Monitoring Tissue Perfusion in Shock

From Physiology to the Bedside

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Editors
Alexandre Augusto Pinto Lima
Department of Intensive Care
Erasmus MC University Hospital Rotterdam
Rotterdam
The Netherlands

Eliézer Silva
Medical School Hospital of the Albert Einstein
Sao Paulo
Brazil

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Preface

The era of modern hemodynamic monitoring begins, in many ways, with the development of the flow-directed pulmonary artery catheter by Swan and Ganz in 1970. This technological achievement contributed to a great extent to the understanding of the pathophysiology of shock and represented an important contribution to the application of physiological principles of circulation to the bedside care of critically ill patients. The ability of measuring cardiac output culminated later on with a wide variety of diagnostic and monitoring technologies that has granted us the ability of monitoring peripheral vascular beds also susceptible to hypoperfusion. As with most recent advances in clinical monitoring, new and useful information has been provided. Evidence produced over the last decade has clearly shown that even though global hemodynamic variables may be normalized, there could be regions with inadequate oxygenation at the tissue level. On these grounds, this book is intended to update the most recent developments in tissue monitoring at the bedside, moving from the physiological principles of global and regional perfusion to their clinical application in guiding resuscitation of shock.

In the first part of this book, the full spectrum of the oxygen transport and its consumption by the tissues is reviewed, incorporating a holistic understanding of the physiology of the processes involved and how it can help to understand and treat problems of tissue oxygenation in critically ill patients. The next part of this book addresses systemic hemodynamic monitoring in the context of cardiac function assessment and its participation in the interaction between systemic oxygen delivery and tissue oxygen demands. This discussion extends to the assessment of global markers of hypoperfusion and their physiologic significance in the understanding of perfusion adequacy to the organs, with emphasis on central venous oxygen saturation, central venous-to-arterial carbon dioxide partial pressure difference, and lactate. Finally, the last part of this book underscores the importance of regional assessment of tissue perfusion with focus on current developments and technological considerations of noninvasive commonly used techniques for assessing peripheral perfusion in shock, moving from clinical assessment to methods based on optical monitoring, transcutaneous measurement of oxygen tension, and regional capnography. Additional information is also provided covering the clinical challenges and therapeutic implications of monitoring tissue perfusion in conditions

in which the cardiovascular system is unable to maintain an adequate global and regional blood flow to the tissues, particularly covering cardiogenic and septic shock.

The book offers a valuable, easy-to-use guide useful for all levels of readers, from the resident in training to the experienced intensivist. Because new concepts of tissue perfusion monitoring are continuously emerging from studies published every year, we consider this book a work in progress and hope that in future editions we can expand upon this field.

Rotterdam, The Netherlands — Alexandre Augusto Pinto Lima
Sao Paulo, Brazil — Eliézer Silva

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Part I

Introduction

Holistic Monitoring and Treatment in Septic Shock

1

Glenn Hernández, Lara Rosenthal, and Jan Bakker

1.1 Introduction

Shock was recently defined, by a taskforce of the European Society of Intensive Care, as a life-threatening, generalized form of acute circulatory failure associated with inadequate oxygen utilization by the cells [1]. In this state, the circulation is unable to deliver sufficient oxygen to meet the demands of the tissues, resulting in cellular dysfunction. The result is cellular dysoxia, i.e., the loss of the physiological independence between oxygen delivery and oxygen consumption, associated with increased lactate levels [1]. Septic shock would thus represent this syndrome in the presence of an acute infection.

In older definitions, much more significance was given to the frequently present clinical symptoms in order to facilitate recognition. In the 1992 consensus definition by an American College of Chest Physicians and Society of Critical Care Medicine consensus conference, both included both volume-refractory hypotension and

G. Hernández
Departamento de Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

L. Rosenthal
Rosenthal Acupuncture, New York, NY, USA

J. Bakker (✉)
Departamento de Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University Medical Center, New York, NY, USA

Department of Intensive Care Adults, Erasmus MC University Medical Center, Rotterdam, Netherlands

Division of Pulmonary and Critical Care, New York University Langone Medical Center – Bellevue Hospital, New York, NY, USA
e-mail: jan.bakker@erasmusmc.nl

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perfusion abnormalities as obligatory components of a septic shock definition [2]. Over the last decade, an even simpler definition has been used, relying mainly on vasopressor requirements [3]. In this definition, perfusion abnormalities were not required for the diagnosis of septic shock. More recently, the Sepsis-3 conference defined septic shock as the combination of hypotension and hyperlactatemia in a patient with infection [4] while disregarding other markers of circulatory dysfunction such as peripheral perfusion abnormalities that were incorporated in the definition of shock by the European Society Task Force [1]. In the Sepsis-3 definition, increased lactate levels in the absence of hypotension do not classify as septic shock.

The purpose of this chapter is to provide a holistic integrative view of perfusion monitoring and treatment based on the pathophysiological definition that includes macrohemodynamic and microcirculatory symptoms and their relation to tissue dysoxia in septic shock [1].

1.2 Holistic View

In the diagnosis of the condition of a critically ill patient, physical exam still has an important place [5] even though some argue that correction of vital signs prevails detailed physical examination [6] and others even think it could be abandoned [7]. A simple assessment of pelvic instability in trauma patients [8], subjective assessment of the peripheral temperature of an ICU patient's skin [9], or even simple assessment of the extent of skin discoloration in septic shock patients [10] reveal important prognostic information. In addition, simple physical exam can even accurately distinguish different categories of shock [11]. On an even more holistic view, an uneasy feeling about the condition of a patient may already contribute the ultimate morbidity and mortality in trauma patients [12].

In the old days, clinical observation was even more important and treatment limited. In traditional Chinese medicine, stasis/stagnation, deficiency, and collapse are important characteristics of the important concepts of energy (Qi), blood, and Yin and Yang. Although the assessment of these concepts doesn't easily translate to modern intensive care medicine, the principles are frequently observed in critically ill patients.

A Qi deficiency may be characterized by lethargy, weakness, and sweating, where a Qi stagnation would be characterized by emotional distress and pain.

Blood deficiency may relate to anemia in traditional Chinese medicine although it may also refer to local blood deficiency as in abnormally perfused areas. Even more interesting is the translation of the Yin and Yang concept. This could be translated into the balance between the branches of the autonomic nervous system. In this context, the Yin would be the parasympathetic restorative branch where the sympathetic system would be the emergency response branch. In the immediate response to critical illness, the sympathetic nervous system plays an important role, and also in the treatment, we frequently use drugs to stimulate this system in order to improve hemodynamics or block this system with beta-blockers. Even using these old concepts, the presence of lethargy, sweating, and abnormal peripheral

perfusion (so a Qi and blood-deficient patient) has been shown to characterize a patient population with high chances of mortality [13].

In Chinese medicine, the concept of balance is extremely important. Optimizing health would imply the restoration of all deficiencies/stagnations. This is an interesting concept when we come to the topic of monitoring. If optimal restorative capabilities should be used to make the patient survive his critical illness, then monitoring cannot be limited to only a few macro-circulatory variables. Additionally, treatment should be targeted on all systems that we can possibly monitor. In the following, we will thus unfold a holistic monitoring plan based on our current knowledge of the (patho)physiology of critical illness.

1.3 Physiology-Based Perfusion Monitoring

A fundamental challenge in septic shock resuscitation, independent of the diagnostic criteria employed, is to evaluate tissue perfusion. During the past decades, several parameters such as gastric tonometry [14]; lactate [15, 16], mixed (SvO_2) [17], or central venous oxygen saturations ($ScvO_2$) [16, 18]; peripheral perfusion [9, 19]; oxygen tissue saturation (StO_2) [20, 21]; and central venous-arterial pCO_2 gradient ($P(cv\text{-}a)CO_2$) [22] or mixed venous to arterial pCO_2 gradient [23] have been used to monitor perfusion status or as potential resuscitation goals in septic shock. More recently, the pathophysiological relevance of septic-related microvascular dysfunction has been highlighted [24–26], and trials testing microcirculatory-oriented therapeutic strategies start to appear in the literature [27]. However, given that sepsis is a pan system disease affecting all aspects of the circulation (myocardium, pulmonary vasculature, systemic vasculature, and microcirculation), none of these markers have earned universal acceptance as *the* unique parameter to be considered as the hallmark to guide septic shock resuscitation. Moreover, they have been tested in rather mutually exclusive protocols [16]. As a result, the lack of an integrative comprehensive approach is evident, with notable exceptions [15]. This trend contrasts with our *holistic* approach. It also contrasts with suggestions to use all available techniques to monitor brain perfusion/function in neurocritical care patients and to not rely on only one or two [28]. However, as with many organ-specific protocols, they lack significant detailing on the other systems [29].

The case of central venous oxygen saturation ($ScvO_2$), a complex physiological parameter, is paradigmatic. It was widely used as *the* resuscitation goal in critically ill patients since the landmark study of Rivers et al. [18] until some recent major trials couldn't confirm these findings [30]. However, using a fixed end point of $ScvO_2$ without including the complicated interpretation of its changes [31–33] or many other parameters that affect $ScvO_2$ precludes a straightforward abandoning of its clinical use. The presence of low $ScvO_2$ clearly indicates an imbalance in the DO_2/oxygen consumption (VO_2) relationship. This finding should prompt an aggressive DO_2/VO_2 optimization strategy as was demonstrated by Rivers et al. [18]. This could already be in part realized by just decreasing oxygen demand [31]. In contrast, the presence of normal $ScvO_2$ values, as frequently observed in ICU patients,

should not be interpreted as evidence of normal global tissue perfusion as $ScvO_2$ is in strict terms a *superior vena cava* territory regional monitor. Thus, its correction does not assure the correction of global tissue hypoxia [31–33]. In addition, severe microcirculatory derangements could theoretically impair tissue oxygen extraction capabilities resulting in normal or even supranormal $ScvO_2$ values despite the presence of tissue hypoxia [33].

The preceding example demonstrates that the idea of a *single* perfusion-related parameter representing the adequacy of the whole cardiovascular system in its essential role to provide oxygenation to tissues according to local demands appears as oversimplistic and anti-physiological under a critical view [33].

In effect, there are several conceptual problems with the *single representative parameter* paradigm:

1. The relative or comparative hierarchy is relatively unknown at least in terms of prognosis. Persistent hyperlactatemia appears as the strongest prognostic factor when analyzing literature [34], although its involved pathogenic mechanisms are complex and time dependent [35, 36] that eventually may represent an unbalanced state rather than a simple manifestation of hypoxia and thus questionable as a target of treatment [37–39]. In contrast to patients with abnormal lactate levels, patients able to maintain normal lactate levels under severe circulatory stress are probably optimal physiological responders and exhibit an extremely low mortality [40]. Thus, besides its prognostic significance, development of hyperlactatemia is a powerful systemic biological signal. However, some guidelines recommend the indistinct use of lactate or $ScvO_2$ as resuscitation goals [41], a too simplistic approach that neglects other important aspects of the circulation.
2. If the hallmark of shock is tissue hypoperfusion or hypoxia, then abnormalities in the proposed parameters should be related to the presence of hypoperfusion. However, this is not the case for several parameters. Hyperlactatemia or a prolonged capillary refill time may be simply related to adrenergic-induced aerobic lactate production or vasoconstriction [33]. Oliguria is frequently multifactorial. Thus, some relevant parameters may be influenced by non-hypoxic conditions and therefore are nonspecific and occasionally unreliable as unique perfusion markers.
3. Currently recommended septic shock treatment strategies are based on the assumption that perfusion-related variables will improve after increasing oxygen delivery (mainly by increasing cardiac output), a concept that can be defined as flow responsiveness [35, 42]. However, parameters traditionally considered as representing tissue perfusion can also be mechanistically determined by non-flow-dependent or mixed mechanisms. Thus, to propose DO_2 increasing maneuvers to normalize any single abnormal parameter without considering specific involved pathogenic mechanisms appears as nonrational and may eventually lead to severe adverse events such as fluid overload and arrhythmias [43, 44], stressing the fact that overstimulation of one system might have significant side effects for the whole. Furthermore, to focus resuscitation efforts on a wrong

target can lead to dangerous unbalanced therapies: e.g., using fluid unresponsiveness as a target might induce fluid overload without any benefit if hypoperfusion has already been corrected [45].

4. The dynamics of recovery for individual parameters has not been well addressed in experimental or clinical studies. A predominant hypoxic versus a non-hypoxic pathogenic mechanism may result in a wide variability in the recovery time courses of individual parameters after DO_2 optimization [19, 35]. This fact should be taken into account when selecting a resuscitation strategy in order to determine the most appropriate target at different time points, to avoid over- or under-resuscitation.
5. The relationship of macrohemodynamics with metabolic, peripheral, regional, or microcirculatory perfusion parameters is controversial and may change throughout the resuscitation process [19, 35, 42].
6. The normalization of one parameter does not necessarily assure the normalization of others. Even more, in case of $ScvO_2$, a normalization trend to supranormal values may occasionally reflect a worsening microvascular dysfunction rather than a systemic flow improvement [32].
7. Normal/adequate values for some parameters are unknown, e.g., microcirculatory perfused vessel density or thenar muscle tissue saturation, among others.

When analyzing potentially useful perfusion-related parameters under the above described considerations, it is clear that all individual parameters have extensive limitations to adequately reflect tissue perfusion during persistent sepsis-related circulatory dysfunction. Therefore, the only rational approach to perfusion monitoring is a multimodal one, integrating macrohemodynamic, metabolic, peripheral, regional, and microcirculatory perfusion parameters to overcome those limitations. This approach may also provide a thorough understanding on the predominant driving forces of hypoperfusion and lead to physiologically oriented interventions. As an example, it is far more easy to understand the underlying mechanism of an increasing lactate level, if a low-flow state is first ruled out by simultaneous assessment of systemic hemodynamics, Scvo2, $P(cv\text{-}a)CO_2$, and peripheral perfusion [33, 46].

1.4 Initial Circulatory Dysfunction

Sepsis-related circulatory dysfunction is usually manifested as an early hypovolemic state that can be completely reversed with initial fluid resuscitation or eventually progresses into a persistent circulatory dysfunction. In contrast to a quite predictable course during the initial phase where all perfusion parameters tend to improve in parallel, persistent circulatory dysfunction can be expressed in complex and heterogeneous patterns. Although many mechanisms are involved in the pathogenesis of sepsis-related circulatory dysfunction, hypovolemia is clearly the predominant factor in pre-resuscitated patients early following hospital admission [1, 33]. Depending on the severity and time course of hypovolemia, patients may

exhibit an impaired peripheral perfusion, hyperlactatemia, low $ScvO_2$, and altered microcirculatory flow, whether or not they are hypotensive.

A couple of studies have explored the relationship between hemodynamic and perfusion parameters in this pre-resuscitative phase. Trzeciak et al. [47] found an early significant correlation between macrohemodynamic parameters, lactate, and microcirculatory flow alterations. Payen et al. [48] confirmed these findings in 43 septic shock patients undergoing initial resuscitation. The cornerstone of initial resuscitation is fluid loading. A series of dynamic studies evaluated the effects of a fluid challenge in this setting. Pottecher et al. [49] observed an improvement in sublingual microcirculatory perfusion after fluid administration in septic shock patients. Interestingly, improvement in microcirculatory flow correlated significantly with changes in global hemodynamics. However, in the presence of an already normal microcirculation, increasing cardiac output or blood pressure by fluids doesn't offer any advantages [45]. In another septic shock study, early fluid loading improved mean arterial pressure (MAP), cardiac index, SvO_2 or $ScvO_2$ values, lactate levels, pulse pressure variation, and microcirculatory flow in parallel [50]. Another study evaluated changes in metabolic and peripheral perfusion parameters at different time points during initial resuscitation. In 41 patients with septic shock, Hernandez et al. [19] found that capillary refill time, lactate, and heart rate improved in parallel during 6 h of fluid-based resuscitation.

These data taken together suggest an intricate relationship between macrohemodynamics, perfusion parameters, and microcirculatory flow indices. All these elements are affected by hypovolemia and tend to improve in parallel in fluid-responsive patients. The clinical expression of these effects is variable according to several preexisting factors such as preload responsiveness, the magnitude of adrenergic-induced redistributive vasoconstriction, or local microvascular dysfunction. The fundamental challenge in this phase is rapid and complete reversal of the low-flow state secondary to hypovolemia. Simple, readily available and validated monitoring tools such as subjective peripheral perfusion and lactate can be used to guide this process. Normalization of these parameters indicates a successful reversal of initial circulatory dysfunction [51].

1.5 Persistent Circulatory Dysfunction

In contrast to the pre-resuscitative phase, more complex mechanisms may lead the pathogenesis of persistent circulatory dysfunction. Vascular dysfunction induces vasoplegia, capillary leak, and distributive abnormalities. Myocardial depression is frequently manifested by a decreased left ventricle ejection fraction [1]. The role of microcirculatory derangements has been highlighted in recent years, and these abnormalities may hasten the development of tissue hypoxia and/or multiple organ dysfunction [26]. It is likely that evolution into different expressions of persistent sepsis-related circulatory dysfunction is influenced by the relative preponderance of any of these mechanisms at the individual level. Several recent publications support the heterogeneity of hemodynamic and perfusion profiles in persistent

sepsis-related circulatory dysfunction. Therefore, in contrast to the pre-resuscitative phase where all perfusion markers tend to improve in parallel, during persistent circulatory dysfunction individual perfusion markers may change in unpredictable or even opposite directions. Consequently, the assessment of perfusion status based solely on one marker can lead to incomplete, inaccurate, or misleading conclusions. This highlights the necessity of a multimodal holistic approach for this phase.

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Part II

Principles of Oxygen Transport and Consumption

Oxygen Transport and Tissue Utilization

2

Ricardo Castro, Glenn Hernández, and Jan Bakker

2.1 Introduction

Tissue oxygenation and regulation is a critical feature for survival of any cell and, by extension, to any organism. The maintenance of an adequate supply of oxygen (O_2) is required to maintain normal cellular function through the production of adenosine triphosphate (ATP) [1] mainly by oxidative phosphorylation in the mitochondrial Krebs cycle [2]. This requires the coordinated action of the three major systems involved in oxygen transport: the cardiovascular system, the respiratory system, and the blood. The cardiovascular and respiratory systems are designed to carry the oxygen that is present in the atmosphere down to the mitochondria.

2.2 Transport of Oxygen

The total amount of oxygen transported (DO_2) can be calculated using the following formula:

R. Castro · G. Hernández
Departamento de Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

J. Bakker (✉)
Departamento de Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University Medical Center, New York, NY, USA

Department of Intensive Care Adults, Erasmus MC University Medical Center, Rotterdam, Netherlands

Division of Pulmonary and Critical Care, New York University Langone Medical Center – Bellevue Hospital, New York, NY, USA
e-mail: jan.bakker@erasmusmc.nl

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$$DO_2 = CaO_2 \times \text{Cardiac Output}$$
$$= \left[1.34 \times Hb \times SaO_2 + \left(0.003 \times PaO_2\right)\right] \times \text{Cardiac Output}$$

CaO_2 = arterial oxygen content
Hb = hemoglobin level
PaO_2 = arterial oxygen partial pressure
SaO_2 = arterial oxygen saturation

From this it is clear that the majority of oxygen is transported to the tissues bound to hemoglobin. Hemoglobin has an oxygenbinding capacity of 1.34 mL O_2 per gram, where the oxygen content mainly depends on oxygen saturation and hemoglobin concentration, as the amount of dissolved oxygen in the blood is minimal. The oxygen partial pressure at sea level is approximately 160 mmHg. From this high initial pressure in the lungs, there is an abrupt fall of about 4–8 mmHg at the mitochondrial level (Fig. 2.1). The level

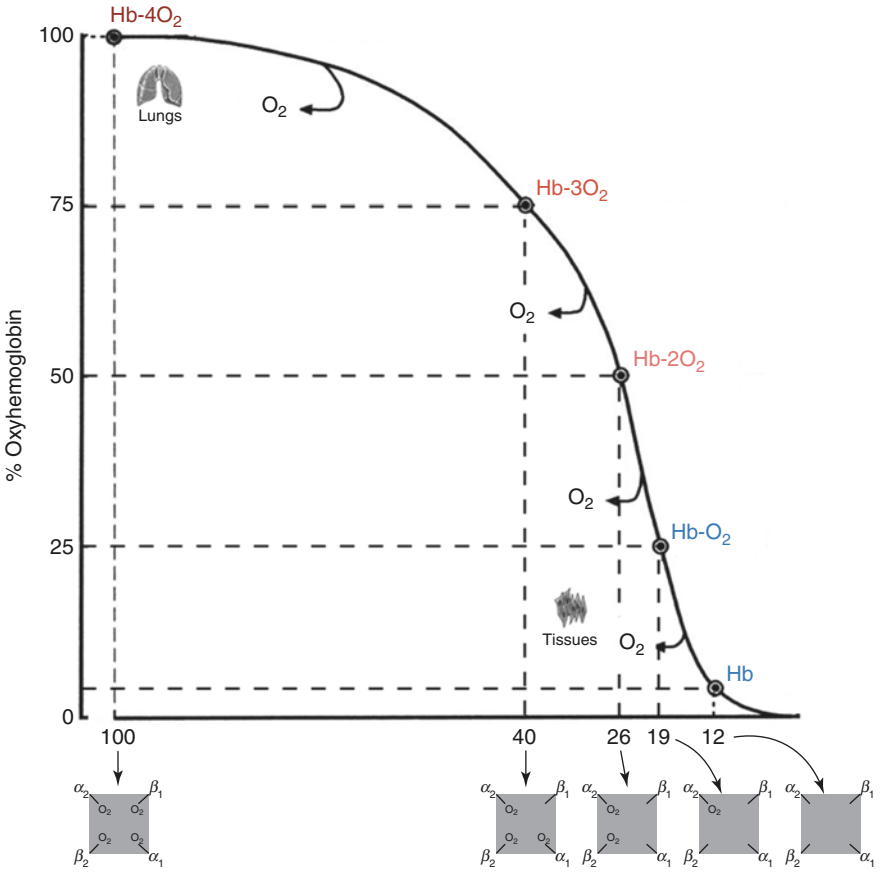

Fig. 2.1 Oxygen fall. Respiration is a cellular phenomenon. Intracellular oxygen partial pressure must be maintained between 5 and 8 mmHg

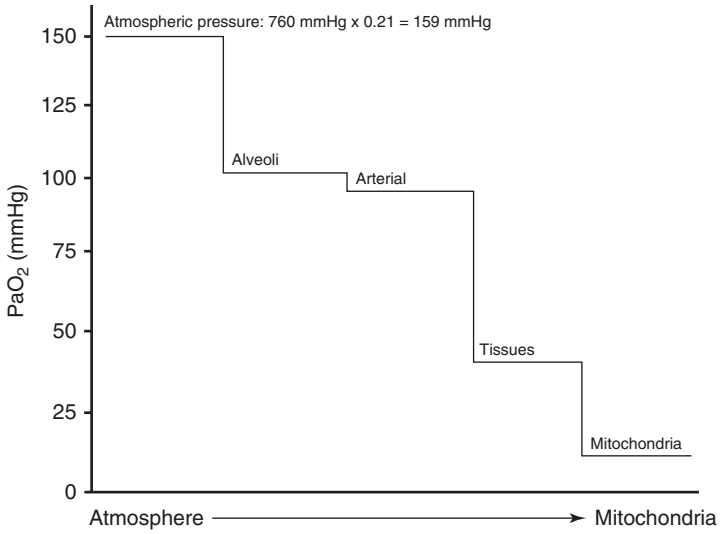

Fig. 2.2 Hemoglobin's oxygen dissociation curve is sigmoidal. The four-subunit arrangement in hemoglobin (α_1, α_2, β_1, β_2) accomplishes a specific function when hemoglobin flows from high oxygen tension in the lungs to the low oxygen tension areas in the tissues and back to the lungs. Oxygen remains tightly bound to hemoglobin in the lungs but will be progressively released as partial oxygen pressure drops in the tissues of the body. The release of the second, and even more so the third, oxygen molecule requires a smaller drop in pressure as the erythrocyte moves farther from the lungs, whereas the reverse occurs when the erythrocyte moves to the lungs (figure constructed from [4])

of saturated hemoglobin (SaO_2) is determined by the oxygen–hemoglobin dissociation curve, where the proportion of hemoglobin in its saturated form is plotted against the prevailing oxygen tension on the horizontal axis. This curve is an important tool for understanding how the blood carries and releases oxygen. This curve is such that when SaO_2 drops to less than 90%, even small variations in PaO_2 are associated to important changes on SaO_2 [3]. Generally speaking, a SaO_2 of about 50% (P_{50}) associates to a PaO_2 of 26 mmHg (Fig. 2.2, [4]). Shifts in the oxygen dissociation curve (resulting in changes in the P_{50}) are related to changes in the off-loading of oxygen. A right shift of the curve (increase in P_{50}) as seen in acidosis, hypercapnia, and fever facilitates oxygen off-loading. Normal DO_2 is approximately 1000 mL/min or 500 mL/min.M^2 if cardiac index is substituted for cardiac output:

Oxygen consumption (VO_2) is the rate at which O_2 is taken up from the blood and used by the tissues. It can either be directly measured or calculated. VO_2 is defined by the Fick equation as the difference between the content of oxygen in the arterial and mixed venous compartment (equaling the amount of oxygen taken up by the periphery) multiplied by the cardiac output (the flow through the system).

$$VO_2 = \left(CaO_2 - CvO_2\right) \times \text{Cardiac Output}$$

$$SvO_2 = \left[1.34 \times Hb \times SvO_2 + \left(0.003 \times PvO_2\right)\right] \times \text{Cardiac Output}$$

CvO_2 = arterial oxygen content
PvO_2 = mixed venous oxygen partial pressure
SvO_2 = mixed venous oxygen saturation

Oxygen extraction ratio (ERO_2) is the relationship between DO_2 and VO_2, and it normally ranges from 0.25 to 0.30. When we reduce the formula for ERO_2 to its main components, we are left with

$$\begin{aligned} ERO_2 &= \left(CaO_2 - CvO_2\right) / \left(CaO_2\right) \\ &\approx 1 - SvO_2 \end{aligned}$$

Therefore, mixed venous oxygenation (or its surrogate, central venous oxygenation) is clinically used to estimate the balance between oxygen delivery and oxygen demand. Under normal conditions oxygen demand equals oxygen consumption. However, when central venous oxygenation falls, it reflects an imbalance between the demand and supply. This is not equal to inadequate oxygen consumption (as this would reflect a state of tissue hypoxia) but rather a compensation for a decrease in delivery either due to a decrease in oxygen content or cardiac output. The transport of oxygen does not equal the delivery of oxygen to the tissues. For this local blood flow is regulated by several tissue factors mainly related to the metabolic rate. So, cardiac output is redistributed among the tissues depending on their relative requirements, where this regulation occurs in the microcirculation [5]. Thus, under normal conditions, cardiac output is demand driven.

Once oxygen reaches the tissues, a part of it passes to the interstitial space and freely diffuses to the intracellular space and mitochondria. The site within the mitochondria at which oxygen is consumed is cytochrome c oxidase, the terminal electron acceptor in the electron transport chain. Mitochondria appear to be able to sustain normal oxygen consumption needed for generating ATP at a maximum rate, until the amount of oxygen in their immediate vicinity acutely falls below a critical value of 4–6 mmHg [6, 7]. In chronic hypoxemia conditions, this threshold is significantly higher, and suppression of oxygen consumption may already start below 40 mmHg [8].

Tissue oxygenation is typically described by one of the following three terms: first, normoxia, being a state where cellular PO_2 is greater than the critical value; second, hypoxia, where some tissue regions have less than adequate oxygen levels and in consequence mitochondria produce ATP at a submaximal rate; and third, anoxia, which is the absence of oxygen in the tissue where mitochondria cease to produce ATP [9]. CO_2 diffuses rapidly through the tissues and across peripheral capillary walls due to its greater solubility. Because of this CO_2 elimination from tissues is seldom a concern of diffusion but rather dependent on the perfusion of the tissues. Therefore, changes in cardiac output relate to changes in central venous CO_2 levels in many disease states [10–12].

Oxygen exchange occurs not only across the walls of capillaries but can be exchanged between any two regions in which a partial oxygen pressure difference occurs or where a gradient is present. Therefore, a significant transarteriolar O_2

gradient is generally present. It was Krogh who presented a more accurate model and description of oxygen transport in tissues. Since all capillaries were assumed to be identical and uniformly spaced, he devised a simple tissue model for oxygen transport and consumption constituted by a single capillary with continuous blood flow, surrounded by a concentric cylinder of oxygenconsuming tissue. This model was refined over time to take into account the variations in capillary hematocrit, the low solubility of O_2 in the plasma, and the resistance to oxygen diffusion between the blood and tissue due to the particulate nature of the blood [13]. Diffusion is the mechanism by which oxygen passes from blood to tissue cells. As red blood cells (RBC) pass through capillaries in single file due to their similar size to the capillary caliber, oxygen is continuously released from the RBC hemoglobin and eventually diffuses to the mitochondria where it is consumed. Although most (≈98%) of the oxygen in the blood is reversibly bound to hemoglobin, the vector or the "driving force" for oxygen movement from the blood to tissue is the PO_2 difference that exists across the vascular wall, not hemoglobin level or arterial oxygenation levels [1, 2].

2.3 Some Clinical Considerations

From the formula for DO_2, it may seem that manipulating oxygen content (oxygen saturation and hemoglobin levels) is as effective as manipulating cardiac output or its distribution. As already mentioned earlier, adaptation to the changing need for oxygen of tissues, these tissues do not influence oxygen content but rather change the flow. In addition, increasing oxygen levels have been associated with adverse effects on tissue oxygenation and outcome [14–16]. Therefore, the judicious use of oxygen has been challenged [17] and clinicians are increasingly willing to apply conservative supplemental oxygen strategies [18]. Although the same holds for blood transfusion given the results from older studies [19–21], more recent studies focusing on the microcirculation have shown beneficial in recruiting the microcirculation [22–24]. Therefore, a transfusion strategy should probably not focus on a static hemoglobin level but rather on the state of the microcirculation.

For almost three decades, DO_2 optimization has been one of the fundamental strategies to improve tissue oxygenation during acute circulatory dysfunction, particularly in high-risk surgical or septic patients. And in the majority of studies, the main manipulated variable was cardiac output next to blood pressure. The pioneer studies by Shoemaker et al. identified an O_2 debt in these patients that was related to organ failures and mortality [25]. In a subsequent study, Shoemaker et al. showed that a strategy of DO_2 maximization to supranormal levels with fluids and vasoactive agents aimed at decreasing or preventing this O_2 debt decreased mortality [10]. Other investigators confirmed that increasing DO_2 to high levels not only increased VO_2 but also improved survival in patients with severe sepsis [26–28]. However, other large studies showed no benefit where one study even showed increased mortality associated with this approach [29, 30].

Although not specifically targeting VO_2 but incorporating all the elements of increasing DO_2, Rivers et al. [31] showed that therapy aimed to improve cardiac

output and oxygen content significantly increased survival in early severe sepsis in emergency department patients. A redo of the concepts of Rivers many years later did not show to have a survival benefit [32–34]. However, the patient population in these studies (among other characteristics) was markedly different from the original study [35]. Nevertheless, it seems obvious that in patients with a risk of under-resuscitation, like postsurgical patients, the concept of early hemodynamic optimization (that mainly manipulates DO_2) is related to improved survival [36, 37].

The resuscitation of patients with hemodynamic dysfunction is more than normalizing hemodynamics as an approach like that might prove to be inadequate [38], but also the therapies might have inherent negative effects. More recently, the risk of fluid overload has been highlighted [39, 40], and it has been recognized that fluid resuscitation to fixed static hemodynamics might induce harm [41, 42]. Therefore, these static clinical endpoints of fluid resuscitation have been removed from the latest sepsis guidelines [43]. Like in the discussion on blood transfusion earlier, aiming for fixed endpoints for fluid resuscitation, cardiac output, and blood pressure, it seems more physiological to aim for the ultimate target: improving microcirculatory perfusion. Although some studies have shown that the microcirculation as the target of resuscitation might be a relevant endpoint [22, 44–46], larger clinical studies incorporating holistic protocols, covering all aspects of tissue perfusion, are necessary.

Another important aspect is that some therapies aimed at improving DO_2 or VO_2 in clinical practice could be harmful not only in terms of toxicity but also detrimental for the purpose for which they were indicated.

Especially the use of vasoactive agents (vasopressors, vasodilators, inotropes) may have unwanted side effects.

Dobutamine increases myocardial VO_2 and might enhance maldistribution of flow between different organs due to unbalanced vasodilatory effects that could be associated with increased mortality [30, 47]. In general, the vasopressor load and the use of multiple vasopressors has been associated with adverse outcome [48–50]. Although vasodilators might improve the microcirculation and have been associated with an increase in oxygen consumption (as a marker of improved tissue perfusion) [51–54], there may be decreases in blood pressure [52] that may have negative [55] or even positive effects [56, 57] in some patients.

Therefore, the management of a patient in shock with the theoretical concepts of the main drivers for transport of oxygen and the subsequent delivery of oxygen to the tissues might lead to a structured approach that might benefit the patient more than using static clinical endpoints for these variables.

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Guyton at the Bedside

3

David Berlin, Vivek Moitra, and Jan Bakker

3.1 Introduction

Beginning in the 1950s, Arthur Guyton and his colleagues performed a series of experiments that culminated in the development of a comprehensive model of the human circulation. This model was codified in his classic textbooks *Medical Physiology* and *Cardiac Output and Its Regulation*. The former is the English language's most popular physiology textbook, and the latter is the definitive treatment of the topic. Guyton developed his model by trying to manipulate individual circulatory factors while keeping other factors constant. The model is most successful in describing the function of the arterioles, veins, and heart. *A major limitation of Guyton's model is the use of the analogy to a direct current circuit. In reality, the*

D. Berlin
Division of Pulmonary and Critical Care Medicine, Department of Medicine, Weill Cornell Medical College, New York, NY, USA
e-mail: berlind@med.cornell.edu

V. Moitra
Division of Critical Care, Department of Anesthesiology, College of Physicians and Surgeons of Columbia University, New York, NY, USA
e-mail: vm2161@cumc.columbia.edu

J. Bakker (✉)
Department of Intensive Care Adults, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands

Departamento de Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

Division of Pulmonary and Critical Care Medicine, College of Physicians and Surgeons of Columbia University, New York, NY, USA

Division of Pulmonary, Sleep Medicine and Critical Care, New York University, Langone Medical Center-Bellevue Hospital, New York, NY, USA
e-mail: jan.bakker@erasmusmc.nl

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circulation behaves more like an alternating current circuit. Guyton's DC model does not account for features of AC circuits: capacitance, inertance, and wave reflections in the arterial system [1]. *The aortic Windkessel model is a more accurate modern model. However, such models are more complex and presently less useful at the bedside.* An understanding of Guyton's model of the circulation is essential for the modern practice of critical care medicine.

3.2 Elements of the Guyton Model

Guyton's model is analogous to an electrical circuit, a technique long used by engineers to describe hydraulic systems. The Guyton model is a lumped model—it consists of discrete idealized segments. These segments are compartments which are connected in series. In Guyton's model, a variety of hydraulic pumps create pressure gradients between the compartments that propel blood forward. Importantly, the atria and ventricles of the heart are just four of these pumps. The respiratory muscles of the thorax, the skeletal muscles of the limbs, and the smooth muscles of the systemic veins also have important roles in generating blood flow and cardiac output. A series of valves help maintain pressure and forward flow in the circuit. Guyton's model demonstrates that the systemic and pulmonary vessels are not mere passive conduits that carry blood. Rather, they are under important regulation. The systemic and pulmonary arteries bifurcate into an extensive network of arterioles which serve as resistors in parallel. The capillaries are the sites of diffusion between blood and tissues. Guyton's model shows that both local and central factors regulate the elements of the circuit. An example of local regulation is the dominant control the tissues exert over systemic arterioles. Additionally, the pulmonary arterioles are mainly under the control of local gas tensions and the degree of lung inflation, while the stretch of the heart by venous return (VR) modulates heart rate and contraction. In addition to local control, there is also central regulation of the circulation, which is mainly provided by the autonomic nervous system.

3.2.1 Cardiac Function

Guyton challenged the traditional concept that heart function alone determines cardiac output. To demonstrate this, he electrically paced the hearts of dogs that had a surgically created arteriovenous fistula between the aorta and inferior vena cava. When the fistula was closed, an increase in pacing rate did not increase cardiac output. Opening the fistula increased the rate of VR to the heart to that cardiac output increased as heart rate increased [2]. In Guyton's model, the normal heart serves as a permissive automaton; it simply pumps out whatever volume of blood returns to it. Guyton demonstrated that by increasing VR, via blood transfusions in dogs, that cardiac output increased and remained elevated independent of heart rate [3, 4]. The heart, however, has a crucial role in maintaining the main circulatory volume and thus preserving the mean circulatory filling pressure (MCFP, see later) in the long run [5].

The heart responds to VR by increasing its force of contraction through the Frank-Starling mechanism. This entails diastolic stretch creating more favorable actin-myosin cross-linking. This mechanism allows matching of the right and left ventricular outputs to prevent accumulation of blood in either ventricle. The heart responds to increased VR by two additional mechanisms. First, stretch of sinoatrial node tissue in the right atrial wall increases its automaticity and raises heart rate. Second, VR activates stretch receptors in the heart which results in sympathetic input to the heart. The sympathetic input increases calcium influx into myocytes. The rise in intracellular calcium raises the contractility of the heart. Together all of these mechanisms help the heart increase its output in response to increased VR.

An essential feature of Guyton's model is that the heart matches its output to the metabolic needs of the end organs. However, the heart is unable to directly measure the needs of the tissues. Instead, the tissues control the heart's output by increasing the return of blood to it. Therefore, cardiac output relates to oxygen consumption that determines organ blood flow by local (metabolites, local hormones, and myogenic and endothelial factors) processes (Fig. 3.1).

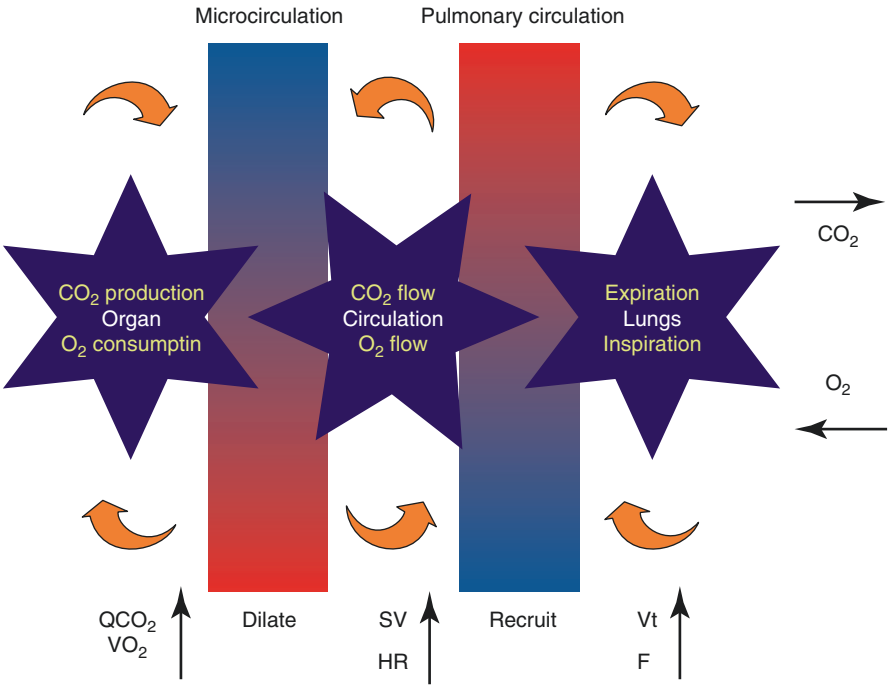

Fig. 3.1 The overall model of the circulation indicating that cardiac output originates from the left part of the figure (i.e., oxygen consumption). By various mechanisms, increases in local oxygen consumption increase local blood flow, thereby generating more venous return causing the cardiac output to increase. This increases pulmonary blood flow that allows to remove the excess of carbon dioxide from the system (produced by increased metabolism) and add oxygen to the system. The blood flow through the system thus is demand driven

3.2.2 Venous Return to the Heart

Guyton's model recognizes the vital importance of the venous system in regulating cardiac output. The systemic veins normally contain two-thirds of the total blood volume. This compartment serves as an adjustable reservoir under systemic control [6]. The veins have smooth muscle in their walls that constricts in response to sympathetic stimulation. The pressure of blood in the synthetic veins is due to the blood volume and the compliance of the vessel walls. An estimate of this pressure is called the MCFP, which normally approximates 6–7 mmHg [7]. The MCFP is the average pressure in the circulatory system *without* cardiac pumping and is build up by the stress volume. Where the unstressed volume only fills the vessels to their normal shape, the stressed volume generates the elastic recoil force that drives blood back to the heart [1]. Experiments can estimate MCFP and the stressed volume by measuring the hydrostatic pressure in the circulation during ventricular fibrillation or circulatory arrest or measure the blood draining from the venous circulation at circulatory arrest [8].

For optimal VR, the diastolic pressure in the right heart should be as low as possible [9]. Guyton showed that there is a near-linear inverse relationship between right atrial pressure and VR. Therefore, the RAP is the consequence of VR and cardiac function (Fig. 3.2) and not the preload parameter of cardiac output as has been misunderstood and misused in clinical practice [9] leading to inappropriate recommendations for fluid resuscitation [10–12].

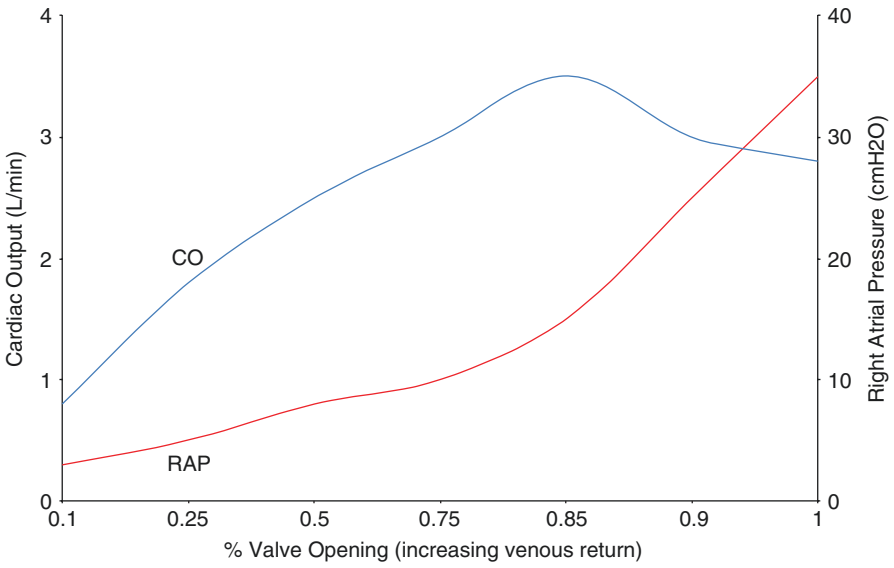

Fig. 3.2 Alternative presentation of the Starling curve with the actual independent variable (opening of the venous return valve) on the *x* axis. From [9]

Under normal conditions, the inspiratory muscles reduce intrathoracic which lowers right atrial pressure to negative values and thus decreases the resistance to venous return (RVR). This negative pressure pulls blood into the right heart. Furthermore, his model suggested that high right atrial pressure due to cardiac failure or positive intrathoracic pressure impedes VR.

$$\mathrm{VR} = \frac{\mathrm{MSFP} - \mathrm{RAP}}{\mathrm{RVR}}$$

Guyton performed a number of experiments to formulate his model. In one, a venous cannula attached to a motorized pump was placed in the right atrium of a dog, and an arterial output cannula was placed in the proximal aorta. The pump speed determined the right atrial pressure (RAP), and the circulating volume determined the MCFP. Through these experiments, Guyton constructed a series of venous return curves, which demonstrated that venous return was determined by the MCFP-RAP gradient [13]. Further proof of the VR concept has been provided by imaging and flow analysis during cardiac arrest: after ventricular arrest, blood continues to flow into the right heart from the systemic circulation until their pressures are equalized and the volume in the systems equals the unstressed volume [8, 14].

3.2.3 Autoregulation of Systemic Blood Flow (Determinants of MCFP)

A key feature of Guyton's model is the dominant role of autoregulation in the control of the circulation. According to Guyton, the tissues control their own blood flow by dilating the arterioles that deliver their blood (Fig. 3.1). The systemic arterioles act as resistors in parallel. The systemic arterioles are normally in a state of active vasoconstriction. Metabolically active tissues secrete acid and other by-products of metabolism which dilate the metarterioles and reduce resistance in that segment. By this mechanism, tissues can accept more arterial blood flow. If there is generalized metabolic signaling, there will be widespread arteriolar vasodilation. The systemic arterioles normally provide the main resistance in the circuit. Therefore, arteriolar vasodilation can reduce the resistance to venous return to the heart. Guyton stated that all causes of chronically elevated cardiac output entailed systemic arteriolar vasodilation. Guyton showed that increasing metabolic rate in mammals by using a metabolic uncoupler dramatically decreased systemic vascular resistance and increased blood flow. As predicted by Guyton's model, pathological states such as thyrotoxicosis, anemia, and arteriovenous fistula all increase cardiac output. He also showed that systemic hypoxia elevates cardiac output.

In the Guyton model, systemic arteries act as conduits for blood flow. The systemic artery compliance is an important determinant of systemic blood pressure. Adequate, systemic blood pressure is essential for autoregulation but not for the distribution of blood flow. During exercise, cardiac output increases significantly

without a change in blood pressure. Only in a high-pressure system can differential relaxation of arterioles allows distribution of arterial blood to tissues needing more flow. Because of the high resistance in the systemic arterioles, blood flow entering the systemic capillaries is nonpulsatile and a low pressure. Blood percolates through the narrow and extensive capillary beds, and gas exchange occurs across the thin-walled vessels.

3.2.4 The Pulmonary Circulation

The pulmonary circulation has a much lower resistance and therefore requires less energy than the systemic circulation. The pulmonary circulation normally imposes much less of a load on the right heart than the systemic circulation imposes on the left ventricle. Guyton's model explains that the pulmonary circulation uses a different mechanism to regulate the distribution of blood flow than the systemic circulation. The lungs regulate the distribution of blood flow through differences in pulmonary vascular resistance. The distribution of ventilation has the greatest effect on the local resistance in the pulmonary arterioles. Hypercapnia, hypoxia, and atelectasis all increase vascular resistance and redistribute blood flow toward the best ventilated lung units. Additionally, gravity has a greater effect on the distribution of blood flow in the pulmonary circulation than in the systemic circulation. Both perfusion and ventilation are greatest in dependent lung regions. The matching of ventilation with perfusion is essential for optimizing gas exchange in the alveoli. Thus, Guyton's model explains the physiologic basis for the differences between the systemic and pulmonary circulations.

3.2.5 Clinical Applications of the Guyton Model

From the Guyton model, three major types of circulatory failure can be depicted (Fig. 3.3). First is the failure of the pump. This can be intrinsic cardiac failure (infarction, myopathy, etc.) or extrinsic cardiac failure (tamponade, pulmonary embolism). Second is the failure of the pipes (severe arterial vasoconstriction or vasodilation). Third is the failure of the (stressed) volume (hemorrhage). A combination of these different primary failures can of course cause different patterns where septic shock, especially in the early phase, can contain elements of all three major types (decreased stressed volume; cardiac failure due to septic myopathy, acidosis, etc.; and severe vasodilation).

3.3 The Pump

3.3.1 Heart Failure

When the heart fails, blood wells up in the heart chambers proximal to the injury. The rise in pressure can cause symptoms (e.g., pulmonary edema or peripheral

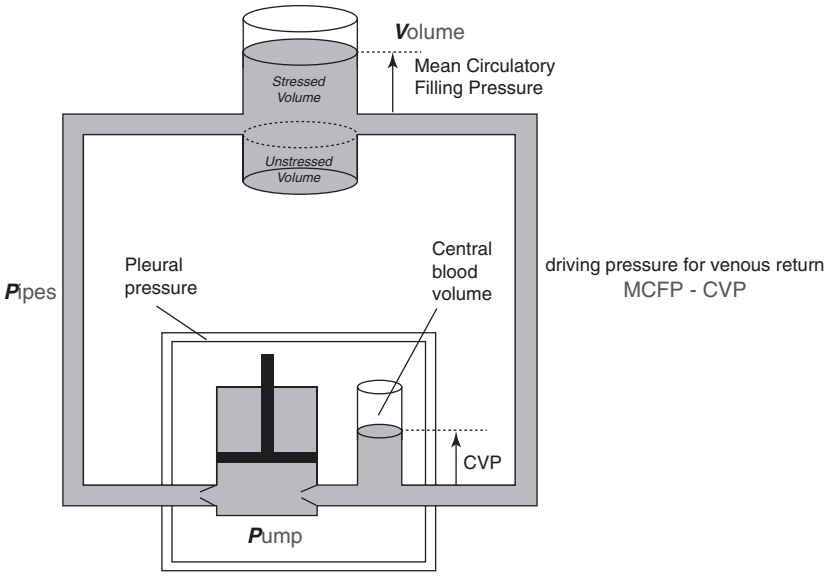

Fig. 3.3 A model of the circulation based on the Guyton principles [8] showing the three major causes for circulatory failure: pipes, pump, and volume. The driving pressure of the circulation is the pressure for venous return: mean circulatory filling pressure (MCFP) and central venous pressure (CVP)

edema) and increase myocardial work. The Guyton model shows that an increase in intracardiac pressure decreases the gradient for venous return. Thus, to maintain cardiac output, the MCFP must increase by expanding blood volume as well as vasoconstriction by sympathetic tone. This compensation creates a vicious self-perpetuating cycle in which increases in cardiac pressure lead to reductions in the pressure for venous return. Therapy for heart failure includes interventions to lower intracardiac pressure (correction of valvular lesion, inotropic and mechanical support, and diuresis) more than the fall in MCFP.

