FUNCTIONAL HEMODYNAMIC MONITORING

UPDATE IN INTENSIVE CARE MEDICINE

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42 Update in Intensive Care and Emergency Medicine

Edited by J.-L. Vincent

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Functional Hemodynamic Monitoring

With 78 Figures and 35 Tables

Springer

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ISSN 0933-6788
ISBN 3-540-22349-5 Springer-Verlag Berlin Heidelberg NewYork

Library of Congress Control Number: 2004110192

Springer-Verlag Berlin Heidelberg New York
a member of Springer Science+Business Media

springeronline.com

Printed in Germany

Editor: Dr. Ute Heilmann, Heidelberg, Germany
Desk Editor: Hiltrud Wilbertz, Heidelberg, Germany
Typsetting: Satz-Druck-Service, Leimen, Germany
Production: Pro Edit GmbH, Heidelberg, Germany
Cover design: design & production GmbH, 69126 Heidelberg, Germany
Printed on acid-free paper 21/3150/Re – 5 4 3 2 1 0

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Common Abbreviations

ARDS	Acute respiratory distress syndrome
COPD	Chronic obstructive pulmonary disease
CVP	Central venous pressure
DO_2	Oxygen delivery
EKG	Electrocardiogram
EVLW	Extravascular lung water
FRC	Functional residual capacity
ICU	Intensive care unit
LVEDA	Left ventricular end-diastolic area
MAP	Mean arterial pressure
NO	Nitric oxide
PAOP	Pulmonary artery occlusion pressure
PEEP	Positive end-expiratory pressure
PPV	Pulse pressure variation
RVEDP	Right ventricular end-diastolic pressure
RVEDV	Right ventricular end-diastolic volume
RVEF	Right ventricular ejection fraction
SPV	Systolic pressure variation
SvO_2	Mixed venous oxygen saturation
SVR	Systemic vascular resistance
SVV	Stroke volume variation
VO_2	Oxygen consumption

Introduction

Functional Hemodynamic Monitoring: Foundations and Future

M. R. Pinsky and D. Payen

Introduction

Hemodynamic monitoring is one of the major diagnostic tools available in the acute care setting to diagnose cardiovascular insufficiency and monitor changes over time in response to interventions. However, in recent years, the rationale and efficacy of hemodynamic monitoring to affect outcome has come into question. We now have increasing evidence that outcome from critical illness can be improved by focused resuscitation based on existing hemodynamic monitoring, whereas non-specific aggressive resuscitation impairs survival. Thus, the stage is set to frame hemodynamic monitoring into a functional perspective wherein hemodynamic variables and physiology interact to derive performance and physiological reserve estimates that drive treatment.

Any discussion on the utility of hemodynamic monitoring must start from the perspective of one scientific truth that is often forgotten when discussing the efficacy of new diagnostic tests or monitoring devices. Namely, that no monitoring device, no matter how simple or sophisticated, will improve patient-centered outcomes useless coupled to a treatment which, itself, improves outcome. Thus, hemodynamic monitoring needs to be considered within the context of clinical condition, pathophysiological state, and sites within the acute care delivery system wherein this monitoring takes place.

Rationale for Hemodynamic Monitoring

A reasonable progression of arguments can be developed to defend the use of specific types of monitoring techniques. At the basic level, the specific monitoring technique can be defended based on historical controls. At this level, prior experience using similar monitoring showed it to be beneficial. Clearly, the mechanism by which the benefit is achieved need not be understood or even postulated. The next level of defense comes through an understanding of the pathophysiology of the process being treated, such as heart failure or hypovolemic shock. Most of the rationale for hemodynamic monitoring lies at this level and, regrettably, is of less secure foundations than would otherwise be assumed. The implied assumption of this level of argument is that knowledge of how a disease process creates its effect and, thus, the ability to prevent the process from altering measured bodily func-

tions, should prevent disease progression and promote recovery. It is not clear from recent clinical studies that this argument is valid, primarily because knowledge of the actual process is often inadequate. The ultimate level of defense of a therapy or monitoring process comes from documentation that the monitoring device, by altering therapy in otherwise unexpected ways, improves outcome in terms of survival and quality of life. In reality, few therapies in medicine can claim this benefit. Thus, we are left with the physiologic rationale as the primary defense of monitoring of critically ill patients. Although defendable at the present time, potentially new information about process of illness or outcome may come to light, negating any aspect of the proposed monitoring paradigms. More than likely, it is through our use of monitoring to direct therapies, defining specific physiological conditions requiring specific treatments with defined end-points of treatment with proven benefits, achieved in a timely fashion, that the benefit of hemodynamic monitoring in any form will be realized.

Tests to Document Effectiveness of Invasive Hemodynamic Monitoring Procedures [1]

1. Information received cannot be acquired from less invasive and less risky monitoring.
2. Information received improves the accuracy of diagnosis, prognosis, and/or treatment based on known physiological principles.
3. The changes in diagnosis and/or treatment result in improved patient outcome (morbidity and mortality).
4. The changes in diagnosis and/or treatment result in more effective use of health care resources.

Importantly, hemodynamic monitoring exists within the context of the patient, pathophysiology, time in the disease process, and area within the healthcare delivery system where it is used. Furthermore, monitoring technologies progress from the most simple and non-invasive to the most complex and highly invasive. As summarized above, the use of increasingly invasive and risky monitoring devices should be considered with reference to the above four points. The site where monitoring takes place has a major impact on type of monitoring, its risks and utility and efficacy. For example, monitoring in the field or in the emergency department is often less invasive that that seen during major surgery in the operating room or intensive care unit. And monitoring on the regular hospital ward can be even less or more invasive depending on the specialized center where it is occurring (e.g., electrocardiographic monitoring post-myocardial infarction in a step-down unit or pulse oximetry on a respiratory ward post-endotracheal extubation). Furthermore, and as alluded to in the previous sentence, the type of disease and treatment options determine the degree to which the same monitoring will be more or less effective. For example, invasive pulmonary artery catheterization with continuous monitoring of cardiac output and right ventricular volumes may be very useful during the intraoperative course of a complex cardiac surgery patient with pulmonary hypertension, whereas the same monitor-

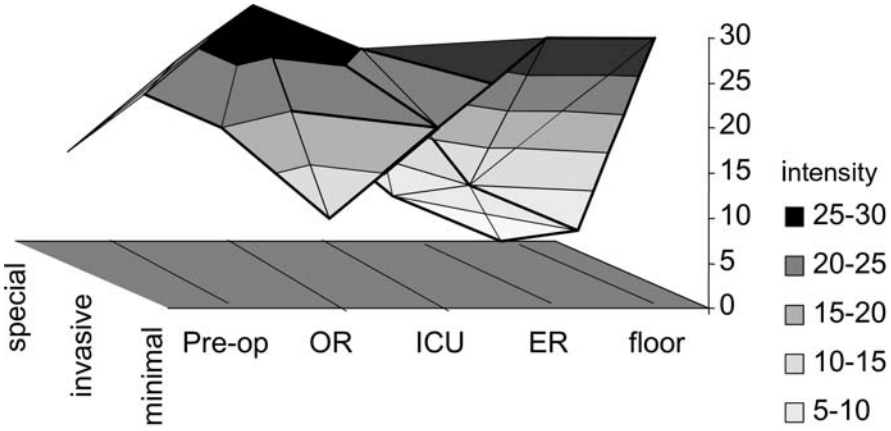

Fig. 1. Schematic representation of the level of intensity of hemodynamic monitoring by place in the health care delivery system and type of monitoring using an arbitrary scoring system from zero to thirty to define level of intensity. Pre-op connotes pre-operative optimization for high risk surgical patients; OR: operating room; ICU: intensive care unit; ER: emergency department; and floor: regular hospital ward. Special monitoring connotes specialized devices such as echocardiography, transcranial Doppler, gastric tonometry and other techniques used in only very specific conditions and patient subgroups.

ing may not alter care in an otherwise uncomplicated cardiac surgery patient with normal cardiac contractility. Where, within the course of disease, the monitoring is used may have profound effects on outcome. Pre-operative optimization of cardiovascular status using invasive hemodynamic monitoring to define therapeutic end-points in high-risk surgery patients (referred to as pre-optimization) has been shown to reduce morbidity, whereas the same monitoring and treatment if applied post-operatively or in otherwise unstable patients already receiving intensive care support does not improve outcome. This point underlies another fundamental aspect of cardiovascular resuscitation form critical illness. Namely, the difference between prevention of tissue ischemic injury in patients presenting in shock and attempts to rescue patients in shock following the development of the ischemic insult.

