAP) decreases the pressure gradient of systemic venous return, and right ventricular preload decreases. If this ventricle is preload responsive, its SV decreases. This decrease is transmitted to the left ventricle, whose preload also decreases. Because of the pulmonary transit time, this decrease occurs at expiration. If, in turn, the left ventricle is preload responsive, the drop in preload results in a decrease in its SV [2] (Fig. 16.1).

Other phenomena also likely play a role in this process. In addition to the decrease in right ventricular preload, positive pressure insufflation decreases the pressure gradient between the inside and outside of the left ventricle, which facilitates its ejection and decreases its afterload. This contributes to the expiratory increase in the left ventricular SV [2]. Also, the increase in intrathoracic pressure increases the transpulmonary pressure (alveolar pressure-intrathoracic pressure). The resulting stretch of the pulmonary vessels propels blood toward the left ventricle, contributing to increase its preload [2] (Fig. 16.1).

In total, all of these phenomena explain that in the case of preload responsiveness of both ventricles, SV increases on expiration and decreases on inspiration. This pattern is sometimes called "reversed pulsus paradoxus."

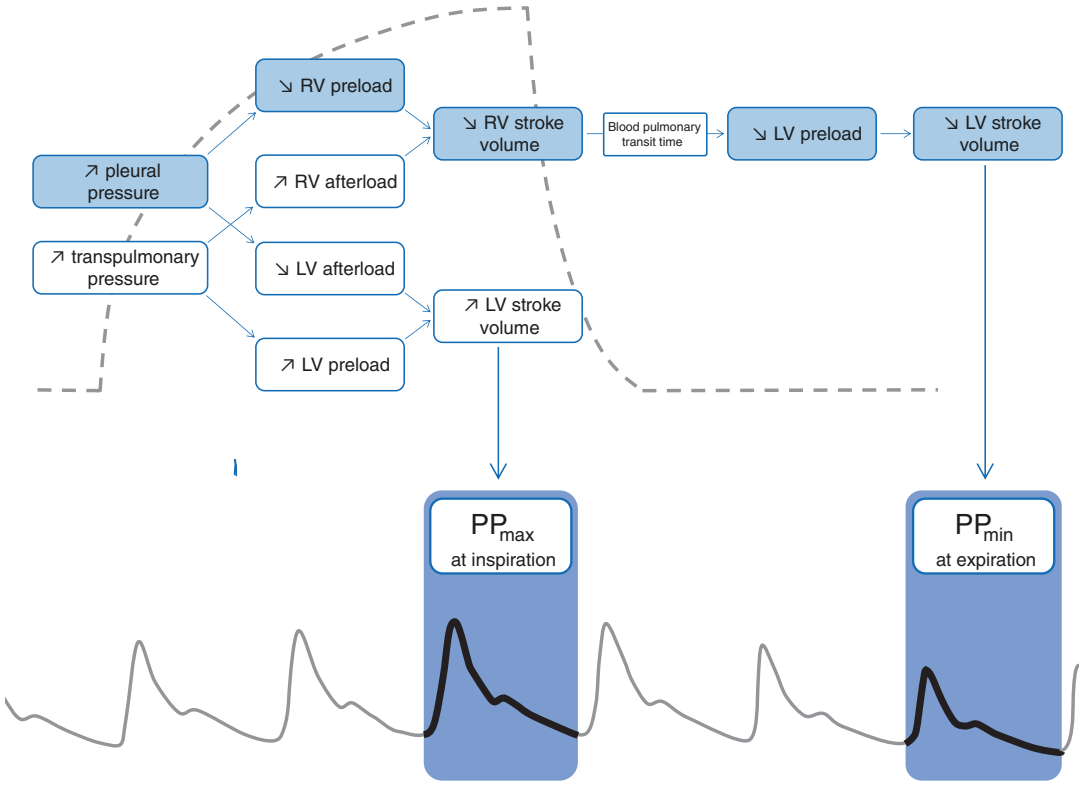

Fig. 16.1 Mechanisms of heart-lung interactions explaining pulse pressure variation. *Top* airway pressure tracing, *bottom* arterial pressure tracing, *LV* left ventricle, *PP* pulse pressure, *RV* right ventricle. (Adapted from [1] with permission)

16.2.2 What Are the Stroke Volume Surrogates Used to Measure Its Respiratory Variation?

In principle, preload responsiveness can be detected by significant respiratory variations in SV (Fig. 16.2). Then, the practical question is to know which indices could be used to estimate SV at the bedside and to quantify its respiratory variation.

16.2.2.1 Arterial Pulse Pressure

The first index whose respiratory variability has been used to reflect that of SV is arterial pulse pressure [3]. Indeed, the difference in systolic and diastolic blood pressure is proportional to SV and inversely related to arterial compliance [4].

Numerous studies have demonstrated that the respiratory pulse pressure variation (PPV) makes it possible to detect the preload responsiveness

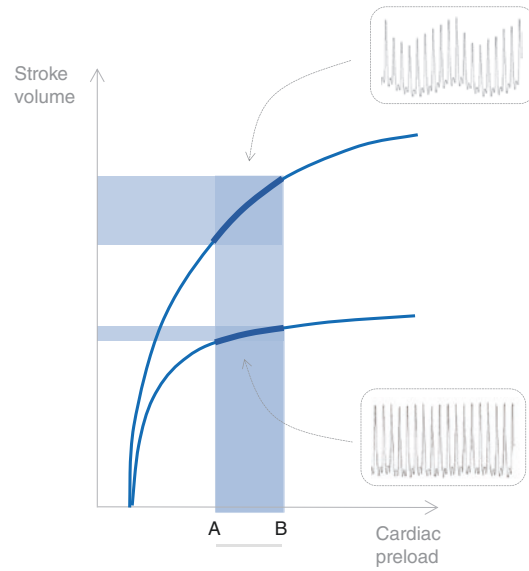

Fig. 16.2 Frank-Starling relationship, preload responsiveness and pulse pressure variation. (Adapted from [2] with permission)

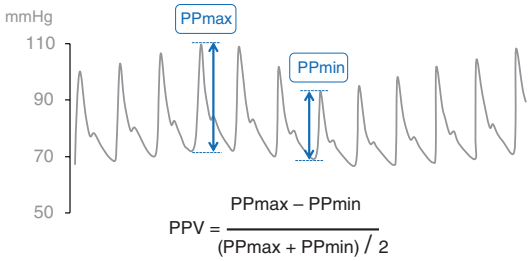

Fig. 16.3 Calculation of pulse pressure variation from an arterial pressure curve. *PP* pulse pressure, *PPV* pulse pressure variation

and to predict the response to volume expansion, and this has been confirmed by some meta-analyses [5]. Among tests and indices predicting fluid responsiveness, PPV has received the highest level of evidence. It is calculated as the ratio between the maximum and minimum pulse pressure difference during a respiratory cycle, divided by the average of the two (Fig. 16.3). The limit diagnostic value is 12% (interquartile range 10–13%) [5].

Initially, PPV was manually measured on arterial pressure traces [3]. Today, all monitoring devices that measure blood pressure continuously display an automatically calculated PPV value. This is of course the case from the arterial pressure curve obtained by an arterial catheter, but also from the pressure curve obtained non-invasively by the volume clamp technique [6, 7].

16.2.2.2 Stroke Volume Estimated by Arterial Pulse Contour Analysis

Pulse waveform analysis estimates SV and therefore cardiac output from an analysis of the blood pressure curve, based on the physiological relationship between SV, arterial pressure, and arterial compliance [8]. Since this estimation is made beat by beat, the technique allows the measurement of respiratory SV variations (SVV) [9].

Clinical studies have shown the validity of SVV to predict the response to volume expansion. In a meta-analysis, SVV predicted fluid responsiveness with greater accuracy than static markers of cardiac preload in mechanically ventilated patients [10]. One might expect that SVV is better than PPV for this purpose, as the variation of pulse pressure is only an estimation of that of SV. However, SVV was significantly less accurate than PPV in that meta-analysis [10]. This is not surprising since the calculation of PPV is prone to fewer errors than the more complex computation of SVV [8]. Another advantage of PPV over SVV is that it requires a simple arterial catheter for its determination.

16.2.2.3 Left Ventricular Outflow

Through pulse Doppler, cardiac ultrasound measures the velocity of blood flow in the outflow tract of the left ventricle during ejection. The signal area, the product of time and speed, is proportional to the stroke volume. Then, the respiratory variation of the left ventricular outflow, reflected by the variation in its maximal velocity, has been shown to detect preload responsiveness [11]. This might be interesting in practice when no monitoring technique is in place and when echocardiography is the only means to assess hemodynamics. However, measuring the respiratory variation of the left ventricular outflow signal is difficult, especially through the transthoracic route since the ultrasound beam must be kept within the outflow in spite of the motion due to ventilation. At least, when an arterial catheter is present, assessing PPV directly through it is much easier.

16.2.2.4 Amplitude of the Esophageal Doppler Signal

Using a Doppler transmitter-sensor located on a probe introduced in the esophagus, esophageal Doppler measures the blood velocity in the adjacent descending thoracic aorta. It reflects SV as does the Doppler of the left ventricular outflow, even if the measurement is made downstream, after the bifurcation toward the head and neck vessels, and even if the signal is influenced by physiological characteristics of the aorta.

Respiratory variations in aortic flow reflect the degree of preload responsiveness and predict the response to volume expansion [12]. This has been demonstrated with an esophageal Doppler device that measured the aortic diameter, and thus took its respiratory variation into account when measuring the variation in the aortic blood

flow [12]. However, the only esophageal Doppler device that is today available does not measure aortic diameter but estimates it from weight, height, and gender. Thus, it considers aortic diameter as constant although it is not since it varies along with arterial pressure [13]. The only respiratory variation that this device takes into account for assessing preload responsiveness is the one of aortic velocity, which is only a part of the flow variation. In spite of that, it has been found to provide an acceptable prediction of fluid responsiveness [14]. Nevertheless, other investigations clearly showed that the respiratory variation of the esophageal Doppler velocity is poorer than that of flow for this purpose [13, 15].

16.2.2.5 Amplitude of the Arterial Doppler Signal

The respiratory variation of the Doppler velocity in some peripheral arteries has also been investigated by few studies as a reflect of SVV and as an index of preload responsiveness. This has been reported with maximal flow velocity measured at the carotid [16, 17] and the brachial [18] levels. The latter seems to be poorer than the former [19]. These indices have not been demonstrated to perform better than PPV, so that they could only be used as surrogates when no arterial pressure curve could be recorded.

16.2.3 Limitations of the Indices Based on Stroke Volume Respiratory Variation

All these indices which detect preload responsiveness by estimating the respiratory changes in SV suffer from the fact that they cannot be used in many clinical conditions (Table 16.1).

16.2.3.1 Spontaneous Ventilation

In spontaneous ventilation, the irregularity of the respiratory efforts respiratory, either in rate or in amplitude, can be at the origin of some SV changes over time which are not related to preload responsiveness. This is thus responsible for some false positives to PPV and SVV (Table 16.1). This is the case even in patients on mechanical ventilation who trigger respiratory cycles because this may still generate irregular alveolar pressure changes [20]. This limitation is important at a time when clinicians are making major efforts to reduce the sedation load of patients under mechanical ventilation.

Table 16.1 Conditions where pulse pressure and stroke volume variations are less reliable

Spontaneous breathing	False +
Cardiac arrhythmias	False +
Low Vt/low lung compliance	False –
Open chest	False –
Increased intra-abdominal pressure	False +
Very high respiratory rate (HR/RR < 3.6)	False –
Right heart failure[a]	False +

HR heart rate, *RR* respiratory rate, *Vt* tidal volume
Adapted from [2], with permission
[a]See text for details

However, some authors have shown that, in case of spontaneous breathing, it is possible to standardize the respiratory efforts of conscious patients by means of a mouthpiece [21]. The variation in SV caused by a deep inspiration through this device was able to detect preload responsiveness reliably. Although they are interesting, these results need to be reproduced. It is doubtful that this method can be used in patients with respiratory distress when a deep inspiration can be sustained.

16.2.3.2 Acute Respiratory Distress Syndrome

In the case of acute respiratory distress syndrome (ARDS), two factors contribute to creating false negatives for the indices of SV respiratory variability. First, the low tidal volume (Vt) that is used to ventilate these patients explains that the variations in intrathoracic pressure are less than in the case of higher Vt. Consequently, for the same degree of preload responsiveness, the cyclic variation of the SV is less. This condition creates some false negatives to PPV [22] (Table 16.1). In practice, it is important to consider that a high PPV in case of low Vt ventilation indicates preload responsiveness, but that a low PPV value does not rule it out.

In case of a small Vt, it is still possible to use PPV to test the preload responsiveness thanks to

the "Vt challenge" [23]. This test, detailed in the next chapter, consists of temporarily increasing Vt from 6 to 8 mL/kg of predicted body weight and observing the effects induced on PPV. It has been shown that if PPV increases by more than 3.5%, preload responsiveness can be strongly suspected [23]. Another way to overcome the limitation of using PPV in case of low V_T is to divide PPV by the respiratory changes in esophageal pressure [24]. The drawback of this method is the need for an esophageal probe.

The second factor limiting PPV and SVV reliability in case of ARDS is the frequent decrease in pulmonary compliance in these patients (Table 16.1). In this case, the alveolar pressure variations linked to ventilation are transmitted to the cardiac cavities and intrathoracic vessels to a lesser extent. It has been shown that when compliance of the respiratory system (Crs) was >30 mL/cmH_2O, PPV predicted fluid responsiveness accurately, whereas when Crs was ≤30 mL/cmH_2O, the prediction was poor, essentially due to a high rate of false negatives [25]. Interestingly, among fluid responders, there was a subset of patients ventilated with a Vt <8 mL/kg, a Crs >30 mL/cmH_2O, and a high PPV and another subset with a Vt >8 mL/kg, a Crs ≤30 mL/cmH_2O, and a low PPV, suggesting that the decreased Crs might play a more important role than the low Vt in the poor predictive value of PPV [25].

16.2.3.3 Cardiac Arrhythmias

It is easy to understand that in the event of atrial fibrillation or frequent extrasystoles, the variability of the volume of systolic ejection is not only due to the preload responsiveness. This is responsible for some false positives for PPV and SVV (Table 16.1).

16.2.3.4 Very High Respiratory Rate

In case of high respiratory rate, the small number of cardiac cycles occurring during a respiratory cycle does not enable the variation of PPV to reach its extreme values. A clinical study showed that PPV cannot be interpreted reliably when the heart rate/respiratory rate ratio is lower than 3.6 [26]. Nevertheless, this corresponds to respiratory rates that are not commonly used in practice (28 cycles/min for heart rate at 100 beats/min, for instance).

16.2.3.5 Right Ventricular Dysfunction

It has been suggested that right ventricular dysfunction could result in false-positive values of PPV due to the predominant effect of mechanical insufflation on the right ventricular afterload through the compression of intra-alveolar microvessels by the transpulmonary pressure. As a failing and dilated right ventricle is more sensitive to its afterload than to its preload, the decrease in right ventricular stroke volume during insufflation would be more related to right ventricular afterload dependence than to right ventricular preload dependence. Two clinical studies reported high PPV values (>12%) despite fluid unresponsiveness in the context of right ventricular dysfunction [27, 28]. However, in these studies, Vt was greater than 8 mL/kg, and it is possible that this phenomenon of right ventricular afterload dependence is attenuated when lower Vt is used. Additionally, in these studies, the way right ventricular function was assessed can be debated.

Practical Advice

If PPV or SVV is low in case of arrhythmias and spontaneous breathing (responsible for false positives), or high in case of low tidal volume and low lung compliance (responsible for false negatives), fluid responsiveness is still likely.

16.2.3.6 Intra-Abdominal Hypertension

An animal study suggests that PPV can still predict fluid responsiveness in cases of intra-abdominal hypertension, but with a higher threshold value than in the case of normal abdominal pressure [29]. Nevertheless, the experimental

conditions (acute rise of intra-abdominal pressure, very high values of intra-abdominal pressure, high Vt and low chest compliance) were extreme and far from those encountered in patients. Conversely, in a clinical study in ventilated patients with acute liver failure, PPV predicted fluid responsiveness, whereas the respiratory changes in the velocity-time integral did not [30].

16.2.3.7 The "Gray Zone" of Pulse Pressure Variations

Using complex statistical methods, a study has demonstrated that there is a "gray zone" of PPV values, between 9% and 13%, where the sensitivity or the specificity is lower than 90% [31]. It was estimated that 24% of PPV values encountered in practice remain within these limits [31]. In fact, the concept of the gray zone analysis expresses the fact that, as for any continuous diagnostic variable, the farther PPV from the diagnostic threshold, the stronger the accuracy of the prediction of fluid responsiveness or unresponsiveness. However, one must keep in mind that a non-negligible proportion of PPV values likely stand within that "gray zone."

Practical Advice

The further PPV/SVV from the diagnostic threshold of 13%, the more likely the diagnosis of preload responsiveness or unresponsiveness.

16.2.3.8 Clinical Context

In practice in the ICU, the conditions where the reliability of PPV and SVV is decreased are quite common. This is particularly true today since patients are less sedated and low Vt ventilation is more common than before and because cardiac arrhythmias are not uncommon. A recent prospective study reported an incidence of 17% of instances where the reliability of PPV and SVV could be used without limitation [32].

In the operating room setting, PPV and SVV monitoring (invasively or non-invasively obtained) retain their predictive value since the conditions of their applicability are generally fulfilled. The limitations of PPV and SVV must always be kept in mind by the intensivists or anesthesiologists, since ignoring them could lead to serious misinterpretations. However, a survey demonstrated that a large proportion of intensivists did not have full knowledge of all factors confounding PPV/SVV interpretation [33].

16.2.4 In Summary

Variations of PP and SV cannot be used in many circumstances, especially in the intensive care unit. Nevertheless, they are the indices of preload responsiveness whose reliability has been best demonstrated. In addition, when they can be used, they have the advantage of being measured automatically by many hemodynamic monitors at the bedside. In addition, PPV analysis is a method of predicting fluid responsiveness that does not require any measurement of cardiac output.

16.3 Respiratory Variations in the Amplitude of the Plethysmography Signal

16.3.1 What Are the Phenomena Causing the Respiratory Variability in the Amplitude of the Plethysmography Signal?

By measuring the oxygen fraction of hemoglobin, plethysmography measures the volume of blood located under the sensor. This varies with the heart cycle. In fact, this signal has two parts, a non-pulsatile one, which does not appear on the display by the monitors, and a pulsatile part, which reflects the variation in the volume of oxygenated blood under the sensor. The ratio

between the two portions, the "perfusion index," is determined by SV and by the degree of vasoconstriction. It also depends on the degree of venous congestion [34].

Thus, the respiratory variability of the perfusion index is believed to reflect that of SV [35]. The perfusion index can be automatically measured by some bedside monitors. Some also automatically calculate its variability and display this "pleth variability index."

16.3.2 How Reliable Is the Respiratory Variability of the Amplitude of the Plethysmography Signal?

In fact, several studies have shown that significant variability in the amplitude of the plethysmographic signal [36, 37] or a high pleth variability index [5, 10] predicts the response to volume expansion. However, it should be noted that several studies have reported less positive results in critical care patients than in the operating room patients [38] and in case of vasopressors administration [39, 40]. This is probably related to the fact that if SV is one of the determinants of the perfusion index, it is not the only one. In particular, the degree of vasoconstriction, which is higher in critically ill patients than in patients undergoing surgery and anesthesia, may account for a lower diagnostic reliability.

In addition, the variation in the amplitude of the pleth signal shares many limitations of PPV and SVV: the presence of spontaneous breathing, cardiac arrhythmias and acute respiratory distress syndrome are obviously responsible for false positives and false negatives for the same reasons.

16.3.3 In Summary

The respiratory variation in the amplitude of the plethysmography signal, or in the pleth variability index, are surrogates of PPV that may be used in the absence of continuous monitoring of arterial pressure. Their reliability is questionable in case of strong vasoconstriction, as suggested by studies performed in critically ill patients.

16.4 Variability of the Diameter of the Venae Cavae

16.4.1 What Are the Phenomena Causing Respiratory Variability in the Diameter of Venae Cavae

Several phenomena are involved in these variations. Regarding those of the inferior vena cava, mechanical ventilation leads to a variability in central venous pressure (CVP) which is greater in the case of preload dependence than in the case of preload unresponsiveness [41]. In other words, the intramural pressure of the inferior vena cava varies. In addition, the transmission of variations in intrathoracic pressure to the abdominal cavity explains cyclic variations in the extramural pressure of the vein. The resulting variations in the diameter of the inferior vena cava are possibly greater if the compliance of the vein is high, which is more likely to occur in hypovolemia than in case of large blood volume. With regard to the superior vena cava, the phenomena are likely identical, except of course that the extramural pressure is the intrathoracic pressure.

Thus, variations in the dimensions of the inferior or superior vena cava are not explained by the changes in SV induced by changes in cardiac preload. These variabilities do not reflect the slope of the Frank-Starling relationship as do PPV or SVV, for instance.

16.4.2 What Reliability?

This may be the reason why the reliability of these indices to reflect preload responsiveness is generally poor. Despite initial positive studies, several subsequent publications have reported moderate or poor diagnostic capabilities. Several

meta-analyses confirmed these results [42, 43]. In a large multicenter study including 540 patients, the area under the receiver operating characteristics curve (ROC) was only 0.65 for variations in the inferior vena cava and 0.74 for those in the superior one [44].

16.4.3 What Limits?

In addition to their lack of reliability, the indices based on the diameter of the cava veins suffer from not being able to be used in several clinical circumstances.

In the same way as PPV and SVV, these indices experience false negatives in the event of low tidal volume and, probably, of low pulmonary compliance. Spontaneous respiratory activity induces false positives, for the same reasons as for PPV and SVV. On the other hand, because the variations are independent of the cardiac cycle, the indices remain valid in the event of cardiac arrhythmia. For the inferior vena cava, intra-abdominal hypertension is another condition in which reliability is reduced.

Practical Advice

If an arterial catheter is present, PPV or SVV should be used instead of the variation of the inferior/superior *venae cavae* diameter for detecting preload responsiveness.

16.4.4 In Summary

The variability of the diameter of the superior or inferior venae cavae does not directly reflect the relationship between stroke volume and cardiac preload, as they are also influenced by the extramural pressures of the vessels. It is now established that these indices of fluid responsiveness are the ones with the lowest reliability. In addition, they share many conditions of use with PPV and SVV.

16.5 Conclusion

The variations in cardiac loading conditions induced by positive pressure ventilation in intubated patients make it possible to test preload responsiveness using indices which are not all equivalent. While PPV and SVV must be considered as very reliable indices, the variability of the diameter of the *venae cavae* has less diagnostic ability. The reliability of the variability of the plethysmography signal has sometimes been questioned. Whatever they are, these indices suffer from being useable only in a limited number of critically ill patients due to very strict conditions of use. It is to get around this important limitation that dynamic tests have been developed.

Keynotes

- Pulse pressure variation is the index of fluid responsiveness that has received the strongest level of evidence.
- The respiratory changes in the diameter of superior or inferior *venae cavae* are the least reliable indices of fluid responsiveness.
- The dynamic indices are less reliable in case of cardiac arrhythmias (false positives), spontaneous breathing (false positives), and acute respiratory distress syndrome (false negatives).
- The respiratory variation of the plethysmography signal is likely less reliable in the setting of the intensive care unit than in the operating room.

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Dynamic Tests

17

Xavier Monnet and Jean–Louis Teboul

Contents

17.1 Introduction

Unlike indices, which are the subject of another chapter and which only require observation of hemodynamic variables under mechanical ventilation, tests that predict preload responsiveness require a brief external intervention. This consists of the administration of small amounts of

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fluid, changes in mechanical ventilation or postural maneuvers that induce significant changes in cardiac preload. The larger the resulting variations in cardiac output (CO), stroke volume or hemodynamic variables estimating them, the larger the degree of preload responsiveness (or of preload dependence), and the more likely the response of CO to volume expansion.

17.2 Fluid Challenge

17.2.1 Standard Fluid Challenge

The most obvious way to detect preload responsiveness dynamically is to administer fluid and measure the response of CO. De facto, the method of injecting 300–500 mL of fluid to guide fluid strategy has been used for many years [1]. Nevertheless, the fluid "challenge" is not a diagnostic test, but the treatment itself. It is not certain that a patient who has just responded to a fluid challenge by a significant increase in CO will still do so during the next one since the 300 or 500 mL of the first challenge may have made the patient already preload independent.

Another disadvantage of the fluid challenge is that it requires a direct measurement of CO (Table 17.1). Indeed, if its effects are assessed by simply measuring the blood pressure, the estimation of its effects on CO is poorly reliable [2] or even not reliable at all [3]. From this point of view, the fluid challenge is not different from the passive leg raising (PLR) test that we will see later. Also, infusion 300 or 500 mL of crystalloid or colloid inevitably induces hemodilution, which is significant and which decreases oxygen delivery [4].

Finally, the major disadvantage of the fluid challenge is that it is not reversible. Repeated use in a patient with multiple hypotensive episodes can only contribute to fluid overload. From this point of view, it is probably necessary to bear in mind the particular risk of fluid challenge in patients for whom fluid overload is particularly deleterious.

17.2.2 Mini-Fluid Challenge

This is the reason why some authors have suggested to administer smaller quantities of fluid to challenge cardiac preload. Muller et al. demonstrated for the first time that the response to volume expansion could be detected by measuring changes in the velocity-time integral of the left ventricular outflow tract measured by echocardiography when 100 mL of colloid were administered [5].

Nevertheless, CO changes induced by a mini-fluid challenge can only be small. Therefore, the method requires a very precise measurement of CO (Table 17.1). From this point of view, echocardiography may not be the ideal method [6],

Table 17.1 Summary of tests predicting preload responsiveness with diagnostic threshold and limitations

"Conventional" fluid challenge (300–500 mL)	Cardiac output	15%[a]	• Requires a direct measurement of cardiac output • Induces fluid overload if repeated
"Mini"-fluid challenge (100 mL)	Cardiac output	6%[b]	• Requires a precise technique for measuring cardiac output • Induces fluid overload if repeated
End-expiratory occlusion test	Cardiac output	5%	• Cannot be used in non-intubated patients • Cannot be used in patients who interrupt a 15-s respiratory hold
Tidal volume challenge	Pulse pressure variation	3.5%	• Cannot be used in non-intubated patients • Requires a monitoring of the arterial pressure curve
Passive leg raising	Cardiac output	10%	• Requires a direct measurement of cardiac output

[a]Thresholds from 12 to 40% have been reported
[b]10% is more compatible with echography precision

especially in non-expert's hands, and more precise techniques might be more appropriate. This is the case, for instance, for pulse contour analysis [7], which is able to detect very small changes in CO [8].

It is likely that there are limits to the reduction of the volume used for the mini-fluid challenge. Very small amounts may fail to significantly increase the stressed blood volume [9]. Even if it does, the induced CO changes in the case of preload dependence may be undetectable if the CO measurement technique is not precise enough. For example, it has been shown that a mini-fluid challenge made of only 50 mL of fluid was unable to detect preload dependence [7].

17.2.3 In Summary

The fluid challenge can be used to predict fluid responsiveness in patients for whom the risk of fluid overload is not excessive. It must be done with small volumes of fluid, but probably not less than 100 mL. Its effects should not be judged by simply observing blood pressure but by measuring CO. In addition, the measurement of CO must be precise enough.

Practical Advice
If a mini-fluid challenge is used for detecting preload responsiveness, the precision of the technique used to assess its effects on cardiac output must be taken into account.

17.3 Respiratory Occlusion Tests

In the wake of pulse pressure variation (PPV), of the distensibility of *venae cavae*, and of other indices predicting fluid responsiveness by observing the hemodynamic effects of heart-lung interactions, some tests based on manipulations of mechanical ventilation have been developed. They are all based on the premise that preload dependence is likely if the preload variations induced by mechanical ventilation affect stroke volume with significant variations. The first of these tests consists in occluding the respiratory circuit at expiration and/or inspiration for a few seconds.

17.3.1 Principle

During mechanical ventilation, each insufflation increases the intrathoracic pressure and, consequently, the right atrial pressure, which opposes the systemic venous return. When mechanical ventilation is interrupted by end expiration for a few seconds, the cyclical decrease in cardiac preload is interrupted. Cardiac preload increases transiently. If, in response, CO increases, it means that both ventricles are preload responsive. Conversely, an end-inspiratory pause should decrease CO in case of preload dependence. Importantly, the duration of the ventilator occlusion should be long enough for the "preload bolus" to pass through the pulmonary circulation. It must also take into account the time on which the device monitoring CO averages it, which delays its maximal change. Five seconds is insufficient [10], and the studies reported a reliable test when occlusions of 12–30 s were performed [10–13].

17.3.2 End-Expiratory Occlusion Test

It has been shown that if CO increases by more than 5% in the last few seconds of an expiratory pause of at least 15 s, the response to volume expansion could be predicted with good reliability [11]. The test has the advantage of being easy to perform, especially when compared with the PLR test [14] (Fig. 17.1).

Practical Advice
The end-expiratory occlusion test should be at least 15-s long in order to allow the increase in cardiac output to appear.

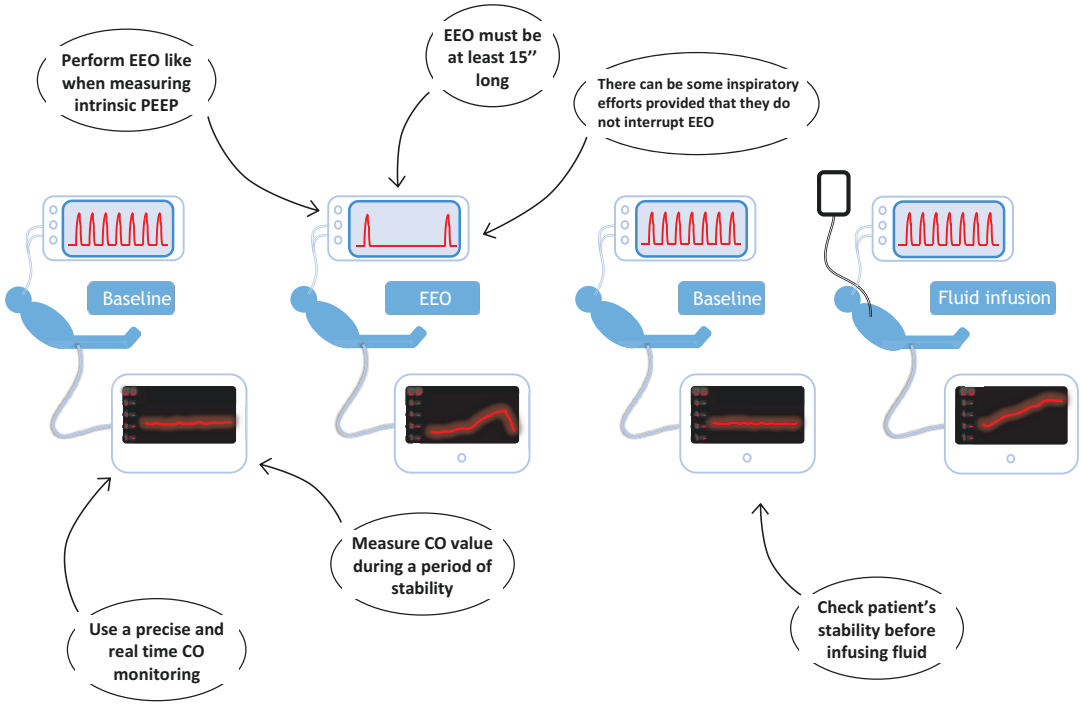

Fig. 17.1 Procedure to perform an end-expiratory occlusion test. *CO* cardiac output, *EEO* end-expiratory occlusion. (Adapted from [14] with permission)

An important practical point is that the technique used to measure CO must be real time, but also precise enough to detect small amplitude changes [14]. From this point of view, the pulse wave analysis is perfectly adapted [8, 15].

17.3.3 Combination of End-Inspiratory and End-Expiratory Occlusions

The increase in the velocity-time integral of the left ventricular outflow measured by echocardiography during an end-expiratory occlusion allows one to predict the response to volume expansion [8, 12]. Nevertheless, the diagnostic threshold might be low compared to the accuracy of echocardiography [6]. Therefore, we proposed to combine a 15-s end-inspiratory pause with a 15-s end-expiratory pause, performed a few seconds apart [16]. We have shown that end-inspiratory occlusion decreased the velocity-time integral of the left ventricular outflow more in preload-responsive patients than in the other ones. Interestingly, if we considered the sum of the effects on the velocity-time integral of the end-expiratory and the end-inspiratory occlusions, the prediction of fluid responsiveness was made with sensitivity and a specificity identical to those obtained with end-expiratory occlusion alone, but with a diagnostic threshold of 13% [16], which is more compatible with the precision of echocardiography [6]. The same combination of end-inspiratory and end-expiratory occlusion tests may be used when esophageal Doppler is used for hemodynamic monitoring, since its precision is not better than the one of echocardiography [17].

The method is somewhat restrictive, since it imposes a careful measurement of the velocity-time integral during two successive respiratory breaks, but it could be an alternative when no other technique than echocardiography or esophageal Doppler is available to estimate CO. Nevertheless, when CO is measured by a technique that cannot reliably detect changes in

CO less than 5%, it seems interesting to combine the end-expiratory and end-inspiratory occlusions.

Practical Advice
When the technique used to measure cardiac output or stroke volume is not precise, like with echocardiography of esophageal Doppler, one should combine a 15-s expiratory occlusion and a 15-s end-inspiratory occlusion and add the effects of both.

17.3.4 Limitations

Respiratory occlusion tests can only be performed, of course, in patients under mechanical ventilation (Table 17.1). In addition, patients must be able to support relatively long breathing occlusions. This is not a problem in the operating room during anesthesia but may be a significant limitation in some critically ill patients.

The level of positive end-expiratory pressure (PEEP) might be theoretically important, since it is the level to which the airway pressure is reduced during end-expiratory occlusion. However, in a previous study in which two levels of PEEP were compared in the same patients, the diagnostic accuracy of the end-expiratory occlusion test was unchanged [18], and this has been confirmed in a meta-analysis [11].

Another factor that might theoretically affect the end-expiratory occlusion test reliability is the tidal volume (Vt). Two studies reported that diagnostic accuracy of the end-expiratory occlusion test was correct with a Vt of 8 mL/kg but poorer if it was 6 mL/kg [14, 21]. However, even if they did not directly compare different Vt levels, some of the other studies which reported excellent diagnostic accuracy had included some patients with low Vt values, as indicated by the mean and standard deviation reported in their whole population. Moreover, the effect of Vt on the end-expiratory occlusion test reliability has not been confirmed in a meta-analysis [11].

17.3.5 In Summary

The reliability of the expiratory occlusion test is established today [11]. The great advantage of the test, if performed by an automatic continuous CO measurement such as pulse contour analysis, is that it is easy to perform. Performing it by means of echocardiography is more restrictive and likely requires both end-inspiratory and end-expiratory occlusions (Table 17.1).

17.3.6 Tidal Volume Challenge

Pulse pressure variation is not reliable for assessing preload responsiveness if Vt is <8 mL/kg as this condition creates some false negatives to the index [19]. Nevertheless, in case of a small Vt, it is possible to use PPV to test preload responsiveness thanks to the "tidal volume challenge" [20]. This test consists of temporarily increasing Vt from 6 to 8 mL/kg of predicted body weight and observing the effects induced on PPV. It has been shown that if PPV increases by more than 3.5% in absolute value (value under Vt = 8 mL/kg (in %) − value under Vt = 6 mL/kg (in%)), preload responsiveness could be strongly suspected [20]. These results have been confirmed in the operating room [21]. The major advantage of this test is not to require CO measurement as a simple arterial line is required to calculate PPV.

17.3.7 Other Tests Using Heart-Lung Interactions

An increase in the level of PEEP from 5 to 10 cmH_2O induces a decrease in cardiac preload that can be used to detect preload dependence. This was shown in a study where the effects of the maneuver were measured on expired carbon dioxide, used as an estimate of CO, in patients who were very stably ventilated [22].

Recruitment maneuvers induce an increase in intrathoracic pressure with similar hemodynamic effects. Concomitant CO changes can predict the response to volume expansion [23]. The

respiratory systolic variation test consists of measuring the effects on the systolic blood pressure of a series of three respiratory cycles performed with increasing airway pressure. The essential advantage of the test is that it does not depend on Vt [24]. The test is allowed automatically by some ventilators used in anesthetic machines.

17.4 Passive Leg Raising

17.4.1 Principle

The transition from the semi-recumbent position to a position in which the lower limbs are raised to 45° and the trunk is horizontal induces the transfer of venous blood from the lower limbs, but also from the splanchnic territory, toward the heart chambers. This results in a significant increase in mean systemic pressure, the upstream systemic venous return pressure [25], and in right and left cardiac preload [26]. Therefore, PLR can be used as a preload-dependence challenge. If CO increases in response to the preload increase, both ventricles are likely preload-dependent and fluid responsiveness is likely. The advantage over pulse pressure or stroke volume variations is that it can be used even in case of spontaneous breathing or cardiac arrhythmias, even in case of low tidal volume and lung compliance in patients under mechanical ventilation. Compared to the standard fluid challenge, the PLR test does not induce hemodilution. As it is reversible, it is not at risk of inducing hydrostatic pulmonary edema. It has been shown that a PLR test was equivalent to about 300 mL of fluid challenge [27], but this is an average value as this volume might highly vary depending on the patient.

17.4.2 Reliability

Many studies have shown that the PLR test can reliably detect preload dependence. The diagnostic threshold for increasing CO during PLR is 10% [28]. A great advantage of the test is that it remains valid even in clinical circumstances where PPV or stroke volume variation cannot be used. In particular, the PLR test retains all its diagnostic value in case of spontaneous breathing, cardiac arrhythmia [29], ventilation at low tidal volume or low lung compliance [29].

Two meta-analyses confirmed the diagnostic value of the PLR test [28, 30]. It has been included in the most recent version of the Surviving Sepsis Campaign's guidelines [31] and in the statements of a consensus conference on hemodynamic monitoring and shock of the European Society of Intensive Care Medicine [32].

17.4.3 Cardiac Output Measurement Techniques

The effects of the PLR test should be measured directly on CO [33]. Indeed, if these effects are assessed on arterial pressure, even pulse pressure, the sensitivity of the test is lower, and the number of false negatives is greater [28, 30]. From this point of view, the PLR test is similar to the fluid challenge, the effects of which can only be reliably assessed by directly measuring CO [2, 3].

Several CO measurement techniques can be used for this purpose. They must meet the requirement to measure flow continuously and in real time, in order to capture the maximum effect of the test (Fig. 17.2). In fact, when the PLR test is positive, the increase in CO occurs during the first minute [34]. Nevertheless, it may occur that CO decreases after reaching this maximum. This effect is particularly observed in patients with severe septic shock, whose vasodilatation is marked. This is, for example, not possible to detect with thermodilution, neither classic pulmonary nor transpulmonary.