3.3.2 Pulmonary Hypertension

Guyton classic experiments revealed the effect of increasing the resistance in the pulmonary vascular bed. By constricting the pulmonary arteries, the load on the right ventricle increased. Pulmonary artery pressures rose in parallel with the vascular resistance, but right atrial and systemic blood pressures were preserved. When the pulmonary resistance was increased beyond the limit of the right ventricle's ability to compensate, the cardiac output fell. The fall in cardiac output leads to a reduction in systemic and pulmonary artery pressure. The clinical relevance is that pulmonary artery pressure may fall when pulmonary vascular resistance increases. However, right atrial pressure will rise as the right heart fails and blood damns up in the right-sided chambers. Guyton showed that the limit of compensation could be

increased by an infusion of epinephrine. It is now known that the benefits of epinephrine in right ventricular failure are due to its inotropic effect as well as the elevation of systemic arterial pressure and the coronary perfusion gradient. Treatment of patients with exogenous catecholamines allows the right ventricle to tolerate greater amounts of obstruction of the pulmonary vascular bed.

3.3.3 Tamponade

Tamponade increases RAP, thereby decreasing the pressure for venous return and hence cardiac output. Although fluid resuscitation has been shown to increase cardiac output in some patients, the majority does not respond to fluids as would be consistent with the Guyton model [15]. Release of the intrapericardial pressure results in an immediate decrease in RAP facilitating an increase in venous return and the rise in cardiac output [16].

3.4 The Pipes

3.4.1 Vasodilation

During acute vasodilatation, the cardiac output will first increase (de Jager-Krogh phenomenon) despite the arterial hypotension [17–19]. When persistent, the increased venous capacitance causes peripheral pooling of blood and decreases venous return into the heart. Fluid administration and venoconstrictors (such as catecholamine vasoconstrictors) can restore the gradient for venous return and increase cardiac output despite the rise in left ventricular afterload [20–23].

3.4.2 Vasoconstriction

In severe vasoconstriction, like in pheochromocytoma, left ventricular afterload impairs left ventricular function and the restorative function of the heart to preserve the filling of the venous system and thus the elastic recoil that maintains venous return [1, 5] resulting in circulatory shock [24].

3.5 The Volume

3.5.1 Acute Hemorrhage

Severe blood loss decreases mean circulatory filling pressure and the gradient for venous return. Hence, cardiac output will decrease unless circulatory reflexes restore venous return. When despite maximum sympathetic tone, the circulatory volume reached the unstressed volume, cardiac output will cease. The

administration of fluid or venoconstriction can increase mean circulatory filling pressure to restore cardiac output [20, 21]. Fluid resuscitation should however not be focused on increasing RAP. Under normal conditions, the cardiac output increases manifold without significant changes in RAP [9, 25]. A significant increase in RAP would thus rather indicate right ventricular dysfunction [1] during ongoing fluid resuscitation. In addition, increases in RAP are associated with decreased microcirculatory perfusion [26] and organ dysfunction [10, 27]. Management of hemorrhage is challenging in conditions such as spinal shock or spinal anesthesia because of impaired circulatory reflexes [28].

3.6 Limitations of the Guyton Model

Guyton developed his model by trying to manipulate individual circulatory factors while keeping other factors constant. The model is most successful in describing the function of the arterioles, veins, and heart. A major limitation of Guyton's model is the use of the analogy to a direct current circuit. In reality, the circulation behaves more like an alternating current circuit. Guyton's DC model does not account for features of AC circuits: capacitance, inertance, and wave reflections in the arterial system [1]. The aortic Windkessel model is a more accurate modern model. However, such models are more complex and presently less useful at the bedside.

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Tissue Response to Different Hypoxic Injuries and Its Clinical Relevance

4

Adriano José Pereira and Eliézer Silva

4.1 Classical Understanding About Tissue Hypoxia

The appearance of oxygen in atmosphere approximately 2.3 billion years ago dramatically changed the life, due to its toxicity related to highly reactive chemical properties. However, a specific and primitive type of unicellular organisms emerged evolving after a symbiotic phenomenon of mitochondria incorporation, representing the origin of the eukaryotic metazoan life on Earth [1–3].

Knowledge about consequences of hypoxia, and the need to intervene when it is identified in critically ill patients, dates to the second half of the nineteenth century, and it is part of the intensive care history, itself [4–7].

Recognizing the importance of measuring oxygen delivery to tissues developed fast since Pflüger performed his first experiments on measuring oxygen content in blood, in 1868. With the development of automated methods to measure blood saturation [8], with the description of techniques to assess hemoglobin concentration [9], and, lately, with the validation of the thermodilution method to measure cardiac output at bedside [10], the basis for oxygen delivery and consumption relationship estimation were launched, considered both of its dimensions: oxygen content and blood flow (cardiac output).

4.1.1 From Global Hemodynamics to Tissues

Different adaptive mechanisms take part in the immediate response to hypoxia. Independently of the hypoxia nature (hypoxic hypoxia, anemic hypoxia, stagnant or circulatory hypoxia, or cytopathic hypoxia), a systemic and coordinated response,

A. J. Pereira (✉) · E. Silva
Hospital Israelita Albert Einstein, Sao Paulo, Brazil
e-mail: adrianojop@einstein.br; silva.eliezer@einstein.br

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aiming to increase oxygen delivery to tissues, is triggered. Arterial oxygen content is dependent on hemoglobin levels, blood oxygen saturation, and oxygen partial pressure. Therefore, from a given FiO_2 (at a specific altitude), oxygen content cannot be acutely changed. During chronic exposure to hypoxia (for instance, during high altitude adaptation), organisms can increase arterial oxygen content through bone marrow stimulation, producing more hemoglobin and increasing hematocrit, basically due to increased erythropoietin production, dependent on iron availability and genetic factors [2]. From this point of view, globally, and in acute sets, flow changes become the main adaptive mechanism available to meet increased oxygen demand or to compensate tissue hypoxia. Such alterations and mechanisms will be discussed in different chapters of this book.

In terms of local hemodynamics, organs can control their flow independently, within physiological limits. This is named blood flow autoregulation. Actually, besides hemodynamic changes, metabolic (low O_2, high PCO_2) and hormonal (vasopressin, NO, angiotensin) factors take part and can contribute to match increased tissue demand to delivery. Moreover, different organs have different oxygen needs. For instance, muscle and the skin are much more tolerant and need much less oxygen to maintain local oxygen consumption (VO_2) than the brain and, therefore, generate different local venous oxygen saturation rates (SvO_2). To illustrate this phenomenon, while most of organs extract about 25–30% of oxygen (resulting in a regional SvO_2 of 70–75%), the heart does the opposite with oxygen extraction rates from 60 to 80%, at rest [11]. In addition, different organs have different local vascular resistances, which determines local flow. Organs with lower oxygen needs, usually extract less oxygen, present higher vascular critical closing pressures, and higher local resistance [12]. More details about microcirculatory changes during hypoxia, tissue oxygen utilization, and vasomotor tonus can be found in other chapters of this book.

4.2 When Adaptive Mechanisms Are Insufficient to Compensate Hypoxia

When global and local adaptive mechanisms fail to meet organ-specific demands, before brain, heart, and kidney VO_2 starts to be limited resulting in organ dysfunction, organisms can try to redistribute flow from tissues more tolerant to hypoxia [13]. Those flow changes seem to be not so intense as seen in shock. Different critical closing pressures and more intense adrenergic-induced vasoconstriction (dependent on the amount of α-adrenergic receptors) in organs like the skin, muscles, and intestines associated to allow blood flow diversion to vital organs as the heart, brain, and kidneys, in cases of critical oxygen delivery [14].

Another important aspect to be considered is that different organs have different tolerance levels to hypoxia. While brain cells cannot tolerate more than 2–3 min of hypoxia, vascular smooth cells can do it for 90 min, and nails, for several days [15]. Still many questions remain to be answered in this regard, but lessons learned from high hypoxic tolerant animals can bring some light into this issue. Aquatic turtles are frequently referred as “facultative anaerobes” given their unique abilities, among

vertebrates, to tolerate hypoxia. Some species can survive in nitrogen-equilibrated water (with no oxygen) for 3–4 months, with lactate levels above 150 mmol/L [16]. What makes turtle brain cells and other tissues so tolerant are basically two factors: to be able to quickly detect hypoxia (oxygen sensors) and to initiate appropriate defense mechanisms [17]. Defense mechanisms involve activation of specific pathways, which leads to a quick change to a kind of hibernation, including anaerobic metabolism (less effective), arrest of facultative cell process and ATP-consuming channels (decrease in cell membrane permeability), protein synthesis and proteolysis blockade, "spike arrest" (downregulation of brain synaptic transmission—adenosine mediated), and suppression of ATP turnover rates [18]. Such adaptations could claim to be species-specific, but some mechanisms were well conserved, and similar phenomena can be observed also in mammalian cells. Oxygen conformance or hypoxic conformance is a concept that describes the ability of certain cell types (as hepatocytes) to reduce metabolism during prolonged moderate hypoxia, keeping only vital processes active, preventing lethal hypoxia damage, and allowing recovery after normoxia [19].

Another factor influences determination of a critical oxygen level that could lead to irreversible hypoxic damage: previous exposure to temporary moderate hypoxia. Hypoxic or ischemic preconditioning are currently well-recognized ways to experimentally improve tolerance to hypoxia, especially in the heart and brain, but also in whole organisms [20]. Despite of theoretically possible, and experimentally promising, clinical application of this concept is still limited.

Systematically observing the evolution of critical illness, it is possible to establish some parallelisms between "multi-organ failure" (MOF) and what happens with hypoxic adaptation in high tolerant organisms. MOF was recently redefined as MODS "multiple organ dysfunction syndrome," since necrosis and apoptosis are rare events in tissues and, usually, organ function can be recovered in survivors without previous significant organ disease [21]. From this point of view, limiting secondary injuries induced by treatment arise as an imperative (and, sometimes, neglected) issue to determine survival. Injuries induced by mechanical ventilation, excessive fluid administration, high load of vasopressors and inotropes, on the other hand, healthcare-related infections, or adverse events are common examples of such conditions which can lead to bad outcomes, even though the initial trigger is controlled. In parallel to the current "golden hours" rule (early treatment is preconized to most of the critically ill conditions), this concept may represent a new paradigm in critical care, allowing rethinking treatment targets and strategies.

4.3 Tissue and Cellular Responses to Hypoxia: The Hypoxia-Inducible Factor

Our understanding about tissue response to hypoxia changed to a new level in the 1990s, when an important hallmark emerged: the discovery of hypoxia-inducible factor (HIF), by Gregg L. Semenza, while studying the mechanisms behind red blood cell production induced by erythropoietin during hypoxia [22]. HIF is a basic-helix-loop-helix-PAS heterodimer, which belongs to the PER-ARNT-SIM

subfamily, regulated by cellular oxygen tension, and since the discovery, increasing evidence has emerged demonstrating its major role not only in disease but also in several metabolic processes as angiogenesis, embryogenesis, wound healing, bone growth, etc. [23].

Centrally, O_2 homeostasis basically depends on two master regulators of the adaptive response to hypoxia called: HIF-1α and HIF-2α. Under normoxia, HIF subunits are stable because they hydroxylated by prolyl hydroxylases (PHD, whose activity is O_2-dependent) and degraded by von Hippel-Lindau (VHL) ubiquitin ligase complex. In other words, hypoxia (which inhibits PHD) or loss of functional VHL promotes HIF-1α activation. HIF-1α dimerizes with subunit HIF-1β, targeting nucleus, where it exerts its transcriptional effect [24] (Fig. 4.1).

Other very important effects of HIF, still to be clinically explored, mainly in critical illness are related to mitochondrial function and inflammation. Regarding mitochondrial function, HIF acts in several ways: (a) promotes glycolytic energy production (inducing both transporters and enzymes) and upregulates lactate dehydrogenase, (b) suppresses Krebs cycle and oxidative phosphorylation within mitochondria (reducing reactive oxygen species—ROS), (c) alters mitochondrial glutamine metabolism from oxidation to carboxylation, (d) suppresses mitochondrial biogenesis, and (e) induces mitophagy (mitochondrial selective autophagy) [24].

4.4 Particularities of Different Hypoxic Mechanisms

Oxygen delivery to tissues (DO_2) is defined by the formulas:

$$DO_2 = CO \times \mathbf{CaO}_2 \times 10$$
$$\mathbf{CaO}_2 = \left(Hb \times SaO_2 \times 1.34 \times 0.01\right) + \left(PaO_2 \times 0.0031\right)$$

where CO is the cardiac output, Hb is the hemoglobin, SaO_2 is the arterial oxygen saturation, and PaO_2 is the arterial oxygen partial pressure.

Hypoxia, in literature, is sometimes synonym of hypoxic hypoxia, but considering DO_2 formula, other two components are related to oxygen delivery (besides oxygen, itself): blood flow (cardiac output) and hemoglobin levels (carrier). Despite not consensual, another mechanism has been proposed to explain hypoxia signs in scenarios in which oxygen, hemoglobin, and flow are preserved or even increased: cytopathic hypoxia. In critically ill patients, not so frequently, such conditions are seen isolated. For example, a trauma patient bleeding with a spleen lesion, evaluating to hemorrhagic shock, will present concomitant anemic and circulatory hypoxia insults. A septic shock patient with pneumonia and ARDS (acute respiratory distress syndrome) will present different grades of hypoxic hypoxia and circulatory hypoxia and even some degree of cytopathic hypoxia.

Adaptive mechanisms discussed so far in this chapter are observed in live organisms facing progressive DO_2 decrease. Usually, in literature, DO_2 decreases are analyzed in quantitative terms, but questions remain opened about the impact of

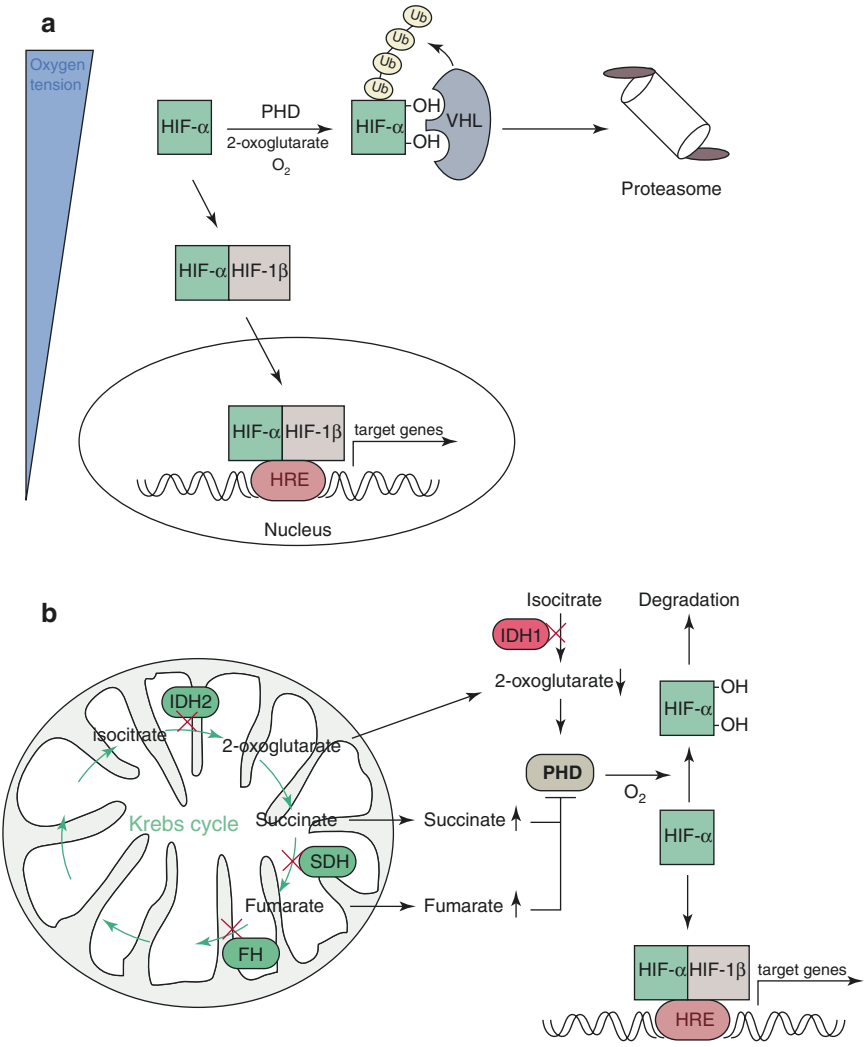

Fig. 4.1 Extracted from Schönenberger MJ [adapted from [24]—Open access. Regulation of HIF-α subunits. (**a**) Hypoxia-inducible factors (HIFs) are transcription factors composed of O_2-regulated α subunits (HIF-1α or HIF-2 α) and a constitutively expressed HIF-1β subunit. Together these subunits bind hypoxia response elements (HRE) to mediate adaptive responses to hypoxia. HIF-α activity is directly linked to oxygen partial pressure. Under normoxia, HIF-α is hydroxylated by prolyl hydroxylase domain (PHD) protein and targeted for proteasomal degradation by the von Hippel-Lindau (VHL) E3 ubiquitin ligase complex. Under hypoxia, hydroxylation is inhibited and HIF-α is stabilized; it dimerizes with HIF-1β and enters the nucleus to induce target gene transcription. (**b**) HIF-α can be stabilized irrespective of O_2 tension due to inhibition of PHDs, a state defined as pseudohypoxia. Mutations in the Krebs cycle enzymes succinate dehydrogenase (SDH) and fumarate hydratase (FH) lead to accumulation of succinate and fumarate, respectively, whereas mutations in isocitrate dehydrogenases (IDH1 and IDH2) lead to low levels of 2-oxoglutarate. Succinate and fumarate inhibit PHDs, while low levels of the co-substrate 2-oxoglutarate decrease the activity of PHDs. Decreased activity of PHDs leads to a low rate of HIF-α hydroxylation under normoxic conditions and stabilization of HIF-α

qualitative changes in DO_2. Mathematically, it is possible to simulate three different scenarios with similarly low DO_2 values, generated by reduced cardiac output, oxygen saturation, or hemoglobin. Would the same low DO_2 elicit standard adaptive global and regional responses or does the altered component matter? Clinically relevant animal experimental models, specific for each type of hypoxia are available, but literature about tissue response in such settings is scarce. Some examples will be discussed below together with the authors' experience working with different animal hypoxia models.

4.4.1 Hypoxic Hypoxia and Anemic Hypoxia

One of the first authors to study the effects of hypoxic hypoxia and anemic hypoxia on the organism was Stephen M. Cain (Texas/USA). Hypoxia models were developed using splenectomized dogs breathing air mixed with nitrogen (reaching oxygen inspired fractions—FiO_2—as low as 6%). Anemia models were developed using dogs after controlled bleeding and infusion of colloids (reaching hematocrits as low as 10%). In one of the first publications, in 1965, Cain studied lactate production in anemic and hypoxia models, it was suggesting that excess of this substance was found at similar points, in terms oxygen transport, in both models. Additionally, it was suggested that such excess was associated with liver dysfunction induced by reduced oxygen content [25]. In a later and more detailed study, considering the markedly hyperdynamic pattern in anemia, the same author studied VO_2 limitation by so-called high-delivery and low-delivery PaO_2 groups. Despite different PaO_2 between groups, after VO_2 was limited (at 9.8 mL/kg min), a linear relationship between DO_2 and VO_2 was found ("pathological dependence") in anemia and hypoxia, equally [26].

Shoemaker WC, in the 1980s, studied hypovolemic, anemic, and hypoxic animals, showing that macrohemodynamic compensation occurs in all models, with some differences: a greater cardiac output increase in anemic dogs and a greater increment in systemic and pulmonary resistances after hemorrhage. This study contributed to the current understanding that VO_2/DO_2 dependency ("oxygen supply dependency") has limited clinical utility except as a marker of impending collapse, since occurs only at near death [27].

Taken together, hypoxic and anemic hypoxia lead to (at least, transitory) hyperdynamic compensatory phases. Similar heart rates are potentially reached but cardiac output is higher during anemia. Viscosity changes contribute to reduced afterload explaining, at least partially, this finding. Hypoxic hypoxia typically induces increased pulmonary vascular resistance (hypoxic vasoconstriction), inducing decrease in pulmonary artery occlusion pressure (PAOP).

Regarding specific tissue responses, myocardium was one of the most studied examples. One of the first reports dates from 1925, demonstrating the impact of "anoxemia" in changing auriculoventricular conduction times [28]. Early evidence from dogs submitted to coronary sinus catheterization showed that the heart changes substrate from free fat acids (FFA) to lactate during hemorrhagic shock [29].

Currently, myocardium is considered a completely atypical tissue in terms of response to hypoxia, since instead of increase oxygen extraction rate (very limited, since basal rates are already very high), cardiomyocytes change energetic substrate, aiming a better energetic efficiency.

4.4.2 Circulatory (or Stagnant) Hypoxia

Similarly to Shoemaker, hemorrhagic shock, as intrinsically includes reduced flow and reduced hemoglobin components, makes difficult to draw conclusions regarding about the specific relevance of each hypoxic component. Not so many studies in literature tried to isolate the anemic component from flow. Experiences with animals with high tolerance to hypoxia (as aquatic turtles) show that they can tolerate anoxia 14 times longer than stagnant hypoxia, suggesting that flow preservation may be very important when oxygen is not available [30]. First references of isolated stagnant anoxia in literature come from studies about its effects on the cerebral cortex, in the 1950s. But only in the 1970s the effects started to be studied in other organs as the heart, liver, and intestines and in the whole organism.

Response to stagnant hypoxia basically depends on flow redistribution. As already discussed, special physiological features (as different critical closing pressures and different intensity of adrenergic activation among organs) make flow be diverted to vital organs, when others more tolerant to hypoxia are sacrificed. Experimentally, stagnant hypoxia is usually induced by pericardial tamponade or preload reduction (inferior vena cava occlusion). Experiments with anesthetized paralyzed and mechanically ventilated dogs after 30 min, with shock induced by tamponade, showed that acid infusions (0.3N HCl) induced increased oxygen delivery away from muscles, probably by flow redistribution and right-shifting oxygen-hemoglobin dissociation curve [31]. Another important physiological consequence of stagnant hypoxia is the changes in venoarterial PCO_2 gradients. For some time was believed that PCO_2 gradients increased as a result of hypoxia an increased anaerobic metabolism, but comparisons between pure hypoxic hypoxia versus ischemic hypoxia [32] showed that the main component is reduced flow. As PCO_2 is a highly diffusible gas (20 times more than oxygen), not overproduction, but local flow is the main determinant of its increase in the regional efferent blood, increasing venous concentration, and enlarging venoarterial gradients.

In comparison with anemic and hypoxic hypoxia, stagnant hypoxia leads to progressive decrease in cardiac output, despite of progressive increase in heart rate. Filling pressures (PAOP and CVP) reach the highest values if tamponade is the mechanism, but the opposite is the rule in case preload reduction (inferior vena cava ballooning). Liver flow is doubly compromised due to reduction in afferent flow (decrease in cardiac output) and due to increased venous pressure (venous congestion and decreased perfusion pressure).

Other authors who studied specific effects of stagnant hypoxia on organism and tissues did it evaluating the impact of superimposed interventions (endotoxemia or vasoactive drugs) on it. In anesthetized mongrel dogs, during tamponade,

dobutamine increased DO_2 with any other special findings [33]. Specific effects of this type of hypoxia on tissues are lacking. More recently, it has regained attention the metabolic side of hypoxia. Vital organs, as the brain and heart, can use lactate not as a secondary but a main energetic substrate in critical situations. The "lactate shuttle" theory, initially associated with exercise, currently can be extrapolated to disease, mainly the critical one, proposing that a net of lactate producers and consumers coexist in live organisms, in cellular, tissular, and systemic levels [34]. This effect is selective and organ specific. Stagnant hypoxia (but other types of critical hypoxia, as well) could trigger it, as an alternative compensatory mechanism. Skeletal muscles but other organs (as lungs) may present as potential lactate sources [35].

4.4.3 Cytopathic Hypoxia/"Dysoxia"

Sepsis is one of the most intriguing critical diseases, still accounting for a high lethality rate. Despite of a linear increment year-a-year in scientific literature, available therapeutic options are still restricted to antibiotics and organs support. Mechanisms involved are growing in complexity but still are not fully understood.

The term "cytopathic hypoxia" was proposed in 1997 by Prof. Mitchell Fink, assuming that hypoxemia, anemia, or inadequate perfusion were insufficient to explain organ dysfunction in sepsis. The concept was used to define the context of reduced ATP production in the setting of normal (or supranormal) PO_2 values inside cells [36]. Over time, the main mechanism linked to cytopathic hypoxia was mitochondrial dysfunction [37]. Experimental and some human evidence were published suggesting that mitochondrial dysfunction could explain this specific kind of tissue hypoxia, and why MODS occurs in sepsis [38]. Moreover, since 2000 when microcirculatory assessment at bedside became possible with orthogonal polarization spectral (OPS) imaging, a new chapter has begun regarding the understanding about organ dysfunction in sepsis [39]. Despite of still non-consensual, mainly because true hypoxia was not demonstrated to occur in almost any organ during sepsis and septic shock [40], and because mitochondrial dysfunction real role in sepsis remains undetermined [41], the denomination "cytopathic hypoxia" seems to be still is appropriated.

During experimental sepsis (peritoneal, since it is closer to human sepsis than LPS or live bacteria-induced sepsis), the highest heart rates are found, and progressively reduced CO is observed (hypodynamic shock, resembling stagnant hypoxia patterns), associated with stable or slightly reduced filling pressures, when compared to other hypoxic insults. Increased oxygen extraction rates may be high (with low mixed venous or central venous values, mainly before resuscitation), normal, or high. Low values are currently understood not related to global hypoxia or "dysoxia," but other players may have important roles. Coronary sinus blood (with the lowest SO_2 values in organism and with blood flow increase being the main mechanism to meet increased metabolic demand in heart) and azygos vein blood (mainly in cases associated with severe respiratory distress and low oxygen content) are considered, at least theoretically, main determinants in such situations [42]. Human

sepsis presents with completely different features due to treatment. Differently from other hypoxic fluid resuscitation, vasopressors and inotropic agents become sepsis hyperdynamic, and sometimes, other hypoxic common tissue responses may be altered. Circulatory shunting is an example, manifested by high mixed venous or central venous oxygen saturation, in the most severe cases. Likewise in a short circuit, oxygen not used by tissues as a consequence of high rates of non-perfused vessels in microcirculation, microthrombosis in the context of disseminated intravascular coagulation, exacerbated by high dose of catecholamines and inotropes, comes back to the heart. Changes in treated sepsis are so dramatically intense that this condition could be considered a "new entity," distinct from the original disease. Actually, large body of evidence is available about how treatment can add morbidity and mortality risk to septic patients.

4.5 Insights and New Concepts

4.5.1 Hypoxia and Inflammation

In Critical Care Medicine, for a long time, it was usual to separate different aspects of critical illness as hemodynamics, oxygenation, inflammation, and metabolism, mainly for therapeutic purposes. Currently it is known that all of those aspects are mixed and interrelated. Hemodynamic changes generate inflammation in cardiogenic shock, low oxygenation is compensated by shift in energetic substrates in the heart, and hypoxia is very close to inflammation and vice versa.

Clinical evidence from persons with mountain sickness (who present cytokine release and vascular leakage, anticipating pulmonary and cerebral edema) and from organ transplantation (ischemia closely correlates with graft failure or rejection) suggests clear links between hypoxia and inflammation [43]. Inflammation also can induce hypoxia simply by increasing metabolic demand, reduced substrate availability (thrombosis, edema inducing reduced oxygen diffusion, or competition with infectious agents) [43]. Intestinal mucosa is normally hypoxic, but during inflammatory bowel disease, the extension is larger and elevated levels of HIF-1α and HIF-2α can be found [43]. NF-κB is an important factor which transcripts signals from Toll-like receptors (e.g., activated by bacteria, during infection) leading to cytokine production and inflammatory response. Several links between NF-κB and HIF pathways were described, even without the context of hypoxia—Fig. 4.2 [43].

HIF is also associated with adaptive and immunity. This could be expected since many immune cells leave the blood and need to act in low-oxygen environments. Its influence in almost all immune cells was already described [1]. Hydroxylases (PHDs, abovementioned) are considered the key oxygen sensors and are currently being targeted for therapeutic purposes, in chronic inflammatory and autoimmune diseases [1].

All of those abovementioned ingredients are frequently found in critically ill patients; however few research are available addressing HIF roles in critical care. The role of HIF and its complex network just begun and there is still a large road to be built [44].

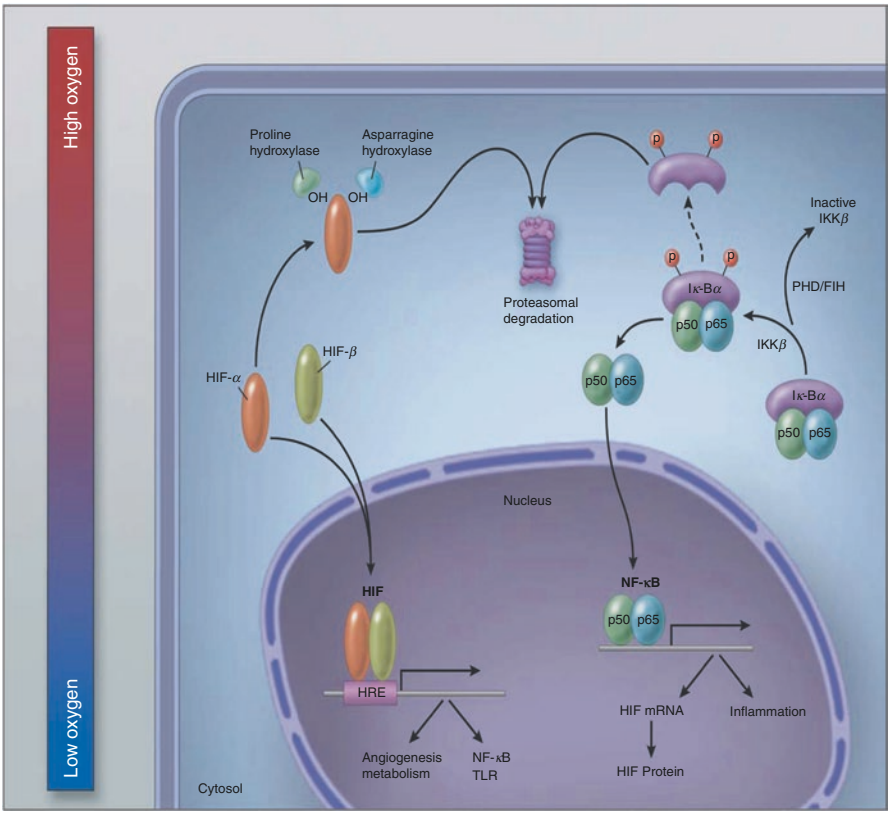

Fig. 4.2 Molecular interaction between the HIF and NF-κB pathways [adapted from [43]—open access]. Hypoxic conditions (left) and resting cells (right)

4.5.2 Obesity Paradox, Adipose Tissue Hypoxia, and Function

Other connections between HIF and disease can be cited here and should inspire critical care scientists to find new promising issues to be explored. While obesity grades 2 and 3 are consistently associated with increased all-cause mortality, obesity grade 1 is associated with lower ones, and this is consistent with different subsets of diseases, including critical care [45]. An emerging concept which supports such so-called obesity paradox is the adipose tissue hypoxia. There is substantial evidence that while adipose tissue mass expands, tissue hypoxia may develop due to reduced capillary density and total tissue blood flow [46]. Adipose tissue is currently recognized as a major endocrine organ, with very complex functions, and tissue hypoxia, associated with chronic inflammation, seems to be linked to insulin resistance, type 2 diabetes, metabolic syndrome, and inflammation in obstructive sleep apnea, for example [47]. Several mechanisms have been explored, among them, mitochondrial dysfunction. Despite of a not clear reason for it, reduced mitochondria number is found

in adipose tissue of obese patients. Chronic hypoxia and HIF-mediated inhibition may be related [47]. In a similar way, ischemic preconditioning seems to benefit organisms and tissues before critical hypoxic insult, and adipose tissue hypoxia may benefit obese patients and represent the reason for better outcomes of this population during critical care.

4.5.3 Permissive Hypoxia

Due to the deleterious effects of high oxygen concentrations in premature lungs, the concept of permissive hypoxia is well established in mechanically ventilated newborns. Nevertheless, in adults, this is not so clear, and it is not uncommonly observed in critical care unit patients with transcutaneous oximetry of 99–100%. From one side, considering intra-uterus life mechanisms and adaptation to high altitude, and in the other side, ROS production (reactive oxygen species) and oxygen toxicity to tissues, permissive hypoxia seems to be plausible and, even promising, in critical care [48]. In a pilot RCT of mechanically ventilated patients for more or equal 24 h, at four intensive care units, a conservative strategy aiming arterial oxygen saturation between 88 and 92% showed to be safe with no difference to another aiming ≥96% [49]. More recently, a single-center trial of conservative oxygen therapy (94–98% vs. 97–100%), with a small occurrence of the primary outcome was early terminated due to difficulties in enrollment, but showed a mortality benefit [mortality: 25 or 11.6% intervention vs. 44 or 20.2% in the control group; relative risk 0.57 (95% CI, 0.37–0.90); $p = 0.01$)] [50]. Despite nonconclusive, those results support the concept and deserve further research in the near future.

4.5.4 VO_2 Manipulation

Optimize DO_2 is currently still the main strategy to treat critical illness. Intensivists are conditioned to always think about how to improve oxygen delivery, but sometimes, this is not possible or harmful (e.g., sepsis with MODS). Assuming that VO_2 should be maintained, even whether temporarily reduced (as it happens in hibernating tissues or in hypoxia high tolerant animals), strategies targeting the "other coin side" could be useful if feasible. Several studies, basically experimental and still underappreciated in human medicine, have shown potentially new therapies that should be tried soon in human medicine. Some examples are permissive hypercapnia, hydrogen sulfide therapy [51], and beta-1-blockade [52].

4.5.5 Chuvash Polycythemia as an Opportunity to Find New Therapeutic Targets

Chuvash polycythemia (CP) is a congenital polycythemia generated by an autosomal recessive disorder, described in 1997, in the central European part of Russia. Those patients have impairment in HIF degradation, presenting with high HIF

levels in the absence of hypoxia [53]. Five patients with this condition were studied in a case control study [53]. CP patients have marked abnormalities of cardiopulmonary function. After exercise, they presented higher muscle acidosis, higher serum lactate levels, and reduced capacity [54]. Muscle biopsies showed elevated transcripts for pyruvate dehydrogenase kinase, phosphofructokinase, and muscle pyruvate kinase [54]. Neither the number nor volume of mitochondria in CP patients (factors potentially affected by HIF activity) were different from controls. HIF-1 may affect regulation of cytochrome oxidase subunit 4 isoforms, but it was not studied in the mentioned study [54].

4.6 Current Challenges and Limitations to Clinical Application

Tissue response to different hypoxia insults is still a field of interest, and several questions remain to be answered. Part of the challenge to reach clinical applications relies on knowledge gaps but also on lack of techniques to be used at the bedside. Examples of relevant techniques and devices to assess tissue response during hypoxia will be discussed in other chapters of this book.

Other difficulties are related to the application of interventions derived from this specific knowledge. For example, ischemic preconditioning has been shown to be a promising intervention, not only for coronary artery disease but also for several conditions. Preconditioning was already tried even for sepsis (an aortic balloon insufflated for 2 min, followed by deflation during 4 min, 4 times before experimental sepsis induction), with apparently positive results in terms of organ function (cardiac output, kidney, and lactate), microcirculation, and survival time [53]. Nonetheless, to predict specific scenarios and patients who could benefit, and even justify making possible such highly invasive procedures remain as big challenges to be overcome in the future. Nevertheless, such difficulties are not so big as the possibilities still opened in this exciting field, ranging from mechanistic studies to clinical trials to test therapeutic options.

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Part III

Measuring Tissue perfusion: Systemic Assessment

Cardiac Function (Cardiac Output and Its Determinants)

5

Loek P. B. Meijs, Alexander J. G. H. Bindels, Jan Bakker, and Michael R. Pinsky

5.1 Introduction

The cardiovascular system subserves the metabolic needs of the body, which itself is highly variable and often unpredictable. Since the primary goal of the cardiovascular system is to sustain adequate oxygen delivery to the metabolically active tissues relative to their demand, the controls for this system are inherently complex yet simple at the same time. The heart serves as a central pumping function to deliver blood under low pressure to the pulmonary circulation and under very high pressures to the systemic circulation, while at all times keeping its filling pressure as low as possible as to maintain maximal filling and minimize tissue edema. The interactions between the right side of the heart, systemic venous return, pulmonary blood

L. P. B. Meijs (✉)
Department of Cardiology, Catharina Hospital, Eindhoven, The Netherlands

Department of Intensive Care, Catharina Hospital, Eindhoven, The Netherlands
e-mail: loek.meijs@catharinaziekenhuis.nl

Alexander J. G. H. Bindels
Department of Intensive Care, Catharina Hospital, Eindhoven, The Netherlands

J. Bakker
Department of Intensive Care Adults, Erasmus MC University Medical Center, Erasmus University Rotterdam, Rotterdam, CA, Netherlands

Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University Medical Center, New York, NY, USA

Department of Pulmonary and Critical Care, New York University, New York, NY, USA

Department of Intensive Care, Pontificia Universidad Católica de Chile, Santiago, Chile
e-mail: jan.bakker@erasmusmc.nl

M. R. Pinsky
Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA, USA
e-mail: pinskymr@upmc.edu

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flow, the left side of the heart, pulmonary venous return, and left ventricular ejection are controlled to a large degree by intrinsic cellular mechanisms that require no external control or feedback. It is both the moment-to-moment changes in venous return induced by breathing efforts (referred to as heart-lung interactions) and the metabolic demands modified by muscular activity, digestion, and mentation that drive steady-state cardiac output. Historically, reviews of cardiovascular system control usually start with descriptions of ventricular pump function. However, except with severe right or left ventricular failure, resting cardiac output remains remarkably constant as cardiac reserve diminishes. In fact, cardiac impairment is assessed not by baseline measures of cardiac output or oxygen delivery to the tissues, but by its responsiveness to a defined exercise challenge, like walking or bicycle exercise. Clearly, when dealing with bedside treatment of critically ill patients in circulatory shock, a broader approach of cardiovascular (dys)function assessment, monitoring, and management is essential. This chapter summarizes in brief terms normal and dysfunctional cardiovascular physiology. The reader will note that though a circuit and closed, each component is uniquely designed and adapted to its specific role(s) which make their monitoring and specific treatment more relevant. Since inadequate oxygen delivery to the tissues represents the end stage of circulation insufficiency, understanding the components of oxygen delivery and metabolic demand becomes central to this analysis. Although increasing oxygen carrying capacity by increasing hemoglobin concentration and increasing its level of oxygen saturation reflect treatment options to increase oxygen delivery to the body, their impact is limited except in the negative. The primary means by which the body and by inference critical care physicians increase oxygen delivery to patients to reverse circulatory shock is by increasing tissue blood flow specifically and cardiac output (CO) in general. This point forms the basis for most hemodynamic monitoring and treatment decisions.

5.2 Cardiovascular Physiology

Under normal conditions the major determinants of CO are metabolic demand of the tissues which varies directly with whole-body oxygen consumption. However, in stressed states, wherein blood volume is diminished, ventricular function impaired or obstruction to flow occurs, and other forces become prominent in determining CO. Within this regard, the heart can only pump what blood it receives. Thus, the primary determinant of CO must be venous return (VR) from the body to the heart, which itself is a function of its developed downstream pressure, called mean systemic filling pressure (P_{ms}). P_{ms} shares a complex relation to total circulating blood volume, peripheral vasomotor tone, and blood flow distribution and will be later explained in detail. From the heart's perspective, each given stroke volume will be a function of how much blood has entered the ventricular chamber during diastole, referred to as preload, heartbeat frequency, or heart rate; the arterial pressure opposing ventricular ejection, called afterload; the innate ability of the cardiac myocytes to vary their force of contraction in response to varying loads, called inotropy; their

ability to actively relax during diastole, called lusitropy; as well as the impact that varying beat frequency has on intrinsic contractility, called chronotropy. Other determinants of cardiac function are architectural and geometrical variables including wall thickness, size, and shape of its cavity as well as global synchrony of myocardial contraction and relaxation [1].

5.2.1 Venous Return

The main function of the venous system is to serve as both the low pressure reservoir for capillary blood drainage and to serve as the upstream reservoir driving blood flow back to the right ventricle (RV) [2, 3]. The cardiovascular system can be artificially divided in systemic and pulmonary compartments, each with 80% and 20% of the blood volume, respectively. In the systemic circulation, the small veins and venules contain most of the systemic blood volume (upward of 75%). However, the amount of blood compartmentalized there is a function of blood flow distribution. If the splanchnic circulation has an increased metabolic demand, as what occurs postprandially, then a greater amount of blood pools in the splanchnic circulation because its outflow is impeded by hepatic parenchymal resistance, as all portal venous blood must traverse the liver before entering the systemic venous circulation. Thus, under resting conditions the splanchnic venous bed stores roughly one third of the blood volume in the venous compartment [3]. Therefore, the venous compartment serves as a capacitance reservoir, whereas the arterial compartment serves as a high-pressure conduit. Things are quite different on the pulmonary side. Although the pulmonary circulation contains only a small portion of the total blood volume, it receives exactly the same CO as the systemic circulation but maintains it in at a much lower pressure. The reason for this is twofold. First, since right atrial pressure (P_{ra}) is the back pressure to venous return, keeping right atrial pressure at or below zero at all times maximizes the driving pressure for venous return. Second, since the primary role of the lung is to exchange oxygen and carbon dioxide between pulmonary capillaries and alveoli, keeping pulmonary capillary pressure as low as possible and minimizing baseline pulmonary vascular resistance allows for maximal capillary-alveolar surface area by minimizing pulmonary edema formation while simultaneously maximizing intrinsic hypoxic pulmonary vasoconstriction matching of blood flow to alveolar oxygen to optimize gas exchange.

Until very recently, most cardiologists and intensivists considered cardiovascular regulation strictly from the perspective of ventricular pump function. In fact, the most common adhered concept of determining CO is that it is only regulated by left ventricular (LV) characteristics [2, 4]. However, as noted above, in a steady state, the heart can only eject what it receives from the vasculature, and the circulation can only return the amount of blood it receives from the heart. Therefore, CO must equal VR, and the heart will always pump out exactly what amount of VR it receives. Thus, as Guyton et al. noted over 50 years ago, VR is the primary determinant of CO [4–10]. According to the Guytonian approach, VR plays a pivotal role in determining CO, and therefore the only thing that cardiac function can do to affect CO is to

reduce it by failing to pump the blood it receives resulting in an increased P_{ra}. However, this is an oversimplification of cardiovascular physiology. Beard et al. questioned Guyton's view on the circulation [11]. They stated that not merely P_{ra}, but flow (CO) itself was the true independent variable through the systemic circulation. This was emphasized by the fact that Guyton had used an artificial rotator pump to maintain flow. He then used a collapsible tube as Starling resistor to vary the right atrial inflow. Grodins et al. reproduced Guyton's experiments without using a Starling resistor, which identified the variable speed pump (CO) as the causal variable [12]. However, this neglects the fact that VR is still key to supplying the heart with blood. Therefore, the truth probably lies somewhere between VR and LV contractility, with the fulcrum balanced more toward the venous return side as being dominant under most conditions and the heart under conditions of severe LV systolic or diastolic heart failure.

From a purely physical basis, there are two main factors regulating venous return: the pressure gradient for venous return, namely, the pressure difference between P_{ms} and P_{ra}, and the resistance to venous return (RVR), stressed volume (V_s) and unstressed volume (V_o) [2]. Each of these terms will be explained.

5.2.2 Mean Systemic Filling Pressure

Already in the 1890s, Bayliss and Starling observed that if blood flow would be stopped or arrested, arterial pressure would drop and venous pressure would rise, until an equilibrium was reached. The equilibrated pressure is what they termed "mean systemic filling pressure" (P_{ms}). Furthermore, they reasoned that P_{ms} would be the same average pressure throughout the whole circulation, independent of mean arterial pressure (MAP), since P_{ms} could be measured during circulatory arrest or absence of pump function in both arteries and veins [13]. This pressure was presumed to be independent of cardiac function, because it was neither raised nor lowered during circulatory arrest. In their studies and others by Guyton et al. in anesthetized dogs, P_{ms} was estimated to be only about 7 ± 2 mmHg (mean ± SD). P_{ms} is lower than capillary pressure, almost equal to portal pressure and higher than P_{ra}. This sequence of pressures is probably of evolutional importance since there is a need for venous compensation to maintain VR despite the orthostatic hypotensive effect of gravity. It is believed that reflex venoconstriction plays a key role in this mechanism; otherwise we would all faint when moving from a supine to standing position. Furthermore, the point of measurement of P_{ms} had to be situated on the venous side because of the higher capacitance of this reservoir, allowing venous pressure to slightly increase during circulation arrest. P_{ms} is regarded as the upstream pressure for VR and arterial constriction trapping arterial blood at a slightly higher value than P_{ms} [14]. Later on, Guyton et al. further developed this concept in a series of experiments which formed the basis for our understanding of the circulation. The methods of these experiments have been elaborately described elsewhere [7–10]. In short, in open-chest anesthetized dogs, arterial pressure and P_{ra} were measured through catheters inserted into the arterial and venous systems. A special cannula

was inserted in the right atrium, and blood was pumped through an external circuit with a variable rate propulsion pump. Blood flow was measured with a flowmeter, and the blood was eventually redirected to the pulmonary artery across a Starling resistor such that at all times the maximal venous return was delivered into the pulmonary circulation. Thus, the system replaced the RV and was called a right heart bypass preparation. P_{ms} was varied by raising or lowering an inflow site for the vascular pump thereby varying the P_{ra} from low negative (−15 mmHg) to very high positive values (+20 mmHg). In different experiments multiple modalities of circulatory arrests, areflexia, administration of vasopressors, types of anesthesia, and hemodynamic circumstances (fluid resuscitation, hypovolemia, distributive shock) were simulated. Based on this massive body of work, a unified understanding of the systemic controls of venous return evolved.

During normovolemia stable dogs' P_{ms} values ranged from 7 to 12 mmHg. However, as expected P_{ms} values will vary greatly and quickly in response to physiologic stresses. For example, slow initial increments of epinephrine infused caused P_{ms} to increase to 16 mmHg, while stopping the heart by constricting the pulmonary artery caused stop-flow P_{ms} to raise to 13 mmHg. Intravascular fluid infusion induced an increase in P_{ms} proportional to total volume infused, consistent with the assumption that vascular capacitance is linear over the physiologic range. Importantly, large-volume fluid infusion increased P_{ra}, P_{ms}, and CO, but the increase in P_{ms} was greater than the increase in P_{ra}, such that the pressure gradient for venous return, namely, $P_{ms} - P_{ra}$, increased proportionally to the CO increase [7–10].

The compliance and resistance of the arterial and venous systems are markedly different and reflect their relative needs in sustaining blood flow. The compliance of the venous system is 30 times higher than the compliance of the arterial system and its resistance 40 times less. The splanchnic circulation receives approximately 20% of the cardiac output and comprises up to 30% of the total blood volume. Because of the high compliance of the venous system, changes in blood volume are associated with relatively small changes in venous transmural pressure. Veins are capable of accepting large volumes of blood with minimal change in P_{ms}. In fact, in an otherwise stable patient, massive fluid infusion will not increase CO or P_{ms} because the newly infused volume is distributed into expanding capacitance vessel's distribution until such time as in the associated increased glomerular filtration rate increases urine output. Thus, the venous system serves as a reservoir for blood and is capable of accommodating large changes in blood volume if not needed to increase CO. Venous capacity is the amount of blood volume contained in a vein (or venous system) at a specific distending pressure [3]. Vascular capacitance is the relationship between total blood volume and distending pressure, whereas vascular compliance is the relation between changing blood volume and changing P_{ms}. The relation between blood volume and P_{ms} is not constant and is a function of blood volume, blood flow distribution among the various vascular beds, and venomotor tone. The veins, when collapsed, can be distended with a certain amount of volume before they start to resist future distention. Conformational changes in their shape as they move from collapsed to distended first passes through a zone in which their volume

increases with any measurable change in distending pressure. The amount of blood volume needed to distend the venous capacitance vessels before any measurable increase in P_{ms} occurs is referred to as the unstressed volume (V_o). Under normal conditions approximately 60–70% of total circulating blood volume is in the unstressed volume. If intravascular volume is increased beyond this amount, P_{ms} increases as the veins resist further distention. The volume above this unstressed volume is referred to as the stressed volume (V_s) and defines the relation between changing blood volume and P_{ms} [14]. Thus, capacitance vessels have both an unstressed volume and a stressed volume. Importantly, the absolute amount of potential unstressed volume in the venous circulation exceeds total circulating blood volume. Thus, under conditions of maximal vasodilation, P_{ms} falls to zero and so does both VR and CO. This is what happens transiently during vasovagal syncope.

For purposes of physiologic definitions, then we can make the following definitions:

- Vascular compliance is defined as the slope of change in intravascular volume and P_{ms} ($\Delta V/\Delta P_{ms}$). Under most conditions over the normal physiologic range, vascular compliance is linear.
- Vascular distensibility/compliance is the fractional change in volume per unit change in pressure ($\Delta V/V_o \Delta P$).
- Static vascular elasticity or elastance is the reciprocal of compliance: $\Delta P/\Delta V$ = slope.
- Unstressed volume (V_o) is the blood volume contained in a vessel without generating a measurable change in P_{ms}. It is not possible to measure V_o in the living human or animal, because values of zero distending pressure are not achievable since there will always be a certain part of distending pressure in the vascular tree. Instead, for both clinical and experimental purposes, it is possible to measure stressed volume (V_s).
- Stressed volume (V_s) is the volume above V_o generating intravascular (and thus distending) pressure thereby reflecting the upstream driving pressure. It is calculated as P_{ms} times compliance ($V_s = C \times P_{ms}$). V_o is calculated by subtracting V_s from the total blood volume (TBV) leading to the equation $V_o = \text{TBV} - V_s$ [2–10, 14].
- Vascular capacitance represents the overall circulating blood volume to P_{ms} relation, which under most conditions is highly variable and of little clinical importance.