Finally, applying protocolized care in the management of critically ill patients reduces medical errors and practice variation, and can reduce ICU length of stay. These points are illustrated in a stylized fashion in Figure 1. Hemodynamic monitoring exists only within the context of the pathophysiology of the disease and its associated complications and potential treatments. However, it is only by identifying the fingerprint of hemodynamic variables that characterize specific disease patterns that one can make specific cardiovascular shock diagnoses and direct specific treatment.

Acknowledgement: This work was supported in part by NIH grants HL67181-02A1 and HL07820-06

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Therapeutic goals

Defining Hemodynamic Instability

M. H. Weil

Introduction

Hemodynamic instability as a clinical state is, for practical purposes, either perfusion failure represented by clinical features of circulatory shock and/or advanced heart failure, or simply one or more measurements which may indicate out-of-range but not necessarily pathological values. Physical signs of acute circulatory failure constitute primary references for shock, including hypotension, abnormal heart rates, cold extremities, peripheral cyanosis and mottling together with bedside measurements of right-sided filling pressure and decreased urine flow. For the purposes of this chapter, our focus is on perfusion failure and more precisely, acute circulatory failure as a systemic complication of underlying diseases. Accordingly, a careful history, if available, is a potentially important asset. Regional perfusion failure such as mesenteric thrombosis or acute vascular obstruction of an extremity due to either arterial or venous occlusion has sometimes been regarded as "regional shock" perhaps because it may ultimately lead to systemic perfusion failure and therefore circulatory shock.

Classification

We define hemodynamic instability and more specifically circulatory shock by a combination of findings. The classification of circulatory shock which was initially published by myself and my late associate, Professor Herbert Shubin, more than 40 years ago [1] and subsequently abbreviated, serves as a useful guide. Four categorical states of shock have the common denominator of decreased effectiveness of systemic blood flow but differing mechanisms (Fig. 1). Critical reductions in intravascular volume produce *hypovolemic* shock due to blood or fluid losses. *Cardiogenic* shock is due to pump failure; its prototype is acute myocardial infarction. *Distributive* shock includes septic shock, in which we have high flows that bypass the capillary exchange bed, presumably due to arteriovenular shunting or by increasing venous capacitance. Distributive shock also follows loss of automatic controls as in the instance of transection of the spinal cord, or drug induced expansion of the capacitance bed by ganglionic drugs or decreased arterial resistance caused by alpha-adrenergic blocking agents. The fourth category is that of *obstructive* shock which is due to a mainstream obstruction of blood flow.

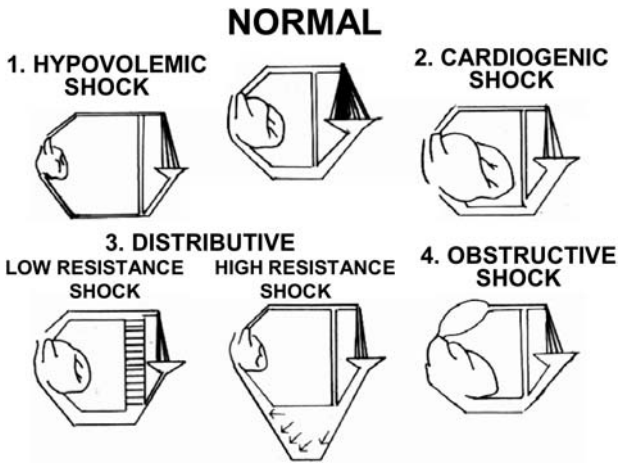

Fig. 1. Diagram representing the hemodynamic features of the four primary etiological shock states. Modified from [15]

Prototypes of obstructive shock include pulmonary embolism, dissecting aneurysm of the aorta, a ball-valve thrombus, or combined obstructive and cardiogenic shock in the instance of pericardial tamponade. In each case, there is a decrease in tissue perfusion although the mechanisms are quite discrete. Moreover, hypovolemia has a high likelihood of complicating circulatory shock of other causes in part because of adrenergically primed venular vasoconstriction with transudation of fluid from capillaries into the interstial space.

Hemodynamic Mechanisms

To understand the sites of the circulatory system which explain hemodynamic stability and, by implication, hemodynamic instability, we identify eight specific loci. They are illustrated in Figure 2 and include:

a) *venous return* to the right side of the heart or preload;
b) the myocardium and *myocardial contractile function*, including heart rate and rhythm which are determinants of stroke volumes and therefore of cardiac output contingent on heart rate and rhythm;
c) pre-capillary *arteriolar resistance* which operates as an *afterload* on the heart;
d) the *capillary exchange circuit* which is the site of substrate exchange, including fluid shifts contingent on capillary hydrostatic pressure;
e) *post-capillary venular resistance* which is an important controller of capillary hydrostatic pressure;
f) *venous capacitance* which in some shock states expands to pool large volumes of blood accounting for critical decreases in venous return or preload and therefore cardiac output.

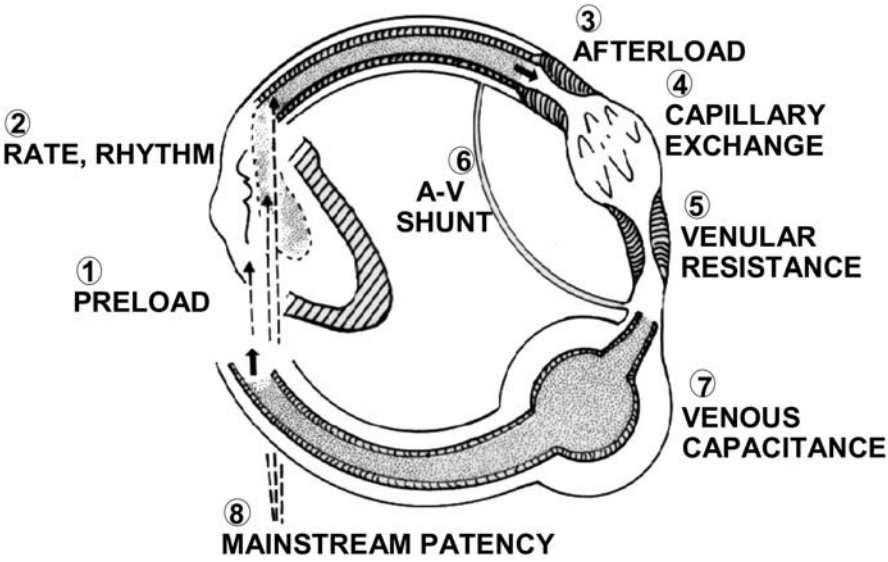

Fig. 2. Hemodynamic loci for identifying mechanisms of perfusion failure. Modified from [15]

g) Finally, systemic blood flow is decreased whenever there is a mainstream *obstruction to blood flow* due to pulmonary embolism or dissecting aneurysm of the aorta.