To monitor the effects of PLR on CO, esophageal Doppler and calibrated or non-calibrated pulse wave contour analysis can be used [34]. With echocardiography, one must look for the increase in the velocity-time integral in the left ventricular outflow tract. An interesting technique is capnography [35–37]. In fact, if the ventilation conditions are perfectly stable, changes in end-tidal carbon dioxide are proportional to changes in CO. It was shown that if this end-tidal carbon dioxide value increased by more than 5%

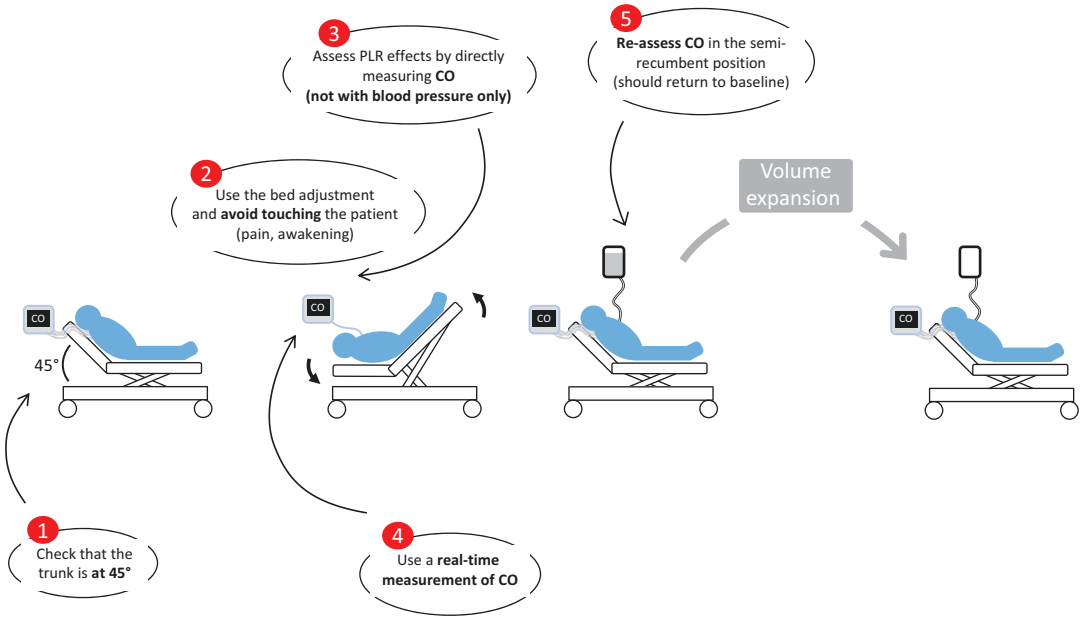

Fig. 17.2 Procedure to perform a passive leg raising test. *CO* cardiac output, *PLR* passive leg raising. (Adapted from [33] with permission)

during the PLR test, fluid responsiveness could be reliably predicted [36, 37].

Finally, a non-invasive assessment of the PLR test is allowed by simply observing its effects on the plethysmography signal. By measuring the oxygen fraction of hemoglobin, plethysmography measures the volume of blood located under the sensor. This signal is made of two parts: a non-pulsatile one, which does not appear on the display by the monitors, and a pulsatile part, which reflects the variation in the volume of oxygenated blood under the sensor. The ratio between the two portions, the "perfusion index," is determined by stroke volume and by the degree of vasoconstriction. It has been demonstrated that the increase in the perfusion index during PLR accurately reflected the changes in CO. The PLR-induced changes in this index, which is automatically measured by some plethysmography devices, detected preload responsiveness accurately [38].

17.4.4 Other Practical Aspects

The position from which the PLR test is started is of great importance (Fig. 17.2). Indeed, if the test is started from the semi-recumbent position, in which the trunk is elevated by 45°, the test mobilizes not only the volume of the venous blood contained in the lower limbs but also the volume of blood contained in the vast splanchnic reservoir, increasing the sensitivity of PLR [27].

The PLR test should ideally be performed using the automatic movements of the bed. Indeed, the "manual" embodiment, which involves holding the patient's heels, can cause discomfort, or even pain, which could distort the analysis of changes in CO [33].

Finally, it is important to measure CO after performing the test, when the patient has been returned to the semi-recumbent position, in order to verify that it has returned to its baseline value and that the changes observed during PLR were only attributable to the test [33] (Fig. 17.2).

Practical Advice

The passive leg raising test should be started from the 30–45° semi-recumbent position. It should use the automatic bed motion. Its effects should be assessed on changes in cardiac output or stroke volume rather than on changes in arterial pressure.

17.4.5 Limitations

As stated above, the main limitation of the PLR test is that it requires a direct measurement of CO (Table 17.1). Also, the test is difficult or impossible to use during a surgical procedure and is reasonably contraindicated in case of intracranial hypertension. It is probably less sensitive in patients with venous compression stocking. Finally, in case of intra-abdominal hypertension, the volume of the splanchnic compartment is reduced, and this condition is responsible for false negatives to the PLR test [39].

17.4.6 In Summary

In adults, the PLR test is a way of predicting fluid responsiveness which reliability is well established. It has the advantage of supplementing PPV and stroke volume variation under the conditions where these heart-lung interaction indices cannot be used. Its major disadvantage is that it requires a direct measurement of CO, even if several non-invasive means can be used to do this.

17.5 Conclusion

Several tests are available to predict fluid responsiveness before performing volume expansion. The mini-fluid challenge is reliable but requires a precise measurement of CO. The end-expiratory occlusion test can be used only in ventilated patients and must be associated with an end-inspiratory occlusion if ultrasound is used to assess its effects. Passive leg raising has received a very large level of evidence. It requires a direct measurement of CO, and it is likely less reliable in case of intra-abdominal hypertension.

Keynotes

- The mini-fluid challenge with 100–150 mL of fluid requires a precise measurement of its effects on cardiac output.
- The end-expiratory occlusion test is easy to perform. It requires a continuous assessment of cardiac output and no active breathing activity.
- The passive leg raising test is now a reference for assessing preload responsiveness. Its effects should not be assessed on arterial pressure but on direct estimates of cardiac output or stroke volume.

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Part V

Monitoring of Microcirculation

Microcirculation: Physiological Background

18

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Contents

18.1 Introduction

Microcirculation is responsible for the regulation and distribution of blood flow in the organs in order to match local tissue perfusion to the oxygen demand. For this purpose, microcirculation reacts to changes in metabolic demand by limiting blood flow in microvascular units with low oxygen demand and increasing blood flow in microvascular units with high oxygen demand. The regulation of arteriolar tone and the regulation of the functional oxygen exchange surface are the two major mechanisms proposed to explain local microvascular regulation of oxygen supply. This microvascular regulation takes place in close collaboration with the microvascular endothelium, which releases various vasoactive compounds, including nitric oxide (NO), reactive oxygen species, and arachidonic acid metabolites. Changes in blood viscosity, endothelial dysfunction, and alteration of glycocalyx are the central elements involved in the alterations in microcirculation observed in ICU patients.

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18.2 Macro- and Microcirculation: Physiological Aspects

Restoring microcirculation and tissue oxygenation are the ultimate goals of hemodynamic resuscitation. During any decrease in volemia, macrovascular and microvascular responses act quickly to compensate for the decrease in blood volume to limit the consequences of low flow, in particular tissue hypoxia. The macrovascular compensatory response involves the autonomic nervous system. Decreased venous return and blood pressure lead to deactivation of cardiopulmonary and arterial baroreceptors, which in turn leads to decreased activation of the vasomotor inhibitor center located in the brainstem causing activation of the vasomotor center (sympathetic center) and inhibition of vagal activity (sinus node). The increased activity of the sympathetic nerves produces an increase in heart rate, cardiac contractility, and arterial and venous tone with activation of the renin-angiotensin-aldosterone system. The magnitude of compensatory vasoconstriction that follows is the net result of the interaction of the effects of norepinephrine released from nerve endings on peripheral vascular adrenoreceptors, epinephrine secreted by the adrenal medulla and non-adrenoceptor mechanisms (*i.e.,* angiotensin and vasopressin). Arterial vasoconstriction rapidly decreases blood flow to non-vital organs (musculocutaneous, splanchnic, and renal blood flow) to maintain perfusion pressure and blood flow to the vital organs (heart and brain).

It is important to keep in mind that sympathetic stimulation exerts arterial and venous α-adrenergic stimulation. Venous vasoconstriction recruits blood from unstressed venous volume and helps to maintain venous return and cardiac output. Thus, the sympathetic system does not only has a role in maintaining arterial blood pressure by increasing arterial tone, but it also has an essential role in maintaining venous return and cardiac output through venous vasoconstriction. This effect of venous vasoconstriction is exerted as soon as there is a slight decrease in venous return.

Microcirculation regulates the distribution of blood flow in the organs to provide an adequate supply of oxygen to meet oxygen needs. To do this, microcirculation responds to changes in metabolic demand by limiting blood flow in microvascular units with low oxygen demand and increasing blood flow in microvascular units with high oxygen demand. This microvascular heterogeneity of blood flow distribution is an essential property of any normal microcirculation to ensure a good match between oxygen supply and metabolic demand. Such metabolic-driven heterogeneity is the guarantee of optimal oxygen extraction. During a drop in volemia, in parallel with the macrovascular redistribution of arterial oxygen transport from the non-vital organs to the vital organs, the blood flow from each organ is redistributed in the capillary networks according to arteriolar tone, rheological factors, and oxygen demand. However, despite the microvascular response, oxygen delivery could be insufficient to cover oxygen demand during shock, and tissues have to downregulate their energy needs to limit tissue hypoxia. In addition, the microcirculatory response to an acute decrease in oxygen supply during shock may be impaired by the development of an inflammatory syndrome which may induce microcirculation dysfunction and alteration of microvascular physiological adaptive mechanisms. In this case, the restoration of macrocirculation, in particular of arterial macrovascular oxygen transport, does not ensure an oxygen microvascular supply adapted to tissue needs. There is then a loss of the physiological link between macro- and microcirculation. Two major mechanisms have been proposed to explain the local regulation of oxygen supply: the regulation of arteriolar tone and the control of the functional oxygen exchange surface.

Practical Advice

The appropriateness of the oxygen supply with the oxygen needs is ensured by the regulation of the microcirculation. The microvascular regulation of oxygen supply involves the regulation of arteriolar tone and the control of the functional microvascular oxygen exchange surface.

18.3 Regulation of the Arteriolar Tone

Microcirculation is a three-dimensional spatial structure made of a network of small vessels (arterioles, capillaries, and venules) with diameters <150 μm. Arterioles are divided into four categories from A1 to A4. A1 includes arterioles with diameters between 70 and 150 μm, A2 those between 40 and 70 μm, A3 those between 15 and 40 μm, and A4 those between 9 and 15 μm. Arterioles are the main regulators of systemic vascular resistances. Mean arterial pressure (MAP) decreases from 80 mmHg in A1 to 30 mmHg in A4.

The arteriolar tone is the net result of the interaction of the autonomic nervous system, the vasoactive substances in the blood (catecholamines, angiotensin, and vasopressin), and the local regulation of the arteriolar tone. The local regulation of the arteriolar tone is a crucial factor of the microvascular regulation for matching oxygen supply to oxygen demand. There is a constant vasoconstrictor tone in arterioles that allows a continuous control of blood flow. As metabolic demand increases, local regulation in the smaller arterioles attenuates the vasoconstrictor tone and leads to vasodilatation in the areas with the highest metabolic needs. In addition, the tone of the larger and more proximal arterioles helps to maintain the MAP necessary to ensure tissue blood flow, while in the smaller arterioles, vasodilation in the more metabolically active areas distributes this tissue blood flow through the microvascular bed, favoring the flow to these areas and decreasing it in the less metabolic areas.

Several mechanisms contribute to the local regulation of the arteriolar tone, including response to intraluminal pressure (myogenic response), shear stress on the endothelial cells (shear-dependent response), and tissue metabolite concentrations (metabolic response).

The vascular myogenic response refers to the intrinsic ability of a blood vessel to constrict to an increase in intraluminal pressure or dilate to a decrease in intraluminal pressure.

The vasodilation induced by shear stress (NO-dependent mechanism) is dependent on endothelial sensing/transduction of the shear induced by blood flow. The proposed mechanosensors on the luminal surface of the endothelium include components of the glycocalyx (glycoproteins and proteoglycans), stretch-activated ion channels, cytoskeletal rearrangements, and cell-cell and cell-extracellular matrix connections.

The metabolic response allows to adapt the vascular tone to cellular oxygen demand. During shock, the decrease in oxygen supply limits the production of adenosine 5′ triphosphate (ATP) and induces an accumulation of adenosine 5′ diphosphate (ADP) and its degradation products (adenosine 5′ monophosphate (AMP), adenosine). In addition, the glycolysis is activated with a production of lactate and hydrogen ion. Adenosine, lactate, and hydrogen ion are arteriolar vasodilators that help in the attempt to maintain an adequacy of arterial oxygen transport to the metabolic demand. CO_2 is also a powerful vasodilator that accumulates in the event of increased cellular metabolism or low CO_2 clearance during tissue hypoperfusion.

Finally, a more and more important role is attributed to the red blood cells (RBCs) and the hemoglobin molecule in the regulation of the microvascular tone and in the matching of oxygen supply to oxygen demand. Ellsworth et al. [1] suggest that the RBCs behave as mobile oxygen sensors and control the vascular tone by means of release of ATP from them. ATP is released from erythrocytes in response to mechanical deformation of their membrane, to an exposure to low PO_2 associated with decrease in the hemoglobin oxygen saturation within erythrocytes or to activation of erythrocyte membrane-bound ß-adrenergic receptors or prostacyclin receptors. The erythrocyte-derived ATP can then interact with endothelial purinergic receptors, inducing release of vasodilator mediators. This vasodilatation may be retrograde, resulting in increased blood flow (oxygen supply) to areas of increased oxygen demand. Certainly, this concept still deserves to be confirmed, but it is an attractive track to explain the microvascular response to oxygen demand. Other mechanisms involving the erythrocyte in the regulation of the vascular tone have been proposed. Stamler et al.

proposed that the erythrocyte could regulate the O_2 delivery through the transport of NO in protected form as *S*-nitrosothiol (SNO) [2, 3]. This vasorelaxant moiety is released by the hemoglobin when the hemoglobin O_2 saturation falls in response to increase in local O_2 demand. Finally, another hypothesis has been proposed in which deoxyhemoglobin would function as a nitrite reductase to transform nitrite (NO_2^-) into NO with resulting vasodilatory action. The possible involvement of other oxygen sensors such as cytochrome oxidase or NADPH oxidase is also of interest but requires further work to establish their respective contributions.

18.4 Control of Microvascular Functional Surface Area for Oxygen Exchange

In order to maintain tissue oxygenation despite a decrease in oxygen supply, such as during shock, more oxygen must be extracted from the incoming blood. Oxygen extraction depends on the incoming blood flow (convective oxygen transport determined primarily by arteriolar tone) and the functional oxygen exchange surface area (diffusive oxygen transport) related to the number of RBCs and the number of capillaries perfused. Thus, oxygen extraction is facilitated by a high capillary density, which increases the oxygen exchange surface area and reduces capillary-to-mitochondrial diffusion distances.

This high capillary density can be achieved by capillary recruitment (*i.e.,* the initiation of a flow of RBCs into previously non-perfused capillaries). However, the capillary recruitment capacity appears to vary according to capillary beds [1, 4]. Capillary resistance and rheological factors (in particular blood viscosity which depends on hematocrit, plasma viscosity, the ability of RBCs to deform under flow, and RBC aggregation-disaggregation properties) determine the distribution of RBCs in the capillary bed [5]. These factors play a crucial role in determining capillary homogeneity and the density of functional capillaries, especially in shock conditions [1]. For example, during the acute phase of hemorrhagic shock, the decrease in capillary pressure leads to an increase in net intravascular fluid absorption, with fluid passing from the interstitium to the vascular compartment, which helps to restore blood volume. This effect associated with hemodilution caused by fluid resuscitation could theoretically decrease the viscosity of the blood and help to reduce the heterogeneity of RBC distribution. However, during the late phase of shock, the inflammatory process may induce extravascular plasma leakage to the interstitial compartment, resulting in increased viscosity and heterogeneity of red cell distribution [4].

Glycocalyx (GC), located at the interface between the endothelium and the cellular and extra-cellular components carried by the blood, plays a decisive role in the functional surface area for oxygen exchange. Glycocalyx is a thin layer negatively charged of glycosaminoglycans and proteoglycans that covers the luminal surface of the microvascular endothelium with an estimated thickness ranging from 150 to 500 nm. It plays an essential role in the maintenance of microcirculatory homeostasis and thus in the microvascular regulation of RBC flow and oxygen transport [6, 7].

Glycocalyx acts as one of the components of vascular permeability, as a mechanotransducer of flow-induced shear stress on endothelial cells and as a regulator of leukocyte-endothelial interactions [8, 9]. Glycocalyx protects the endothelium through anti-adhesive, anti-thrombotic, and anti-oxidative stress properties [10–12]. There is a growing body of evidence suggesting that GC degradation is one of the elements responsible for the microcirculatory alterations observed in shock [13, 14] and chronic diseases such as atherosclerosis, diabetes mellitus, chronic renal failure, and cerebrovascular disease [15]. Indeed, the degradation and loss of the protective barrier properties of GC will contribute to (1) an alteration of the physiological responses of the microcirculation, in particular an alteration of the production of NO, (2) an increase in the adhesion of circulating blood cells to the endothelium, (3) a decrease in the endothelial anticoagulant properties with the formation of microthrombus, and (4) an increase in capillary permeability with

an increase in tissue edema. All these elements contribute to a decrease in microcirculatory flow with an increase in the heterogeneity of the distribution of this flow within the organs and consequently to a decrease of functional surface area for oxygen exchange.

18.5 Alterations of Microcirculation in Critically Ill Patients

In all types of shocks, alterations in microcirculation have been described both in preclinical models and in critically ill patients. A decrease in arterial oxygen transport leads to a decrease in microcirculatory blood flow and functional capillary density with an increase in flow heterogeneity within the organs. If this decrease is rapidly corrected by early resuscitation, the microvascular alterations will be reversible. But, if the decrease in arterial oxygen transport cannot be quickly corrected by fluid resuscitation and/or vasopressors, then the microcirculatory changes may persist and become impossible to correct despite adequate macrovascular resuscitation. Changes in blood viscosity and endothelial dysfunction are two central elements involved in alterations in microcirculation (Fig. 18.1).

18.5.1 Changes in Blood Viscosity

The viscosity of blood is non-linearly dependent on the hematocrit and is proportional to the suspension phase, the plasma viscosity. The viscosity of the blood is lowered by structuring the two-phase plasma/RBC microcirculatory flow with a concentration of RBCs in the center of the vessels surrounded by the plasma. The plasma acts as a lubricant and minimizes the friction between the RBCs and the endothelium (Fahræus-Lindquist effect). Pressure gradient and velocity also impact viscosity. Indeed, at low speed and low shear rate, many aggregates of RBCs are formed. These aggregates of RBCs have a very important contribution to the viscosity of the blood. Increasing the shear rate leads to a decrease in these aggregates, and therefore a decrease in the viscosity of the blood. In addition,

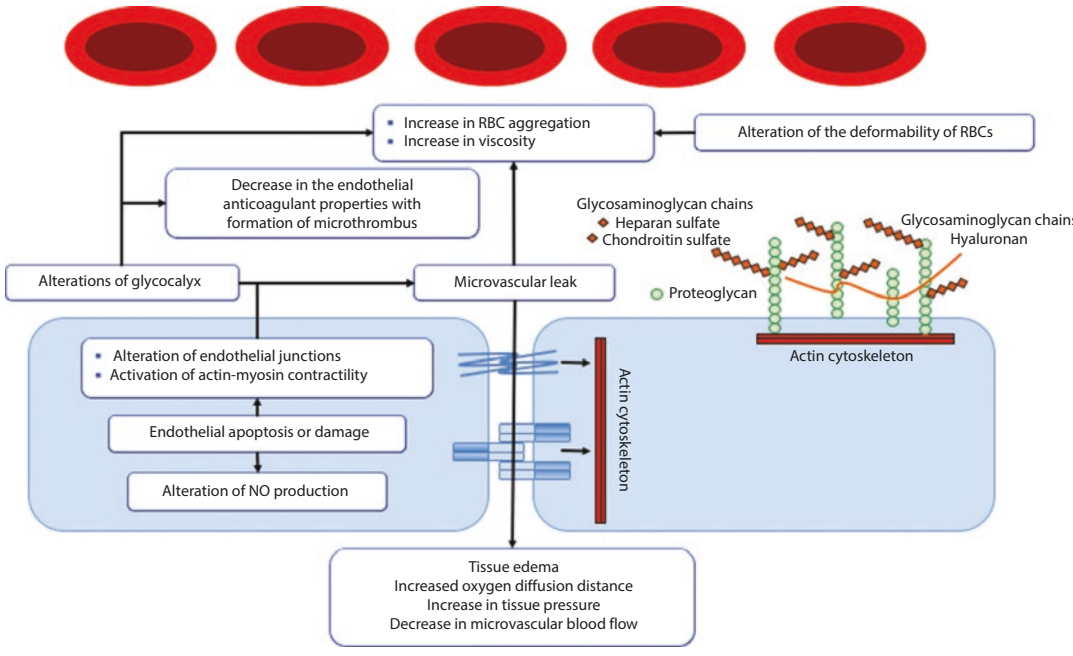

Fig. 18.1 Mechanisms of alterations in microcirculation. *RBC* red blood cells

at high shear rates, the RBCs, due to the mechanical properties of their membrane, change shape until they become flat ellipsoids oriented along the current lines with a decrease in viscosity.

In ICU patients, an increase in blood viscosity may be induced by an increase in microvascular leakage, a decrease of microvascular flow, and an alteration of the deformability of the RBCs. This last point has been clearly demonstrated in patients in septic shock. Indeed, sepsis reduces the deformability of RBCs by reducing the sialic acid content of the membrane glycophorin A, which promotes their aggregation and modifies the microvascular functional surface for oxygen [16].

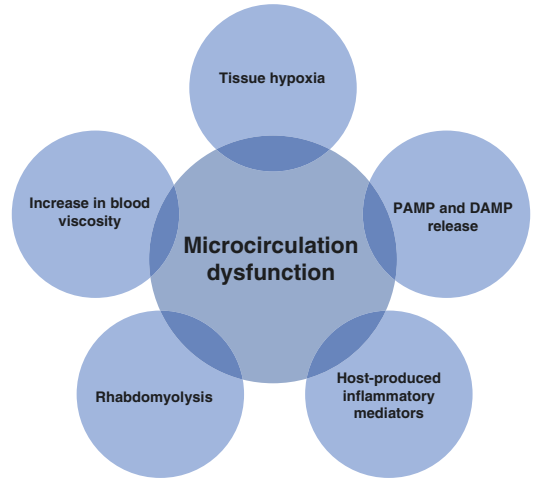

Fig. 18.2 Dysfunction of endothelium and microcirculation in critically ill patients. *PAMP* pathogen-associated molecular patterns, *DAMP* damage-associated molecular patterns

18.5.2 Endothelial Dysfunction

It is obvious that endothelial dysfunction plays a central role in microcirculatory dysfunction. Depending on the etiology of the shock, an alteration in the function and structure of the microvascular endothelium may be induced by (1) hypoxemia and tissue hypoxia induced by the decrease in arterial oxygen transport, (2) pathogens (bacterial, fungal, or viral agents) with exogenous PAMPs (pathogen-associated molecular patterns) and endogenous DAMPs (damage-associated molecular patterns) release, (3) host-produced inflammatory mediators, (4) products released by rhabdomyolysis, and (5) increased blood viscosity (Fig. 18.2). The microvascular endothelial dysfunction results in a shift toward a proapoptotic, pro-inflammatory, pro-adhesive, and procoagulant phenotype.

Both DAMPs and PAMPs, inflammatory mediators derived from pathogens, tissue injuries, and activated immune cells that initiate, signal, alert, and guide the immune system to fight infection, also mediate host cell damage. DAMP and PAMP act on endothelial cells by acting on pattern recognition receptors (PRRs, including Toll-like receptors) to activate downstream signaling *via* members of the MAPK (*i.e.,* p38, JNK, and ERK5) and the NF-kB family and induce gene transcription of pro-inflammatory cytokines, chemokines, adhesion molecules, and procoagulant factors. Upregulation of adhesion molecules (integrins (CD 62E/P), VCAM-1 (vascular cell adhesion molecule-1), PECAM (platelet endothelial cell adhesion molecule-1), and ICAM-1/2 (intercellular cell adhesion molecule-1/2)) and alteration of glycocalyx cause an increase in the adhesion of circulating cells (leukocytes and platelets) mainly in the venous part of the microcirculatory network. This upregulation of VCAM-1 and ICAM-1 is associated with the development of multi-organ dysfunction in patients with sepsis and septic shock [4]. Furthermore, the regulation of arteriolar tone and functional surface area for oxygen exchange is totally modified by the overproduction of NO, prostacyclin, and endothelin. The activation of microvascular endothelium provokes iNOS upregulation resulting in the overproduction of NO which can interact with reactive oxygen species (superoxide anion O_2^-) and create high reactive oxygen species as peroxynitrite ($ONOO^-$) which is a major mediator of lipid peroxidation and protein nitration.

Increased microvascular leak occurs due to alterations of the glycocalyx and loss of intercellular junctional integrity (especially phosphorylation of constituents of adherent junctions with vascular endothelial cadherin proteins internalization), remodeling of the cellular cyto-

skeleton and causing interendothelial gaps. Accumulation of interstitial fluid is detrimental to tissue oxygenation and organ function as edema (1) increases the diffusion distance for oxygen and nutrients and (2) compresses capillaries by increasing the interstitial pressure in organs with non-expendable interstitial volumes (kidney, brain, muscle). In addition, edema in the lungs leads to alveolar flooding and hypoxemia. Preclinical studies suggest that preventing microvascular leak may represent a viable therapeutic strategy to decrease organ dysfunction [16, 17]. Given the emerging role of glycocalyx as an essential component of capillary permeability, further studies on therapeutic agents that may stabilize glycocalyx are needed.

Under normal conditions, endothelium is a natural anticoagulant that ensures the fluidity of the blood. Endothelium regulates coagulation and fibrinolysis by (1) GC which is negatively charged and rich in heparin-like molecules such as glycosaminoglycans (heparan), (2) activation of the protein C/thrombomodulin system which inactivates factors Va and VIIIa, (3) tissue factor pathway inhibitor (TFPI) which limits fibrin deposition by binding to factor Xa and inhibits TF-factor VIIa complex, (4) regulation of fibrinolysis by tissue plasminogen activator (tPA) through inhibition of plasminogen activator inhibitor-1 (PAI-1), and (5) endothelial release of NO and prostacyclin. Shock disrupts this balance by altering the function of the endothelium with a transition from hypo- to hypercoagulability. Trauma-induced coagulopathy (TIC) is characterized by activation of protein C system, coagulation factors depletion, and fibrinogen deficiency [18] with evidence of endogenous heparinization due to release of heparin-like constituents from the glycocalyx [19, 20]. In septic shock, endothelial damage participates to the shift toward a procoagulant state with microvascular thrombosis by shedding and decreased expression of endothelial protein C receptor, thereby limiting the activation of protein C. In addition, the fibrinolytic pathway is suppressed in sepsis by the increased release of PAI-1 by the endothelium [21–23]. Finally, endothelial lesions promote platelet adhesion and the generation of microvascular thrombosis.

18.6 Conclusion

The essential function of microcirculation is to regulate the distribution of blood flow in the organs for providing an adequate supply of oxygen to meet oxygen needs. To do this, microcirculation responds to changes in metabolic demand by limiting blood flow in microvascular units with low oxygen demand and increasing blood flow in microvascular units with high oxygen demand. Two major mechanisms have been proposed to explain the local regulation of oxygen supply: the regulation of arteriolar tone and the control of the functional oxygen exchange surface. Alterations in microcirculation play a major role in the organ dysfunctions that are observed in ICU patients during shock and high-risk cardiovascular surgery. Changes in blood viscosity and endothelial dysfunction are two central elements involved in these microcirculation alterations. In order to better prevent and correct microvascular alterations, it is necessary to continue to explore the behavior of the various microcirculations during shock and surgery with high cardiovascular risk in preclinical models and in ICU patients.

Keynotes

- The microcirculation regulates the distribution of blood flow in the organs in order to adapt the oxygen supply to the oxygen needs.
- The regulation of arteriolar tone and the modulation of functional microvascular oxygen exchange surface are the two mechanisms that allow the oxygen supply to be adapted to the oxygen needs.
- Alterations in microcirculation play a major role in the organ dysfunctions that are observed in ICU patients.
- Changes in blood viscosity and endothelial dysfunction are two central elements involved in microcirculation alterations.
- The microvascular endothelial dysfunction results in a shift toward a proapop-

totic, pro-inflammatory, proadhesive, and procoagulant phenotype.
- Increased microvascular leak occurs due to alterations of the glycocalyx and loss of intercellular junctional integrity.

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Vital Microscopy

19

Benjamin Bergis, Anatole Harrois, and Jacques Duranteau

Contents

19.1 Introduction

Optimization of tissue microcirculation and oxygenation are the ultimate objectives of hemodynamic resuscitation. The aim of hemodynamic resuscitation must be to prevent tissue hypoperfusion in order to limit organ dysfunction. Recent advances in imaging techniques allow us to observe that the behavior of microcirculation may be different from that of macrocirculation in critically ill patients. Indeed, alterations in microcirculation may persist in spite of optimization of macrovascular hemodynamic parameters. However, despite the fact that it is becoming evident that we need to take microcirculation into account in optimization strategies, we lack microcirculation monitoring tools that can be used at the bedside in clinical practice. In this chapter, we propose to examine the vital microscopy for these purposes.

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19.2 Handheld Vital Microscopes: Parameters and Devices

With the introduction of handheld vital microscopy (HVM) techniques almost 20 years ago, it became possible to assess the microcirculation in a non-invasive manner at the patients' bedside. Handheld vital microscopes (HVMs) allow direct non-invasive bedside assessment of microcirculation by visualizing flow of red blood cells (RBCs) through the capillaries (convective transport of oxygen) and the density of perfused capillaries (diffusive transport of oxygen) (Fig. 19.1) [1]. Handheld vital microscope measurements are mainly performed in the sublingual area, so we will limit ourselves to this microvascular bed in this chapter. The emitted light, corresponding to the hemoglobin wavelength absorption, displays each erythrocyte in black on a light background. Images acquisition and analysis have to be performed according to international guidelines [2]. The greatest care has to be provided in order to avoid pressure artifacts. Sequence quality has to be systematically evaluated using the "Microcirculation Image Quality Score" described by Massey and co-workers [3].

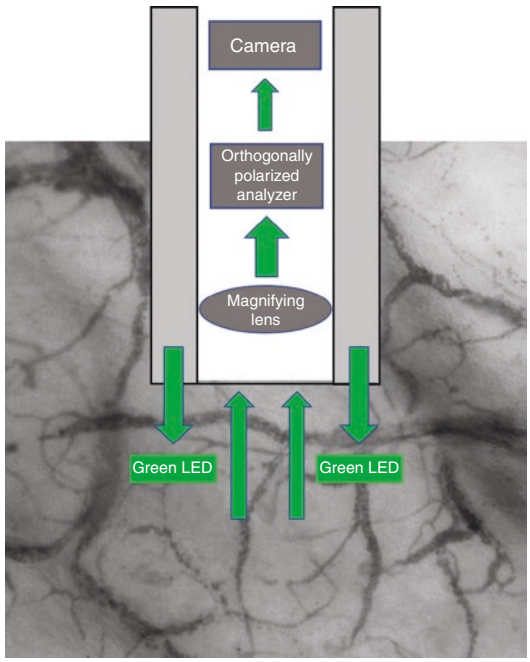

Fig. 19.1 General principle of handheld vital microscope. Handheld vital microscope imaging consists of a light guide surrounded by green light-emitting diodes (LEDs; wavelength 530 nm) whose light penetrates the tissue and illuminates the microcirculation. Green light is linearly polarized to illuminate the tissue. A magnifying lens projects the image onto a video camera. Polarized reflected light is blocked by an orthogonally polarized analyzer while depolarized scattered light passes through to the camera. The light is absorbed by hemoglobin of the red blood cells and scattered by leukocytes

Usually four microcirculatory parameters are analyzed:

1. The microvascular flow index (MFI), which is a qualitative evaluation of the microvascular flow. The image is divided into four quadrants, and the predominant type of flow in very small vessels (*i.e.,* diameter less than 20 μm) is assessed in each quadrant using an ordinal score (0 = no flow, 1 = intermittent flow, 2 = sluggish flow, 3 = normal flow). The overall score, called microvascular flow index, is the sum of each quadrant score divided by the number of quadrants.
2. The percentage of perfused vessels (PPV), which is calculated as follows: 100 × (total number of vessels – [no flow + intermittent flow])/total number of vessels.
3. The perfused vessel density (PVD) (which can also be referred to as functional capillary density), which is calculated by dividing the area of perfused vessels by the total area of interest.
4. The heterogeneity index, which is calculated as follows: (highest site microvascular flow index – lowest site microvascular flow index) divided by the mean of the microvascular flow index of all sublingual sites.

Microcirculatory images can be analyzed by real-time visual evaluation, offline manual analysis (*e.g.,* grid-based or complete screen-based), and offline software-aided analysis. It is obvious that offline analysis is very time-consuming and is not suitable for clinical intensive care practice. Thus, development of online automatic analysis of microcirculatory images would be a decisive step toward the use of HVMs in critically ill patients.

In addition to qualitative assessment, quantitative evaluation of microcirculatory flow is required for a more precise characterization of the microcirculatory flow patterns in the microvascular network. This would allow a better assessment of the heterogeneity of microvascular flows and analysis of the flow-oxygen delivery relationship. Currently, quantitative RBC velocity profiles could be analyzed by space–time diagrams (Automated Vascular Analysis (AVA) software, MicroVision Medical, Amsterdam, The Netherlands) or by averaged perfused speed indicator (CytoCamTools software, CytoCam, Braedius Medical, Huizen, The Netherlands).

Practical Advice
Development of online automatic analysis of microcirculatory images would be a decisive step toward the use of handheld vital microscopy in critically ill patients.

19.3 Clinical Relevance of Sublingual Microvascular Perfusion Parameters

The sublingual surface is an easily accessible mucosal surface for visualizing the microcirculation in ICU patient, so studies on MVH have largely focused on this area. However, what is the clinical relevance of studying sublingual microcirculation?

A key argument for the clinical relevance of sublingual microcirculation is the fact that the parameters derived from the analysis of sublingual microcirculatory perfusion are associated with the outcome of critically ill patient. Indeed, De Backer et al. [4] reported that sublingual microcirculation parameters are stronger predictors of mortality than microcirculation parameters and lactate. Furthermore, Sakr et al. [5] found that restoration of sublingual microcirculatory perfusion was possible in surviving patients, whereas it was not possible to restore sublingual microcirculatory perfusion in non-surviving patients. More recently, Massey et al. [6] in a sub-study of the ProCESS (Protocolized Care in Early Septic Shock) study showed an association between sublingual microcirculatory parameters at 72 h and mortality. In patients with hemorrhagic shock, Tachon et al. [7] and Hutchings et al. [8] found that sublingual microvascular parameters are associated with organ dysfunction. Recently, in a monocentric prospective observational study in a general intensive care population (MicroDAIMON study) with daily assessment of sublingual microcirculation from admission to discharge or death, Scorcella et al. showed that abnormal microcirculation at ICU arrival (defined as MFI < 2.6) was an independent predictor of mortality (odds ratio 4.594, $p = 0.015$) [9].

Thus, the association between alterations in sublingual microvascular parameters and patient outcomes validates the fact that these parameters are clinically relevant for the assessment of ICU patients.

Practical Advice
Sublingual microvascular parameters allow us to observe that the behavior of microcirculation may be different from that of macrocirculation in critically ill patients.

19.4 Is Sublingual Microcirculation a Reflection of Other Microvascular Beds?

This question remains debated because the architectures of microcirculation are different according to the organs. Several studies have shown that changes in sublingual microcirculation are correlated with changes in other microvascular beds, in particular intestinal microcirculation [10–14] and renal microcirculation [15, 16]. For example, in a septic shock model, the course and severity of intestinal microcirculatory damage were similar to that of sublingual microcirculation [10]. Similar results were reported in a sheep model of hemorrhagic shock [13]. De Bruin et al. [14] reported that in patients undergoing elective

gastrointestinal surgery, analysis of the intestinal serosa microcirculation was similar to the assessment of sublingual microcirculation. Lima et al. [15] demonstrated, in an endotoxic shock model, that sublingual microcirculation could reflect the renal microvascular alterations detected by contrast-enhanced ultrasound during shock and fluid resuscitation.

Further studies are still needed to clarify whether the behavior of sublingual microcirculation is representative of the microcirculation of other organs. Another element to be considered is the fact that even if the sublingual microcirculation does not behave in the same way as the other, it may be a microcirculation that is affected at an early stage in situations of hypovolemia or cardiac dysfunction and which may therefore alert us to the fact that hemodynamic optimization is insufficient or inadequate. Similarly, alterations in sublingual microcirculation may precede the appearance of microvascular dysfunctions in other organs. These assumptions should be documented by additional pre-clinical and clinical studies.

19.5 Sublingual Microcirculation: Ultimate Goal of Resuscitation?

The interest of the evaluation of sublingual microvascular perfusion parameters is not limited to the analysis of the impact of microvascular alterations on the patient's outcome. Indeed, the evaluation of sublingual microcirculation also allows us to analyze the microvascular response to the different hemodynamic strategies we use in patients. Indeed, the parameters of sublingual microvascular perfusion are dynamic variables that provide immediate indications for therapeutic interventions. For example, it is currently accepted that fluid administration is only justified if the patient is preload dependent. Preload dependency is defined as a condition in which an increase in right ventricular volume and/or left ventricular volume at the end of diastole leads to an increase in stroke volume. Dynamic indices, such as respiratory changes in pulse pressure or systolic ejection volume, are used to detect preload dependence and are used to predict vascular filling response. However, while fluid resuscitation guided by these dynamic indices leads to optimization of macrocirculation, it is not clear whether it also leads to improved microcirculation. Indeed, the possibility of achieving microvascular improvement depends on the preservation of the microvascular response and the functional relationship between microcirculation and macrocirculation. Thus, despite an increase in stroke volume, the sublingual microvascular response may be negative due to microvascular alterations. Therefore, the further optimization of macrocirculation by vascular filling no longer makes sense as it does not lead to an improvement in tissue oxygenation and may even be harmful (increase in capillary leakage and interstitial edema).

Ideally, fluid administration should therefore be considered on the basis of an analysis of the microcirculation and/or tissue oxygenation. Thus, for example, the finding of a lack of microvascular response after vascular filling should lead to consideration of other therapies such as vasopressors, transfusion or specific microvascular vasodilators. Similarly, the finding of normal microcirculation prior to fluid administration should also raise the question of the need for giving fluids.

Therefore, the future for guiding therapeutic interventions such as vascular filling at the patient's bedside lies in the use of techniques assessing microcirculation and/or tissue oxygenation.

To reinforce the fact that the assessment of sublingual microcirculation can be a valuable tool for the optimization of microvascular perfusion and the personalization of hemodynamic resuscitation, Tanaka et al. [17] have shown that RBC transfusion improves sublingual microcirculation independently of macrocirculation and systemic hemoglobin level in patients in hemorrhagic shock. The positive microcirculatory response that was observed by these authors after blood transfusion was not dependent on the baseline hemoglobin concentration, a parameter that is currently used in clinical practice for deci-

sion regarding RBC administration. In this study, only microvascular perfusion parameters predicted the microcirculatory response to transfusion. This microcirculatory improvement could involve local microvascular mechanisms in which the RBCs could play a central role. This example highlights the fact that a therapeutic strategy can improve microcirculatory perfusion in a way that cannot be fully explained by macrocirculatory effects alone.