There are two ways that a subject can increase their CO in response to a metabolic stress. Either they decrease their V_o by diverting blood flow away from high capacitance circuits, like the splanchnic circulation, and into circuits with low unstressed volume, like muscle vascular beds, or they decrease the resistance to venous return (RVR) by increasing the parallel number of venous conducting circuits draining the venous system or by vasodilating the large venous resistance vessels (e.g., vena cavae). In practice, they do both. The arterial circuit vasoconstricts

blood flow to the splanchnic circulation thus decreasing V_o while also vasodilating the large venous conduit vessels such as the inferior vena cava.

Several clinical examples illustrate these dynamic interactions. Non-specific arterial vasoconstriction will cause a decrease in arterial flow, decreasing venous blood volume and thus CO, as seen with phenylephrine infusion in normal adults. Whereas a combined increased arterial tone and contractility, as created by norepinephrine infusion, will result in the pooled central blood being ejected for completely increasing CO for the same increase in arterial pressure as induced by phenylephrine. When CO decreases due to ventricular failure, P_{ra} also increases causing VR to decrease pooling blood in the venous reservoirs, increasing both venous vascular pressure and peripheral edema formation. With isolated LV failure causing decreased forward blood flow, baroreceptors induce a reactive vascular vasoconstriction. This causes LV afterload to increase further impeding LV ejection while also increasing P_{ra}, if backward failure impairs RV function. Similarly, the increased sympathetic tone increased venomotor tone thereby decreases V_o increasing P_{ms}. To the extent that P_{ra} can be kept low by decreasing LV afterload, then CO will not decrease and may even go up. An active response of capacitance vessels in response to smooth muscle activity (caused by reflexes or sympathetic nerve stimulation) causes a change in the venous pressure/volume (compliance). In times of increased sympathetic tone, V_o decreases and for the same circulating blood volume causing P_{ms} to increase. This dynamic process is the primary mechanism used to sustain CO as metabolic demand rapidly changes, as with sudden exercise [14].

5.2.3 Pressure for Venous Return

An important concept of VR is the net driving pressure estimated as the upstream pressure (P_{ms}) relative to P_{ra}, often deferred the driving pressure for venous return (P_{vr}). Steady-state CO is determined by factors collectively grouped into preload, heart rate, intrinsic contractility, and afterload. From this perspective, the only way that cardiac function can modulate VR is by changing P_{ra}, which in turn changes P_{vr}. P_{ra} represents the downstream pressure to VR, whereas P_{ms} is the upstream pressure [2–4]. As Funk et al., inspired by Bressack and co-workers, recently opined that P_{vr} calculations can be deducted from the knowledge as to the V_s value, P_{ms} in turn can be calculated by subtracting V_s from total blood volume, divided by systemic compliance ($P_{ms} = (V_{total} - V_s)/C$) (derived from Hagen-Poiseuille's equation Q (flow) = $P_1 - P_2/R$, where Q represents the flow, P_1 the upstream pressure, P_2 the downstream pressure, and R the resistance to flow). Under influence of vasomotor effects, catecholaminergic stress responses, intravascular fluid infusion, exsanguination, changes in autonomic tone, or endo-/exogenous vasoactive substances can all change both vascular compliance and V_s [2]. Thus, VR can be increased or decreased by changing either P_{ms} (either by influencing stressed volume) or P_{ra} (as a measure of ventricular contractile reserve) or changes in RVR. VR can therefore be calculated as VR = $(P_{ms} - P_{ra})$/RVR [14].

5.2.4 Resistance to Venous Return

Resistance to flow, which counts for both arterial vascular resistance RVR, is calculated by various methods depending on the vascular circuit and flow characteristics each circuit creates. Poiseuille's Law states that the pressure drop across a length of conducting vessel will be a function of the length of blood vessels (l), π, and blood viscosity (η) while inversely related to the radius (r) of blood vessel, resulting in the equation [2]:

$$R = \left[\frac{8\eta l}{\pi r}\right]^4$$

The net change of blood volume redistribution coincides with a change in venous resistance. This occurs because the change in volume is related to the second power of the vessel diameter, whereas a change in vascular resistance is related to the fourth power of diameter. Small veins and venules have a smaller radius, but with a very large cross-sectional area in comparison to the much larger (in diameter) vena cava and large veins, they serve as an excellent reservoir. The caval and larger veins on the other hand act primarily as conduits, but due to their larger diameters, according to the equation for resistance, they account for the majority of venous resistance. Also, the speed of flow through a vascular bed largely determines RVR. Specifically, lengthy vascular beds with slow blood flow account for a higher venous resistance than short beds with fast flow. Thus, when a given percentage of venous conduit vessels experience a decrease in vessel diameter, resistance to blood flow will increase to the fourth power of the mean radius. The increase in resistance will lead to a decrease in flow, but an increase in upstream pressure (P_{ms}), accumulation of blood in the venous circuit, and peripheral edema (see also Fig. 5.1) [14].

Another factor influencing RVR is respiratory cycling. Normally, P_{ra} exceeds pleural pressure and serves as the downstream pressure opposing VR. However, during spontaneous inspiration intrathoracic pressure becomes negative which is transferred to the right heart. P_{ra} progressively decreases, and at that point it becomes subatmospheric, thus making atmospheric pressure the major downstream pressure opposing VR. Venous pressures and P_{ra} ultimately fall below the atmospheric pressure during forceful inspiration, causing the veins to collapse, limiting any further increase in flow despite further increases in P_{vr}. This phenomenon is reversed during spontaneous expiration [14]. Downstream pressure cannot decrease below zero, because as external tissue pressure exceeds intravascular pressure causing the veins to collapse as they enter the thorax [7–10]. Guyton reasoned that due to vascular compliance, resistance decreased to only a small extent when P_{ms} rose. Importantly, in life P_{ra} cannot increase to a value greater than P_{ms} because otherwise there would be total circulatory arrest. At best, when the circulation is halted and VR becomes zero, P_{ra} and P_{ms} also equal. Thus, stop-flow P_{ra} if measured before reflex vasoconstriction or metabolically induced vasodilation is an accurate estimate of P_{ms}. In practice, Guyton measured the equilibrium pressures of arterial and venous pressure as he stopped flow and then rapidly pumped blood into the veins from the arteries,

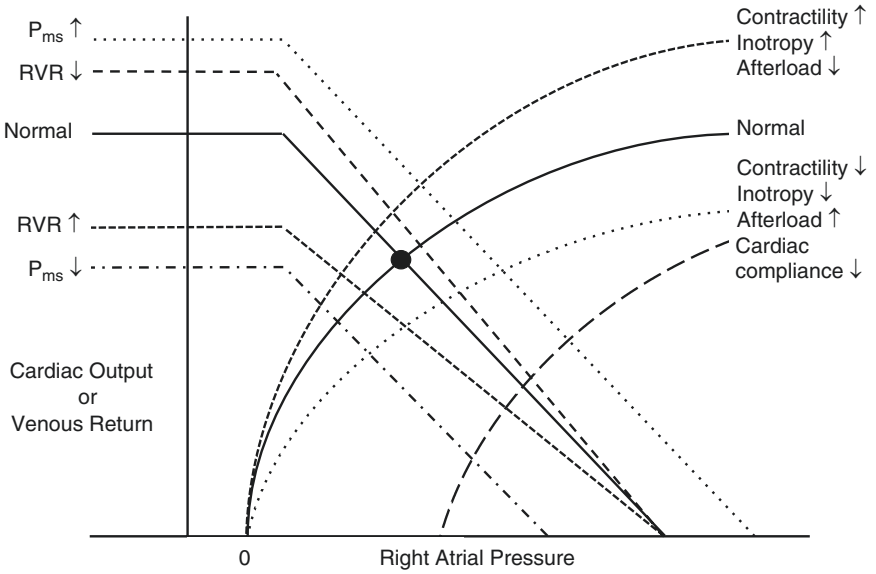

Fig. 5.1 Integration of venous return curve and cardiac output curve as exemplified by Guyton and co-workers. Flow is presented on the *y*-axis. Right atrial pressure is presented on the *x*-axis. Black solid lines tagged "normal" represent the venous return and cardiac output curve in steady-state condition. The intersection of both curves (black dot) represents the optimal integration of CO and VR (equilibrating point). When increasing P_{ms} (upper dotted curve), the VR curve shifts upward, thereby also shifting upward along the CO curve in order to reach a new equilibrium with a higher CO as a result. The opposite occurs when decreasing P_{ms} (lowest dash-dotted curve), reaching a new equilibrium at the cost of a lower CO. Changes in RVR are represented as a change in slope. An increase in RVR will limit VR, flattening the slope of the curve, without changing P_{ms} (small dashed curve). In contrast, a decrease in RVR causes the slope to increase (large dashed curve). By stimulating contractility, use of positive inotropes or by decreasing ventricular afterload, the slope of the CO changes resulting into an increase in CO. Opposite effects occur when decreasing contractility, lowering inotropy dosage, or increasing ventricular afterload. When cardiac compliance decreases (i.e., ischemia, diastolic dysfunction), the CO curve shifts upward along the *x*-axis reflecting higher diastolic filling pressures at the cost of a lower CO, higher P_{ra} and P_{ms}

which took about 3 s. Furthermore, P_{ms} represents the upper limit of the P_{ra} values possible [7–10]. Newer techniques show that one can wait ~20 s and still get an accurate estimate of P_{ms} from venous pressure (infra vide).

A decrease in arterial flow (e.g., by increasing arterial resistance or cross clamping the aorta) leads to a decrease in volume within the venous system, shifting blood from the venous system to the heart and thereby instantaneously increasing VR and CO.

Venous compliance is a change in blood volume associated with a change in distending pressure in a vein of venous system. Venous compliance reflects the relation between changing venous pressure and blood volume, whereas venous capacity is a static measure of the total blood volume generating a certain P_{ms}. An increase in

effective circulating blood volume can be achieved by either a decrease in vascular capacity or a decrease in compliance or both. For example, pharmacologic venoconstrictors (i.e., alpha-adrenergic agonists) decrease venous capacity without changing compliance by decreasing unstressed volume [3]. The resistance to venous return can thus be considered to be the sum of the venous and arterial resistance, multiplied by the ratio of total arterial and venous capacitances ($RVR = R_v + R_a C_a / C_t$) where R_v is venous resistance, R_a is arterial resistance, C_a is arterial capacitance, and C_t is total vascular capacitance [11].

5.3 Integrating Mean Systemic Filling Pressure and Cardiac Output

The relationship between CO and P_{ms} is complex. P_{ms} is a variable rather than a parameter which is dependent on blood volume, vascular compliances, and (un) stressed volumes. Previous studies have found that a 1 mmHg increase in P_{ms} is equivalent to 4% change in blood volume [2, 14]. CO further depends on cardiac contractility, heart rate (HR), and diastolic filling (influenced by P_{ms} and venous resistance). Guyton et al. integrated the venous return curve and the cardiac output curve (Fig. 5.1) to show how they are linked [7–10].

5.4 Clinical Application of P_{ms} Measurements

There are multiple ways of measuring P_{ms} at the bedside, based on our understanding of the determinants of P_{ms} described above. Logically, the methods developed by Guyton et al. of creating a right heart bypass system and measuring vascular equilibrium pressure during transient stop-flow conditions would be the most accurate of means, but except under conditions of on-pump cardiopulmonary bypass during cardiovascular surgery, these are not clinically feasible.

Furthermore, the measures of P_{ms}, achieved during stop-flow preparations, are independent of the prior measures of P_{ra} before discontinuation of flow, which could trouble the interpretation of resistance to venous return [15]. In 1984 Pinsky postulated that, according to the concept of the VR curve (Fig. 5.1) and based on the assumption that changes in right ventricular (RV) stroke volume (SV_{RV}) and VR are the same during small tidal volume (VT) breathing (VT < 10 mL/kg), gradually increased intrathoracic pressure applied by increasing positive-pressure ventilation resulted in an increase in P_{ra} without affecting P_{ms}. SV~~RV~~ and P_{ra} were then plotted (P_{ra} *x*-axis), resulting in a relation with a negative slope, equal to the resistance to venous return with a positive-pressure SVRV intercept approximating P_{ms} [16]. Maas et al. applied older techniques validated in animals, as published by Versprille and Jansen in 1985 [17] in humans to assess P_{ms}, showing that transiently increasing P_{ra} using inspiratory breath-hold maneuvers of 10–15 s at different plateau airway pressures of 0, 2.5, 5, 7.5, and 10 cm H_2O caused P_{ra} to increase and instantaneous CO, measured by minimally invasive arterial pulse pressure waveform analysis, to

decrease. The resultant plot of these P_{ra} and CO values describes a VR curve, which when extrapolated to zero CO closely approximated P_{ms} [18, 19]. If the inspiratory hold maneuver is held just slightly longer (e.g., ~20 s), the resultant CO decrease is associated with an arterial pressure decrease because baroreceptor response is too slow to change arterial tone. One can then plot a MAP to CO graph similar to the P_{ra} and CO graph, because the CO is the same for both P_{ra} and MAP measures. The zero flow MAP to CO graph ends not at P_{ms} but at a pressure much higher than P_{ms}, reflecting the arterial critical closing pressure, otherwise referred to as a vascular waterfall, which will be described in greater detail below. Schipke et al. measured arterial and venous pressures in patients undergoing cardioverter/defibrillator implantation during cessation of flow caused by longer fibrillation/defibrillation sequences. Although this resembled the Guyton experiments, no equilibrium of pressures was achieved, probably due to the short cessation of circulation which kept the arterial critical closing pressure functional [20]. One step further, Repessé et al. measured venous and arterial pressures in critically ill patients who died at the ICU 1 min after circulation arrest. One-minute P_{ms} was 12.8 ± 5.6 mmHg with no difference in patient characteristics [21]. The group of Pinsky and Maas recently analyzed different bedside modalities of P_{ms} measurements in humans [18]. According to the hypothesis-generating work by Anderson, a stop-flow vascular pressure in a peripheral artery or vein could be used as an approximation of P_{ms}. The group of Maas compared transient stop-flow forearm arterial and venous equilibrium pressure (P_{arm}) with both P_{ms} achieved by inspiratory breath-hold maneuvers and an estimated value of P_{ms} calculated by a recent monitoring computerized algorithm developed by Parkin and Leaning which incorporates the Guytonian approach to measure P_{ms}. It assumes a lump sum arterial resistance 40 times greater than venous resistance and arterial compliance 20 times less than venous compliance. Thus, if one knows P_{ra}, MAP, and CO, P_{ms} is easily calculated. This value is referred to as P_{ms} analogue (P_{msa}). Although its clinical significance is still under investigation, it is a good example of how estimates of P_{ms} could be made in a minimal invasive clinical setting [22–26]. Maas et al. found that P_{arm} correlated well with P_{ms} as measured by inspiratory hold maneuvers, whereas P_{msa} had a systemic bias which could be accounted for by dividing P_{msa} by 0.7. Consequently, they compared changes in volume status by passive leg raising and volume infusion between P_{ms}, P_{arm}, and P_{msa}, which showed that all three measures of P_{ms} reliably tracked the changes in effective circulating blood volume status. Cecconi and co-workers used estimates of P_{msa} using this methodology to measure P_{ms} and P_{vr} in postsurgical patients in response to volume resuscitation. They observed that all volume challenges increased P_{msa}, but only in volume responders, defined as those whose CO increased by >15%, did P_{vr} also increase. In the non-volume responders, P_{ra} increased in proportion to the increase in P_{msa}. Thus, if a patient is given a fluid challenge and P_{ra} increases, that fluid challenge should be stopped and the patient reassessed because they are probably not volume responsive [27]. Another technique studied is the vascular stop-flow equilibrium method. If peripheral venous and arterial pressures are being simultaneously measured in the same arm and a vascular blood pressure cuff is rapidly inflated to greater than systolic arterial pressure, one

sees the venous and arterial pressure merging toward a common value after about 20 s that closely tracks P_{ms} and its change in response to fluid loading. This stop-flow measure can be made from a radial arterial pressure catheter alone. Thus, there are several methods available to estimate P_{ms} at the bedside. Recently, clinical studies have shown that the changes in P_{ms}, P_{vr}, and RVR can be readily measured and performed in a fashion consistent with Guytonian physiological principals in post-operative cardiac surgery patients given norepinephrine to increase MAP and in septic patients during withdrawal from norepinephrine [19, 21].

5.5 Cardiac Physiology

5.5.1 Atrial Physiology in General

The atrium has five main functions. First of all, as described earlier, it has a major function as reservoir. Second, its presystolic contractile function optimizes emptying and thereby delivering blood into the chambers (atrial kick). Third, after opening of the atrioventricular (AV) valves, it functions as a conduit by transferring blood to the chambers down a pressure gradient. Fourth, it serves as a blood volume sensor which releases atrial natriuretic peptides during states of increased atrial wall stretch, thereby increasing diuresis and contributing to the restoration of normal intravascular volume state. And fifth, it contains receptors from afferent fibers answering to increased venous return (Brainbridge reflex) [28, 29].

Inspired by the experiments from Starling, Mitchell, Sarnoff, and Guyton, Anderson investigated in several experiments what he termed “the mechanical nature of the heart as a pump” [5, 13, 30]. With a similar extracorporeal circulatory design using subsequently a sucking and non-sucking pump in mongrel dogs, he found that the output of the sucking pump was dependent on the rate of the pump. Output of the non-sucking pump was more dependent on external (or likewise extra-cardiac) factors, e.g., flow rate to the heart. Changing pump rate in a non-sucking model merely changed the stroke volume but not the total (cardiac) output. Clamp-tubing experiments proved atrial function as (distensible) reservoirs to avoid stop flow during closure of AV valves. Anderson concluded that since the heart is non-sucking, continuous-inflow (atria) and intermittent-outflow pump atria function more as conduits at rest and supplemental pump during exercise [5]. Without atria the heart needs a four-time higher inflow pressure to achieve (venous pressure), but the atrial systole only attributes up to 15–25% of blood flow from the atria to the ventricles. This has been confirmed by many studies [13, 28, 31]. Additionally, atria in sinus rhythm are more effective because they do not contract during venous filling and do not interrupt inflow during ventricular systole, i.e., the atria remain distensible enough. Even during atrial contraction, their lumen never narrows to the extent in which venous resistance increases. Of note, atria never reach a negative pressure and are therefore to be considered non-suction pumps. On the contrary during atrial fibrillation and flutter, the atria prohibit atrial relaxation and thus venous inflow. This proves that atrial kick does not necessarily play a pivotal role in

contributing to CO, but moreover the reservoir and conduit function, which fall short during atrial (tachy)arrhythmias.

5.6 Right Atrium

P_{ra} should not be considered as the independent variable determining CO. It is clearly linked to RV function, stressed blood volume, and intrathoracic pressure. Still, P_{ra} plays a pivotal interacting role in defining P_{vr} and thus CO. There are three mechanisms which influence P_{ra}. The first describes a decrease in P_{ra} when CO increases, as a result from transferring blood from the venous part to the arterial tree. Second, relaxation of smooth muscle resulting in venodilation decreases P_{ms} which eventually leads to a decrease in cardiac filling, reflected by a decrease in P_{ra}, CO, and arterial pressure. Finally, a reduction of blood volume also leads to a decrease in P_{ra}. Since P_{ra} is influenced by cardiac function (i.e., the ability to transfer the amount of blood which it receives) and thus increases when CO diminishes or the opposite, it is not a good parameter of venous return and intravascular filling status [14]. The atria are relatively empty after ventricular diastole, combined with the atrial contraction, allowing continuously venous inflow. Therefore, the atria serve both as a reservoir and a conduit, but their contraction plays only a minor role in comparison to its capacitive function except under circulatory stress and exercise conditions. The fact that the atria are capable of distension during ventricular systole allows venous drainage into the atria to be continuous, despite only episodic ventricular filling [5].

5.7 Left Atrium

In addition, atrial remodeling (which occurs mainly on the left side of the heart because of the following processes) is a combination of ion, structural, contractile, and metabolic changes induced by elevated left atrial pressures in several disease states. For example, it occurs as a result of as well as induces atrial tachyarrhythmias. Left atrial stretch or enlargement either resulting from long-time left ventricular diastolic dysfunction, hypertrophy, or otherwise elevated LV pressures caused by systolic LV failure can lead to poor atrial contractile performance and increased initiation and perpetuation of atrial fibrillation [32].

5.7.1 Ventricular Physiology in General

Preload is the load present before contraction has started, usually defined by the end-diastolic pressure or end-diastolic volume. It could better be defined as wall stress at the end of diastole. Afterload is the load opposing the ventricle during ejection and is considered to be the wall stress during LV ejection. When preload increases, ventricular end-diastolic volume increases, thereby increasing

contraction force according to the Frank-Starling mechanism. Preload and afterload are interlinked, meaning that preload is related to the extent to which myocardial fibers are stretched during end diastole and afterload is related to the wall stress generated by these fibers during systole. This tight linkage of end-diastolic myocardial fiber tension and developed pressure has greatly improved knowledge of ventricular function to date.

5.8 Frank-Starling Effect

In the 1890s Starling and co-workers observed that when myocardial muscle strips were stretched, the force of their contraction increased. Sudden increases in developed tension (caused by increased preload) induce an immediate increase in developed pressure. This is referred to as heterometric autoregulation, to accent the fact that the autoregulation is due to external forces (i.e., preload). Since end-diastolic myocardial fiber length is a major determinant of LV end-diastolic volume, the Frank-Starling relation has been simplified to state that sudden increases in LV end-diastolic volume can cause an immediate increase in LV force of contraction. This process is essential to match over short time periods RV and LV outputs so as to maintain central blood volume constant. Since venous return varies widely during positive-pressure breathing owing to the effect of intrathoracic pressure on P_{ra}, RV filling and thus output also vary widely across the ventilatory cycle, and parallel changes in LV end-diastolic volume are caused with a two- to three-heartbeat delay. The Frank-Starling effect keeps these two ventricles cycling their stroke volumes to these dynamic changes in preload [13]. Interestingly, the exact mechanism(s) causing this effect is poorly understood but must relate in some way to conformational changes in myocyte orientation or calcium proximity to troponin, because the effect is instantaneous.

5.9 Anrep Effect

An acute increase in ventricular afterload causes intrinsic contractility to increase by complex cellular mechanisms associated with ischemia that includes phosphorylation of the calcium channel receptor activator protein increasing calcium transits during systole. This effect takes about 2–3 min to be fully developed, but once present results in a lower LV end-diastolic volume and filling pressure for a greater stroke volume. This process is referred to as the Anrep effect of homeometric autoregulation to contrast its Frank-Starling effect because it is intrinsic to the cardiac myocyte metabolic processes. Von Anrep proposed a sudden release of myocardial stores of catecholamines by mechanical stretch, although more recent data suggest that increased calcium transiting due to changes in T-tubal associated flux is a more likely mechanism [33]. The Anrep effect is an important mechanism to support increased contractility for short intervals of stress, such as exercise, but usually subsides after a few hours.

5.10 Ventricular Wall Stress

Wall stress, according to Laplace's law, is created when tension is applied to a cross-sectional area, measured in unit force per unit area. For a sphere, wall stress is calculated as = (pressure × radius)/(2 × wall thickness). This portends two important features. The first is that the larger ventricular size and radius, the greater the wall stress. The second is that at any given radius, the greater the pressure generated by the ventricle, the greater the wall stress. Thus, an increase in either ventricular size or intraventricular pressure will increase wall stress and thereby myocardial oxygen uptake. Under normal conditions maximal LV wall stress occurs at the start of ejection when the aortic value initially opens because the product of diastolic arterial pressure and end-diastolic volume is maximal. During normal LV ejection as LV volume decreases, the radius decreases much more than systolic arterial pressure increases. Thus under normal conditions, the left ventricle unloads itself during ejection to end systole. A good example of adaptation of the heart to increased wall stress is that of ventricular concentric hypertrophy. However, hypertension increases wall stress across all LV ejection. Increased wall thickness in response to systemic hypertension counterbalances increased intraventricular pressure thereby compensating increased wall stress; the radius does not change. However, this compensatory mechanism holds up to a certain limit, after which, as known in hypertensive heart disease, the ventricle eventually starts to dilate. Ventricular dilation is a good example of increased wall stress, as the radius increases. In systolic heart failure, decreased contractile function is compensated by dilation, thereby increasing wall stress. However, in systolic heart failure, radius stays too high throughout the contractile cycle, leading to both elevated end-systolic and end-diastolic wall stress. This pathological process underlies the logic in afterload reduction to treat systolic heart failure, because wall stress remains high during ejection in the setting of LV dilation. Therefore, overall reduction in ventricular size reduces wall stress and improves ventricular function [28].

5.11 Chronotropy

Heart rate (HR) changes inversely alter diastolic filling time. The faster the HR, the less time in diastole and thus the lower the LV end-diastolic volume causing a proportional decrease in stroke volume without a change in CO. However, in heart failure states, wherein P_{ra} is elevated and both RV and LV end-diastolic volumes limit filling such that SV is fixed, HR increases initially increase CO until P_{ra} decreases to a point where it no longer allows for an increased P_{vr}. Second, as HR increases from 90 to approximately 110 beats/minute, intrinsic contractility also increases (Treppe or Bowditch effect). This effect is usually what is referred to as chronotropy and has a maximum response at heart rates 150–180 beats/minute in young adults and probably at low beat frequencies in the elderly. However, the first effect secondary to decreasing P_{ra} described above is usually lumped into the overall effect because it is not possible to separate the two processes from each other. The cause of the

HR-induced increased force of contraction is still unclear but probably related to nonsteady-state increases in calcium availability for troponin coupling because it has not had sufficient enough time to return completely to the t-tubules during diastole.

5.12 Work of the Heart

The work of the heart (external work) is calculated as pressure x volume. Volume work generally demands less energy (oxygen) than pressure work. Stroke volume (or cardiac output) is the volume moved against blood pressure, whereas the pressure work consumes an increased pressure or heart rate. In this relationship three components can be regarded determining myocardial oxygen uptake: preload, afterload, and heart rate, usually defined in the formula minute work = systolic blood pressure (SBP) × stroke volume (SV) × heart rate (HR). Following this formula of the pressure-work index, the double product of SBP × HR and SV × HR (i.e., CO) reveals that a lot of myocardial oxygen demand is involved (up to 40%). See also Fig. 5.2.

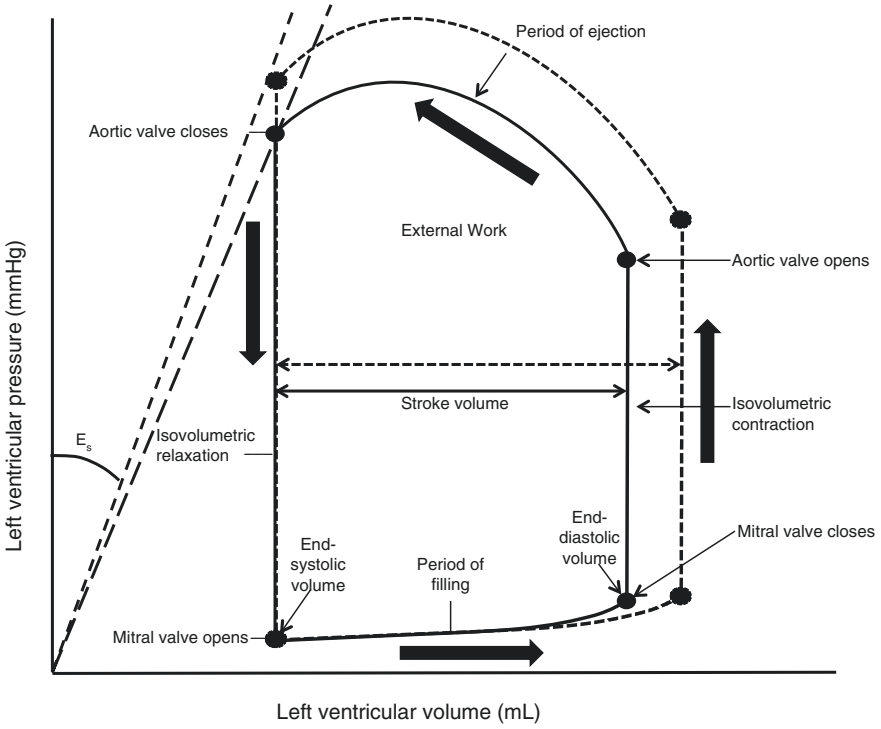

Fig. 5.2 Graphical presentation of ventricular function and its pressure-volume relationship. The slope of the end-systolic pressure-volume relationship (E_{es}) is displayed. Total external work of the heart is represented by the area of the pressure-volume curve. When cardiac output increases, the area of the external work curve becomes larger

5.13 Right Ventricle

5.13.1 Right Ventricular Anatomy

The RV is the cardiac chamber which is situated most anteriorly behind the sternum and marks the inferior border of the cardiac silhouette [34, 35]. It is defined by the presence of the annulus of the tricuspid valve and the pulmonary valve. There are three important RV anatomical compartments: (1) inflow tract (sinus), consisting of the tricuspid valve, chordae tendineae, and the papillary muscles; (2) the trabeculated apical myocardium; and (3) the infundibulum (conus), which represents the right ventricular outflow tract (RVOT). Furthermore, there are three muscular bands which characterize the right ventricle: (1) the parietal band, which, together with the infundibular septum, forms the crista supraventricularis, and (2) the septomarginal band, which continues into the moderator band (3) eventually attaching to the anterior papillary muscle. The ventriculo-infundibular fold, separating the tricuspid and pulmonary valves, is another specific marker of RV anatomy, as in contradiction to the LV, where fibrous continuity exists between the mitral and aortic valves. The RV has a triangular shape seen from aside but appears to have a half-moon shape on cross-sectional slides [34, 35]. The design of the RV is primarily aimed at volume capacity. It consists of coarse trabeculae (reaching from the sinus to the conus) which cause the RV to contract in an almost peristaltic pattern. The myofiber architecture of the RV consists of two layers (instead of three layers in the LV), where the superficial layer arrays more or less parallel to the atrioventricular groove, circumferentially surrounding the RV and eventually continuing into the superficial layer of the LV around the apex. Although the RV also has helical fibers (as is the case in the LV), it does not have an oblique middle layer of circumferential fibers (as present in the LV wall) and is therefore largely dependent on longitudinal shortening, in combination with torsion along with the LV. Furthermore, it moves along with the rotation of the LV apex relative to basal segments. The merged superficial layers of the RV and LV permit binding of the two ventricles together and forms the basis of ventricular interdependence (see further) [34].

5.13.2 Right Ventricular Physiology

In contrast to LV diastole, there is not an active RV diastolic relaxation-related ventricular sucking. Over 100 years ago, Starling demonstrated that the primary determinant effect of cardiac function on CO is how it inhibits venous return, not how contractile the myocardium is [3]. They and many others observed that the heart pumps out as much blood as it receives. Venous inflow (preload) or venous return, rather than P_{ra}, determines CO. Starling made a striking comparison to a petrol engine when reviewing the function of the heart; the output only increased with an increase with venous inflow. Thus, the greater the volume of the heart, the more contractile the heart becomes [13]. This is not entirely true

when it comes to RV physiology. In steady-state conditions, the RV can be ablated without causing a substantial increase in systemic venous pressures [36]. The primary role of the RV is to deliver all blood it receives into the pulmonary circulation. An acute increase in pulmonary vascular resistance (PVR) causes acute RV dilation and RV pump failure. A gradual increase in pulmonary artery pressure allows the RV to hypertrophy similar to LV remodeling due to an increase in systemic arterial pressure. Furthermore, Starling et al. observed that CO is independent of mean arterial pressure (MAP), albeit up to physiologic limits according to his experiments (>220 mmHg), after which the heart dilates and fails. Nevertheless, he also found that MAP is major determinant of coronary perfusion. Indeed, within physiological ranges of systemic arterial pressure, RV outflow is not impaired by changes in arterial pressure so long as venous return is sustained. Therefore, the right ventricle is the primary determinant of CO [14].

The primary function of the RV is to receive systemic venous return and pump it into the cardiopulmonary circulation. As explained earlier, RV function should be considered as the determinant of cardiac output, where LV function is a determinant of tissue organ perfusion, which will be focused on later on. RV contraction starts with contraction of the inlet and trabeculated myocardium followed by contraction of the infundibulum, the latter with a 25–50 ms later onset. The RV contraction pattern follows a three-step sequence, initiated by inward movement of the free wall (creating a bellowing effect), followed by contraction of the longitudinal fibers, shortening the long axis and drawing the tricuspid valve apparatus to the apex, and finally with traction on the free wall at the attachment points where RV is connected with the LV, secondary to its latter contraction [34].

RV contraction results in an early peaked and rapidly declining ventricular pressure curve, due to its low resistant and highly distensible pulmonary vascular tree into which blood is expelled. Also isovolumetric contraction phase is shorter than the LV, because RV systolic pressure rapidly exceeds the low pulmonary artery diastolic pressure earlier than LV systolic pressure exceeds aortic diastolic pressure.

Concerning afterload, the RV is more sensitive for afterload changes than the LV. RV stroke volume decreases almost 50 times faster with increasing intravascular pressure in comparison to the LV. In this light Guyton already questioned the flow-resistive properties of the pulmonary circulation, guided by the observation that a Fontan circulation falls short when pulmonary resistance increases too much. He wondered if it was purely an example of the RV falling short or that it could also be a lack of mean systemic filling pressure [37]. Although pulmonary vascular resistance (PVR) is the most commonly used parameter for RV afterload, a more complete model with both static and dynamic indices, as well as vascular impedance, intracavitary resistive properties, and valvular anomalies, would be more adept [34]. RV filling has an earlier onset in comparison to LV filling and finishes later. As with RV isovolumetric contraction phase, RV isovolumetric relaxation is

shorter than LV, and RV filling pressures (*E* and *A*) are lower, with a lower *E*/*A* ratio. The influence of the respiratory variations on the RV filling is however higher than compared to LV.

5.14 Left Ventricle

5.14.1 Left Ventricular Anatomy

The design of the left ventricle is aimed at pressure capacity. Normal LV contraction is made possible by three key elements in LV construction. First, its helical layer of fibers which course between subendocardium and subepicardium determines both conical shape and movement pattern. However, this layer only contributes for 15% of length shortening in the LV contraction process and therefore contraction of LV oblique fibers further contributes to LV ejection. Furthermore, LV contains a middle layer consisting of circumferential constrictor fibers which cause the decrease of the internal diameter and thus being the driving force of the LV. The third important component of ejection is the rotation of the left ventricle from LV apex to the basal segments. LV contains three layers, obliquely oriented superficial myofibers, longitudinally oriented myofibers in the subendocardium, and circular fibers in between [1]. Its movement is a combination of torsion, translation, rotation, and thickening.

5.14.2 Left Ventricular Physiology

The basic hemodynamics of the heart are determined by three essential basic pump characteristics: (1) passive filling, (2) atrial effect (allows continuous uninterrupted venous inflow by dilation of the atria), and (3) intermittent or pulsatile outflow. With regard to the first characteristic, in vivo, this is shown in the fact that the heart is not sucking, though the chest is (raising negative pressure during forceful inspiration, creating negative intrathoracic pressure). Normally the end-systolic volume in the heart and the rapid filling from the normal inflow pressure never allow the heart to develop any negative pressure. The circulation rate is determined by extra-cardiac factors, as well as the balance between the systemic and pulmonary compartments. In addition, pulsatile outflow is shown to have a better diffuse perfusion of the body. Increases and decreases in diastolic pump filling correlate with elevations and decreases in arterial blood pressure. Vasopressors increase MAP by increasing P_{ms} (as mentioned previously) and not by increasing resistance. Increased cardiac contraction in response to drugs, increased strength of myocardial contraction to increased diastolic filling (Starling), and increased heart rate are all observed in situations of increased cardiac output. They have been misinterpreted in the past as a cause of increased cardiac output, because they occurred concomitantly with an increase in cardiac output [5]. In this light, the primary function of the LV is to maintain arterial pressure (P_{sa}) and flow, in order to guarantee organ perfusion [14].

5.14.3 Systolic Function

The systolic function of the left ventricle could be best explained by the pressure-volume relationship. The complex interaction between contractility, afterload, and preload of ventricular function (both RV and LV) is usually depicted in a pressure-volume relationship, with ventricular volume on the *x*-axis and ventricular pressure on the *y*-axis (Fig. 5.2).

It represents the ventricular pressure-volume changes within one cardiac cycle and can be divided into four phases:

1. Filling phase. When ventricular pressures are at its minimum (end systole) and thus lower than atrial pressures, this allows for opening of the mitral/tricuspid valves and subsequently emptying of the atrial blood volume into the ventricles (diastole). This filling period consists thus of the early rapid filling phase, followed by diastasis and atrial systole. The slope of the passive ventricular distention is diastolic compliance. At the end of diastole, the pressure-volume relationship is at its minimum, and this point is considered to be a measure of diastolic compliance. However, it is influenced by extra-cardiac factors such as pericardial pressure, intrapulmonary pressure, and its neighboring ventricle based on the principle of interventricular dependence (see later section). As mentioned before, end-diastolic pressure is synonymous with preload.
2. Isovolumetric contraction phase. When mechanical contraction occurs, intraventricular pressure increases, which allows the AV valves to close. Then the isovolumetric contraction phase follows, which is termed so because the volume of the ventricle does not change because all valves are closed.
3. Ejection phase. When pressure further rises, the semilunar (aortic and pulmonary) valves open as soon as ventricular pressure exceeds aortic or pulmonary artery pressure. At this point, the curve represents maximal ventricular wall stress which is considered to be a measure of afterload (see earlier section). Under normal conditions maximal wall stress occurs at the beginning of ventricular ejection. The end-systolic pressure-volume relation, which can be approximated by a linear relationship with the slope of its relationship, is referred to as end-systolic elastance and is considered to be a good load-independent index of contractility (E_{es}; end-systolic pressure-volume relationship) [28, 38, 39]. Time-varying elastance (E_{τ}) is a marker of progressive stiffening of the ventricle during systole and its relaxation during diastole. It is calculated as a pair of isochronic pressure-volume relations during ejection and increases progressively from end diastole to end systole. Maximal elastance (E_{max}) is the maximal LV pressure-volume ratio and usually occurs just after end systole [39].
4. Isovolumetric relaxation phase. Once ejection has finished, ventricular relaxation commences. Diastolic relaxation or lusitropy, initiated by the isovolumetric pressure decline/isovolumetric relaxation phase, is an active process which requires energy. The semilunar valves close and ventricular pressures fall back to the diastolic pressure level.

5.14.4 Diastolic Function

Diastolic relaxation is an active process, which causes left ventricular intracavitary pressure to decrease fast and allow the ventricle to fill adequately without an abnormal increase in left atrial pressure. As mentioned before, the phases of diastole are isovolumic pressure decline and filling, of which the latter is divided into early rapid filling phase, followed by diastasis and atrial systole. The early rapid filling phase, driven by the LA-to-LV pressure gradient, contributes up to 80% of LV filling and decreases with aging. It is a complex combination of factors in which myocardial relaxation, LV elastic recoil, LV diastolic stiffness, LA pressures, ventricular interaction, pericardial constraint, pulmonary vein properties, and mitral orifice area play an important part. Diastasis contributes less than 5% to LV filling. Atrial systole only contributes up to 25% of LV filling; however, as mentioned before, its importance remains debated in the light of the reservoir and conduit function of the atria. Nevertheless, since the atrial kick is part of LV diastolic filling, it is worth mentioning that its function is dependent on the duration of the PR interval, atrial inotropic state, atrial preload, atrial afterload, autonomic tone, and heart rate. The process of LV filling consists of active relaxation and the recoil/suction, thereby "pulling" blood into the left ventricle. This enhances the LA-to-LV pressure gradient [40]. The isovolumic pressure decline can be quantitatively observed by measuring the peak rate of pressure fall (dP/dt.min) along with the time constant τ which is a marker of the rate of LV pressure decline during the isovolumetric relaxation process. A higher dP/dt.min signifies that relaxation rate is decreased and a larger value of τ implies it takes longer for the LV pressure to fall which is a sign of impaired relaxation. During systole potential kinetic energy is stored in the elastic elements of the myocytes, which is released during relaxation as the elastic element recoil and return to their original length and orientation. This greatly enhances LV pressure to fall which contributes to an early diastolic pressure gradient from LA to LV.

5.15 Ventricular Interdependence

Ventricular interdependence is characterized by the transmission of forces from one ventricle to another through the myocardium and pericardium. Systolic interaction refers to the positive contribution of both ventricles to each other [41]. The interventricular septum (IVS) plays a major role in modulating interventricular dependence in close conjunction with the pericardium. As mentioned in the anatomical section of both LV and RV, the latter is literally draped around the LV and has a more compliant character than the LV. Following contraction of the LV, the RV profits from its neighbor with a roughly 30% contribution to RV contraction and pulmonary flow [42]. This is explained by the concept of mechanical entrainment of both ventricles within the pericardium, but also LV contribution to systemic blood pressure, which is essential for RV coronary perfusion. Diastolic ventricular interaction accounts for

the competition of space between the ventricles within the non-distensible pericardium. When LV end-diastolic volume (LVEDV) increases, this shifts the IVS toward the right, increasing RV end-diastolic pressure (RVEDP). Similarly, when RV end-diastolic volume (RVEDV) increases, this causes the IVS to shift leftward during diastole due to restrictions imposed by the pericardium on the RV cavity. This leftward shift impairs LV function by reducing LV volume, decreasing both LV filling and compliance which greatly decreases cardiac output eventually. It also increases muscle stiffness and LV wall tension [43].

5.16 Ventriculo-arterial Coupling

A proper physiologic function of the cardiovascular system is determined by the dynamic interaction between heart and systemic circulation. Both left ventricular systolic performance in terms of contractility and loading conditions (preload and afterload) and the arterial system (systemic arterial compliance, stiffness, and resistance) are in close conjunction. This phenomenon is termed ventriculo-arterial (VA) coupling. VA coupling can be defined as the ratio between arterial elastance and ventricular elastance (E_{es}). An optimal E_a/E_{es} ratio implies an adequate left ventricular stroke volume at the lowest energy consumption. It is therefore an effective index of maximal cardiac performance and dynamic modulation of the arterial system. Also, at this point the lowest myocardial oxygen demand is required. As explained earlier, E_{es} or the end-systolic pressure-volume relationship defines the intrinsic contractility of the heart. The steeper the slope, the greater contractility. E_a consists of the total arterial afterload opposing the LV, taking into account systemic arterial compliance, stiffness, and resistance, which can be regarded as the ability of the vessels to process the increased pressure when LV stroke volume increases. It can be depicted as the slope from the LV end-diastolic volume to the LV end-systolic pressure as presented in Fig. 5.3 [44].

5.17 Coronary Physiology

Myocardial oxygen uptake can be increased by preload, afterload, increased heart rate, or contractile function caused by beta-adrenergic stimulation. Both increased preload and afterload increase diastolic and systolic wall stress, respectively, which demands a higher oxygen uptake. Moreover, the concept of increased wall stress generating increased oxygen uptake is of crucial importance in relation to heart size, as a larger radius increases wall stress (see previous sections). Since LV coronary flow occurs only in diastole, the LV may be subjected to (subendocardial) ischemia with increased LV wall stress (i.e., with increased LV end-diastolic pressure, LVEDP). This is slightly different in the RV, where the myocardium is being perfused during both diastole and systole, because RV wall stress is usually low and can easily be overcome by coronary artery pressure. However, in pulmonary

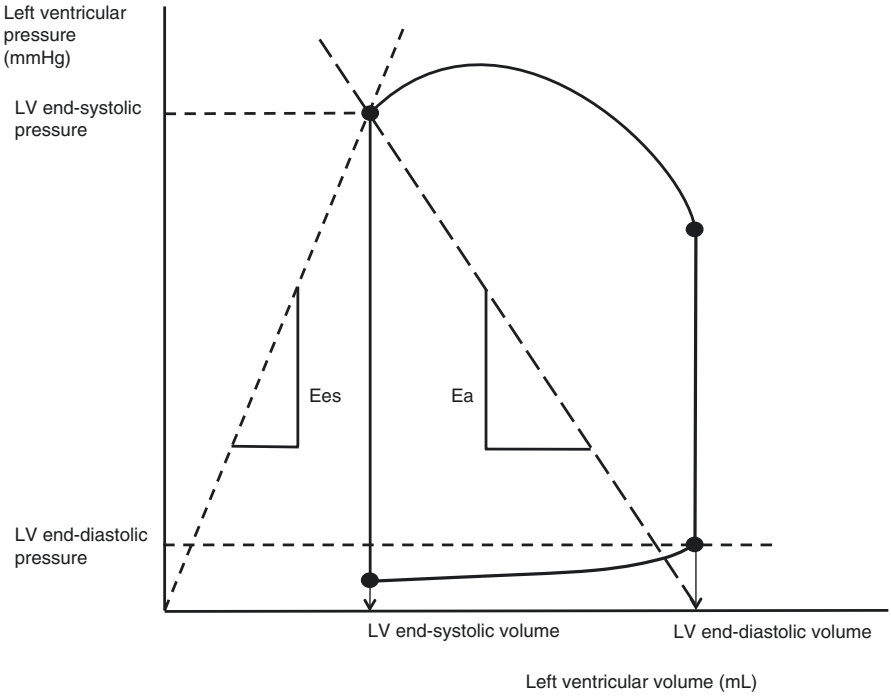

Fig. 5.3 Left ventricular pressure-volume loop with LV ventricular elastance (E_{es}) and arterial elastance (E_a) slopes. Note the optimal point of VA coupling where both slopes intersect

hypertension states, treatment must increase diastolic arterial pressure greater than pulmonary artery pressure to insure right ventricular blood flow and prevent acute cor pulmonale [45].

5.18 Pericardium

The most important function of the pericardium is its modulation of cardiac volume on which it has a restraining effect. This is obtained by the elasticity of the pericardium which reaches a limit at a certain point, thereby inhibiting the cardiac chambers from further dilating or overdistension. In this light, more specifically pericardial contact pressure, which is the pressure representing transmission of the pericardial pressure, determines to a great extent the upper limits of normal cardiac filling. This goes especially for the right-sided heart, since those filling pressure are lower than left-sided. Furthermore, it augments contractility of the RV through systolic ventricular interdependence and augments LV contractility by limiting energy loss by rotational changes during contraction. The normal pericardium also contributes to diastolic interaction between the ventricles via interventricular dependence.

Thus it contributes to intracavitary filling pressures both through direct external contact pressure and because of increased diastolic interaction [46–48].

5.19 Concluding Remarks

In this chapter the interplay of the systemic circulation and the heart has been discussed. Clearly, there is a role for mean systemic filling pressure (P_{ms}) in the determination of intravascular fluid status and its consequences for the amount of preload. Where it comes to the right side of the heart, preload is essential for its primary role which by its volume-pump function supplied by venous return greatly determines cardiac output. In between, the atrial function was highlighted, where it became clear that atrial kick does not portend the major contributor to cardiac output, but the atrial reservoir and conduit function do. The left ventricle on the contrary has a primary role in the determination of organ perfusion. Together, via its complex interaction of interventricular dependence and physiology of the pericardium, they determine total work of the heart in both steady state as during strenuous exercise and critical illness circumstances. Each of these parts in the chain plays their own major role, and failure of one of each has great implications for the performance and prognosis of the patient.

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Oxygen Transport Assessment

6

Arnaldo Dubin and Eliézer Silva

6.1 Introduction

The systemic oxygen transport (DO_2) is the amount of oxygen convectively delivered from the central circulation to the tissues. The DO_2 is calculated as the product of cardiac output (CO) by arterial oxygen content (CaO_2):

$$DO_2 = CO \times CaO_2$$

$$CaO_2 = Hb \times 1.34 \times \text{arterial } O_2 \text{ saturation} + \text{arterial } PO_2 \times 0.00309$$

Consequently, the DO_2 results from the joined contributions of cardiovascular, respiratory, and hematopoietic systems. Since several methods are available for the CO measurement and arterial gases and O_2 saturations are routinely measured, the DO_2 can be easily computed in critically ill patients.

Although the reduction in tissue DO_2 and the subsequent decrease in oxygen consumption (VO_2) is the underlying mechanism of every type of shock, the relevance of the actual value of systemic DO_2 is an uncertain issue because of:

1. In physiological conditions, the VO_2 is primarily determined by metabolic oxygen needs, not by the DO_2. Thus, DO_2 is a dependent variable, which is adjusted for satisfying the changing oxygen demands. Consequently, the frequently

A. Dubin (✉)
La Plata, Argentina

Cátedra de Farmacología Aplicada, Facultad de Ciencias Médicas, Universidad Nacional de La Plata, Buenos Aires, Argentina

Servicio de Terapia Intensiva, Sanatorio Otamendi y Miroli, Buenos Aires, Argentina

E. Silva
Medical School Hospital of the Albert Einstein, Sao Paulo, Brazil
e-mail: silva.eliezer@einstein.br

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quoted DO_2 normal range of 300–600 mL/min/m^2 might be worthless. Lower values might be adequate in patients with decreased oxygen demands (e.g., sedated and paralyzed patients on mechanical ventilation), while higher than normal DO_2 might be needed to satisfy metabolic oxygen needs in agitated and febrile patients [1]. Therefore, the key question is not what the actual value of DO_2 is, but if such DO_2 is enough to meet oxygen demands.

2. Most of patients have a form of shock, the microcirculatory shock, characterized by the presence of tissue hypoxia and hypoperfusion regardless of the normalization of systemic hemodynamics and DO_2 [2]. This condition might be present not only in septic shock but also in every type of shock. Consequently, normal or even high DO_2 does not exclude the presence of shock.

According to this discussion, the assessment of DO_2 requires measurements of the actual value of DO_2 as well as an evaluation of the adequacy of a given DO_2 to satisfy tissue perfusion and oxygen demands.

6.2 The Measurement of DO_2

Traditionally, DO_2 has been estimated from thermodilution-measured CO along with the CaO_2 calculated from hemoglobin concentration and arterial oxygen saturation and pressure. Nowadays, real-time monitoring of DO_2 is possible because of the availability of technology that allows continuous measurements of not only CO [3] and oxygen saturation but also hemoglobin [4]. Nevertheless, the performance of continuous noninvasive hemoglobin monitoring device might be inadequate [5]. As previously discussed, however, the actual value of DO_2 should not be isolated considered but in the context of several variables of systemic and tissue perfusion and oxygenation.