Measurements

Physical Signs and Bedside Observations

Against this background of classification and hemodynamic mechanisms, the bedside clinician seeks methods for more refined diagnosis of acute perfusion failure [2]. Arterial (blood pressure), heart rate and rhythm, the rate of capillary refill of skin after blanching, the urine output, the mental status of the patient, and the effects of body position on blood pressure continue to be valuable clinical signs (Table 1). The presence of cyanosis of the ear lobes, nose and fingertips, and of the extremities, including mottling of cool and moist extremities, are characteristic of hypovolemic, cardiogenic, and obstructive shock states. The disarmingly simple technique of measuring the temperature of the great toe remains an attractively simple quantitative indicator for diagnosis of circulatory shock [3]. Each of these measurements is fallible, however [4]. The early onset of septic shock, for instance, is characterized by a hyperdynamic circulation with wide blood pressure, warm extremities, and early confusion.

An electrocardiogram (EKG) may be indicative of myocardial ischemia and complements the physical signs of shock. Pulse pressure represented by the differ-

Table 1. Clinical parameters for estimating severity of circulatory shock

Stage	Pa	HR	CR (2 min)	Urine ml/h	Mental Status	% Loss
					normal	
1	normal	normal	<2	>39	or anxious	<15
2	↓Tilt +	>100	>2	20	anxious	>20
3	↓	>120	>2	5–15	confused	>30
4	↓	>140	>2	0–5	lethargic	>40

Pa: arterial pressure; CR: capillary refill; HR: heart rate

ence between the systolic and diastolic pressure is a non-invasive correlate of stroke volume. Within the past decade, echocardiography has proven to be an excellent alternative to invasive hemodynamic measurements for estimating cardiac output and filling pressures with the bonus of identifying structural and functional cardiac abnormalities, including the valuable distinction between systolic and diastolic dysfunction in settings of cardiac pump failure [5]. More recently, efforts to interpret the microcirculation in patients have been experimentally, but not as yet clinically, useful [6].

Invasive Measurements

Hemodynamic assessments may be refined by the use of more invasive procedures and specifically central venous catheterization for measurement of central venous pressure and oxygen saturation and/or pulmonary artery catheterization with a flow-directed catheter for measuring pulmonary artery and pulmonary artery occlusive (wedge) pressure (PAOP). This method also provides for thermodilution cardiac output and more secure measurement of oxygen saturation of mixed venous (pulmonary artery) blood. These measurements have a high likelihood of establishing or confirming the mechanism of circulatory shock based on history and physical signs. Hypovolemic shock, for instance, is characterized by decreased right-sided filling pressures, decreased cardiac output, and decreased oxygen saturation or oxygen content of mixed venous blood. This contrasts with cardiogenic shock in which there is an increase in left-sided filling pressures also with decreases in cardiac output and oxygen content of mixed venous blood. In the instance of obstructive shock due to pulmonary embolization, right-sided filling pressures are elevated proximal to the obstruction. There is a high likelihood that both pulmonary artery and right ventricular systolic and diastolic pressures are increased but without increases in PAOP. In the initial stages of

distributive shock due to sepsis, both cardiac output and mixed venous oxygen concentration are increased. Bedside echocardiography has the likelihood of providing comparable information excepting only mixed venous oxygen. Measurements on expired gases and specifically end-tidal carbon dioxide ($ETCO_2$) are of special value not only for guiding ventilation but also as indirect indicators of cardiac output when cardiac output is critically reduced [7]. Thoracic impedance also provides an estimate of cardiac output. Unfortunately, we lack the capability of quantitating blood volumes as a clinical routine. Without measurements of intravascular volumes, together with cardiac output and filling pressures, there is but little objective indication of venous capacitance.

Metabolic Measurements

Perhaps the oldest and most readily available of laboratory measurements is the base deficit. Metabolic acidosis during circulatory shock states reflects generation of excess hydrogen ions when the anaerobic threshold is exceeded. More precisely, the anaerobic threshold represents the transition from aerobic metabolism through the tricarboxylic acid cycle to the emergency pathway in which pyruvate is "shunted" to form lactate [8]. The capability of the body to maintain energy production by the utilization of oxygen and generation of carbon dioxide is compromised. Excesses of hydrogen ions are primarily accounted for by generation of lactic acid through the emergency pathway. In addition, high and intermediate energy phosphates are used up rapidly and their degradation generates excesses of hydrogen ions. Concurrently, there is likely to be hyperventilation, especially in settings of septic shock and reduced arterial carbon dioxide tension which therefore minimizes changes in pH of blood. Since effects of treatment, including the administration of both unbuffered and buffered electrolyte solutions, are routine, they also impact on the base deficit quite independently of the severity of anaerobic metabolism. Accordingly, base deficits have limited reliability. Nevertheless, the value of base deficit stems from the fact that it is routinely available both as part of routine hospital chemistry analyses and blood gas measurements without additional effort or cost. However, arterial blood lactate serves as a much more specific indicator of the metabolic consequence of perfusion failure and, more specifically, the failure to maintain capillary oxygen delivery leading to anaerobiosis [9].

There is a close relationship between the maximum levels of lactate in patients with circulatory shock and the outcome (Fig. 3) which has been fully confirmed for more than 40 years. However, the lactate measurements also have limitations. First, marked increases in lactate may follow vigorous physical exertion caused by shivering, convulsions, or even struggling of the patient in bed, independent of the presence of shock. These physiological increases in lactate indicate only that the anaerobic threshold has been exceeded. Yet, it differs from circulatory shock in that there is a rather prompt decline in the lactic acid concentration usually within one half hour or less after physical exertion ceases. This contrasts with circulatory shock in which as long as 12 or more hours are required for lactate clearance. Nevertheless, when the lactate concentration exceeds 6 mmol/l and remains at that level for

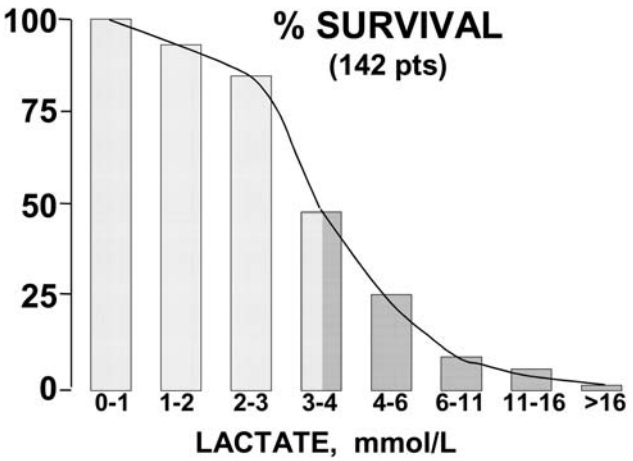

Fig. 3. Prognostic value of arterial blood lactate levels. Modified from [15]

4 hours or more in the absence of physical exertion, it confirms the diagnosis of the perfusion failure characteristic of circulatory shock and prognosticates a mortality of between 80 and 90%.