19.6 Sublingual Microvascular Perfusion Parameters at the Patient's Bedside

While studies confirm the clinical relevance of sublingual microvascular parameters, the use of these parameters in clinical practice is only conceivable if the HVM can be easily used at patient bedside with real-time image analysis.

Real-time evaluation by visual image assessment provides quantitative information on microvascular flow and capillary density and detects obvious alterations. This approach can be linked to a visual evaluation of the left ventricular ejection fraction by echocardiography. Indeed, when a rapid diagnosis is required, visual evaluation of the left ventricular ejection fraction can easily provide an accurate assessment. Real-time evaluation by visual image assessment can provide quantitative information on microvascular flow and capillary density and can detect obvious alterations of microcirculation. The examples of sublingual microcirculation are presented at (in septic shock) and at (in hemorrhagic shock). Reduction in microvascular flow and density is observed. This visual evaluation of the sublingual microcirculation is therefore in line with the idea of alerting us to a marked alteration of the sublingual microcirculation and of questioning the relevance or sufficiency of the optimization of the macrocirculation.

Ideally, the nurses should be able to produce and interpret the videos in order to have a real follow-up at the bedside. This is why we tested the possibility for nurses to take measurements of microcirculatory parameters in real time at the bedside in intensive care (MICRONURSE study) [18]. This work concluded that nurses were able to qualitatively assess the MFI and total vessel density with good agreement with offline software analysis by a physician and a very good sensitivity and specificity to detect impaired microvascular flow (MFI < 2.5) and low capillary density. Naumann et al. [19] described a five-point ordinal scale (the Point of Care Microcirculation (POEM) rating system) of microcirculatory flow and heterogeneity that can be used at the patient's bedside. The authors found minimal variability between users among healthcare professionals after only 1 h of training with good agreement with offline software analysis. The development of automated microcirculatory analysis software is the next step in obtaining quantitative analysis at the patient's bedside and in ensuring the adherence of caregivers to the use of this technique. It is also important to work on an analysis of sublingual oxygenation in order to have an assessment of oxygen transport in addition to microvascular hemodynamic parameters.

19.7 Conclusions

Handheld vital microscopes must be easy to use and provide easily interpretable data to ensure their adoption by all medical and paramedical staff. However, despite continuous improvement of HVMs, we are still a few steps away from routinely applying microcirculatory monitoring in ICU. Thus, the impact of the use of sublingual microcirculation analysis as a therapeutic guide on the patient's outcome remains to be proven. For this, we need clinical studies demonstrating that taking into account sublingual microvascular alterations and their treatment can prevent organ failure or mortality in critically ill patients.

Keynotes

- Recent advances in imaging techniques allow us to observe that the behavior of microcirculation may be different from that of macrocirculation in critically ill patients.

- The association between alterations in sublingual microcirculation and patient outcomes proves that it is clinically relevant to evaluate sublingual microcirculation.
- Further studies are still needed to clarify whether the behavior of sublingual microcirculation is representative of the microcirculation of other organs.

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Other Techniques for Assessment of Microcirculation

20

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Contents

20.1 Introduction

Optimizing microcirculation and tissue oxygenation requires that clinicians should have microcirculation monitoring tools that can be used at the bedside to guide therapeutic strategies.

Vital hand microscopes (Chap. 18) are a very attractive method because they allow a direct visualization of the microcirculation at the patient's bedside and an indirect evaluation of the endothelial glycocalyx. In addition to vital hand microscopes, it is essential to validate other techniques that can be easily used in the patient's bed.

20.2 Mottling and Capillary Refill Time

Clinical assessment of skin perfusion is used in clinical practice to detect skin hypoperfusion. Mottling and capillary refill time (CRT) that are easy to assess can be an interesting tool to alert and guide patient management.

Mottling, defined as patchy skin discoloration, is part of the classic examination of ICU patient. It has previously been found that the mottling score (Fig. 20.1), measured 6 h after initial ICU resuscitation, is an important predictor of mortality in patients with septic shock whatever vasopressor

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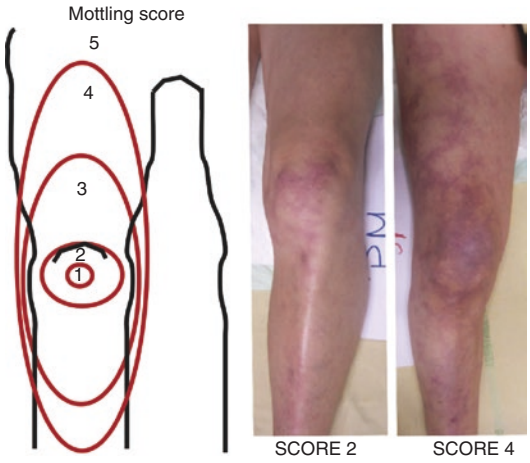

Fig. 20.1 Mottling score. Score 0 indicates no mottling; score 1, a modest mottling area localized to the center of the knee; score 2, a moderate mottling area that does not exceed the superior edge of the kneecap; score 3, a mild mottling area that does not exceed the middle thigh; score 4, a severe mottling area that does not go beyond the fold of the groin; score 5, an extremely severe mottling area that goes beyond the fold of the groin (with permission from Ait-Oufella H, Lemoinne S, Boelle PY, Galbois A, Baudel JL, Lemant J, Joffre J, Margetis D, Guidet B, Maury E et al: Mottling score predicts survival in septic shock. *Intensive Care Med* 2011, 37(5):801–807)

dosage [1, 2]. A pilot study also shows that CRT and mottling score correlate with the echographic pulsatility indices of the visceral organs in early septic shock (kidney and intestines) [3].

Capillary refill time is defined as the time it takes for a distal capillary bed to regain its color after pressure has been applied to cause bleaching. This test is easy to perform making it simple and very attractive for clinical use for perfusion monitoring in resource-limited or pre-ICU settings. However, it needs to be standardized to be correctly interpreted. Ait-Oufella et al. [4] demonstrated that CRT is highly reproducible in septic shock patients with an excellent interrater concordance. In this study, CRT was a strong predictive factor of 14-day mortality. Among patients with septic shock, a resuscitation strategy targeting normalization of CRT, compared with a strategy targeting serum lactate levels, did not reduce all-cause 28-day mortality [5]. In a predefined subgroup of patients with less severe organ dysfunction, peripheral perfusion-targeted resuscitation was associated with beneficial effects on the secondary outcome of SOFA score at 72 h and lower 28-day mortality. The combination of CRT with a passive leg raising maneuver could be accurate to predict the improvement in peripheral tissue perfusion of volume expansion [6].

20.3 Glycocalyx Assessment

The use of handheld vital microscopes allows indirect evaluation of endothelial glycocalyx in microvessels (Fig. 20.2). The hypothesis is that there is a certain distance between the central flow of RBCs (RBCs) and the endothelium which is assumed to be partly due to the presence of glycocalyx [7]. Degradation of the glycocalyx allows RBCs to penetrate the glycocalyx and move closer to the endothelium. The perfused boundary region (PBR), which measures the radial movement of RBCs away from the central flow to endothelial cells (μm), is used to assess the microvascular glycocalyx layer. The more impaired the glycocalyx is, the deeper the RBCs penetrate into the glycocalyx and the higher the PBR.

Several studies in ICU patients have shown that the PBR is markedly increased in critically ill patients compared to healthy controls [8–10].

Measurement of markers of glycocalyx degradation also allows to assess the damage to glycocalyx [11]. These markers most often include syndecan-1, heparan sulfate, and hyaluronan. For example, significant correlations between these markers and SOFA scores were found in sepsis [12, 13]. Increased levels of syndecan-1 and heparan sulfate in plasma have been found to be associated with an increase in the PBR and degree of sublingual microvascular dysfunction [8, 14].

Practical Advice

- Glycocalyx analysis can help in the understanding of endothelial alterations and capillary permeability disorders.
- The perfused boundary region is an interesting marker to evaluate the microvascular glycocalyx layer. Studies are still needed to evaluate this method of analysis.

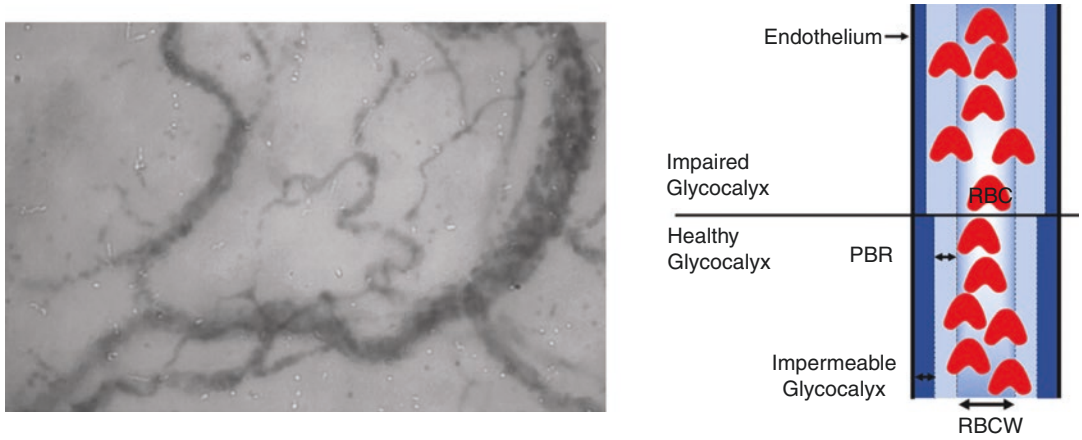

Fig. 20.2 Glycocalyx assessment. Image acquisition using sidestream-darkfield camera with analysis of glycocalyx by GlycoCheck™ System. GlycoCheck™ detects the dynamic lateral movement into the glycocalyx, which is expressed as the perfused boundary region (PBR in μm). An impaired glycocalyx allows more RBCs to penetrate deeper toward the endothelial surface that is reflected by an increase in PBR. *PBR* perfused boundary region, *RBC* red blood cell, *RBCW* red blood cell width (with permission from Rovas A, Lukasz AH, Vink H, Urban M, Sackarnd J, Pavenstadt H, Kumpers P: Bedside analysis of the sublingual microvascular glycocalyx in the emergency room and intensive care unit - the GlycoNurse study. *Scand J Trauma Resusc Emerg Med* 2018, 26(1):16)

20.4 Contrast-Enhanced Ultrasound

Contrast-enhanced ultrasound (CEUS) is a recent non-invasive imaging modality that allows quantification of microcirculation. This technique has the advantage of being able to explore the microcirculation of solid organs and can be carried out at the patient's bedside. Kidney and liver are the most investigated organs. For example, renal CEUS has been proposed to quantify renal microcirculation in patients under various conditions such as kidney transplantation [15, 16], cardiac surgery or shock [17–19].

Contrast-enhanced ultrasound uses microbubbles of gas surrounded by a stabilizing shell (phospholipid or protein envelope). Their size (1–6 μm), similar to that of RBCs, allows the microbubbles to pass through the capillary bed of the pulmonary circulation and reach the capillaries of the various organs. At the same time, their size is large enough so that they do not cross the endothelium, making them true intravascular agents. After a few minutes, the microbubbles are eliminated through the respiratory tract and are not nephrotoxic. Ultrasonic waves induce a non-linear oscillation of the microbubbles, and the backscattered signal therefore contains an additional frequency range to that of the incident ultrasonic field with a high echogenicity difference between the gas of the microbubbles and the soft tissue. The microbubbles can be injected as a bolus or continuous infusion. When a constant infusion is administered, a "destruction-replenishment technique" can be applied (Fig. 20.3). The destruction phase consists of an ultrasound flash of high mechanical index (mechanical index ≥ 1) that instantaneously destroys the contrast ultrasound agent in the ultrasound plane observed with the probe. The replenishment phase using low-powered ultrasonic pulses corresponds to the progressive contrast enhancement of the kidney ultrasound plane after destruction.

In ICU patients, Schneider et al. [20] were the first authors who tested the feasibility of the CEUS to assess cortical renal microcirculation. At 24 h postoperatively, the authors observed a 50% overall decrease in perfusion index indicating a decrease in renal cortical perfusion. In septic shock, Harrois et al. [19] using CEUS observed that cortical renal microcirculation was

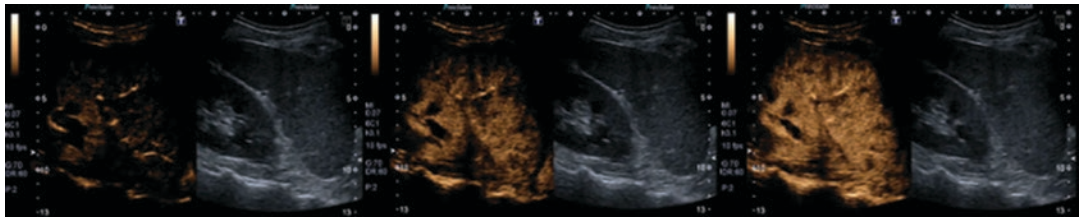

Fig. 20.3 Example of destruction-replenishment technique. Immediately after the destruction phase, the refilling of the renal blood vessels (replenishment) with new microbubbles can be recorded and evaluated. The course of this vascular replenishment precisely reflects blood flow in the image plane (from Creteur J, *Curr Opin Crit Care* 2020;26(6):543–548)

highly variable from patient to patient despite satisfactory restoration of systemic hemodynamic parameters. It was either normal or decreased or even increased during septic shock, despite a comparable restoration of macrocirculatory hemodynamic parameters confirming that it is impossible to predict renal microvascular perfusion based on the restoration of macrocirculatory data because renal microvascular alterations are complex and heterogeneous. In addition, perfusion of renal cortical microcirculation was significantly reduced in patients with septic shock who develop severe acute kidney injury (AKI) of KDIGO stages 2 or 3 compared to those who do not develop AKI. Contrast-enhanced ultrasound may also be useful for testing the renal microvascular effects of fluid resuscitation and vasopressor therapy in ICU patients. Schneider et al. [18] used CEUS to estimate the effect of norepinephrine-induced increase in mean arterial pressure (MAP) on renal cortical perfusion in critically ill patients (83% of these patients had septic shock). No difference could be found between measurements obtained with a MAP level of 60–65 mmHg and those obtained after an increase in norepinephrine-induced MAP to a MAP level of 80–85 mmHg. However, at the individual level, large variations were observed with increases or decreases in renal cortical perfusion. Thus, targeting MAP to achieve optimal renal microcirculation perfusion estimated on CEUS parameters could be interesting.

Practical Advice

- Contrast-enhanced ultrasound can explore the microcirculation of solid organs and can be performed at the bedside.
- More evidence is needed for this technique to be adopted in clinical practice to guide patient management.

20.5 Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) is a non-invasive technique that has been proposed as a tool to assess tissue oxygenation (StO_2) of different organs, including muscle. Near-infrared light (700–1100 nm) is absorbed by three chromophores: hemoglobin, cytochrome oxidase, and myoglobin, but the last two participate to a much lesser extent in the signal. Oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin (Hb) have different absorption spectra. Therefore, when the tissue is subjected to near-infrared light which passes easily through the tissue, the emission signal is proportional to the state of oxygenation of the hemoglobin present in the volume of tissue explored by the excitation light. Near-infrared spectroscopy on the thenar eminence can also be used by performing an arterial occlusion test with a pneumatic cuff inflated to approximately 30–50 mmHg above systolic pressure

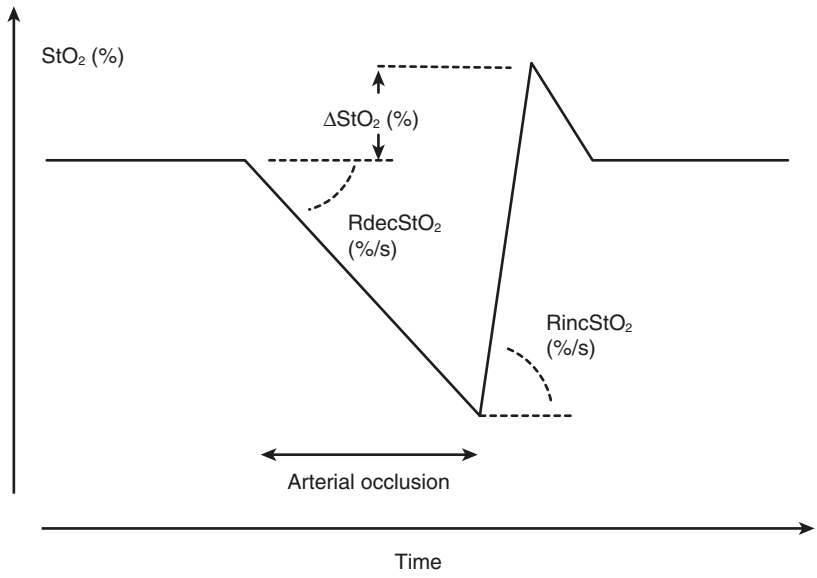

Fig. 20.4 Schematic StO_2 curve during an arterial occlusion maneuver. *D* difference between maximum StO_2 value during the reperfusion period and baseline StO_2. *RdecStO*$_2$ the rate of the decrease in StO_2 during the ischemic period. *RincStO*$_2$ the rate of the increase in StO_2 during the reperfusion phase (from Creteur J, *Curr Opin Crit Care* 2008;14:361–366)

(Fig. 20.4). During this ischemic period, the decrease in local oxygen is monitored by NIRS with a decrease in HbO_2 and a simultaneous increase in Hb (decrease in StO_2), while the total Hb remains constant. The rate of decrease in StO_2 during this ischemic period is linked to the consumption of muscular oxygen. After deflation of the pneumatic cuff, the hyperemic response is accompanied by an increase in HbO_2 and a rapid washout of Hb (increase in StO_2). This phase could be a reflection of the microvascular recruitment capacity [21].

Several studies have shown that thenar eminence StO_2 can be helpful in the emergency and early resuscitative phases of care of trauma patients [22–24] and in the management of goal-directed resuscitation [24]. In trauma, StO_2 measurements at admission <75% predict the need for blood products and emergency surgical procedures (thoracotomies, pericardial windows, exploratory laparotomies, and bone fractures fixation) and can be used as a complementary method to identify shock [25].

During sepsis, StO_2 values <75% may be associated with poor clinical outcomes [26, 27]. However, a recent study provides no evidence for any potential benefit from targeting muscle StO_2 in addition to CVP, MAP, and $ScvO_2$. Thus, targeting muscle StO_2 for early goal-directed therapy failed to significantly increase muscle StO_2 in most patients, and it was associated with prolonged mechanical ventilation, increased blood transfusions, and increased doses of dobutamine [28]. However, it has been recently shown that StO_2 may be interesting to personalize the MAP target in septic shock [29].

In acute brain injury, despite some interesting research approaches, insufficient evidence on the value of NIRS monitoring means that NIRS cannot be used to guide management [30]. Indeed, the NIRS signal does not appear to be sufficiently consistent with other brain oxygenation or brain perfusion monitors.

Practical Advice

- Near-infrared spectroscopy is a non-invasive technique for evaluating tissue oxygenation.

- During sepsis, StO_2 values <75% may be associated with poor clinical outcomes. However, there is no evidence for any potential benefit from targeting muscle StO_2.
- In acute brain injury, NIRS cannot be used to guide management.

20.6 Laser Doppler Flowmetry

Laser Doppler flowmetry is a non-invasive method of measuring microcirculatory blood flow in tissue. The technique is based on measuring the Doppler shift induced by moving RBCs to the illuminating coherent light. A laser Doppler instrument output often gives flux, velocity, and concentration of the moving RBCs. The Doppler laser is used to evaluate the microvascular blood flow of the volume of the vascular network scanned by the ultrasonic signal under the probe. The measurement takes into account each arteriole, capillary, and venule of the explored tissue volume (1 mm^3).

This technique is mainly used in experimental models. Its use in ICU patients is limited to clinical research. This technique has been used on many areas of the body and even on the gastric mucosa [31]. Transient ischemia following arterial occlusion can also be tested with a pneumatic cuff placed around the arm to assess the capacity of the microcirculation to recruit arterioles. A decrease in cutaneous hyperemia has been described in septic patients [32]. Recently, this technique has been used to test the effect of an L-arginine infusion in septic patients [33]. Prolonged intravenous L-arginine administration does not improve local perfusion and organ function despite an increase in NO synthesis.

20.7 Conclusion

Most methods for assessing microcirculation in ICU patients are still techniques that are primarily used in clinical research. Recent advances in imaging techniques, such as the contrast-enhanced ultrasound, open up new perspectives that need to be studied and positioned in order to individualize patient treatment. In addition to sophisticated techniques, it is important to keep in mind simple tissue perfusion evaluation techniques such as evaluation of mottling and capillary refill time. Near-infrared spectroscopy and laser Doppler flowmetry are techniques that must be technically advanced to become efficient tools for analyzing microcirculation in ICU patients.

Keynotes

- Simple techniques for evaluating tissue perfusion, such as evaluation of mottling and capillary refill time, should continue to be used and studied as they can provide valuable information and be used widely.
- The evaluation of glycocalyx may lead to a better understanding of microvascular and endothelial dysfunction in the future.
- Recent advances in imaging techniques, such as the contrast-enhanced ultrasound, open up new perspectives to individualize patient treatment.
- StO_2 can be helpful in the early resuscitation of shock patients, but there is no evidence for any potential benefit from targeting StO_2.
- The impact of microcirculation assessment on ICU patient outcomes remains to be proven.

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Part VI

Hemodynamic Monitoring and Therapy in Perioperative Medicine

21 Hemodynamic Monitoring and Optimization in Cardiac Surgery

Gerd Klinkmann, Daniel A. Reuter, and Sebastian A. Haas

Contents

21.1 Introduction

Demographic developments shifting population to older patients require that cardiac surgery is of increasing importance in the future. Even though older patients are often afflicted with many comorbidities, complex interventions are frequently needed. Many patients are inadequately diagnosed preoperatively, particularly with regard to right ventricular function and/or the presence of pulmonary arterial hypertension [1]. As a consequence, the perioperative care, as well as management in the intensive care unit (ICU) of cardiac surgery patients, is becoming more and more challenging. Routine use of both neurological and advanced hemodynamic monitoring in combination with goal-directed perioperative hemodynamic optimization aimed at optimizing systemic and cerebral oxygen balance promises to reduce postoperative morbidity and improve mortality in this high-risk population. Therefore,

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this chapter covers multiple aspects of advanced hemodynamic and cerebral monitoring and focuses on established and future monitoring.

21.2 Near-Infrared Spectroscopy

So far, the major focus of hemodynamic monitoring was the assessment of macrocirculation. However, knowledge about perioperative hemodynamic effects on microcirculation, pathophysiologically at least as important, is small. One monitoring device has been developed to monitor oxygenation of an end organ and therefore might stand for a surrogate of microcirculation: near-infrared spectroscopy (NIRS). Taking microcirculation into the clinical context, numerous investigations point to an increasing evidence that NIRS-derived regional cerebral oxygen saturation ($rScO_2$) levels are linked to both general and especially neurological perioperative outcome parameters. Cerebral desaturation has been reported to be associated with complications like postoperative delirium, encephalopathy, and finally increased mortality rates [2]. Hence, the prevention of cerebral desaturation by means of a goal-directed strategy seems obvious and may help to reduce perioperative complications. Furthermore, NIRS may deliver supporting data to assess the functionality of cerebral blood flow autoregulation and thus facilitate the adjustment of individual goals for mean arterial pressure (MAP) [3]. NIRS is further used to appropriately position the carotid cannula of the cardiopulmonary bypass and subsequently to adjust cerebral directed blood flow during surgery of the thoracic aorta with cardiocirculatory arrest in deep hypothermia and selective perfusion of supra-aortal vessels [4].

The technique might have the capability of monitoring both microcirculation and macrocirculation since NIRS-derived cerebral oxygenation has been reported to correlate with mixed venous oxygen saturation. Hence, the application of a cardiac output measurement device for patients with intermediate perioperative risk might not be necessary and might be replaced by NIRS [5–8]. However, due to a lack of RCT, there is no consistent opinion regarding the general applications of NIRS in cardiac surgery. Explicit expert recommendations comprise special interventions, *e.g.,* thoracic aortal surgery, heart transplantations, and cardiac surgery with simultaneous carotid surgery. A further indication for NIRS is seen in patients having a left ventricular assist device where conventional hemodynamic monitoring is hindered by lack of a pulsatile blood flow. Various investigations substantiate the application of cerebral oximetry within the scope of comorbidities like severe arterial hypertension, preceded neurological deficit, and high-grade carotid artery stenosis [3]. Moreover, especially patients undergoing cardiac surgery with low perioperative risk have been reported to show beneficial effects of a prevention of cerebral desaturation ($rScO_2 < 50\%$), just as an association of the perioperative use of NIRS with a significant reduction of delirium as well as a shortened length of ICU stay [9].

Practical Advice

A drop in cerebral oxygen saturation below the preoperative baseline, as determined by NIRS, represents perioperative cerebral desaturation and is associated with an increased rate of delirium or postoperative cognitive dysfunction (POCD). Avoiding cerebral desaturation can reduce these complications.

21.3 Arterial Pressure

Continuous invasive measurement of arterial pressure is still a fundamental tool to monitor high-risk patients. Nowadays, in cardiac surgery, the absence of invasive blood pressure monitoring is not imaginable since critical periods of hemodynamic instability are immediately noticed. Further, blood pressure can be monitored sufficiently as predominant nonpulsatile perfusion pressure at runtime of cardiopulmonary bypass (CPB). During CPB, devices depending on pulsatile perfusion such as noninvasive

blood pressure measurements or oximetry fail or are invalid. Primarily, the arterial cannulation is performed in the radial artery of the patient nondominant arm. To avoid the cannulation of the femoral artery, which is basically possible but may be required for circulatory support systems, it is admissible to provide high-risk patients with an indwelling catheter in the brachial artery.

Furthermore, the analysis of the arterial pressure waveform enables further parameters of advanced hemodynamic parameters like stroke volume (SV) or functional parameters of preload such as stroke volume variation (SVV) and pulse pressure variation (PPV). To optimize the incoming arterial signal leading to best possible validity of parameters, the disturbance variables causing over- or under-damping of the signal have to be identified and eliminated. Apart from technical impreciseness, an aorto-radial pressure gradient is frequently found in cardiac surgery patients as a consequence of a peripheral vasodilatation. This is particularly actual after start of CPB, leading to an underestimation of the actual central perfusion pressure [10]. The most important disturbance variables of arterial pressure measurement are summarized in Table 21.1.

There is a still ongoing debate on optimal MAP both at runtime of CPB as well as afterward. Until now, there are no fixed limits for the correct blood pressure corridor; in fact, it has to be assumed that blood pressure has to be aligned individually to ensure best possible end-organ perfusion. One of the main goals of the adjustment of blood pressure is to perpetuate the autoregulation of the cerebral blood flow. However, autoregulation is difficult to determine. There are various surrogate parameters for cerebrovascular integrity. Both the measurement of cerebral oxygenation by means of oximetry and the measurement of flow velocity in the basal arteries of the brain using transcranial Doppler to assess relative changes in flow, to diagnose focal vascular stenosis, or to detect embolic signals within these arteries may act as alternatives. It has been shown that there is a correlation between MAP and cerebral oximetry signals. However, significant inter--individual differences have been detected in this correlation, and only low-level evidence links the $rScO_2$ decrements from baseline to poor neurologic outcomes [11]. Additionally, the available data are insufficient to conclude that interventions for correcting $rScO_2$ decreases result in a

Table 21.1 The most important disturbance variables of arterial pressure measurement

Disturbance variable	Cause
Slinging spikes	Usually occur when an extra-long supply line is connected to an 18-Gauge cannula in the radial artery. A small air bubble in the supply line can dampen the curve
Attenuated curve	If the curve is damped, systolic blood pressure is measured too low and diastolic blood pressure too high. The most common causes are: • Air bubbles in the system • Blood clot in cannula or system
Transducer cannot be calibrated	• Pressure transducer defective • Pressure sensor connected incorrectly • Amplifier defective
Pressure curve drifts	• Warm-up time too short • Cable kinked
Pressure is displayed too low	• Curve damped, air bubbles, thrombus, vascular spasm • Pressure sensor not correctly calibrated • Pressure sensor not placed at reference height
Pressure is displayed too high	• Pressure sensor placed too low • Pressure sensor not correctly calibrated
No curve on the monitor	• Pressure sensor connected incorrectly • Pressure sensor defective • Amplifier defective
Direct pressure measurement does not correspond to cuff pressure	Direct pressure measurement is usually more accurate, especially in hypotension, low cardiac output, and peripheral vascular constriction

lower risk for stroke, delirium, or POCD [12]. Hence, current recommendations focus on adjustment of MAP individually with regard to the preoperative situation and to adapt to alterations of the cerebral oxygenation.

Monitoring and management of intravascular volume status plays a crucial role in cardiosurgical patients. Functional preload parameters such as the left ventricular SVV and PPV, describing the specific interplay of the heart and the lungs under mechanical ventilation, have been reported to be beneficial for predicting fluid responsiveness. However, a sufficient assessment of cardiac preload of the left ventricle using functional parameters is only clinically valid if controlled mechanical ventilation with a tidal volume of at least 8 mL/kg predicted body weight occurs, a steady sinus rhythm is present and pressure curves are free of artifacts. It has to be underlined that functional parameters of preload only reflect preload of the left ventricle. Severe right ventricular dysfunction can counterfeit volume deficit showing high SVV and PPV. Therefore, especially in high-risk cardiosurgical patients suffering from hazards of right ventricular contractility and pulmonary arterial hypertension, dynamic preload parameters are frequently insufficient to provide significant benefits and improve the macrocirculation [13].

Practical Advice

Invasive arterial blood pressure measurement is one of the basic monitoring procedures in cardiac surgery patients, allows continuous monitoring of blood pressure in all phases of potential hemodynamic instability, and is essential for determining the predominantly nonpulsatile perfusion pressure during CPB.

21.4 Central Venous Pressure

A central venous catheter (CVC) is often used for administration of fluids, vasopressors, and inotropes and for measurement of central venous pressure (CVP). Since transmural CVP is substantially related to right ventricular (RV) preload, intrathoracic pressure changes which are largely influenced by mechanical ventilation have to be taken into account for CVP interpretation. Thus, CVP changes with associated cardiac output (CO) variations indicate RV function as well as global cardiac function and potential peripheral venous congestion [11].

Besides the continuous invasive measurement of arterial pressure and CO, the monitoring of CVP is still of high importance in cardiac surgery. Although CVP has been rightly criticized for the inability to sufficiently predict volume responsiveness, a substantial decrease of CVP with a concomitant reduced CO has been reported to be associated with hypovolemia. The course of CVP in combination with CO can be very helpful to assess cardiac and especially right ventricular function. In fact, a sudden CVP increase might unmask an overshooting volume application and a beginning of right ventricular decompensation.

Additionally, continuous CVP monitoring has an extended impact to cardiac anesthesiology. Analyzing the shape of the CVP wave may refer to pathologies like tricuspid regurgitation with a "*v*" wave during systole and detection of hemodynamically relevant AV-node rhythm, or it may serve to monitor an adequate venous return during cannulation of superior vena cava as well as to optimize the adjustment of an AV-sequential pacemaker. Hence, CVP values provide important information about the cardiocirculatory status of the patient and should not be abandoned. Although the CVP has many limitations to predict fluid resuscitation, it is crucial to understand and consider these limitations rather than to discard the CVP completely from hemodynamic monitoring.

Furthermore, it was shown that the absolute value of the CVP is a prognostically relevant parameter not only in the cardiological but also in the cardiac surgery setting. To what extent this is due to reduced visceral and renal perfusion in the context of a high CVP, *i.e.,* a decrease in effective systemic perfusion pressure, or to a leading right ventricular dysfunction, cannot be conclusively assessed at present. However, one important

message regarding CVP remains unaffected: "A healthy heart never has an elevated CVP."

Practical Advice
In addition to arterial blood pressure, continuous monitoring of central venous pressure (CVP) is one of the fundamental parameters in monitoring of cardiac surgery patients. Continuous monitoring of CVP should not be dispensed with in cardiac surgery patients.

21.5 Transesophageal Echocardiography

Perioperative transesophageal echocardiography (TEE) was introduced in cardiac anesthesia some decades ago, and it was initially considered to serve as monitoring tool for left ventricular function only. Since then, its role has changed fundamentally. Nowadays, perioperative TEE plays an integral role in the setting of a multitude of surgical procedures. It constitutes an excellent intraoperative diagnostic tool, which facilitates beneficial information in cardiac surgery and interventional cardiology particularly. By providing high-resolution real-time data of the entire heart and the surrounding large vessels, and, in particular, the assessment of wall motion, the functional morphology of the valve apparatus and the volume state of the patient, TEE influences both surgical and anesthetic management profoundly. Valve surgery and coronary bypass grafting have been reported to especially benefit from TEE by outcome enhancement [14].

Every patient undergoing TEE should have an encompassing examination of the heart over the course of cardiac surgery. The detection of unexpected pathologies is owing to this systematic approach. Miscellaneous versions of a comprehensive examination have been recommended. Besides these, in 2013, Hahn et al. have published an abridged, focused version of the basic perioperative TEE examination [15].

Compared to other advanced hemodynamic monitoring tools, TEE is reported to deliver a multitude of additional information with—in many situations—direct clinical consequences. Several studies report that information derived by perioperative TEE induce changes in therapeutic decisions in up to 52% of the cases, in particular with regard to volume and catecholamine administration as well as the assessment of valvular function after valve replacement surgery [16–24]. As a beneficial feature, TEE facilitates the direct visualization of the major determinants of the stroke volume, namely, preload, intrinsic contractility, and valvular function. Hence, TEE is predestined to evaluate cardiovascular system on a complex base [25, 26].

TEE is of superordinate significance concerning the analysis of regional differences of the ventricular function and therefore represents a highly sensitive indicator to detect myocardial ischemia [27]. In addition, TEE enables clinicians to determine the left ventricular ejection fraction (LVEF) besides the quantitative gathering of various diameters and flow parameters. During echocardiography, LVEF is defined as a ratio of SV to the left ventricular end-diastolic volume (LVEDV): (SV/LVEDV × 100%) [28]. LVEF is of prognostic value to describe the severity of congestive heart failure [29]. The determination of the fractional area change (FAC) using the transgastric midpapillary short axis view represents an alternative option to estimate LVEF. Left ventricular dysfunction is commonly considered as FAC < 35% in patients under general anesthesia including controlled ventilation, taking into account gender-specific reference values (male 37%, female 34%) [30, 31].

In clinical practice, the end-diastolic area (EDA) or the end-diastolic cross-sectional area index (EDAI) in short axis view at the level of the middle papillary muscles is usually used as a preload parameter. Despite some limitations, the Task Force on Transesophageal Echocardiography of the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists concluded that echocardiography provides more reliable information about cardiac preload than

pulmonary artery catheter (PAC). The recording of volumes, which is possible by echocardiography, reflects the cardiac preload better than the pressure ratios measured by PAC. Fontes et al. reported a significantly higher informative value of TEE compared to PAC concerning the hemodynamic condition of patients suffering from left ventricular dysfunction (LVEF less than 40%) and divergent preload parameters in patients who underwent coronary artery bypass grafting [32].

Finally, echocardiography can be used to measure SV or CO using the Doppler method. Compared to the reference method of CO measurement, the pulmonary arterial thermodilution, a large number of perioperative studies of echocardiography showed acceptable correlation results both for cardiosurgical [33, 34] and non-cardiosurgical patients [35, 36].

TEE is the tool of choice to explain the pathology in an unclear, acutely occurred hemodynamic instability. It is the diagnostic tool that can most directly clarify the etiology of circulatory shock (distributive, hypovolemic, cardiogenic, obstructive). Therefore, its use in circulatory shock of unclear origin is also a Class Ia recommendation [37].

Furthermore, the TEE can also be helpful in the instrumentation of catheters (multi-stage venous inguinal cannulas in minimally invasive cardiac surgery, or venous cannulas on the neck, including PAC).

A major disadvantage of TEE is its discontinuity, the user dependence, and its relative invasiveness. Recently, miniaturized TEE probes have therefore been developed which can remain in the esophagus for 72 hours and offer the possibility of a comparatively more frequent hemodynamically focused TEE ("hTEE"). After training of the intensive care physicians on this probe, hTEE is suitable for diagnosing pericardial tamponade [38].

Knowledge of the limitations of echocardiography is of utmost importance for the reviewer to interpret the results accurately, as wrong conclusions can be drawn. Regardless of the frequency of its use, there are still challenges and cases where it can lead to wrong conclusions, unless the sharp eye and interpretation of the experienced operator ensure that the results are interpreted correctly. Similarly, as technology advances, new techniques and tools will become available to the sonographer. However, it is the responsibility of the echocardiography specialist to have a full understanding of the advantages and limitations of each instrument available and to know how to interpret the results accurately.

Based on the current literature, it is obvious that TEE is an invaluable diagnostic and monitoring tool for patients undergoing heart surgery.

Practical Advice

Intraoperative TEE is an excellent method of cardiovascular differential diagnosis and monitoring that is useful in developing a surgical strategy, managing hemodynamic interventions, and immediately assessing surgical outcomes. As soon as the anesthesiologist is appropriately qualified to apply the method, its importance in perioperative medicine increases, as it provides clinical information that is essential for the surgical procedure.

21.6 Transpulmonary Thermodilution

Optimizing the balance between oxygen demand and delivery is a fundamental aim of goal-directed therapy (GDT). This includes the targeted influencing cardiac preload, afterload, and contractility with the help of dynamic parameters. Various studies have shown positive effects of this concept in cardiac surgery patients, which, in addition to the beneficial influence on various outcome parameters, ultimately led to a reduction in morbidity and mortality [39, 40].

Further results of GDT for the hemodynamic management of high-risk patients in cardiac surgery are encouraging. Kapoor et al. presented the importance of targeted hemodynamic optimization for improved outcomes in high-risk heart patients undergoing off-pump coronary

artery bypass surgery (OPCAB). Both the length of hospitalization and ICU stay and the duration of support with inotropes were significantly reduced in the GDT group compared to the control group [41].

Smetkin et al. also postulated the benefit of an algorithm capable of influencing perioperative hemodynamics and fluid management as well as the duration of postoperative ICU and hospital stay during OPCAB. In the conventional monitoring group, therapy was controlled by CVP, MAP, and heart rate (HR), in the advanced monitoring group—by intrathoracic blood volume index, MAP, HR, central venous oxygen saturation ($ScvO_2$), and cardiac index (CI). Measurements were performed before and during surgery and at 2, 4, and 6 h postoperatively. This GDT algorithm based on advanced hemodynamic monitoring and continuous measurement of $ScvO_2$ facilitated the early detection and correction of hemodynamic changes and influenced the strategy of fluid therapy decreasing ICU stay after OPCAB [42].

The optimization of the global end-diastolic volume index (GEDVI) may also be a promising concept. Thus, therapy control using a GEDVI--based algorithm led to a reduced need for vasopressors, catecholamines, mechanical ventilation and ICU therapy after cardiac surgery [43]. In another investigation, Goepfert et al. were able to enroll 100 patients undergoing coronary artery bypass surgery and/or aortic valve replacement in a prospective, controlled, parallel arm, open--label study and demonstrated that early targeted hemodynamic therapy based on CI, SVV, and optimized GEDVI reduces complications and shortens postoperative ICU stay [44].