6.3 CO Surrogates

In the absence of direct CO measurements, some surrogates might be useful as an approximation to CO.

6.3.1 Central and Mixed Venous Oxygen Saturation

Venous oxygen saturation reflects the balance between VO_2 and DO_2 [6]. Consequently, reductions in central and mixed venous oxygen saturation ($S\bar{v}O_2$ and $ScvO_2$, respectively) show both decreases in DO_2, regardless of the compromised factor (CO, Hb, or arterial oxygenation), and increases in VO_2 and oxygen extraction (e.g., exercise, fever, agitation, etc.). The presence of a low venous oxygen saturation frequently points out to a low DO_2 and might be useful to guide

resuscitation. Nevertheless, recent large randomized clinical trials showed that this approach is useless in the resuscitation of septic shock [7–9]. In addition, high $ScvO_2$ has been associated with worse outcome [10]. Also, the interchangeability of $S\bar{v}O_2$ and $ScvO_2$ is controversial [11]. On the other hand, low venous oxygen saturations cannot be a sign of tissue hypoxia in stable patients with chronic cardiac failure [12].

6.3.2 Central Venoarterial PCO_2 Difference

According to Fick's principle, variations in CO are inversely correlated with the central venoarterial PCO_2 difference (Pcv-aCO_2). In contrast to oxygen venous saturation, Pcv-aCO_2 primarily reflects changes in CO and is insensitive to drops in DO_2, if CO is preserved [13]. A Pcv-aCO_2 > 6 mmHg might identify patients with hypoperfusion even when $ScvO_2$ is ≥70% [14]. Nevertheless, it should be emphasized that venoarterial PCO_2 differences mainly express systemic or regional hypoperfusion, but not tissue hypoperfusion. In an experimental model, the administration of endotoxin induced reductions in CO and superior mesenteric blood flow, which were associated with increases in systemic and intestinal venoarterial PCO_2 differences and tissue minus arterial CO_2 gradient (ΔPCO_2). After the normalization of systemic and intestinal hemodynamics by fluid resuscitation, systemic intestinal PCO_2 gradients normalized. ΔPCO_2, however, remained elevated as an expression of the alterations in villi microcirculation [15] (Fig. 6.1).

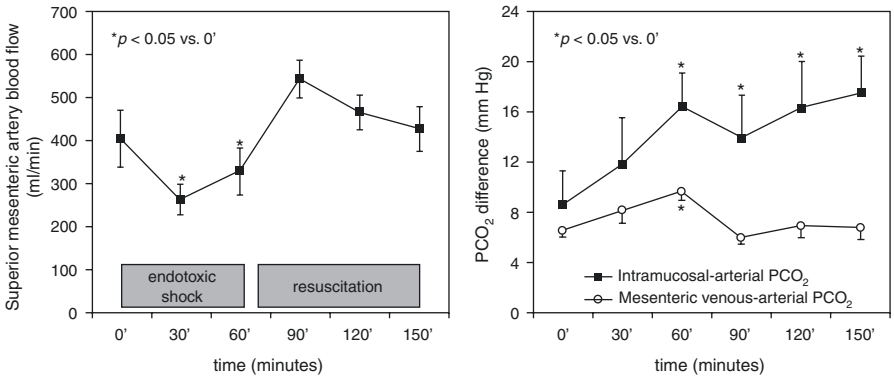

Fig. 6.1 Behavior of superior mesenteric artery blood flow (left panel) and mesenteric venous minus arterial and mucosal minus arterial PCO_2 differences (right panel), in endotoxemic shock and resuscitation. During the low flow, both PCO_2 increased as expression of global hypoperfusion. After the normalization of regional blood flow, the intestinal venoarterial PCO_2 difference returned to basal values, but mucosal minus arterial PCO_2 difference remained elevated because of persistent alterations in villi microcirculation (modified from reference [15])

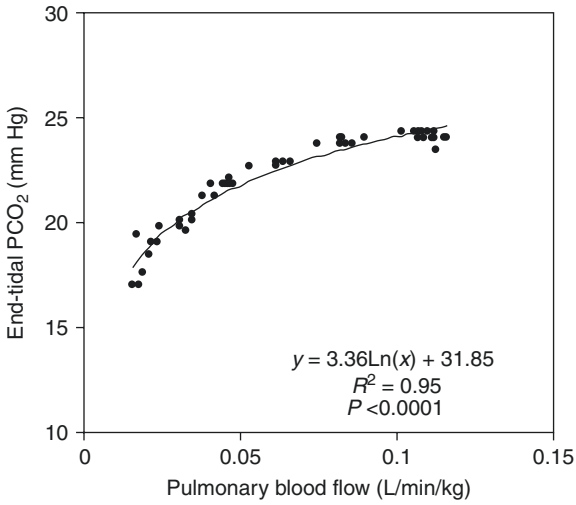

Fig. 6.2 Logarithmic relationship between end-tidal PCO_2 and pulmonary blood flow during progressive bleeding (modified from reference [16])

6.3.3 End-Tidal PCO_2

The end-tidal PCO_2 ($PETCO_2$) depends on interactions between the pulmonary ventilation/perfusion relationship and the CO_2 production (VCO_2) [16]. Consequently, if pulmonary ventilation and VCO_2 remained unchanged, decreases in CO and pulmonary perfusion result in reductions in $PETCO_2$. Indeed, variations in $PETCO_2$ may reflect changes in CO. The CO/end-tidal PCO_2 relationship, however, is not linear but logarithmic (Fig. 6.2). The greatest reduction in $PETCO_2$ observed with critical CO decreases might be attributed not only to a lessening of its excretion but also to a decrease in its production, during the phase of oxygen supply-dependent metabolism. $PETCO_2$ may be useful for tracking changes in pulmonary blood flow and for warning of ongoing anaerobic metabolism [16].

6.4 The Involved Factor of DO_2

The reductions in DO_2 can be produced by decreases in CO, arterial oxygen saturation, or hemoglobin levels and eventually result in the three basic types of hypoxia (i.e., ischemic, hypoxic, and anemic hypoxia, respectively). Nevertheless, the impact of each kind of hypoxia on tissue oxygenation, as well as the body tolerance, may differ each other. Compared to ischemic hypoxia, similar reductions in DO_2 induced by anemic hypoxia are associated with lower oxygen extraction ratio (O_2ER) and more severe microcirculatory alterations [17]. Moreover, the feasibility for the therapeutic correction of the different compromised factors of DO_2 may also differ each other. In addition, attempts to increase DO_2 might be unsuccessful to improve tissue perfusion, regardless of the improvement in a particular factor. For example, blood transfusions can correct low hemoglobin levels but fail to ameliorate tissue hypoxia because of the characteristics of transfused red blood cell [18].

6.5 Evaluation of the Adequacy of DO_2 for Systemic and Tissue Oxygenation

6.5.1 Oxygen-Derived Variables

6.5.1.1 VO_2/DO_2 Relationship

The final goal of DO_2 is to meet oxygen demands. Thus, plateau values of VO_2 might assure the adequacy of DO_2. This assumption is based on the model of physiological oxygen supply dependency [19], which consists in a biphasic VO_2/DO_2 relationship (Fig. 6.3, Panel A). During DO_2 reductions produced by hypoxemia, isovolemic anemia, or low CO, VO_2 remained unchanged because of progressive increases in the O_2ER. When a critical DO_2 is reached, further reductions result in VO_2 falls, and anaerobic metabolism ensues [20]. The lineal VO_2/DO_2 relationship beyond the critical DO_2 implies that O_2ER reaches its maximal values. The model also presumes two defined zones of aerobic and anaerobic metabolism. Nevertheless, the assumptions of this simple model could be challenged in

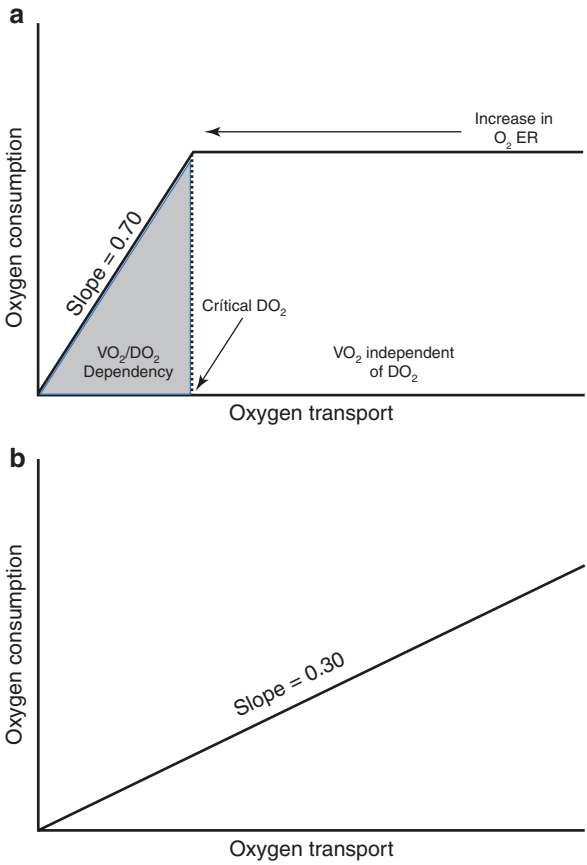

Fig. 6.3 Panel A: Physiological dependency of oxygen consumption on oxygen transport. Panel B: Pathological dependency of oxygen consumption on oxygen transport

some ways: (1) Probably, the VO_2/DO_2 relationship is not biphasic but logarithmic. (2) Accordingly, there is no plateau of VO_2, since the relationship seems asymptotic. The explanation is that the maintenance of high DO_2 requires higher oxygen demands and VO_2 (higher cardiac workload, increased renal filtration and electrolyte reabsorption, etc.). (3) The lack of modifications in VO_2 not necessarily guarantees tissue perfusion and oxygenation. For example, a bleeding of 20 mL/kg in sheep was unable to modify systemic and intestinal VO_2. In spite of this, mucosal hypercarbia and gut lactate production developed [21]. (4) There is no a real critical DO_2 for the whole organism. Each organ and tissue has its own critical DO_2. Consequently, during the reductions in DO_2, anaerobic metabolism is an earlier phenomenon in the skin and subcutaneous tissue, while the compromise is delayed in the brain and heart. (5) There is no maximal O_2ER at the critical DO_2 because O_2ER continues increasing until the final stages. (6) Finally, the model assumes constant oxygen needs, which is not true in critically ill patients [1].

In contrast, the VO_2/DO_2 relationship has been characterized as lineal in some groups of critically ill patients (Fig. 6.3, Panel B). The underlying cause for the so-called pathological oxygen supply dependency is an inability to modify O_2ER in response to changes in DO_2. O_2ER, which is the slope of the VO_2/DO_2 relationship, remained fixed in values of about 0.25–0.30 [22]. This behavior of the VO_2/DO_2 relationship has been associated with the presence of hyperlactatemia, multiorgan failure, and death [23]. Nevertheless, the actual meaning of the pathological oxygen supply dependency is debatable. An alternative interpretation is that this is a physiological phenomenon, in which cardiac output and DO_2 change to satisfy the variable oxygen demands [24]. Finally, the pathological oxygen supply dependency might be an artifact that results from the use of thermodilution CO for the calculation of both, VO_2 and DO_2. Since the measurement of CO has an error inherent to the method, such error might propagate to the calculation of each variable and generate mathematical coupling of data and a spurious correlation [25]. Independent calculation of VO_2 and DO_2 by means of expired gases analysis, however, has found the same linear relationship [26]. In addition, similar findings were also described in experimental models of septic shock [27]. Therefore, the evidence suggests that alterations in the O_2ER and the VO_2/DO_2 relationship are present in critical conditions.

In brief, the assessment of the adequacy of DO_2 through the analysis of its correlation with VO_2 is methodologically unreliable and difficult to perform and interpret and should not be carried out in critically ill patients. Unfortunately, the extensive research performed on this issue is inconclusive.

6.5.1.2 Respiratory Quotient

The respiratory quotient (RQ) is the ratio between VCO_2 and VO_2. It is measured by analysis of expired gases. Under aerobic conditions, the RQ is fixed and dependent on the caloric fuel. When the metabolism becomes anaerobic, the RQ increases as the consequence of an anaerobic source of CO_2. Anaerobic VCO_2 results from bicarbonate buffering of strong acid generated during tissue hypoxia. The rise in RQ might identify the beginning of anaerobic metabolism (anaerobic threshold) not

only during the increasing DO_2 that characterizes progressive muscular workload [28] but also in the other extreme of physiology, during the O_2 supply dependency [16, 29] (Fig. 6.4).

As a simplification of Fick's principle, the ratio between Pcv-aCO_2 and arterial-central venous O_2 content difference (Pcv-aCO_2/Ca-vcO_2) might be a surrogate for RQ that does not require analysis of expired gases. Observational studies have

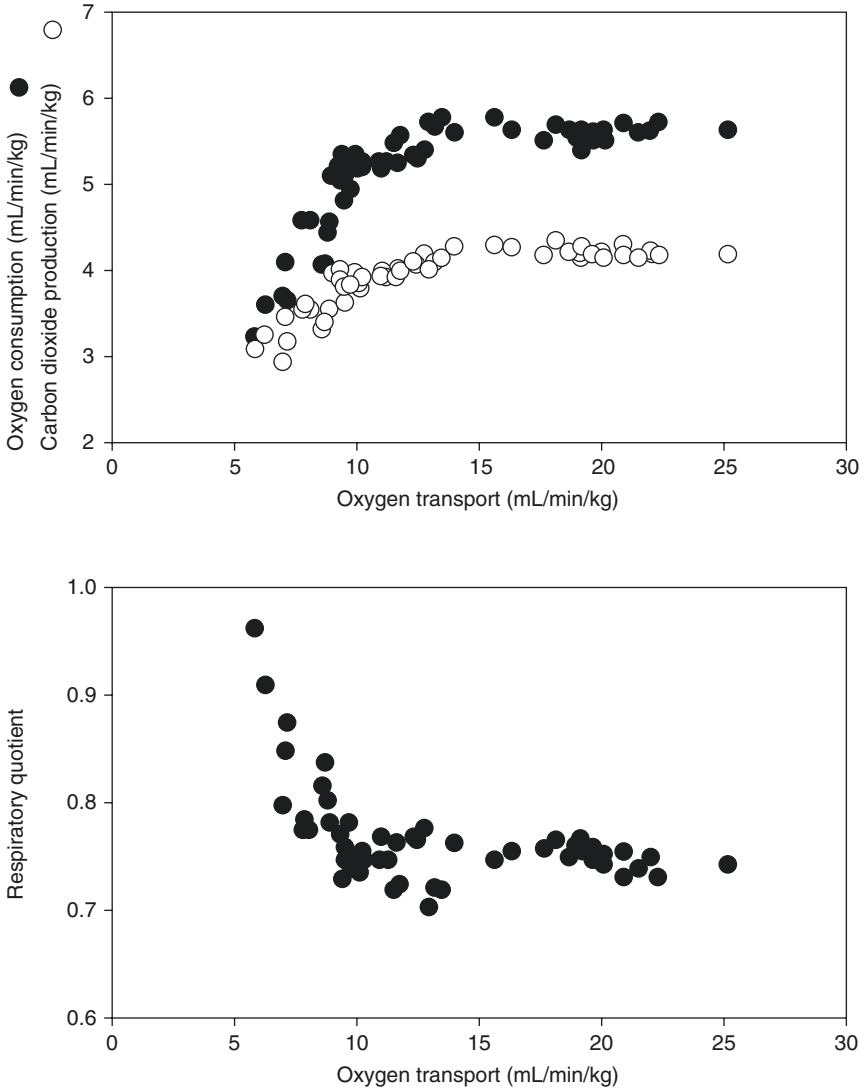

Fig. 6.4 Effects of progressive bleeding on oxygen consumption (VO_2), carbon dioxide production (VCO_2), and respiratory quotient. Panel A. After critical reductions in DO_2, VO_2 and VCO_2 decreased. Panel B. After critical reductions in DO_2, respiratory quotient increased

suggested that it might identify critically ill patients with hyperlactatemia and worse outcome [30]. Although Pcv-aCO_2/Ca-vCO_2 has been included in algorithms of resuscitation [31], this recommendation lacks of physiological bases and clinical evidence. On the contrary, experimental studies showed that Pcv-aCO_2/Ca-vCO_2 is poorly correlated with the actual RQ in conditions such as hemorrhagic shock, retransfusion, and isovolemic anemia [32, 33]. The main explanation is the change in the dissociation of CO_2 from Hb induced by metabolic acidosis, hemodilution, and Haldane effect. Therefore, Pcv-aCO_2/Ca-vCO_2 might be a misleading surrogate for tissue oxygenation.

6.5.2 Assessment of Tissue Perfusion and Oxygenation

The evaluation of the following variables may help to assert if the DO_2 is adequate to oxygen demands. Alterations in these variables might warn about tissue hypoxia or hypoperfusion, independently of a particular value of DO_2. Specific therapeutic interventions directed to increase systemic DO_2, however, could fail to correct such disorders while other succeed. For instance, in septic patients, similar increases in DO_2 induced by dopamine and dobutamine have contrasting effects on tissue perfusion. While dopamine decreases gastric mucosal blood flow and does not modify mucosal PCO_2, dobutamine improves both variables [34]. The assessment of the effects of DO_2 on tissue perfusion and oxygenation includes the following variables:

6.5.2.1 Peripheral Perfusion

Clinical assessment should be the first approach to determine the adequacy of DO_2. Typical features of low DO_2 are arterial hypotension, oliguria, depressed consciousness, and alterations in the skin perfusion. Many years ago, a seminal study showed that toe temperature is a strong predictor of cardiac output and outcome of shock patients [35]. Recently, several studies confirmed these findings [36–38].

6.5.2.2 Lactate and Base Excess

Lactic acidosis is a common feature of tissue hypoxia. Its association with shock [39], as well as its strong predictor ability [40], is well known from a long time ago. An increased anion gap metabolic acidosis usually reflects the hyperlactatemia. In septic shock, however, the increase in anion gap is not completely explained by hyperlactatemia. Other anions, which source and characterization are uncertain, also contribute to its increase [41]. These unmeasured anions are the most common cause of metabolic acidosis in critically ill patients and also behave as independent predictors of outcome [42]. In addition, 20% of the critically ill patients with severe hyperlactatemia on ICU admission may exhibit normal bicarbonate and base excess because of concurrent hypochloremic metabolic alkalosis [43]. Although hyperlactatemia is usually defined as values >2.2 mmol/L, the normal lactate concentration is 0.5–1.0 mmol/L. Actually, increases in lactate levels, even in the normal range, might be associated with worse outcome. A large observational study showed that

concentrations >0.75 mmol/L identify patients at higher risk of death [44]. Moreover, the source of hyperlactatemia in shock states, mainly after resuscitation, is not anaerobic glycolysis resulting from inadequate DO_2, but exaggerated aerobic glycolysis through Na^+K^+ ATPase stimulation [45]. A clinical randomized study showed that in patients with hyperlactatemia on ICU admission, lactate-guided therapy significantly reduced hospital mortality when adjusting for predefined risk factors. Although these patients were more aggressively resuscitated and presumably had higher DO_2, the reduction of lactate was similar to that of control group [46]. Consequently, hyperlactatemia can be a misleading indicator of insufficient DO_2. Nevertheless, lactate levels and lactate clearance are strong predictors of outcome [47].

6.5.2.3 Tissue PCO_2

The local increase in tissue PCO_2 is a sensitive indicator of tissue hypoperfusion. To avoid the impact of changes in arterial PCO_2, it is convenient to use the tissue-arterial gradients (ΔPCO_2). Tissue PCO_2 can be measured in different territories by means of different technologies. In contrast to Pvc-aCO_2, which is a marker of systemic perfusion, ΔPCO_2 reflects microcirculatory perfusion [15, 48].

Theoretically, increases in venous and tissue PCO_2 can be produced from two basic mechanisms: (1) hypoperfusion and subsequent reduction in CO_2 removal and (2) anaerobic production of CO_2 as a consequence of bicarbonate buffering of anaerobically generated protons. Experimental studies [49–51], as well as a mathematical model [52], showed that venoarterial PCO_2 and ΔPCO_2 are unable to reflect tissue hypoxia when blood flow is preserved. Venous and tissue PCO_2 results from interactions among aerobic and anaerobic VCO_2, CO_2 dissociation curve, and blood flow [13]. During the oxygen supply dependency, there are opposite changes in aerobic and anaerobic VCO_2. Aerobic VCO_2 decreases as a consequence of depressed aerobic metabolism, while anaerobic VCO_2 starts because of bicarbonate buffering derived from strong acids. Total VCO_2, however, does not increase or even decreases. As there is a more severe decrease in VO_2, the respiratory quotient increases. Nevertheless, this relative increase of VCO_2 in respect to VO_2 only can induce venous and tissue hypercarbia in low flow states, in which CO_2 clearance is reduced. Even though systemic and regional flows and DO_2 are commonly elevated in sepsis, increased ΔPCO_2 is a frequent finding that follows the alterations in microcirculatory perfusion [15, 48].

The development of gastrointestinal tonometry was an important step in the monitoring of tissue hypoxia. It rapidly became a useful tool in basic research. In addition, and for the first time, a regional parameter was used to detect and to treat hypoperfusion in critically ill patients. Gastrointestinal tonometry consists in the PCO_2 measurement in a silicone balloon inflated with saline solution or air, which are equilibrated with the surrounding environment.

Many experimental and clinical studies have shown that ΔPCO_2 is more sensitive than systemic markers to reflect hypoperfusion. In normal volunteers, gastric tonometry is the earliest indicator of hypoperfusion during progressive bleeding compared to other parameters commonly used in this setting [53]. In addition,

gastric tonometry is useful to predict perioperative complications, gastric bleeding [54], weaning from mechanical ventilation [55], assessment of response to vasoactive drugs [34] and fluids [56], and outcome of critically ill patients [57, 58]. Moreover, its use as a guide for resuscitation might contribute to improve the outcome of critically ill patients [59].

Gastrointestinal tonometry has limitations and sources of errors that can reduce its reproducibility. In spite of this, there is no real justification for the fact that this technique has not used anymore. Sublingual capnometry seems to be an equivalent alternative to gastric tonometry [48]. It provides continuous measurements and could also avoid technical problems associated with gastric tonometry. Also, ear capnometry has been reported as a valuable option [60].

In conclusion, (1) tissue capnography is a sensitive indicator of tissue perfusion but fails to reflect tissue hypoxia when blood flow is preserved. (2) It also shows relevant information about complications, outcome, and therapeutic responses. (3) Resuscitation guided by tissue capnography not only could ameliorate hypoperfusion but also improve the outcome of critically ill patients. Despite these evidences, no technologies are now available for these purposes.

6.5.2.4 Microcirculation

The crucial goal in the assessment of DO_2 is to show the preservation of tissue oxygenation, which is finally accomplished at microcirculatory level. Microcirculatory alterations are present in every type of shock but they play a major role in the pathophysiology of septic shock and other distributive forms of shock. In those settings, hypoperfusion and tissue hypoxia can be present regardless of a normal or high DO_2 [2]. So, the evaluation of the microcirculation might be more relevant in these settings.

In septic shock, microcirculation can be affected by several mechanisms, which include endothelial dysfunction, glycocalyx degradation, capillary leak, loss of vascular reactivity and autoregulation, and microthrombosis [61]. Experimental studies showed that the microcirculatory alterations include a large number of stopped-flow capillaries, a reduced perfused capillary density, and an increased perfusion heterogeneity [62, 63]. Consequently, oxygen might shunt from arterioles to venules, leaving the microcirculation hypoxic. This shunting may underlie the reduced O_2ER present in septic shock [64].

In the last few years, technological developments have allowed the direct and noninvasive visualization of the microcirculation. For this purpose, the sublingual mucosa is the window more easily accessible. Patients with septic shock frequently exhibit sublingual microcirculatory abnormalities [65, 66]. The alterations are more manifest in nonsurvivors [65, 66], improve over time only in survivors [67], and are independent predictors of outcome in septic shock [68]. In contrast, in these studies, systemic DO_2 was not related to either outcome or microvascular alterations. Although some correlation can be present during the initial steps of resuscitation [69], microcirculation and systemic hemodynamics are commonly dissociated [65–67]. In this way, microcirculatory alterations are similar in hyperdynamic and normodynamic septic shock [70]. Even in patients with high CO and DO_2, the septic microcirculation is hypodynamic (Fig. 6.5).

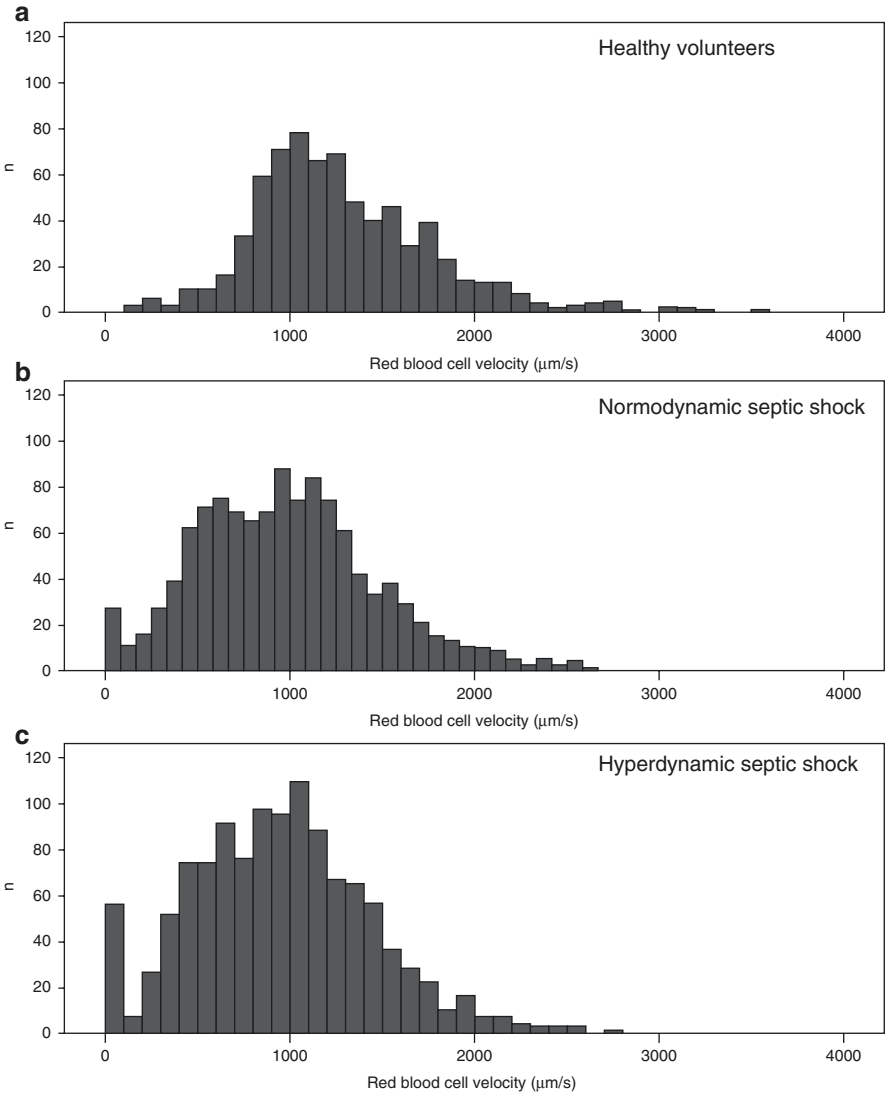

Fig. 6.5 Histograms of sublingual red blood cell velocity in healthy volunteers (Panel A) and patients with normodynamic (Panel B) and hyperdynamic (Panel C) septic shock. Sublingual red blood cell velocities were similarly reduced in both normo- and hyperdynamic septic shock compared to healthy volunteers (Modified from reference [70])

Consequently, microvascular perfusion cannot be predicted by any of the systemic variables. In patients who die from septic shock, the more severe microvascular abnormalities coexist with lactic acidosis, tachycardia, and high requirements of vasopressors [66, 71].

The monitoring of microcirculation might also contribute to the assessment of the response to fluids [72], vasopressors [73], and inotropes [74].

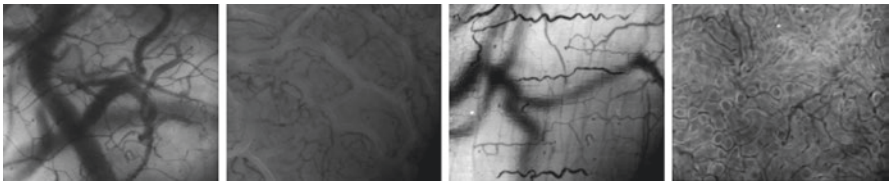

Fig. 6.6 Microphotographs of some microcirculatory beds

The different microvascular beds differ each other in structure and regulation (Fig. 6.6). Besides, their behavior might be dissociated. In these circumstances, sublingual microcirculation can fail to reflect alterations in territories such as intestinal mucosa [15, 75, 76].

In brief, the monitoring of microcirculation is an appealing approach to assert the adequacy of DO_2. A main limitation of these techniques is the time required for the analysis of the images. Unfortunately, the development of automatic analyses has been unsuccessful. Also, point-of-care techniques for the bedside assessment of microcirculation have not been validated.

6.5.2.5 Near-Infrared Spectroscopy (NIRS)

NIRS is a noninvasive technique that continuously measured microvascular tissue oxygen saturation (StO_2) [77]. NIRS measurements have been taken in different places. Last studies have been focused in the thenar eminence because its anatomic characteristics minimize variability, allow a better approach to muscle, and facilitate dynamic tests. Besides the measurements of basal state of muscle oxygenation, it is possible to track the behavior of StO_2 during a vascular occlusion test (VOT). The VOT consists in the inflation of a pneumatic cuff above systolic arterial blood pressure, during 3 min or until StO_2 decrease to 40% of baseline. After deflating the cuff, a reactive hyperemia arises. The slope of StO_2 recovery is a functional test of capillary recruitment. Basal values are decreased in low flow states such as traumatic and hemorrhagic shock, while StO_2 might be normal in septic shock. On the contrary, dynamic tests are altered in this condition and give valuable prognostic information. Moreover, they might be modified by the treatment and be useful for vasopressor titration.

Conclusions

The assessment of the adequacy of DO_2 is a complex task. Isolated values of DO_2 could be misleading since metabolic oxygen needs can be quite variable and changing in critically ill patients. A comprehensive approach should include (1) measurements of CO and DO_2 or surrogates such as $S\bar{v}O_2$ and $ScvO_2$, $Pcv\text{-}aCO_2$, and end-tidal PCO_2 and (2) an evaluation of the adequacy of DO_2 to satisfy tissue perfusion and oxygen needs. For this purpose, physical examination, laboratory determination, tissue capnography, and microcirculatory studies should be taken into account.

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Central and Mixed Venous O_2 Saturation: A Physiological Appraisal

7

Guillermo Gutierrez

7.1 Historical Perspective

The oxygen saturation of mixed venous, and that of central venous blood, have been used widely to monitor tissue oxygenation and also as markers of adequate resuscitation in critically ill patients [1,2]. The development of these techniques paralleled rapid advances in physiology that occurred during the past century. Adolf Eugen Fick (1821–1901) first proposed the idea that blood flow to an organ could be estimated as the ratio of the organ's O_2 uptake to the O_2 concentration difference of arterial and venous blood [3]. When applied to cardiac output, Fick's principle becomes

$$\text{Cardiac output} = \left(\dot{V}O_2\right)_{SYS} / \left(\left[O_2\right]_a - \left[O_2\right]\right)_{mv} \tag{7.1}$$

where $[O_2]_a$ and $[O_2]_{mv}$ are the arterial and mixed venous O_2 contents and $(\dot{V}O_2)_{sys}$ is the rate of systemic or total body O_2 consumption. Samples of arterial and pulmonary artery blood are needed to calculate $[O_2]_a$ and $[O_2]_{mv}$ as the sum of O_2 bound to hemoglobin and that dissolved in plasma:

$$\left[O_2\right] = 13.9 \times SO_2 \times \left[Hb\right] + 0.031 \times PO_2 \ \ mL \cdot L^{-1} \tag{7.2}$$

where [Hb] is the hemoglobin concentration ($g \cdot dL^{-1}$), SO_2 is the fractional hemoglobin O_2 saturation, and PO_2 is the plasma O_2 partial pressure (mmHg). The units of $[O_2]$ are mL O_2 per liter of blood.

Many years would pass before Fick's principle could be applied to measure cardiac output in humans. The delay may be partly attributed to technical difficulties inherent in sampling pulmonary artery blood, but the main obstacle was the notion

G. Gutierrez
Pulmonary, Critical Care and Sleep Medicine Division, The George Washington University School of Medicine, Washington, DC, USA
e-mail: ggutierrez@mfa.gwu.edu

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that passing a catheter into the heart would prove fatal. Instead, cardiac output was estimated by measuring the CO_2 concentration of expired gases and arterial blood [4]. This cumbersome and error-prone technique was particularly unreliable in patients with diseased lungs [5].

In 1929, while working in a clinic in Eberswalde, Germany, Werner Forssmann (1904–1979), a young surgeon who had trained under Fick, passed a thin ureteral catheter from the antecubital vein into his right atrium and confirmed its placement with fluoroscopy. Once satisfied of the safety of the procedure, he inserted an atrial catheter in a terminally ill woman, instilling a preparation of epinephrine and digitalis aiming at improving the heart's contractility [6]. A year later, working in Prague, Otto Klein (1881–1968) performed 30 heart catheterizations using Forssmann's technique and measured cardiac output by Fick's principle [7]. He presented his findings at a meeting in Boston but was ignored by the medical community. A decade later, André Cournand (1895–1988) and Dickinson Richards (1895–1973), while at Bellevue Hospital in New York, perfected the technique of right heart catheterization [8]. They also reported leaving a pulmonary artery catheter in place for an extended time with no harm to the patient [9]. Forssmann, Cournand, and Richards shared the 1956 Nobel Prize in Physiology or Medicine for "their discoveries concerning heart catheterization and pathological changes in the circulatory system." The reason why the Nobel Prize Committee failed to likewise honor Professor Klein remains a mystery.

The need for fluoroscopic guidance limited the use of right heart catheterization to a few well-equipped medical centers. This state of affairs changed dramatically in 1970 with the invention of the flow-directed pulmonary artery catheter (PAC) by Jeremy Swan (1922–2005) and William Ganz (1919–2009). The PAC could be floated with relative ease into the pulmonary artery without fluoroscopic guidance [10] allowing continuous monitoring of pulmonary artery and central venous pressures, as well as providing ready access to mixed venous blood. Technical improvements to the PAC followed in rapid order, including the thermodilution indicator technique to measure cardiac output directly [11] and infrared reflection spectrometry to monitor mixed venous blood O_2 saturation ($S_{mv}O_2$) continuously [12, 13]. The direct measurement of cardiac output by thermodilution superseded Fick's principle and the need to measure $S_{mv}O_2$.

The unhindered access to pulmonary artery blood provided by the PAC led to $S_{mv}O_2$ becoming one of the variables most commonly monitored in the care of critically ill individuals. To date, however, the clinical significance of $S_{mv}O_2$, and that of its surrogate, central venous O_2 saturation ($S_{cv}O_2$), remains a topic of intense and continuing debate [14, 15]. At various times, $S_{mv}O_2$ has been endorsed as an indicator of cardiac output [16], as a marker of peripheral tissue oxygenation [17], and as a predictor of morbidity and mortality [18, 19]. Particularly during the past decade, $S_{cv}O_2$ also has been touted as a reliable guide to resuscitation in sepsis [20]. The validity, or lack thereof, of these claims is best explored by reviewing the physiological foundations of $S_{mv}O_2$ and $S_{cv}O_2$.

7.2 Physiological Principles

Neglecting gas exchange across the skin, the rate of pulmonary O_2 uptake measured by the expired gases method $(\dot{V}O_2)_{Exp}$ is equivalent to systemic O_2 consumption, $(\dot{V}O_2)_{Sys}$. The timed collection of expired air into a Douglas bag represents the "gold standard" in measuring $(VO_2)_{Exp}$:

$$\left(\dot{V}O_2\right)_{exp} = V_E\left(1 - F_ECO_2 - F_EO_2\right)/\left(1 - F_IO_2\right)\ \text{mL}\cdot\text{min}^{-1} \tag{7.3}$$

In this expression, V_E refers to the expired gas volume collected in the bag over a finite period of time; F_ECO_2 and F_EO_2 are the volumetric fractions of CO_2 and O_2 in expired gas, respectively; and F_IO_2 is the inspired O_2 fraction or 0.21 for room air. Given the nature of the denominator, $(\dot{V}O_2)_{Exp}$ cannot be calculated for $F_IO_2 = 1.0$, and becomes clinically unreliable for $F_IO_2 > 0.60$ [21].

An alternative method is to compute $(\dot{V}O_2)_{Exp}$ continuously using a calibrated pneumo-tachometer and O_2 and CO_2 analyzers. Due to the small differences in O_2 concentration between the inspired and expired gases at high F_IO_2, the reliability of this method also deteriorates for $F_IO_2 > 0.60$ [22].

In clinical ICU practice, $(\dot{V}O_2)_{Sys}$ is most commonly estimated as the product of cardiac output (Q) measured by thermodilution and the O_2 content difference between arterial and mixed venous blood (the "reverse" Fick's method):

$$\left(\dot{V}O_2\right)_{Sys} = Q\left(\left[O_2\right]_a - \left[O_2\right]_{mv}\right)\ \text{mL}\,\text{min}^{-1} \tag{7.4}$$

It should be noted that Eq. 7.4 does not account for pulmonary O_2 consumption, since the deep bronchial veins drain on the left side of the circulatory system, either via the pulmonary vein or directly into the left atrium. Therefore, the reverse Fick's method will underestimate $(\dot{V}O_2)_{Sys}$ in conditions associated with substantial pulmonary O_2 consumption, such as pneumonia [23] or acute lung injury [24, 25].

7.3 $S_{mv}O_2$ as a Measure of O_2 Extraction Ratio

The efficiency of O_2 uptake by the tissues is characterized by the O_2 extraction ratio $(ERO_2)_{Sys}$:

$$\left(ERO_2\right)_{Sys} = \left(\dot{V}O_2\right)_{Sys}/\left(\dot{D}O_2\right)_{Sys} \tag{7.5}$$

The rate of O_2 delivered to the tissues per unit time, $(\dot{D}O_2)_{Sys}$, is calculated as

$$\left(\dot{D}O_2\right)_{Sys} = Q \times \left[O_2\right]_a\ \text{mL}\,\text{min}^{-1} \tag{7.6}$$

The clinical interpretation of $(ERO_2)_{Sys}$ requires detailed knowledge of the physiological conditions prevailing at the time of its measurement. In normal individuals,

resting $(ERO_2)_{Sys}$ is approximately 20–30%. During high-intensity exercise, it increases to 60% and may even reach 80% in highly trained athletes [26]. On the other hand, in critically ill individuals, an $(ERO_2)_{Sys}$ in the neighborhood of 60% implies the onset of anaerobic metabolism [27].

Substituting the definitions for $[O_2]$, $(\dot{V}O_2)_{Sys}$, and $(\dot{D}O_2)_{Sys}$ (Eqs. 7.2, 7.4, and 7.6) into Eq. 7.5, while neglecting the contribution of plasma PO_2 to blood O_2 content, yields an expression for $(ERO_2)_{Sys}$ in terms of $S_{mv}O_2$ and S_aO_2:

$$\left(ERO_2\right)_{Sys} = \left(1 - S_{mv}O_2 / S_aO_2\right) \tag{7.7}$$

Under most clinical conditions, S_aO_2 values are confined to the narrow range of 90–100%. Therefore, for all practical purposes, $(ERO_2)_{Sys}$ becomes a complementary function of $S_{mv}O_2$:

$$\left(ERO_2\right)_{Sys} \approx \left(1 - S_{mv}O_2\%\right) \tag{7.8}$$

Figure 7.1 shows data from a cohort of critically ill patients ($n = 53$) [28]. The graph illustrates the intimate coupling between $(ERO_2)_{Sys}$ and $S_{mv}O_2$. The dashed lines represent $(ERO_2)_{Sys}$ values derived from Eq. 7.7 under constant conditions of S_aO_2 equal to 90% and 100%, respectively. These lines delineate the narrow boundaries imposed on $(ERO_2)_{Sys}$ by Eq. 7.7.

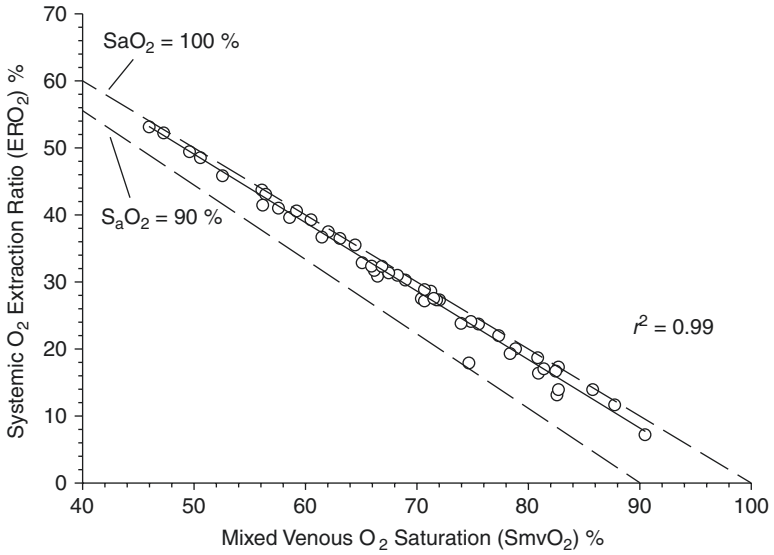

Fig. 7.1 ERO_2 as a function of $S_{mv}O_2$ for a heterogeneous cohort of critically ill patients ($n = 53$). The solid line represents the linear correlation ($ERO_2 = 100.3 - S_{mv}O_2$; $r^2 = 99$; $p < 0.01$), and the dashed lines are $(ERO_2)_{Sys}$ are values calculated using Eq. 7.7 under constant conditions of S_aO_2 equal to 90% and 100%, respectively

From the foregoing analysis, it can be concluded that $S_{mv}O_2$ is a reliable indicator of $(ERO_2)_{Sys}$. As such, $S_{mv}O_2$ provides insight into the fraction of the O_2 offered by the circulation taken by the tissues. The clinical meaning of $(ERO_2)_{Sys}$, however, is strongly dependent on prevalent physiological conditions. In other words, changes in $(ERO_2)_{Sys}$ may be the result of decreases in $(\dot{D}O_2)_{Sys}$, increases in $(\dot{V}O_2)_{Sys}$, or a combination of both. It should be noted that $S_{cv}O_2$ cannot be used to estimate $(ERO_2)_{Sys.}$ Should $S_{cv}O_2$ be substituted for $S_{mv}O_2$ in Eq. 7.7 or 7.8, the computed value would refer exclusively to the ERO_2 of organs draining into the superior vena cava.

7.4 $S_{mv}O_2$ as a Measure of Cardiac Output

A study in patients with myocardial infarction published in 1968 [29] reported an association between the signs of heart failure and decreases in $S_{cv}O_2$, but warned against the use of $S_{cv}O_2$ to predict cardiac output. A subsequent study [30] reported decreases in $S_{mv}O_2$ in patients following cardiopulmonary bypass with cardiac index <2.0 L min^{-1} m^{-2}. Other investigators also have found that decreases in $S_{mv}O_2$ correspond to lower cardiac output in shock states [31] and in severe trauma [32].

The relationship between cardiac output and $S_{mv}O_2$ is obtained by rearranging Eq. 7.4 as

$$Q = \left(\dot{V}O_2\right)_{Sys} / \left[13.9 \bullet \left[Hb\right] \bullet \left(S_aO_2 - S_{mv}O_2\right)\right] \tag{7.9}$$

According to Eq. 7.9, there is a positive but complex relationship between $S_{mv}O_2$ and Q, one that must account for the other variables in the equation, in particular $(\dot{V}O_2)_{Sys}$. The complexity of the relationship expressed by Eq. 7.9 introduces considerable uncertainty when estimating Q purely in terms of $S_{mv}O_2$. This is exemplified by Fig. 7.2, where Q is plotted as a function of $S_{mv}O_2$ using data from the patient cohort previously shown in Fig. 7.1. Although there is a positive relationship between Q and $S_{mv}O_2$, the correlation is weak ($r^2 = 0.17$).

A poor correlation between $S_{mv}O_2$ and Q also has been noted in several studies performed under diverse clinical conditions. These include the induction of anesthesia [33], cardiothoracic surgery [34–37], vascular surgery [38], general surgery [39], congestive heart failure [40–43], myocardial infarction [44], acute lung injury [45], general ICU population [46], and septic shock [47, 48]. The same uncertainty in estimates of cariac output is present when measuring $S_{mv}O_2$ continuously, where changes in cardiac output are predicted only 50% of the time [49].

Notwithstanding the above discussion, low $S_{mv}O_2$ values in a critically ill individual are likely to mirror decreases in cardiac output, rather than increases in tissue O_2 requirements. Therefore, sequential measures of $S_{mv}O_2$ in a given patient are likely to mirror fluctuations in Q, as long as $(\dot{V}O_2)_{Sys}$, [Hb], and S_aO_2 remain relatively constant.

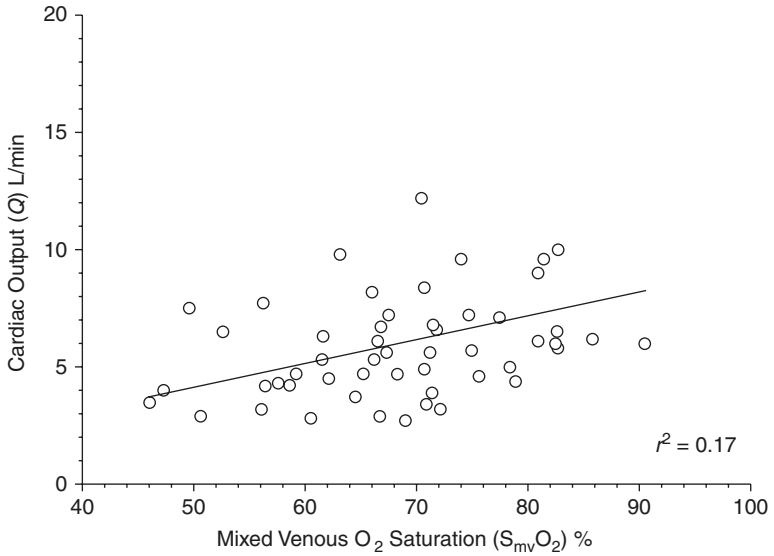

Fig. 7.2 Cardiac output (Q) as a function of $S_{mv}O_2$ for the patient cohort shown in Fig. 7.1 ($n = 53$). The solid line represents the linear correlation ($Q = 0.99 + 0.1\ S_{mv}O_2$; $r^2 = 0.17$; $p < 0.01$)

7.5 $S_{mv}O_2$ and Right-to-Left Pulmonary Shunt Fraction

The right-to-left pulmonary shunt fraction (Q_{Shunt}/Q_{Total}) is estimated with the patient breathing 100% F_IO_2 as

$$\frac{Q_S}{Q_T} = \frac{[O_2]_c - [O_2]_a}{[O_2]_c - [O_2]_{mv}} \tag{7.10}$$

where $[O_2]_c$ represents the idealized pulmonary capillary O_2 content.

Arterial and pulmonary artery blood samples are required for the computation of $[O_2]_a$ and $[O_2]_{mv}$, whereas $[O_2]_c$ is calculated from the alveolar air equation, coupled to the assumption of equality between pulmonary capillary and alveolar PO_2. Some have proposed [50] substituting O_2 saturations for O_2 contents in Eq. 7.10 as a bedside estimate of Q_S/Q_T:

$$\frac{Q_S}{Q_T} = \frac{1 - S_aO_2}{1\text{-}S_{mv}O_2} \tag{7.11}$$

This equation is incorrect and can seriously underestimates Q_S/Q_T. For example, applying Eq. 7.10 to the case where arterial PCO_2 = 40 Torr, PO_2 = 60 Torr, S_aO_2 = 90%, and $S_{mv}O_2$ = 60% (corresponding to $P_{mv}O_2$ = 31 Torr), results in Q_S/Q_T

of 38%. This compares to 25% when using Eq. 7.11. In fact, regardless of its true value, Q_S/Q_T calculated from Eq. 7.11 will be nearly zero for any value of S_aO_2 approaching 1.0, which is usually the case for patients breathing 100% F_IO_2.

7.6 $S_{mv}O_2$ as a Measure of Tissue Oxygenation

In 1919, August Krogh (1874–1949) developed a conceptual model of the microcirculation to quantify the process of O_2 transfer from capillaries to tissue parenchyma [51] . In Krogh's model, the tissues are represented by a cylinder surrounding a single, non-branched capillary (Fig. 7.3). The red blood cells (RBC) release O_2 into capillary plasma, whence it diffuses radially into the tissues. Among the variables that determine plasma PO_2 are the rate of O_2 dissociation from hemoglobin, the O_2 solubility in plasma, and capillary transit time, the latter defined as the ratio of capillary length to RBC velocity. Transit time increases with capillary cross-sectional area and decreases with greater blood flow [52].

Tissue O_2 uptake, or O_2 flux, is driven primarily by plasma PO_2. As the RBCs traverse the length of the capillary, hemoglobin-bound O_2 and plasma PO_2 are depleted. According to Krogh's model, capillary plasma PO_2 and O_2 flux reach a nadir at the venous end, giving rise to a region of tissue potentially at risk of hypoxia. This is labeled the "lethal corner." Another important property of Krogh's model is the assumption that end-capillary is exactly equal to venous blood PO_2.