Tissue Hypercarbia

My associates and I first identified marked increases in the CO_2 tension (PCO_2) of mixed venous blood in settings of cardiopulmonary resuscitation. The mixed venous PCO_2 in blood sampled from the pulmonary artery typically exceeded 70 mmHg in contrast to arterial PCO_2 which was less than 20 mmHg [9]. We subsequently traced these increases in mixed venous PCO_2 to even greater increases in the PCO_2 of ischemic organs during shock, including the heart, the brain, the gut, and the kidneys. The changes were extreme. In the heart, for instance, the myocardial tissue PCO_2 increased to levels as high as 500 mmHg during cardiac arrest. When levels exceeded 300 mmHg, attempts to restore spontaneous circulation with cardiopulmonary resuscitation (CPR), including defibrillation, were unavailing. Tissue hypercarbia correlated closely with reductions in blood flow through organs as measured in pigs and rats with microspheres. The findings were consistent with the principles that led to gastric tonometry, although the methods popularized by Fiddian-Green et al. [10] reported gastric intramucosal pH (pHi) as the parameter of interest. Gastric tonometry was a useful research measurement which predicted severity and outcome of shock. Increases in tissue PCO_2 cleared rapidly after reversal of shock in but minutes and, unlike lactate, provided prompt indication of the effects of treatment. Unfortunately, gastric tonometry presented major practical limitations and inherent errors for clinical use. The method provided for a balloon to be incorporated near the distal end of an oral- or naso-gastric tube. The tube was advanced into the stomach. The balloon was then

filled with normal saline. At the end of 45, 60, or 90 minutes after which PCO_2 had equilibrated between the stomach wall and the saline in the balloon, the saline was sampled and subsequently analyzed in a conventional blood-gas analyzer. The pHi, was computed from measurements of PCO_2 on the aspirated saline, bicarbonate which was computed from pH, and PCO_2 of arterial blood with the Henderson-Hasselbalch equation [10]. Because gastric acid interfered with the measurement, patients were pre-treated with an H_2-blocker. The rationale of using arterial HCO_3^- to calculate pHi was subsequently invalidated [11]. The complexity of this intermittent measurement prompted a refinement of the technique with measurements of CO_2 on gas instead of saline in the gastric balloon.The technique then called for analysis of the PCO_2 in the balloon with an infrared CO_2 meter. Unfortunately, this method never gained prominence, also because of inconsistency of results and cost.

A series of studies by our own group in which we subsequently measured the PCO_2 of tissues directly with methods now incorporated in the commercially available Capnoprobe® demonstrated that tissue hypercarbia during tissue ischemia was a universal phenomenon not limited to the stomach or viscera more generally. We therefore elected to measure sublingual tissue PCO_2 by a technique only slightly more demanding than measuring oral temperature. We found a highly significant correlation between sublingual PCO_2, gastric PCO_2, cardiac index, and arterial blood lactate. It applied to all types of shock, including sepsis. Like arterial blood lactate, it identified the metabolic defect characteristic of critically reduced systemic blood flow [12, 13].

Mediators Indicative of Perfusion Failure

Over the last half-century, a large number of mediators and acute phase reactants have been proposed to facilitate the diagnosis and predict the severity and outcomes of shock states of diverse causes and most especially septic shock. These include endotoxins and polysaccharide binding proteins, cytokines, leukotrienes, clotting factors, C-reactive protein, histamine, uric acid, catecholamines, and procalcetonin, to name but a few. We recognize the commonality of cascades that are triggered and which are implicated in settings of acute circulatory failure. Nevertheless, none of the mediators has yet been shown to be sufficiently characteristic to serve as diagnostic or prognostic measurements and potentially decrease the burden of depending on clinical and hemodynamic measurements.

The measurement of tissue PCO_2 under the tongue has now proven to be a very useful non-invasive and reliable alternative to the gastric tonometer [13]. Sublingual PCO_2, like gastric wall PCO_2, is increased during shock. High correlations between tonometric and gastric PCO_2 and sublingual PCO_2 based on 76 measurements on 22 patients by Merrick [14] have confirmed the rationale. In subsequent studies, we specifically confirmed that sublingual PCO_2 also increases during sepsis produced by intravenous infusion of live *Staphylococcus aureus*. In patients in the emergency department or in medical and surgical intensive care unit settings, sublingual PCO_2 rapidly identifies the presence of shock. However, it does not

pinpoint mechanisms and thereby still requires classification for treatment based on both clinical and hemodynamic measurements.

Conclusion

Hemodynamic instability caused by perfusion failure (circulatory shock) is best defined by measurements which initially pinpoint the presence or absence of circulatory shock and subsequently the underlying mechanism. Once the mechanism of shock has been identified, the priority is to treat the underlying cause of hypovolemic, cardiogenic, distributive, or obstructive shock. There are eight primary sites of altered function in the circulatory system which explain the hemodynamic impairment. Clinical recognition therefore proceeds from physical signs to bedside measurements of blood pressure, the electrocardiogram and, echocardiography, end-tidal CO_2, and urine flow together with measurements of sublingual PCO_2 and metabolic measurements in blood, including lactate. Invasive measurements, including pulmonary artery catheterization, may be required for additional precision in differential diagnosis but will be likely to give way to increasingly simplified methods of Doppler-echocardiography.

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Determinants of Blood Flow and Organ Perfusion

E. Calzia, Z. Iványi, and P. Radermacher

Introduction

In organisms up to 1 mm in diameter, materials are transported within the body by diffusion. In larger species, convective transport, which requires a propulsive organ and conduits, is mandatory to ensure the transport of oxygen and nutrients to the tissues and the simultaneous removal of the waste products of cellular metabolism [1]. In the context of the circulatory system, the heart and the vascular system assume these functions, the latter being responsible for the distribution of cardiac output to the organs and tissues [2] (Table 1). The distribution of cardiac output may vary markedly in response to the underlying pathophysiology and/or ongoing therapy. Focusing as far as available on human data, this chapter reviews the main alterations in regional blood flow with respect to different stress states as well as the individual response to standard day-to-day therapeutic measures in the intensive care unit (ICU) except for vasoactive treatment which has been reviewed elsewhere [4–8].

Table 1. Regional blood flow distribution in a 70 kg healthy normal volunteer at rest. Adapted from [3].

Organ	Organ size [kg]	Blood flow [l/min]	Blood flow [l/kg/min]
Kidneys	0.3	1.2	4.0
Liver	1.5	1.4	0.9
Heart	0.3	0.25	0.8
Brain	1.4	0.75	0.5
Muscle	2.5	0.2	0.08
Skin	30	0.9	0.03

Normal Physiology

Cardiac Output

Cardiac output is defined as the blood volume that one ventricle ejects during 1 minute, i.e., the product of heart rate and stroke volume. Figure 1 summarizes the determinants of cardiac output. Besides vagal and sympathetic innervation, heart rate is determined by the electrical properties, while stroke volume is governed by the mechanical properties of the cardiac muscle as well as neural, hormonal, and chemical factors [2], the most important among the latter being tissue partial pressures of oxygen (PO_2) and carbon dioxide (PCO_2), pH as well as nitric oxide (NO), carbon monoxide, purine nucleotides, and eicosanoids [1]. Moreover, cardiac output depends on the characteristics of the conduit system, i.e., mainly the resistance of the vascular tree. Blood flow is inversely related to this resistance and directly proportional to the effective perfusion pressure, i.e., the pressure gradient between the arterial and the venous end of the system [1, 2], except for the renal and cerebral perfusion which remain rather constant despite marked variations in perfusion pressure, a phenomenon called *autoregulation* (see below). According to Poiseuilles law, one major resistive component is the vascular diameter, and consequently, blood velocity, i.e., the flow divided by the cross-sectional area, is highest in the aorta, the pulmonary artery, and the large veins. By contrast, due to the considerable increase in cross-sectional area, it markedly decreases in the capillaries, thereby allowing for substance exchange between the blood and the tissues (Table 2). While the distensible arterial walls serve as a pressure buffer and