Practical Advice

Early goal-directed hemodynamic therapy based on cardiac index, stroke volume variation, and optimized global end-diastolic volume index reduces complications and length of ICU stay after cardiac surgery.

21.7 Pulmonary Artery Catheter

PAC was introduced in 1970, and since then, its use gained in importance. However, owing to its invasive nature, its potentially deleterious effects on patient outcome, as well as the advancing development of less invasive hemodynamic monitoring technologies, the intraoperative use of the PAC has significantly decreased [45].

PAC measurement enables the determination of CO, right ventricular end-diastolic volume (RVEDVI), and right ventricular ejection fraction (REF) semi-continuously, as well as the continuous determination of pulmonary artery pressure (PAP) and mixed venous oxygen saturation (SvO_2). Furthermore, the fields of application of PAC include intermittent detection of the pulmonary artery occlusion pressure (PAOP) as surrogate parameter for left ventricular preload, the calculation of oxygen supply and consumption, and the continuous determination of the right ventricular pressure [46]. The main indications for the use of PAC in cardiac surgery are presented in Table 21.2.

The perioperative goal-directed implementation of PAC in high-risk patients using CI or oxygen delivery as targets has been reported to

Table 21.2 Indications for extended hemodynamic monitoring with the pulmonary artery catheter

The use of a pulmonary artery catheter (PAC) is recommended:	PAC should also be used:
– In a cardiosurgical high-risk patient with a complex intervention	– In patients with preoperative right ventricular dysfunction
– To differentiate between left or right ventricular dysfunction	– In patients at risk for right heart dysfunction and/or pulmonary arterial hypertension
	– To differentiate the cause and control the therapy of a severe low cardiac output syndrome
These recommendations are evaluated with the evidence level D according to the criteria of the Oxford Centre for Evidence-Based Medicine	

significantly reduce mortality and the use of fluids, inotropes, and vasoactive drugs [47].

Judge et al. conducted a survey among the members of the Society of Cardiovascular Anesthesiologists to assess the use of the PAC and other hemodynamic monitoring tools in patients undergoing cardiac surgery. The majority of the respondents selected the use of PAC. However, TEE remained the most popular hemodynamic monitoring tool [48].

In conclusion, PAC is still indicated in a subgroup of patients suffering from circulatory or respiratory failure, particularly in association with pulmonary hypertension or right heart dysfunction. A reliable usage requires a high level of expertise in insertion as well as interpretation of measurements appropriately.

Practical Advice

When using a PAC, it must be taken into account that the pulmonary arterial occlusion pressure in chronic changes of the pulmonary tract (*e.g.,* in patients with long-term post-capillary pulmonary arterial hypertension) only imprecisely reflects the left atrial pressure (LAP). This can be avoided by determining the LAP *via* an intraoperatively inserted catheter.

Given the rising risk profile of the patients to be treated and the increasing complexity of cardiac surgery, it is important to select the optimal modalities for making skillful use of the available monitoring procedures and controlling the therapy for the individual patient. Echocardiography and advanced hemodynamic monitoring should not be seen as competing but rather complementary procedures.

21.8 Promising Future Technologies

21.8.1 Noninvasive Techniques

In recent years, several technologies for continuous, noninvasive blood pressure measurement have attracted increasing attention and use in the clinical field. However, one method might be highlighted in this context. This method is based on a volume clamp technique, which was first presented in the 1970s by the Czech physiologist J. Peñáz [49]. With this method, the arterial blood pressure is measured on the finger using a finger cuff. Through further development of the method, several products with different technological implementation concepts have been brought onto the market in the last 10 years, which make continuous blood pressure and CO measurements based on pulse contour analysis possible. Several studies have been published which investigated the accuracy of this method in comparison to invasive blood pressure, but also to oscillometrically measured noninvasive blood pressure in everyday clinical practice. However, the patient samples as well as the results of these studies are inconsistent.

Noninvasive technology has also been used in studies with cardiosurgical patients. Fischer et al. investigated the accuracy of the Nexfin System in 50 postoperative cardiosurgical patients. An acceptable correlation between radially invasive and noninvasive blood pressure values was shown. However, in the further investigation, a high percentage error of 50% was found when comparing the CI measured by thermodilution and Nexfin System using pulse contour analysis [50].

Continuous noninvasive blood pressure measurement could provide an alternative to invasive measurement in hemodynamically stable patients. Owing to the large number of limitations that have not been further investigated (patients in shock, arrhythmias, pronounced hypotension), the evidence base is currently still low, and indication for using these systems is so far not to be seen primarily in patients undergoing major cardiac surgery.

However, these systems could be of interest for cardiac surgery patients undergoing minor operations such as vacuum-assisted closure (VAC) therapy, sternal closure, intracardiac device implantation, and other procedures.

21.8.2 Monitoring of the Sublingual Microcirculation

During cardiac surgery, pathophysiological mechanisms such as reduced CO, non-pulsating

blood flow during CPB, inflammation, hemodilution, and hypothermia are not uncommon and may therefore be associated with microvascular dysfunction and reduced tissue oxygenation. The microcirculation can be permanently damaged perioperatively and remain dysfunctional, although the macrohemodynamic target constellation has been achieved. The handheld microscopy allows a direct visualization of the microcirculation. In this field, a lot of scientific knowledge has been gained in recent years. This has contributed significantly to a better understanding of microcirculatory perfusion during cardiac surgery, opens up new perspectives in the diagnosis and treatment of microvascular changes, and thus has an important influence on the management of perioperative complications and patient outcome [51, 52].

The measuring principle is based on incident dark-field imaging and light-emitting diodes with a wavelength of 530 nm. Due to the light absorption of hemoglobin, the resulting image shows red blood cells as dark moving spheres, while the surrounding tissue is shown as a bright blur. Thus, for vessels to be displayed, they must contain red blood cells. Therefore, sublingual microscopy (SM) does not give direct information about tissue oxygenation but rather evaluates microcirculatory perfusion and convective and diffusive oxygen transport. The technique of SM can provide fundamental insights into microcirculatory changes in cardiac surgery, which may help to establish an individual hemodynamic approach. However, further research is needed to prove that SM-based monitoring has a positive effect on the postoperative outcome of patients. Therefore, the use of SM in clinical practice is currently not recommended [53, 54]. The importance of microcirculation monitoring in perioperative interventions such as fluid management and the administration of catecholamines and other therapies should also be the subject of further research.

21.9 Conclusion

Changing demographics and the increased severity of cardiac surgery patients require an increasingly comprehensive monitoring of both neurological and hemodynamic function in anesthesiological care. Echocardiography and extended monitoring should be considered as complementary procedures. A targeted optimization of the systemic and cerebral oxygen balance allows an adaptation of the therapy to the individual needs of a patient both intra- and postoperatively and seems to be suitable to reduce morbidity and mortality.

Keynotes

- Cardiac surgery patients have a significantly increased risk of neurological complications. Avoiding a drop in regional cerebral oxygen saturation below the preoperative baseline may reduce the rate of delirium or POCD.
- Transesophageal echocardiography is a standard procedure in cardiac surgery patients to evaluate cardiac function and outcome after valve replacement/reconstruction.
- To evaluate the frequently complex hemodynamic patterns of cardiac surgery patients, extended monitoring using transpulmonary thermodilution, pulmonary artery catheter, and echocardiography is often required. Continuous monitoring of the arterial and central venous pressure curve is mandatory.

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Hemodynamic Monitoring and Optimization in Noncardiac Surgery

22

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Contents

22.1 Rationale for Hemodynamic Monitoring in Noncardiac Surgery

Yearly, more than 200 million surgical procedures are performed worldwide, most of which are in high-expenditure countries. Based on epidemiological and observational data, the overall mortality risk is as low as 0.5% [1]. However, it seems that among high-risk population, the risk of dying is 25–50 times higher making this group extremely prone to consume most of the resources of perioperative care. Moreover, complication rate in intermediate-to-high surgical cases is frequent (exceeding 30%), and complication occurrence has been repeatedly associated with increased long-term mortality [2]. Since Shoemaker's seminal papers [3], perioperative organ hypoperfusion and resulting oxygen debt

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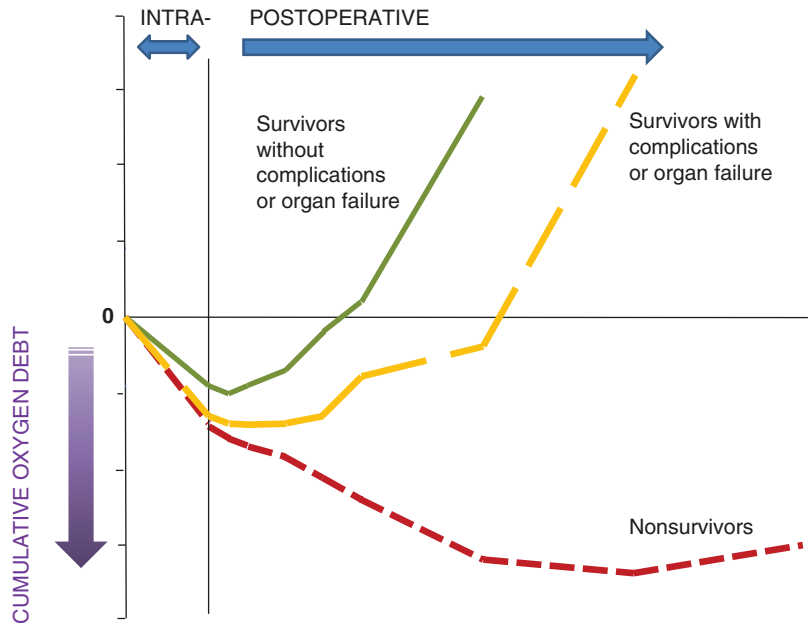

Fig. 22.1 Impact of cumulative oxygen debt on postoperative outcome. Legend: Net cumulative VO_2 deficit for non-survivors, survivors without organ failure and survivors with organ failure calculated for intraoperative period and each successive time period after surgery—picture adapted and based on the data by Shoemaker et al. [3]

are recognized causes of such adverse events (Fig. 22.1). Unlike surgery-associated complications, which dropped down given the improvement in surgical techniques, the risk of hypoperfusion seems to decrease only mildly, even though our monitoring techniques of cardiovascular dynamics improved significantly over the last 40 years.

Generally, acceptable lowest value of MAP (which is able to maintain tissue perfusion) is 65 mmHg. If the pressure drops below this level, we speak about intraoperative hypotension. However, we must admit that there is no uniform definition of intraoperative hypotension. Bijker et al. found a total of 140 different definitions of it [4]. Moreover, MAP value that may be associated with organ hypoperfusion is highly individual. For example, in patients with chronic hypertension, MAP of 65 mmHg can be too low because of impaired vascular autoregulation [5, 6]. Recent studies confirmed that perioperative hypotension adversely affects postoperative morbidity and mortality [7–10] and is associated with myocardial infarction, renal failure, and stroke [9, 11–13]. Not only the depth of hypotension is important but also its cumulative length and dose (area under the line of lowest acceptable MAP). With less severe hypotension, negative impact can occur in more than 10 min [12, 13], but with a MAP around 50 mmHg, the patient may be harmed earlier [8]. Therefore, it is important to monitor blood pressure with high frequency and ideally continuously in high-risk procedures and/or patients.

However, perioperative hypotension (nevertheless how detrimental) is only the tip of the iceberg [14]. Meregalli found in his study that occult hypoperfusion can be present also in patients without evident signs of shock who were hemodynamically stable [15]. Hence, besides perfusion pressure, the important factor for adequate organ perfusion is sufficient cardiac output. However, to recognize inadequate cardiovascular performance, we need one of the more advanced hemodynamic monitors. These monitors allow us to measure cardiac output and determine the individual parameters that affect cardiac output, namely, preload, contractility, and afterload. Knowing these variables, we are able to optimize the individual parameter of cardiac output in order to keep its value within the required limits and thus guarantee sufficient tissue perfusion.

In recent years, it has been repeatedly demonstrated that early detection and targeted treatment of insufficient cardiac output and thus the oxygen supply to tissues, the so-called perioperative goal-directed therapy, have a positive effect on

outcome, especially in high-risk noncardiac surgery patients [16–20]. In this chapter, we will discuss the most frequently used techniques of hemodynamic monitoring in noncardiac surgery as well as their utility in perioperative goal-directed therapy.

Practical Advice

Hypotension during perioperative period is never "benign." It frequently points toward profound alterations of cardiovascular dynamics induced either by disease or surgery or as medication side effect.

The general definition of hypotension is MAP <65 mmHg. However, this is not a universal value. In patients with chronic hypertension, we are aiming to keep it ≥70–75 mmHg or in a range ± 20% of patient's normal preoperative value.

Tissue hypoperfusion may occur even in "stable" patients with normal blood pressure readings (so-called occult hypoperfusion).

In high-risk procedures and/or patients, monitoring of cardiac output is highly recommended and is associated with improved outcomes of noncardiac surgery.

22.2 Blood Pressure Monitoring

Intermittent noninvasive blood pressure measurement is one of the basic monitoring modalities during perioperative period. It is generally recommended that blood pressure should be measured at least every 5 min throughout anesthesia. However, especially in high-risk procedures and/or patients, noninvasive blood pressure monitoring may be insufficient. Some studies point to the frequent occurrence of hypotension and late response to it when blood pressure is monitored intermittently and noninvasively by an oscillometric cuff [11, 12, 21, 22].

For this reason, it is preferable to monitor blood pressure continuously. Invasive monitoring *via* an intra-arterially inserted cannula (most often into the radial artery) is still considered to be the gold standard for continuous blood pressure monitoring, although it carries a risk of complications [23]. Nevertheless, invasive blood pressure monitoring should be still the standard for all procedures where we expect large blood loss and rapid changes in blood pressure such as major vascular surgery, liver resections, or intracranial neurosurgical procedures.

In addition to invasive techniques, noninvasive modalities of continuous blood pressure monitoring have been marketed recently. These monitors are based on either the volume clamp principle (first introduced by the Czech professor of physiology Peňáz) or applanation tonometry. The volume clamp method is based on measuring the volume of arteries on the fingers using infrared photoplethysmography. The measured volume is kept constant throughout the cardiac cycle by means of a pressure cuff embracing the finger, which is inflated and deflated in a rate of 100 Hz. The pressure required to maintain a constant volume of the artery corresponds to the intra-arterial pressure within the finger arteries. Blood pressure at the level of brachial artery is reconstructed either *via* external calibration or *via* using a sophisticated mathematical model. The method allows the continuous measurement of arterial pressure and graphical reconstruction of the arterial curve. Currently, several devices are at hand: CNAP (CNSystems Medizintechnik AG, Graz, Austria)—integrated within few other monitoring platforms, ClearSight (Edwards Lifesciences, Irvine, CA, USA)—which is a "second" generation to former Nexfin (Bmeye, Amsterdam, Netherlands) and rather novel NICCI monitor (Pulsion, Maquet Getinge group, Sweden) based on CNAP technology—further developed, but not clinically evaluated yet. There are several papers documenting the utility of these devices in clinical practice and their effect on reducing the incidence of episodes of perioperative hypotension [12, 22] and optimizing perioperative hemodynamics [24]. In addition to continuous blood pressure measurement, advanced hemodynamic calculations are provided including estimation of cardiac output, calculation of pulse pressure/stroke volume variation, and several other hemodynamic parameters.

The second method of noninvasive blood pressure measurement is applanation tonometry. During the measurement, a part of the arterial wall is compressed against the bone, which allows its flattening (applanation). The device uses Imbert Fick's law to determine blood pressure. Applanation tonometry is used by the T-line monitor (Tensys Medical Inc., San Diego, CA, USA). The big disadvantage of this device is the high sensitivity to the exact position of the sensor above the radial artery. There are relatively few studies evaluating the usefulness of the T-line, but in the meta-analysis performed by Kim, the accuracy of both types of noninvasive continuous blood pressure measurement techniques was comparable [25]. At present, the limitations of the use of these devices are conditions associated with reduced peripheral perfusion—hypothermia, severe shock with peripheral vasoconstriction, and high doses of catecholamine. In these situations, it is better to use intra-arterial catheter, which also enables blood sampling.

Practical Advice

Continuous measurement of blood pressure should always be preferred in situations, in which we expect blood pressure fluctuations.

Invasive monitoring *via* intra-arterial line is recommended in case of impaired peripheral perfusion.

22.3 Cardiac Output Monitoring

Previous studies have repeatedly shown a negative effect of perioperative hypoperfusion on patient morbidity and mortality [15, 26]. The usual pressure-centric approach to hemodynamics does not allow us to identify the underlying cause of hypotension/hypoperfusion. Therefore, advanced monitoring is often recommended based on the patients and procedure-related risk stratification (Fig. 22.2). Currently, a number of devices enable monitoring of cardiac output and/or associated variables (Table 22.1).

Historically, the first CO monitoring method was the Swan-Ganz pulmonary artery catheter (PAC) introduced into clinical practice in 1970. Although PAC is still considered the gold standard of cardiac output monitoring and novel devices are compared to it, its use is associated with a number of risks that may increase perioperative morbidity and mortality, and it is not recommended for routine care in noncardiac cases nowadays [27]. It has been replaced by less and minimally invasive devices over the last 20 years. Similarly, less invasive devices needing transpulmonary thermodilution calibration (*i.e.,* PiCCO, VolumeView) seem to be too cumbersome and time consuming for perioperative setting. Thus, we use these monitors only in very complex cases especially in major vascular and liver surgery [28].

In daily clinical practice in the operation room, we measure CO most frequently by ultrasonography (esophageal Doppler—ED) or we estimate it by monitors based on arterial pressure waveform analysis (PWA). These monitors brought one important factor into the perioperative cardiovascular monitoring—the factor of time: continuous monitoring and trending ability. Especially, non-calibrated monitors based on PWA either obtained invasively (*via* radial artery) or noninvasively are currently the most frequently used hemodynamic monitoring tools in intermediate- to high-risk patients. The mathematical principles, which may differ based on device used, are described in detail in Chap. 8. Their preference by clinicians is based on the easiness of use (so-called plug-and-play) combined with sophisticated and ergonomic monitor-user interfaces. The PWA-based monitors offer wide range of hemodynamic parameters derived from arterial pressure curve (PPV/SVV, dP/dtmax, *etc.*). It is important to note that these devices share some common limitations. First of all, they are dependent on the quality of pressure tracing (damping, *etc.*) and reliability of the mathematical model especially under specific situations (high doses of vasopressors, sepsis, liver surgery, *etc.*) [29, 30]. To avoid this, some devices enable external calibration, but in general, the trending ability seems to be less affected [31].

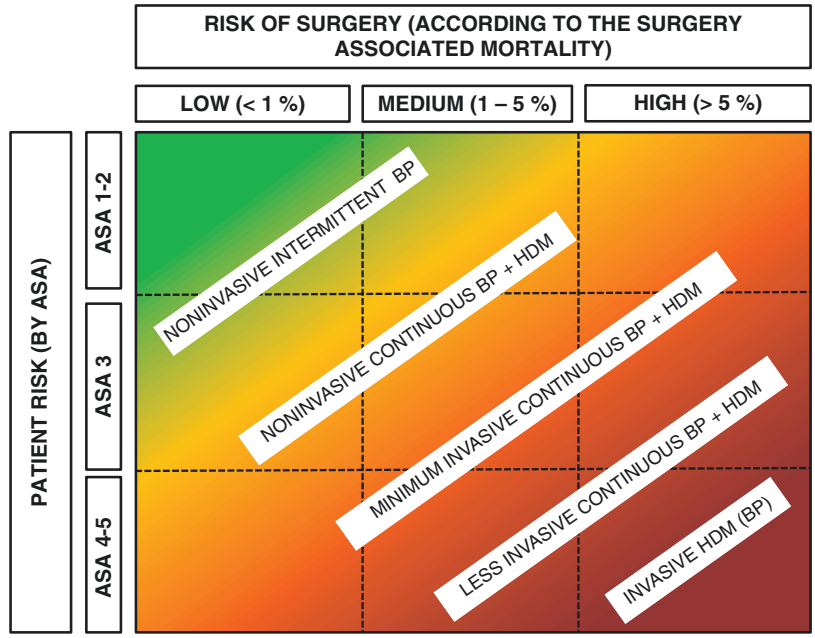

Fig. 22.2 Complexity of hemodynamic monitoring based on the patients and procedure-related risk stratification. Legend: Based on the patients and procedure-related risks, the optimal monitoring tool may be chosen. *ASA* American Society of Anesthesiologists score, *BP* blood pressure, *HDM* hemodynamic monitor. Adapted from Kirov et al. [45]

Table 22.1 Methods of measuring cardiac output and their distribution according to the degree of invasiveness

	Method	Device
Invasive	Thermodilution: Pulmonary catheter	Swan-Ganz catheter
Less invasive	Transpulmonary indicator dilution + analysis of the arterial pressure curve	LiDCO, PiCCO, VolumeView
Minimally invasive	Arterial pressure curve analysis	FloTrac/HemoSphere, ProAQT/PulsioFlex, LiDCORapid, MostCare/PRAM
	Esophageal Doppler	CardioQ
Noninvasive	Transthoracic Doppler	Echocardiographic devices
	Fick principle: Re-inhalation of CO_2	NICO
	Bioreactance, bioimpedance	NICOM, BioZ, ECOM
	Peňáz volume clamp technology	CNAP, ClearSight, NICCI
	Applanation tonometry	T-line
	Pulse wave transit time	Vismo

Esophageal Doppler was the first less-invasive modality of cardiovascular monitoring replacing the use of the PAC in perioperative setting. Doppler probe inserted *via* esophagus to the level of descending aorta enables to monitor stroke volume, but also several specific hemodynamic parameters (peak velocity, corrected flow time). The method is described in detail in Chap. 9. Currently, the only monitor available for clinical practice is CardioQ (Deltex Medical, Chichester, West Sussex, UK). Although the agreement of ED and invasive CO measurement is only moderate, there are multiple studies demonstrating positive effect of the perioperative goal-directed therapy (pGDT) based on ED [32]. The major limitation of ED is that it is not well tolerated by awake patients and sensitive to proper probe placement [33].

Recently, fully noninvasive monitoring tools have been introduced into clinical setting. Some of them (PWA analysis based on noninvasive continuous blood pressure—CNAP, LiDCO Unity, ClearSight, or bioreactance—NICOM) have already been utilized in some clinical scenarios [24, 34, 35]. Others, like bioimpedance, pulse wave transit time, and re-inhalation of CO_2,

are used exceptionally in daily clinical practice based on their uncertain reliability [36]. Nevertheless, the use of fully noninvasive techniques of CO measurement is spreading among clinicians changing the paradigm from pressure-centric to perfusion-centric.

Practical Advice
Less invasive and noninvasive monitors of cardiac output are easy to use and should be a standard monitoring in intermediate- to high-risk surgery.

22.4 Hemodynamic Optimization and Perioperative Goal-Directed Therapy

Based on their findings in the late 1980s, Shoemaker et al. tested the hypothesis whether improvement of high-risk patients' cardiovascular performance would affect their postoperative outcome [3]. Process of reaching predefined hemodynamic goals (obtained as median values of survivors) with the use of fluids, pressors, and inotropes has been proposed as the so-called hemodynamic optimization. Shoemaker's targets were used by multiple others with mostly positive results in the perioperative setting [37]; however, several negative results [38] and decreased use of PAC led to abandonment of the supranormal targets concept. Meanwhile, ED technology and PWA-based monitors started to replace PAC leading to rethinking of the concept of pGDT.

In the following years, more than 100 studies using the pGDT concept were published, which protocols no longer aimed at achieving supramaximal DO_2 values [17, 20]. In these studies, new parameters of functional hemodynamic monitoring (fluid responsiveness assessment and analysis of the pressure upstroke or peak velocity of Doppler signal curve) were tested. In general, these studies have shown a positive effect on the morbidity and mortality of operated patients, especially in the subgroup of moderate and high-risk noncardiac surgery [17, 18].

Nowadays, we may identify three major concepts within the pGDT trials: (1) hemodynamic optimization to Shoemaker's supranormal targets; (2) maximization of stroke volume (Fig. 22.3); and (3) fluid optimization based on dynamic variation of stroke volume/pulse pressure (Fig. 22.4). The latter two are sometimes limited to fluid loading only but mostly use further hemodynamic parameters to optimize cardiac function and perfusion pressure.

The following variables have been proposed most frequently in pGDT protocols as treatment targets: cardiac output/index (CO/CI), stroke volume (SV), indexes of oxygen delivery and con-

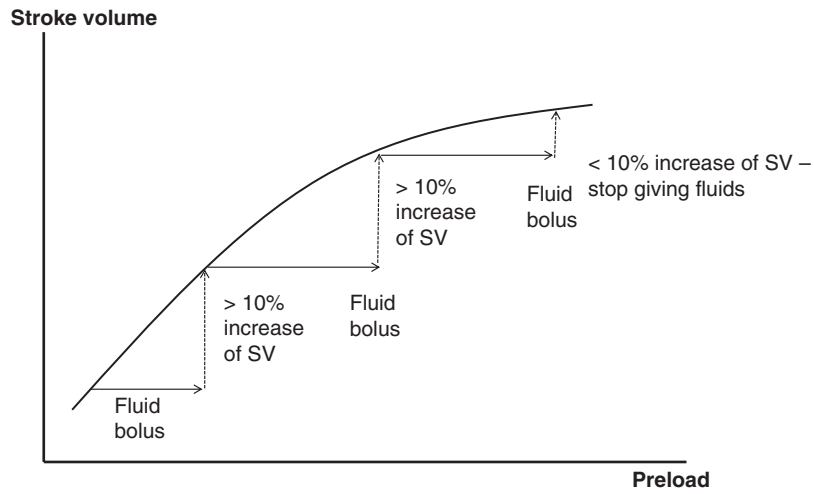

Fig. 22.3 Fluid optimization concept based on maximization of stroke volume. Legend: *SV* stoke volume

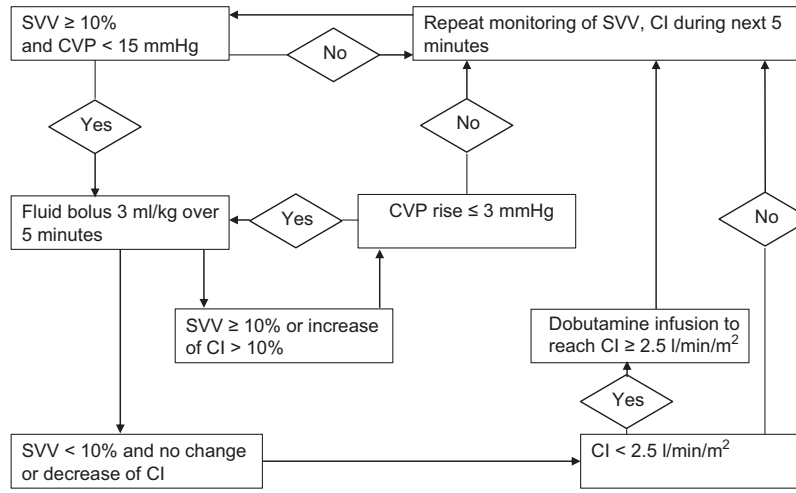

Fig. 22.4 The example of optimization protocol based on stroke volume variation. Legend: Protocol based on FloTrac monitoring system as used by Benes et al. [46]. *SVV* stroke volume variation, *CVP* central venous pressure, *CI* cardiac index

sumption (DO_2I and VO_2I), and variation of stroke volume/pulse pressure (SVV and PPV).

Since Shoemaker, CO/CI remains the core variable of pGDT protocols. In studies aiming at supranormal values, the target CI is usually >4.5 L/min/m^2. Humble targets (>2.0–2.5 L/min/m^2) have been used in modern fluid optimization protocols. In reality, this minor target aims more at avoiding inadequately low CI than optimizing cardiovascular performance.

The SV-guided pGDT aims usually at maximizing the value of SV by steps of fluid challenges dictated by 10% increase to previous administration (Fig. 22.3). Afterward, the SVmax value identified should be maintained throughout the perioperative period. This approach has been proposed by NICE/NHS recommendations in the United Kingdom. However, some authors have questioned the extent of fluid loading in patients with high cardiovascular reserve [39]. Moreover, SV is a complex parameter, and not all fluctuations of SV throughout the surgical procedure are always attributable to preload change.

Global oxygen delivery (DO_2I > 600 mL/min/m^2) has been proposed by Shoemaker; this target is still aimed by multiple studies especially coming from the United Kingdom. Frequently, reaching such value is not possible without accepting higher transfusion threshold (*i.e.,* 10 g/dL) and/or the use of inotropes to further increase CI. In addition, increased global oxygen delivery does not mean adequate tissue supply. Therefore, the use of local tissue oxygen saturation as measured using near-infrared spectroscopy has been proposed as an interesting alternative (yet not tested in large studies).

Global parameters of oxygen consumption such as mixed/central venous oxygen saturation, oxygen extraction, or VO_2I were used by several authors as markers reflecting the adequacy of oxygen delivery. Disadvantage of this approach is disproportion between consumption in anesthetized and awake state making these parameters difficult to use in protocols of perioperative care.

In addition to these variables, multiple protocols have used SVV/PPV or even similar noninvasive parameters (plethysmography variability index—PVI) to optimize the preload and fluid loading during high-risk procedures under general anesthesia. Based on published meta-analysis, this approach seems to be safe and associated with improved postoperative outcomes [18]. However, it poses several limitations. First, these parameters could be used only in patients without spontaneous breathing efforts, with tidal volume large enough and with regular heart rhythm. The prevalence of these contraindications differs between populations and procedures, but in general, up to one-third of the patients presents with at least one. Secondly, rather large "gray zone" has questioned the use of liberal targets of SVV/PPV within 10–12% used in former studies. Nowadays, more reserved 13–15% are recommended as targets.

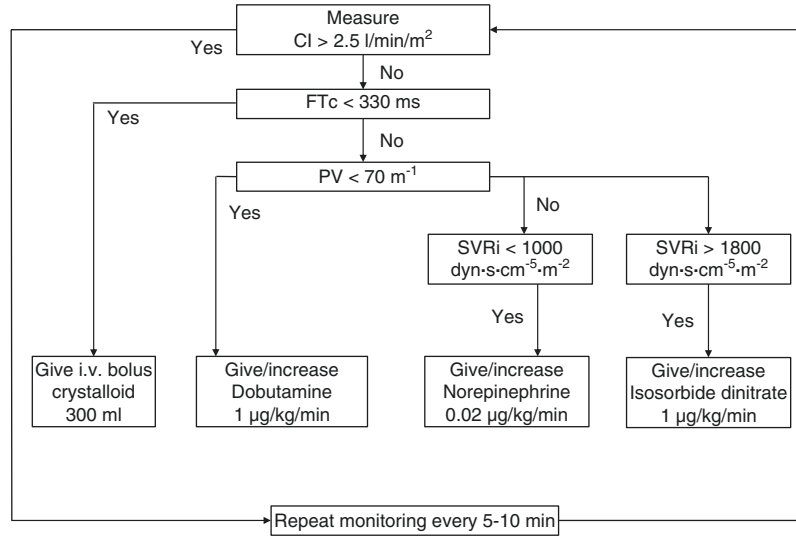

Fig. 22.5 The example of multiparametric optimization protocol. Legend: Protocol based on the use of esophageal Doppler by Szturz et al. [40]. *CI* cardiac index, *FTc* flow time corrected, *PV* peak velocity, *SVRi* systemic vascular resistance index

Besides these general parameters, variables more specific to each domain (preload, afterload, contractility) are sought to enable specifically aimed treatments. For instance, SVV/PPV are parameters enabling preload assessment. Similarly, corrected flow time is used in ED studies to guide fluid loading more appropriately. Recently, parameters as dynamic elastance (EaDyn), maximal pressure-time derivate (dP/dtmax), or peak velocity (PV) have been proposed to specifically identify changes in afterload or inotropy. These parameters have not been studied in detail yet, but several signals have demonstrated positive effect on perioperative hemodynamic stability and postoperative outcomes [40] (Fig. 22.5). It is important to note that rational goals of pGDT include also maintaining adequate blood pressure values, not just cardiac output [9].

Further on, the concept of personalized hemodynamic management is currently being developed. Within this concept, the goal is to keep the values of cardiac output and blood pressure as close as possible to individual patient's normal values adapted to the particular clinical situation. Wider implementation of this concept in the nearest future depends on the availability of fully noninvasive cardiac output monitors for ambulatory monitoring. Studies showing the positive effect of this concept have already been published, and others are underway [41]. Another step will be closed loop system management and monitoring of microcirculation.

Practical Advice

Especially in high-risk cases, we should carefully look for occult hypoperfusion by using advanced hemodynamic monitoring and optimally prevent it by using perioperative goal-directed therapy.

Treatment of hypotension/hypoperfusion should follow three strict rules:

- All possible preventive measures should be used to avoid periods of hypotension/hypoperfusion.
- If hypotension/hypoperfusion occurs, a fast normalization of normal perfusion pressure using short-acting vasopressors should be initiated immediately.
- Meanwhile, underlying cause of instability should be identified and treated appropriately (*i.e.,* fluids, inotropes).

22.5 Future Perspectives

There are several concepts of hemodynamic monitoring which could help to increase the safety of operated patients in the nearest future:

- Concept of multimodal monitoring—including advanced hemodynamic monitoring combined with global oxygen equilibrium parameters (lactate, $ScvO_2$, *etc.*) and monitoring of microcirculation [42].
- Personalized hemodynamic management—aiming to optimize hemodynamic parameters based on the patient's personal hemodynamic profile found preoperatively [43].
- Closed-loop system management—because the compliance of anesthetists to pGDT protocols is suboptimal, we could use monitors which automatically direct the treatment response to changes of hemodynamic variables [44].
- Prediction of upcoming hemodynamic derangement using machine-learning—this principle has already been applied by the Acumen hypotension probability indicator (HPI), a novel feature of HemoSphere monitor (Edwards Lifesciences, Irvine, USA)—a parameter able to predict hypotension development in next 10–15 min with high accuracy.

22.6 Conclusion

Hypoperfusion and hypotension (as its most prominent, but not always present symptom) are still occurring frequently in noncardiac surgical patients. Especially in intermediate- and high-risk patient, they may lead to decreased tissue oxygen delivery and are associated with perioperative complications. Choosing the right monitoring system, including continuous advanced hemodynamic monitoring, is the first step to recognize the problem. Perioperative goal-directed therapy is a preventive approach to regulate the patient's cardiovascular performance during surgery and adjacent time with the aim of minimizing tissue hypoperfusion and hypoxemia. Based on multiple studies, this approach of individualized hemodynamic care is associated with improved postoperative outcome in intermediate- to high-risk noncardiac surgery.

Keynotes

- Advanced perioperative hemodynamic monitoring and perioperative goal-directed therapy have been repeatedly demonstrated to improve postoperative outcomes of intermediate- to high-risk noncardiac surgical patients. Hence, pGDT should be incorporated as a standard part of care for such patients.
- Several protocols and target values may be used to define the best one(s) for the individual patient.
- The use of less invasive and noninvasive hemodynamic monitors allows monitoring to be extended to moderate- and low-risk surgery and can further help increase the safety of operated patients.
- In the nearest future, noninvasive monitors would allow the development of personalized hemodynamic management of patients and thus start the era of true individualization of perioperative hemodynamic care.

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Part VII

Hemodynamic Monitoring and Therapy in Intensive Care Medicine

23 Hemodynamic Monitoring and Therapy in Hypovolemic Shock

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Contents

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23.1 Pathophysiology of the Hypovolemic Shock

Adequate vascular filling, together with cardiac contractility and vascular tone are the three major determinants of the functional cardiovascular system. The term "volemia" is physiologically well defined, but only indirectly measurable in clinical conditions. The human body consists of 60% of water, divided into several separated compartments: intracellularly (40%), then in interstitial space (15%), and intravascularly (5%). In routine critical care, intravascular fluid compartment plays a major role. It has a direct impact on patient's hemodynamics, but first of all, it is the only one we may get into therapeutically. The

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fluid interchange between compartments is tightly regulated with membranes and transport systems. Classic Starling equation describing the vascular-interstitial barrier has been challenged by the exploration of the function of the endothelial glycocalyx, and the simple mechanistic rules of oncotic pressures and back filtration are no longer considered to be true [1]. Glycocalyx and its disruption seem to play major role in the fluid shifts during critical illness, including shock of different origins.

Hypovolemia in acute situations is mainly caused by blood loss and hemorrhagic shock. Subacute or chronic fluid depletion can occur in the case of inadequate intake, losses through the gastrointestinal system like prolonged vomiting or diarrhea, polyuria, or diseases affecting systems of humoral regulation (*e.g.,* central diabetes insipidus in brain injury). Many states, which were believed to be hypovolemic (*i.e.,* sepsis, pancreatitis, or effect of general anesthetics), are now considered to be mainly a problem of fluid distribution and sequestration (relative hypovolemia) rather than the true (absolute) hypovolemia. However, the central reaction to both relative and absolute hypovolemia is very similar (Fig. 23.1): a decrease of circulating blood volume leading to a drop of venous return. This results in the lowering of both ventricles preload and causes the fall of the cardiac output (CO). Hypovolemia, CO decline, and drop of blood pressure directly stimulate receptors in the heart, aorta, and carotid sinus and lead to activation of the sympathetic system and parasympathetic damping.

Compensatory neurohumoral regulations are started to maintain sufficient CO and oxygen delivery, with β_1-adrenergic-mediated increase in contractility and tachycardia as the initial step. Next, catecholamine α_1 receptor-mediated vasoconstriction of capacitance veins provides additional volume from the unstressed venous compartment to the functional circulation (the "stressed" one) [see Chap. 1]. This compensatory response is usually blocked in relative hypovolemia, but when adequate volume mobilization is elicited *via* external stimuli (mostly vasopressors), it may help to partially reverse the low venous return.

Besides this mechanism, blood flow redistributes from the skin and splanchnic region *via* α_1-mediated arteriolar constriction, causing a rise of the left ventricle afterload and maintaining oxygen and nutritional supply for the heart and brain.