The concept of the "lethal corner", along with the assumption of equality between end-capillary and venous PO_2, gave rise to the notion of venous SO_2 as a marker of tissue oxygenation. Extension of Kroghian theory to the body as a whole provides

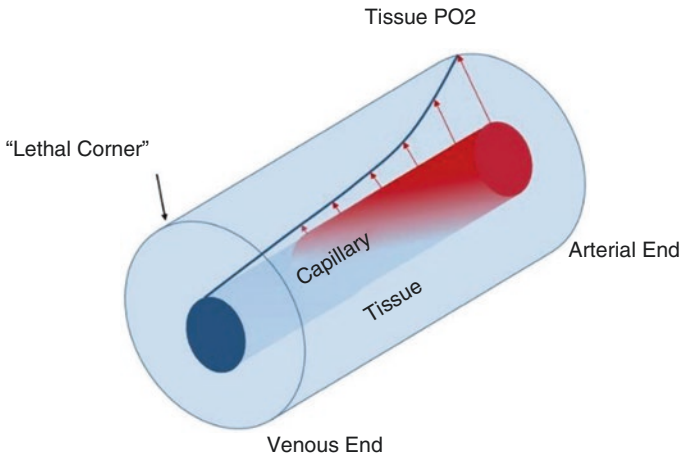

Fig. 7.3 Krogh's cylinder model of capillary-tissue oxygenation

the foundation for assuming that $S_{mv}O_2$ reflects the state of systemic tissue oxygenation [53]. This is a precarious assumption, since it fails to consider the intricate macro- and microcirculatory adjustments attendant to sepsis and hypoxemia.

The elegant simplicity of Krogh's model provides a lucid physiological construct for the process of tissue oxygenation but does not account for the spatial and temporal heterogeneity of the microcirculation [54]. Second-order processes, including capillary recruitment [55], O_2 diffusion between adjacent capillaries [56], time-dependent hemoglobin O_2 unloading [57], and perpendicular and countercurrent flow [58], combine to produce a remarkably homogeneous distribution of tissue oxygenation, one lacking "lethal corners" [59]. It is possible, however, that in the intestinal villi and the renal medulla, tissues exhibiting a peculiar microvascular arrangement of countercurrent flow, a "lethal corner" may exist where cells live on the edge of hypoxia, vulnerable to even mild ischemic or hypoxic insults [60, 61].

Venous blood from all organs mix in the pulmonary artery, giving rise to $S_{mv}O_2$, which can be defined as the flow-weighted average of all venous effluents SO_2:

$$S_{mv}O_2 = \sum \left[S_vO_2\right]_i \times Q_i / Q \tag{7.12}$$

where $[S_vO_2]_i$ and Q_i represent the individual organ's venous SO_2 and flow. As defined by Eq. 7.12, organs with the greatest Q_i are the primary determinants of $S_{mv}O_2$.

The mixing of venous blood in the RA adds another level of complexity to the relationship of $S_{mv}O_2$ and systemic tissue oxygenation. Under pathological conditions, such as sepsis, a normal or even a high $S_{mv}O_2$ may occur along with regional tissue hypoxia. For example, loss of regional microcirculatory control could apportion greater Q_i to some organs, above that required by their metabolic rate. The venous effluent from these overly perfused organs would have a high $[S_vO_2]_i$, in effect creating a functional left-to-right peripheral shunt. Conversely, tissues with decreased $Q_i/(\dot{V}O_2)_i$ and a low $[S_vO_2]_i$ would have a meager impact on $S_{mv}O_2$ given their reduced Q_i.

Skeletal muscle is an organ capable of inducing a sevenfold increase in blood flow by trebling the number of open capillaries through capillary recruitment [62]. This is a beneficial response during exercise, as it directs the bulk of the cardiac output to working skeletal muscle. During critical illness, however, a pathological increase in blood flow to *resting* skeletal muscle would result in venous blood of high SO_2, potentially overwhelming the hypoxic signals emanating from underperfused organs. This condition, termed "covert tissue hypoxia" [63], is defined by a normal or even elevated $S_{mv}O_2$ present in conjunction with regional tissue hypoxia [64]. This appears to be a case in patients with sepsis or septic shock, in whom $S_{mv}O_2$ is poorly predictive of splanchnic regional O_2 delivery [65–67] and who display significant gradients between hepatic and mixed venous SO_2 [68]. Experimental studies also have noted a weak correlation between $S_{mv}O_2$ and regional venous SO_2, with large decreases in sagittal sinus and portal vein SO_2 occurring with no changes in $S_{mv}O_2$ [69].

Alternatively, low $S_{mv}O_2$ values may occur in the absence of tissue hypoxia during aerobic exercise. Trained athletes are known to experience a very low $S_{mv}O_2$, in the neighborhood of 40%, prior to reaching the anaerobic threshold [70]. Far from signaling tissue hypoxia, these low $S_{mv}O_2$ values reflect the ability of trained skeletal muscle to maintain aerobic metabolism by extracting O_2 maximally from capillaries.

Another confounder in the interpretation of $S_{mv}O_2$, vis-à-vis tissue oxygenation, is the manner by which $\dot{D}O_2$ may decrease. Animals subjected to decreases in $\dot{D}O_2$ by hypoxemia or by isovolemic anemia reach a state of anaerobiosis at similar $(\dot{D}O_2)_{sys}$ levels, defined as the critical O_2 delivery $(\dot{D}O_2)_{critical}$. Remarkably, $S_{mv}O_2$ is much lower in hypoxemia than in isovolemic anemia at $(\dot{D}O_2)_{critical}$ [71, 72]. This phenomenon is also known to occur at the organ level [73], as resting skeletal muscle preparations exposed to hypoxemia and isovolemic anemia show similar tissue PO_2 distributions and $\dot{D}O_{2critical}$ but significantly different S_vO_2 values.

The discrepancy in $S_{mv}O_2$ between hypoxemia and isovolemic anemia at $(\dot{D}O_2)_{critical}$ may be explained by rearranging Eq. 7.9 with $S_{mv}O_2$ as the dependent variable:

$$S_{mv}O_2 = S_aO_2 - \left(\dot{V}O_2\right)_{Sys} / \left(13.9 \bullet [Hb] Q\right) \tag{7.13}$$

In this equation, $S_{mv}O_2$ is a function of the variables that may produce a decline in DO_2, that is, S_aO_2, [Hb], and Q. It should be noted that $(\dot{V}O_2)_{Sys}$ is relatively constant above $(\dot{D}O_2)_{critical}$, being solely a function of the intrinsic metabolic rate. This deceptively simple expression becomes quite complex when $(\dot{D}O_2)_{sys}$ falls below $(\dot{D}O_2)_{critical}$, since $(\dot{V}O_2)_{sys}$ then becomes a function of the other variables of the equation.

To estimate the effect on $S_{mv}O_2$ of a decrease in [Hb], let's assign values for Q = 5 L min^{-1}, $(\dot{V}O_2)_{sys}$ = 250 mL min^{-1}, and S_aO_2 = 100%. A decrease in [Hb] from 15 g dL^{-1} to 12 g dL^{-1} results in decreases in $(\dot{D}O_2)_{sys}$ from 1043 mL L^{-1} to 840 mL L^{-1}, a value still considered to lie above $(\dot{D}O_2)_{critical}$, resulting in a small decrease in $S_{mv}O_2$ from 76 to 70%. Under similar physiological conditions, but holding [Hb] constant at 15 g dL^{-1}, a decrease in S_aO_2 from 100 to 80% produces a fall in $(\dot{D}O_2)_{sys}$ similar to that of the anemic case, but it is now accompanied by a dramatic and equivalent decrease in $S_{mv}O_2$ from 76 to 56%. This proportional relationship between S_aO_2 and $S_{mv}O_2$ expressed by Eq. 7.13 has been shown to occur in humans [74].

In summary, the relationship of $S_{mv}O_2$ either to $(\dot{V}O_2)_{Sys}$ or to tissue PO_2 is tenuous at best. $S_{mv}O_2 \geq 70\%$ does not guarantee adequate tissue oxygenation. Conversely, $S_{mv}O_2 < 70\%$ may result from factors other than a low tissue PO_2. Another issue to consider is that, although a most important variable in the oxygen delivery process, tissue PO_2 does not by itself determine the adequacy of mitochondrial adenosine triphosphate (ATP) production in relation to cellular needs. The fundamental issue in caring for critically ill patients is to discern the level of regional $(\dot{D}O_2)$ required to sustain aerobic ATP turnover rate by all cells, in all organs, at all times. This information is not forthcoming from measurements of $S_{mv}O_2$.

7.7 Central Venous as a Measure of Mixed Venous SO_2

Confidence on the use of the PAC was shaken by an observational study published in 1996 showing increased mortality rate associated with its use [75]. This prompted calls for a large study to assess the PAC's safety and effectiveness or, failing that, a moratorium on its use [76]. A subsequent multicenter, randomized study showing neither benefit nor harm in the use of PACs in critically ill patients [77] definitely cooled the critical care community's enthusiasm toward the PAC. The use of PACs in the United States plummeted by 65% from 1993 to 2004 [78], a downward trend continuing to date.

Given the concerns regarding the use of PACs, the notion of replacing this catheter with a shorter central venous catheter (CVC) had a definite appeal. This notion led to the concept of $S_{cv}O_2$ as a surrogate for $S_{mv}O_2$ [79]. The substitution of $S_{cv}O_2$ for $S_{mv}O_2$, however, begs the question of how do these variables relate? In other words, how reliable is $S_{cv}O_2$ as an estimate of $S_{mv}O_2$? As shown in schematic form in Fig. 7.4, the right atrium (RA) is a complex hydrodynamic chamber where venous blood of different provenance mix. The resulting $S_{mv}O_2$ is the flow-weighted average of blood SO_2 from the inferior vena cava (IVC), the superior vena cava (SVC), and the coronary sinus (CS).

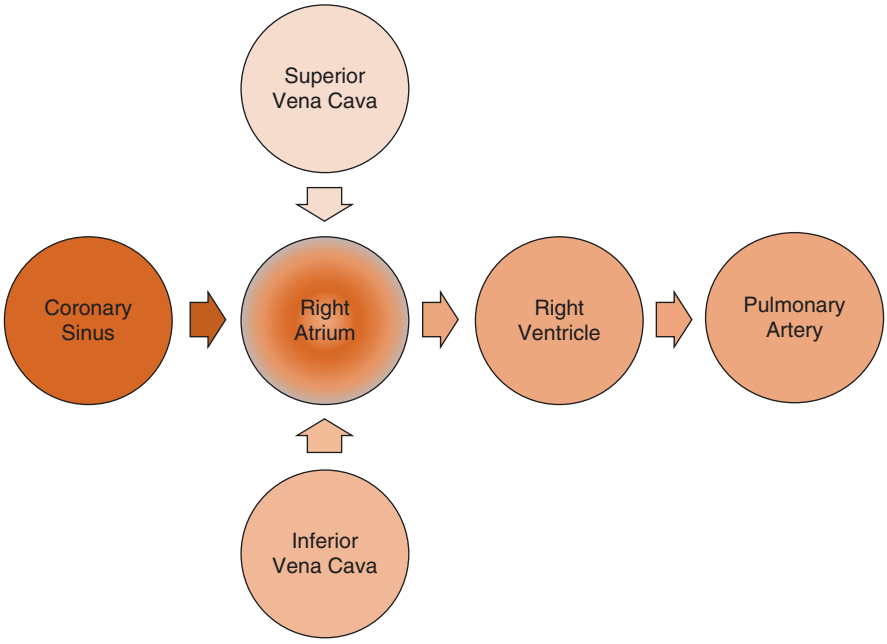

Fig. 7.4 Conceptual model of blood mixing in the right atrium

Studies in children with heart defects gave the initial impetus to the development of formulas that estimate $S_{mv}O_2$ based on simultaneously drawn blood samples from the SVC and IVC. The expression [80–83] gaining the widest acceptance is:

$$S_{mv}O_2 = \frac{3S_{cv}O_2 + S_{IVC}O_2}{4} \tag{7.14}$$

Eq. 7.14 was derived empirically and does not imply a physiological model of RA blood mixing. Its utility is constrained to the range of measured SO_2 values and the clinical conditions present at the time of blood sampling. Eq. 7.14, however, does point to the large influence exerted by $S_{cv}O_2$ on $S_{mv}O_2$, and further indicates these variables to be closely correlated. It should be noted that Eq. 7.14 does not account for the contribution of CS blood toward the development of $S_{mv}O_2$. The SO_2 of CS blood ($S_{CS}O_2$) is usually low, nearly 40% [84], but given the low CS flow relative to cardiac output, the effect of $S_{CS}O_2$ on $S_{mv}O_2$ is likely to be modest at best. On the other hand, $S_{CS}O_2$ may play a role in determining the direction (or sign) of the SO_2 gradient, defined here as the difference between $S_{cv}O_2$ and $S_{mv}O_2$:

$$SO_2 = S_{cv}O_2 - S_{mv}O_2 \tag{7.15}$$

Table 7.1 lists 28 studies where paired values for $S_{cv}O_2$ and $S_{mv}O_2$ were compared in critically ill medical and postsurgical adult patients. Shown are the number of patients, blood samples per study and the mean values for $S_{cv}O_2$ and $S_{mv}O_2$. Also shown are ΔSO_2, the coefficient of determination for the correlation between $S_{cv}O_2$ and S_{mv} (r^2), the 95% limits of agreements (LOA%), and whether the authors of the study concluded that $S_{cv}O_2$ was an adequate surrogate for $S_{mv}O_2$. The overall average for the variables are shown at the bottom of the table. They were obtained by weighing the data according to the number of patients in each study. This is more accurate than weighing by the number of samples measured, since some studies reported multiple determinations in a single patient, including one in which 580 measurements were drawn from only seven patients!

Table 7.1 shows a significant difference in weighted means for $S_{cv}O_2$ and $S_{mv}O_2$ (74.0% and 71.2%, respectively, $p < 0.001$, paired t-test), with $\Delta SO_2 = 2.4\%$. There is a linear correlation between $S_{cv}O_2$ and $S_{mv}O_2$ ($p < 0.01$), a finding consistent with the conceptual model shown in Fig. 7.4. The r^2 value of 0.61 indicates that nearly 40% of the variation in $S_{mv}O_2$ is related to factors other than $S_{cv}O_2$, most likely mixing with IVC and CS blood. Finally, the mean LOA% of 13.1% imparts a high degree of uncertainty to estimates of $S_{mv}O_2$ based on measures of $S_{cv}O_2$. As shown in Table 7.1, and based mainly on the wide LOA% values, the overwhelming majority of the studies listed in Table 7.1 rejected the use of $S_{cv}O_2$ as a reliable surrogate for $S_{mv}O_2$.

Table 7.1 Studies comparing paired values for $S_{cv}O_2$ and $S_{mv}O_2$ in critically ill and postsurgical adult patients

Study	Patient type	*n*	Samples	$S_{cv}O_2$%	$S_{mv}O_2$%	ΔSO_2%	r^2	LOA%	$S_{cv}O_2 = S_{mv}O_2$
Berridge [85]	ICU patients	51	76	73.2	70.8	3.4	0.95		Yes
Barrat-Boyes [86]	Healthy subjects	26	49	76.8	78.4	−2	0.53	7.0	N/A
Bouchacourt [87]	Cardiac surgery	18	18	76.4	71.9	4.5	0.90	10.4	N/A
Chawla [28]	ICU patients	53	53	73.9	68.8	5.2	0.88	10.4	No
Dueck [88]	Neurosurgical	70	64			−0.5	0.76	13.5	No
Edwards [89]	Shock	30	27	74.2	71.3	2.9	0.37	21.3	No
El Masry [90]	Liver transplant	50	450	88.0	85.5	2.5	0.96	3.6	No
Faber [91]	Shock	24	211			5	0.75		No
Gasparovic [92]	Cardiac surgery	156	468			1.2	0.73	13	No
Goldman [93]	Cardiac medical	27	27	66.2	64.9	1.3			Yes
Gutierrez [94]	Pulmonary HTN	9	9	69.0	64.5	4.4	0.99	3.1	N/A
Gutierrez [95]	ICU patients	45	45	74	69	5.2			N/A
Ho [96]	Shock	20	40			6.9	0.64	11.9	No
Kopterides [97]	Septic shock	37	37	78.6	70.2	8.5	0.86	11.8	No
Ladakis [98]	ICU patients	61	61	69.4	68.6	0.8	0.95		Yes
Lee [99]	Shock	15	19	66.1	56.0	10.1	0.73		No
Lee [99]	No shock	29	35	68.3	72.1	−3.8	0.88		Yes
Lequeux [100]	Cardiac surgery	15	Continuous			−4.4		18.1	No
Lorentzen [101]	Cardiac surgery	20	236			1.9		10.1	No
Martin [102]	ICU patients	7	580	68	67	1.1	0.62	20	No

Reinhart [103]	ICU patients	29	150	82.3	74.5	7.1	0.87	7.95	No
Sander [104]	Cardiac surgery	60	300			0.3	0.72	12.2	No
Scheinman [105]	ICU patients	16	29	57.9	53.3	4.6	0.86		Yes
Scheinman [105]	Shock – cardiac	8	23	58	47.5	10.5	0.55		No
Suehiro [106]	Cardiac surgery	102	102	79.9	77.5	2.3			N/A
Tahvanainen [107]	ICU patients	42	64	72.0	70.8	0.2	0.88		No
Turnaoglu [108]	Sepsis	41	41	76.9	70.5	6.4	0.69	14.6	No
Turnaoglu [108]	Cardiac surgery	32	32	76.9	78.5	−1.6	0.49	13.2	No
Van Beest [109]	Sepsis	53	265	72.0	71.8	1.7		13.8	No
Varpula [110]	Septic shock	16	72	70	66	4.2	0.89	12.3	No
Yazigi [111]	Shock cardiac	60	60	66	65	0.6	0.46	18.6	No
	Total	**1222**	**3643**						
	Weighted mean			**74.0**	**71.2**	**2.4**	**0.61**	**13.1**	

Shown are values for the number of patients in the study (*n*), the number of determinations and values for $S_{cv}O_2$, $S_{mv}O_2$, ΔSO_2, r^2, and the 95% limits of agreements (LOA%). The average for the variables was obtained by weighing according to the number of patients in each study

7.8 The $S_{cv}O_2$ to $S_{mv}O_2$ Gradient

Continuous measurements of $S_{cv}O_2$ and $S_{mv}O_2$ often show them running in parallel [88, 103]. Therefore, it may be possible to use continuous measurements of $S_{cv}O_2$ to monitor the adequacy of systemic O_2 delivery, with the caveat that the information has limited value in the absence of cardiac output measurements [112].

Some have proposed subtracting 5% from $S_{cv}O_2$ to obtain an estimate of $S_{mv}O_2$ [113]. This assumption was given further credence by the Surviving Sepsis Campaign calling for either $S_{cv}O_2$ of 70% or $S_{mv}O_2$ of 65% as one of the initial goals of resuscitation [114]. The notion that $S_{cv}O_2$ and $S_{mv}O_2$ are separated by a fixed SO_2 % value is not supported by clinical data. ΔSO_2 may assume positive or negative values in the same patient [102], at different times [108, 109] and under varying clinical conditions [86, 100, 103].

The ΔSO_2 gradient develops as blood from the SVC mixes with IVC and CS blood. Early studies [87, 99] reported $S_{cv}O_2 > S_{IVC}O_2$ with a negative ΔSO_2 ($S_{mv}O_2 > S_{cv}O_2$) in patients in shock, and vice versa in patients not in shock. These findings have been interpreted to mean that individuals in shock experience greater O_2 extraction by infra-diaphragmatic organs when compared to upper body organs, with the opposite occurring in the absence of shock [115].

Table 7.2 shows weighted mean values for the variables of Table 7.1, separated according to whether the enrolled patients were identified as septic or in shock (shock/sepsis group) or as postoperative or ICU patients ("not in shock" group). In both groups, the mean-weighted values for $S_{cv}O_2$ are greater than those for $S_{mv}O_2$, resulting in a positive ΔSO_2, this gradient being larger for the sepsis/shock group ($p = 0.02$). The sepsis/shock group also shows significantly lower r^2 and wider LOA% ($p < 0.05$), likely the result of unstable hemodynamic conditions.

The gradient ΔSO_2 is not constant, but varies widely from patient to patient and in the same patient at different times in response to changes in clinical condition. A complete understanding of the relative influences on ΔSO_2 of IVC and CS blood is hindered by a dearth of clinical data. A study on patients with pulmonary hypertension [94] showed a ΔSO_2 of 4.4% with no differences between $S_{IVC}O_2$ and $S_{cv}O_2$. These data suggested mixing or RA blood with CS blood of lower SO_2 is the mechanism producing the positive ΔSO_2 gradient.

The only study reporting SO_2 from all blood streams converging in the RA is an observational study in patients undergoing elective cardiac surgery [87]. The authors found a positive ΔSO_2 (4.5%), no differences between $S_{IVC}O_2$ and $S_{cv}O_2$, and a

Table 7.2 Weighted mean values for the variables of Table 7.1, separated according to whether the enrolled patients were identified as septic or in shock (shock/sepsis group) or as postoperative or ICU patients ("not in shock" group)

Patient type	*n*	Samples	$S_{cv}O_2$ %	$S_{mv}O_2$ %	ΔSO_2%	r^2	LOA %
Not in shock	918	2848	75.0	72.8	1.6	0.70	11.2
Sepsis/shock	304	795	71.7	67.7	4.4	0.42	15.4

significantly lower $S_{CS}O_2$ (46.6%). They concluded that CS blood is an important contributor to the generation of ΔSO_2.

Studies measuring lactate concentrations in SVC and PA blood report a step-down in lactate concentration from SVC to PA [95, 97, 102]. Lactate is a preferred myocardial substrate and its concentration in CS blood is usually low, giving further credence to the role played by CS blood in generating ΔSO_2. This observation raises the interesting possibility that ΔSO_2 could provide useful insight into myocardial O_2 utilization in a select group of patients [28, 84, 97].

The clinical significance ΔSO_2 is not clear. A large retrospective study of patients undergoing right- and left-sided cardiac catheterizations [116] showed a $\Delta SO_2 \geq 5\%$ occurring in 5.4% of cases, mainly those with elevated pulmonary capillary wedge and pulmonary artery pressures. A multicenter study of postoperative and medical ICU patients measured ΔSO_2 at 6-h intervals [117] and found a strong association between survival and a positive ΔSO_2. A subsequent study, restricted to septic patients, showed survivors with a trend toward positive ΔSO_2 values ($p = 0.13$), but as acknowledged by the authors, the study was probably underpowered to detect a difference in survival. Conversely, studies in cardiac surgery patients suggest that a *negative* ΔSO_2 gradient is associated with better outcome and less inotropic support requirements [92].

In summary, measures of $S_{cv}O_2$ are not reliable surrogates for $S_{mv}O_2$, especially in regard to septic patients where the influence of IVC and CS blood on $S_{mv}O_2$ may predominate. Further, the notion that $S_{mv}O_2$ may be estimated by subtracting 5% from $S_{cv}O_2$ is not supported by clinical data. Only in clinical conditions where the pathophysiology is well ascertained can alterations in systemic O_2 extraction be derived from continuous measures of $S_{cv}O_2$.

7.9 $S_{mv}O_2$ and $S_{cv}O_2$ as Predictors of Morbidity and Mortality

The utility of a monitored variable rests on its ability to warn of an impending clinical calamity. Studies in critically ill patients relating morbidity and mortality to measures of $S_{mv}O_2$ or $S_{cv}O_2$ are remarkably few in number. Moreover, the nature of the data is ambiguous, given that poor ICU outcomes may occur with either high or low $S_{mv}O_2$ or $S_{cv}O_2$ values.

There appears to be consensus that mortality is greater in patients with $S_{mv}O_2$ or $S_{cv}O_2$ values <70%, although the boundary between decedents and survivors varies according to study. A study in patients with septic shock ($n = 20$) in which $S_{mv}O_2$ was measured continuously with fiber-optic PACs noted increased mortality for patients with a preponderance of $S_{mv}O_2$ readings <65% [118]. A retrospective case-control analysis [119] of septic patients with pre-existing left ventricular dysfunction ($n = 166$) showed decedents (34%) with lower initial mean $S_{mv}O_2$ than survivors (61% vs. 70%). Somewhat confusing, the control group ($n = 168$) showed decedents (26%) had similar $S_{mv}O_2$ as survivors (70% vs. 71%). Greater mortality rate (29% vs. 17%) was also noted in patients with $S_{cv}O_2 < 60\%$ admitted to a multidisciplinary ICU ($n = 98$) [120]. Similarly, patients with septic shock

(n = 363) experience greater mortality rates when ICU admission $S_{cv}O_2$ < 70% (38% vs. 27%) [121].

To complicate matters, high $S_{cv}O_2$ values are also associated with greater ICU mortality. A secondary analysis of septic patients [122] using data culled from prospectively collected registries (n = 619) showed patients with both low *and high* $S_{cv}O_2$ (<70% or >89%) having greater mortality rates than patients with "normal" range $S_{cv}O_2$ (70–89%). A retrospective study of 169 septic patients showed those with "high" or "low" admission $S_{cv}O_2$ values (78.8% and 51.1%, respectively) experiencing significantly higher mortalities than those with "normal" $S_{cv}O_2$ (70.9%) [123].

It is possible that the time a patient is exposed to a low $S_{mv}O_2$ or $S_{cv}O_2$ affects outcome more than sporadic decreases in O_2 saturation. In a retrospective analysis of septic shock patients (n = 111), decreases in $S_{mv}O_2$ <70% for a prolonged time during their first 24 h in the ICU were associated with greater mortality (33%) [124].

It should be noted that low $S_{mv}O_2$ values occur infrequently in septic ICU patients. A study monitoring $S_{mv}O_2$ continuously (n = 15) found values for $S_{mv}O_2$ < 65% in only 10% of monitored events, with mean $S_{mv}O_2$ ranging from 72 to 82%. Another study measuring $S_{cv}O_2$ continuously in ICU patients (n = 32) reported $S_{cv}O_2$ < 70% to be present in 4.3% of monitored events in survivors, compared to 12.6% in decedents [103]. This finding suggests that isolated measures of $S_{cv}O_2$ are neither sensitive nor specific in predicting ICU mortality.

The majority of surgical and trauma studies show an association between low values for $S_{mv}O_2$ and $S_{cv}O_2$ and postoperative complications. A retrospective analysis of 488 postoperative cardiac patients found a greater incidence of both postoperative complications and mortality (9.4%) for patients with $S_{mv}O_2$ < 55% on arrival to the ICU [125]. Patients with cardiac index <2.0 L min^{-1} m^{-2} following coronary artery bypass grafting (CABG; n = 36) experienced low $S_{mv}O_2$ values (58.5% vs. 63.7% in control) and prolonged intensive care unit course [126]. Decreases in $S_{cv}O_2$ have been independently associated with postoperative complications following major surgery (n = 117) [127] . Patients experiencing complications had lower $S_{cv}O_2$ during surgery (63% vs. 67%). A multicenter study of 60 patients with intra-abdominal surgery also reported greater complication rate in patients with intraoperative $S_{cv}O_2$ of 60%, compared to those with 64% [128].

As with septic and general ICU patients, the relationship of postoperative complications to low $S_{cv}O_2$ measurements is not clear. Greater mortality rates have been noted in patients undergoing elective cardiac surgery (n = 205) [129] with either low (<61%) or high (>77%) $S_{cv}O_2$ values.

The trauma literature reports patients sustaining more serious injuries and greater blood loss to have lower admission $S_{cv}O_2$ (<65%; n = 10) [130], but a subsequent observational study in a similar population of trauma patients failed to confirm this finding [131]. More recently, it has been reported that $S_{cv}O_2$ < 70% is associated with poor outcome following trauma, with an optimal cutoff for complications of 66.5% [132].

Given the uneven ability of $S_{cv}O_2$ to forecast outcome, some advocate combining early measures of $S_{cv}O_2$ either with blood lactate concentration ([Lac]) or with lactate clearance. Blood lactate concentration ([Lac]) may be more reliable as predictor of postsurgical complications than $S_{cv}O_2$. Patients following CABG (n = 629) had fewer complications when [Lac] < 3.9 mmol/L, irrespective of $S_{cv}O_2$ values [133]. The combination of $S_{cv}O_2 < 70\%$ and [Lac] ≥ 4 mmol L^{-1} upon ICU admission in patients following CABG (n = 18) was found to be associated with longer ICU length of stay [134]. The story may be different in sepsis, as admission values for [Lac] or $S_{cv}O_2$ in septic patients (n = 25) fail to differentiate between survivors and decedents [135].

A study in septic shock patients showed no difference in mortality when comparing therapy aimed at increasing lactate clearance ≥10% to that of raising $S_{cv}O_2 \geq 70\%$ (n = 150 each group) [136]. A subsequent study by the same investigators [137] (n = 203) showed achieving lactate clearance ≥10% was more strongly associated with survival than achieving $S_{cv}O_2 \geq 70\%$.

Decreases in $S_{mv}O_2$ or $S_{cv}O_2$ are prone to reflect increased extraction by the respiratory muscles; therefore, monitoring these variables during the process of weaning patients from mechanical ventilation appears to be useful. A study in hemodynamically stable ICU patients undergoing weaning (n = 73) found that a decrease in $S_{cv}O_2 > 4.5\%$ was the only independent predictor of reintubation [138]. Others have reported maintaining $S_{mv}O_2 > 60\%$ during weaning to be a reliable index of success [139], whereas a decrease in $S_{mv}O_2 > 20\%$ has been associated with weaning failure [140]. When $S_{mv}O_2$ has been monitored continuously, weaning failure (n = 8) was associated with progressive declines in $S_{mv}O_2$, in contrast to weaning success (n = 11) where $S_{mv}O_2$ did not change [141].

7.10 $S_{cv}O_2$ as a Guide to Resuscitation in Sepsis

The concept of "pathologic supply dependency" during sepsis arose from the confluence of two observations. The first was that septic patients often experience increases in [Lac], suggesting the activation of anaerobic glycolysis by tissue hypoxia [142]. The second observation was that increasing $(\dot{D}O_2)_{Sys}$ in septic patients is often accompanied by an upsurge in $(\dot{V}O_2)_{Sys}$ [143, 144]. According to the pathologic supply dependency hypothesis, septic tissues are affected by defective O_2 utilization. This leads to a “covert” hypoxic condition [145] that can be unmasked by increases in $(\dot{D}O_2)_{Sys}$ accomplished either by a dobutamine-mediated rise in cardiac output [146] or by the transfusion of blood [147]. A clinical trial tested this hypothesis in a heterogeneous ICU population in which one group (n = 253) was targeted to achieve a high cardiac index and another (n = 257) at maintaining $S_{mv}O_2 \geq 70\%$. Neither group, however, showed improved survival when compared to control [148]. At the time, some ascribed the trial’s lack of effectiveness to tardiness in enrollment (after 48 h in the ICU) and the time separating $S_{mv}O_2$ measurements (at 12-h intervals) [149].

Several years later, a study was conducted in septic shock patients ($n = 263$) that emphasized alacrity in therapeutic response. Treatment was dictated by a resuscitation algorithm called early goal-directed therapy (EGDT) implemented during the patient's initial six hours in the hospital [150]. Therapy in the study group was partly guided by $S_{cv}O_2$ measured continuously with a spectrophotometric CVC [151]. Among the treatment arms of the EGDT algorithm, was the maintenance of $S_{cv}O_2 \geq 70\%$ mediated by increases in $(\dot{D}O_2)_{Sys}$. This was initially effected by RBC transfusion and, failing that, by infusing dobutamine to increase cardiac output. The study showed a substantially lower mortality (30.5% vs. 46.5%) in patients treated with EGDT.

Based on the impressive results of the EGDT study, beginning in 2004 [152] and continuing until recently [113], the Surviving Sepsis Campaign Management Guidelines Committee (SCC) had recommended that septic patients failing to maintain $S_{cv}O_2 \geq 70\%$, despite aggressive fluid infusion during the first 6 h of treatment, should be transfused with packed red blood cells to a hematocrit ≥30% and/or infused with dobutamine to a maximum of 20 μg kg^{-1} min^{-1}. The Institute of Healthcare Improvement (IHI) [153] and the Joint Commission on the Accreditation of Hospitals (JCAHO) [154] promptly accepted the SCC recommendation as part of a bundle concept to treat patients admitted with sepsis or septic shock.

Three large prospective randomized studies enrolling a total of 4183 patients have tested the hypothesis that EGDT improves ICU survival in septic patients. All three of these trials, the Protocolized Care for Early Septic Shock (ProCESS) [155], the Autralasian Resuscitation in Sepsis Evaluation (ARISE) [156], and the Protocolised Management in Sepsis (ProMISe) [157], failed to show a survival advantage by implementing EGDT.

Not delving into all possible causes leading to the divergent outcomes of the EGDT study and the recent trials, it may be instructive to examine one aspect of these trials heretofore ignored. It concerns the low initial $S_{cv}O_2$ values reported by the Rivers et al. EGDT study of 49 ± 11%. By most standards this is a very low value, one at odds with data from a Dutch multicenter study reporting only one in 150 septic patients with $S_{cv}O_2 < 50\%$ within 6 h of hospital admission [158]. For comparison, initial $S_{cv}O_2$ was 71 ± 13% in the ProCESS, 73 ± 11% in the ARISE, and 65 ± 20% in the ProMISe study (estimated from a graph).

Figure 7.5 depicts the Gaussian functions corresponding to these initial $S_{cv}O_2$ values. Obviously, the $S_{cv}O_2$ distribution reported in the EGDT trial differs substantially from the other three trials ($p < 0.001$), a finding that suggests patients enrolled in the EGDT trial differed fundamentally from those enrolled in the subsequent negative trials. A possible explanation for this discrepancy may be found by noting the location in the SVC where $S_{cv}O_2$ is measured (The reference: Gutierrez G. Work of breathing, not dysoxia, as the cause of low central venous blood O2 saturation in sepsis. Crit Care. 2016 Sep 19;20:291 - should be added here).

Correct positioning of the CVC should be with its tip in the SVC, below the anterior first rib and above the RA [159]. On the chest radiograph, the CVC tip should lie slightly above the carina [160], placing it just below the opening of the

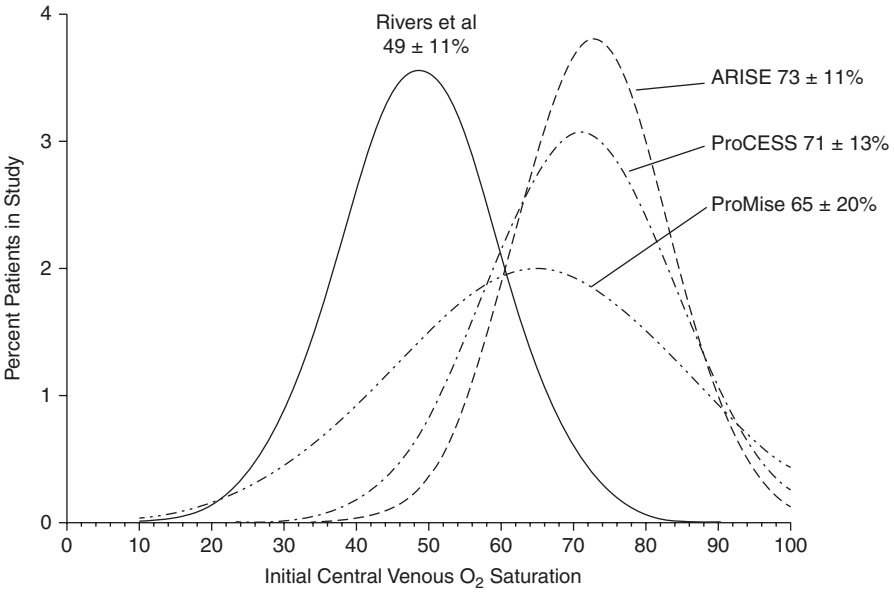

Fig. 7.5 Hypothetical $S_{cv}O_2$ Gaussian population distributions derived from mean ± standard deviation values published in the various EGDT trials

azygos vein, a unilateral vessel carrying blood from the posterior intercostal muscle and diaphragmatic veins. The outlet of the infrared spectrophotometer fiber-optic lumen, where $S_{cv}O_2$ is measured, is also located at the CVC tip.

Patients in the EGDT study developed severe metabolic acidosis. They also experienced considerable respiratory distress, with 53% requiring invasive mechanical ventilation, compared to 26%, 20%, and 22% for patients in the ProCESS, ARISE, and ProMISe trials, respectively. Compensatory ventilation, with the concomitant increased work by respiratory muscles, particularly by the intercostal muscles, may have led to the azygos vein discharging venous blood of very low O_2 saturation into the SVC, in close proximity to the CVC tip. Therefore, the low $S_{cv}O_2$ values reported in the EGDT trial possibly reflected increased work of breathing, not global tissue hypoxia. In that instance, the indicated therapy was mechanical ventilation, not RBC transfusion or dobutamine infusion. Supporting this hypothetical series of events is a study in septic patients showing increases in $S_{cv}O_2$ from 64 to 71% before and after emergent intubation and institution of mechanical ventilation [161].

In summary, $S_{cv}O_2$-guided resuscitation does not improve the survival of septic patients. This does not mean that therapy grounded on the early treatment of septic patients is futile. The early application of some treatment modalities, such as low tidal volume mechanical ventilation [162] and rapid fluid infusion with reversal of hypotension [163] may improve survival in severe sepsis or septic shock.

7.11 Parting Thoughts on $S_{cv}O_2$

The ideal ICU-monitored variable must be (1) easy to measure, (2) easy to interpret, (3) amenable to treatment, and (4) measured noninvasively. Pulse oximetry is the quintessential monitoring device meeting these criteria. $S_{cv}O_2$ monitoring, on the other hand, falls far short of expectation.

$S_{cv}O_2$ is relatively easy to measure, either intermittently or continuously with a fiber-optic catheter, but, due to its invasiveness, the decision to insert a CVC solely for the purpose of measuring $S_{cv}O_2$ should be tempered by the risk associated with the procedure.

Changes in $S_{mv}O_2$ are inversely related to changes in systemic ERO_2. The same concept applies to $S_{cv}O_2$ in regard to upper body organs. As previously reviewed, however, $S_{cv}O_2$ is not easy to interpret. Even experienced clinicians may be confused by the information conveyed by $S_{cv}O_2$. Hemodynamic phenotypes based on arterial blood pressure, [Lac], $S_{mv}O_2$, and $S_{cv}O_2$ have been proposed [165], but the resulting taxonomy is intricate and unlikely to be of significant clinical utility. Perhaps continuous monitoring of $S_{mv}O_2$ or $S_{cv}O_2$ may be useful in selected cases where the patient's pathophysiology is well understood, i.e., cardiomyopathy with reduced cardiac output. This is not the case in most other conditions affecting critically ill individuals, in particular that of severe sepsis in which both high and low $S_{mv}O_2$ or $S_{cv}O_2$ values carry a dire prognosis.

Lastly, the lack of a clearly defined therapeutic response is the Achilles heel of $S_{cv}O_2$. The difficulty in ascribing pathological causation to changes in $S_{cv}O_2$ during sepsis is compounded by the lack of a defined therapeutic response. Whether the therapeutic aim is to decrease O_2 consumption by mechanical ventilation or to increase O_2 delivery by transfusing RBCs or infusing dobutamine, this cannot be easily discerned from measures of $S_{cv}O_2$.

Until a proven therapy in response to changes in $S_{mv}O_2$ or $S_{cv}O_2$ is clearly established, monitoring these variables in critically ill patients cannot be supported by physiological principles nor by current literature. .

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Central Venous-to-Arterial Carbon Dioxide Partial Pressure Difference

8

Xavier Monnet and Jean-Louis Teboul

8.1 Introduction

One of the main goals of haemodynamic resuscitation of patients with acute circulatory failure is to detect, prevent and correct tissue hypoxia. In this regard, a crucial question is to know whether oxygen (O_2) supply is in adequacy with oxygen requirements. This question is particularly important when interpreting cardiac output values since no "normal range" of cardiac output can defined as a target for haemodynamic resuscitation. As a matter of fact, the correct value of cardiac output is the value that ensures a flow of oxygen that fits the metabolic demand, which is highly variable.

To answer the question of adequacy between oxygen supply and demand, clinical examination is limited. At best, urine output reflects the function of one organ only. Moreover, in case of acute tubular necrosis, diuresis cannot be used anymore as an indicator of the kidney function. Lactate is a sensitive marker of global anaerobic metabolism, but it has many false positives. Moreover, the delay required by its metabolism precludes using it as a real-time marker of tissue metabolism. The oxygen saturation of the mixed (SvO_2) or the central ($ScvO_2$) venous blood is often in the normal range in septic shock in spite of tissue anaerobic metabolism because of alteration of oxygen extraction, in part due to microcirculatory failure. The gradient in the carbon dioxide (CO_2) tension between veins and arteries (PCO_2 gap or ΔPCO_2) overcomes many of the limitations of the previous indices to indicate tissue anaerobic metabolism. In the following chapter, we will review its physiologic meaning and detail the way it should be interpreted at the bedside.

X. Monnet (✉) · J.-L. Teboul
AP-HP, Hôpitaux universitaires Paris-Sud Hôpital de Bicêtre,
Service de réanimation médicale, Le Kremlin-Bicêtre, France

Univ Paris-Sud, Faculté de médecine Paris-Sud, Inserm UMR_S 999,
Le Kremlin-Bicêtre, France
e-mail: xavier.monnet@aphp.fr; jean-louis.teboul@aphp.fr

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8.2 What Does the PCO_2 Gap Mean?

8.2.1 How Is CO_2 Produced?

Under **normoxic conditions**, CO_2 is produced in the cells during oxidative metabolism. The CO_2 production (VCO_2) is directly related to the global O_2 consumption (VO_2) by the relation: $VCO_2 = R \times VO_2$, where R is the respiratory quotient. R may vary from 0.7 to 1 depending on the predominant energetic substrate (0.7 for lipids, 1 for carbohydrates). Therefore, under aerobic conditions, CO_2 production should increase either because the aerobic metabolism increases or, for a given VO_2, because more carbohydrates are used as energetic substrates.

Under **hypoxic conditions**, CO_2 is produced in the cells through buffering of excessively produced protons by local bicarbonate ions (HCO_3^-). Protons are generated by two mechanisms [1]. First, the production of lactate increases, as a result of the accumulation of pyruvate due to the blockade of the Krebs cycle [1]. Second, CO_2 increases because of the hydrolysis of adenosine triphosphate and of adenosine diphosphate that occurs in anaerobic conditions. Another potential but minor source of CO_2 production under anaerobic conditions is the decarboxylation of some substrates produced by intermediate metabolism (α ketoglutarate or oxaloacetate) [1].

8.2.2 How Is CO_2 Transported?

CO_2 is transported in the blood in three forms: dissolved CO_2 (10%), carried in bicarbonate ions (60%) and associated with proteins as carbamino compounds (30%). Compared to what happens for O_2, the dissolved form of CO_2 plays a more significant role in CO_2 transport because CO_2 is approximately 20–30 times more soluble than O_2. The main proportion of CO_2 is carried in bicarbonates, which result from the reaction of CO_2 and water molecules ($CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$).

In the tissue capillaries, CO_2 diffuses into the red blood cells where erythrocytic carbonic anhydrase catalyses CO_2 hydration, converting most CO_2 to HCO_3^- and H^+ [2]. In the red blood cells, dissolved CO_2 can also be fixed by haemoglobin. This fixation depends on the oxidation state of haemoglobin: CO_2 has a greater affinity for reduced than for oxygenated haemoglobin [3]. This is called the "Haldane effect" [4]. In the peripheral capillaries, this phenomenon facilitates the loading of CO_2 by blood, while O_2 is delivered to the tissues. By contrast in the lungs, the Haldane effect enhances the unloading of CO_2, while O_2 is transferred to haemoglobin.

Finally, the carbamino compounds are formed by combining the CO_2 with the terminal NH_2 groups of proteins, especially with the globin of haemoglobin. This reaction is also favoured by the deoxygenation of haemoglobin.

8.2.3 How Is CO_2 Eliminated?

The three forms of CO_2 are carried by the blood flow to pulmonary circulation and eliminated by ventilation. CO_2 is eliminated by passive diffusion from the capillaries to the alveoli, depending on the difference in the gas tension between both spaces.

8.2.4 What Is the Relationship Between Blood CO_2 Content (CCO_2) and PCO_2?

The relationship between CCO_2 and PCO_2 is almost linear over the physiological range: $PCO_2 = k \times CCO_2$. Thus, the veno-arterial difference in CCO_2 can be estimated at the bedside by the veno-arterial difference in PCO_2 (PCO_2 gap) [5]. In fact, the relationship between CCO_2 and PCO_2 is not perfectly linear and is influenced by the degree of metabolic acidosis, the haematocrit and the arterial O_2 saturation [6, 7].

8.2.5 What Are the Determinants of the PCO_2 Gap?

According to the Fick equation applied to CO_2, the CO_2 excretion (which equals VCO_2 in steady state) equals the product of cardiac output by the difference between mixed venous blood CCO_2 ($CvCO_2$) and arterial blood CCO_2 ($CaCO_2$): VCO_2 = cardiac output × ($CvCO_2 - CaCO_2$).

As mentioned above, under physiological conditions, CCO_2 can be substituted by PCO_2 ($PCO_2 = k \times CCO_2$) so that $\Delta PCO_2 = k \times (CvCO_2 - CaCO_2)$. Thus, VCO_2 can be calculated from a modified Fick equation: $\Delta PCO_2 = (k \times VCO_2)$/cardiac output where k is the factor defining the relation between PCO_2 and CCO_2.

This relationship between cardiac output and ΔPCO_2 expresses the fact that, if cardiac output is low, the CO_2 peripheral clearance rate decreases, CO_2 stagnates at the peripheral venous side and $PvCO_2$ increases relatively to $PaCO_2$ at the peripheral venous level. In other words, for a given VCO_2, a decrease in cardiac output results in an increased PCO_2 gap and vice versa. This was found by experimental studies in which, when cardiac output was gradually reduced under conditions of stable VO_2, ΔPCO_2 was observed to concomitantly increase [8, 9]. Conversely, in a clinical study performed in normolactatemic patients with cardiac insufficiency, the increase in cardiac index induced by dobutamine was associated with a decrease in ΔPCO_2, while VO_2 was unchanged [10].

8.3 How to Use the PCO_2 Gap in Clinical Practice?

8.3.1 Can ΔPCO_2 Be Used as a Marker of Tissue Hypoxia? No!

It is often believed that ΔPCO_2 is a marker of tissue hypoxia. This was mainly suggested by studies observing large increases in ΔPCO_2 during cardiac arrest [11, 12].

However, because of the physiologic facts explained above, ΔPCO_2 is not a straightforward indicator of anaerobic metabolism.

Indeed, in the case of tissue hypoxia, the determinants of ΔPCO_2 can change in opposite directions so that ΔPCO_2 can increase, decrease or remain unchanged. As mentioned above, the *k* factor (defining the relationship between PCO_2 and CCO_2) increases in case of tissue hypoxia, increasing the PCO_2 gap even if the veno-arterial difference in CCO_2 does not change.

During tissue hypoxia, VCO_2 should decrease as result of the decrease in VO_2, both being linked by the respiratory quotient. This tends to decrease ΔPCO_2. In an animal study where cardiac output was experimentally decreased by tamponade, Zhang and Vincent observed that, below a critical level of O_2 delivery, the further decrease in cardiac output and O_2 delivery resulted in a progressive decrease in VCO_2 along with the decrease in VO_2 [8]. Similar results were reported in a model of tissue hypoxia created by application of incremental levels of PEEP in pigs [9].

Because VCO_2 must decrease and *k* must increase during tissue hypoxia, the resultant effect on PCO_2 gap will mainly depend on cardiac output [13]. Therefore, two situations should be distinguished: tissue hypoxia with reduced blood flow and tissue hypoxia with maintained or high blood flow.

In case of *tissue hypoxia with reduced systemic blood flow*, $PvCO_2$ increases relatively to $PaCO_2$ due to the venous stagnation phenomenon. In this regard, higher than normal ΔPCO_2 values have been reported in patients with congestive heart failure and low cardiac index but normal lactate [10].

In experimental studies where tissue hypoxia was induced by reducing blood flow, high values of ΔPCO_2 were also found [9, 14]. In addition to the venous stagnation phenomenon, the increase of ΔPCO_2 was explained in these studies by the fact that *k* also increases with decreased cardiac output. In such conditions, ΔPCO_2 can dramatically increase in spite of the decrease in VCO_2 [9, 14].

In case of *tissue hypoxia with maintained or high systemic blood flow*, PCO_2 gap should be normal or even reduced. In such conditions, CO_2 produced by aerobic metabolism should decrease as a result of a decrease in VO_2, even if some CO_2 is generated through anaerobic pathways as described above. Whatever the resultant VCO_2, the high efferent venous blood flow should be sufficient to washout the CO_2 produced by the tissues, and hence, ΔPCO_2 should not increase.

Results from several clinical studies have supported this hypothesis. Bakker et al. [15] found that most patients with septic shock had a $\Delta PCO_2 \leq 6$ mmHg. Cardiac index obtained in this subgroup of patients was significantly higher than that obtained in the subgroup of patients with a $\Delta PCO_2 > 6$ mmHg. Interestingly, the two subgroups did not differ in terms of blood lactate. Although VCO_2 and VO_2 were not measured directly, these data suggest that differences in CO_2 production did not account for differences in ΔPCO_2. In other words, many patients had a normal ΔPCO_2 despite tissue hypoxia, probably because their high blood flow had easily removed the CO_2 produced at the periphery. Similar findings were reported by Mecher et al. [16]. Clearly, these latter studies [15, 16] underline the poor sensitivity of ΔPCO_2 to detect tissue hypoxia.

Normal or low ΔPCO_2 was also reported by Wendon et al. [17] in a study including ten hypotensive patients with fulminant hepatic failure. These patients were assumed to have significant tissue hypoxia, as they demonstrated an increase in VO_2 after prostacyclin infusion. At baseline, ΔPCO_2 was very low, which was probably explained by the fact that VCO_2 was low—as suggested by the low VO_2—and by the fact that cardiac output was very high. These findings support the fact that tissue hypoxia under conditions of high-flow states should rather result in decreased than increased ΔPCO_2.