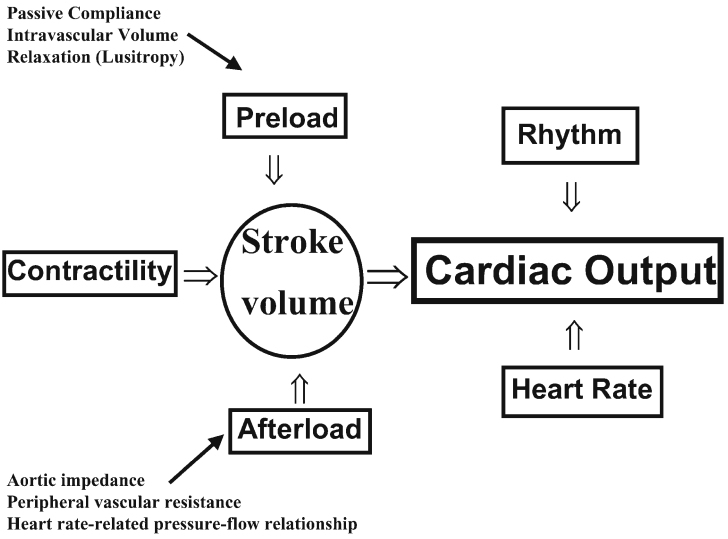

Fig. 1. Determinants of cardiac output

Table 2. Distribution of blood volume, intravascular pressures and blood velocity within the circulatory system. Adapted from [3].

Vessel	Volume [ml]	Pressure [mmHg]	Velocity [cm/s]
Aorta and large arteries	400	100 –40	40–10
Arterioles	50	40– 30	10–0.1
Capillaries	250	30–12	< 0.1
Venules	300	12–10	< 0.3
Vena cava and large veins	2500	105 (–2)	0.3–20

attenuate the pulsation-related flow oscillations, the highest resistance is located in the arterioles, which therefore contribute most to the pressure drop over the vascular bed, and consequently, due to selective constriction, control flow distribution to the tissues (Table 2).

The distribution of blood volume within the vascular bed is also fairly uneven (Table 2): the venous system contains approximately three fourths of the total blood volume [9], and, hence, serves as a low-pressure reservoir. Consequently, since there is no blood stock in the heart [10], the venous system assumes crucial importance for the regulation of cardiac output, namely via changes in cardiac preload related to variations in venous vascular tone [9]. Venous return is driven by the pressure gradient between the pressure in the veins and the right atrium, the former being the *mean circulatory filling pressure*, which is defined as the steady-state pressure within the circulation under no-flow conditions, e.g., cardiac arrest. Being approximately 8–10 mmHg, this pressure describes the relation between the amount of intravascular fluid volume and the space available for this fluid, and consequently, blood volume and venous tone are its determinants [11]. Depending on the vascular tone, up to 75 % of the intravascular volume may be referred to as the *unstressed volume*, i.e., the blood that may be contained in the circulation without exerting a transmural pressure, while the remainder, i.e., the *stressed volume,* is responsible for the mean circulatory filling pressure [9].

Except for strenuous exercise affiliated with extremely high flow rates, laminar flow profiles are present in undivided vessels with smooth walls. Due to the higher flow velocity, blood cells accumulate in the center of a vessel, which reduces the difference between the velocity in the center and adjacent to the vessel wall, and thereby flattens the velocity profile [2]. Moreover, *plasma skimming* occurs so that small side vessels have a lower hematocrit, such as in the gut villous circulation [12, 13]. By contrast, laminar flow is impossible in capillaries where the diameter of a red cell exceeds that of the vessel. The physico-chemical properties of the blood, namely blood viscosity, also contribute to vascular resistance: normal plasma viscosity is approximately 1.8 times that of water, and, mainly due to the presence of erythrocytes, blood at 37°C is 3–4 times more viscous than water [1].

Physiology of the Regional Circulation during Normal Conditions

Kidney blood flow

Renal blood flow comprises 20–25% of the cardiac output, i.e., the perfusion rate per tissue mass exceeds that of any other organ. Under normal conditions, *autoregulation* of the arteriolar resistance guarantees that blood flood is preserved despite wide variations in perfusion pressure (80–180 mmHg) [14]. By contrast, in pathologic situations, such as shock and sepsis, autoregulation is lost, and consequently renal plasma flow becomes pressure dependent [15]. The renal cortex receives approximately two thirds of the total organ blood, thus favoring glomerular filtration, while the relatively low flow rate to the medulla maintains osmotic gradients and thereby enhances water reabsorption [14].

Cerebral blood flow

Normal cerebral blood flow represents approximately 15 % of cardiac output (see table 1). The cerebral circulation is unique inasmuch as the target organ is contained in a rigid box – the skull – so that the relationship between the volume of the tissues within this box, i.e., brain parenchyma, blood, and cerebrospinal fluid, and the space allowed for the content, determines the pressure inside this box, i.e., the intracranial pressure (ICP) [16]. Intracranial pressure rises when the increase in intracranial mass exceeds the displaceable volume of (venous) blood and cerebrospinal fluid and thereby determines the downstream pressure of the cerebral circulation [16]. Consequently, the effective cerebral perfusion pressure is defined as the difference between mean arterial pressure (MAP) and ICP [16, 17].

Similar to renal blood flow, *autoregulation* keeps cerebral perfusion rather constant during variations of MAP between 50–150 mmHg [18]. In hypertensive subjects, the threshold values of effective autoregulation are displaced [17], and autoregulation disappears during hypercapnia and after intracranial hemorrhage or brain injury [17, 18].

Gut and liver blood flow

The hepato-splanchnic system, which receives about one fourth of total cardiac output, comprises both a serial and a parallel vascular net (Fig. 2), so that three fourths of liver blood are supplied via the portal vein, i.e., via a low pressure system representing the outflow of the mesenteric circulation, and, hence, with a normal pressure gradient of about 4–5 mmHg only between the portal and the hepatic vein; the hepatic artery contributes the remainder [13, 19]. Consequently, the portal circulation is particularly sensitive to changes in the downstream pressure of the hepatic vascular bed, namely increased right atrial pressure. Variations in portal venous flow are compensated for by changes in hepatic arterial flow in order to maintain total liver oxygen supply, an intrinsic regulatory mechanism called the hepatic arterial buffer response [20, 21] which is mainly determined by