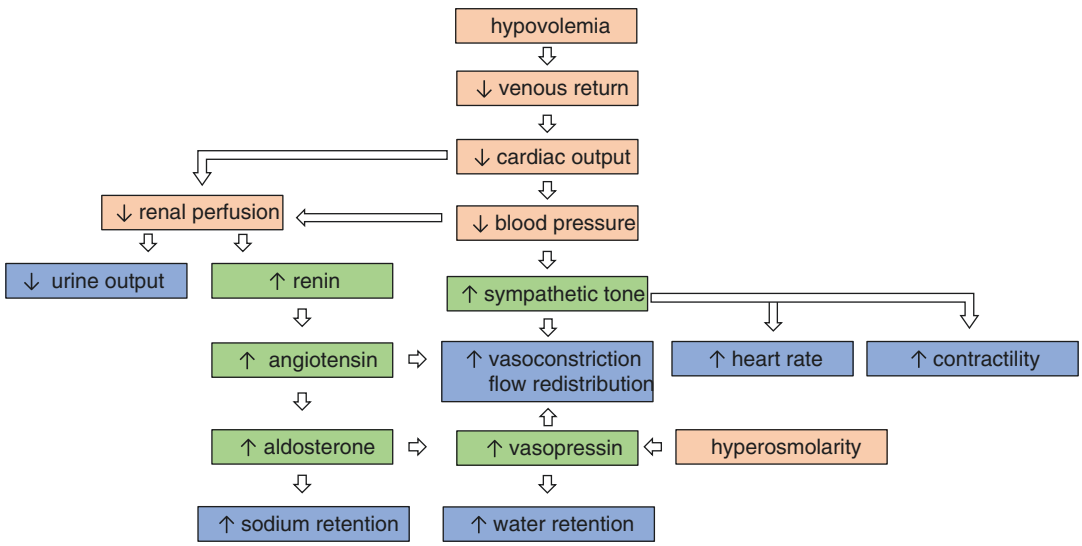

Fig. 23.1 Physiological response to hypovolemia. Legend: Pathological states and their natural consequences (in orange boxes) trigger neurohumoral response (in green) leading to contra-regulatory effects on cardiovascular and renal systems (blue boxes)

Table 23.1 Body reaction to the loss of the intravascular volume

Class of hemorrhagic shock				
	I	II	III	IV
Blood loss (ml)	>750	750–1500	1500–2000	>2000
Blood loss (%)	>15	15–30	30–40	>40
Heart rate (bpm)	<100	100–120	120–140	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal/increased	Decreased	Decreased	Decreased
Respiratory rate (bpm)	14–20	20–30	30–40	>35
Urine output (ml)	>30	20–30	5–15	Anuria
Mental status	Slightly anxious	Anxious	Confused	Lethargic

Ml milliliters, *bpm* beats/breaths per minute

Moreover, other humoral regulations are established. Renal hypoperfusion and low sodium/chloride levels at *macula densa* lead to increased renin secretion activating the renin-angiotensin-aldosterone system. Aldosterone helps to preserve circulation volume by water and sodium retention in the kidney, whereas angiotensin II leads to direct vasoconstriction *via* the AT1 receptors. Vasopressin is another important regulatory peptide. Its production within hypothalamic neurosecretory cells and further release by posterior pituitary is stimulated by hypothalamic osmoreceptors and by other hormones (aldosterone). Through different receptor types, vasopressin has a direct vasoconstrictive effect (V1a) and causes water reabsorption in the kidney through aquaporin channels regulation (V2). In addition, it causes glycogenolysis in the liver (V1a) and secures the connection with an adrenocortical system in the hypophysis (V1b).

The intensity of the compensatory reactions is dictated not only by the extent (see Table 23.1) but also by the speed of development of the hypovolemic state. Acute blood loss (combining loss of circulating volume, drop in cardiac output and decrease in hemoglobin levels) is much worse tolerated than a hypovolemic state, which develops by loss of water and ions in diarrhea or dehydration. Nevertheless, protracted activation of compensatory mechanisms and blood flow redistribution lead to hypoperfusion of distant organs and result in multi-organ failure. Among global parameters, an increase in oxygen extraction may be observed *via* decreased central/mixed venous oxygen saturation. Because some organs suffer from hypoxia given their limited blood supply, lactate level—as a marker of anaerobic glycolysis—starts to increase. The low flow state in the splanchnic circulation can cause bacterial translocation and inflammatory activation. Renal vasoconstriction leads to acute kidney injury, and hypoperfusion of the skin and extremities may result in peripheral necrosis. Dysfunction of endothelium (so-called shock-induced endotheliopathy) leads to damage of endothelial glycocalyx, coagulation activation, thromboses, and dysfunction of the vascular barrier. If left untreated, the shock becomes decompensated, oxygen delivery falls below a critical threshold and with progressive hypoperfusion of vital organs, resulting in imminent death (Fig. 23.2).

23.2 Diagnosis of Hypovolemia

23.2.1 Clinical Symptoms

Most cases of the hypovolemic shock can be diagnosed quickly using clinical examination and eventually ultrasound, which can help to state the diagnosis in view of the relatively low specificity of leading clinical symptoms (Table 23.2). Identification of the cause is extremely important, especially if hypovolemia is acute and the patient's state is progressively deteriorating. History of any trauma, recent surgery, blood in vomits or tarry stool, or anticoagulation treatment leads to high suspicion of hemorrhage. The same issue is the history of any gastrointestinal,

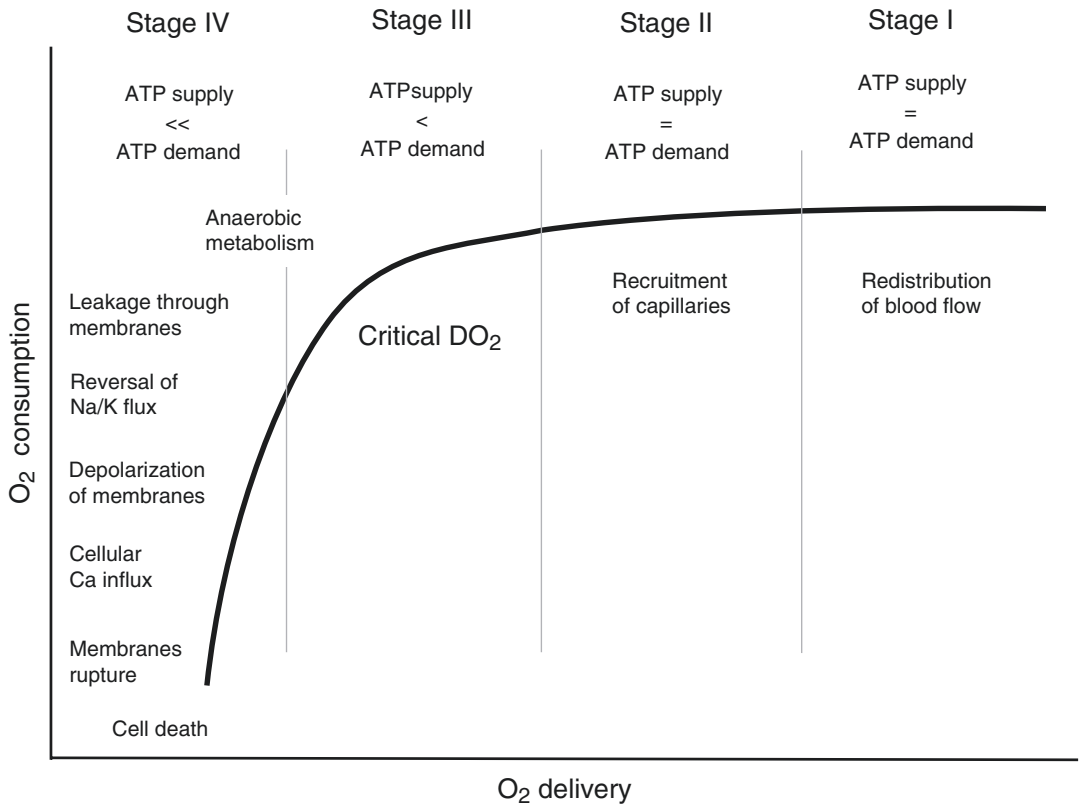

Fig. 23.2 Relationship of the oxygen delivery and consumption in different stages of shock. Legend: With decreasing global oxygen delivery, the patients shift from the right to the left on the VO_2/DO_2 curve: from the area of VO_2 independence (stage I and II) to the point of critical DO_2 (stage III), under which the VO_2 is fully dependent on the amount delivered (stage IV)

Table 23.2 Clinical examination in hypovolemic shock

Symptom	Finding	Possible confounders
Heart rate	Tachycardia	Atrial fibrillation with rapid ventricular response other sympathetic activation, *e.g.,* pain Use of β-blockers
Breathing	Tachypnoea, dyspnoe	Sedation, pain, psychological distress, or mental disorder
Consciousness	Confusion, obtundation	Sedation, brain injury, psychological distress, or mental disorder
Skin perfusion	Pallor, mottling Prolonged CRT, acrocyanosis	Peripheral vascular disease, *e.g.,* Raynaud's disease hypothermia
Hydration	Skin turgor, dry mucosae	Pre-existing heart or renal failure with edema
Diuresis	Oliguria Urine concentration	Pre-existing renal dysfunction use of diuretics central nervous system disorder

CRT capillary refill time

endocrine and renal disease, or medication causing possible fluid loss.

Thorough head-to-toe clinical examination can reveal symptoms of blood loss and/or increased sympathetic tone—tachycardia (which can be mitigated by the use of β-blockers), pale skin and conjunctivae, and the signs of the reduced cardiac output (weak palpable pulse,

cold extremities, acrocyanosis). Obtundation, decreased level of consciousness, as well as dyspnea can be seen in more profound shock. Centralization of the circulation, as described above, causes skin hypoperfusion, which is manifested as mottling, usually starting above kneecaps, later spreading proximally and distally (Fig. 23.3). Mottling score [2] was developed and correlates well with mortality. Another important basic test is the capillary refill time (CRT). Although used frequently, proper compression time of the nail bed and evaluation is not well

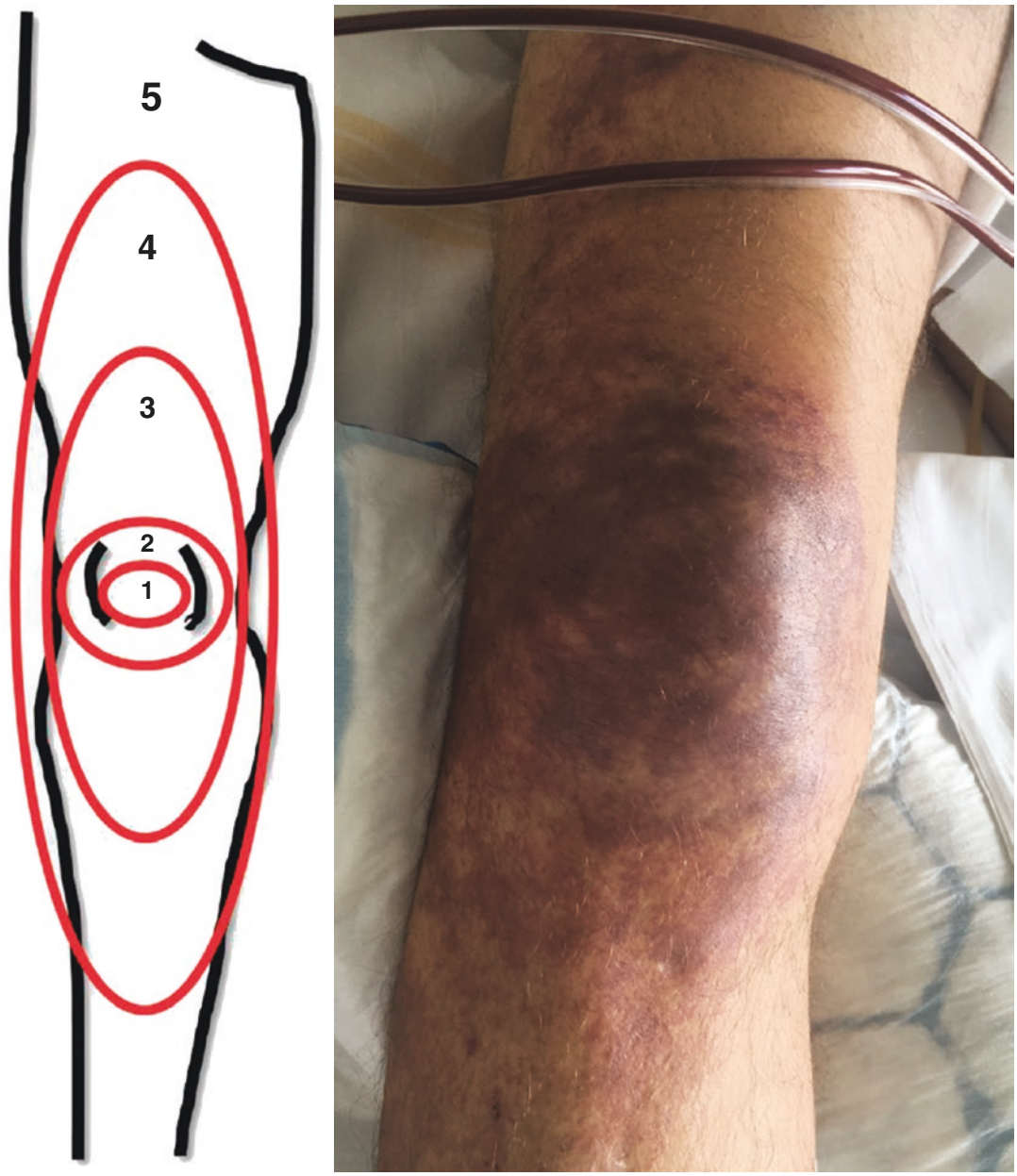

Fig. 23.3 Spread of the skin mottling and mottling score. Legend: Mottling score proposed by Ait-Oufella [2] describes the area of hypoperfused skin of the knee/lower leg area in defined five stages (left panel). Picture of stage 3 mottling in a patient with septic shock (right panel)

defined (normal CRT is described as 2.3–4.5 s after compression of the index/middle finger's distal phalanx lasting 5 s [3]). Examination of the CRT can be complicated in profound hypothermia or pre-existing peripheral vascular disorders. Another easily obtainable marker of hypoperfusion is oliguria, especially in the first hours of shock. The usual definition is urine production less than 0.5 mL/kg/h for more than 3 h. However, oliguria is a nonspecific marker with limited use in the presence of established kidney disease or diuretics intake.

23.2.2 Point-of-Care and Laboratory Evaluations

Point-of-care ultrasound (POCUS) is nowadays almost a mandatory part of the clinical examination in the critically ill. Its repeatability and the steep learning curve permit rapid diagnosis of the hypovolemia and the shock type. Different simplified ER and ICU protocols were developed (*e.g.,* eFAST, FEEL, RUSH). In hypovolemia, basic echocardiography examination shows poor ventricular filling often coupled with hypercontractile wall motions (called "kissing ventricle") and small diameter/collapse of the inferior vena cava. The main benefit of POCUS is immediate recognition and differential diagnosis of other low flow/shock types: heart failure (ventricular dysfunction, valvular disease), cardiac tamponade, pulmonary embolism (enlarged right heart), and tension pneumothorax [4]. In traumatic patients, eFAST became a standard of care over the last years.

Practical Advice

- Clinical examination together with ultrasound is a cornerstone for rapid identification of the hypovolemia.
- Three clinical "shock windows" are mentation, skin perfusion, and diuresis.
- Capillary refill time and skin mottling score are fast and clinically verified indicators of peripheral vasoconstriction and low cardiac output.

Laboratory diagnostics, especially point-of-care (POCT) methods, bring important insight into blood gases, acid-base state, blood count, and clot formation. Hypoperfusion in hypovolemic shock, causing inadequate CO and oxygen delivery, leads to acute metabolic (lactate) acidosis, manifested by low pH and base deficit. Increased oxygen extraction is measurable as a decrease in central venous oxygen saturation. Increased lactate production, presumably caused by tissue hypoperfusion, is traditionally used as a marker of shock severity. Its changes in shock and adequate clearance may serve as a target of the volume resuscitation [5]. One has to note that adrenergic activation *per se* may lead to increased lactate production even without tissue hypoperfusion. More profound acidosis (pH < 7.1) is better to correct with the buffer solution because enzymatic processes in the body (*i.e.,* blood clotting and vasopressor effect) are tightly dependent on pH. Contrary, in the case of milder acidosis or the absence of severe clinical manifestations, the use of the bicarbonate buffer is controversial due to risk of induced intracellular acidosis.

In hemorrhagic shock, frequent analysis of hemoglobin/hematocrit and platelet count is essential to guide blood products substitution. In the past years, POCT clotting analysis, based on viscoelastic methods (VEM)—thromboelastography (TEG) and rotational thromboelastometry (ROTEM)—has changed completely the therapeutic approach of the hemorrhagic shock. These methods allow tailored therapy with targeted substitution of platelets, fibrinogen, and clotting factors.

Analysis of osmolality, ion levels in blood and urine, as well as blood-urea-nitrogen and creatinine levels can bring important information about the underlying pathologic processes—especially in cases of non-hemorrhagic hypovolemic shock. Isolated urea elevation with normal creatinine, reduced excretion of the water, and sodium retention are the classical picture of incipient renal failure, caused by hypovolemia. In the established critical illness, sodium balance and fractional excretion have very complex regulation, and the analysis of these processes is of limited use [6].

23.2.3 Standard Non-invasive Monitoring

Basic monitoring techniques (ECG, non-invasive blood pressure, pulse oximetry) confirm clinical suspicion on shock state. Pulse oximetry is working properly even in deep anemia [7] but brings only limited information on the adequacy of oxygen delivery. Measurement can be unreliable or impossible due to hypothermia, peripheral vasoconstriction, and hypoperfusion. Non-invasive blood pressure (BP) measured by the oscillometric technique is a standard initial examination. Drop in the BP, with narrowing of the pulse pressure, caused by reduced CO and increase of the systemic vascular resistance, is usually found. Hypotension can be less pronounced in the early phase of the hypovolemic shock. Blood pressure drop is compensated in many cases and can be a sign of developed shock in some populations like children and pregnant [8]. Limitation of the oscillometric method is poor accuracy in deeper hypotension when the measurement can be overestimated [9]. Shock index, a ratio of the heart rate (HR) and systolic BP, or modified shock index (ratio of HR and mean arterial pressure) can be easily calculated and is a good predictor of the hemorrhagic shock presence [10].

Practical Advice

- Hypovolemic shock can be already developed despite normal blood pressure.
- Hypotension in hypovolemia is a sign of significant patient deterioration and exhausted compensatory regulations.
- Shock index (HR/BP > 0.9) is an easy-to-use indicator of the decompensation in hypovolemia.

23.2.4 Invasive Monitoring

Signs of protracted hypoperfusion after initial fluid loading and vasopressor support are usually a stimulus for escalation to invasive pressure monitoring. Although radial artery cannulation is a standard approach in most units, there is evidence of inaccurate measurement in patients requiring high-dose catecholamine support [11]. Therefore, more proximal artery (mostly femoral) is a better choice in severe shock. Most modern monitors allow automatic calculation of pulse pressure variation, which can be used as a predictor of fluid responsiveness in mechanically ventilated patients. Normal arterial access also allows the use of uncalibrated CO monitoring. For a long time, central venous pressure (CVP) has been believed to reflect the fluid status and is still recommended as a fluid resuscitation target by Surviving Sepsis Guidelines [12]. However, CVP is under the influence of many factors and has very poor correlation with intravascular volume, cardiac output, and fluid responsiveness [13]. Currently, CVP should not be used as a target of fluid therapy but can be applied as a safety limit with the absolute high values (12–15 mmHg) or the rise of 3–5 mmHg after a fluid bolus as markers of the possible fluid overload.

23.2.5 Advanced Hemodynamic Monitoring

During the resuscitation phase, advanced hemodynamic monitoring is usually not necessary. However, after patient's salvage, it may be difficult to find the right balance between further fluid administration and use of other pharmacological support. Advanced hemodynamic monitoring has been demonstrated to enable better recognition of actual therapeutic goals in hypovolemic or trauma patients [14]. Non-calibrated pulse wave analysis hemodynamic monitors or esophageal Doppler may be used for trending. However, in complex cases, the calibrated devices, mostly transpulmonary thermodilution (TD) monitoring systems (PiCCO, VolumeView), offer more reliable hemodynamic parameters. Static volumetric parameters of preload (like intrathoracic blood volume or global end-diastolic volume) can amend the picture of fluid status, although their correlation with fluid responsiveness is only slightly better than CVP [15]. Other TD-derived

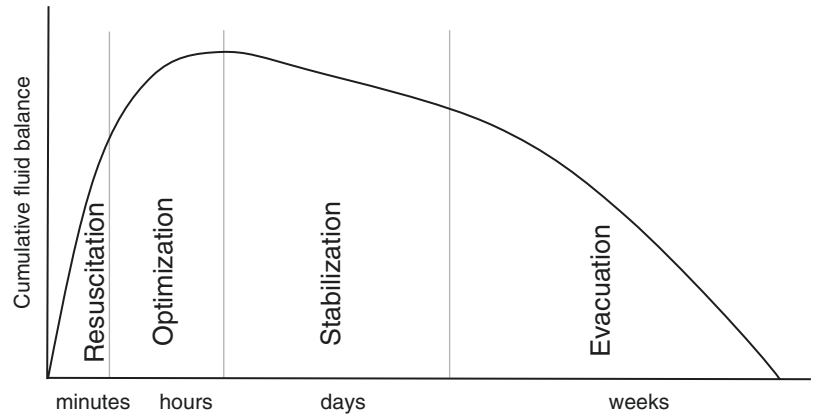

Fig. 23.4 ROSE concept of the fluid therapy. Legend: Four stages of the ROSE concept describing the extent of the cumulative fluid balance over the course of time/illness

parameters, namely, extravascular lung water and pulmonary vasculature permeability combined with continuous pulse wave analysis, can provide valuable information in complex shock complicated by ARDS and pulmonary edema (*e.g.,* in sepsis, brain injury, large pulmonary contusions, near drowning, burns) for guiding fluid and vasopressor therapy [see Chap. 26].

23.3 Treatment of the Hypovolemic Shock

23.3.1 Treatment Goals and ROSE Concept

In hypovolemic shock, rapid recognition and treatment of the underlying cause are the most important therapeutic interventions. Along with that, restoration of the circulating volume with intravenous fluids or blood products is indicated. However, overzealous fluid administration may be harmful leading to hemodilution, promoting endothelial dysfunction and tissue edema. This idea was incorporated also in the resuscitation-optimization-stabilization-evacuation (ROSE) concept proposed by Manu Malbrain [16] (Fig. 23.4), which is focused on adequate and minimal necessary fluid therapy. Thus, separating the treatment of hypovolemic patient into these four distinct phases of hemodynamic care deserves major attention.

Resuscitation (called also "salvage" by some) is a short period of initial management. Within this phase, the patients should never be left alone, without the close supervision of the treating team. Only basic monitoring, clinical evaluation and ultrasonography are usually needed at this moment. In the case of apparent hypovolemic shock, boluses of 250–500 mL of crystalloids should be given, with a careful check of effect. Early use of blood products and aggressive treatment of the hypothermia and acidosis is warranted in actively bleeding patients, simultaneously with damage control surgery. The target in the resuscitation phase is to reach the lowest perfusion pressure within the autoregulation range (mostly 60–65 mmHg). Early co-administration of vasopressor (norepinephrine as a first-line) is often beneficial to reach sufficient BP but can contribute to significant visceral and peripheral vasoconstriction. In the case of hemorrhagic shock caused by penetrating or blunt trauma, the concept of permissive hypotension (systolic BP target >90 mmHg in the absence of brain injury) and fluid restriction leads to lower mortality. General targets for resuscitation are summarized in Table 23.3.

Practical Advice

- Every fluid bolus applied to the patient has to have a defined therapeutic target and safety measure.
- Treatment goals differ in dedicated phases of therapy based on the ROSE concept.

Optimization phase is the moment when initial goal to save the patient life is already achieved: bleeding is controlled, minimal perfusion pressure is reached, and flow into vital organs is

Table 23.3 Resuscitation targets

SBP ≈ 90–100 mmHg, MAP ≈ 60–65 mmHg in the absence of acute brain injury
HR < 110/min
CI > 2.0–2.5 L/min/m^2 (measured directly in few cases)
Lactate and $ScvO_2$ (first check of values)
CRT and skin mottling: Reversal of the worst pathology
Hemoglobin about 10 g/dL in the case of ongoing bleeding 7–9 g/dL in non-bleeding subjects
Normal coagulation parameters, ideally guided by VEM

SBP systolic blood pressure, *MAP* mean arterial pressure, *HR* heart rate, *CI* cardiac index, *$ScvO_2$* oxygen saturation of the central venous blood, *CRT* capillary refill time, *VEM* viscoelastic methods

restored. Unlike the resuscitation phase, which usually lasts minutes, optimization takes normally hours to reach the right balance. The cornerstone is the concept of fluid responsiveness, fluid challenge, and mindful examination of the balance between preload, contractility, and afterload. Only fluid, which results in CO rise, should be administered, but the increase in CO should never be chased only for itself. Prior any fluid administration, we should be well aware of hemodynamic targets (CO/DO_2 rise, normalization of peripheral perfusion, CRT, lactate levels) and safety measures (defined CVP increase, extravascular lung water value) (Table 23.4). This practice is very important and, according to FENICE trial [17], still not widely accepted in daily care. Fluid responsiveness is a physiological state, and in case of sufficient oxygen delivery, CO should not be overresuscitated to "supranormal" values. It is important to note that in some cases (especially in chronic hypovolemia and in patients with low cardiovascular reserves), too fast application of fluid boluses aiming at rapid normalization of perfusion can easily lead to ventricle overload, loss of vasoreactive compensatory regulations, and devastating results at the end.

Stabilization and evacuation (de-escalation) phases are less well defined especially in terms of time frames and treatment targets. Daily fluid balance should play an important role as well as global behavior of the circulation, dependence on vasoactive drugs, and resolution of the primary insult. Active evacuation of the fluid surplus is necessary for some patients using diuretics or renal replacement therapy.

Table 23.4 Possible optimization targets

SBP/MAP ≈ patients' normal values ±20%
HR ≈ 70–90/min
CI > 2.5 L/min/m^2; SVI > 30–35 mL/m^2; DO_2I 400–600 mL/min/m^2
PPV/SVV ≈ 15% (in case of mechanical ventilation and regular heart rhythm)
Lactate and $ScvO_2$ normalization
CRT and mottling normalized
Hemoglobin ≈ 7–9 g/dL (higher in specific population)
Normal coagulation parameters, consider thromboprophylaxis
Safety margins: CVP rise >3 mmHg/absolute value >12 mmHg EVLWI >15 mL/kg while PVPI ≤2.5; EVLWI >10 mL/kg while PVPI >3

SBP systolic blood pressure, *MAP* mean arterial pressure, *HR* heart rate, *CI* cardiac index, *SVI* stroke volume index, *DO_2I* oxygen delivery index, *PPV* pulse pressure variation, *SVV* stroke volume variation, *$ScvO_2$* oxygen saturation of the central venous blood, *CRT* capillary refill time, *CVP* central venous pressure, *EVLWI* extravascular lung water index, *PVPI* pulmonary vascular permeability index

23.3.2 Types of Fluids

Fluid selection depends on the pathophysiologic cause of the central hypovolemia, but crystalloid solutions are the first choice in most situations. The most widely used normal saline (NS) is an isotonic solution of sodium chloride, containing 154 mmol/L of both ions. Large volumes of infused NS are associated with hyperchloremic metabolic acidosis and possibly cause acute kidney injury by the constriction of afferent arterioles. Unfortunately, this was not confirmed in any outcome-centered randomized trial [18], and the NS remains widely used as a fluid of choice in non-European countries. Normal saline is indicated in situations with sodium and chloride depletion, *e.g.,* caused by losses from the upper gastrointestinal tract. It is also recommended by guidelines in hypovolemia associated with the diabetic ketoacidosis [19], but the evidence is lacking.

Buffered or balanced solutions (Ringer lactate (LR), Hartmann's solution, *etc.*) were developed with the idea to reduce chloride content and approximate the constitution of the solution to plasma. To preserve electroneutrality, different, mostly metabolizable, organic acids (*i.e.,* lactate, gluconate, or acetate) replace chlorides. There are small differences in ion contents, mainly in

sodium, calcium, and magnesium, but the clinical impact is dubious if any. Only rational risk is low sodium level in LR and its relative hypotonicity when used in patients with acute brain injury.

Colloids represent currently the most controversial part of fluid therapy. These solutions have been used to allow more effective and long-lasting plasma expansion with larger molecules and its oncotic effect. Unlike in theory based on body fluids compartmentalization, these effects were never demonstrated in clinical reality [20], at least at hemodynamic stability endpoint. Hydroxyethyl starches (HES), most popular colloid solutions in the past years, were restricted for use in critically ill by the FDA and EMA [21]. Accumulating evidence from large randomized studies showed a higher incidence of renal failure and the need for renal replacement after HES administration. Gelatin shares many adverse effects with HES, but due to less usage, most evidence comes from animal and *in vitro* studies. Historically, the possible association with anaphylaxis and long storage in the reticuloendothelial system is noticed [22]. Although gelatin is still used in many countries, its application is avoidable and arguable based on current evidence. Summarized, probably the only acceptable indication for synthetic colloids is hypovolemia from acute blood loss, in the case of blood derivatives unavailability.

Practical Advice
Balanced crystalloid or NS is fluid of choice for most cases of hypovolemic shock.

Nowadays, human albumin is the most used natural colloid solution in critical care due to restrictions of synthetic colloids. Albumin is prepared for use as a hyperoncotic (20 or 25%) or iso-oncotic (4 or 5%) solution. Benefits of the albumin administration over crystalloids were never demonstrated by large trials. There is small evidence of possible mortality reduction in cirrhotic patients and patients in sepsis [23, 24]. We should avoid albumin in patients with traumatic brain injury, but the evidence is also not very strong [25]. No clear target plasmatic level of albumin for the substitution can be given.

In the setting of the significant blood loss, oxygen transport capacity is markedly reduced as the hemoglobin level decrease, further contributing to tissue hypoxia. Moreover, coagulation derangement occurs because of the clotting factors consumption, dilution caused by fluid resuscitation, and acid-base disorders. The traditional approach was to start with crystalloid substitution and after insufficient reaction to a specific amount (*e.g.,* 2000 mL as proposed by ATLS algorithm [26]) go on with blood products.

In the 1990s, this scheme has changed; thanks to accumulating evidence as experience coming from the Middle East war showed benefit with early massive transfusion protocols—*e.g.,* early administration of red blood cells (RBCs), plasma, and platelets. The use of larger volumes of crystalloids to normalize perfusion in bleeding patient leads to dilution and worsens coagulopathy and hypothermia. Moreover, normalization of perfusion may increase the bleeding if control of hemorrhage has not been provided. Massive transfusion protocols, consisting of the similar ratio of RBCs, plasma, and platelets (*e.g.,* 1:1:1), together with aggressive treatment of the hypothermia and acidosis were associated with better outcome [27].

Recently, viscoelastic methods have further changed this paradigm with the targeted treatment of coagulation disorders using fibrinogen, platelets, and clotting factors, limiting the use of plasma. Recombinant-activated factor seven (rVIIa), considered to be a "magic bullet" in trauma-induced coagulopathy, is now used only as a last resort and seems to be associated with the long-term thrombotic complications. Maintaining normal pH and ionized calcium is crucial to keep the coagulation system working. Early, even prehospital application of tranexamic acid effectively reduces the rate of hyperfibrinolysis, now with proven minimal side effects [28].

Practical Advice
In hemorrhagic shock, limiting a crystalloid use, early start of the massive transfusion protocol, and damage control resuscitation approach are reasonable. Early application of tranexamic acid is safe and beneficial for outcome.

23.4 Conclusion

Hypovolemic shock is a state of decreased intravascular volume, mainly caused by hemorrhage, resulting in reduced cardiac output. With regular clinical examination together with the point-of-care ultrasound, it is possible to diagnose nearly all cases of hypovolemic shock. Early escalation of monitoring to the more invasive methods is beneficial in the mixed types of shock and poor response to the initial therapy. Fluid therapy with crystalloids and blood in severe bleeding, together with immediate treatment of the underlying cause, is a treatment of choice in hemorrhagic shock. After the resuscitative measures, the amount of given fluid has to be guided by clinical and monitoring targets.

Keynotes

- Hypovolemic shock is characterized by the intravascular volume drop, followed by decreased venous return and low cardiac output. Fall of the oxygen delivery causes tissue hypoxia and, if unopposed, could lead to cellular death.
- Clinical examination and point-of-care ultrasound are the first and often the most important diagnostic tools. Extension of the hemodynamic monitoring to the minimally invasive and invasive methods is useful in mixed types of shock and severe comorbidities.
- Crystalloids are the fluid of choice for the start of treatment. Even at the beginning of the fluid resuscitation, a clear therapeutic target for fluid has to be defined.
- In the case of hemorrhagic shock, damage control resuscitation is indicated. Bedside viscoelastic methods allow to tailor blood therapy in massive bleeding and reduce the amount of applied plasma.

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Cardiogenic Shock

24

Evgeny V. Grigoryev and Sergey M. Efremov

Contents

24.1 Pathophysiology

Cardiogenic shock (CS) is characterized by microcirculatory derangement due to a decrease in cardiac output accompanied by compensatory vasoconstriction. The aim of vasoconstriction is centralization of circulation by mobilization of blood from splanchnic organs and peripheral tissues in order to increase preload and retain blood volume predominantly for vital organ perfusion (*i.e.,* brain and heart). According to a recently

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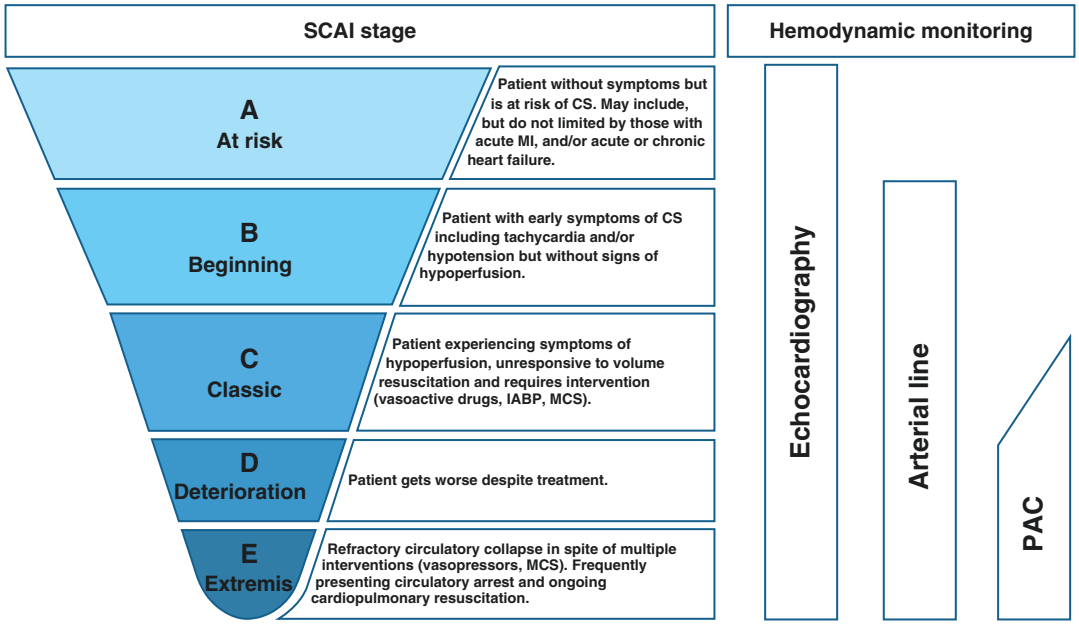

Fig. 24.1 Recommended volume of hemodynamic monitoring according to SCAI stage of cardiogenic shock. *CS* cardiogenic shock, *MI* myocardial infarction, *IABP* intra-aortic balloon pump, *MCS* mechanical circulatory support, *PAC* pulmonary artery catheter

published consensus statement, CS is classified into five stages labeled A–E (Fig. 24.1) [1].

Activation of microcirculation is generally considered as an essential component of microcirculatory alterations in shock. The process of microthrombi formation is associated with fibrin deposits in microvessels, reduced antithrombin level, decreased number of perfused capillaries, development of systemic inflammation, cell activation, and endothelial damage [2, 3].

Activated platelets and leukocytes play a key role in the onset of microcirculatory alterations. They roll and firmly adhere to the endothelial lining, disrupting the normal transit of cells through the microcirculation. A loss of deformability in red blood cells (RBCs) and subsequent nitric oxide production result in the adhesion of damaged RBCs to the endothelium, causing relaxation of the arteriolar smooth muscles [4, 5]. Thus, CS is often accompanied by multiple organ dysfunction [6]. Typical pathophysiologic causes of CS are presented in Fig. 24.2.

24.2 Microcirculatory Monitoring

24.2.1 Indirect Signs of Microcirculatory Alterations

Lactate and venous-to-arterial gradient of carbon dioxide are the most frequently used markers of microvascular perfusion, inversely related to cardiac output [7–9].

Practical Advice
The probability of increased serum lactate without hypoperfusion as well as the presence of hypoperfusion without hyperlactatemia should be considered.

Contrast-enhanced ultrasound perfusion imaging is a novel promising method for assessing microcirculatory perfusion. Contrast

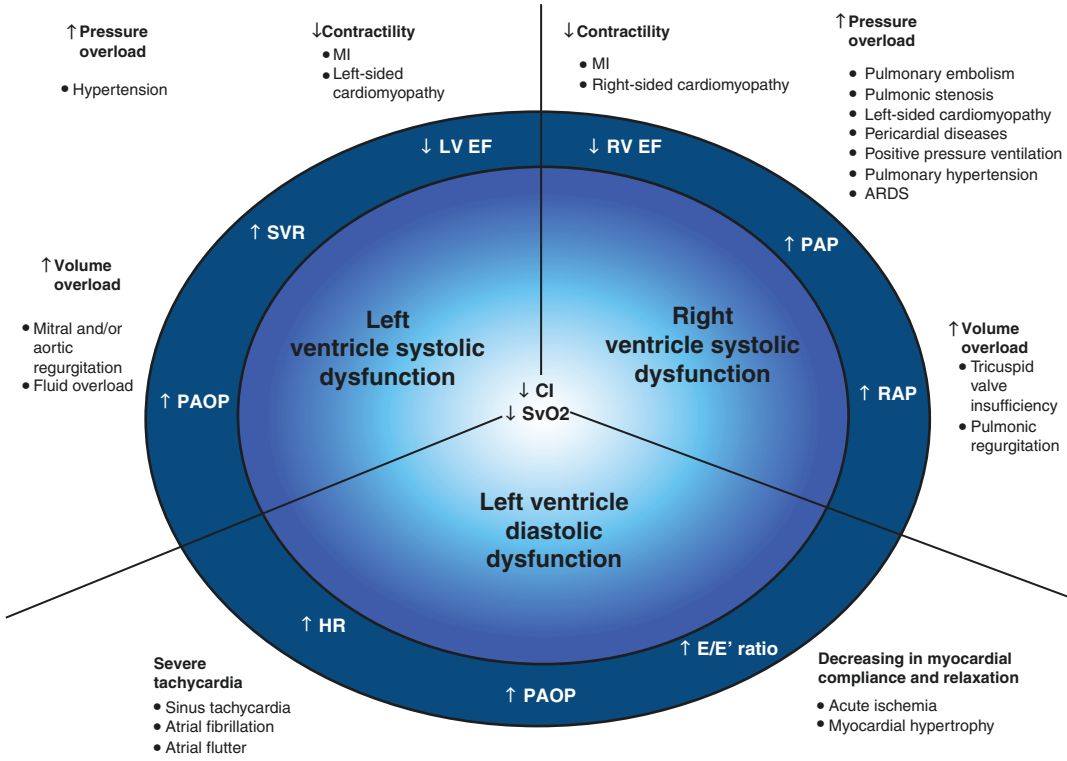

Fig. 24.2 A schematic presentation of possible causes of cardiogenic shock. Legend: Most common causes and typical signs of cardiogenic shock are presented. Adapted from [43]. *ARDS* acute respiratory distress syndrome, *CI* cardiac index, *E* early flow velocity at the level of the mitral valve, *E′* early velocity of the mitral annulus (myocardial Doppler imaging), *EF* ejection fraction, *HR* heart rate, *LV* left ventricle, *PAP* pulmonary artery pressure, *PAOP* pulmonary artery occlusion pressure, *RAP* right atrial pressure, *RV* right ventricle, *SVR* systemic vascular resistance, SvO_2 mixed venous oxygen saturation, *MI* myocardial infarction

enhancement in the organ (most often the kidney and liver) depends on cardiac output and perfusion in a region of interest. The limitations of method include the risk of contrast-induced nephropathy, the heterogeneity of microcirculation in the organ, the inability to assess regional perfusion, and the operator dependence [10].