The major role of the cardiac output in the widening of ΔPCO_2 was demonstrated in animal studies comparing changes in ΔPCO_2 in ischaemic hypoxia and in hypoxic hypoxia [18, 19]. Ischaemic hypoxia was created by reducing blood flow using progressive bleeding in pigs [18] or in sheep [19]. Hypoxic hypoxia was created either by a progressive reduction of inspired oxygen concentration in pigs [18] or by progressive instillation of hydrochloric acid in sheep [19]. In both studies, cardiac output remained unchanged in the hypoxic hypoxia group. In both studies, ΔPCO_2 increased in the ischaemic hypoxia group, whereas it remained unchanged in the hypoxic hypoxia group [18, 19]. Similar results were reported by Vallet et al. in a model of vascularly isolated dog hindlimb [20]. Indeed, ΔPCO_2 significantly increased when limb hypoxia was induced by ischaemia, while it remained unchanged when hypoxia was induced by hypoxemia with maintained blood flow [20].

All these experimental [18–20] and clinical [15–17] studies have confirmed that during tissue hypoxia, ΔPCO_2 can be either high or normal depending on cardiac output. A mathematical model analysis also confirmed that cardiac output represents the major determinant in the elevation of ΔPCO_2 [21]. Thus, a normal ΔPCO_2 does not exclude the absence of tissue hypoxia. This is what should happen in high blood flow shock states. On the other hand, ΔPCO_2 can be elevated in cases of low cardiac output in the absence of tissue hypoxia.

8.3.2 In Summary, How to Interpret the PCO_2 Gap in Practice?

An increased PCO_2 gap suggests that cardiac output is not high enough with respect to the global metabolic conditions. Under anaerobic conditions (increased blood lactate), a high PCO_2 gap could incite to increase cardiac output with the goal of reducing tissue hypoxia (Fig. 8.1). Under aerobic conditions, this condition can be associated with an increased oxygen demand. In this regard, PCO_2 gap, as well as SvO_2, can serve to titrate β_1-agonists better than cardiac output because of potential thermogenic effects of these agents [10].

In a patient with a high initial value of ΔPCO_2, following the time course of ΔPCO_2 can also be helpful to assess the global metabolic effects of a therapeutic intervention aiming at increasing cardiac output. Under conditions of oxygen supply dependency when cardiac output increases, the decrease in anaerobic metabolism tends to decrease ΔPCO_2, but the increase in VO_2 tends to increase ΔPCO_2. As a result, ΔPCO_2 is expected to decrease to a lesser extent than in the case of oxygen supply independence. Consequently, unchanged ΔPCO_2 with therapy would not mean that the therapy has failed but rather that the treatment should be intensified

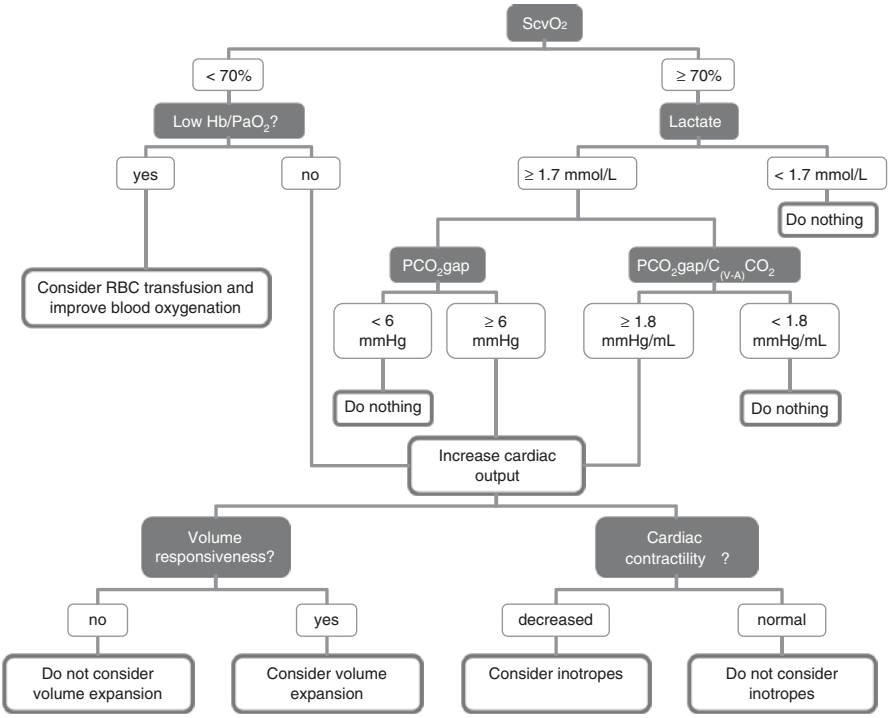

Fig. 8.1 Do oxygen delivery fit oxygen requirements? $C_{(V-A)}O_2$ arteriovenous difference in oxygen content, *Hb* haemoglobin, PaO_2 arterial oxygen tension, PCO_2 *gap* veno-arterial difference in carbon dioxide tension, *RBC* red blood cells, $ScvO_2$ central venous oxygen saturation

until obtaining a frank decrease in ΔPCO_2, indicating that the critical level of O_2 delivery has been actually overcome.

A normal PCO_2 gap suggests that cardiac output is enough to washout the amount of the CO_2 produced from the peripheral tissues (Fig. 8.1). This suggests that increasing cardiac output has little chance to improve global oxygenation even in cases of hypoxic conditions and thus that such a strategy cannot be a priority. In this regard, it must be remembered that increasing cardiac output to supranormal values was not demonstrated to be beneficial in critically patients [22, 23].

8.4 Combined Analysis of ΔPCO_2 and Oxygen-Derived Parameters

From the Fick principle, two equations can be written:

$$VCO_2 \times k = \text{cardiac output} \times \quad PCO_2$$

VO_2 = cardiac output × $C_{A-V}O_2$, where $C_{A-V}O_2$ is the arteriovenous difference in O_2 content (i.e. arterial blood O_2 content—mixed venous blood O_2 content).

During tissue hypoxia, k increases, while VCO_2 decreases less than VO_2 (due to generation of CO_2 through anaerobic pathways). Therefore, the $(VCO_2 \times k)/VO_2$ ratio should increase. Since the $(VCO_2 \times k)/VO_2$ ratio equals the $\Delta PCO_2/C_{A-V}O_2$ ratio (after eliminating cardiac output present on both the numerator and the denominator), the $\Delta PCO_2/C_{A-V}O_2$ ratio should increase during hypoxic conditions and thus could be used to detect global anaerobic metabolism (Fig. 8.1). In other words, indexing VCO_2 by VO_2 (and ΔPCO_2 by $C_{A-V}O_2$) allows one to interpret ΔPCO_2 independently from the changes in VO_2.

In a series of 89 critically ill patients (148 measurements) where the mixed venous blood was sampled through a pulmonary catheter and analysed, a close correlation was found between blood lactate concentration and the $\Delta PCO_2/C_{A-V}O_2$ ratio, while no correlation was found between blood lactate concentration and ΔPCO_2 alone and between blood lactate concentration and $C_{A-V}O_2$ alone [24].

This was confirmed in another series of 51 critically ill patients, where blood gas analysis of the venous blood was performed on the central and not on the mixed venous blood [25]. In patients where volume expansion increased cardiac output, the $\Delta PCO_2/C_{A-V}O_2$ ratio was able to follow the changes in VO_2, while the PCO_2 gap did not [25]. This confirmed that the PCO_2 gap rather reflects the adequacy of cardiac output to tissue metabolism than the adequacy of VO_2 to O_2 delivery.

In summary, $\Delta PCO_2/C_{A-V}O_2$ ratio should be considered as a marker of global anaerobic metabolism. It seems that it can be measured from the central as well as from the mixed venous blood.

8.5 $ScvO_2$- Versus PCO_2-Derived Indices

An advantage of the PCO_2 gap over $ScvO_2$ is that it remains a valid marker of the adequacy of cardiac output to the metabolic conditions even if the microcirculation is injured and the oxygen extraction properties are impaired (Fig. 8.1). This could be due to the fact that CO_2 is about 20 times more soluble than oxygen [26]. The microcirculatory impairment, with large veno-arterial shunts, impedes the diffusion of O_2 between cells and red blood cells, while the diffusion of CO_2 remains unaltered [26]. Another hypothesis is that, in septic shock, O_2 extraction is impaired because of the dysfunction of the mitochondria ("dysoxia"), an abnormality that would alter the consumption of O_2 but not the production of CO_2.

Aiming at illustrating the superiority of the PCO_2 gap over SvO_2, Vallée et al. included 50 septic shock patients where a $ScvO_2$ higher than 70% had been achieved [27]. Central PCO_2 gap was abnormally high (>6 mmHg) in half of the patients [27]. In that subgroup, blood lactate level tended to be higher and cardiac output to be lower than in patients with a central PCO_2 gap ≤6 mmHg. The authors concluded that $ScvO_2$ may not be sufficient to guide therapy and that when the 70% $ScvO_2$ value is reached, the presence of a central PCO_2 gap >6 mmHg might be useful to identify patients who still remain inadequately resuscitated [27]. Another study

showed that the combination of $ScvO_2$ and central PCO_2 gap predicted outcome in 172 critically ill patients resuscitated from septic shock better than $ScvO_2$ alone [28]. Patients who met both targets appeared to clear lactate more efficiently [28]. Similar results were reported in a series of septic shock patients [29].

Regarding the comparison of $ScvO_2$ with the $\Delta PCO_2/C_{a-v}O_2$ ratio, our team performed a study where 51 critically ill patients received a volume expansion [30]. Blood gas analysis of the venous blood was performed on the central and not on the mixed venous blood [30]. In patients in whom volume expansion increased cardiac output, ΔPCO_2 was able to follow the changes in cardiac output. This suggests that ΔPCO_2 allows one to follow changes in cardiac output even when it is measured in the central venous blood. Among patients in whom cardiac output increased, VO_2 increased in around half of the cases (indicating dependency between VO_2 and O_2 delivery), while VO_2 remained stable in the other ones (indicating independency between VO_2 and O_2 delivery). The increase of VO_2 was detected by changes in the $\Delta PCO_2/C_{A-V}O_2$ ratio and not by the changes in ΔPCO_2 [30]. This confirmed that, conversely to the $\Delta PCO_2/C_{A-V}O_2$ ratio, the ΔPCO_2 allows the assessment of the decrease in tissue hypoxia. Interestingly also, $ScvO_2$ could not detect changes in VO_2, because of the large proportion of septic shock patients in whom $ScvO_2$ was normal due to oxygen extraction impairment. This showed the superiority of the $\Delta PCO_2/C_{A-V}O_2$ ratio over $ScvO_2$ to assess tissue oxygenation in septic shock patients. Finally, the changes in lactate were also able to detect changes in VO_2, but lactate was measured 3 h after volume expansion, while the $\Delta PCO_2/C_{A-V}O_2$ ratio was measured immediately after the end of fluid administration [30]. This shows that one advantage of the $\Delta PCO_2/C_{A-V}O_2$ ratio over lactate is that it changes immediately after changes in VO_2.

In summary, all these arguments suggest that in case of septic shock with O_2 extraction impairment, in contrast with $SvO_2/ScvO_2$, the PCO_2 gap remains a reliable marker of the adequacy of cardiac output with the metabolic condition and the $\Delta PCO_2/C_{A-V}O_2$ ratio remains a valid indicator of the adequacy between O_2 delivery and VO_2. Moreover, compared to lactate, the CO_2-derived variables have the advantage to change without delay and to follow the metabolic condition in real time.

8.6 Errors and Pitfalls of the PCO_2 Gap

First, some errors in the PCO_2 gap measurements may occur because of technical issues when sampling the venous blood: incorrect sample container, contaminated sample by air or venous blood or catheter fluid [31]. Second, a too long delay of transport of blood sampling may lead to significant changes in the blood gas content at the venous and the arterial site.

Third, if the central venous blood is used rather than the mixed venous blood for gas analysis, one must check that the tip of the central venous catheter corresponds to the position of the right atrium on chest X-ray.

Fourth, it is important to remind that blood gas analysers have an imprecision of ±1 mmHg, which is not negligible if compared to the normal range of the PCO_2 gap.

Finally, due to the non-linear relationship between CCO_2 and PCO_2 at high cardiac output levels, this condition may be associated with largest changes in CO_2 but less significant increases of ΔPCO_2.

Conclusion

A proper analysis of the physiology of CO_2 metabolism reveals that the PCO_2 gap indicates the adequacy of cardiac output with the metabolic condition. The adequacy between O_2 delivery and O_2 consumption is better indicated by the $PCO_2/C_{A-V}O_2$ ratio. The CO_2-derived indices seem to be reliable when measured in the central venous blood as if measured in the mixed venous blood. In contrast to $SvO_2/ScvO_2$, they remain useful in septic shock patients with an impaired O_2 extraction.

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Lactate

9

Glenn Hernández Poblete, Maarten W. Nijsten, and Jan Bakker

9.1 Introduction

Since the first description of the measurement of lactate levels in humans, increased levels have been related to morbidity and mortality in many clinical situations [1, 2]. The prevailing hypothesis is that decreases in tissue blood flow cause tissue hypoxia that increases anaerobic lactate production due to low mitochondrial oxygen availability [3]. The subsequent tissue injury resulting from impaired oxygenation then leads to organ failure and subsequent morbidity and mortality. As has been shown in many experiments, decreasing oxygen delivery to the tissues indeed results at a critical point in oxygen delivery in the increase in serum lactate levels.

G. H. Poblete
Departamento de Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

M. W. Nijsten
Department of Critical Care, University Hospital Groningen, University of Groningen, Groningen, Netherlands
e-mail: m.w.n.nijsten@umcg.nl

J. Bakker (✉)
Departamento de Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University Medical Center, New York, NY, USA

Department of Intensive Care Adults, Erasmus MC University Medical Center, Rotterdam, Netherlands

Division of Pulmonary and Critical Care, New York University Langone Medical Center—Bellevue Hospital, New York, NY, USA
e-mail: jan.bakker@erasmusmc.nl

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The mechanism by which oxygen delivery decreases doesn't impact this principle [4] although decreases in blood flow and associated decreased microcirculatory perfusion seem to be important clinical features [5]. And although this critical point of oxygen delivery is different for different regional circulations [6], the principle of tissue hypoxia, critical oxygen delivery, and increased lactate levels has been well accepted. In addition, the existence of a critical oxygen delivery level and its association with increased lactate levels has also been shown in patients [7–9].

However, as lactate is a normal end product of glucose metabolism, levels may be increased due to other causes than impaired oxygenation. As has been long established, increasing sympathetic tone or accelerating glucose metabolism [10, 11] can significantly increase lactate levels in the presence of normal oxygenation. In addition, although seizures are frequently associated with high lactate levels, mortality is extremely low. Also, increased physical activity is frequently accompanied by a rise in lactate levels without clinical consequences. Finally, decreased clearance of lactate has also been associated with increased serum lactate levels [12].

Therefore, although there is a definite coupling between increased lactate levels and decreased oxygen delivery outcome in critically ill patients, its metabolism and causes of increased levels need to be thoroughly understood to optimize its clinical use. In this chapter we will integrate new and old knowledge on lactate metabolism and lactate monitoring that were obtained from experiments, sports physiology, and studies in critically ill patients.

9.2 Biochemical and Physiological Role of Lactate

Just like plants, animals have two key processes in generating energy to sustain life: glycolysis and oxidative phosphorylation (OxPhos) in the tricarboxylic acid. Each of these ATP-generating processes provides specific advantages (Table 9.1) where

Table 9.1 Glycolysis and oxidative phosphorylation

Glycolysis	OxPhos
~3.5 billion years	~1 billion years
Substrate-level phosphorylation	Cectorial biochemistry
In cytosol	In mitochondria
Very fast and adaptive	Oxygen dependent
Low yield (2 ATP)	High yield (32 ATP)
Produces pyruvate/lactate	Utilizes pyruvate/lactate
All animal cells	Many animal cells

As pyruvate and lactate connect glycolysis with oxidative phosphorylation (OxPhos), circumstances that induce tissues to utilize enhanced glycolysis may lead to increased lactate production, which can lead to increased circulating lactate levels

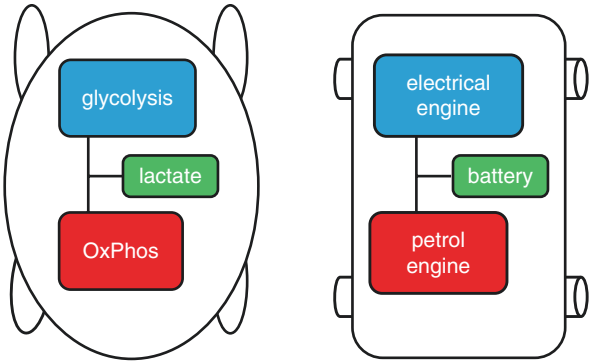

Fig. 9.1 Hybrid metabolism. Combination of two energy generating systems in animals and hybrid cars. Hybrid cars can outperform conventional cars and 100% electrical cars since they combine two complementary engines. But without a battery that serves as a buffer between the two engines, a hybrid car makes no sense. Thanks to the battery it can quickly accelerate and thanks to the high-yield petrol engine it has a large range. All animals are hybrid in that they combine both glycolysis and OxPhos with lactate serving as the indispensable buffer

lactate integrates these processes thereby creating a hybrid and exceptional flexible and efficient system (Fig. 9.1). Just like high-end hybrid cars use two systems for acceleration (electrical engine) and range (petrol engine), animals utilize glycolysis to facilitate acute or local high ATP requirements (acceleration power), while OxPhos provides a sustained overall supply of ATP (range). Without the use of lactate and lactate dehydrogenase (LDH), which are apparently evolutionary at least as old as mitochondria, this would not be possible.

9.2.1 Lactate at the Biochemical Level

Although lactate (La^-) and lactic acid (HLa) are not the same, the terms are often interchanged.

Since carbohydrates have the overall formula $(CHOH)_n$, with glucose $(CHOH)_6$, it can be appreciated that lactic acid $(CHOH)_3$ is equivalent to half a glucose. Therefore, two molecules of lactic acid are generated after the glycolysis of one molecule of glucose. With a pK_a of 3.8, lactic acid is nearly fully dissociated, even under pathophysiological conditions, into La^- and H^+. In the presence of oxygen, carbon backbones such as glucose and fats can be fully oxidized to CO_2 by the mitochondria. In the absence of oxygen, glucose is the only fuel that can generate ATP through glycolysis producing 2 mmol ATP and 2 mmol lactate for every mmol of glucose. The accumulation of pyruvate with this fast metabolic process will halt glycolysis until pyruvate is reduced to lactate by LDH, present in all animal cells, with concomitant conversion of NADH to NAD^+.

9.2.2 Lactate at the Cellular Level

When cells are stressed, glycolysis can be rapidly increased. Although the yield of glycolysis is only 2 ATP per glucose compared to a yield of 34 by OxPhos, glycolysis can be scaled up very rapidly and a much larger extent than OxPhos. Figure 9.2 provides an overview of three distinct cellular states. The upper panel shows the nonstressed condition when a steady amount of glucose is converted by glycolysis into pyruvic/lactic acid which is oxidized by OxPhos to CO_2. The middle panel shows a stressed state where the cell takes up much more glucose while maintaining OxPhos. Under these conditions, lactate production by glycolysis can exceed the ability of OxPhos to metabolize lactate, even in the presence of sufficient oxygen.

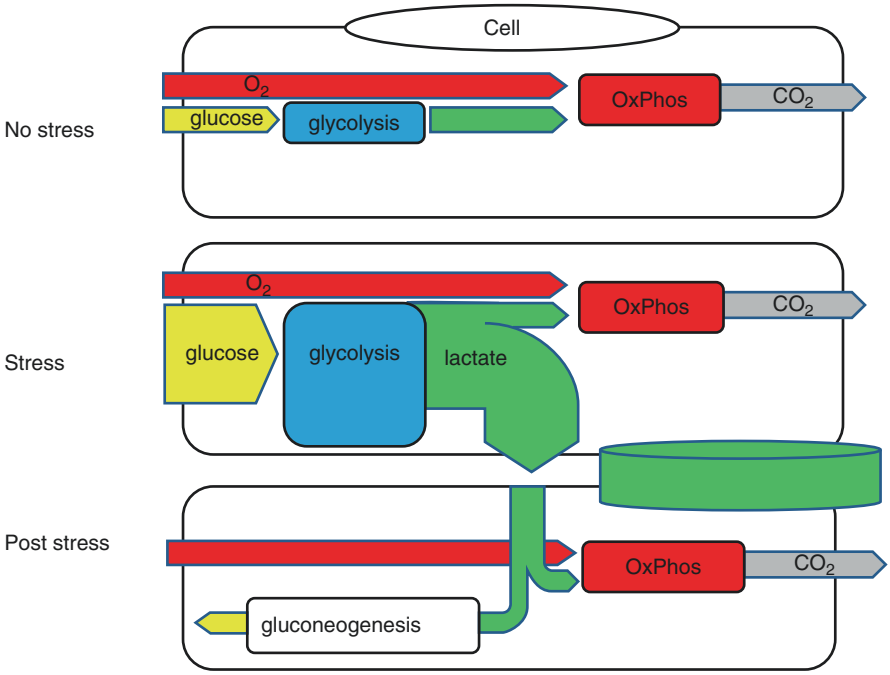

Fig. 9.2 Glycometabolism at the cellular level. Three different conditions regarding lactate production and consumption at the cellular level. The upper panel shows a stable state where a nominal amount of glucose (yellow) is converted by glycolysis into pyruvic/lactic acid (green) which is oxidized by OxPhos to CO_2. The middle panel shows a stressed state where the cell takes up much more glucose while maintaining OxPhos. Lactate production by glycolysis can easily outstrip the ability of OxPhos to metabolize lactate by a large margin. Lactate can be exported for use elsewhere or later use. The lower panel shows how in a post-stress state a cell reuses accumulated lactate for energy generation in OxPhos or to (re)synthesize glucose or glycogen through gluconeogenesis

Thus, lactate accumulates and can be exported out of the cell for later reuse. The lower panel recovery following stress is shown. Cells reuse the accumulated lactate for energy generation in OxPhos or to (re)synthesize glucose or glycogen through gluconeogenesis. Thus, lactate is not a "waste product" but rather a fuel that can ultimately be reused by cells [13, 14].

9.2.3 Lactate at the Tissue Level

In mammals, fuel delivery (fat and glucose) at the tissue level is far higher than oxygen delivery. If all delivered oxygen could be consumed, still >75% of the fuel passes the tissue without being used for ATP generation. As complete oxygen extraction is not possible, this underscores the importance of glycolysis and lactate production (Fig. 9.3). Although fuel preference of organs varies (e.g., the heart prefers fatty acids and the brain prefers glucose), maximal aerobic metabolism will always leave considerable fuel surplus at the venous side. Thus in case of acutely increased ATP demands even under fully aerobic conditions, a large amount of glucose is available to be converted in lactate [15]. As depicted in Fig. 9.3b, lactate production occurs on top of OxPhos in many physiological but also pathophysiological stress conditions [16, 17]. Thus, in much of pathophysiology, lactate production happens in the context of adequate oxygenation but increased ATP requirements.

9.2.4 Lactate at the Whole-Organism Level

The liver and kidneys, the main metabolic organs, can remove circulating lactate and convert it back to glucose through gluconeogenesis (Fig. 9.4). During physical exertion part of the glucose consumed by muscles is converted into lactate and excreted into the circulation to be converted back into glucose by the liver and kidneys. This so-called Cori cycle was described Cori in 1931 [15]. The Cori cycle allows stressed tissues to generate more ATP than otherwise would be possible. In addition, in many cases lactate is directly oxidized by other tissues, without any overall ATP loss (Fig. 9.4). Increased lactate production could thus be driven by increased energy demands rather than reduced supplies. In stress conditions, like shock, increased energy demand stems from different sources. The adrenergic system, in particular adrenalin, is known to directly stimulate glycolysis as well as glycogenolysis by its β_2-receptor stimulation [15–17]. The rapid release of glucose leads to hyperglycemia and thus increased circulating "acute" fuel levels with the concomitant stimulation of glycolysis which immediately increases ATP levels. The acute systemic adrenergic stress response can be followed by the slower response of the adrenal cortex with rising cortisol levels. It has been shown that the glucocorticoid response increases glucose levels and induces gluconeogenesis, but it also increases glycolysis and lactate production [18, 19].

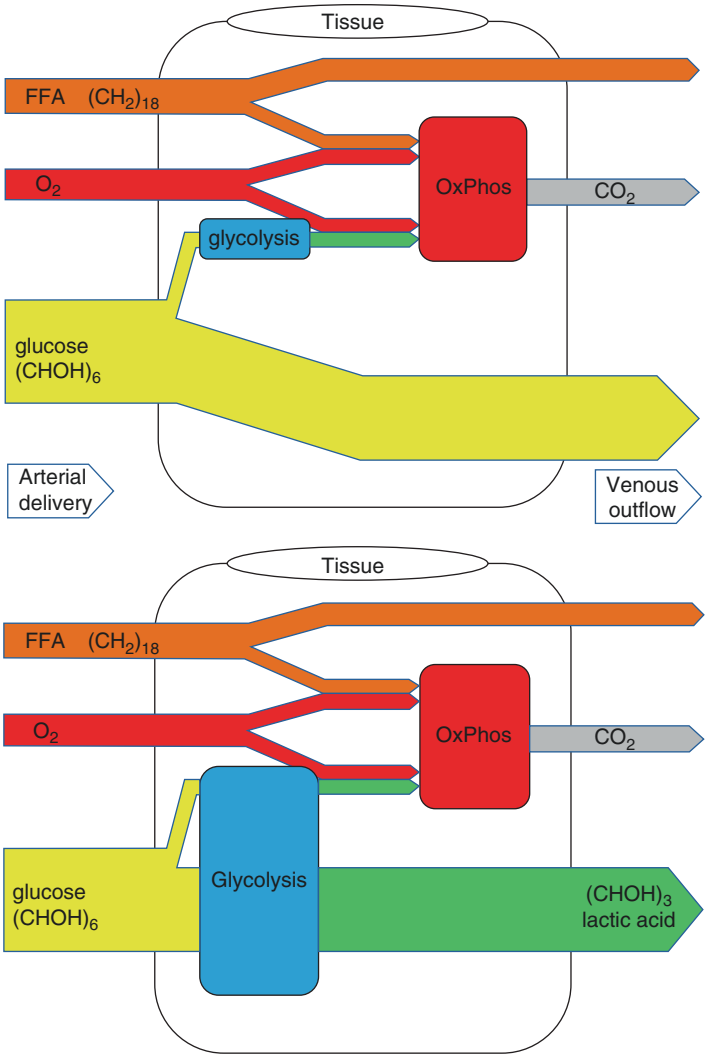

Fig. 9.3 Fuel and oxygen delivery at the tissue level. (**a**) Scheme that relates fuel and oxygen delivery to tissues or organs. Theoretical maximal pure aerobic metabolism at the tissue level. Delivery and outflow of key metabolites under stable conditions is shown in this theoretical example where a tissues is assumed to extract all avialable oxygen. The thickness of the flows of fatty acid (FFA) and glucose flows correspond to the oxygen required to fully oxidize them. (**b**) Theoretical maximal pure aerobic metabolism + maximal glycolysis at the tissue level. Although all delivered oxygen is consumed, compared to the situation in the upper panel, the excess remaining glucose is now converted into lactic acid to generate additional ATP and excreted. This phenomenon is called 'aerobic glycolysis', since it is glycolysis not resulting from anaerobic conditions, but from increased energy demands by the cell. The assumed arterial values are [O_2] 9 mmol/L, FFA (as $(CH_2)_{18}$; oleic acid) 0.5 mmol/L and glucose 5 mmol/L). The fuel delivery is $0.5 \cdot 18 + 5 \cdot 6 = 39$ carbon atoms that require 39 O_2 molecules to be fully oxidized to CO_2. Note that the fuel : oxygen ratio is thus ~39:9 or ~4.3. Over the past decades it has has become apparent that this cause of lactate generation is much more frequent than a shortage of oxygen

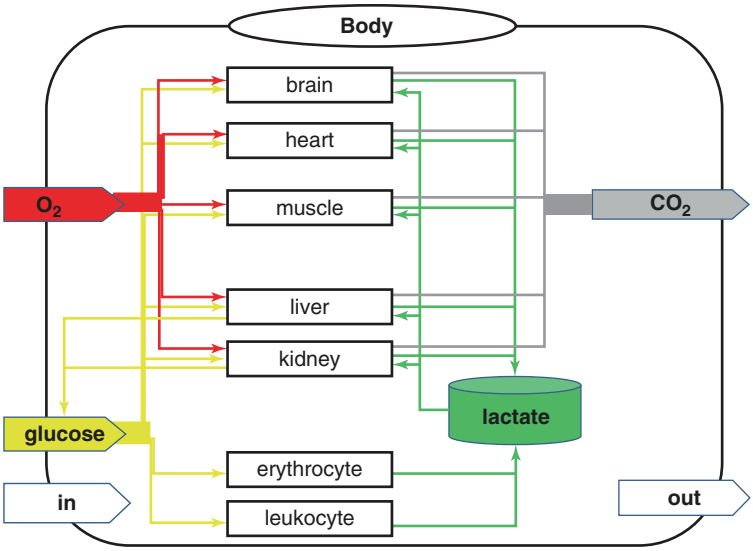

Fig. 9.4 Macroscopic lactate shuttles. Lactate's role as an intermediate metabolite at the organism level. The ability of all cells in mammals to generate lactate and of most cells to metabolize lactate has given rise to various lactate shuttles. Cells that possess mitochondria can take up lactate from the circulation. Note that since erythrocytes and (many) leukocytes lack ATP-generation from OxPhos, they are completely dependent on glycolysis. Further note that only the liver and kidney can convert lactate back into glucose (gluconeogenesis at the cost of 6 ATP) and export this glucose into the circulation. The arterial consumption of glucose and venous production of lactate by the muscles and its conversion into glucose and its release back into the circulation by the liver, is called the Cori cycle. Note that lactate is a true intermediate metabolite an animal will nourish itself with carbohydrates or fat and excrete CO_2, but that it will not feed or excrete relevant amounts of lactate

9.3 Persistent Hyperlactatemia in Clinical Practice

Given the above importance of glucose and lactate metabolism, the use of lactate levels in clinical practice is not as straightforward as has been suggested. For instance, parameters next to lactate that are frequently used to monitor tissue perfusion might have a different time constant when increasing tissue perfusion by resuscitation [20]. As an example, central venous oxygen saturation has been shown to respond almost instantly, where lactate levels decrease much slower in response to decreases in oxygen demand or increases in oxygen delivery [2]. Although tissue hypoperfusion has been traditionally considered the most common cause of hyperlactatemia, there is increasing evidence for concomitant non-hypoxic and thus non-flow-dependent mechanisms [21, 22] that may influence the time course of lactate recovery rate. The distinction between these two scenarios (flow-dependent vs. non-flow-dependent hyperlactatemia) should strongly affect the therapeutic approach [21]. As an example, treatment of the latter with sustained efforts aimed at

increasing DO_2 could lead to detrimental effects of excessive fluids or inotropes. In a recent study by Hernandez et al. [23], lactate exhibited a significant decrease of almost 30% of basal median values during the first 6 h of resuscitation, and this was associated with a rapid normalization of other metabolic and peripheral perfusion parameters. However, further decrease in lactate was very slow since complete normalization was observed only in half of a cohort of ultimately surviving patients at 24 h. Thus, it appears that lactate decrease can be characterized by a biphasic evolution: an early rapid response followed by a slower recovery trend potentially explained by non-flow-dependent mechanisms.

The role of hyperadrenergia and the stress response in muscle aerobic lactate production has been recently highlighted as a very important contributing factor in persistent hyperlactatemia [20, 21]. However, much less attention or research has been focused on the potential role of impaired hepatic lactate clearance in this setting. Indeed, the splanchnic contribution to hyperlactatemia may be secondary to an increased hypoxic or non-hypoxic gut lactate production, a decreased hepatic lactate clearance secondary to hypoperfusion or dysfunction, or a combination of both [24–27]. In a recent study by Hernandez et al., septic shock patients with a 6 h-lactate clearance <10% presented an increased gastric intramucosal to arterial pCO_2 gap and a decreased indocyanine green–plasma disappearance rate (ICG-PDR) to extremely abnormal values (medians of 33 mmHg and 9.7%, respectively) compared to patients with a higher lactate clearance, suggesting the presence of sustained hepatosplanchnic hypoperfusion despite a global hyperdynamic flow status at least in some cases [22].

Lactate clearance is frequently used when referring to the process of changes in serial lactate levels in response to therapy. However, the latter is the consequence of both production and the actual clearance. Therefore, a decrease in serum lactate levels could be caused either by a decreased production or increased clearance, where the inverse is also true [28]. Although the liver plays a major role in systemic lactate clearance [29], persistent hyperlactatemia has only been related to impaired hepatic clearance in cases of severe shock with a comorbidity of liver ischemia or advanced cirrhosis [24, 30]. In contrast to this view, Levraut et al. evaluated whole-body net lactate clearance and lactate production in 34 stable septic patients with normal to slightly elevated lactate levels by modeling the lactate kinetics induced by an exogenous lactate bolus [12]. They found that patients with increased lactate levels, as compared to patients with normal levels, exhibited approximately 50% lower lactate clearance after the challenge. In addition, Hernandez et al. demonstrated that endotoxic (LPS) shock induces a very early and severe impairment of 90% in exogenous whole-body net lactate clearance that is not related to total liver hypoperfusion or evident biochemical dysfunction [31]. Moreover, a very low difference in lactate concentrations between the portal and hepatic veins suggested at least a metabolic inability of the liver to handle increased lactate loads. This appeared to be a specific rather than generalized metabolic dysfunction as the clearance of sorbitol, a polyol molecule with a 96% first pass liver extraction, was preserved. This dramatic decrease in clearance was observed very early after LPS

administration (a mean of 80 min after initial bolus of LPS) and was not restored by systemic resuscitation [31]. Taken together, these two studies suggest that impaired lactate clearance develops very early in septic shock, varies in severity according to the magnitude of the septic insult, and persists over time considering that 12 out of 34 patients in Levraut's study [12] were enrolled after 3 days of septic shock. Additionally, liver biochemistry was almost normal in both studies, suggesting a selective metabolic dysfunction not easily recognizable by systemic hemodynamics or common liver function tests.

9.4 Circulatory Dysfunction with Normal Lactate Levels

The ability of some patients to maintain normal lactate levels even under severe circulatory stress provides additional valuable information. Both adrenergic-driven aerobic and hypoxia-related anaerobic lactate production may increase during septic shock. However, similar to what happened in sports physiology [14], our understanding of lactate in pathophysiology has changed dramatically during the last decade, shifting from a *bad* to a *good* lactate conception. Lactate appears to exert fundamental metabolic and signaling effects. Thus, patients able to maintain normal lactate levels despite a massive aerobic release from muscles in this setting, probably represent a physiological compensated state eventually associated to a high survival rate. We addressed this subject in a previous study where 302 patients diagnosed as septic shock according to the 2001 Consensus Conference were treated with a common perfusion-oriented management algorithm and registered in a prospective dataset [32]. In a retrospective analysis, Hernandez et al. found that one third of patients never displayed elevated lactate and exhibited a very low mortality risk (<8%), less organ dysfunction, and lower norepinephrine requirements. Interestingly, patients with at least one elevated lactate value exhibited a mortality of 43%, which was even higher (61%) in patients with a delayed peak value as compared with those in whom peak lactate levels were registered at admission. Although all patients fulfilled the 2001 Consensus Definition and required vasopressors, patients without hyperlactatemia exhibit a physiologic pattern and clinical evolution incompatible with a true shock state.

In a subsequent study, the clinical, hemodynamic, perfusion, and microcirculatory profiles associated with the absence of hyperlactatemia during septic shock resuscitation in 124 patients were studied [33]. Thirty percent evolved without hyperlactatemia and showed less severe microcirculatory abnormalities and higher platelet counts. Systemic flow parameters were not related to the presence or absence of hyperlactatemia. These data suggest a relationship between coagulation, microcirculatory derangements, and lactate levels and tend to support the notion that patients with persistent sepsis-induced hypotension without hyperlactatemia exhibit a distinctive clinical and physiological profile within the spectrum of septic shock.

9.5 Practical Approach to Increased Lactate Levels

In a septic patient, the foremost priority is to rule out a hypoxic cause for hyperlactatemia. Concomitant analysis of central venous O_2 saturation ($ScvO_2$), central venous–arterial pCO_2 gradient ($P(cv–a)CO_2$), and peripheral perfusion may be helpful [20]. The presence of a low $ScvO_2$ in the context of persistent hyperlactatemia clearly indicates an imbalance in the DO_2/oxygen consumption (VO_2) relationship thus suggesting a flow-dependent hyperlactatemia. This finding should prompt an aggressive DO_2/VO_2 optimization strategy as was demonstrated by Rivers et al. [34]. In contrast, the presence of normal or even supranormal $ScvO_2$ values, as frequently observed in ICU patients, should not be interpreted as evidence of a normal tissue perfusion because of several reasons. First, Vallee et al. found persistent abnormal $P(cv–a)CO_2$ values in 50% of septic shock patients who had already achieved normal $ScvO_2$ values after initial resuscitation, and this was associated with hyperlactatemia [35]. Second, $ScvO_2$ is in strict terms a regional monitor. We demonstrated that the maneuver of sedation and connection to mechanical ventilation rapidly normalizes this parameter in septic patients subjected to emergency intubation by decreasing regional oxygen extraction, but this does not assure the correction of global tissue hypoxia [36]. Third, since severe microcirculatory derangements could theoretically impair tissue oxygen extraction capacities, a normal DO_2/VO_2 relationship may coexist with profound tissue hypoxia [37]. Increases in the $P(cv–a)CO_2$ gradient have been reported in different classes of shock, and an inverse curvilinear relationship between $P(v–a)CO_2$ and cardiac output has been described [38], highlighting the importance of blood flow on venous CO_2 accumulation. More recently it was suggested that a high $P(v–a)CO_2$ could identify septic patients who remain inadequately resuscitated despite achieving other targets, reinforcing the notion of $P(cv–a)CO_2$ as a marker of global perfusion due to its ability to track blood flow alterations [35] or even detect anaerobic CO_2 generation, thus aiding in identifying a flow-dependent lactate. In addition, analysis of the venous–arterial CO_2 to arterial–venous O_2 content difference ratio ($C(v–a)CO_2/D(a–v)O_2$ ratio) could serve as a surrogate of the respiratory quotient [39], thereby adding context to increased lactate levels. A ratio > 1.0 could identify anaerobic CO_2 generation. Thus, in the presence of hyperlactatemia, a high $C(v–a)CO_2/D(a–v)O_2$ may indicate anaerobic metabolism as the possible source of lactate, while a normal $C(v–a)CO_2/D(a–v)O_2$ may suggest that lactate accumulation is due to non-flow-dependent causes [39]. Interestingly, hyperlactatemic patients evolving with a high $C(v–a)CO_2/D(a–v)O_2$ 6 h after initial resuscitation had a lower VO_2 compared with those evolving with normal $C(v–a)CO_2/D(a–v)O_2$, despite similar DO_2 values [39]. This suggests that a high $C(v–a)CO_2/D(a–v)O_2$ coupled with hyperlactatemia could identify ongoing VO_2/DO_2 dependence.

The assessment of peripheral perfusion in the context of hyperlactatemia may provide additional physiological information. An abnormal peripheral perfusion may be caused by a low cardiac output, and thus a complementary evaluation of cardiac function through invasive or noninvasive techniques is obligatory. It should also prompt a reassessment of preload status, since triggering of adrenergic response

by ongoing hypovolemia could induce peripheral vasoconstriction [40]. So the simultaneous finding of abnormal peripheral perfusion together with hyperlactatemia may suggest a flow-dependent mechanism.

In conclusion, the physiological and pathophysiological role of lactate has been steadily unraveled. The basic principles of lactate metabolism are well understood, and it is now clear that hyperlactatemia reflects a vital compensatory response. We are optimistic that in the near future, the various underlying mechanisms will be further clarified. In the meantime, lactate has firmly established itself as an important and unique marker of severity of critical disease [41].

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Part IV

Measuring Tissue Perfusion: Regional Assessment

Clinical Assessment

10

Roberto Rabello Filho and Thiago Domingos Corrêa

10.1 Introduction

During circulatory failure, a decreased oxygen supply and blood flow redistribution result in tissue hypoperfusion [1]. While vital organs such as the brain, heart, and kidneys have vasomotor regulation that may maintain blood flow even in hypotensive states, cutaneous circulation is deprived of blood flow autoregulation [1].

The physiological rationale for monitoring peripheral perfusion is based on the concept that low arterial blood pressure triggers a sympathetic neurohumoral response that predominates on peripheral tissues, resulting in decreased perfusion and consequently low cutaneous temperature [2, 3]. Thus, monitoring clinical parameters of tissue perfusion at the bedside may allow access compensatory mechanisms induced by shock states in early stages of the disease [4].

Attempts in correlate clinical parameters of the skin and shock are not recent. In 1969, Joly and Weil identified cold toe as an easily accessible parameter circulatory shock severity [5]. The authors also observed a significant correlation between cardiac output (CO) and toe temperature [5]. More than 30 years later, the subjective assessment of peripheral perfusion during acute circulatory shock continued to be a matter of debate, in particular, the evaluation of skin-derived parameters to identify critically ill patients at high risk of poor outcomes [6–8].

Thompson and colleagues studied the time course of clinical features of meningococcal disease in 373 children and adolescents before hospital admission [6]. The authors showed that hemorrhagic rash, meningism, and impaired consciousness developed late (median onset 13–22 h), while more than two thirds of patients exhibited early symptoms of peripheral hypoperfusion (leg pains, cold hands and feet, abnormal skin color) that first developed at a median time of 8 h [6].

R. R. Filho (✉) · T. D. Corrêa
Department of Critical Care Medicine, Hospital Israelita Albert Einstein, São Paulo, Brazil
e-mail: roberto.rabello@einstein.br

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Aiming to determine whether physical examination can accurately track hypoperfusion, Kaplan and colleagues divided patients accordingly extremities skin temperature as cool extremities and warm extremities [7]. The authors found no differences between groups regarding macrohemodynamic parameters such as heart rate, systolic blood pressure, diastolic blood pressure, and pulmonary artery occlusion pressure [7]. Nevertheless, CO, blood pH, and central venous oxygen saturation (SvO_2) were lower and blood lactate levels higher in patients with cool extremities [7]. The authors demonstrated that hypoperfusion might occur despite normal macrohemodynamic parameters [7].

Furthermore, the subjective assessment of peripheral perfusion can also provide important prognostic information [8]. Hasdai and colleagues' study demonstrated that parameters derived from physical examination, such as cold and clammy skin, were independent predictors of 30-day mortality [8]. A more recent prospective observational study showed that clinical evaluation of tecidual perfusion can discriminate patients with a more severe organ dysfunction, as expressed by high sequential organ failure assessment (SOFA score) in patients with abnormal peripheral perfusion [4].

In this chapter, we briefly revised the role of clinical assessment of peripheral circulation and presented the evidence supporting the use of capillary refill time, peripheral temperature and temperature gradients, and skin mottling at bedside.

10.2 Clinical Assessment of Peripheral Circulation

10.2.1 Capillary Refill Time (CRT)

Capillary refill time is a quick, reproducible, and noninvasive method for assessing circulatory status in critically ill patients [9]. The first mention of CRT measurement in literature was done by Beecher in 1947, who proposed this measure as a shock assessment parameter [10]. CRT is measured by applying firm pressure to the distal phalanx of the index finger for 15 s [1]. Thus, a chronometer must be used to record the time for return of the normal color [1, 4].

The CRT varies with age, gender, and temperature [11]. As an example, it has been shown that applying the 2-s limit results in a false-positive rate of 4.0% for the pediatric and adult male volunteers, 13.7% for the adult female volunteers, and 29.0% for the elderly volunteers [11]. Therefore, it has been suggested that the upper limit of normal for adult women should be 2.9 s, and the upper limit of normal for the elderly should be 4.5 s [11].

Several methodological aspects should be acknowledged for a correct measurement of CRT: (1) limb choice is important, since lower limbs may have longer CRT compared with the upper limbs [12]; (2) adequate ambient light should be available; (3) the limb should be positioned above the level of the heart to avoid venous refill [13]; and (4) low ambient temperature can prolong capillary recharge time [14].

The correlation between CRT and hemodynamic parameters was assessed in many studies [9–15]. Bailey and colleagues evaluated the relationship of indicators

of peripheral perfusion (CRT, quality of pedal pulses, and toe or finger core temperature gradient) with thermodilution cardiac index (CI) and systemic vascular resistance immediately after cardiac surgery [15]. They did not find significant relationship between CRT and global hemodynamics during the first 8 h following ICU admission [15].

However, in the pediatric population, CRT correlates better with other clinical and laboratory perfusion parameters [9, 16]. Prolonged CRT has been found to be a good predictor of dehydration, reduced stroke volume, and increased blood lactate levels [9, 16].

These findings raise doubts about the validity of CRT as a diagnostic marker of circulatory status peripheral perfusion especially in adults, mainly because factors other than global hemodynamics, including normal thermoregulatory responses, may affect the peripheral vasculature [17]. However, the association of CRT with worse clinical outcomes is important and should not be overlooked. New studies aimed at the evaluation of the use of CRT in combination with serum tissue perfusion monitoring tools should still be encouraged.

10.2.2 Peripheral Temperature and Temperature Gradients

Two components are responsible for the peripheral cutaneous circulation: (1) capillary flow and (2) arteriovenous shunts (which are mostly thermoregulated) [18]. Skin surface temperature gradients correlate reasonably well with capillary blood flow, but the total finger blood flow may be influenced by thermoregulatory changes [18].

Since Ibsen [19] and Joly [5] studied the toe temperature as a parameter of the circulatory shock, body temperature gradients have been used as a measure of peripheral perfusion. Temperature measurements are objective and available without discomfort to the patient and would require only a minor investment. Therefore, their potential value for routine monitoring was especially attractive [5].

In 1967 Ibsen published the first study involving temperature gradients evaluating the difference between rectal and skin temperature before and after administration of vasodilator in 150 patients with different types of shock [19]. Significant drop of this gradient was observed after vasodilator administration was observed and this study opening the doors to a series of new experiments [19].

Two years later, in the Joly and Weil study, peripheral temperature was measured with standard thermistor probes at five sites: the digital pad of the third finger, the large toe, the deltoid region of the arm, the lateral portion of the thigh, and the rectum [5]. This study investigated whether quantitative changes in skin temperature might provide reliable indication of the presence and severity of circulatory shock [5]. The authors demonstrated that a critical reduction in CI to levels of less than 2 L/min/m^2 was associated with a decline in toe temperature to less than 27 °C in 42 of 44 cases (95%) and when toe temperature exceeded 29.2 °C, the CI exceeded 2 L/min/m^2 in each case [5]. Moreover, the authors confirmed a highly significant correlation between CI and toe temperature ($r = 0.71$; $P < 0.01$), and this correlation

coefficient was improved after correction for differences in ambient temperature (0.73; $P < 0.01$) [5].

Ruiz and colleagues investigated 34 patients with circulatory shock associated with myocardial infarction, bacteremia, or hypovolemia before and after the treatment with dopamine [20]. Increases in toe temperature were correlated with increases in CO, and reduction in arterial blood lactate and increases in toe temperature during dopamine treatment were a good indicator of favorable outcome [20].

In the presence of a constant environmental temperature, changes in the skin temperature reflect changes in skin blood flow [21]. The peripheral skin temperature can be measured using a temperature probe placed on the ventral face of the great toe, and fingertip temperature can be measured using a temperature probe attached to the ventral face of the finger [1]. Considering a constant environment temperature condition, temperature gradients peripheral-to-ambient (dTp-a) decreases and central-to-peripheral (dTc-p) increases during vasoconstriction [22]. A gradient of 3–7 °C occurs in patients with stable hemodynamics [23].

Forearm-to-fingertip skin-temperature gradient (Tskin-diff) has also been used as an index of peripheral circulation to identify the initiation of thermoregulatory vasoconstriction [24, 25]. The Tskin-diff concept is based on assumption that the reference temperature is a skin site exposed to the same ambient temperature as the fingertip [24, 25]. Experimental studies have established a Tskin-diff threshold cut-off of 4 °C for severe vasoconstriction [24, 25].

A number of studies have examined the correlation between these temperature gradients and global hemodynamic variables [7, 26]. Kaplan and colleagues compared distal extremity skin temperature (evaluated by subjective physical examination) with hemodynamic markers of hypoperfusion in adult ICU patients [7]. This study found a relationship between cold periphery signals and lower cardiac output besides higher blood lactate levels as a marker of more severe tissue hypoxia [7].

Henning and colleagues studied temperature gradient between the ventral surface of the first toe and the ambient temperature in 71 critically ill patients with circulatory failure caused by acute myocardial infarction, primary bacteremia, and hypovolemia [26]. The dTp-a was a more predictable indicator of survival than either arterial pressure or cardiac index in each group of patients [26]. Moreover, a gradient of less than 3 °C over an interval of 12 h was typically observed in patients who subsequently died [26].

Vincent et al. [27] evaluated the value of dTp-a for assessing peripheral perfusion in cardiogenic shock and found that a low cardiac index was associated with a decrease in dTp-a lower than 5 °C. Further, the increase in dTp-a occurs earlier than the increase in skin oxygen partial pressure during recovery of patients [27].

In conclusion, clinical assessment of peripheral perfusion with temperature gradients has already well-described value in relation to macrocirculatory variables, especially CI, besides an important prognostic measure in critical ill patients. These gradients can easily be obtained and may be an additional tool in the hemodynamic monitoring of severe patients with different types of shock.

10.2.3 Skin Mottling

In 1941 Ebert et al. described that patients with severe infection developed circulatory failure characterized not only by a marked fall in arterial pressure but also by a decrease in peripheral blood flow as shown by "pallor and cold extremities" [28]. Later, in an analysis of 100 patients with septic shock, moist and cool skin on patients were associated with a worse prognosis [29].

Skin mottling, a common and easy to assess clinical sign in critical ill patients, is defined as a red-violaceous discoloration of the skin that usually starts around the knees due to skin hypoperfusion [30].