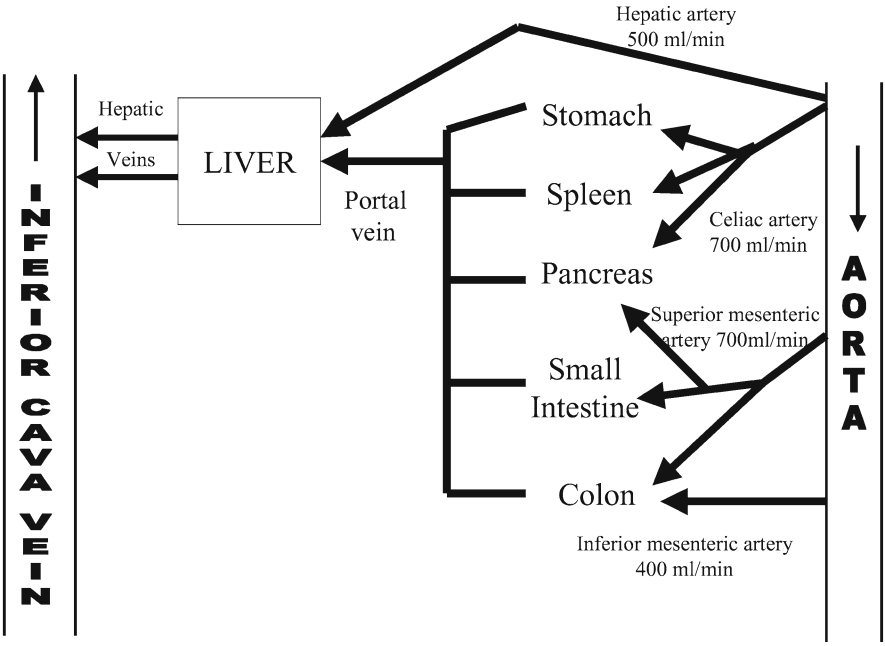

Fig. 2. Macrovascular anatomy and blood flows of the hepato-splanchnic organs in normal healthy volunteers at rest. From [8] with permission.

local adenosine concentrations. Moreover, NO and carbon monoxide formation also assume importance for the regulation of hepatic arterial and portal venous resistance [22]. Recent experimental data suggest that the celiac trunk also contributes to the regulation of blood flow distribution between the hepato-splanchnic organs, in particular during low-flow states [23].

Circulatory adaptations to physiologic stress: Exercise

As during any other physiological challenge, regulation of the cardiac output during exercise is to meet tissue oxygen and substrate demands. Therefore, blood flow to skeletal muscle may be increased up to 20-fold, and in addition oxygen extraction may triple [1]. Both neural and local mediators, in particular tissue PO_2 and PCO_2, are responsible for this response [1], and decreased peripheral resistance and enhanced venous return resulting from muscular pumping of the veins allow for this rise in tissue perfusion. The increase in cardiac output necessary to guarantee the rise in peripheral blood flow is mainly due to an increase in heart rate [1]. Nevertheless, despite the fall in filling and ejection time, stroke volume also rises by approximately 50% because of the catecholamine-related inotropic effect [1]. Maximum cardiac output in a healthy adult is approx. 25 l/min, which, however, does not suffice to equalize maximal regional perfusion in all vascular

beds [9]. Consequently cardiac output is unevenly distributed during exercise: muscle perfusion increases at the expense of the hepatosplanchnic system [24] and the kidney [1]. This response is mediated by catecholamine-related vasoconstriction in these vascular beds and thereby guarantees the above-mentioned increase in venous return. It may account for a reduction in splanchnic blood flow of up to 80% [25]. This particular response of the visceral circulation to physical effort is by no means only of academic interest for the ICU physician: during weaning from mechanical ventilation spontaneous breathing may present as exercise [26] potentially compromising visceral blood flow. In fact, the inability to breathe spontaneously, which ultimately resulted in weaning failure, was reported to be associated with impaired gastric mucosal perfusion as assessed with laser Doppler flowmetry [27] and mucosal tonometry [28] despite a significantly increased cardiac output [27]. This phenomenon is enhanced when weaning coincides with fever. Physical effort under warm environmental conditions is a particular challenge for the maintenance of blood pressure that is mandatory to sustain blood flow to the working muscle: under these conditions cutaneous vasodilation occurs to allow for heat dissipation, which results in increased skin blood volume, and in turn may compromise venous return and thereby cardiac preload due to a redistribution of blood volume at the expense of the intrathoracic compartment [9].

Pathophysiology

Hypovolemia and Hemorrhage

Taking into consideration the distribution of blood volume discussed above, hypovolemia will reduce the mean circulatory filling pressure and, consequently, venous return. Since the stressed volume accounts for only 25% of the total blood volume, theoretically venous return would in fact completely cease unless adaptive mechanisms come into existence [10]. In fact, overall, vasoconstriction occurs [29] to maintain intrathoracic blood volume at the expense of the venous capacitance, which is mediated by endogenous catecholamine-release [31]. Reduced hepatosplanchnic [12, 24, 29, 30] and renal [24, 30] blood flow contribute most to this compensatory response, but skin and muscle circulations also assume importance [9, 29]. It is trivial that fluid resuscitation - which will increase the stressed volume and thereby improve venous return - is the essential therapeutic measure when hypovolemia is present. It has to be noted however, that even apparently adequate fluid administration as judged by restored systemic vascular resistance may not overcome the hypovolemia-induced vasoconstriction; sustained splanchnic vasoconstriction was present in healthy volunteers after transient simulated normotensive hypovolemia despite normalization of systemic hemodynamics [29]. Moreover, aggressive volume resuscitation with large amounts of fluids may be necessary to restore venous return when the unstressed volume is increased, for example during sepsis-induced vasodilation [9].

Fluid resuscitation, no matter whether colloids or crystalloids are used, will result in decreased hematocrit and, hence, blood viscosity will markedly decrease.

Taking into account that volume expansion with colloids and crystalloid is probably the most frequent measure to increase cardiac output and thereby to improve oxygen delivery, studies in patients on the effects of hemodilution on organ blood flow and tissue perfusion are surprisingly scarce. From the available large animal and human data it seems unequivocal that moderate (hematocrit > 25) normovolemic hemodilution as a result of reduced vascular resistance leads to increased systemic [31] and thereby regional, e.g., coronary [32], renal [33], hepatosplanchnic [34–36], and cerebral [37] blood flows. Moreover, the fall in oxygen transport capacity associated with the decreased hemoglobin content not only does not impair but might even improve organ function [38–40].

Increased Airway Pressure and Mechanical Ventilation

Increasing intrathoracic pressure and, thereby, lung volume has marked hemodynamic effects which comprise both the diastolic and the systolic function of the heart as documented by the effects of Valsalva and Muller maneuvers on left heart volume and ejection fraction [41]. These phenomena have been masterly summarized elsewhere [42, 43]. Briefly, four different mechanisms have to be considered [44]:

1. Positive airway pressure increases the transpulmonary and thus the central venous pressure although right atrial transmural pressure decreases, which results in a fall of the driving pressure for venous return [45]. This is the primary cause of reduced cardiac output [46] associated with positive end-expiratory pressure (PEEP) [9, 47] and may be reversed by blood volume expansion [48, 49].
2. PEEP may cause ventricular interdependence characterized by a leftward shift of the interventricular septum that may impede left ventricular filling [49, 50].
3. The increase in functional residual capacity (FRC) affiliated with PEEP may change the perfusion of the pulmonary vascular bed and thereby increase right ventricular afterload [51–53].
4. As already mentioned above, changes in airway pressure may also affect left ventricular systolic function, i.e., left heart afterload [41]. An extreme manifestation of this phenomenon is the cough-induced maintenance of a sufficiently high stroke volume to maintain consciousness in patients with ventricular fibrillation [54]. Consequently, ventilation with PEEP is a unique adjunct for the treatment of the failing heart [55]: in fact, in patients with terminal congestive heart failure stroke volume markedly improved when high fequency jet ventilation-pulses were synchronized with the electrocardiogram (EKG) [56], while such a response was not observed when left ventricular ejection fraction was normal or only moderately depressed [57]. The improved left ventricular afterload associated with positive pressure breathing may also explain unsuccessful weaning from mechanical ventilation in some patients: when airway pressure returns to normal, hypervolemia may occur with a subsequent deterioration of the left ventricular function curve [48, 58].