Laser Doppler flowmetry and near-infrared spectroscopy allow measurement of regional blood flow and oxygen saturation of hemoglobin in a region of interest. However, the application of both methods is limited by the heterogeneity of the skin and organ microcirculation [11–13].

24.2.2 Vasoreactivity Testing

Vasoreactivity testing allows the evaluation of maximum vasodilation in response to physical stimuli (*e.g.,* temperature or temporary limb compression). A decrease in the rate of restoration of vasoreactivity may correlate with the severity of organ dysfunction. However, this method is limited by the assessment only in one region and by dependence on different causes violating the blood supply to the limbs, such as chronic ischemia.

24.2.3 Video Microscopy

Intravital video microscopy is the gold standard technique for studying microcirculation, as it allows direct assessment of microcirculatory perfusion and imaging of microcirculatory tissue beds. To date, a variety of technologies have been used, including orthogonally polarized spectroscopy, incident dark-field illumination, and side-

stream dark-field microscopy. All these techniques are based on high-penetration sharp contour visualization of the microcirculation and red blood cells through the reflected direct light. The probe is commonly placed under the tongue. The lack of a proven correlation between sublingual microcirculatory perfusion and microvascular circulation in other organs remains an issue of concern. None of the devices allows direct visualization of blood circulation [14–19].

Despite a large number of methods for studying microcirculation, the authors have not chosen any specific option for microcirculatory monitoring in critically ill patients. Moreover, there are currently no existing algorithms that would consider microcirculatory alteration as one of the factors for selecting the treatment strategy.

The alteration in oxygen extraction is a well-known clinical consequence of shock. Thus, a 50% reduction in capillary density, leading to heterogeneous blood flow, is associated with a decrease in oxygen consumption and, consequently, tissue hypoxia resulting from increased distance for oxygen diffusion. It is assumed that the restoration of microcirculation depends not only on increasing oxygen delivery to normal levels but also on the effectiveness of the microcirculatory recruitment, which is needed to ensure the restoration of homeostasis with a decrease in shunting, normalization of intravascular coagulation, and attenuation of cell activation.

24.3 Hemodynamic Profiles and Considerations for the Initial Treatment of Cardiogenic Shock

Vasoactive support is the first-line therapy of CS aimed at improving contractility, preload, and afterload. The effects of this therapy depend on maintenance of normal acid–base status, electrolyte balance, normothermia, and ventilation. A summary of commonly used inotropes and vasopressors is provided in Table 24.1.

Common hemodynamic characteristics according to shock type are presented in Table 24.2.

Practical Advice
Surgical or percutaneous transcatheter treatment of CS should always be considered when applicable.

24.3.1 Classic "Wet and Cold" Cardiogenic Shock

This is the most frequent phenotype of CS, accounting for the majority of myocardial infarction (MI)-associated CS. Absolute cutoffs of cardiac index (CI) are likely to be clinically impractical and a threshold of <1.8–2.2 L/min/m^2 should be used in combination with assessment of signs of end-organ hypoperfusion [20]. Available data suggest norepinephrine as the first-line vasopressor for the treatment of classic CS [21–23]. Dobutamine is also recommended for initial treatment of classic CS and is commonly used in combination with norepinephrine. Dopamine may also be considered in bradycardia, but it increases the risk of arrhythmia. Diuretics and/or ultrafiltration are necessary to decrease pulmonary artery occlusion pressure (PAOP) and normalize filling pressures in all "wet" types of CS. Furthermore, PAOP and right atrial pressure (RAP) are stronger predictors of outcomes than CI in patients with advanced heart failure [24].

24.3.2 Euvolemic "Cold and Dry" Cardiogenic Shock

This type of CS is typically present in patients with subacute chronic heart failure (CHF) decompensation. However, MI also accounts for euvolemic CS in nearly 30% of cases [25]. Euvolemic CS is less likely to be associated with

Table 24.1 Properties of vasoactive agents

Medication	Dosages	Receptors				Effects	Side effects
		α_1	β_1	β_2	D		
Drugs, recommended for initial treatment of CS							
Norepinephrine	0.05–0.4 μg/kg/min	++++	++	+	–	↑↑SVR, ↑CO	
Dobutamine	2.5–20 μg/kg/min	+	++++	++	–	↑↑CO, ↓SVR, ↓PVR	Arrhythmia, tachycardia
Drugs, may be used for improving hemodynamics in CS							
Levosimendan	0.05–0.2 μg/kg/min	Myofilament Ca^{2+} sensitizer				↑CO, ↓SVR, ↓PVR	Arrhythmia, hypotension
Milrinone	0.125–0.75 μg/kg/min	PD-3 inhibitor				↑CO, ↓SVR, ↓PVR	Arrhythmia, hypotension, thrombocytopenia (less than enoximone)
Vasopressin	0.02–0.04 U/min	V_1 receptors of vascular muscle				↑↑SVR, ↔PVR	Myocardial ischemia, ventricular arrhythmia
Isoproterenol	2.0–20 μg/min	–	++++	+++	–	↑↑CO, ↓SVR, ↓PVR	Arrhythmia, tachycardia
Drugs, not recommended for initial treatment of CS							
Epinephrine	0.01–0.5 μg/kg/min	++++	++++	+++	–	↑↑CO, ↑↑SVR	Lactic acidosis, hyperglycemia, splanchnic ischemia
Dopamine	0.5–2 μg/kg/min	–	+	–	+++	↑CO	May worsen renal injury in CS
	5–10 μg/kg/min	+	+++	+	++	↑↑CO, ↑SVR	Tachycardia
	10–20 μg/kg/min	+++	++	–	++	↑↑SVR, ↑CO	Arrhythmia, tachycardia

Adapted from Ref. [20]
Abbreviations: *CS* cardiogenic shock, *PD* phosphodiesterase, *CO* cardiac output, *SVR* systemic vascular resistance, *PVR* pulmonary vascular resistance

Table 24.2 Typical hemodynamic profiles of different types of cardiogenic shock

Variable	Classic "wet and cold" CS	Euvolemic "cold and dry" CS	Mixed vasodilatory "warm and wet" CS	Right ventricular shock	LV diastolic dysfunction	Normotensive CS
SAP, mmHg	< 90					>90
CI, L/min/m^2	< 2.2					
PAOP, mmHg	⇑	⇔	⇑	⇓ ⇔	Variable	Variable
SVR, dynes-s/cm^{-5}	⇑	⇑	⇓ ⇔	⇔ ⇑	⇔ ⇑	⇔ ⇑
CVP, mmHg	⇔	⇔	⇔	⇑	⇔	⇔
PAPi	⇔	⇔	⇔	⇑	⇔	⇔

SAP systolic arterial pressure, *CI* cardiac index, *PAOP* pulmonary artery occlusion pressure, *SVR* systemic vascular resistance, *CVP* central venous pressure, *PAPi* pulmonary artery pulsatility index defined as the ratio of PA pulse pressure (PA systolic pressure minus PA diastolic pressure) to right atrial pressure: (PAS − PAD)/RAP

previous MI and chronic kidney disease. Initial vasoactive therapy considerations for euvolemic CS are similar to those of classic CS. In CS caused by decompensation of CHF, the most important predictors of outcomes reflect the volume state, specifically PAOP and RAP [24].

24.3.2.1 Mixed or Vasodilatory "Warm and Wet" Cardiogenic Shock

Systemic inflammation is associated with different causes of CS, including MI, CHF, and cardiac surgery [26–28]. Low systemic vascular resistance index (SVRI) typical for systemic inflammation is associated with an increased risk of sepsis and mortality [29]. Norepinephrine is a first-line drug for hemodynamic support of patients with vasodilatory CS.

24.3.2.2 Right Ventricular Shock

Prevalence of RV shock is relatively uncommon and reported in 5.3% of patients with MI-related CS [30]. As pulmonary artery pressure (PAP) is one of the main targets in the management of RV dysfunction, the pulmonary artery catheter (PAC) is very useful in guiding the treatment. Fluid boluses are commonly well tolerated by patients with RV shock. Pulmonary-inhaled vasodilators should always be considered for the treatment of RV shock. Vasopressin is a reasonable vasopressor for RV shock management as it has a neutral effect on pulmonary vascular resistance (PVR) [31, 32]; however, this statement is contradictory [33].

Milrinone is an appealing agent for use in RV shock because of its combined characteristics of an inotrope and a pulmonary vasodilator [34, 35].

Practical Advice

Decreasing the LV preload with diuretics, nitrates, and noninvasive ventilation are common initial therapeutic approaches in LV dysfunction. Decreasing the RV afterload is a primary goal in the therapy of RV dysfunction.

24.3.3 Normotensive Cardiogenic Shock

This is another uncommon type of CS occurring in 5% of cases [20]. Normotensive CS may reflect SCAI stage B pre-shock (normotensive hypoperfusion), and PAC may be critically important for diagnosing the CS at the early stage of compensation [1]. However, routine use of PAC is not recommended for normotensive patients with congestion because of acute heart failure decompensation, who are responsive to initial treatment

with diuretics and vasodilators [36]. Considering that normotensive CS is associated with relatively high SVR, dobutamine is the first-line inotropic agent used for perfusion restoration. Normotensive CS is associated with a lower risk of mortality than classic CS, but it poses a higher risk of the same than that in hypotensive cases with no signs of hypoperfusion [37].

24.3.4 Cardiogenic Shock Caused by Left Ventricle Diastolic Dysfunction

Diastolic dysfunction of the LV is a state of diminished LV contractile function accompanied by preserved global systolic performance. This state is characterized by the inability of LV to accept an adequate diastolic blood volume despite normal preload [38].

The utility of PAC is limited by the inability to measure LV pressure and transmitral flow. Echocardiography is a validated and practical tool for assessing LV diastolic function [39]. Maintaining filling pressures (fluid boluses), systemic vascular resistance (norepinephrine), atrioventricular synchrony, and prevention of tachycardia (beta blockers) are the main initial treatment options. The use of inotropes as first-line drugs should be avoided. However, when heart filling, heart rate, and afterload are controlled, inotropes with lusitropic effects (levosimendan and milrinone) may be considered [40].

24.3.5 Heart Valve Diseases

Cardiogenic shock caused by aortic stenosis is afterload-dependent, for which initial treatment with vasopressors (norepinephrine of vasopressin) is commonly recommended. Addition of dobutamine should be considered when aortic stenosis is associated with reduced left ventricular ejection fraction (LVEF). It is also recommended to guide inotropic therapy by PAC in these cases [20].

Therapy of CS caused by aortic regurgitation is aimed at decreasing left ventricular end-diastolic filling. Thus, temporary pacing and inotropes with chronotropic effects (dopamine) may be appropriate for initial treatment.

In contrast, CS caused by mitral stenosis is a preload-dependent state and requires prolonged diastole to maintain sufficient end diastolic LV volume. Thus, chronotropic agents should be avoided. Phenylephrine and vasopressin can be used in combination with beta blockers (esmolol) and amiodarone.

Mitral regurgitation as a result of organic valve disease or MI may be complicated by CS. Therapy targeted to decrease the LV afterload commonly helps to improve CI and decrease the regurgitation fraction. Administration of intra-aortic balloon pump can be useful in the treatment of CS with mitral regurgitation as it decreases afterload and improves systemic perfusion [41].

Practical Advice

The insertion of pulmonary arterial catheter is recommended when initial CS therapy is not effective [1].

24.3.6 Hemodynamic Monitoring during Mechanical Circulatory Support in Cardiogenic Shock

In all patients with CS undergoing or planning MCS, the use of PAC can be helpful to guide the therapy. Hemodynamic monitoring is highly useful for initial decision-making and when choosing the type of MCS that best matches the needs of a particular patient. Pulmonary artery catheter is critical for the effective monitoring of MCS and necessary for its escalation or combination. As an example, elevation of PAOP during initiation of venoarterial extracorporeal membrane oxygenation (ECMO) resulting from an increase in left ventricle end-diastolic pressure may indicate the need for implantation of left ventricle assist device (such as Impella) in addition to ECMO. Furthermore, PAC is important for weaning and assessment of prognosis in patients

requiring MCS and for considering MCS as a bridge for heart transplantation [42].

24.4 Conclusions

Advanced hemodynamic monitoring could be critical for timely diagnosis, appropriate management, and prognosis of patients with CS. The volume of monitoring and utility of derived data are highly dependent on the etiology and stage of CS. Blood lactate and venous-to-arterial carbon dioxide ratio are affordable and routinely used methods, whereas direct methods of microcirculation assessment have a limited clinical use. Patients with CS receiving PAC represent a higher risk cohort with worse prognosis, highlighting the importance of hemodynamic monitoring in clinical evaluation.

Keynotes

- Cardiogenic shock is a clinical entity characterized by inadequate tissue perfusion resulting from primary myocardial dysfunction.
- There are no currently existing algorithms that would consider microcirculatory alterations as one of the factors for selecting the treatment strategy.
- Vasoactive support is the first-line therapy of CS.

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Distributive Shock

25

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Contents

25.1 Introduction

Distributive shock (DS), which is also known as vasodilatory shock, is the type of shock in which tissue dysoxia occurs mainly due to the loss of vasomotor tone in the absence of primary cardiac dysfunction and severe hypovolemia [1–3].

Distributive shock can be caused by different etiological factors: sepsis, anaphylaxis, endocrine, and neurogenic abnormalities—all these conditions lead to profound vasoplegia mainly involving venous part of the microcirculation and result in tissue hypoperfusion. Although DS occurs under different physiological abnormalities, its hemodynamic pattern is usually similar

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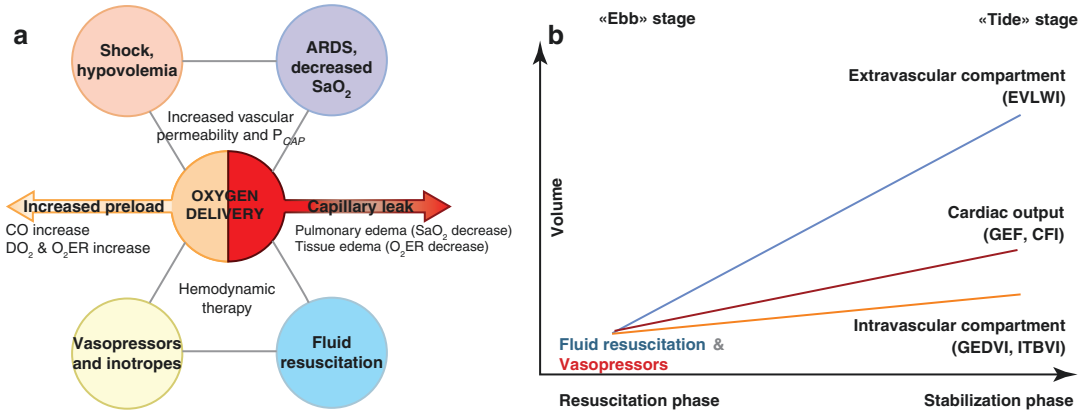

Fig. 25.1 Panel (**a**) The balance between preload and pulmonary edema. Panel (**b**) The dynamic changes in the body compartments in distributive shock. *CO* cardiac output, SaO_2 arterial oxygen saturation, O_2ER oxygen extraction ratio, DO_2 oxygen delivery, P_{CAP} pulmonary capillary pressure, *ARDS* acute respiratory distress syndrome, *EVLWI* extravascular lung water index, *GEF* global ejection fraction, *CFI* cardiac function index, *GEDVI* global end-diastolic volume index, *ITBVI* intrathoracic blood volume index

and includes low systemic vascular resistance (SVR), normal-to-high cardiac output (CO), and, in some cases, increased stroke volume (SV). Of note, DS is the only type of shock associated with primary decrease in SVR and eventually hyperdynamic state [3–7].

25.2 Epidemiology

Undoubtedly, DS shock is the most common type of shock in critically ill patients. A study published by De Backer et al. has revealed that DS occurred in 68% of patients with dysoxia, when 62% of patients had septic shock and only 4% demonstrated other etiology of DS [8].

25.3 Etiology

Septic shock represents the most frequent cause of DS and is defined as a combination of sepsis-induced hypotension requiring vasopressors infusion despite adequate fluid resuscitation and hyperlactatemia [9]. Other etiological factors of DS resulting in severe systemic inflammatory response syndrome (SIRS) or "cytokine storm" include severe necrotizing pancreatitis, anaphylaxis, endocrine (*e.g.,* acute severe adrenal insufficiency), and neurogenic disorders [2, 3, 10, 11]. Neurogenic shock results from injury to the spinal cord or severe brain injury and is associated with the loss of sympathetic tone and an unopposed parasympathetic response [12]. Distributive shock can also be caused by ischemia-reperfusion injury (reperfusion shock after cardiopulmonary bypass, patients with a massive acute myocardial infarction or prolonged cardiopulmonary resuscitation) [10, 13–15].

25.4 Pathophysiology

Distributive shock is associated with profound vasodilation (vasoplegia, vasorelaxation) affecting primarily the venous segment of the systemic circulation. This condition is associated with organ dysfunction, endothelial injury, and cellular dysregulation. The key pathophysiological features of DS are as follows (Fig. 25.1):

- Unfavorable redistribution of blood flow (opening of precapillary arterial-venous systemic and pulmonary shunting)
- Impaired cellular oxygen consumption and extraction (dysoxia) due to microcirculatory-mitochondrial distress syndrome (MMDS)

- Increased capillary permeability and capillary leak syndrome, leading to relative hypovolemia due to the shift of fluid and plasma proteins into the interstitial space
- Impaired humoral regulation of vascular tone involving hypothalamic-pituitary-adrenal axis, decreased sensitivity of alpha-adrenergic receptors (mainly venous α_1), vasopressin receptors (V_1), angiotensin-2 receptors (AT-2), and nuclear glucocorticoid receptors
- Relative and/or absolute deficiency of endogenic vasopressors
- Enhanced production of endogenous vasodilators (nitric oxide—NO), cytokines (interleukins-1 and -6, tumor necrosis factor), and inflammatory mediators, changes in cellular signaling
- Severe immunosuppression and dysregulation of the immune response
- Dysregulation of the circulation by central sympathetic mechanisms (brain)

Hemodynamic pattern of DS includes the decrease in SVR, systolic, mean, and, particularly, diastolic arterial blood pressure (often associated with an increased pulse pressure). In many cases, especially in young patients, an increased cardiac output (CO) can be observed related to either tachycardia or, less commonly, an absolute increase in stroke volume. This specific hemodynamic pattern readily distinguishes DS from other types of shock and facilitates differential diagnosis [16–20].

Practical Advice
The distributive shock is the most common type of circulatory shock in critically ill and is the only type associated with primary decrease in systemic vascular resistance.

The most frequent organ dysfunctions in DS are acute kidney injury, cardiomyopathy (mainly primary diastolic dysfunction), acute respiratory distress syndrome, and disseminated intravascular coagulopathy (Table 25.1). Metabolic signs of dysoxia associated with impaired oxygen extraction and MMDS include hyperlactatemia, as well as increased central venous saturation ($ScvO_2$) and venoarterial carbon dioxide gradient ($Pv–aCO_2$) [21–23]. Hypervolemia and tissue edema that are typical for DS can further promote organ dysfunction and tissue hypoperfusion (Table 25.1).

Table 25.1 Organ-specific symptoms of distributive shock and complications of capillary leak and fluid overload

Organ	Symptoms	Effects of edema/"polycompartment" syndrome	Comments
Central nervous system	Delirium, cognitive function impairment, agitation, or decreased level of consciousness	• Brain edema and increased ICP • Cognitive dysfunction and delirium • Increased intraocular pressure • Stroke	Often, central nervous system dysfunction is one of the earliest organ-specific signs (*e.g.,* sepsis in the elderly!)
Cardiovascular system	Hypotension (MAP <65 mmHg or a decrease of BP more than 40 mmHg from the baseline values) and tachycardia are often observed. Possible signs of local ischemic injury/ myocardial necrosis	• Edema of myocardium. Diastolic dysfunction and disorder of contractility. Myocardium depression • Increased CVP and PAOP. Reduced venous return • Pericardial effusion	Hyperdynamic type of blood circulation is specific in distributive shock. Diastolic myocardial dysfunction (filling disorder) is common. Mixed or isolated systolic myocardial dysfunction also occurs as well

(continued)

Table 25.1 (continued)

Organ	Symptoms	Effects of edema/"polycompartment" syndrome	Comments
Lungs	Hypoxia, edema, impaired lung functions. Development of pulmonary edema and/or ARDS is possible due to excessive fluid resuscitation	• Pulmonary edema and increased EVLWI • Pleural effusion • Changes in lung and chest compliance. Increased work of breathing • Hypoxemia and hypercapnia • Weaning-associated heart failure	Oxygenation impairment may be associated with an increase in shunting during hypoperfusion. ARDS may result from reperfusion, sepsis, and massive transfusion therapy
Kidneys	Oliguria/anuria, increased creatinine concentration, and biomarkers of kidney injury (NGAL, cystatin, *etc.*), decreased GFR	• Interstitial edema and renal compartment syndrome • Acute kidney injury • Reduced creatinine clearance, reabsorption of electrolytes, and water	Acute kidney injury is defined by an increase in serum creatinine level by 26.5 μmol/L or more within 48 h, or an increase in creatinine concentration by 1.5 times or more compared with the baseline level or urine output less than 0.5 mL/kg/h in 6 h
Liver	Increased bilirubin concentration and lever enzymes, increased blood lactate concentration, hypoglycemia, thrombocytopenia, clotting factor deficiency	• Interstitial edema and hepatic compartment syndrome • Synthetic function disorder and cholestasis • P450 function disorder and reduced clearance of ICG	Clinical symptoms are rarely observed
Gastrointestinal tract	Gastric paresis, evacuation impairment, and colonization of pathogen flora. Paralytic ileus, ischemia, intestinal wall edema, translocation of gut microorganisms, and acute ulcers. Rise in intra-abdominal pressure	• Ascites and edema of gut wall • Malabsorption and ischemia (reduced gastric pHi) • Intestinal obstruction (reduced peristalsis) • Intra-abdominal hypertension and abdominal compartment syndrome • Translocation of bacterial flora • Disorder of splanchnic microcirculation • Anastomosis leakage	Evacuation impairment and colonization of pathogenic flora may lead to intra-abdominal hypertension and abdominal compartment syndrome. Translocation of microorganisms is considered an important trigger of SIRS and MOF
Skin and muscular tissue	Skin can be pale and cold. Acrocyanosis, zones of hypostasis ("spotting," "mottle"), peripheral necrotic changes. In septic shock, hyperemia and warm skin may be observed	• Rhabdomyolysis (?) • Critical illness polyneuromyopathy • ICU-acquired weakness	Acute decrease in skin blood flow (centralization), sympathetic activation (vasoconstriction), microcirculation disorders during bacteremia. The hyperdynamic stage of septic shock can be manifested by dilation of skin vessels

ARDS acute respiratory distress syndrome, *SIRS* systemic inflammatory response syndrome, *MOF* multiorgan failure, *NGAL* neutrophil gelatinase-associated lipocalin, *CNS* central nervous system, *ICP* intracranial pressure, *ICG* indocyanine green, *pHi* interstitial pH, *CARS* compensatory anti-inflammatory response syndrome, *CVP* central venous pressure, *PAOP* pulmonary artery occlusion pressure, *EVLWI* extravascular lung water index, *IAP* intra-abdominal pressure, *GFR* glomerular filtration rate

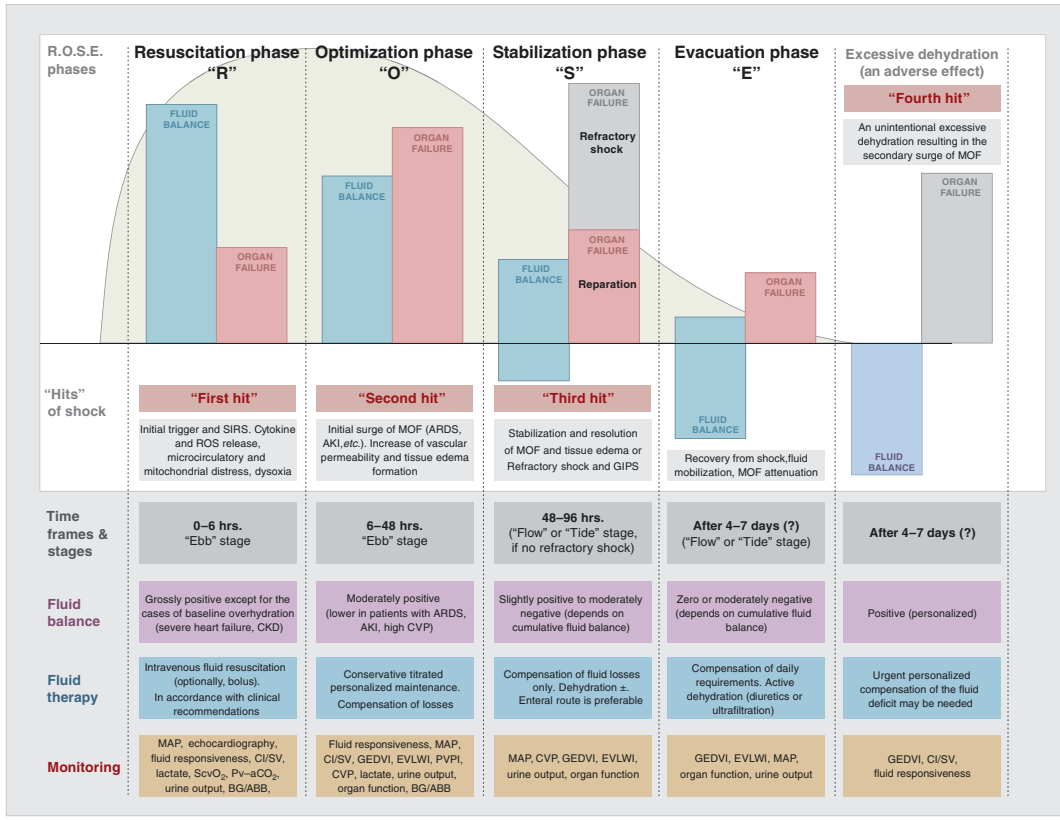

Fig. 25.2 Phase course of distributive shock: the concept of "hits," monitoring, and therapy. *SIRS* systemic inflammatory response syndrome, *ROS* reactive oxygen species, *MOF* multiorgan failure, *ARDS* acute respiratory distress syndrome, *AKI* acute kidney injury, *MAP* mean arterial pressure, *CVP* central venous pressure, *CI/SV* cardiac index/stroke volume, *GEDVI* global end-diastolic volume index, *GIPS* global increased permeability syndrome, *EVLWI* extravascular lung water index, *PVPI* pulmonary vascular permeability index, *BG/ABB* blood gases/acid-base balance, $ScvO_2$ central venous oxygen saturation, $Pv–aCO_2$ venoarterial gradient of blood partial carbon dioxide pressure, *CKD* chronic kidney disease, *RRT* renal replacement therapy

An early "Ebb" hyperdynamic stage of DS is characterized by decreased SVR due to vasodilation, increased capillary permeability, and severe absolute or relative intravascular hypovolemia poorly responding to fluids. The next stage which is known as "Tide (or 'Flow') phase" is referred to as the initial stabilization [24]. After initial resuscitation, the excessive interstitial fluid spontaneously mobilizes back to the intravascular space and can be associated with polyuria, decrease in extravascular lung water (EVLW), and resolution of the peripheral and pulmonary edema (Fig. 25.2).

25.4.1 Refractory Distributive Shock

According to the current consensus, the DS associated with the profound hypotension requiring high doses of vasopressors (more than 0.5 μg/kg/min for norepinephrine) to maintain blood pressure >65 mmHg and severe multiple organ failure may be defined as refractory (Fig. 25.2) [25]. The severe capillary leakage (global increased permeability syndrome) develops and limits the attempts to correct hypovolemia despite fluid responsiveness. Commonly, the use of adjuvant vasopressors is recommended to decrease the

dose of norepinephrine and reduce the risk of tissue ischemia (epinephrine, vasopressin and its analogs, angiotensin-2, *etc.*) [26–28].

25.5 Diagnosis

Diagnosis is based on a complex interpretation of many clinical parameters with limited sensitivity and specificity. The following signs and symptoms are the most specific for DS:

1. **Symptoms of severe multiple organ failure (MOF) and SIRS**. The DS is characterized by severe MOF including encephalopathy, acute kidney injury, acute respiratory distress syndrome, disorders of peripheral blood flow, disseminated intravascular coagulation (DIC) syndrome, and acute gastroenteropathy (Table 25.1). The inflammatory response is accompanied by an increase in the concentrations of C-reactive protein (nonspecific) and procalcitonin (more specific for septic shock caused by gram-negative infections).
2. **Hemodynamic pattern** of DS is characterized by hyperdynamic type of blood circulation manifested by increased cardiac output, arterial hypotension, a decrease in SVR, and, in some cases, a moderate increase in pulmonary vascular resistance. After the initiation of hemodynamic support (fluids and vasopressors), a rapid increase in central venous pressure (CVP) is associated with splanchnic congestion, disturbed arterial-ventricular coupling, and acute kidney injury.
3. **The metabolic changes** resulting from the impairment of tissue oxygen extraction include hyperlactatemia, metabolic acidosis, and increased $ScvO_2$ and $Pv–aCO_2$.

25.6 Hemodynamic Monitoring

The DS is a life-threatening situation that requires multimodal and personalized diagnostic and therapeutic approaches. The monitoring complies the phases of shock (Fig. 25.2) and is, therefore, time dependent.

25.6.1 Mean Arterial Pressure

According to ESICM 2014 Consensus conference on circulatory shock and hemodynamic monitoring, compensatory mechanisms can preserve blood pressure during hypotension [29], so absolute hypotension is no more recommended to be considered as DS formal criterion yet is a frequent symptom. However, relative or absolute decrease in mean arterial pressure (MAP) is an important criterion within the current definition of septic shock.

Mean arterial blood pressure is one of the most available parameters for hemodynamic monitoring and assesses the net response to fluid and vasoactive therapy. In shock, it should be measured continuously using invasive approach (Chap. 2). According to current sepsis guidelines, monitoring and targeting MAP values are the essential part of fluid and vasopressor therapy [30]. Several studies have indicated that maintaining MAP above 65 mmHg in addition to other hemodynamic parameters has beneficial effects on outcome [31–33]. However, in refractory distributive shock, the safe range of arterial pressure can be a subject for individualized management depending on the patient age, comorbidity, and preexisting pressure levels. Thus, although the target MAP for majority of patients with septic shock is within 65–75 mmHg, the elderly patients with preexisting arterial hypertension in some cases can benefit from higher MAP (up to 75–85 mmHg) [34].

25.6.2 Preload Parameters

Traditionally, CVP is frequently used to monitor volume status in ICU patients. However, static pressure preload parameters like CVP and pulmonary artery occlusion pressure (PAOP) reflect the end-diastolic pressure in ventricles and preload indirectly. Thus, numerous studies and meta-analyses demonstrated the failure of both CVP and PAOP to predict fluid responsiveness in sepsis that limits their use in DS as targets for hemodynamic therapy [18, 35, 36].

The static volumetric parameters of preload have a better diagnostic value. To assess cardiac volumes and diagnose hemodynamic disorders, echocardiography should be used in patients with DS as a first-line technique already at the rescue stage [16, 29]. Global end-diastolic volume index (GEDVI) is a volumetric parameter measured by transpulmonary thermodilution technique (Chaps. 12 and 13). Several studies indicate that GEDVI is a better indicator of cardiac preload than CVP in septic patients [37–40]. Nevertheless, in DS, both pressure and volumetric preload parameters are influenced by multiple factors including vascular tone, intrathoracic pressure, and changing ventricular compliance [41].

25.7 Fluid Responsiveness: Dynamic Variables and Functional Tests

Since the primary reason for hypotension in DS is profound vasodilation but not absolute hypovolemia, the attempts to increase preload with fluid load should be strictly personalized. Although the current guidelines recommend a crystalloid bolus of 30 mL/kg within 3 h after diagnosis of septic shock [30], the excessive infusion during capillary leak can promote tissue edema and further compromise oxygen transport. Thus, fluid administration beyond initial resuscitation requires careful assessment of fluid responsiveness including dynamic parameters and functional tests.

The role of dynamic variables is described in detail in Chap. 16. During positive pressure mechanical ventilation, cardiac output variably depends on the cyclic heart-lung interactions. In case of the preload deficit, a tidal increase in intrathoracic pressure decreases stroke volume and pulse pressure that is reflected on the arterial waveform. Many studies demonstrated the ability of arterial waveform analysis, including stroke volume variation (SVV), and pulse pressure variation (PPV) during mechanical ventilation, to predict fluid responsiveness accurately [18, 35, 42, 43]. Thus, both SVV and PPV are recommended for monitoring in shock by several guidelines [27, 29, 30]. However, these parameters have a limited value in spontaneous breathing, non-sinus rhythm, high-dose vasopressor support, and several other clinical scenarios [44, 45].

Practical Advice

Among the current hemodynamic parameters, the combination of global end-diastolic volume index with pulse pressure and stroke volume variations seems to have a reliable association with changes in preload and cardiac output in distributive shock.

In these situations, the functional tests can represent a method of choice (see Chap. 17). Among the functional tests, passive leg raising (PLR) when 200–300 mL of blood from lower extremities transiently returns to the heart is, probably, the most popular alternative technique to the classic irreversible IV fluid challenge. If the patient is fluid-responsive, CO and SV will increase by 10–15% after functional test or fluid challenge as assessed by continuous CO monitoring, echocardiography, or indirectly end-tidal carbon dioxide monitoring [22]. Functional tests can include several other approaches: positive and-expiratory pressure test (PEEP-test), mini-fluid load test, assessment of dynamic arterial elastance, *etc.* [35, 42]. It is worth to note that in the DS-associated severe capillary leak, even if the patient is a fluid responder, the intravascular volume can rapidly become deficient again after the initial increase of the preload and CO/SV [46–48].

Practical Advice

It is important to measure SV and CO during PLR maneuver or fluid challenge since these parameters indicate fluid responsiveness better than change in blood pressure.

25.8 Extravascular Lung Water Index (EVLWI)

Pulmonary edema is the most frequent adverse effect of fluid overload and ARDS. Monitoring of EVLWI during DS is a valuable tool to detect capillary leak that can increase during optimization of preload. Therefore, the dynamic changes in EVLWI can be used to guide and personalize fluid management in the critically ill patients with DS. Recent studies demonstrated that EVLWI-guided fluid therapy in septic shock attenuates organ dysfunction and improves survival [24]. For more detailed information on EVLWI, see Chaps 7, 12, and 14.

25.9 Central Venous Oxygen Saturation and Venoarterial Carbon Dioxide Gradient

Central venous oxygen saturation ($ScvO_2$) describes the relationship between oxygen delivery (DO_2) and consumption (VO_2). Decreased $ScvO_2$ indicates either a decrease in DO_2 or an increase in VO_2. During distributive shock, $ScvO_2$ may be high or normal despite local tissue hypoxia due to impaired microcirculation and shunting of the capillaries. Therefore, $ScvO_2$ is an unspecific parameter to detect tissue hypoxia [48].

The increased mixed venous to arterial gradient of carbon dioxide ($Pv–aCO_2$) has been proposed to be a valuable indicator of tissue dysoxia for many years ago and is still listed among the "metabolic" sepsis markers. The increase in $Pv–aCO_2$ is related to tissue hypercarbia associated with low-flow state [49]. However, comparing with lactate and $ScvO_2$, it changes without delay being a plausible indicator of peripheral tissue perfusion not depending on the decreased oxygen consumption [22]. Under normal conditions, this difference should not exceed 6 mmHg (0.8 kPa) [50]. In septic shock, this parameter is higher in the non-survivors, which is associated with higher lactate concentrations and decreased lactate clearance, decreased cardiac index, and, probably, severity of ARDS [49]. The prognostic potential of $Pv–aCO_2$ increase can be further improved in non-ventilated patients with septic shock [51].

25.10 Basic Principles of Hemodynamic Management

Key elements of the initial treatment of DS include early recognition of cause of the shock (*e.g.,* life-threatening infection, anaphylaxis), hemodynamic correction, source control, and early antibiotic therapy (in case of infection). Hemodynamic management is aimed to the assessment of volume status, fluid responsiveness, need for vasopressor or inotropic support, and identification of complications (*e.g.,* hypovolemia in the presence of pulmonary edema). Thus, therapeutic interventions should restore tissue perfusion by optimizing intravascular volume and cardiac function.

The term early goal-directed therapy (EGDT) in septic shock was first suggested by Rivers et al. [52]. The proposed EGDT protocol during the first 6 h of septic shock optimized oxygen delivery by maintaining CVP 8–12 mmHg, MAP 65–90 mmHg, and $ScvO_2$ of $\geq$70% and markedly reduced mortality in septic shock [52]. However, the efficacy of this protocol was questioned by several randomized clinical trials [53–56]; thus, it was excluded from the current Surviving Sepsis Campaign guidelines [30].

The modern approach to the hemodynamic management of DS takes into account the phases of shock (ebb/flow, SOSD and ROSE concepts), consisting of salvage/rescue, optimization, stabilization, and de-escalation/evacuation [24, 57–59]. First two phases correspond to the ebb phase and latter two phases to the flow phase of DS [24]. The phases of monitoring and therapy modified for DS are shown in Fig. 12.2.

In addition to fluids and catecholamines, the hemodynamic management of refractory DS can additionally include hydrocortisone, vasopressin or its analogs, detoxication, and organ replacement therapy [18, 25, 26, 30, 60]. Several novel approaches are still under debates [13, 61, 62].

25.11 Conclusion

Distributive shock is the most frequent type of shock, representing a serious challenge for physician in terms of differential diagnosis, monitoring, and management. Despite all efforts and the latest achievements in therapy, the mortality rate in patients with DS remains unacceptably high. The development of personalized and phase approaches to hemodynamic monitoring of DS is of paramount importance. Particularly, further attention should be paid to the advanced management of shock phases associated with globally increased permeability and microcirculatory-mitochondrial distress syndromes. In parallel with the routine invasive arterial pressure and cardiac output monitoring, the volumetric approach comprising a complex assessment of preload, fluid responsiveness, myocardial contractility, and pulmonary edema may be beneficial.

Keynotes

- Distributive circulatory shock is usually related to sepsis representing a unique hemodynamic pattern of the profound vasodilation associated with preserved or increased cardiac output.
- In contrast to other circulatory shock subsets, the course of distributive shock is associated with consecutive phases requiring the personalized time-dependent changes in monitoring and management.
- Despite the consensus recommendation to maintain mean arterial pressure above 65 mmHg, in refractory distributive shock the safe range of arterial pressure can be a subject for individualized management depending on the patient age, comorbidity, and preexisting pressure levels.
- In distributive shock, the volumetric monitoring is a promising approach facilitating the personalization of hemodynamic therapy.