Pathophysiologically, the formation of mottling skin occurs through the action of chemical mediators in small vessels acting in high noradrenergic receptors density mainly located in knees, ears, and fingers [31]. In mottled territories the near-infrared spectroscopy (NIRS) showed a reduction of tissue oxygen saturation, suggesting a decrease in local perfusion [32].

A skin mottling score (SMS) was developed to quantify the extent of mottling on the legs [30]. This score ranges from 0 to 5 and is based on the area of mottling from the knees to periphery [30]. A score 0 indicates no mottling; score 1, a small mottling area localized to the center of the knee; score 2, a mottling area that does not exceed the superior edge of the knee cap; score 3, a mottling area not exceeding the middle thigh; score 4, a mottling area not going beyond the fold of the groin; and score 5, an extremely severe mottling area going beyond the fold of the groin [30].

From the development of the SMS, two studies reported the incidence of skin mottling over the knee in a subset of patients admitted for septic shock [30, 32]. In these studies, mottling was frequent, occurring in 46 and 70% of the patients [30, 32].

Several studies have also evaluated this signal as a prognostic factor in different populations of severe patients [30, 33, 34]. A prospective observational study with septic shock patients found that the SMS had an excellent agreement between independent observers and high arterial lactate level and SMS was strongly associated with 14-day mortality [30]. More recently, another study analyzed SMS as a 28-day death predictor in ICU septic patients and was demonstrated that the time to death was shorter in patients with higher SMS [33].

Coudroy and colleagues evaluated 791 critically ill patients aimed to analyze the overall incidence in ICU of skin mottling, and it impacts on mortality, without the use of SMS [34]. They found that mortality was 8% in patients without mottling, 30% in patients with short skin mottling and 40% in patient with persistent (no reversion) skin mottling [34]. Moreover, in the overall population, skin mottling over the knee was associated with in-ICU mortality independently from SAPS II [34].

It is possible to conclude that skin mottling, a noninvasive and easy to assess clinical sign, occurs frequently in severe ICU patients and can predict poor outcomes, independently of global hemodynamic parameters and ICU severity scores.

Conclusion

Abnormal microcirculation has been identified as the main cause of organ dysfunction and consequently poor outcomes [27, 35], whereas systemic hemodynamic parameters were not [36]. Therefore, it is important to understand different parameters available at the bedside to assess microcirculation and organ perfusion. There are simple, noninvasive, and low-cost tools to assess clinically peripheral perfusion that are often neglected but can predict poor outcomes in ICU patients.

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Optical Monitoring

11

Alexandre Augusto Pinto Lima and Daniel De Backer

11.1 Introduction

Optical methods apply light with different wavelengths directly to tissue components using the scattering characteristics of tissue to assess different states of these tissues [1]. Light can be used in two ways, the first being the use of its absorption capacities to evaluate oxygenation states or to visualize red blood cells. Commonly used optical methods in the clinical setting include near-infrared spectroscopy, plethysmographic signal of pulse oximetry that is able to monitor tissue oxygenation at the bedside and videomicroscopic techniques to directly visualize the sublingual microcirculation. The second way is to use the properties of moving cells to alter the wavelength of the reflected wave (the Doppler effect). The laser Doppler uses this property to evaluate microvascular perfusion.

At physiologic concentrations, the molecules that absorb most light are haemoglobin, myoglobin, cytochrome, melanins, carotenes and bilirubin. These substances can be quantified and measured in intact tissues using simple optical methods. As haemoglobin is far more abundant, most of the absorption of light is related to haemoglobin and the so-called tissue oxygenation that represents in fact tissue microvascular oxygenation. The assessment of tissue microvascular oxygenation is based on the specific absorption spectrum of oxygenated haemoglobin (HbO_2) and deoxygenated haemoglobin (Hb). Near-infrared spectroscopy,

A. A. Pinto Lima (✉)
Department of Intensive Care, Erasmus MC University,
Rotterdam, The Netherlands
e-mail: a.pintolima@erasmusmc.nl

D. De Backer
CHIREC Hospitals, Université Libre de Bruxelles, Brussels, Belgium
e-mail: ddebacke@ulb.ac.be

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plethysmographic signal of pulse oximetry and laser Doppler flow will be discussed here. Direct visualization of sublingual microcirculation is discussed at greater length in the chapter 6 (in *Microcirculation*).

11.2 Near-Infrared Spectroscopy

Near-infrared radiation consists of light with wavelengths near that of the visible portion of electromagnetic spectrum. First described in 1800 by William Herschel [2], it was not until 1968 that the agricultural engineer Karl Norris described the near-infrared spectrum using spectroscopy [3]. In 1977, Frans F. Jobsis demonstrated the usefulness of near-infrared spectroscopy (NIRS) for the noninvasive monitoring of tissue oxygenation, and he is also considered the frontrunner of research into the use of NIRS to assess cell oxygenation and metabolism [4]. This pioneer's work opened a new area of monitoring tissue oxygenation using NIRS, both in patients and in healthy subjects [5–7]. NIRS uses specific and calibrated wavelengths of near-infrared light to noninvasively illuminate the tissue below a sensor placed on the skin.

11.2.1 Technical Considerations

A detailed description of the physical bases of NIRS can be found in articles that focus specifically on this subject [8, 9]. Briefly, NIRS analysis is based on the use of different near-infrared wavelengths. The different absorption and dispersion characteristics of light of various wavelengths can be used to both quantitatively and qualitatively evaluate biological tissue contents. When light reaches a biological tissue, its subsequent path depends on reflection, dispersion and absorption. Whereas reflection is dependent only on the angle of incidence of the light, dispersion and absorption depend on the light's wavelength. Light with longer wavelengths is less dispersed into the tissues, thus favouring infrared transmission, as it has longer wavelength within light spectrum. Absorption, however, is determined by the molecular properties of the tissue. Light in the visible portion of the spectrum (below ~700 nm) is completely absorbed by haemoglobin (Hb) and myoglobin. Moreover, visible light is highly dispersed, limiting its penetration into tissues. Near-infrared (between 700 and 1300 nm) has superior tissue penetration ability; it can pass through the skin into subcutaneous tissue, the underlying muscles or any other tissue. Therefore, the emitted light is not directly transmitted to the receptor, which is generally parallel to the emitter. The light path through the tissue (known as the 'optical path length', or PF) acquires a curved shape (the 'banana shape'), and the distance covered is longer than the emitter-receptor distance. Knowledge of the DPF is essential for quantitative NIRS measurements and is one of the primary components of the algorithm used in a given NIRS device. Near-infrared penetration is primarily dependent on the

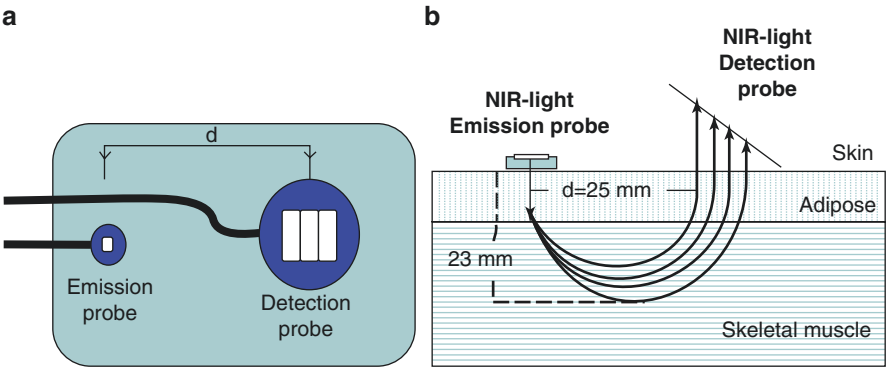

Fig. 11.1 Diagram of a distal tip of the NIRS optical cable. (**a**) With 25 mm spacing (d) between emission and detection probes, approximately 95% of the detected optical signal is from 23 mm of tissue penetration. (**b**) Note the curved shape of the light path (banana shape)

optical path through the tissue. The majority of sensors have a D-value between 2.5 and 3 cm, providing a tissue penetration ability of between 2.0 and 2.5 cm (Fig. 11.1). Therefore, near-infrared light crosses the skin, subcutaneous tissue, muscle and bone; brain and muscle tissues are therefore the easiest tissues to assess using NIRS.

11.2.2 Methodological Considerations

The difficulty to quantify the NIRS signal led to the development of different measurement methods. Currently, near-infrared spectrophotometers have variable degrees of sophistication, applicability, algorithms and wavelengths. It is generally accepted that at least four near-infrared wavelengths are required to differentiate the absorption spectra of different tissue chromophores. Continuous wave (CW) spectrophotometers are commonly used commercial devices. These apparatuses, however, do not provide quantitative measures of absolute chromophore concentrations but rather determine changes in concentrations from a baseline value, reflecting, therefore, changes in tissue oxygenation. This methodological limitation is based on the need to obtain accurate PF values for each wavelength and estimations of tissue light dispersion. Phase modulation and spatially resolved spectroscopy employ different algorithms to obtain tissue absorption coefficients and consequently are able to calculate absolute concentrations of tissue chromophores. These devices also use multichannel NIRS technology, i.e. several detectors at different distances within a same sensor, providing measurement of a larger portion of tissue. Although these spectrophotometers can quantify tissue chromophore concentrations, few studies have compared the different measurement methods currently in use. As these spectrophotometers use different algorithms, their quantifications will also differ,

rendering their clinical application making direct comparison of results obtained by different devices more difficult [10].

With the aim of designing devices for bedside use, some manufacturers have developed more easily operated spectrophotometers using simpler algorithms. Even though these do not provide absolute tissue chromophore concentrations, their ability to measure continuous StO_2 and other variables provides a continuous evaluation of tissue oxygenation at the bedside. At a technical level, NIRS spectrophotometers comprise a light detection microprocessor and a monitor. The device is connected to an optical fibre cable that has a light source connected to an optical sensor. The distance between the light emitter and the light receptor of the optical sensor varies from 12 to 25 mm. An optical converter is used to export the collected signals to the monitor, where the data are graphically displayed.

11.2.3 Parameters Measured with NIRS

Tissue oxygenation-related molecules that absorb near-infrared are primarily haemoglobin, myoglobin and mitochondrial cytochrome oxidase ($citaa_3$). The absorption peaks of these three components in the near-infrared region differ; deoxyhaemoglobin (Hb) and oxyhaemoglobin (HbO_2) have absorption peaks at 760 nm and 920 nm, respectively (Fig. 11.2). Although both Hb and HbO_2 are more strongly absorbed in the visible light spectrum (~500–600 nm), this wavelength of light cannot penetrate the tissue as deeply. $Citaa_3$ is the final electron transportation chain receptor in the internal mitochondrial membrane and is the endpoint for cellular aerobic metabolism. The absorption peak for $citaa_3$ in the near-infrared spectrum is between 800 and 865 nm. During hypoxaemia, $citaa_3$ is in the reduced state, altering its absorbance properties in the infrared spectrum.

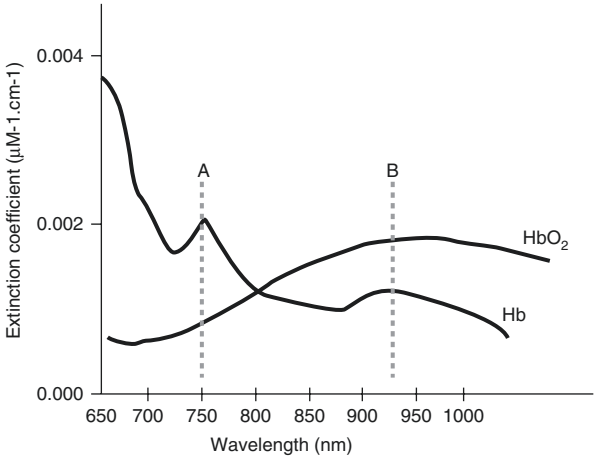

Fig. 11.2 Near-infrared spectrophotometer absorption spectra for oxyhaemoglobin (HbO_2) and deoxyhaemoglobin (Hb). Dotted lines correspond to peak Hb (line A) and HbO_2 (line B) absorptions [79]

Table 11.1 Directly near-infrared spectrophotometer measured parameters

Parameter	Unit	Modality	Physiological intervention to obtain the parameter
Peripheral tissue O_2 saturation (StO_2)	%	D	None
ΔHbO_2 and ΔHb	AU, μM	D (with PMS, SRS) or I	AO, VO
$Citaa_3$	μM	D	None
Peripheral O_2 consumption	$mLO_2\ min^{-1}\ 100\ g^{-1}$	I	AO, VO
Peripheral blood flow	$mLO_2\ min^{-1}\ 100\ g^{-1}$	I	VO
Deoxygenation velocity	%/min	D	AO
Reoxygenation velocity	%/min	D	AO

O_2 oxygen, *HbO_2* oxyhaemoglobin, *Hb* deoxyhaemoglobin, *Δ* difference in value prior to and following physiological intervention, *AU* arbitrary unit, *D* direct, *I* indirect, *AO* arterial occlusion, *VO* venous occlusion, *PMS* phase modulation spectroscopy, *SRS* spatially resolved spectroscopy, *s* seconds

NIRS-measured parameters may be calculated either direct or indirectly (Table 11.1). Directly calculated measurements depend on the device used. For example, phase modulation and spatially resolved spectroscopy provide absolute HbO_2 and Hb concentrations. Most NIRS devices provide information regarding changes in concentration from a baseline value at an arbitrary unit and tissue oxygen saturation, which is the clinically most relevant direct parameter. Measures calculated indirectly are obtained using physiological interventions to alter circulation at the assessed area; this is most frequently performed using arterial and, sometimes in addition, venous occlusion [5, 11]. This technique provides quantitative information regarding blood flow and local oxygen consumption.

11.2.3.1 Tissue Muscle Oxygen Saturation (StO_2)

Based on the Hb and HbO_2 concentration ratio, NIRS provides data to calculate StO_2, which is also expressed as tissue oxygenation index. This information can be derived from the equation $[HbO_2/(HbO_2 + Hb)] \times 100$, which is defined as the functional saturation percentage. StO_2 is a measure of blood oxygen saturation in the tissue area assessed by the spectrophotometer. Based on the tissue's blood distribution, the contribution of arteriolar, capillary and venous compartment to the NIRS signal is estimated to be 10%:20%:70%, respectively. Thus, resting StO_2 values measured by NIRS in normal conditions reflect mainly the venous compartment. However, the contribution of the different compartments is affected by many factors. In hypovolaemia, the decrease in effective circulating volume is more severe in the venous than in the arterial compartment, as there is severe constriction of the venous reservoir in order to redistribute blood to central compartments. Accordingly, StO_2 can be preserved for long periods of times even when cardiac output, tissue perfusion and venous saturations fall, as the respective contribution of arterial blood to venous blood will increase. On the other hand, in low cardiac output states with venous

congestion (cardiogenic shock and obstructive shock), the combination of arteriolar constriction, severe venous desaturation and venous stasis makes StO_2 decrease very rapidly. In sepsis, the microvascular shunting makes StO_2 minimally affected as it reflects the average value of the relatively large piece of tissue and it is thus unable to detect focal pouches of hypoxaemia [12]. Accordingly, several studies have failed to show a correlation between NIRS-determined StO_2 and actual venous blood saturation, in conditions other than low cardiac output [13–17]. Another application is the evaluation of the balance between peripheral tissue perfusion and local metabolic demand. During exercise the proportion of blood in the different vascular compartments is changed due to capillary recruitment together with some blood flow redistribution. Although venous, arterial and capillary blood contributions cannot be practically determined, StO_2 has been shown to be an excellent parameter for determining the balance between oxygen supply and oxygen demand [18].

11.2.3.2 Muscle Oxygen Consumption and Regional Blood Flow

Arterial and venous occlusion can be used to estimate muscle oxygen consumption. Using the venous and arterial occlusion methods, NIRS can be applied to measure oxygen consumption (mVO_2) and regional blood flow (BF) by following the rate of HbO_2 and Hb changes. In the venous occlusion method, a conventional pneumatic cuff is inflated in a stepwise manner to a pressure of approximately 50 mmHg, while measurements are obtained at several pressure levels. Such a pressure blocks venous occlusion, but does not impede arterial inflow. As a result, venous blood volume and pressure increase. NIRS can reflect this change by an increase in HbO_2, Hb and total haemoglobin [19]. Blood flow (BF) measurements using NIRS are calculated using venous occlusion method, which results in a volume increase of the distal part of examined limb due to continuous arterial blood flow combined with blocked venous outflow. BF is calculated as a linear function of total haemoglobin (HbO_2 + Hb) during occlusion. Absolute concentration variations of HbO_2 and Hb (ΔHbO_2 and ΔHb) are expressed as $\mu M\ s^{-1}$. Using laboratory-assessed blood haemoglobin levels, BF is calculated and converted into units of $mL\ min^{-1}\ 100\ mL^{-1}$. These calculations can only be obtained from NIRS devices that provide quantitative HbO_2 and Hb data. Muscle VO_2 is thereafter computed from the flow and the difference between StO_2 at fully arterialized state and baseline values.

The arterial occlusion method is much simpler and provides estimates of muscle VO_2 and microvascular reactivity but no information on absolute blood flow. In this technique, the pneumatic cuff is inflated to a pressure of approximately 30 mmHg greater than systolic pressure, blocking both venous outflow and arterial inflow. Depletion of local available O_2 is monitored by NIRS as a decrease in HbO_2 and a simultaneous increase in Hb, whereas total Hb remains constant. For venous occlusion, mVO_2 is calculated using the rate of Hb increase. As venous blood flow is blocked, the increase of Hb levels is primarily due to conversion of HbO_2 to Hb, therefore reflecting mVO_2. The calculation of mVO_2 using arterial occlusion is based on the same principle as venous occlusion. The difference is that blocking both arterial and venous blood flow results in a static blood compartment where HbO_2 levels drop as a direct result of mVO_2, which displaces oxygen from

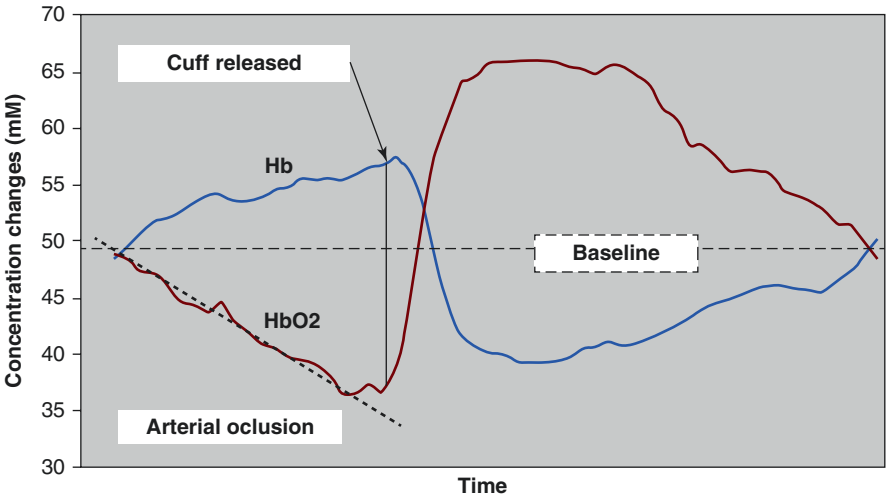

Fig. 11.3 Quantitative NIRS measurements during arterial occlusion. After the release of the occluding cuff, blood volume increases rapidly, resulting in an increase in HbO_2 and a quick washout of Hb, followed by a hyperaemic response. Oxygen consumption is calculated as the rate of decrease of HbO_2 indicated by the dotted line

haemoglobin (Fig. 11.3). Absolute HbO_2 and Hb concentration changes (ΔHbO_2 and ΔHb) are expressed in units of $\mu M\ s^{-1}$. Considering the molecular relationships between haemoglobin with oxygen (i.e. 1:4) and the molecular weight of haemoglobin, mVO_2 can be indirectly obtained and converted into units of $mLO_2\ min^{-1}\ 100\ g^{-1}$. The release of the clamp and computing of the ascending slope are an excellent reflection of microvascular reactivity (see below).

11.2.3.3 Rate of StO_2 Deoxygenation

An alternative method exists for estimating mVO_2 using devices that do not return absolute concentrations, which is determining the rate of StO_2 decrease during an ischaemic period, normally calculated during a 3-min arterial occlusion and expressed as StO_2 variation in %/min (Fig. 11.4). This parameter was only recently introduced in the intensive care setting and has not been properly evaluated. The drop in StO_2 during arterial occlusion is believed to reflect the local oxygen extraction rate at the NIRS-assessed area; this analysis may provide an important estimate of the balance between oxygen supply and oxygen demand [5].

11.2.3.4 Rate of StO_2 Reoxygenation

The rate of StO_2 reoxygenation is calculated as the velocity of StO_2 increase between the end of arterial occlusion (starting after the pneumatic cuff is emptied) and the degree of maximal reoxygenation during reactive hyperaemia. After the release of the occluding cuff, a hyperaemic response is observed (Fig. 11.4). Blood volume

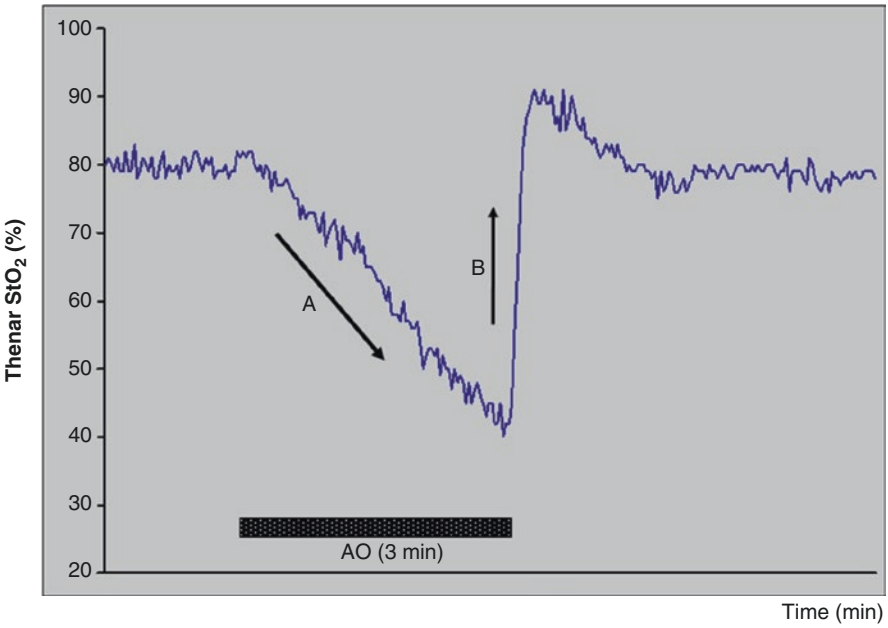

Fig. 11.4 Tissue muscle oxygen saturation (StO_2) during 3 min of arterial occlusion (AO). (**a**) Rate of StO_2 deoxygenation: the velocity at which StO_2 decreases during AO, expressed as %/min. Rapid deoxygenation rate corresponds to higher oxygen extraction rates. (**b**) Rate of StO_2 reoxygenation: the velocity at which StO_2 increases from cuff release to the maximal reoxygenation during reactive hyperaemia. Reflect mainly microcirculatory vascular reactivity

increases rapidly, resulting in an increase in HbO_2 and a quick washout of Hb. This overshoot of StO_2 represents the balance between arterial blood inflow and mVO_2 and depends mainly on microcirculation function. Delayed reoxygenation velocity implies microcirculatory changes, e.g. those that occur with severe sepsis. Of note, microvascular reactivity, as assessed by NIRS, may differ from microvascular perfusion. Indeed, the hypoxic challenge represents an extreme stimulation. One may make the following analogy: NIRS ascending slope represents the maximal acceleration of a car, while microvascular perfusion represents the actual speed of this car in the actual traffic conditions.

11.2.3.5 Mitochondrial Cytochrome Oxidase ($Citaa_3$)

$Citaa_3$ remains reduced during oxygen deprivation, resulting in a loss of its near-infrared absorbance. NIRS is able to detect this change during intracellular dysoxia conditions; however, monitoring this parameter is still technically complicated because tissue $citaa_3$ concentrations are low compared to haemoglobin and because these changes are not synchronized with the ischaemic insult. Simultaneous $citaa_3$ and StO_2 measurements allow for the detection of cellular

dysoxia secondary to mitochondrial dysfunction. In normal conditions, changes in StO_2 and $citaa_3$ are coupled, i.e. when StO_2 decreases, $citaa_3$ is in the reduced state, and when StO_2 levels increase, $citaa_3$ is less reduced. When StO_2 and $citaa_3$ changes are disparate (e.g. more reduced $citaa_3$ with normal or high StO_2 levels), one may anticipate that it reflects either microvascular shunting or mitochondrial dysfunction.

11.2.4 Clinical Uses of NIRS

NIRS is currently useful in a number of clinical conditions, and although it can be applied in any organ, it has been primarily used for the assessment of brain and muscle tissue oxygenation. Cerebral NIRS monitoring is used in surgical procedures with high brain ischaemia risks, such as carotid endarterectomy, brain aneurism surgeries, brain perfusion monitoring during extracorporeal circulation and head trauma. A recent application of cerebral NIRS is veno-arterial ECMO, especially when there is a risk of desaturation of ascending aortic blood flow. Apart for cerebral NIRS in these specific settings, the use of NIRS in the intensive care setting and in emergency medicine has mostly focused on peripheral muscle oxygenation [20]. Monitoring muscle oxygenation is used for the following reasons: (a) peripheral muscle tissue is easily accessible compared to brain tissues; (b) during shock, brain oxygenation is maintained at the expense of blood flow redistribution from peripheral tissues to vital organs; and (c) vascular control mechanism in the muscle tissue is more sensitive to systemic perfusion alterations due to its predominant sympathetic control. Therefore, the physiological base for the use of NIRS in critically ill patients is based on the fact that monitoring peripheral perfusion can be used as early marker of tissue hypoperfusion [21].

11.2.4.1 Trauma

Experimental models of animal haemorrhagic shock have shown that NIRS-determined StO_2 can be used as a resuscitation parameter [22–25]. In these studies, a predefined 50% StO_2 value in peripheral muscle was showed to reflect appropriate systemic oxygen supply. Moreover, muscle StO_2 values were shown to be low even with normal systemic resuscitation parameters, corroborating the idea that normalizing conventional haemodynamic parameters does not restore oxygenation to all tissue vessels.

Studies investigating the usefulness of NIRS for peripheral monitoring in trauma patients have been focused mainly on shock resuscitation. The primary differences among these trials were related to the part of the body at which StO_2 was assessed, which were the deltoid area and the thenar eminence [18, 26–30]. From these studies, it is clear that StO_2 is lower in the deltoid muscle than at the thenar eminence. This difference may be explained by the larger subcutaneous tissue layer in the deltoid region, which may faint the NIRS signal from the muscle, as will be discussed below. In addition, some studies performed in healthy subjects have showed

low sensitivity of thenar StO_2 to detect changes in central blood volume in a model of hypovolemia induced by lower limb negative pressure [31, 32]. However, the advantage of assessing StO_2 at the thenar eminence is the feasibility of the arterial occlusion test, allowing the mVO_2 and microcirculation function to be estimated, i.e. a more complete evaluation of peripheral perfusion. In spite of this difference, independent of the assessed region, the prognostic value of StO_2 comes from repeated measurements performed within the first hours of resuscitation and not from one time point.

11.2.4.2 Severe Sepsis and Septic Shock

Although a large number of clinical trials have investigated StO_2 in septic patients, few were able to report any predictive value of baseline StO_2. Even when differences exist between survivors and non-survivors, the overlap between groups is large and does not allow individual prediction. Some authors have even shown similar StO_2 values for healthy subjects and septic patients, while others have shown lower StO_2 values for septic shock patients when compared with healthy subjects. This inconsistency is speculated to be related to different types of resuscitation as well as to the time of measurement. However, a prospective observational study demonstrated that repeated StO_2 assessments in septic patients within the first hours of ICU admission were predictive of unfavourable outcomes [33]. In this study, the lack of StO_2 normalization, as shown by a sustained StO_2 below 70% within the first 8 h following resuscitation, was reported to be associated with organ and metabolic dysfunctions.

NIRS can be used in sepsis to evaluate the integrity of the microvasculature and mVO_2 with the analysis of changes in StO_2 during the vascular occlusion test. Studies applying these methods have shown discrepant mVO_2 results and challenge the effectiveness of NIRS as a noninvasive regional oxygenation assessment method [34, 35]. However, these differences are most likely related to the different device models and the study designs used, e.g. measurements did not include repeated mVO_2 assessments prior to or following any therapeutic intervention. The rate of StO_2 deoxygenation was also observed to be significantly correlated to the SOFA (sequential organ failure assessment) score ($r = 0.79$). The pathophysiological mechanism of StO_2 deoxygenation during the ischaemic period is related to alterations in the diffusive transport of oxygen in microcirculation [16].

The predictive value of StO_2 reoxygenation rate has been shown to be strongly associated with the severity of organ dysfunction and mortality in patients with septic shock, highlighting the ability of NIRS to continuously monitor microcirculation reactivity in septic patients [36–39]. Of special note, these studies applied different methods of VOT. This is of special interest because there is a lack of agreement on standardization for the appropriate method for performing a VOT [40, 41]. When measured at the thenar eminence, NIRS-derived measurements are influenced by the peripheral circulation condition [42]. Nevertheless, when used in

conjunction with other peripheral perfusion methods, repeated StO_2 monitoring has the potential to assess the effect of therapeutic intervention on the peripheral microvascular circulation in various shock states [43–45].
Other clinical uses in intensive care medicine include diagnosing lower limb compartment syndrome [46–48] and the assessment of brain vascular reactivity in sepsis [49]. Some studies have compared central venous oxygen saturation with thenar StO_2 measurements in septic patients and failed to show a strong correlation between these two parameters [50]. A plausible explanation may be that StO_2 is much more related to the peripheral perfusion status than with the systemic haemodynamic, emphasizing that microcirculation and macro-haemodynamic measurements cannot be directly related [42].

11.2.5 NIRS Limitations

The main limitations of NIRS include the following: (a) the influence of the bone or fatty tissue thickness on assessments performed in the brain and muscle, respectively; (b) the role of myoglobin on tissue oxygenation assessments; (c) the influence of interstitial oedema on the NIRS signal; and (d) lack of standardization for VOT technique. Regarding brain oxygenation monitoring, modern devices can account for bone thickness by the appropriate modification of the distance between the light emitter and the receptor, thereby improving NIRS sensitivity [51]. The role of fatty tissue interference is still controversial in the literature, most likely due to the different methodologies and devices used in the trials. However, tissue oxygenation variations are considered primarily from regions of the muscle, even when fatty tissues are as thick as 1.5 cm [52, 53]. Haemoglobin and myoglobin absorption spectra are superimposed, and because their absorption spectra are identical, NIRS is not able to discriminate between them. Experimental studies have shown that the signal from myoglobin corresponds to only 10% of the absorbed light and that myoglobin saturation is stable even during conditions that impair cell oxygen transportation [6, 54]. Therefore, the majority of the NIRS signal is considered to come from haemoglobin. The effect of tissue oedema gained interest following the introduction of NIRS for the assessment of peripheral oxygenation in septic shock patients with interstitial oedema from vascular leakage syndrome. One study showed that the degree of interstitial oedema may affect NIRS oxygenation measurements. However, this influence is less important when NIRS is used in muscle areas that are less impacted by oedema, such as the thenar region [55]. The technique for using VOT has not been standardized. Currently, various types and degrees of deflation thresholds (StO_2 of 10 or 40%; duration of 3 or 5 min) are used, and no supporting evidence in the literature shows which of the methods is superior and more reliable to assess the VOT-derived StO_2 slopes. These highlight a necessary further step in evaluating the NIRS clinical utility and its possible use in predicting complications and early identification of patients at risk for microcirculatory failure. Even though

attractive by its fully noninvasive nature, we have to admit that this technique failed to reach routine clinical use. The main reason is that it was relatively insensitive, alterations in basal StO_2 occurring only when major blood losses already occurred, so that the severity of these patients was often already recognized by classical means, including clinical evaluation.

11.3 Plethysmographic Signal of Pulse Oximetry

The plethysmographic signal of pulse oximetry or peripheral perfusion index (PPI) has been used to evaluate changes in peripheral vasomotor tone. Pulse oximetry is a monitoring technique used in probably every trauma, critically ill and surgical patient. The principle of pulse oximetry is based on two light sources with different wavelengths (660 and 940 nm) emitted through the cutaneous vascular bed of a finger or earlobe. The Hb absorbs more light at 660 nm, and HbO_2 absorbs more light at 940 nm. A detector at the far side measures the intensity of the transmitted light at each wavelength, and the oxygen saturation is derived by the ratio between the red light (660 nm) and the infrared light (940 nm) absorbed. As other tissues also absorb light, such as connective, bone and venous blood, the pulse oximetry distinguishes the pulsatile component of arterial blood from the non-pulsatile component of other tissues. Thus, using a two-wavelength system, the non-pulsatile component can be discarded, and the pulsatile component is used to calculate the arterial oxygen saturation. The overall haemoglobin concentration can be determined by a third wavelength at 800 nm, which resembles the spectrum for both Hb and HbO_2. The resulting variation in intensity of this light can be used to determine the variation in arterial blood volume (pulsatile component). The PPI is calculated as the ratio between the pulsatile component (arterial compartment) and the non-pulsatile component (other tissues) of the light reaching the detector of the pulse oximetry, and it is calculated independently from the patient oxygen saturation (Fig. 11.5).

While pulse oximetry has limited value in the evaluation of tissue perfusion, PPI can be used to evaluate peripheral perfusion. Altered peripheral vascular tone is accompanied by variation in the pulsatile component and as the non-pulsatile component does not change the ratio changes. As a result, the value displayed on the monitor increases with peripheral vasodilation and decreases with peripheral vasoconstriction. This was first demonstrated in a model of axillary plexus-induced vasodilatation, and the analgesic effect of this nerve block could be predicted within minutes using the increase in PPI as a measure of concomitant peripheral vasodilatation in patients undergoing hand surgery [56]. Similarly, the PPI was shown to be rapidly reduced following sympathetic response-induced vasoconstriction after the introduction of a nociceptive skin stimulus [57] or an intravenous injection of epinephrine [58] or norepinephrine [59]. Furthermore, in a lower body negative pressure model, the PPI also rapidly decreased following sympathetic activation in healthy volunteers who underwent stepwise decreases in venous return [60]. In a large population of healthy volunteers, the median PPI value was

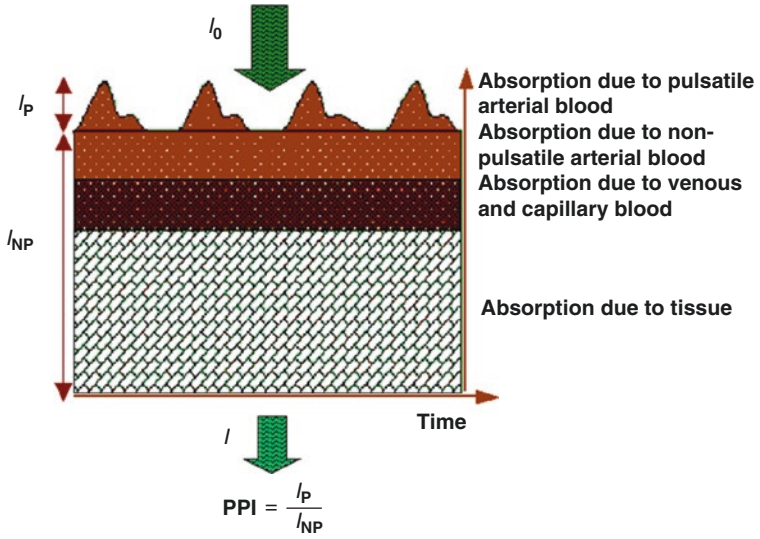

Fig. 11.5 The pulsation of arterial blood causes a pulsating volume variation. PPI is calculated as the ratio between the arterial pulsatile component (I_P) and the non-pulsatile component (I_{NP}). *PPI* peripheral perfusion index, I_0 source light intensity, *I* light intensity at the detector

1.4% [61]. In critically ill patients, the same value was found to represent a very sensitive cutoff point for assessing peripheral vasomotion, with values lower than 1.4% indicating peripheral vasoconstriction, as defined by a prolonged CRT and an increased skin temperature difference [61–63]. This cutoff value, however, may vary depending on the device manufacturer. For example, a different cutoff value of PPI < 0.2 was found to be associated with a poor outcome in a series of 46 septic shock patients [64].

One of the main limitations of PPI measurements is the influence of the movement artefacts associated with the pulse oximeter signal. This can be either by patient motion or by fibre movements in the pulse oximeter probe. Nevertheless, the inclusion of PPI into the pulse oximetry signal is a recent advance in clinical monitoring, and it can be easily obtainable for monitoring peripheral vascular tone in critically ill patients.

11.4 Laser Doppler Flowmetry

Laser Doppler flowmetry (LDF) is a noninvasive, continuous measure of microcirculatory blood flow, and it has been used to measure microcirculatory blood flow in many tissues including the neural, muscle, skin, bone and intestine. The principle of this method is to measure the Doppler shift—the frequency change that light undergoes when reflected by moving objects, such as red blood cells. LDF works by illuminating the tissue under observation with a monochromatic laser from a probe.

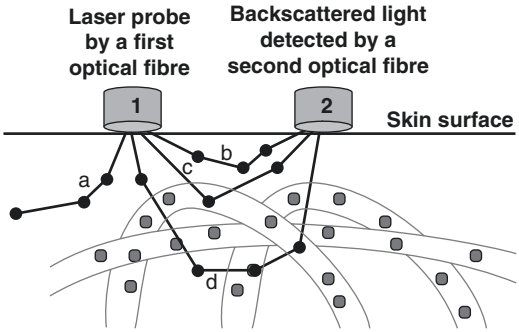

Fig. 11.6 Schematic diagram of the laser Doppler flowmetry. When the tissue is illuminated by a laser source (1), 93–96% of the light is either absorbed by various structures or undergoes scattering (**a**, **b**). The remaining 3–7% is reflected by moving red blood cells (**c**, **d**) and returns to the second optical fibre (2). Microvascular perfusion is defined as the product of mean red blood cell (RBC) velocity and mean RBC concentration in the volume of tissue under illumination from the probe

When the tissue is illuminated, only 3–7% is reflected. The remaining 93–96% of the light is either absorbed by various structures or undergoes scattering. Another optical fibre collects the backscattered light from the tissue and returns it to the monitor (Fig. 11.6). As a result, LDF produces an output signal that is proportional to the microvascular perfusion [65]. Depending on the device and the degree of invasiveness, it can be used to assess blood flow in muscle, gastric, rectal and vagina mucosae [66, 67]. But as a noninvasive measure of peripheral blood flow, its use is limited to the skin [65]. LDF has been applied to obtain information on the functional state of the skin microcirculation during reactive hyperaemia in several conditions, such as diabetes mellitus, essential hypertension, atherosclerosis, cardiopulmonary bypass and sepsis [67, 68]. A major limitation of this technique is that LDF does not take into account the heterogeneity of blood flow as the velocity measurements represent the average of velocities in all vessels of the window studied. In addition, skin blood flow signal varies markedly depending on probe position. No current laser Doppler instrument can present absolute perfusion values (e.g. mL/min/100 g tissue), and measurements are expressed as perfusion units, which are arbitrary.

LDF has been useful to evaluate endothelium-dependent vascular responses in the skin microcirculation during either reactive hyperaemia [68, 69] or the noninvasive local application of acetylcholine or sodium nitroprusside [70–72]. This characteristic of LDF was used in critically ill patients to evaluate endothelial dysfunction in sepsis. Observational studies have shown that the hyperaemic response in septic patients is decreased, and a relationship between changes in vasculature tone and severity of sepsis has been described [73–75]. In addition, restored vasomotion in patients with sepsis evaluated by LDF seems to be associated with a favourable prognosis [74]. The ability of LDF to assess abnormalities of skin blood flow

control in sepsis could be of clinical use for early detection of microcirculatory derangements in high-risk patients.

A recent advance in LDF is laser speckle contrast techniques based on speckle contrast to develop techniques for measuring skin perfusion [76]. Conventionally, speckle flow techniques are based on the changes over time of the dynamic speckle sequence generated by movement, and this changing speckle sequence is recorded with a camera. The movement of the particles alters the speckle sequence over time, and this dynamic behaviour is mainly caused by the Doppler shifts of the light that interacts with the moving particles. Since laser speckle is a scanning technique, clinical research applications are mainly used where a non-contact measurement is a necessity. Therefore, gastric surgery and neurovascular surgery are some examples of clinical application of laser speckle imaging [77, 78].

11.5 Conclusions (or Summary)

Advances in tissue monitoring technologies have established noninvasive optical monitoring as a modality of considerable value in the critical care setting for tissue monitoring in shock. Different optical techniques are available for evaluation of tissue perfusion at bedside. These mostly provide indirect information and changes over time, either spontaneous or during occlusive tests.

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Transcutaneous O_2 and CO_2 Monitoring

12

Diego Orbegozo-Cortès and Daniel De Backer

12.1 Introduction

Electrodes to measure transcutaneous blood gases were initially developed for the noninvasive evaluation of arterial blood gases. The first experimental device was presented in 1960 by Severinghaus [1]. Rapidly different groups started to work with a modified Clark-type electrode to measure the transcutaneous (TC) PO_2, and their results were presented in the 1970s by different publications [2]. The same modification was performed in the CO_2 electrode to obtain TC PCO_2 values and presented in 1978 [3].

Taking into account that cutaneous PO_2/PCO_2 measurements are affected by perfusion, this technology can also be used to evaluate tissue perfusion.

12.2 Determinants of Tissue PO_2 and PCO_2

Tissue PO_2 represents the balance between local metabolism and local oxygen delivery. Local oxygen delivery depends on arterial PO_2, hemoglobin, and local perfusion. Local perfusion is influenced by cardiac output and perfusion pressure, which regulate perfusion of the whole organ. At the tissue level, microvascular perfusion plays a critical role.

Tissue PCO_2 also represents the balance between local metabolism (CO_2 production) and perfusion but is also affected by the arterial PCO_2. Hence, it is often more useful to report PCO_2 gap, the difference between tissue and arterial PCO_2, than

D. Orbegozo-Cortès
Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium

D. De Backer (✉)
Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium

CHIREC Hospitals, Université Libre de Bruxelles, Brussels, Belgium
e-mail: ddebacke@ulb.ac.be

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Table 12.1 Interpretation of tissue PO_2/PCO_2

	Tissue PO_2	Tissue PCO_2	Tissue PCO_2 gap
Normal condition	40 mmHg	45 mmHg	<7 mmHg
Increased metabolism	↓	↔	↔
Decreased metabolism	↑	↔	↔
Low flow	↓↓	↑↑	↑
Stagnant hypoxia	↓↓↓	↑↑↑	↑↑↑
Anemia	↓↓	↔	↔
Anemic hypoxia	↓↓↓	↔	↔
Hypoxemia	↓↓	↔	↔
Hypoxic hypoxia	↓↓↓	↔	↔
Hypercapnia	↔	↑	↔
Heterogeneous perfusion	↑	↑	↑
Heterogeneous perfusion + tissue hypoxia	↑	↑↑↑	↑↑

tissue PCO_2 alone. To overcome the influence of $PaCO_2$ on tissue PCO_2, it is convenient to use the PCO_2 gap (tissue-arterial CO_2 gradient, normal $\leq$ 6 mmHg). Very high PCO_2 gap values may in addition suggest the presence of tissue hypoxia [4], while moderately elevated PCO_2 gaps may represent either flow stagnation or tissue hypoxia. Of note in anemic and hypoxic hypoxia, PCO_2 gap may remain constant as a result of the washout phenomenon induced by the high perfusion.

The interpretation of PO_2 and PCO_2 is summarized in Table 12.1. In normal conditions, tissue metabolism (thus, VO_2 and VCO_2) is coupled with tissue perfusion. When metabolism increases, all the CO_2 produced is washed out so that PCO_2 gap remains constant. However, there is some reserve in O_2 extraction in order to spare cardiac output, so that tissue PO_2 slightly decreases when metabolism increases (and PO_2 increases when metabolism decreases).

The most difficult situation to interpret is when heterogeneity in perfusion occurs, as in sepsis [5, 6]. In these conditions, the heterogeneity in perfusion is associated with heterogeneity in PO_2 and PCO_2. Interestingly, the electrodes used for tissue PO_2/PCO_2 monitoring are sensitive to the highest value in the environment: these will capture the high PO_2 of the shunted vessels while being insensitive to the low values of the dysoxic areas. On the other hand, the PCO_2 electrode will capture the high PCO_2 values of the stagnant/not perfused areas while being insensitive to the highly perfused areas. Hence, tissue PCO_2 monitoring, including transcutaneous PCO_2 [7] as well as venous PCO_2 [8], can reflect microvascular alterations in heterogeneous flow conditions such as in sepsis.

12.3 Basic Concepts of Transcutaneous PO_2/PCO_2 Measurements

The main problem to measure the TC CO_2 and O_2 pressures is the potential pollution of the measurements by room air making necessary to create a microenvironment enclosing a selected skin area and then using some technology to measure the gas

pressures or concentrations. The commercially available machines measuring TC O_2 and CO_2 use the same technology found in the Stow-Severinghaus-type electrode to measure CO_2 and in the Clark-type electrode to measure O_2. By the way, this is the exactly the same principle used every day in blood gas analyzers. The principle of the measurements is quite simple. Initially blood gases must diffuse through the skin into a closed liquid-filled chamber. From there CO_2 and O_2 must diffuse through a special semipermeable membranes to reach the space where the CO_2 and O_2 electrodes are placed. The Clark-type electrode generates a current that is proportional to the O_2 tension. For the Stow-Severinghaus-type electrode, the dissolved CO_2 generates a change in the H^+ and $HCO3^-$, thus modifying the pH in proportion to the CO_2 concentration.

The first version for a TC PO_2 electrode was available in 1972 [2] and the first version for a TC PCO_2 electrode in 1978 [3]. Rapidly, the TC probes were modified to incorporate in the same case both electrodes with special membranes [9].

An important limit to O_2 and CO_2 monitoring through the skin is that the diffusion of these gases is limited by the skin barrier (epithelium) and, more importantly, that the measurement represents a mixture of venous, capillary, and arterial values.

Heating the skin was suggested, as heating the skin from 37 to 45 °C increases the skin blood flow by three to four times [10]. Accordingly, heating opens the precapillary sphincters, increasing importantly the contribution of arterial blood flow. Indeed the TC O_2 and CO_2 values became closest to the arterial values by increasing the temperature of the probe [9, 11–14].

Also the diffusion of the gases is affected by the temperature. Hence heating reduced the response time of this technology to 10 s [9, 11, 12]. This allows this technology to track continuous changes in the blood gas contents noninvasively.

Of note all TC monitoring systems require some time before displaying PO_2 and PCO_2 results, as there are first a calibration period (exposing the probe to known CO_2 and O_2 concentrations) and then a stabilization period to allow diffusion of the gases into the probe case [12]. The calibration time differs according to the manufacturer but does not take more than few minutes, and the stabilization time is around 10–15 min but sometimes needing 22 min [9].

Even with new TC O_2 and CO_2 monitors, the probe temperature is a key factor, and higher temperature is related to lower stabilization times before to start the definitive measurements and with more precision and lower bias when comparing the TC values to the BGA values [12].

However, heating the probes is associated with several potential issues.

First, heating increases local metabolism, affecting local PCO_2 and PO_2. During the first studies using this technology, some researchers noted that at higher temperatures the electrode sometimes measured lower values for the O_2 [9] and a paradoxical increase in the TC CO_2 with increases in the temperature [3]. This finding can be explained by an increased skin local metabolism leading to a higher oxygen consumption and a higher CO_2 production [3, 9]. Subsequent experiments showed that using special liquids that reduce the local metabolism (putting them in the closed liquid filling chamber between the skin and the electrode membranes) improved the accuracy of the measurements [15, 16]. However, the magnitude of

this effect on the TC O_2 and CO_2 measurements is limited, and these liquids are rarely used.

Second, heating the skin can thermally injure the skin. The probability of thermal injury is related to the used temperature and the time of exposure [17]. Exposure of the skin to 44 °C can lead to some degree of thermal injury if the time of exposure is as long as 5 or 6 h [17]. Heating the probe may not be a problem if the monitor is not used for a prolonged time; however the probes are often kept in place for long periods. Some studies in babies have reported some degree of erythema in the explored area [18, 19]. However, major adverse events have never been reported some major adverse event with this technology. To prevent potential thermal injury, manufacturer recommendations propose to reposition the electrode every 6 h.

The main limitation of heating the probe is that it "arteriolizes" the area so that the measurement reflects arterial blood gases rather than tissue PO_2/PCO_2. It has been suggested recently to use these monitors with a probe at usual skin temperature (37 °C) in order to evaluate regional tissue PO_2/PCO_2. The risk of thermal lesion will be limited; however the calibration time and equilibration times remain important limitations.

There are some other limitations independent of heating the probe that also affect tissue PO_2/PCO_2 estimation. The corneal stratum and the skin thickness can limit blood gas diffusion and diminish the TC-obtained values. Gently rubbing the skin and partially removing the stratum corneum before applying the probes to the skin can increase the TC O_2 values and diminish the gap between the TC and arterial values [10, 20, 21]. The potential role of tissue edema has not been investigated.

Finally, a drift can occur during prolonged periods of monitoring. Sometimes the TC values tend to increase or decrease progressively with prolonged monitoring periods (drift). Janssens and colleagues monitored the TC CO_2 during 8 h at 43 °C, and they did not detect any drift in the signal [22]. Similarly, Rodriguez and colleagues registered continuously the earlobe TC CO_2 in 50 critically ill patients for a mean of 17 h without any change deterioration in bias and limits of agreement with repeated measurements [13]. Whether this may or not occur without heating the probe remains to be determined.