It is self-evident that the marked effects of increased intrathoracic pressure on heart function will also profoundly affect regional organ blood flow. In this context, the primary cause of a positive pressure breathing-related fall in cardiac output, i.e., reduced venous return, assumes crucial importance: PEEP ventilation increases the right atrial pressure and thereby the backstream pressure of the systemic circulation, which is associated with a displacement of blood volume away from the intrathoracic compartment into the periphery [9,59], in particular in the hepatosplanchnic region [60–62]. In fact, splanchnic blood flow falls in parallel to cardiac output with increasing airway pressure [63, 64]. Because of the small pressure gradient between the portal and the hepatic vein (normally 5–8 mmHg only), liver blood flow via the portal bed is particularly sensitive to increases in the intrathoracic pressure [65], i.e., the downstream pressure of the hepatic circulation, albeit the hepatic arterial buffer response mentioned-above compensates for the drop in portal venous flow. Interestingly, this deleterious effect of PEEP disappears when the increments in airway pressure are titrated according to the thoraco-pulmonary pressure-volume curve [66], i.e., when the PEEP maneuver restores FRC and thereby optimizes the relation between pulmonary vascular resistance and lung volume such as in patients with acute respiratory distress syndrome (ARDS) in contrast to patients with exacerbated chronic obstructive pulmonary disease (COPD) [67].

Although already investigated for some decades [68, 69], the deleterious effect of positive pressure breathing on renal blood flow is still a matter of concern [70]. Although the fall in creatinine clearance was reported to parallel a PEEP-related drop in cardiac output [71] and to be reversed by aggressive fluid resuscitation in dogs [39], glomerular filtration rate remained depressed after PEEP removal [71] and did not respond to volume redistribution using a military antishock trouser [72]. Hence, hormonal factors involving the antidiuretic hormone [73], the renin-angiotensin-aldosterone system [74] and, in particular, the atrial natriuretic factor [75] assume importance in this context. The interaction of mechanical ventilation with renal blood flow and glomerular filtration rate also is an example of the dual-faced role of spontaneous breathing: while allowing the patient to breathe spontaneously may potentially impair hepatosplanchnic blood flow due to the exercise-related redistribution of cardiac output (see above), it may in turn improve renal blood flow and glomerular filtration rate [73, 76] even when airway pressures are not modified [77].

Several direct and indirect mechanisms are regarded as contributing to the deleterious effects of positive pressure breathing on the ICP and thereby the cerebral circulation [78]. In fact, lung recruitment maneuvers may markedly depress cerebral blood flow and thus even cause brain tissue hypoxia despite improve arterial oxygenation [79]. It should be noted, however, that this effect is not due to the increased airway pressure *per se*: when MAP and thus cerebral perfusion pressure were well-maintained during PEEP increments, ICP did not rise, even in patients with pathologically high baseline levels [80], while the opposite was observed when the PEEP maneuver was associated with a fall in blood pressure and, consecutively, in mean cerebral artery velocity [81].

Ventilation during kinetic rotation or in the prone position are some of the most frequently used supportive measures in patients with acute respiratory failure.

Although only scarce human data are available from the literature, the bottom line seems to be that provided increases in intraabdominal pressure are prevented, prone positioning affects neither renal [82], intestinal [83, 84], nor liver blood flow [85]. By contrast, continuous rotational therapy has been reported to result in a marked increase in right ventricular end-diastolic dimensions, and consequently cardiac output, when the patients were in the extreme left dependent position, while the opposite response was observed in the right dependent position [86]. How this response translates into variations of regional blood flow remains to be elucidated.

Changes in O_2 and CO_2 Tensions

As outlined above, the cardiac output ensures the transport of oxygen and nutrients to the tissues and the simultaneous removal of the waste products of cellular metabolism, the tissue PO_2 and PCO_2 being main determinants of the regulation of the distribution of blood flow. Consequently, it is conceivable that variations of *arterial* PO_2 and PCO_2 may also affect organ perfusion. In fact, a fall in arterial PO_2 or an increase in arterial PCO_2 leads to a rise in cardiac output and organ blood flow such as at high altitude [1] or during deliberate hypercapnia [87–89]. Hyperoxemia has the opposite effect: it is well-known that pure oxygen breathing at supra-atmospheric ambient pressures is associated with a fall in cardiac output due to both reduced heart rate and systemic vasoconstriction [90]. Under these conditions of increased, i.e., "arterial" PO_2 levels in the venous blood, the affinity of NO to the *S*-nitrosohemoglobin binding is enhanced, and the reduced local free NO concentrations inhibit the endothelial vasodilation [91]. Normobaric hyperoxia also causes systemic vasoconstriction [92, 93] with a subsequent fall in regional blood flow [93, 94]. Interestingly, the administration of oxygen free radical scavengers, such as *N*-acetylcysteine or vitamin C, may reverse this effect [92, 94].

While the circulatory responses to hyperoxia are often overlooked during day-to-day ICU routine, manipulating arterial PCO_2 plays an important role as a therapeutic measure: as mentioned above, the autoregulation of cerebral blood flow disappears after intracranial hemorrhage or brain injury, and therefore hyperventilation-induced hypocapnia is used to control ICP due to reduced cerebral blood flow and thereby intracranial blood volume. In fact, several authors have reported a virtually linear relationship between arterial PCO_2 (between 29 and 54 mmHg) and cerebral blood flow [95–97], the reduced overall brain blood flow potentially leading to regional ischemia [96, 97]. While a similar vasodilatory response to hypercarbia was observed in the coronary circulation [88], the hepatosplanchnic system showed a different response pattern: neither moderate hyperventilation (arterial $PCO_2 \approx 27$ mmHg) in patients with brain trauma [98] nor moderate hypercarbia induced by increased dead space ventilation (rise in arterial $PCO_2 \approx 7$ mmHg) in patients with acute respiratory failure [99] significantly affected regional blood flow to these organs.

Conclusion

The mechanical and electrical properties of the heart together with the circulatory system determine the cardiac output, which ensures the transport of oxygen and nutrients to the tissues and the simultaneous removal of the waste products of cellular metabolism. The regional distribution of cardiac output may vary markedly according to both the underlying pathologic conditions as well as ongoing standard day-to-day routine treatment, and, furthermore, the response of cardiac output to therapeutic interventions may differ from that of regional blood flow, so that classical hemodynamic monitoring does not suffice to evaluate the impact of therapeutic interventions on organ perfusion.

Acknowledgements: Dr. Iványi was supported by a grant of the Deutscher Akademischer Austauschdienst and the Land Baden-Württemberg.

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Determining Effectiveness of Regional Perfusion

D. M. Payen

Introduction: Definitions and Concepts

Several approaches can be used to analyze regional perfusion, which focus on different determinants. From the macrocirculation point of view, regional perfusion can be considered as the locally regulated regional blood flow. Since the systemic circulation is not the limiting factor, regional blood flow is essentially regulated by local factors that adapt organ blood flow according to organ function. Of these local factors, metabolic demand is of major importance. Regional perfusion can thus also be seen as the flow sufficient to cover the energetic demand, to ensure organ function. Such regulation predominates over the systemic circulation in physiological conditions. Depending on the function, this metabolic demand can be chronically high, such as kidney oxygen consumption, or low, such as in skeletal muscle at rest. Within an organ, the metabolic demand may vary area to area: cerebral blood flow, a composite of regional blood flows, is heterogeneous as are the local activities of the brain. As a consequence, global cerebral blood flow can vary differently from the local flow, and independent of systemic blood flow; regional and global blood flows then have different determinants.