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Pulmonary Edema

26

Mikhail Y. Kirov and Vsevolod V. Kuzkov

Contents

26.1 Introduction

Pulmonary edema (PE) is a life-threatening clinical phenomenon observed in many critically ill patients. In most cases, a type of PE that is conventionally defined as "cardiogenic" is associated with acute or chronic decrease of systolic heart function, whereas "non-cardiogenic" PE is mostly caused by increased vascular permeability and frequently referred to as acute respiratory distress syndrome (ARDS) [1]. Despite differentiation to cardiogenic and non-cardiogenic types, PE often represents an "overlap" syndrome involving both acute filtration phase and edema resolution [2, 3]. The key mechanisms of PE comprise increased outflow (pulmonary veins) pressure, related either to left heart failure or to the direct pulmonary venular constriction, as well as capillary leak due to microvascular injury caused by systemic inflammatory response. The migration of inflammatory cell, disturbances of lymphatic flow, and fluid reabsorption as well as protein exudation can promote accumulation of extravascular lung water (EVLW), a hallmark of PE [1].

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There are many "specific" subtypes of PE including neurogenic (mostly related to encephalitis, severe head trauma, and subarachnoid hemorrhage) [4], postpneumonectomy (probably due to volumotrauma of reduced pulmonary tissue) [5], post-obstructive (manifesting after resolution of airway obstruction) [6], re-expansion (associated with evacuation of pneumothorax) [7], and weaning-associated (after the discontinuation of mechanical ventilation associated with cardiac dysfunction) [8]. In addition, there are various "environmental" forms of PE associated with extreme outward conditions such as high altitude, immersion, swimming, poisoning, and severe physical exercises [9]. The factors involved into PE formation in critically ill patients include pulmonary vascular permeability, capillary and interstitial hydrostatic pressures, multilevel oncotic pressures, and lymphatic drainage [1, 10] (Fig. 26.1). These factors are reflected in the classic Starling's equation that has been recently adjusted according to discovery of the role of endothelial glycocalyx as an independent oncotic compartment.

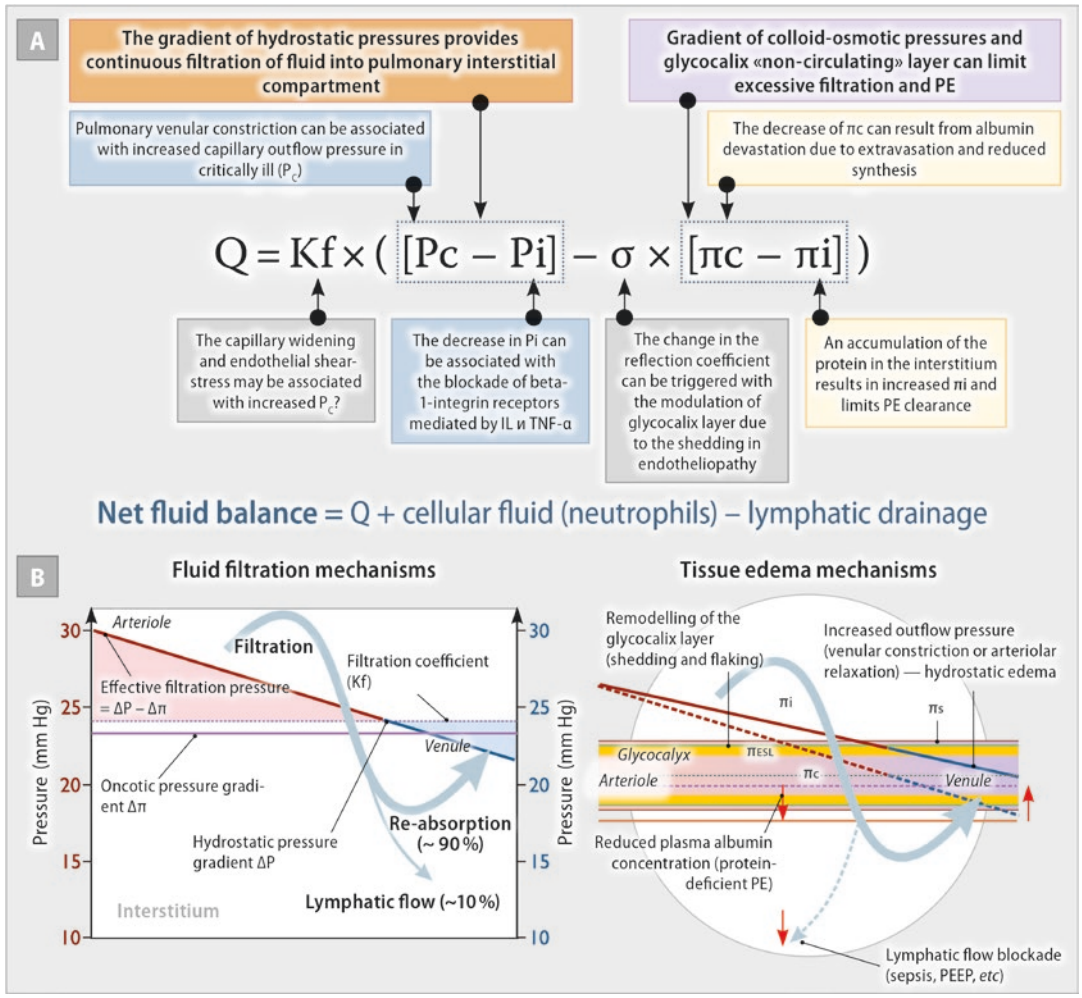

Fig. 26.1 Lung fluid balance and mechanisms of pulmonary edema. (**a**) Equation of Starling. (**b**) Factors, influencing lung fluid filtration in critical illness. *Q* fluid flow through the capillary wall, *Kf* capillary filtration coefficient, *PE* pulmonary edema, *Pc* capillary hydrostatic pressure, *Pi* interstitial hydrostatic pressure, *σ* reflection filtration coefficient (closely related to glycocalyx integrity), *πc* capillary oncotic (colloid-osmotic) pressure, *πi* interstitial oncotic pressure, *ESL* endothelial surface layer, π_{ESL} endothelial surface layer oncotic pressure, *πs* sub-glycocalyx layer oncotic pressure

Practical Advice
In many critically ill patients, both permeability and hydrostatic mechanisms may be involved; thus, it can be difficult to differentiate "non-cardiogenic" and "cardiogenic" types of pulmonary edema.

The Starling's equation describes the process of fluid transport to the interstitial space and thereafter to the alveoli. The Kf coefficient is related to the properties of capillary wall. The capillary hydrostatic pressure depends on pulmonary zone and method of assessment. For the lung vasculature, Pc approximates 7 mmHg, whereas for other tissues, Pc varies between 17 and 25 mmHg. The Pi values are usually negative (−3 to −4 mmHg). The value of σ coefficient is closely related to the glycocalyx integrity and is associated with the proportion of molecules reflected by the capillary endothelium (in case of total impermeability, σ = 1; if all molecules leave the capillary lumen, σ = 0). The values of πc and πi represent oncotic pressures in capillaries and interstitium (for lungs, 24 and 14 mmHg, respectively). In summary, modern model highlights a complex interplay involving up to four oncotic zones with an addition of endothelial surface layer (π_{ESL}) and sub-glycocalyx (πs) oncotic pressures and assuming that πs is lower than πi. The oncotic pressures are mainly dependent on the concentration of colloid molecules (mainly, albumin) in plasma and interstitium as well as on the integrity of ESL and glycocalyx lining.

26.2 Monitoring of Pulmonary Edema

Among numerous invasive and noninvasive approaches, only transpulmonary indicator dilution technique is clinically approved to quantify extravascular lung water index (EVLWI) and to estimate vascular permeability in critically ill patients [11–13]. Historically, EVLWI was assessed first with double (dye and thermal) indicator transpulmonary dilution technique. Later, this robust approach was replaced by a simpler, less expensive, and less invasive single (thermal indicator only) transpulmonary dilution (STD). This technique is described in detail in Chap. 7.

Practical Advice
Thermodilution-derived extravascular lung water index provides a direct quantification of pulmonary edema at the bedside.

Despite a number of limitations (Fig. 26.2), EVLWI assessed by STD demonstrates a strong correlation with "gold standard" *postmortem* gravimetry, as well as with invasive and noninvasive *in vivo* techniques applied in different settings [13–15]. Thus, despite potential value of lung ultrasound, bioimpedance tomography, and quantitative computed tomography, to date STD can be referred as a "clinical gold standard" for EVLWI quantification [13, 16].

The bedside EVLWI measurement provides us with an important piece in the puzzle of personalized hemodynamic management in shock, ARDS, heart failure, and multi-organ dysfunction syndrome. The assessment of EVLW helps to estimate the severity of PE and to reach a precise balance between efficacy and safety of fluid resuscitation [12, 17]. Moreover, when integrated into protocols of personalized hemodynamic management, the use of EVLWI as a target for therapy might have a strong potential to improve clinical outcome [17, 18]. In ICU patients, the increase in EVLWI both at onset of critical illness and during treatment is strongly associated with severity of ARDS and mortality [19, 20]. Thus, the monitoring of PE using EVLWI has shown a clear prognostic value in septic shock, cardiothoracic surgery, severe trauma, cardiac arrest, and many other conditions [12, 13, 20–22].

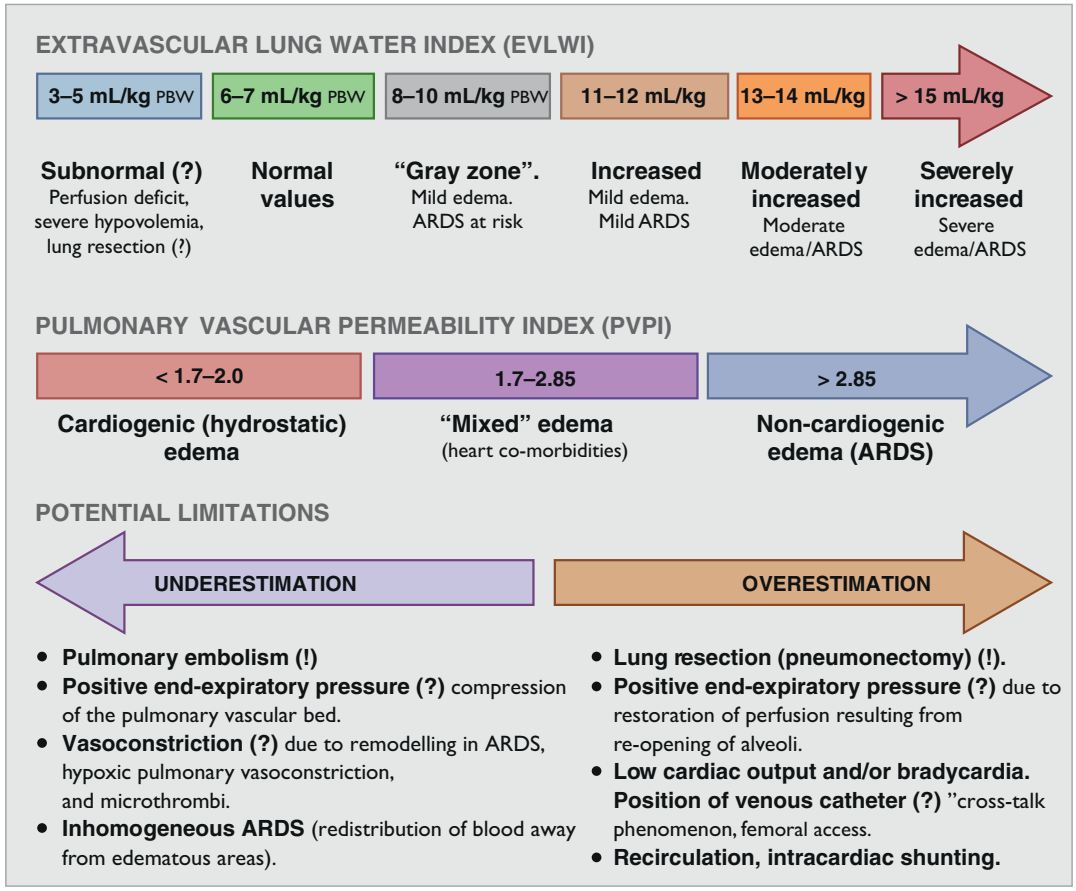

Fig. 26.2 A practical approach for the interpretation of extravascular lung water index and pulmonary vascular permeability index

26.3 Methodology of Single Transpulmonary Thermodilution to Quantify Pulmonary Edema: The Brief Insight

As has been described in Chap. 7, estimation of cardiac output (CO) based on the Stewart–Hamilton equation applies the analysis of thermal indicator dilution curve (cold crystalloid). Along with *intrathoracic thermal volume* and *pulmonary thermal volume*, thermodilution module computes *pulmonary thermal volume* consisting of *pulmonary blood volume* (PBV) and EVLW [22, 23].

In addition, the STD-derived variables allow to calculate *pulmonary vascular permeability index* (PVPI = EVLW/PBV) that can help to distinguish cardiogenic, non-cardiogenic, and "mixed" PE (Fig. 26.2) [20, 21].

The accuracy of STD to estimate PE can be compromised by multiple factors associated with "heat sink" phenomenon related to the shifts in heat conductivity of intrathoracic structures (pleural cavities, thermal losses to the myocardium, and great vessels), as well as low cardiac output, intracardiac shunting, and inhomogeneity of pulmonary blood flow [12, 21, 23].

Both diagnostic and predictive value of EVLWI significantly increases when indexing to

predicted body weight ($EVLWI_{PBW}$) [24]. The "normal range" of EVLWI is usually referred to as 4–7 mL/kg; however, Tagami et al. have shown in autopsy normal $EVLWI_{PBW}$ values of 7.4 ± 3.3 mL/kg [14]. Currently, $EVLWI_{PBW}$ in the range of 8–10 mL/kg can be clinically interpreted as a "gray zone" for developing PE [14, 21]. The optimal cutoff value for $EVLWI_{PBW}$ associated with PE and diffuse alveolar damage is 10 mL/kg [21, 25]. In moderate PE, the EVLWI range is within 10–15 mL/kg, whereas the threshold exceeding 15 mL/kg corresponds to severe ARDS and increased mortality [12, 13, 21] (Fig. 26.2).

26.4 Lung Ultrasonography for Diagnosing Pulmonary Edema

Currently, the use of lung ultrasound (LUS) recognizing B-lines becomes a reasonable and not expensive bedside alternative to STD for screening and semiquantitative assessment of PE in different categories of ICU and perioperative patients [16, 26].

The cause of lung congestion is the accumulation of extravascular water that appears as multiple B-lines or "comet tail" artifact during LUS (Fig. 26.3). The number of B-lines is directly proportional to the degree of extravascular water accumulation and is typically evaluated using an 8-zone method (four zones on each side), although a 28-zone method has recently become widespread. The severity of pulmonary edema can be semiquantified by summing the amount of B-lines in the zones or by determining the number of affected zones. When counting the B-lines in isolated zone, a result of ≤3–5 is considered indicative of no fluid accumulation, while 6–15, 16–30, and 30 more lines indicate minor, moderate, and severe edema, respectively. In addition, B-lines can merge to form wide bands, which can progress to the "white lung" appearance (also known as LUS "ground glass") [26, 27].

Ultrasonography is more sensitive for diagnosing lung congestion compared with plain chest radiography [26]. Although B-lines are a nonspecific sign of extravascular fluid accumulation, they should be combined with EVLWI measurement, echocardiography, and biomarker testing to clearly determine the cause of heart failure and to assess the severity of PE [28].

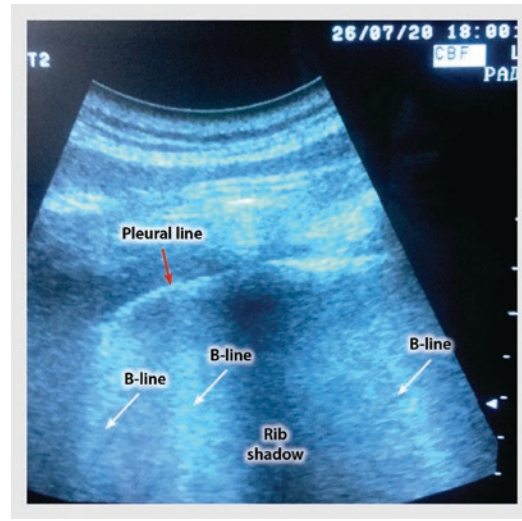

Fig. 26.3 Pulmonary edema associated with multiple B-lines in patient with COVID-19 (courtesy of Dr. Konstantin S. Lapin, Severodvinsk, Russian Federation)

26.5 Pulmonary Edema in Sepsis

Sepsis and septic shock are the most prevalent triggers of ARDS and PE. In septic shock, an increase in EVLWI by more than 10% from baseline (or the absolute value of EVLWI >10 mL/kg) may be considered as a limit for further infusion load, being a guidance for maintaining zero or negative fluid balance [22, 29–31]. Further horizons of EVLWI-guided personalization of fluid therapy can be approached with complex algorithms involving other volumetric, hemodynamic, and metabolic parameters [32–34].

Importantly, the detection of PE in sepsis by assessment of EVLWI occurs before changes in oxygenation and chest radiogram [22, 30]. Thus, Martin et al. have shown that more than 50% of patients with sepsis not meeting the ARDS criteria demonstrated increased EVLWI, representing subclinical lung injury [30].

Practical Advice
Being the major cause of ARDS and shock, sepsis is one of the most frequent indications for monitoring of pulmonary edema in ICU.

26.6 Pulmonary Edema in ARDS

Non-cardiogenic PE has been referred among the most important mechanisms of ARDS for decades; therefore, its assessment has a great potential to personalize fluid balance, respiratory and pharmacological interventions [12, 13, 21].

In ARDS, both EVLWI and PVPI are increased in most patients. These changes are more prominent in non-survivors peaking at days 2–4 after the onset of ARDS [20, 30]. The values of EVLWI > 10 mL/kg PBW and PVPI > 2.85 can serve as important clinical thresholds of ARDS. [12, 13, 35]. Moreover, these volumetric parameters are strongly associated with severity of ARDS in accordance with Berlin criteria [35].

In addition, it has been shown that the bedside quantification of PE in ARDS in parallel with monitoring of other hemodynamic variables can facilitate the clinical decisions associated with decreased duration of mechanical ventilation, ICU stay, and hospitalization period [23, 34, 36].

26.7 Pulmonary Edema in Heart Failure

Monitoring of EVLW is also valuable in hydrostatic PE and cardiogenic shock [21, 37] with diagnostic thresholds for EVLWI and PVPI of 10 mL/kg and <2.0, respectively [25, 35]. The measurement of EVLWI for estimation of PE can be of particular value after sudden cardiac arrest [38].

26.8 Other Applications for Monitoring of Pulmonary Edema

In mixed ICU, the assessment of EVLWI for monitoring of PE can also be considered for personalization of hemodynamic management in multiple clinical scenarios, including necrotizing pancreatitis [39], solid organ transplantation [40], and renal replacement therapy [41].

The assessment of EVLWI and PVPI in the perioperative settings of cardiac surgery can contribute to the differential diagnosis between cardiogenic and non-cardiogenic (postoperative ARDS) origins with EVLWI as one from the targets for therapy [42, 43].

In neuro-ICU, the quantification of EVLWI might be useful to control neurogenic PE in subarachnoid hemorrhage and prevent secondary delayed cerebral injury, vasospasm, and brain edema [44, 45]. In severe traumatic brain injury, the rise in EVLW is associated with trauma severity and increased intracranial pressure [46, 47].

In combined trauma complicated by hypotension and hypoxemia, monitoring of PE results in modifications of fluid and vasopressor support, reducing fluid balance and improving outcome [48]. Extravascular lung water and other volumetric variables also provide guidance of fluid therapy in adults and children with severe burns involving more than 25–30% of body surface area [49, 50].

26.9 Conclusion

The monitoring of PE has an obvious potential to provide additional information regarding fluid status and to personalize therapy in both ICU and perioperative settings. Grading the severity of PE with EVLWI has proved to be an important diagnostic and prognostic tool in sepsis, ARDS, cardiogenic shock, neurocritical care, severe trauma, and perioperative period of major surgery. Transpulmonary thermodilution remains a bedside "gold standard" for quantitative assessment of lung water in critically ill, whereas LUS can be method of choice for screening of PE in other clinical scenarios.

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Conflict of Interest Mikhail Y. Kirov is a member of the Medical Advisory Boards of Pulsion/Getinge and Philips.

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Keynotes

- Pulmonary edema occurs in many critically ill patients and requires thorough monitoring and active dehydration in case of fluid overload.
- Both baseline value and dynamic changes of extravascular lung water index can reveal pulmonary edema and are associated with severity of acute respiratory distress syndrome and outcomes.
- Currently, single transpulmonary thermodilution is a bedside reference technique for quantification of extravascular lung water index and other volumetric parameters.
- A clinical decision based on volumetric parameters including extravascular lung water index represents an attractive approach for personalized therapy in critically ill.

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Part VIII

Future of Hemodynamic Monitoring and Therapy

New Methods and Sensors for Hemodynamic Monitoring

27

Frederic Michard

Contents

For decades, the hemodynamic assessment of critically ill patients relied almost exclusively on invasive dilution techniques and on echocardiography evaluations done with cumbersome devices designed for cardiologists. Things dramatically changed over the last decade with the development of multiple less invasive blood pressure and cardiac output monitoring techniques and the miniaturization of ultrasound devices [1]. The continuous acceleration of hardware and software innovations makes it difficult to accurately predict what hemodynamic monitoring will be like in the future [2]. However, key trends can be envisioned and are discussed in this chapter.

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27.1 The Rise of Noninvasive Techniques

Many recent cardiac output monitoring techniques are noninvasive, from bioimpedance tracheal tubes to bioreactance surface electrodes, applanation tonometry, and volume clamp methods [3]. Carbon dioxide (CO_2) rebreathing methods are not new but have recently been revisited [4]. They would have strong potential for wide clinical adoption if they were integrated into anesthesia machines or mechanical ventilators. Electrical impedance tomography (EIT), currently used for noninvasive and continuous functional lung monitoring, also has potential for cardiac output monitoring [5]. Novel tiny and flexible experimental sensors can "feel" our pulse and record high-quality blood pressure curves [6]. When used in combination

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with pulse contour algorithms, these sensors will allow continuous monitoring of pressure and flow [7], the two main determinants of organ perfusion. Electronic tattoos, still under development, will enable the measurement of lactate, electrolytes, and other metabolites in sweat [8]. These noninvasive tools will help to reduce thrombotic, hemorrhagic, and infectious complications associated with invasive techniques and to improve patient comfort and satisfaction.

27.2 Ease of Use as a Key Element of Clinical Adoption

Gastric tonometry has been used in the past to assess gastric mucosa perfusion and titrate hemodynamic therapy with proven survival benefits [9]. However, this technology disappeared from our monitoring arsenal because of an inability to match with clinicians' workflow. Echocardiography is a good example of how simplification and miniaturization of medical devices can boost clinical adoption. Pocket echo probes are now available and have potential to replace the stethoscope in the pocket of many clinicians, in the ICU, and beyond (Fig. 27.1). Although miniaturized, these tools have proven to be useful for a qualitative (*e.g.,* pericardial effusion, right ventricular dilation, left ventricular dysfunction) or even quantitative assessment of cardiac function (*e.g.,* estimation of left ventricular ejection fraction or inferior vena cava variations) [10]. The rise of echocardiography was recently highlighted by an international survey of intensivists and anesthetists treating COVID-19 critically ill patients [11].

Practical Advice
Pocket echo devices will replace the stethoscope in the pocket of many acute care physicians.

The concept of intraoperative stroke volume optimization with fluid was initially described with esophageal Doppler, and many studies reported postoperative outcome benefits [12]. However, today, most anesthetists are using uncalibrated pulse contour methods to monitor high-risk patients undergoing major noncardiac surgery [13]. Pulse contour methods are not more accurate and precise than Doppler techniques [14]. However, they are plug-and-play techniques, not operator dependent, not influenced by electro-cautery, and easy to use in high-risk surgical patients who, anyway, have a radial catheter in place for continuous blood pressure monitoring.

Practical Advice
Uncalibrated pulse contour techniques are easy to use in high-risk surgical patients who have a radial catheter in place for continuous blood pressure monitoring.

Fig. 27.1 Example of pocket echo devices enabling a quick and qualitative evaluation of cardiac function. From left to right: Lumify from Philips with permission, IQ from Butterfly with permission, VScan from GE Healthcare with permission

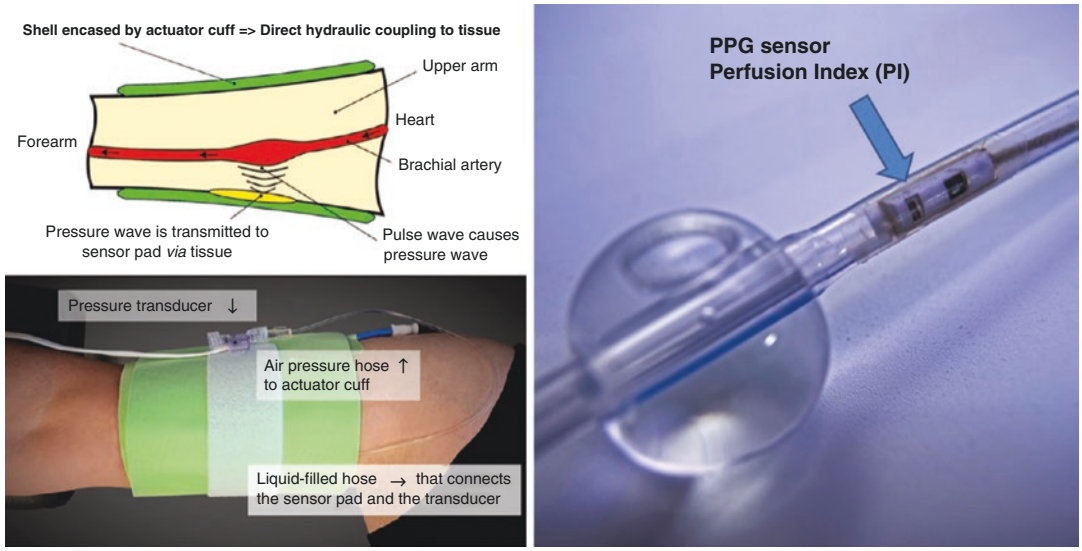

Fig. 27.2 Smart upgrade of existing tools would facilitate clinical adoption. Left panel: Oscillometric brachial cuff revisited with a rigid conic shell and a hydraulic sensor pad enabling the high-fidelity recording of a brachial arterial pressure waveform, from Philips with permission. Right panel: Bladder catheter with a photoplethysmographic sensor enabling the continuous monitoring of tissue perfusion, from Vygon with permission

Upgrading tools already used in critically ill patients (*e.g.,* a brachial cuff or a pulse oximeter or a bladder catheter) might be very efficient to increase clinical adoption. Oscillometric upper-arm cuffs have recently been revisited. These new cuffs include a rigid conic shell and a hydraulic sensor pad (Fig. 27.2, left panel). It does improve their accuracy and precision when measuring blood pressure [15]. It also enables the recording of an arterial pressure waveform for about a minute that could be used in the nearest future to compute pulse pressure variation (PPV) and cardiac output. Bladder catheters have recently been upgraded [16] to include a photoplethysmographic sensor enabling the continuous monitoring of urethral mucosal perfusion (Fig. 27.2, right panel). Monitoring microcirculation and tissue perfusion from a Foley catheter may be useful to individualize hemodynamic therapy without changing our clinical habits. Pulse oximeters are ubiquitous tools used to monitor oxygen saturation. According to recent studies, they could be used as well to detect changes in blood pressure and trigger oscillometric measurements [17]. Another desirable evolution to facilitate clinical adoption and make clinicians' life easier is the integration of multiple sensors into ergonomic tools such as rings, shirts, or bracelets [18] (Fig. 27.3).

27.3 Wireless and Wearable Sensors

Wireless technologies are part of our daily life but are uncommonly used in the operating room and ICUs. This may change in the nearest future, given the fast pace of technological and computer innovations. First, this would make clinicians' life easier by eliminating cables and wires that engulf patients. Second, it would give the opportunity to monitor patients beyond the operating room and ICU. On hospital wards, nurses classically spot-check vital signs only every 4–8 h and therefore may detect clinical deterioration with delays [19]. A recent and prospective observational study [20] conducted in a leading US hospital, where patients were continuously but blindly monitored, revealed that nurses who were checking blood pressure every 4 h missed about half of hypotensive events. Another study from the same group [21] showed

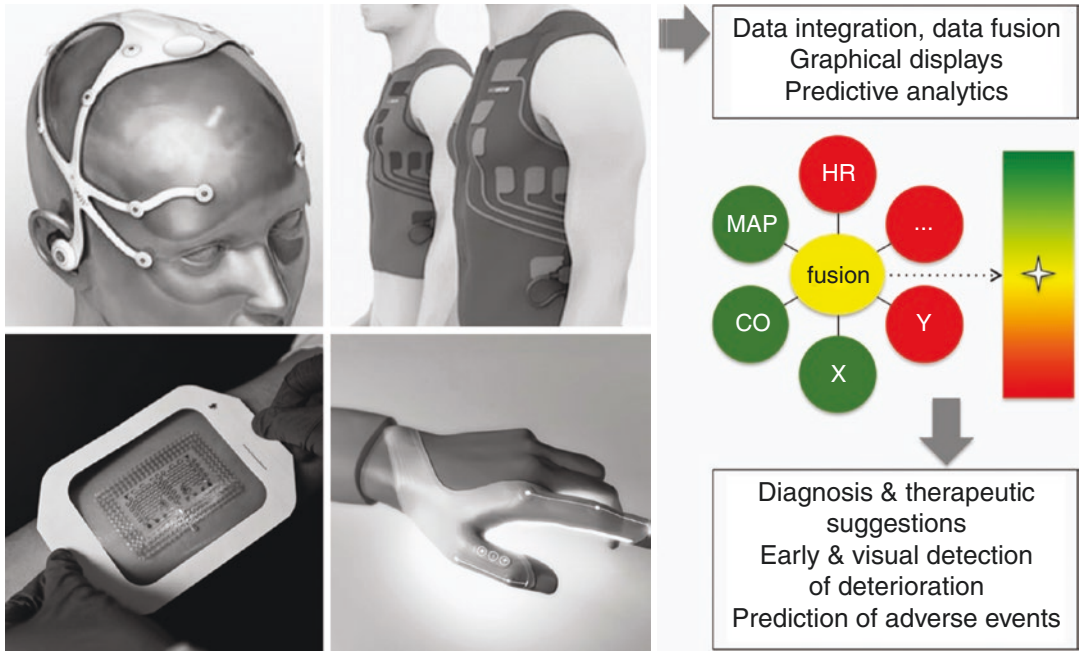

Fig. 27.3 The evolution of physiologic monitoring toward ergonomic tools integrating multiple sensors, data fusion, and visual decision support (from [18] with permission)

that hypotensive events between day 1 and day 4 after surgery (when most patients are on the wards) are associated with a 183% increase in myocardial infarction and death. Therefore, continuous monitoring of blood pressure may help to improve quality of care. Unfortunately, blood pressure remains a variable difficult to measure noninvasively and continuously [22]. Volume clamp and tonometric sensors are part of tethered monitoring systems that have been designed for the operating room, not for mobile ward patients. Other monitoring systems, combining chest electrodes (to detect the ECG R wave) and a finger pulse oximeter (to detect a peripheral pulse), are able to predict blood pressure from the estimation of changes in pulse wave transit time [22]. Weller et al. [23] used such systems in ward patients and reported a significant decrease in the number of rapid response team calls. In the future, adhesive, conformable, and wireless patches may become available for the continuous monitoring of carotid, brachial, or radial blood pressure and derived parameters [6, 7]. Ultrasound probes are also becoming wireless, and Doppler patches placed on the carotid artery may have value to predict preload responsiveness [24] (Fig. 27.4).

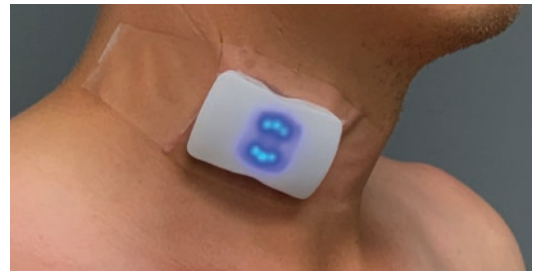

Fig. 27.4 Example of wireless Doppler patch (from Flosonics with permission)

Practical Advice

Postoperative hypotension is frequent and often under-recognized on surgical wards because patients are not monitored continuously.

27.4 Smart Software and Algorithms

With improved software and algorithms, monitoring systems will become smarter. First, signals and data recorded by noninvasive and wireless sensors will be filtered to eliminate artifacts and prevent false alarms and alarm fatigue. Real alarms will be seen or heard exclusively at central monitoring stations or on nurses' mobile tools in order to create a sleep-friendly environment for patients [18]. Second, data coming from multiple sensors will be integrated to recognize specific patterns and suggest diagnosis and therapeutic options (decision support tools). Third, data fusion and predictive analytics will be used to create warning scores or visual indicators helping clinicians to quickly recognize adverse events, such as hemodynamic instability (Fig. 27.3). Finally, knowing that the brain processes visual information 60,000 times faster than text, the use of graphical displays will continue to expand [7]. Visual decision support systems or target screens are already available to guide clinicians following hemodynamic protocols [25]. Hemodynamic variables and targets can be selected by clinicians who need to adapt their hemodynamic strategies to specific clinical situations and the individual patient. These decision support tools are useful to quantify the time spent in target [25] and to enhance protocol adherence [26].

Practical Advice
A picture is worth a thousand numbers, and visual information has the potential to improve quality of care.

Predictive analytics are statistical methods analyzing current and historical data to make prediction about the future. They are susceptible to detect specific patterns or signatures of clinical deterioration before it becomes visible to clinicians. Predictive algorithms have recently been proposed to predict intraoperative hypotension. Studies have yielded conflicting results with sensitivities and specificities within the 65–85% range [27]. A recent study [28] suggests that the prediction of hypotension may be associated with a reduction in hypotension time. Whether it may impact outcome remains to be determined.

27.5 Automation and Closed-Loop Systems

Due to its potential to make clinicians life easier, automation of simple diagnostic tests may soon become available. For instance, assessing the hemodynamic impact of respiratory maneuvers (transient rise in tidal volume, end-inspiratory or expiratory pause, lung recruitment maneuver) is known to be useful to predict fluid responsiveness [29]. Patients who do not experience significant changes in hemodynamics during such maneuvers should not receive fluid boluses. These simple tests could be automatized on anesthesia machines and mechanical ventilators so that anesthetists and intensivists would know at regular intervals, and without any additional workload, about the fluid responsiveness status of their patient [30].

Closed-loop systems are currently under development for the automatic administration of hemodynamic therapy, but there are still multiple challenges ahead. Obstacles to the development of safe and effective systems include the number of confounding factors (*e.g.,* the influence of positive end-expiratory pressure and abdominal pressure on input variables, such as cardiac filling pressure and PPV) and the need for sensor redundancy (multiple sensors are desirable to guarantee the quality of signals triggering automatic interventions). In surgical patients, classical intraoperative goal-directed fluid therapy protocols recommend stopping fluid boluses if they do not increase stroke volume (non-responder patients). But truly hypovolemic patients may not respond to a fluid bolus by a rise in stroke volume if they are bleeding at the same time. A clinician would obviously notice and continue to give fluid, whereas an automated system designed to fluid

optimize stroke volume would not. Two recent randomized controlled trials investigating the clinical impact of a closed-loop system delivering fluid boluses (according to a predefined protocol) failed to show significant benefits [31, 32]. The automatic titration of vasopressors to ensure a stable blood pressure during surgery is also technically feasible, but it does not mean that vasopressors are always the right therapeutic answer to a decrease in blood pressure [33]. Depending on the root cause of hypotension, it may actually be better to give fluid, or red blood cells, or inotropes, or simply to decrease the depth of anesthesia [33].

27.6 Affordability

The adoption of hemodynamic monitoring techniques remains poor, particularly in surgical patients [34]. Surveys suggest that only 1/3 of eligible patients are monitored, and a recent real-life audit revealed it may actually be much less (<1/10 of eligible patients) [35]. One of the major headwinds to clinical adoption is the cost associated with the use of hemodynamic monitoring techniques. The "MERCI" equation [13, 36] enables an easy estimation of the possible Investment (I) to implement perioperative hemodynamic monitoring at no net costs. It takes into account the current morbidity rate (M), the expected reduction (ER) in postoperative morbidity, and the current cost (C) of complications:

$$M \times ER \times C = I$$

As an example, if the morbidity rate after colorectal surgery is 25% (M = 25%), the expected reduction in postoperative morbidity is 20% (ER = 20%), and the average cost of complications per patient is €10,000, the investment to implement hemodynamic monitoring at no net cost is €500 per patient:

$$0.25 \times 0.20 \times €10,000 = €500$$

If the actual cost of the monitoring is greater than €500/patient, the monitoring cost above €500/patient would represent new net cost to the health system. If the cost of monitoring is less than €500/patient, the difference would be savings to the health system.

If the baseline morbidity rate and cost of complications are lower, and the clinical impact of hemodynamic monitoring is not as significant, then the investment, or "breakeven point" will logically be lower as well. For example, if the morbidity rate after femur and hip fracture repair is 15%, the expected reduction in postoperative morbidity is only 10%, and the average cost of complications in this specific population is €5000 [13], then the investment to implement hemodynamic monitoring at no net cost is only €75/patient:

$$0.15 \times 0.10 \times € 5000 = € 75$$

If the cost of implementing the monitoring is greater than €75/patient, the cost above €75/patient would represent new net cost to the health system. It is clear that the greater the incidence and cost of complications, the greater the cost of monitoring can be while maintaining either net cost savings or no net cost ("breakeven").

Practical Advice
When assessing the return on investment of hemodynamic monitoring techniques, it is necessary to take into account potential savings associated with a decrease in complications and hospital length of stay.

To improve the adoption of perioperative hemodynamic monitoring, several medtech companies are now offering more affordable solutions with a flat fee for monitoring an unlimited number of patients. Given the growing body of evidence supporting the clinical value of uncalibrated pulse contour methods [37], one may also expect from bedside monitoring companies to develop or acquire pulse contour algorithms so that cardiac output values, or at least trends, will become available next to blood pressure numbers in all patients with a radial catheter.

27.7 Conclusion

In the future, acute care clinicians will have an echo probe in their pocket and, to monitor patients, will increasingly use noninvasive, wireless, and wearable sensors, which will be part of ergonomic tools such as rings or bracelets. Oscillometric brachial cuffs will assess the determinants of blood pressure, namely, cardiac output and vascular tone; and changes in pulse oximetry waveform will tell them when to inflate (smart triggering). Anesthesia machines and mechanical ventilator will estimate cardiac output from the CO_2 rebreathing method and automatically detect preload responsiveness. All physiologic signals and data will be filtered, analyzed, and fused by smart software and algorithms, and it will then become possible, at a glance (thanks to visual information), to predict and prevent adverse events, as well as to receive and follow rational therapeutic suggestions.

Keynotes

- Minimally invasive and noninvasive hemodynamic monitoring techniques are increasingly used in the operating room and in intensive care units.
- Uncalibrated pulse contour techniques are useful to predict fluid responsiveness and to track changes in cardiac output during high-risk surgery.
- Future bedside monitors will integrate pulse contour algorithms so that cardiac output will become a new vital sign, next to blood pressure and heart rate.
- Echocardiography is indispensable to identify hemodynamic phenotypes in ICU patients with shock.
- Pocket echo devices are affordable and enable a quick and qualitative evaluation of cardiac function.
- Wireless wearable sensors are emerging as a solution for continuous monitoring on the wards and for the early detection of clinical deterioration.