12.4 Validation Studies

Several studies show a good correlation between the TC values and the BGA, especially for the CO_2 with a good linear correlation and a small bias [23–26]. In general half of the TC CO_2 values would be inside ±5 mmHg (compared to the $PACO_2$), and almost all values are inside ±10 mmHg (compared to the $PACO_2$) [23, 25]. As an example Bendjelid and colleagues evaluated the performance of the earlobe TC CO_2 in a mixed population of ICU patients, obtaining 19% of the measurements outside of a tolerable clinical relevant zone of ±7.5 mmHg, so concluding that BGA is still needed in critically ill patients [23]. Some researchers have tried to identify the different factors that can affect the agreement between TC O_2 and CO_2 measurements

[24, 27]. In a cohort of critically ill patients, Hasibeder and colleagues described the PaO_2 and mean arterial pressure only explaining 40% of the variability. The main factors affecting the TC CO_2 were the $PaCO_2$ and cardiac index, but these contributed to only 66% of the variability [28]. That confirms that other not measured factors (skin characteristics, edema, local blood flow, etc.) can affect the obtained TC values and that probably they need to be taken into account when interpreting the results.

Another interesting finding was reported using earlobe transcutaneous PCO_2 monitoring during cardiac arrest: lower TC CO_2 values were correlated with shorter times to achieve a restore of the spontaneous circulation (ROSC) and that a progressive increase in their values was correlated with worse outcomes [29]. Unfortunately, arterial PCO_2 was not measured in that study, so that it is difficult to determine whether the elevated TC CO_2 represented higher arterial PCO_2 levels or impairments in tissue perfusion.

12.5 Indirect Evaluation of Tissue Perfusion with Transcutaneous PO_2/PCO_2 Measurements

Rapidly, the relevance of local blood flow on the PO_2/PCO_2 values has been recognized [11, 13, 30–33]. In an elegant experimental study, Tremper and colleagues monitored the TC CO_2 in anesthetized dogs while manipulating cardiac output [11]. They reported that a decrease in cardiac output was accompanied by an increase in the TC CO_2 despite that $PaCO_2$ remained constant, and this effect was even more important when the probe temperatures were lower (not heated). Similar observations have been obtained in humans: in conditions where $PaCO_2$ remained stable, changes in the TC CO_2 were mainly explained by important hemodynamic changes. In some cases sometimes an increase in the TC CO_2 value preceded the development of cardiac arrest or low cardiac output states [30–33]. Critically ill patients with poor skin perfusion present high gaps between the measured TC CO_2 and the $PaCO_2$ [13].

To evaluate tissue perfusion in critically ill patients in a more standardized way, two alternatives have been used: (a) to do not heat the probes and collect data at skin temperature and (b) to perform a functional test.

Using the probe at skin temperature led to higher TC CO_2 values and lower TC O_2 values, increasing the gap with the $PaCO_2$ and PaO_2 and increasing the probe response time [9, 11, 12]. By applying the probe at a standardized 37 °C temperature, lower values of TC PO_2 were observed in patients with arterial occlusive disease than in healthy volunteers and higher values of TC PCO_2 in diabetic patients than in healthy volunteers or nondiabetic patients [34].

Vallée and colleagues monitored the earlobe TC CO_2 at 37 °C and calculated the difference between TC PCO_2 and $PaCO_2$ as a surrogate of the tissue blood flow in a cohort of septic and non-septic patients. They found higher TC CO_2 and TC-$PaCO_2$ values in septic patients than in the control group and higher TC-$PaCO_2$ values in the non-survivors than in the survivors with a progressive increase over the time [7].

Also in a recent study, Neuschwander and colleagues monitored the earlobe TC CO_2 at 37 °C in patients undergoing pump cardiac surgery showing that TC CO_2 values are affected in some degree by the $PaCO_2$, the mean arterial pressure and the temperature, but the TC CO_2 or the TC-$PaCO_2$ was not correlated with the postoperative outcomes [27].

The second option is to perform a functional or provocative test while continuously monitoring the TC CO_2 or CO_2 values. Initial reports performed a vascular occlusion test (VOT) using a cuff that was inflated over the arterial systolic pressure for a transient period of time while monitoring the TC O_2 [34–38]. These reports show a good reproducibility of the test while observing a transient increase of the TC O_2 values after the ischemic periods.

An alternative functional test is to increase the FiO_2 and look for the changes in the TC O_2 monitoring with a heated electrode [39–41]. This approach has been largely studied in the arterial occlusive diseases used and is recommended in the vascular field: patients with arterial occlusive diseases increasing the TC O_2 by more than 10 mmHg after 10 min of a high FiO_2 less frequently require amputation, and this test was a better predictor of amputation than the basal TC O_2 or other regularly used clinical parameters [39]. A similar approach has been investigated by different teams in septic patients [40, 41]. The basal TC CO_2 or TC O_2 values were not different when comparing survivors with non-survivors, but the increase in the TC O_2 after increasing the FiO_2 to 100% for 10 min was higher in the survivors than in non-survivors [40, 42]. Of note, Mari et al. [43] however noticed that these oxygen challenge tests should be cautiously interpreted in patients with altered pulmonary function, as the impairment in respiratory function can alter the test independently of any hemodynamic alteration.

Conclusions

The TC monitoring of CO_2 and O_2 is a relatively simple and promising noninvasive technic that has evolved during the last decades. While performing measurements at a skin temperature of 43–45 °C, obtained values are highly affected by the arterial values for the $PACO_2$ and PO_2, and measurements at 37 °C can be used to indirectly evaluate tissue blood flow. Promising results have been reported using this technology in functional tests like vascular occlusion tests or oxygen challenge tests.

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Regional Capnography

13

Jihad Mallat and Benoit Vallet

13.1 Introduction

Early recognition and adequate correction of tissue hypoperfusion are of great importance in the management of critically ill patients with shock to prevent the development of multiple organ dysfunctions and to improve outcome [1, 2]. Early aggressive resuscitation targeting macrocirculatory parameters has been recommended for the management of shock states [3, 4]. However, even if optimizations of macrocirculatory parameters are achieved, inadequate oxygen supply and compromised tissue perfusion can persist, leading to organ failure [5, 6]. Indeed, global hemodynamic and oxygen-derived variables may be normal despite evidence of tissue hypoxia and, therefore, fail to reflect both the imbalance between oxygen demand/oxygen supply and the microcirculatory deficit, especially in sepsis [7]. This causes difficulties in interpreting oxygen-derived variables in revealing tissue hypoxia: a low oxygen consumption may be due to a diminished oxygen demand without hypoxia [8] or to tissue hypoxia by a whatsoever process (e.g., sepsis, hypovolemia). This may be a consequence of the microcirculatory shunting and/or the inability of the tissues to use oxygen (cytopathic hypoxia) [9–11]. Thus, systemic oxygen-derived variables are nonspecific and not capable of detecting regional hypoperfusion.

While commonly measured in critically ill patients, elevated blood lactate is an insensitive marker of tissue hypoxia and hypoperfusion [12–18]. Other non-hypoxic

J. Mallat (✉)
Department of Anesthesiology and Critical Care Medicine, Service de Réanimation polyvalente, Centre Hospitalier du Dr. Schaffner de Lens, Lens, France

B. Vallet
Department of Anesthesiology and Critical Care Medicine, Centre Hospitalier Universitaire de Lille, Lille, France
e-mail: Benoit.VALLET@chru-lille.fr

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mechanisms such as accelerated aerobic glycolysis induced by sepsis-induced inflammation [19], inhibition of pyruvate dehydrogenase [20], and impaired lactate clearance [21] may contribute to increased blood lactate level found in septic patients. In endotoxic states, lactate levels failed to distinguish between hypoxia and aerobiosis [22]. Moreover, given the nonspecific nature of lactate elevation, hyperlactatemia alone is not a discriminatory factor in defining the nature of the circulatory failure.

Increase in tissue partial pressure of carbon dioxide (PCO_2) has been observed in low-flow states of cardiac resuscitation for a long time [23, 24]. It has been demonstrated that the PCO_2 of the heart, the liver parenchyma, the kidney, and the cerebral cortex were increased during the low-flow states of circulatory shock and cardiac arrest [25–27]. The rise in tissue PCO_2 has been proposed to be an early and better marker of tissue hypoxia than global metabolic markers [28–30], although potential mechanisms involved remain debated. These findings underlined the potential importance of monitoring tissue PCO_2, which may allow the detection of early signs of microcirculatory hypoperfusion. The measurement of tissue PCO_2 can be performed by using different technologies that can be applied to a variety of sites that are accessible for use in clinical practice (gastric, sublingual, and skin).

In the present chapter, we will first discuss the determinants of tissue PCO_2 in shock states and then review the current knowledge about the several available regional capnography methods for measuring tissue PCO_2, their applicability, and limitations, to evaluate organ perfusion in critically ill patients. Transcutaneous PCO_2 measurement will not be treated in this review as it is discussed in another chapter of this book.

13.2 Physiological Background of Increase in Tissue PCO_2

Augmented tissue PCO_2 has been mainly used to detect tissue hypoxia, the situation in which oxygen supply (DO_2) can no longer maintain oxygen consumption (VO_2) [31]. However, the interpretation of tissue PCO_2 is relatively complex and depends on three variables: regional blood flow, arterial CO_2 content, and tissue CO_2 production. In stable respiratory situations when arterial CO_2 content is constant, tissue CO_2 content mainly reflects the balance between tissue blood flow and local CO_2 production. Theoretically, tissue PCO_2 can increase by two mechanisms [32]. First, rises in aerobic metabolism are associated with greater CO_2 generation by the cells, which is usually linked to similar rises in blood flow, due to the regulatory role of oxygen demand in tissues, so that tissue PCO_2 does not change (washout phenomenon). Conversely, in low-flow situations, tissue CO_2 content rises because of an imbalance between CO_2 generation and a decreased CO_2 clearance [33], even in the absence of tissue hypoxia. Indeed, due to the decreasing of transit time, a higher than usual addition of CO_2 per unit of blood passing the peripheral efferent microvessels results in venous and tissue hypercarbia (CO_2 stagnation phenomenon). Second, under conditions of tissue hypoxia, there is an increased generation of H^+ ions from an excessive generation of lactic acid due to an acceleration of anaerobic glycolysis

and the hydrolysis of high-energy phosphates [34]. These H^+ ions will then be buffered by bicarbonate existing in the cells so that CO_2 will be produced, which may result in an increased PCO_2 that would reflect tissue hypoxia in such case. Experimental studies showed evidence supporting intramucosal PCO_2 as an indicator of tissue hypoxia in low-flow models when VO_2 decreases [32, 35]. Schlichtig and Bowles [32], in a dog model of cardiac tamponade, demonstrated that below critical oxygen supply threshold, mucosal PCO_2 increases because of anaerobic CO_2 production. Also, Dubin et al. [35] identified an anaerobic source of gut intramucosal CO_2 production with increased PCO_2 in a model of hemorrhagic shock.

However, all studies that had addressed the issue of detecting tissue hypoxia by analysis of tissue PCO_2 had used experimental protocols of decreasing blood flow to produce reduced VO_2, which may act as a potential confounder because of the impossibility of separating tissue hypoxia from hypoperfusion [36]. Moreover, anaerobic CO_2 generation in hypoxic tissues is not simple to identify. Indeed, under situations of tissue hypoxia, with a reduced VO_2, there is a decreased aerobic CO_2 generation counterbalanced by an anaerobic CO_2 production with the net result is a reduction in total CO_2 generation. As a consequence, the resultant effect on tissue PCO_2 depends mainly on the flow state. Therefore, when tissue hypoxia is associated with a preserved blood flow, tissue PCO_2 should remain relatively unchanged because the smaller quantity of CO_2 generated should be easily removed by a normal tissue blood flow. Conversely, in stagnant hypoxia where blood flow is decreased, increased tissue PCO_2 should be observed due to altered clearance.

Vallet et al. [36] have addressed this issue in a canine model of isolated dog hind limb. These authors nicely demonstrated that when oxygen delivery was decreased below the critical threshold by reducing blood flow (ischemic hypoxia), this was associated with an increased venous-to-arterial PCO_2 gap in the limb because of the tissue CO_2-stagnation phenomenon even if the total CO_2 production decreased. Conversely, when blood flow was maintained but arterial PO_2 was reduced by decreasing the input oxygen concentration (hypoxic hypoxia), the PCO_2 gap did not increase in spite of similar declines in DO_2 and VO_2, implying similar degrees of tissue hypoxia. This because the maintained blood flow was sufficient to clear the CO_2 generated in excess (anaerobic CO_2 production) (Fig. 13.1). Nevière et al. [37] and Dubin et al. [38, 39] both in their experimental studies confirmed that increased intramucosal-arterial PCO_2 gap was mainly related to the decrease in blood flow as the PCO_2 gap was increased during ischemic hypoxia, but not during hypoxia. Interestingly, Creteur et al. [40] found that sublingual tissue PCO_2 correlated with the proportion of sublingual perfused capillaries (evaluated using orthogonal polarized spectroscopy) and the reperfusion of impaired microcirculation was associated with normalized sublingual tissue PCO_2 in septic shock patients (Fig. 13.2).

In summary, taken together, these findings support the concept that the widening of tissue-arterial PCO_2 gap reflects only microcirculatory stagnation, not tissue hypoxia. Tissue PCO_2 is an insensitive indicator of hypoxia and purely a marker of tissue hypoperfusion. These results were confirmed by a mathematical model [41].

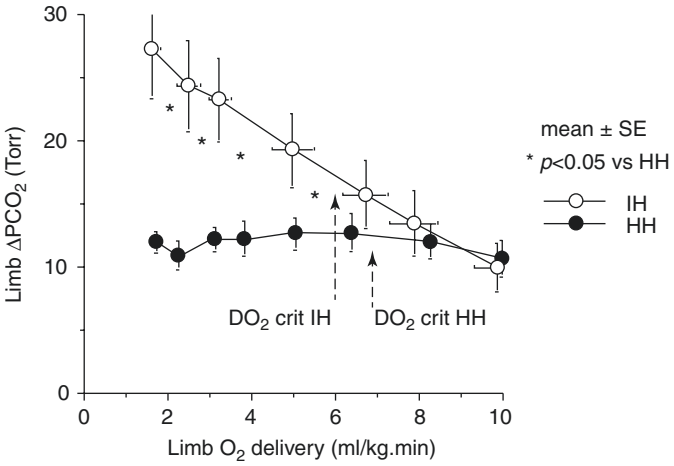

Fig. 13.1 Hindlimb PCO_2 gap (ΔPCO_2) as function of limb oxygen delivery (DO_2) for ischemic hypoxia (IH) and hypoxic hypoxia (HH). Critical DO_2 ($DO_{2\,Crit}$) was not different in IH and HH. From [36] with permission

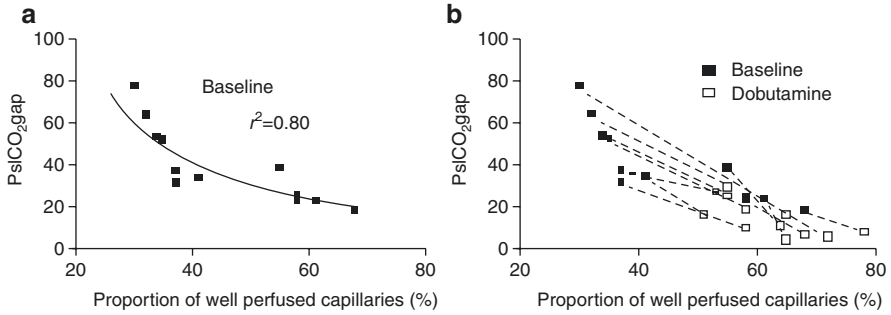

Fig. 13.2 (**a**) Relation between sublingual to arterial PCO_2 gradient ($PslCO_2$ gap) and the proportion of well-perfused capillaries. (**b**) Individual effects of a dobutamine infusion on $PslCO_2$ gap and the proportion of well-perfused capillaries. From [40] with permission

13.3 Gastric Tonometry

Gastric tonometry is a technique aimed to measure PCO_2 in the lumen of the stomach by inserting a nasogastric tube with a silicone balloon at its distal end. The CO_2 generated in the mucosal cells can freely diffuse into the lumen of the stomach and equilibrates with the content inside the balloon (saline or gas) across its semipermeable membrane. The PCO_2 within the balloon can be measured by one of the two ways: (1) saline tonometry, where the balloon is filled with saline solution and then withdrawn after an equilibration period and the PCO_2 of the fluid determined using a blood gas analyzer, or (2) air tonometry, where air is aspirated through the balloon

and the PCO_2 is semicontinuously measured by an infrared analyzer. The advantages of air tonometry are a quicker full equilibration and automated sampling and measurement, which may eliminate potential sources of error associated with saline tonometry.

The gut mucosa is highly sensitive to reduced tissue perfusion because of the countercurrent flow of its microcirculation and the higher critical O_2 requirements of its cells than other vital organs [42]. Splanchnic hypoperfusion may cause the release of inflammatory cytokines and structural changes in the gut mucosa with augmented permeability and bacterial translocation, which has been strongly associated with the development of multi-organ failure and death in critically ill patients [43–45]. It has been suggested that the gastrointestinal tract may be the "canary of the body," with gastrointestinal ischemia as 'an early cautionary of imminent danger" [46]. The stomach is a relatively easy organ to access and may deliver crucial information to the rest of the splanchnic bed. Monitoring the splanchnic perfusion by using gastric tonometry may help lessen or avoid incidents of mesenteric ischemia and ameliorate the outcome in critically ill patients. Indeed, temporary normotensive hypovolemia may result in splanchnic vasoconstriction [47], and this early alteration could be detected by gastric tonometry [48].

13.3.1 Prognostic Capability of Gastric Tonometry

Monitoring of gastric intramucosal PCO_2 ($PgCO_2$) and gastric intramucosal pH (pHi) was initially proposed to assess splanchnic hypoxia. Gastric intramucosal hypercarbia and acidosis have been demonstrated to be an index of gastric mucosal hypoxia and a predictor of morbidity and mortality in critically ill patients [15, 17], with a strong prognostic value [49, 50]. However, the determination of pHi assumes that serum arterial bicarbonate equals gastric mucosal bicarbonate, which may be incorrect. Indeed, simulations of splanchnic ischemia show that use of the arterial bicarbonate will result in errors in the calculation of gastric pHi [51]. Furthermore, acid-base disorders could lead to low pHi without an excess accumulation of gastric CO_2 [52]. Consequently, the calculation of pHi was abandoned, and interest was turned to the increase in $PgCO_2$ [53]. Nevertheless, since gastric PCO_2 is straightforwardly linked to arterial PCO_2, it is, indeed, the difference between $PgCO_2$ and $PaCO_2$ ($PgCO_2$ gap) that should be considered to determine perfusion to the stomach as it more precisely reflects the adequacy of gastric mucosal blood flow [54].

Levy et al. [30] measured the $PgCO_2$ gap using air-automated tonometer in 95 consecutive critically ill patients on admission to the ICU and at 24 h. Interestingly, the authors found that the $PgCO_2$ gap and the organ failure score measured at 24 h after admission were independent prognostic factors for 28-day mortality. The best threshold value for $PgCO_2$ gap to predict 28-day mortality was 20 mmHg [30]. This study suggests that the persistence of splanchnic hypoperfusion within 24 h after ICU admission is associated with worse outcome.

Monitoring gastric tonometry-derived variables intraoperatively also has a prognostic value in the prediction of postoperative complications [55, 56]. It has been

demonstrated an association between intraoperative splanchnic hypoperfusion and increased intestinal permeability, exaggerated acute phase response, and postoperative septic complications in patients undergoing esophagectomy [57]. Lebuffe et al. [58], in a European multicenter observational study, found that the intraoperative gradient between $PgCO_2$ and end-tidal PCO_2, which was considered as a surrogate of arterial PCO_2, could be used as a prognostic index to predict postoperative morbidity, in high-risk surgical patients during major surgery. In multiple trauma patients, it has been demonstrated the superiority of gastric capnography over other clinical variables in predicting the development of multiple organ dysfunction syndrome and death [59].

13.3.2 Gastric Tonometry as a Guide to Therapy

Some reports have tested the usefulness of gastric tonometry as a guide to therapy using pHi as a goal of resuscitation [28, 60–64]. Unluckily, these studies yielded conflictive results, mainly as some of the resuscitation strategies that were used failed to alter effectively pHi [62].

In a large multicenter trial, Gutierrez et al. [28] randomized 260 critically ill patients to a standard resuscitation protocol group or a protocol group in which resuscitation was guided to maintain pHi $\geq$ 7.35. Those individuals with an initial pHi $\geq$ 7.35 and whose resuscitation was titrated by pHi had a greater 28-day survival compared to those patients who were treated according to a standard protocol. This study gives additional support to the argument that early detection and treatment of splanchnic tissue hypoperfusion may influence the outcome of critically ill patients. However, five other randomized controlled trials [60–64] failed to establish patients' benefit from this treatment strategy. Indeed, Gomersall et al. [62] did not notice a difference in survival when resuscitation to a gastric pHi > 7.35 was compared to a standard reanimation protocol in critically ill patients with diverse illness. Also, the Miami Trauma Clinical Trials Group was a prospective randomized study that compared a therapeutic approach to treat hypoperfusion guided by gastric tonometry with a standard approach to shock management based on conventional indicators of hypoperfusion, in 151 trauma patients admitted to ICU [63]. There were no statistically significant differences in mortality rates, ventilator days, or length of stay between the two approaches. Furthermore, in a randomized controlled trial of 130 septic shock patients, Palizas et al. [64] compared a gastric intramucosal pHi-guided resuscitation protocol aimed to obtain pHi $\geq$ 7.32 with a standard approach targeted at normalizing cardiac index. These authors failed to demonstrate any survival benefit of using pHi compared with the cardiac index as resuscitation goal in septic shock patients. Nevertheless, a normalization of pHi within 24 h of resuscitation was a strong sign of therapeutic success, and in contrast, a persistent low pHi despite treatment was associated with a very poor prognosis.

Unfortunately, most of these studies did not have the statistical power to detect significant differences in resuscitation approaches. Nevertheless, a constant finding in all of these reports has been that a decreased gastric pHi correlates with outcome.

Recently, Zhang et al. [65] undertook a systematic review and meta-analysis of these six studies to investigate whether gastric tonometry-guided therapy could be of benefit for critical care patients. The authors found that resuscitations guided by gastric pHi reduced total mortality of critically ill patients when compared with control groups (*OR* = 0.732; 95% *CI*, 0.536–0.999; $p = 0.049$). However, there was no difference regarding ICU and hospital mortalities neither ICU nor hospital length of stay.

Silva et al. [66] reported the effects of fluid challenge on $PgCO_2$ gap and systemic hemodynamic and global tissue oxygenation variables in septic shock patients. While the fluid challenge was associated with an increase in cardiac index and a decrease in $PgCO_2$, global measures of tissue oxygenation remained unchanged. Furthermore, neither changes in cardiac index and $PgCO_2$ gap were related nor baseline indices of preload and changes in the $PgCO_2$ gap. However, the changes in $PgCO_2$ gap were highly associated with the baseline $PgCO_2$. These findings provide further evidence that regional markers of tissue hypoperfusion (such as $PgCO_2$ gap) rather than global parameters should be used when starting and titrating resuscitative measures in critically ill patients.

Gastric tonometry has many limitations, even after the arrival of air-automated tonometry [67], including discontinuation of enteral feeding and the need for the concomitant use of H_2-blockers. All these drawbacks have prevented its widespread adoption as a practical tool for routine tissue PCO_2 monitoring.

13.4 Sublingual Capnography

It has been hypothesized that the sublingual space, the very proximal and easily accessible part of the gastrointestinal tract, may be used as a suitable location for measurement of tissue PCO_2 [68]. The vascularization of the sublingual mucosa emanates from branches of the external carotid arteries, and thus, the sublingual area is not part of the splanchnic region. However, the sublingual mucosa, which shares a similar embryologic origin with the digestive mucosa, may present identical alterations. Interestingly, experimental studies have demonstrated a good correlation between $PgCO_2$ and sublingual mucosa PCO_2 ($PslCO_2$) [68–70]. These studies observed that changes in $PslCO_2$ during hemorrhagic and septic shock were parallel to variations in $PgCO_2$ and systemic indicators of hypoperfusion such as arterial blood lactate concentration in different animal models. Sublingual capnography has many advantages over gastric tonometry. The method is easy to implement, is noninvasive, does not need premedication and interruption of enteral feeding, and yields an instant result, and therefore, it is a simple technique of monitoring tissue perfusion at the bedside in ICU.

Two different devices have been used for $PslCO_2$ measurement: MI-720 CO_2 electrode (Microelectrodes; Londonderry New Hampshire) and CapnoProbe SL Monitoring System (Nellcor; Pleasanton, California). MI-720 is a CO_2 electrode that requires being calibrated in standard gasses with known percent values of CO_2 before use, and it was essentially utilized in animal studies for $PslCO_2$ measurements [69, 70].

The CapnoProbe was mainly designed for analysis of $PslCO_2$ and has been used in most of the clinical studies on this topic [29, 40, 71, 72]. It consists of a disposable PCO_2 sensor (placed under the tongue), which is actually a CO_2-sensing optode. The optode contains a fluorescent indicator, which is excited by light conducted through an optical fiber, which then transmits the fluorescent back to the instrument where they are converted to a numerical value of PCO_2 [73].

Five clinical studies using sublingual capnography in critically ill patients have been reported [29, 40, 71, 72, 74]. Weil et al. [74] found higher $PslCO_2$ values in patients with acute circulatory shock and observed that $PslCO_2$ value at admission was predictive of the probability of hospital survival. Initial $PslCO_2$ values were very well associated with blood lactate levels but diminished more rapidly during resuscitation, implying that reductions in $PslCO_2$ arise faster than blood lactate concentration. The authors concluded that sublingual capnography was a trustworthy technique for diagnosis and assessment of severity of acute circulatory failure in critically ill patients.

Similarly, Marik et al. [29, 71] tested the clinical usefulness of $PslCO_2$ gap ($PslCO_2$—arterial PCO_2) as an indicator of tissue hypoperfusion in a prospective study of hemodynamically unstable critically ill patients. They observed that $PslCO_2$ gap was a better prognostic factor of outcome than traditional markers of tissue hypoxia (mixed venous oxygen saturation, cardiac index, oxygen delivery, and arterial lactate level) and more responsive to therapeutic interventions.

Using the orthogonal polarization spectral (OPS) imaging technique, De Backer et al. [10] observed that microcirculatory impairments in the sublingual area were common in septic shock patients with decreases in capillary density and in the percentage of perfused capillaries compared with control patients. In septic shock patients, it has also been demonstrated that microvascular blood flow quickly improved in survivors but persisted altered in non-survivors [5]. These results suggest that persistent impairments in microcirculation are incriminated in the development of multiple organ failure and death in septic patients. Interestingly, in an elegant study of patients in septic shock, Creteur et al. [40] examined the association between impairment in sublingual microcirculatory perfusion (assessing using OPS) and $PslCO_2$ gap. They showed that the reperfusion of damaged sublingual microcirculation was associated with normalized $PslCO_2$ gap levels (Fig. 13.2). The authors concluded that sublingual capnography could serve as a simple, noninvasive tool to monitor the sepsis-induced microcirculation impairments during the resuscitation of septic shock. However, no study has evaluated the clinical utility of $PslCO_2$ gap as an endpoint resuscitation target in critically ill patients. Also, unfortunately, CapnoProbe is no longer commercially accessible. A newly developed sublingual tonometric method using a specially coiled silicone rubber tube is under investigation [75], but it is not yet available in the marketplace.

Conclusion

In critically ill patients, tissue hypoperfusion is an important cause leading to multi-organ dysfunction and death, and it cannot always be detected by measuring standard global hemodynamic and oxygen-derived parameters. Experimental

and clinical studies have demonstrated that low-flow states are consistently associated with important PCO_2 increase affecting virtually all tissues. Monitoring regional PCO_2 by gastric tonometry has been recognized to be useful as a prognostic factor and as an endpoint of therapeutic interventions. However, this technique has several limitations that have hampered its implementation in clinical practice. Sublingual capnography seems to be the ideal noninvasive monitoring tool to evaluate the severity of shock states and the adequacy of tissue perfusion. The clinical experience with sublingual capnography is, however, limited, and further studies are needed to determine the clinical utility of $PslCO_2$ monitoring, particularly as an endpoint to guide resuscitation.

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Clinical Implications of Monitoring Tissue Perfusion in Cardiogenic Shock

14

John Moore and John F. Fraser

14.1 Introduction

Cardiogenic shock is a clinical state of acute circulatory failure secondary to a reduction in cardiac output to a level that is inadequate to supply tissues with sufficient oxygen for cellular metabolism. The vast majority of cases of cardiogenic shock are due to acute myocardial infarction (AMI) and subsequent LV dysfunction. Cardiogenic shock can also be caused by ventricular wall rupture, acute mitral valve regurgitation, valvular heart diseases, dysrhythmias or cardiomyopathy.

The critical care management of cardiogenic shock remains challenging, as reflected in the mortality rates of up to 50% of patients with AMI [1]. Common pharmacological agents used to improve cardiac output and reverse tissue malperfusion, by definition, increase the myocardial oxygen demand with potentially deleterious consequences [2]. For this reason it is critical to employ a strategy of augmenting cardiac output just enough to realise adequate organ perfusion without further exacerbating the supply/demand mismatch that the failing heart represents. The attainment of this balance point remains extremely difficult, exacerbated by the inherent inadequacies of our current technologies and biological markers that

J. Moore (✉)
Department of Intensive Care, Sunshine Coast Institute for Critical Care Research (SCICCR), Sunshine Coast University Hospital, Birtinya, QLD, Australia

The School of Medicine, The University of Queensland, Brisbane, QLD, Australia

Critical Care Research Group (CCRG), The Prince Charles Hospital, Brisbane, QLD, Australia
e-mail: john.moore@health.qld.gov.au

J. F. Fraser
The School of Medicine, The University of Queensland, Brisbane, QLD, Australia

Critical Care Research Group (CCRG), The Prince Charles Hospital, Brisbane, QLD, Australia

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poorly, if at all, determine this endpoint. Consequently there is a fundamental requirement to develop technologies and treatment strategies with tissue perfusion at their core.

14.2 Microcirculatory Analysis in Diagnosis and Monitoring

The clinical diagnosis of cardiogenic shock is based on well-established criteria [1]: (1) systolic blood pressure < 90 mmHg for >30 min or vasopressors required to achieve a blood pressure ≥ 90 mmHg, (2) pulmonary congestion or elevated left ventricular filling pressures and (3) signs of impaired organ perfusion with at least one of the following criteria: (a) altered mental status; (b) cold, clammy skin; (c) oliguria; and (d) increased serum lactate. While some of these criteria inarguably identify cardiac dysfunction at the core of the clinical problem, the markers of malperfusion at the tissue level remain flawed. Lactate levels may correlate well with poor outcome, but hyperlactataemia can be caused by a number of clinical conditions and pathological processes in shock states including mitochondrial dysfunction, reduced hepatic clearance and directly resulting from catecholamine therapy. Given these compounding factors, lactate levels cannot be viewed as markers of malperfusion and tissue hypoxia, but rather as useful surrogate markers of shock severity [3].

There are a number of reliable monitoring modalities [4] for the differentiation of the components of a shock state including highly invasive methods such as pulmonary arterial catheters, through to various modalities of continuous indicator dilution and pulse waveform analysis, to different modes of echocardiography. Only the PAC and central venous catheters, providing SvO_2 and $SCVO_2$, respectively, offer any information as to the balance of supply and demand of oxygen at the tissue level. While this information can be used to titrate therapies, it does not offer direct or specific information as to the state of the microcirculation, and their influence on patient outcome remains controversial [5, 6]. Contrast echo, which employs contrast microspheres coupled with contrast-specific ultrasound imaging modalities, allows bedside assessment of the coronary microcirculation. The technique uses microspheres (approximately 1–8 μm in diameter) which are haemodynamically inert and have the same intravascular rheology as red blood cells. Higher intensity wavelengths of ultrasound are uses to destroy the microbubbles. The 'seep-back' rate of the microbubbles into the myocardial circulation is then analysed.

The critical importance of derangements in microcirculatory perfusion in disease, and its uncoupling from macrohaemodynamics, was first suggested by Freedlander in 1922 [7]. This has been confirmed in cardiogenic shock by a small number of studies [8–12].

Fundamentally, the presence of normal macrohaemodynamic values in a shock state does not guarantee that end-organ perfusion is normal. This is a phenomenon seen across all subtypes of shock [3] and across a spectrum of cardiac disease. In atrial fibrillation, microcirculatory perfusion is improved by electrical cardioversion despite unchanged systemic pressures; [13] in decompensated heart failure without shock, microcirculatory perfusion is impaired but responds to therapy [11]. This

clinical situation may represent a pre-shock state, in that the observed normal blood pressure belies a reduced blood flow rate. If identified, and appropriate intervention undertaken, this clinical state could be prevented from deteriorating into fulminant shock. This study highlights a fundamental point in the management of all shock states. While blood pressure is frequently and easily measured, it is not only a poor surrogate of end-organ perfusion, it is also unreliable as a marker of macrovascular blood flow, even in non-shock states. This emphasises the importance of the development of accurate and reliable tissue-level monitoring.

14.3 Prognostication

The importance of using a genuine assay of microcirculatory perfusion extends beyond the simple diagnosis of the shock state. A relationship between poor outcome and microcirculatory perfusion has been demonstrated using simple bedside examination [14] and more specific microcirculatory analysis [8]. More recently, Den Uil et al. studied 68 patients who had suffered myocardial infarctions complicated by a clinical diagnosis of shock. When measured at baseline, reduced microcirculatory perfusion levels as described by perfused vessel density (PVD) were only weakly correlated with associated level of cardiac dysfunction and macrohaemodynamic derangements. Importantly however, reduced PVD was strongly associated with an increased mortality [9] and a high level of PVD predicted improvements in organ function (SOFA score) over the next 24 h. The study repeated measurements at 24 h, with the failure to increment PVD being strongly associated with a significantly increased risk of death. Conversely, in patients with a reduced PVD at baseline, those who improved over 24 h had a much-improved chance of survival [9]. At the severe end of the spectrum, an observational study of 24 patients requiring VA-ECMO for cardiogenic shock demonstrated that a reduced perfused vessel density at initiation of VA-ECMO predicts non-survival, despite similar blood pressure and heart rates [15].

This data not only points to a poor correlation of macrohaemodynamic parameters with tissue perfusion, but a strong association of microcirculatory perfusion with outcome and that improvement in perfusion itself results in an increased chance of survival. Taken together, this data supports the notion that the microcirculation offers promise as a therapeutic target in cardiogenic shock and that until therapies are developed to fulfil this role, patients are suffering adverse clinical outcomes.

14.4 Pathogenesis of Microcirculatory Malperfusion in Cardiogenic Shock

An understanding of the mechanisms behind microcirculatory malperfusion in cardiogenic shock is required to explain the impact current therapies have upon the microcirculation.

The compensatory responses to cardiogenic shock share similarities with the clinical entities of hypovolaemic and haemorrhagic shock, but the perfusion of the

heart itself is of particular relevance to cardiogenic shock. The high metabolic rate and oxygen extraction ratio of cardiac tissue render it particularly vulnerable to malperfusion. Ischaemic cardiogenic shock thus represents a vicious cycle of cardiac malperfusion hypoxia and dysfunction. Reduced cardiac output results in an increased sympathetic outflow [16] and redistribution of blood from the splanchnic and cutaneous circulations [17]. Simultaneously, there is activation of the renin-angiotensin-aldosterone system and release of vasopressin favouring vasoconstriction and salt and water retention [18].

Changes in autonomic function resulting from modulation of central processing of afferent signals have been implicated in the pathogenesis of critical illness [19]. This is in part due changes in sympathetic outflow and the effects upon cardiovascular function. In cardiogenic shock a sympathetic-vagal imbalance has been observed, and it is theorised that the consequential arteriolar vasoconstriction underpins the observed microvascular malperfusion [8] [20].

Interestingly, such changes in the balance of autonomic output are known to be influenced by routine parts of critical care support including physical inactivity, sedation and neuromuscular blockade as well as psychological stress [19]. This offers support to well-established intensive care practices such as minimising sedation levels, increasing physical activity and minimising the occurrence of painful or distressing procedures. Furthermore, it hints that these interventions may positively modulate the shock state and even improve microcirculatory perfusion.

The increased tendency to vasoconstriction mediated by increased sympathetic activation may be compounded by a reduction in the production of nitric oxide. Such reductions have been demonstrated in chronic left ventricular failure [21] possibly due to reduced transcription or inhibition of the endothelial isoform of nitric oxide synthase (eNOS) [22, 23]. This has adverse downstream effects on ventricular, vascular endothelial function and microcirculatory perfusion. Indeed studies of acute heart failure have revealed that nitric oxide donors reverse microvascular malperfusion independent of changes to macrohaemodynamic indices [24, 25]. In cardiogenic shock the role of nitric oxide is more complex. Data from the SHOCK [26] trial registry point to a distributive component of cardiogenic shock [27], particularly post-myocardial infarction. This supports the notion of an inflammatory response or immune activation as part of these patients' clinical presentation. Based on both animal [28–30] and clinical studies [31–34], it is postulated that the excess inducible nitric oxide synthase (iNOS)-derived NO released following myocardial infarction is a major contributor to this vasodilatory component of cardiogenic shock. However, attempts to improve mortality using blockade of NO production with the non-selective nitric oxide synthase inhibitor tilarginine (L-N^G-monomethylarginine, L-NMMA) in the TRIUMPH trial failed [35]. This trial was stopped early for futility but excluded patients who were not revascularised post-MI. Some of these patients may have been profoundly unwell and therefore had the most to gain from the drug. Blockade of the non-inducible forms of NOS by L-NMMA may also be a factor underlying the drug's lack of efficacy. These isoforms may be important in modulating the sympathetically driven vasoconstriction seen in cardiogenic shock in order to preserve the matching of supply and demand

at the tissue level. As yet there have been no trials examining specific inhibition of the inducible isoform of nitric oxide synthase (iNOS).

In addition to the vasomotor changes above, there are also rheologic changes associated with cardiogenic shock, with initial increases in viscosity due to increased protein and fibrinogen levels, increased red cell aggregation and reduced red cell deformability [36]. The driving factors for such endothelial and rheologic changes have not been extensively investigated, but they may be mediated by a combination of increased levels of circulating catecholamines, reperfusion injury and a systemic inflammatory response [37–40]. Finally, given that acute ischaemia underlies the bulk of clinical presentations of cardiogenic shock [1] and the majority of these patients are managed early in the disease with revascularisation, anticoagulants and/or antiplatelet drugs, it has been postulated that microvascular thrombosis is not likely to be significantly involved in the pathogenesis of malperfusion [8].

14.5 Microvascular Perspective on Available Treatments

While it is important to monitor responses to therapy to ensure adequacy, it is also vital to ensure that efforts to resuscitate patients are not excessive. Standard monitoring will effectively show that cardiac output, perfusion pressure and even oxygen supply/demand have been restored. It is well established in the microcirculation literature that such macrohaemodynamic parameters are poor surrogates of perfusion at the tissue level. Without monitoring the microcirculation directly, it is possible that treatments targeted at the macrocirculation run the risk of overshoot, driving physiological parameters to levels that offer no additional benefit. This would expose the patient to unnecessary harm from therapies, whether mechanical or pharmacological [41].

The mainstays of treatment of cardiogenic shock are revascularisation, antiplatelet/antithrombotic medication, inotropes/chronotropes, nitrates, fluids, mechanical support and if necessary blood transfusion. There is a paucity of data supporting the use of any of these technologies from the standpoint of cardiogenic shock and in particular resuscitating the microcirculation.

Given that there is evidence for the uncoupling of microcirculatory perfusion from cardiac function and macrovascular parameters [13, 24, 25] and that a complicating distributive shock picture can occur in established shock, it is logical to try and intervene as early as possible. Indeed, early revascularisation in cardiogenic shock complicating myocardial infarction is associated with improved delayed mortality rates [26]. While it has not been specifically studied, it is expected that coronary revascularisation and subsequent restoration of cardiac function would improve microvascular perfusion. This would parallel the finding that in patients with dysrhythmia but normal macrovascular parameters, the restoration of sinus rhythm results in improved microvascular perfusion [13]. While not studied specifically, similar effects could reasonably expected to occur with any intervention directed to correcting the underlying pathology in cardiogenic shock. The indications for most definitive therapies in cardiogenic shock extend far beyond acute resuscitation and

have broader implications for a patient in terms of symptoms, quality of life and overall prognosis. The effects on resuscitating the microcirculation are of secondary consequence and have not been extensively studied. In contrast, the supportive therapies employed within the intensive care unit aimed at resuscitation and prevention of further organ failure are fundamental to the process of bridging a patient to definitive management or recovery. Unfortunately the available therapies have little supporting evidence as to their efficacy at augmenting perfusion at the tissue level.

14.6 Medical Management

Judicious fluid therapy is indicated in some clinical situations where preload is suboptimal and is titrated to simple clinical endpoints. While this may result in some early haemodynamic benefits and improve microcirculatory perfusion [11, 42], excess fluid may exacerbate microvascular malperfusion [43, 44]. Similarly, in patients where anaemia may be contributing to a reduced myocardial oxygen supply, blood transfusions might reasonably be employed. The efficacy of blood transfusions in shock both in general terms and from a microvascular standpoint remains highly controversial [3] and is associated with a worse outcome in acute coronary syndromes [45].

Catecholamine therapy is the mainstay of medical augmentation of cardiac output, and current guidelines recommend dobutamine as the agent of choice for ischaemic shock [46].

Beyond this, it is perhaps surprising that there is little data on the efficacy of individual vasoactive agents [47]. Catecholamines in general should be used with caution in ischaemic conditions [48]; by definition they increase myocardial oxygen demand that may predispose to dysrhythmias. Dopamine in particular is associated with both increased risk of dysrhythmia and poor outcome as compared to noradrenaline [49].

In order to restore perfusion pressure, vasopressors are often co-administered with inotrope therapy; however, they may paradoxically adversely affect microcirculatory perfusion [50, 51]. Given that high-dose inotrope therapy is associated with adverse outcome [2], a conservative approach to dosing is advisable.

Levosimendan offers potential as an alternative to standard inotropic therapy. It acts independent of beta-adrenoceptors and does not increase myocardial oxygen demand. It may be superior to dobutamine in restoring macrohaemodynamic [52] and microcirculatory [53] perfusion, as yet this has not been demonstrated to result in improved patient outcome and it cannot be recommended over more traditional catecholamine-based therapies [47].

Given the lack of genuine end-organ perfusion data that clinical or standard haemodynamic parameters offer, there is an urgent need to develop monitoring technologies that will provide accurate and reliable measures of metabolic and microcirculatory function. Such technology would permit truly individualised management and allow the use of the lowest possible dose of inotrope or vasopressor that results in adequate perfusion. Rather than direct further more aggressive

management in order to target perceived 'normal' endpoints, it would offer the opportunity to reduce the harm from unnecessary interventions whether fluid, blood or inotropes.

14.7 Mechanical Support

A major modern component of management of cardiogenic shock is mechanical support. As yet, there are little clinical outcome data supporting the use of any modality. Very careful case selection is fundamental to the success of any intervention but if correctly done may offer outcome benefit over best medical therapy [54, 55]. The decision-making process requires an integrated approach to the complications of individual techniques, availability of destination therapies, underlying cause of cardiac dysfunction, left and right ventricular reserve, presence of valve disease, patient size, projected time course of recovery, severity, phase of illness and importantly the presence and severity of respiratory failure.

The available percutaneous techniques include intra-aortic balloon counterpulsation (IABP), veno-arterial extracorporeal membrane oxygenation (VA-ECMO), ventricular assist devices (VADs), the Impella pump and the TandemHeart. The use of VADs in cardiogenic shock results in poor patient outcome [56, 57], and VADs are recommended in use for more chronic cases of compensated cardiac failure [58].

14.7.1 Intra-aortic Balloon Counterpulsation

The use of IABP for cardiogenic shock remains controversial. It improves coronary and cerebral perfusion via diastolic augmentation and reduces aortic impedance and cardiac afterload. There is evidence that it is effective in improving perfusion at the tissue level [51]. In contrast, in non-shocked patients undergoing high-risk PCI, IABP inhibits normal microvascular flow [59] despite normal systemic blood pressure. IABP therapy would therefore only be expected to be of benefit to those patients who are shocked, and some measure of microcirculatory assessment might have a role to play in case selection. By extension, it suggests that once the underlying cardiac disease has resolved, IABP therapy may adversely affect the microcirculation. In a study of patients deemed clinically ready to cease IABP therapy, there was a significant increase in microvascular perfusion (PVD) (5.47 ± 1.76 to 6.63 ± 1.90; $p = 0.0039$) when the IABP was stopped despite unchanged blood pressure and $SVCO_2$ [60]. Taken together, this evidence indicates that without a microvascular component to diagnosis and monitoring, there may be clinical situations or phases of illness, where an IABP would be either ineffective or even harmful and that this might result from paradoxical tissue malperfusion. Interestingly, the recent large IABP-Shock II study failed to demonstrate any benefit either from IABP use in cardiogenic shock due to myocardial infarction in terms of physiological endpoints, ICU-related outcomes or mortality overall or in any subgroup [61]. This was

a pragmatic study with timing of IABP therapy left to individual clinicians, and no microvascular assessments were made to help direct this. It is possible there existed a subgroup of patients in whom initiation and cessation of IABP therapy was poorly timed with reference to microvascular perfusion. This may have subjected them to unnecessary complications of IABP therapy or hampering tissue perfusion while providing no haemodynamic benefit.

14.7.2 Percutaneous Left Ventricular Assist Devices: The Impella Pump and TandemHeart™

The Impellas (2.5 and 5.0) are a family of axial flow pumps, with different flow rates, placed across the aortic valve and designed to unload the left ventricle or as adjuncts to VA-ECMO. While these devices show promise in terms of macrohaemodynamic indices, patient outcome is limited to observational studies [62, 63]. Their use is limited by a lack of oxygenation support, the significant risks associated with bleeding, limb ischaemia and haemolysis. The effects on the microcirculation are largely unknown, but they may improve perfusion in combination with IABP and in the context of STEMI and PCI [64, 65].

The TandemHeart™ provides ECLS by using a continuous flow centrifugal pump draining the left atrium with return to the lower abdominal aorta or iliac arteries. Similar to the Impella family has little supportive patient outcome data and as yet no data on microcirculatory perfusion.

14.7.3 VA-ECMO

With recent developments in technology, there has been a proliferation in the use of VA-ECMO [66] for cardiogenic shock, but clinical data showing improved patient outcome is limited to a single-centre retrospective study with historical controls [67]. Consequently only class IIb/C recommendations exist for its use in cardiogenic shock [46]. Despite this, the flexibility in modes of support and broad scope of indications beyond cardiac support make ECMO a practical and viable option. There are numerous configurations of VA-ECMO broadly classified into central and peripheral strategies. A description of the various modes of support is beyond the scope of this chapter but has been well described elsewhere [68]. The decision-making process of case selection, timing and mode of support are highly complex and significantly impact on patient outcome.

From the perspective of the microcirculation, there are a number of highly significant facets of ECMO therapy. By augmenting cardiac output, ECMO does result in an improved microcirculatory perfusion [69, 70]; however, ECMO therapy is much more complex than the simple restoration of blood flow. It has itself been implicated as a discrete cause of multi-organ failure by virtue of its interactions with the inflammatory response. The interaction between leucocytes and the non-endotheliased surface of the circuit may promote and amplify the generation of

pro-inflammatory mediators. This in combination with the presence of an ischemia-reperfusion phenomenon, and damage to the glycocalyx will superimpose a component of distributive shock state and a corresponding microcirculatory malperfusion phenotype. Prolonged and severe cardiogenic shock already predisposes to generation of this effect, and ECMO is likely only to compound this.

This complex combination of factors is likely to generate a variable clinical state and an uncoupling of the macrocirculation and microcirculation. With the limitations current methods of assessing systemic blood flow have with regard to microcirculatory perfusion, the titration of output from extracorporeal support devices is necessarily targeted at a surplus of blood and oxygen supply. Despite recent developments in technology, coagulation management and an increased clinical experience leading to more judicious case selection, VA-ECMO has a significant side effect profile including limb ischaemia, compartment syndrome, stroke, renal failure [71], infection and most significantly major bleeding [72]. The principles of applying the minimum amount of support for the minimum period of time apply in a similar way to mechanical support as to pharmacological interaction. Such close titration of therapy could be improved with the incorporation of microcirculatory analysis techniques such as IDF imaging. The use of The IDF imaging has been shown to be of use in predicting weaning success from VA-ECMO. A single centre observational study demonstrated that the preservation of microcirculatory perfusion during a reduction of flow rate to 50% of baseline was predictive of successful weaning of VA-ECMO. This not only suggests that microcirculatory parameters may be useful for the determination the likelihood of weaning success, but that they may be able to determine the efficacy of VA-ECMO flow rate [73].

The very recent single-centre study showing that IDF imaging can be reliably and regularly performed by bedside nurses shows that the incorporation of microcirculatory assessment and in particular IDF imaging can be readily incorporated into clinical practice [74]. Any useful integration of microcirculatory analysis into treatment algorithms will fundamentally rely on frequent reliable and reproducible measurements. Bedside nurses are the ideal personnel to undertake this task.

The deployment of ECLS techniques must be carefully considered in terms of choice of technique, timing of initiation, titration to effect and cessation.

Without reference to these issues, the restoration of blood flow can only be considered a measure of technical success of the chosen technique and may not result in the prevention or reversal of multi-organ dysfunction or even improved survival [75].

Conclusion

The advent of new mechanical assist technologies in the treatment of cardiogenic shock is heralding a new era for patients who suffer this often devastating clinical condition, but case selection remains a fundamental clinical challenge. It is not only important to determine which patients will benefit, but when it is optimal to intervene with a complex therapy which carries with it significant side effect and economic burden. It is only once best medical therapies have failed or are highly

likely to fail that strategies such as ECMO are considered; however the data above suggest that there is significant scope to improve our medical therapies by titrating them against clinical endpoints which have real relevance to tissue perfusion. Furthermore, such clinical endpoints might offer potential to minimise the exposure of a patient to a therapy in dose or duration, thus diminishing the risk of complications. The development of these endpoints remains a work in progress [74] but is fundamental to any progress in the treatment of cardiogenic shock.

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