Disclosure FM is the founder and managing director of MiCo (michardconsulting.com), a Swiss consulting and research firm. MiCo does not sell any medical products and FM does not own any shares from any medtech company.

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Closed-Loop Hemodynamic Management

28

Brenton Alexander, Joseph Rinehart, and Alexandre Joosten

Contents

28.1 Introduction

Anesthesia providers have developed an ever-increasingly complex relationship with the various devices that surround them throughout the perioperative process. These technologies have continuously advanced at a remarkable pace ever since the initial development of ether dribbled masks almost 175 years ago [1]. Significant steps toward completely automating individual aspects of perioperative patient care are already occurring, and one category receiving particularly large amounts of interest is hemodynamic optimization and management. The reasons for this specific expansion are plentiful but largely consist of advancements in computing, monitoring devices, evidence-based data-driven protocols,

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reduced physician workload, and improved affordability. Automation of perioperative hemodynamics has been mainly focused on two key areas: fluid delivery and vasopressor administration [2]. Significantly more literature addressing the automation of fluid therapy has been disseminated as various goal-directed fluid therapy (GDFT) protocols known to decrease perioperative morbidity for specific patient populations have become widely accepted. Vasopressor automation is also gaining significant traction [3, 4] and will likely continue to expand in the upcoming years given the high number of published papers reporting a link between perioperative hypotension and postoperative complications [5–10].

The aim of this chapter is to provide an overview of the recent evidence addressing various closed-loop systems designed to optimize perioperative hemodynamics. We will accomplish this by first examining if there are hemodynamic targets worth automating and the benefits of implementing that automation, and then more closely reviewing the individual variables being automated.

28.2 Do We Need Hemodynamic Targets and Protocols?

The simple answer is YES. In order to avoid periods of hypo- and hyperperfusion, which are unfortunately very difficult to directly quantify, perioperative physicians have instead aimed to optimize the best available hemodynamic surrogates. These include arterial pressure, cardiac function, fluid status, end-organ function, oxygenation, and many other clinical variables known to affect oxygen delivery. Using these surrogates, the broad strategy of goal-directed hemodynamic therapy (GDHT) is to decrease potential malperfusion *via* a clinical optimization of fluid status, vasopressors, and inotropes [11]. Although likely less significant than previously thought, there is still a strong trend toward improved morbidity with GDHT mainly in high-risk surgical patients [12–14], as low- to moderate-risk surgeries require significantly larger sample sizes to demonstrate meaningful clinical benefit.

Moreover, physicians have significant inconsistencies in their fluid administration practices (both intra- and interindividual variability), which could contribute to inconsistencies in surgical outcomes [15, 16]. In fact, it has been demonstrated that the major factor in determining the average volume of fluid given to surgical patients is whoever happens to be the clinician assigned to that case, which leads to unjustified variability in care delivery instead of treatment based on best clinical evidence [17].

Regarding the administration of vasopressors, we have recently completed a study at two large international academic centers examining patients in both the ICU and operation room (OR) under continuous noradrenaline infusion therapy [18]. This study demonstrated that patients only remained in their predefined arterial pressure target range for less than 50% of the treatment period (vasopressor administration period), with most patients being kept above the target range (which was likely to allow for a "safety margin" if blood pressures were to decrease) [18]. Moving beyond the inability for providers to keep patients in a therapeutic target zone, there have also been multiple studies directly highlighting the importance of arterial pressure control in the operating room and intensive care unit [9, 19–29].

When looking at all of this data cohesively, it appears that GDHT protocols do consistently decrease perioperative morbidity in moderate- and high-risk surgical patients although conclusive effects on LOS and mortality still require additional clinical research [30]. Furthermore, there is some evidence that automating both fluid and vasopressor infusion in the perioperative setting would provide significant improvements in stroke volume and arterial pressure management [31–35] compared to routine management.

28.3 What Are the Benefits of Automation?

When addressing current fluid administration practices, it is very important to realize that multiple trials have concluded that there is extremely large variability in fluid administration through-

out the perioperative and critical care environments [15, 16, 36], with extremes of fluid therapy being associated with increased morbidity [16, 36]. This variability is the nemesis of protocolized treatment and has been found to be largely due to provider-specific preferences, which can be further complicated by a lack of vigilance and evidence-based knowledge. Even when governmental and institutional guidelines are in place [37], significant variability and an overall poor compliance have still been demonstrated [38–42] independent of the discipline, ranging from glucose control to bleeding management [43].

Luckily, as computing has advanced, a novel and efficient approach to this problem has emerged: automation. Automation in anesthesia coupled with or without artificial intelligence and machine learning is a very hot topic today as demonstrated by the increasing volume of recent literature published in the past 2–3 years [44–49]. The definition of automation in this context includes any system that uses real-time information to partially or completely guide therapeutic interventions, which include both closed- and open-loop technology [2]. Closed-loop systems are completely automated and use input variables (physiologic variables in this context) to change output variables (fluid, vasopressors, and inotropes in this context) without the required input of clinicians. Open-loop systems do the same task but require a minimal amount of clinician input prior to therapies being automatically initiated or adjusted (*e.g.,* final approval before actually administering the fluid bolus or adjusting the vasopressor infusion rate). These systems can remove many aspects of repetitive provider workload, and when combined with the incredible ability for computer systems to never lose vigilance and make thousands of observations and adjustments every second, they allow for vastly improved compliance, decreased instability [50], and are beginning to independently demonstrate improved outcomes for patients automatically treated with GDHT systems.

These systems have a distinct and recognizable design. Typically, there is a computer with input connections receiving a patient's hemodynamic data and output connections to one or more standardized interventions (fluid therapy, vasopressors, and/or inotropes). As the case progresses, the computer has software that is constantly (usually many times per second) analyzing the collected data and using well-established protocols to adjust the output interventions. In its simplest form, these systems are perfectly positioned to increase adherence to established GDHT protocols while also decreasing provider workload.

28.4 Existing Closed-Loop Hemodynamic Management Systems

28.4.1 Fluid Therapy

Fluid therapy was one of the earliest interventions to be automated by clinical researchers. A group from Utah, USA, linked a fluid pump to an electronic measurement of urine output in the late 1970s [51]. A variety of technologies have been since used to guide fluid therapy, including blood pressure [52, 53], near-infrared spectroscopy [54], dynamic predictors of fluid responsiveness [55], or a combination of hemodynamic variables [56].

The algorithmic approach used by many GDFT protocols [57–59] lends itself very naturally to computer assistance. Our team has personally performed multiple clinical studies using a closed-loop GDFT system, and we have demonstrated increased protocol compliance [35, 60, 61], decreased length of hospital stay, and decreased postoperative complications in a variety of clinical settings [60]. We also used our closed-loop system to answer questions in ways not previously thought to be possible such as: "Would it be better to optimize a patient's stroke volume with either a crystalloid or a colloid solution within a GDFT strategy?" [62, 63]. Table 28.1 summarizes studies performed in the last 10 years using our closed-loop GDFT administration system. Importantly, many additional groups are currently working on closed-loop fluid resuscitation algorithms, and we feel

Table 28.1 Studies performed with the authors' closed-loop fluid administration system

Author	Institution(s)	Main findings
Joosten et al. [60]	Erasme University Hospital, Brussels, Belgium	Closed-loop GDFT protocol reduced postoperative complications and LOS when compared with routine care
Joosten et al. [64]	Erasme University Hospital, Brussels, Belgium	Closed-loop GDFT had similar cardiovascular endpoints to protocolized fluid therapy
Joosten et al. [65]	Erasme University Hospital, Brussels, Belgium	Combining two independent closed-loop systems (hypnosis/analgesia and fluid) is feasible
Joosten et al. [62]	Erasme University Hospital, Brussels, Belgium	Closed-loop GDFT systems were used to compare two types of fluid (colloid and crystalloid)
Lilot et al. [66]	Lyon University Hospital, Lyon, France	Cardiac index increased more in closed-loop group versus manual control, otherwise no differences noted
Joosten et al. [67]	Erasme University Hospital, Brussels, Belgium	Dual closed-loop systems (hypnosis and GDFT control) are possible
Joosten et al. [61]	University of California, Irvine, USA	Intraoperative closed-loop GDFT control using a noninvasive finger-cuff hemodynamic monitoring device is feasible
Rinehart et al. [35]	University of California, Irvine, USA	Closed-loop GDFT control group spent more time in a preload independent state compared to manual GDFT group
Rinehart et al. [68]	CHU Pitié Salpêtrière, Paris, France and UC Irvine, USA	Closed-loop GDFT control is possible and reproducible
Rinehart et al. [69]	University of California, Irvine, USA	Closed-loop GDFT control during hemorrhage is effective with low variability
Rinehart et al. [55]	University of California, Irvine, USA	Closed-loop GDFT control of simulated patient hemorrhages outperforms manual control
Rinehart et al. [56]	University of California, Irvine, USA	Closed-loop system is an effective volumetric resuscitator in simulated hemorrhage scenarios and improved physician management of the simulated hemorrhages

GDFT goal-directed fluid therapy, *LOS* length of stay

that this is a field that is likely to expand rapidly in the coming years [66, 70–73]. Implementation of this technology at our academic institution as a real-time decision support system ("Assisted Fluid Management") allows patients to spend less time during surgery with a stroke volume variation above 13% compared to a hand-titrated GDFT strategy [74].

Practical Advice

This real-time clinical decision support system ("assisted fluid management system") currently has the CE mark allowing commercial release in Europe since March 2017 and soon will be approved by the FDA in the United States.

Figure 28.1 shows our closed-loop fluid administration system in an operating room in Erasme Hospital, Brussels, Belgium, during a major abdominal surgery.

28.4.2 Vasopressor

Vasopressor infusions have also demonstrated an exponential increase in automation, especially as it is a distinct variable that is commonly measured and treated in the perioperative and critical care environments [61–63]. As stated above, there is a substantial amount of evidence indicating the clinical importance of arterial pressure optimization in the operating room and intensive care unit, while there is also some evidence that the manual titration of vasopressors can be inef-

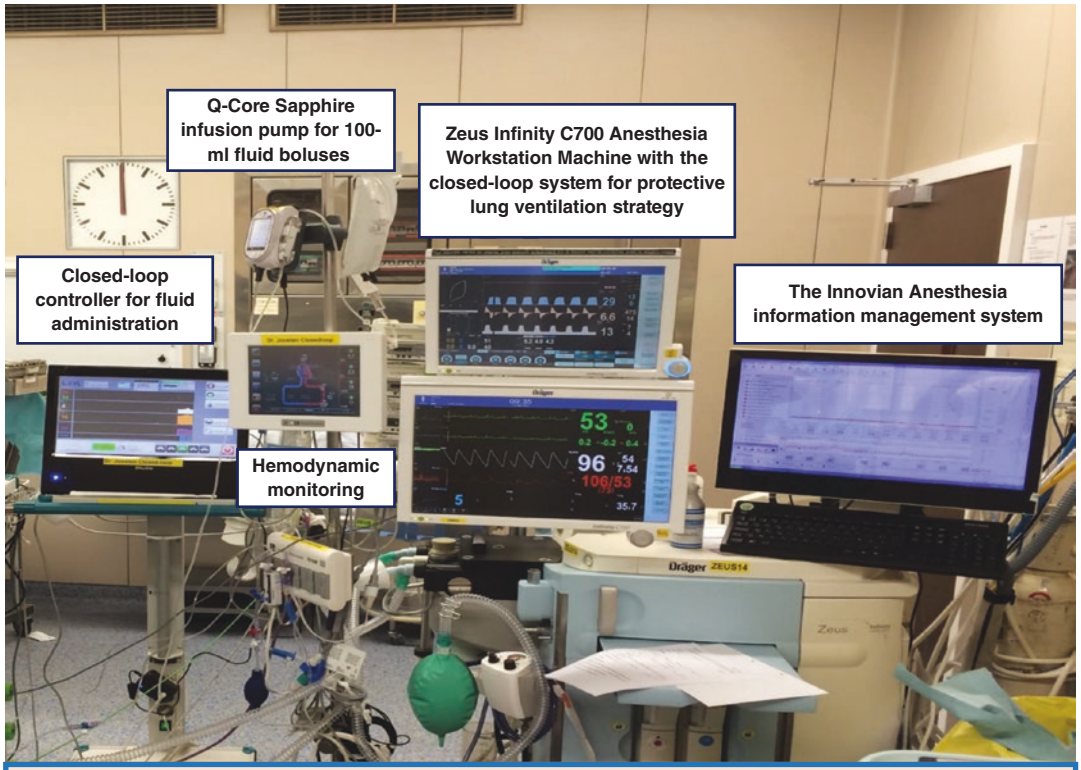

Fig. 28.1 Closed-loop fluid administration system at Erasme University Hospital, Brussels, Belgium

ficient and imprecise [20]. Modern automated vasopressor systems are currently being developed for perioperative and intensive care use, obstetrics and spinal-induced hypotension [75–77], and septic shock [78]. In a recent proof of concept study, we reported that using such system to titrate a noradrenaline infusion significantly minimizes the incidence of perioperative hypotension to less than 3% of treatment time [31]. Our team is currently conducting multiple randomized controlled trials comparing closed-loop vasopressor titration to manual management in different types of surgery. Figure 28.2 shows our closed-loop vasopressor infusion system in an operating room in Erasme Hospital, Brussels, Belgium.

28.4.3 Cardiac Function

Cardiac function has not been as prolifically studied a topic for closed-loop pharmacologic interventions. This is likely a natural result of the types of physiologic effects resulting from cardiac medication (adjusting the rate and/or increasing inotropy), as many of these effects are nonlinear and have ceiling effects, even at low infusion rates. The obvious exception to this is implantable cardiac pacemakers, which are quite advanced and contain many layers of control algorithms governing their operation [79].

That being said, there are groups that have explored pharmacologic rate control *via* closed-loop algorithms [80], particularly in the setting of

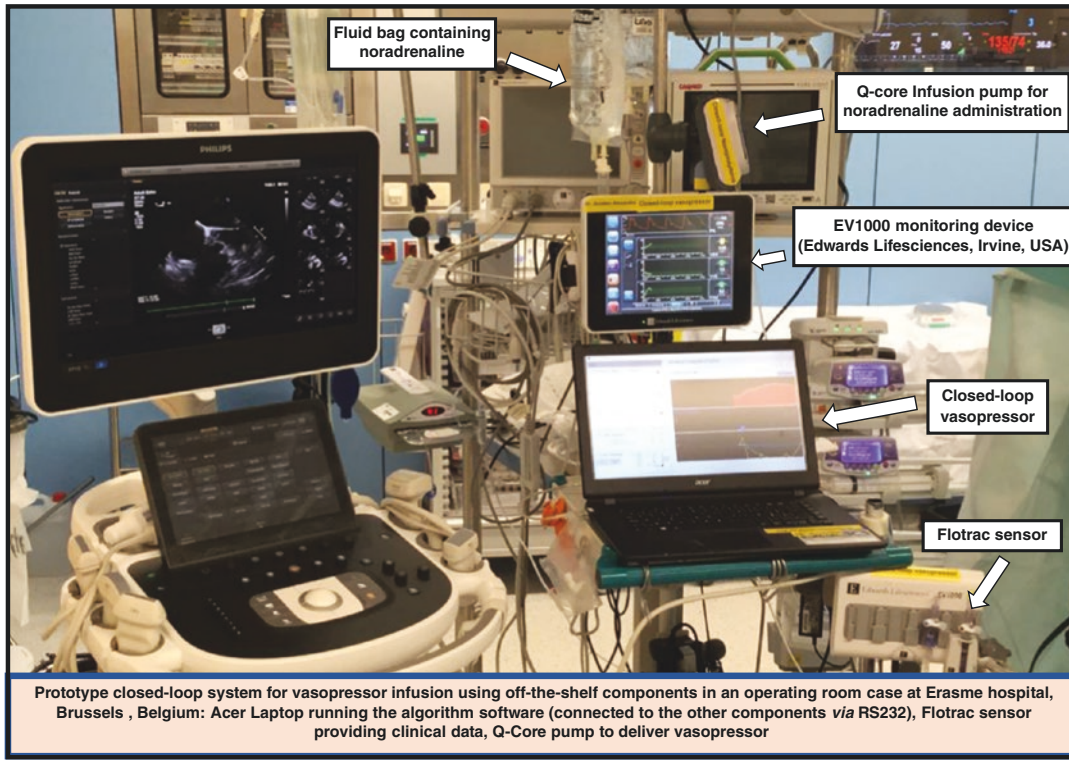

Fig. 28.2 Closed-loop vasopressor administration system at Erasme University Hospital, Brussels, Belgium

cardiac stress tests where isoproterenol is often used, though other drugs have also been trialed [81]. Limited studies have also been performed using inotropes, but additional clinical research is needed [82, 83].

28.4.4 Vasodilator

Vasodilators, like vasopressors, use arterial blood pressure as a control variable, and their titration was another very early prototyped system [84]. Despite this, relatively few studies have explored vasodilator titration, possibly due to the relative rare need for vasodilation drips and the increased risk of overtreatment. Two studies did explore automatic titration *via* closed-loop systems for both intracranial surgery [85] and following open-heart surgery [86].

28.5 Future Directions

Moving forward in this arena is an exciting and challenging prospect. One group in Paris, France, is starting to explore the feasibility of automating the simultaneous co-administration of both vasopressor and fluid infusions with promising results [87]. This is definitely a step in the right direction as fluid and vasopressor administrations are interdependent and need to be treated by a system that is "aware" of both. In the same way, our group has already reported the feasibility of conducting anesthesia in high-risk patients with multiple closed-loop systems working simultaneously, although independently, with excellent performance metrics [65, 67].

There is also significant interest in combining these "simple" automated systems with the increasingly popular field of artificial intelligence

(AI) and machine learning. Allowing an adaptive AI system to control the administration of fluids and vasopressors (along with other future therapies) would likely lead to a more patient-specific and robust system that could handle unexpected and unique scenarios safely and effectively. This eventual partnership will require large amounts of engineering and clinical cross talk, but the potential benefits would be quite significant. A future example of this would be if an optimal hypotension threshold might be determined for each patient using predictive analytics, thus further personalizing hemodynamic treatment. Additionally, it is likely that personalized titration of drugs will be based on intelligent systems that could compare active patients to previous patients with similar demographics. These systems would be able to more accurately predict the response of a given patient to specific drugs and use specific predictive treatment models within their clinical protocols. This would allow for true "precision medicine," an active goal of both the critical care and perioperative communities in recent years. Finally, AI and advanced analytics will be used to better understand the interactions between various closed-loop systems working together and will help refine the way these systems work. Ultimately, it is important to always remember that the overall goal of these closed-loop systems is to improve each patient's management and clinical outcome [88].

28.6 Conclusions

In summary, the clinical benefits for establishing and ensuring proper adherence to GDHT protocols are well established. Automation (both closed- and open-loop systems) increases compliance to such protocols while also decreasing hemodynamic variability. Closed-loop hemodynamic systems have primarily focused on fluid and vasopressor management in recent years although there are novel research systems that can combine multiple automated systems together, with potential AI integration in the future. These are all strong areas of future exploration that will require additional basic and clinical research.

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Keynotes

- The practice of anesthesiology is inevitably dependent upon technology. Anesthetics were first made possible, then increasingly made safer, and now are more innovative and functional mainly due to advances in monitoring devices and delivery technology.
- Closed-loop hemodynamic systems are evolving at an unprecedented pace and are able to increase compliance to GDHT strategies while also potentially improving patient outcomes when compared to manually adjusted systems.
- The overall goal of using closed-loop systems is to try to help clinicians in becoming more standardized in their delivery of care. The authors and developers of these systems strive to provide solutions to make the perioperative setting ever safer and more consistent (when appropriate) for our patients.

- Closed-loop hemodynamic systems should always be used as an aid to assist clinicians and not as a replacement. The human qualities that we offer patients and their families cannot and should not be replaced by machines.

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29 Artificial Intelligence and Predictive Analytics

Ilonka N. de Keijzer, Simon T. Vistisen, and Thomas W. L. Scheeren

Contents

29.1 Introduction

Artificial intelligence (AI) is a very broad term that has had multiple definitions over the years and even several interpretations of these definitions. The term *AI* appears therefore to be used in numerous societal contexts, also in medicine. In particular, *machine learning*—a subset of AI techniques—is a methodology frequently applied in hemodynamic monitoring in order to predict future hemodynamic events. The term *predictive analytics* is likewise a term with broad definitions and interpretations. However, since this chapter focuses on *artificial intelligence and predictive analytics* within the area of hemodynamic monitoring, it will focus on the prediction of adverse hemodynamic events, such as hypotension or tachycardia, based on advanced analyses of hemodynamic monitoring time series data.

We will first introduce the general methodology of applying advanced predictive analytic techniques to continuous hemodynamic monitoring data along with defining the terms used within this methodology. This is best done with a practical example.

29.2 General Terminology of Predictive Analytics

Let us assume that we want to predict the risk of tachycardia to occur within the coming 5 min, defined by a heart rate exceeding, say, 130 beats per minute, because this could be thought of as an adverse hemodynamic event [1]. Obviously, we

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would need to base that prediction on data, and analysis of the ECG seems an intuitive starting point. Perhaps other vital time series monitoring modalities, such as plethysmography and arterial blood pressure, or baseline characteristics such as patient demographics and medication may also be on the list of data sources, which the researcher hypothesizes to contain predictive information of the future heart rate.

Having defined the required data sources, the researcher has to think and plan for the various steps of the final data analysis leading to a result on the performance in predicting tachycardia. The final goal for the clinical example is a *prediction model*, which at any point in time can predict whether or not tachycardia will happen within the next 5 min. A prediction model is essentially a more or less advanced mathematical model, which is trained to output one prediction score typically based on several input data sources, termed *features*, and this prediction score is thought to be able to predict the outcome of interest with a certain accuracy. The outcome is often dichotomized as an event or nonevent (so-called *labels*), *i.e.,* tachycardia or non-tachycardia, which often means that the prediction score is high, when (in the example) the risk of tachycardia is high as compared to when the risk is low. If the prediction model works well, the prediction score summarized from the features can predict the labels correctly and only with a low number of false predictions.

The input features can be the single numbers for, *e.g.,* age and gender, but for hemodynamic monitoring, we would rarely think of the raw ECG as a feature in itself. The ECG is a high-resolution time series (*i.e.,* a voltage level measured perhaps 100–1000 times per second and signal processed with filtering). Each individual millisecond-wise number for a voltage level is virtually never used for prediction; rather characteristics (*i.e., features*) of the ECG waveform are derived to summarize the information held in the ECG. For prediction of tachycardia, an obvious feature is the derived identification of heart rate comprised by a detection of the individual R spikes and calculation of the time interval between them, possibly calculated as a mean of several RR intervals. Other features of the ECG could be measures of heart rate variability, the QT interval, possibly a derived respiratory rate, or the change in heart rate over the last couple of minutes, *etc*. The QT interval may intuitively be less relevant as a feature compared with the change in heart rate, but the researcher can choose any summarizing feature of potential interest in this explorative development phase and possibly discover unknown physiologic relations if the prediction model allows for such interpretation. And the features can also be derived from other signals, like the arterial blood pressure waveform or the photoplethysmographic signal.

To summarize the overall workflow of predictive analytics in hemodynamic monitoring, we want to be able to predict some clinical problem, the *label*, based on the *acquisition* of a lot of (*pre-processed*) time series *monitoring data*, which is summarized into a number or *features*. The *feature extraction* may or may not be followed by *feature evaluation*, *e.g.,* for evaluation of the features' internal correlation, after which they are fed into one or more *prediction models* that finally outputs its *prediction score* to predict the label, which is evaluated; see Fig. 29.1.

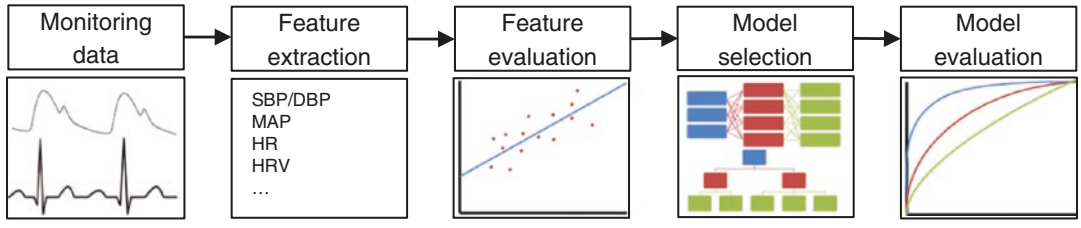

Fig. 29.1 Predictive analytics workflow for hemodynamic time series monitoring

The prediction score is often an interpretable number for the calculated probability of the event as we know it from, *e.g.,* the hypotension prediction index (HPI) [2], or it could have an arbitrary level, depending on the choice of features and prediction model. Either way, the prediction score intends to predict the *label*, *i.e.,* a certain threshold of the prediction score should be able to predict the label with a certain accuracy, *i.e.,* predict upcoming events distinct from nonevents.

Practical Advice

The aim of predictive analytics is to be able to predict some clinical problem, based on the *acquisition* of a lot of (*pre-processed*) time-series *monitoring data*, which is summarized into a number or *features*. Features can be evaluated for internal correlation before they are fed into one or more *prediction models.* Finally, model performance can be compared between different models to select the model, which is best suited to predict the clinical problem.

29.3 Evaluation of Predictive Analytics

The typical approach for evaluating a prediction model is—after collection of all required data—to subdivide the entire dataset into a training and test dataset (and preferably a third validation dataset that may be acquired externally). By doing so, the prediction model can be developed on the training set as described above, while the model knows nothing about the test set. Once the model is built, model performance is evaluated by inspecting how well the model developed based on the training dataset is able to predict events in the test dataset and possibly in a third external validation dataset; see Fig. 29.2.

Model performance is typically reported using receiver operating characteristics (ROC) curve statistics, when the prediction task concerns a dichotomous outcome (such as tachycardia *present* or *not present* in the near future). The ROC curve is a graphical visualization of how well the prediction score identifies events (*e.g.,* tachycardia) and nonevents (*e.g.,* no tachycardia) at all possible thresholds, *i.e.,* what is the combined sensitivity and specificity at each possible threshold.

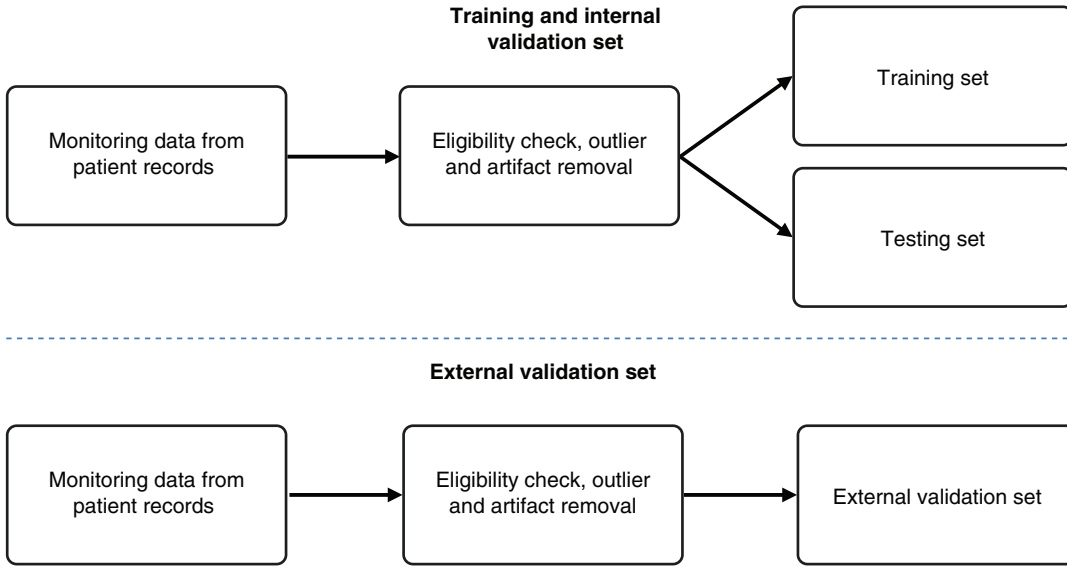

Fig. 29.2 Schematic representation of how predictive analytics models are evaluated

At the extreme (typically lowest) value of the prediction score, all events of, say tachycardia, will be correctly predicted—100% sensitivity—whereas all nonevents will be misclassified—0% specificity. If the model works well, gradually increasing the prediction score threshold from the extreme level will significantly increase specificity without reducing sensitivity much. This will happen until the threshold reaches a level, where increased specificity is on an unacceptable expense of sensitivity. Varying the threshold in this way from one extreme to the other is essentially how the ROC curve is created/drawn. Various algorithms exist in order to select the optimal threshold such as the Youden index, maximizing the sum of sensitivity and specificity, but at the end of the day, the threshold should be informed by the clinical setting, which may even vary over time. In addition, identifying optimal thresholds in predictive analytics for hemodynamic monitoring can be thought of as a screening task, where specificity is typically preferred over sensitivity (excluding the Youden Index approach). This is because over time deteriorations are rare events relative to predominant periods with hemodynamic stability, and because usually a high frequency of false alarms will lead to *alarm fatigue* among clinicians.

In the model development phase, however, researchers often want to make sure that the model is developed based on a balanced representation of cases and non-cases in both the training and the validation dataset. Windows with data prior to an event and a nonevent are equally extracted even though this may not reflect clinical reality. If the existence of an event is used in the creation of the training and validation datasets, then the model is fundamentally acausal. All evaluation measures are predicated on knowing who gets the event, *e.g.,* tachycardia, and knowing when they get it. A subsequent clinical implementation of a model derived in this way is expected to perform dramatically differently in practice, as the set of continuous data presented to the model is likely to markedly differ [3].

Another important aspect of evaluation is comparison of model performance against a sensible reference model. The researcher doing predictive analytics should feel obliged to show that his/her advanced model is not just a big Humvee used to crossing the river to get water. In the case of tachycardia prediction, the model performance reporting should not be limited to ROC curve area and other ROC statistics and a test against the flip-a-coin ROC curve area of 0.5. A simple and clinically intuitive prediction model based on, *e.g.,* heart rate and its development over time (such as the derivative for 1 min) could serve as a sensible comparator model, which the developed and often much more advanced predictive analytics algorithm should preferably outperform. In the event of outperforming the simple model, the next question of interpretability arises. A clinician being informed by a difficult-to-interpret algorithm to prepare for and possibly proactively treat, *e.g.,* upcoming tachycardia is less likely to trust that prediction if tachycardia does not appear clinically eminent and if the prediction model is known to only marginally (even if statistically significantly) better predict the event compared to a sensible reference model, which is more intuitive to the clinician. For example, if the current heart rate is rather low (say, 50 bpm), the patient is less likely to develop tachycardia in the near future compared to when the current heart rate is around 120 bpm. The predictive analytics data scientist should think of an inverse relation between the demand for model interpretability and the demand for high prediction performance. The less interpretable the algorithm is, the higher the demand for excellent prediction accuracy if the goal is clinical acceptance and implementation.

Practical Advice

In developing predictive models, the model complexity and interpretability should be weighed against the added prediction performance compared with simpler, physiologically intuitive models. The less interpretable the algorithm is, the higher is the demand for excellent prediction accuracy if the goal is clinical acceptance and implementation.

29.4 Application of Predictive Analytics

Several studies have been conducted on the topic of predicting hypotension in the ICU setting [2, 4–11]. The Medical Information Mart for Intensive Care (MIMIC) databases have been used to develop and train the predictive models in the majority of these studies. The MIMIC databases hold information from several thousands of patient records from ICU admissions. From these data, vital sign-derived features and demographics were used in the different models in order to predict arterial hypotension. All of these articles reported on feature extraction methods that were used. Of these studies, only two [6, 10] were subject to acausal data extraction. Another two algorithms were the only ones who compared their model to a reference model [5, 7]. The HPI [5] showed the largest area under the ROC curve (AUROC) in predicting arterial hypotension 5 min in advance (AUROC 0.97, sensitivity 92%, specificity 92%, positive predictive value (PPV) 88.8%, negative predictive value (NPV) 94.4%). The HPI was tested in a real-time setting using retrospective data from two centers and showed a high predictive value 5 min before a hypotensive event (AUROC 0.926, sensitivity 85.8%, specificity 85.8%) and thereby outperformed reference models of only mean arterial pressure and change in mean arterial pressure over a 3-min window [2]. Another well-performing algorithm was the super learner algorithm (AUROC 0.929, sensitivity 59%, specificity 96%, PPV 77%, NPV 91%, accuracy 89%) [11]. Not all articles reported AUROCs; however, in two of them, sensitivity and specificity were reported [6, 10], and the last one reported only a 13.7% better accuracy compared to prediction based on mean arterial pressure [7].

Three different studies focused on the prediction of arterial hypotension occurring immediately after the induction of anesthesia (post-induction hypotension), probably as a result of the vasoplegic and negative inotropic effects of most anesthetics [12–14]. In these studies, models were built with demographics, vital signs, comorbidities, and administered medications as features. Different prediction windows were used; the time from start of anesthesia until intubation was used as window in one study [12], the second used only first mean arterial pressure and first peak inspiratory pressure combined with other features [13], and the last one used baseline heart rate and arterial blood pressures [14]. None of these models were tested in real time, compared to a reference model, or were subject to acausal data extraction. The artificial neural network model developed by Lin et al. showed the best predictive values with an AUROC of 0.893 (sensitivity 76.4%, specificity 85.6%, accuracy 82.3%), which was surprising since the features that were used were chosen by clinicians and were not statistically selected based on discriminating abilities between an event and nonevent [14].

Additionally, two studies aimed to predict tachycardia in the ICU [1, 15]. Both of them used features derived from vital signs to predict tachycardia, one selected features using regularized lasso logistic regression [1], while the other used heart rate variability (HRV) features selected in a previous study and added three respiratory rate variability (RRV) features [15]. None of the developed models were compared to a reference method or tested in real time, and both cohorts were subject to acausal data extraction. In both studies, events were 1:1 matched with nonevents. The artificial neural network model with 11 HRV and 3 RRV features [15] outperformed the other model and was able to predict tachycardia 1 hour in advance with an AUROC of 0.93 (sensitivity 88.2%, specificity 82.4%, PPV 83.3%, NPV 87.5%, accuracy 85.3%). Another study aimed to predict post-intubation tachycardia by assessing the predictive abilities of different models [16]. A logistic regression model with eight hand-crafted features (promising features were selected by an exploratory data analysis process) showed the best results with an AUROC of 0.85 (accuracy 80.5%, precision 79.9%, recall 85.1%). This model was also not compared to a reference model, nor was it tested in real time.

In conclusion, evidence for the clinical use of predictive analytics in foreseeing adverse hemodynamic events is emerging and shows promising results. However, before implementing these

models in routine clinical care, more real-time testing needs to be done, and it needs to be assessed whether the complexity of most models significantly improves prediction compared to simpler models which are more intuitive and easier to understand.

Practical Advice

Comparing different models remains difficult. Model performance is typically reported using receiver operating characteristics (ROC) curve statistics, sensitivity, and specificity. Specificity is typically preferred over sensitivity because a high frequency of false alarms may lead to *alarm fatigue* among clinicians.

Keynotes

- Predictive analytics—a subset of AI techniques—is a methodology frequently applied in order to predict future hemodynamic events, based on advanced analyses of hemodynamic monitoring time series data.
- Input features for predictive models can be the single numbers for, *e.g.,* age and gender, but for hemodynamic monitoring, ECG or blood pressure-derived features are more commonly constituting the basis for the algorithms.
- To create a predictive model, features need to be extracted from monitoring data and preferably evaluated before they are fed to one or more predictive models. Models can then be compared in order to select the best performing model.
- Model performance is typically reported using receiver operating characteristics (ROC) curve statistics, when the prediction task concerns a dichotomous outcome (such as tachycardia *present* or *not present* in the near future).
- Predictive models should be compared against sensible reference models in order to assess their additional value.
- Predictive models show promising results, yet only few are currently used in clinical practice.

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Part IX

Conclusions

Conclusive Remarks

30

Mikhail Y. Kirov, Vsevolod V. Kuzkov, and Bernd Saugel

This book gives an overview of hemodynamic monitoring methods. Levels of hemodynamic monitoring are summarized in Fig. 30.1. Noninvasive routine monitoring is sufficient in low-risk surgical patients and hemodynamically stable ICU patients, whereas patients with cardiorespiratory comorbidities, critical illness, and high-risk surgical interventions require more invasive approaches, *e.g.,* invasive blood pressure monitoring, Doppler techniques, and pulse wave analysis (Levels I–III) in complex elective surgery or indicator dilution methods (Levels IV–V) in patients having cardiac surgery or refractory shock. Echocardiography can complement hemodynamic monitoring. Functional hemodynamic monitoring considers patient physiology at a given point of time in the clinical course and thus helps individualizing treatment. Methods for microcirculation monitoring as well as other novel techniques still warrant further validation in different patient groups and clinical settings.

The arsenal of monitoring techniques should increase along with both severity of illness and risk of invasive treatment (*i.e.,* extracorporeal life support, renal replacement therapy). Thus, complex invasive hemodynamic monitoring is reserved for the most severely critically ill patients, where the risk of unfavorable outcome and complications is high. Finally, the safety and efficacy of any hemodynamic monitoring method should always be considered in the context of evidence-based treatment protocols because not monitoring *per se* but interventions titrated based on monitored hemodynamic variables can eventually improve patient outcome.

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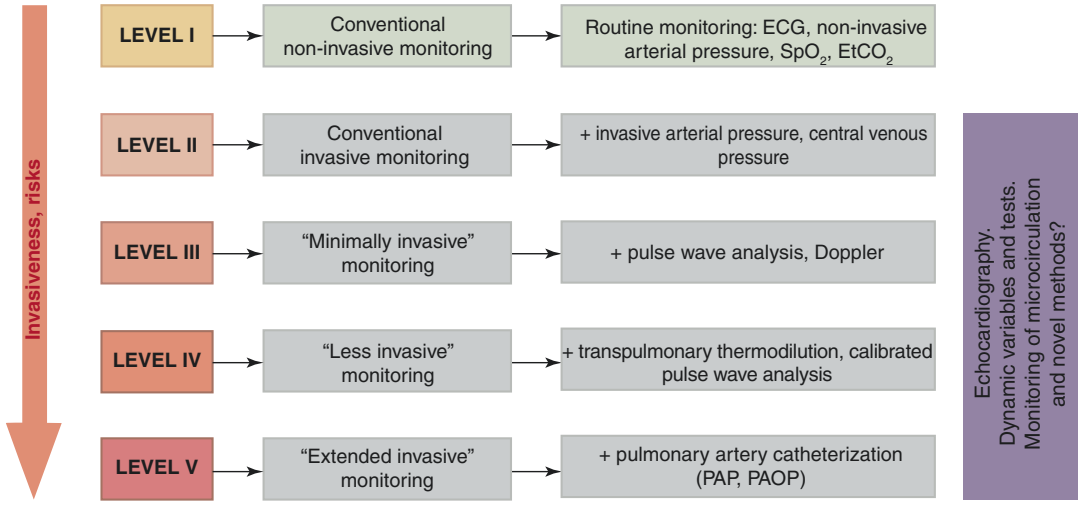

Fig. 30.1 The levels of hemodynamic monitoring. *ECG* electrocardiography, SpO_2 pulse oximetry, $EtCO_2$ end-tidal carbon dioxide, *PAP* pulmonary artery pressure, *PAOP* pulmonary artery occlusion pressure