Regional perfusion can be seen also as a partition of flow within a tissue at the microcirculatory level. Global organ blood flow does not provide information on tissue perfusion at the cellular level, which is dependent microcirculatory factors, and may have a major impact in pathological conditions such as septic shock, which is a distributive shock with a very heterogenous microcirculation. The determinants of microvessel recruitment then need to be considered.

The Concept of Autoregulation

Peripheral organ perfusion can be classified in two major physiological categories: organs with an efficient blood flow autoregulation system, and those with very limited blood flow autoregulation.

Strongly autoregulated blood flow occurs in organs that require the most efficient protection, because of their key functions: the brain, to a lesser extent the heart, and the kidney. This concept implies local regulation of vessel caliber in relation to the perfusion pressure. When the pressure increases, the vessel caliber decreases, maintaining the flow. Conversely, when the perfusion pressure de-

creases, the vessel caliber increases to maintain the flow. While the precise vascular mechanism(s) involved remain a matter of debate between the myogenic and the metabolic theory, autoregulation is of particular importance to protect perfusion of organs such as the brain.

The Concept of Waterfall

The flow within an organ can be seen as a function of the difference between the inflow pressure and the outflow pressure. For a given perfusion pressure, the flow depends on the regional vascular tone or resistance. While this remains true for many organs, especially the musculo-cutaneous territory, it may not be so for others. The above concept is no longer correct when organ vessels are surrounded by a pressure different to atmospheric pressure. If this pressure is positive, it can at least induce vessel collapse. The perfusion pressure/flow relation is then more complex and surrounding pressure has to be integrated. If such external pressure becomes higher than intravascular pressure, the vessel is narrowed, with a reduced flow. The outflow pressure is not the venous pressure, but the intra-vascular pressure elevated by the positive pressure surrounding the tissue. The waterfall phenomenon occurs in the lung, the heart, the brain, and to a lesser extent the portal vein in the liver.

Phasic Blood Flow [1]

Arterial flow is a phasic phenomenon, with systolic and diastolic components. At the aortic level, flow is only present during systole, with no flow in diastole. At the microvessel level, flow is more continuous, which is a witness to the buffer role of arterial vessels that transform phasic flow into continuous flow. It is important to note that arterial organ blood flow is phasic, with systolic and diastolic components that differ from organ to organ (Fig.1) [2]. For example, forearm blood flow is essentially during systole with no flow during diastole, whereas cerebral blood flow is systolo-diastolic, and left coronary blood flow is purely diastolic (Fig. 2) [3]. This implies different determinants for these organ blood flows, according to the systolic and diastolic vascular tone. As for systolic pressure, systolic blood flow depends on aortic stroke volume, vessel compliance, and vascular tone. During an acute situation, compliance modification has a limited impact on the observed variations, because it cannot change in any large extent. The stroke volume and the vascular tone are the major factors of systolic blood flow. Diastolic blood flow is positive mainly in organs with an efficient autoregulation. These organs have a relatively low vascular tone during diastole, allowing a passive diastolic run off. Extravascular compressive forces are markedly different in the right and left ventricle under normal conditions. As a consequence, systolic flow expressed as a fraction of diastolic flow is much greater in vessels that perfuse the right ventricle than the left ventricle [4]. During diastole, coronary vascular tone is low, with a large perfusion pressure, generating a diastolic blood flow. On the right coronary vascular bed, perfusion is present both during systole and diastole. The systolic

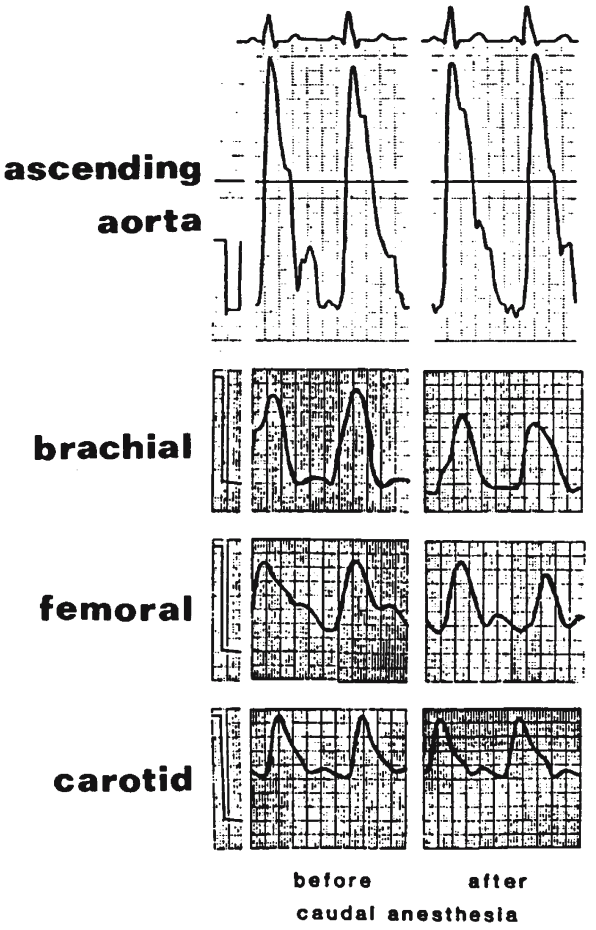

Fig. 1. Phasic ascending aortic, brachial, femoral, and carotid blood flows before and after caudal anesthesia in infant [2]. Note the absence of diastolic flow in aorta and skeletal muscle circulation. Note the positive diastolic flow in common carotid blood flow.

flow is positive because of a high systolic perfusion pressure (aortic systolic pressure – systolic pulmonary pressure). As in left side, the diastolic right coronary blood flow is positive related to a large perfusion pressure (diastolic aortic pressure – diastolic right ventricular pressure). In intensive care unit (ICU) patients, the determinants of the phasic components of flow should be integrated into the understanding and the therapeutic strategy.

Oxygen Supply/Oxygen Demand [5]

It is agreed that oxygen deprivation may cause tissue damage directly, owing to exhaustion of ATP and other high energy intermediates needed to maintain cellular structural integrity. In addition, oxygen deprivation may cause damage indirectly during reperfusion, when oxygen radical "storms" are formed and destroy

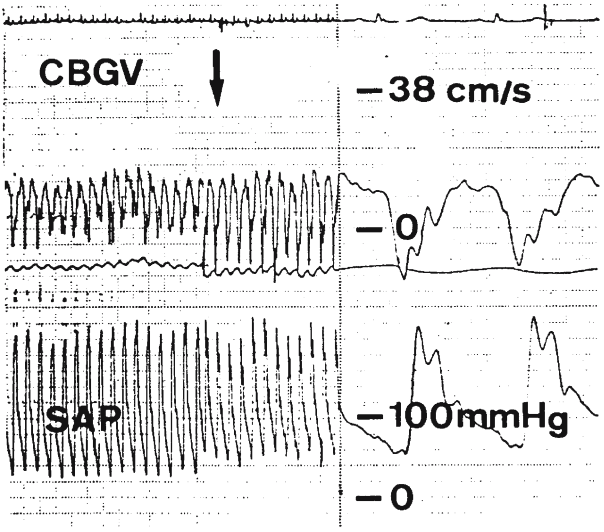

Fig. 2. Phasic left coronary bypass blood flow velocity: top tracing shows phasic flow velocity with no systolic flow, with a large diastolic blood flow. The arrow indicates the impact on coronary bypass blood flow velocity of the closing of the chest [3].

cell structure and function. The relationship between oxygen transport and tissue well-being is of interest to intensivists. As mentioned above for circulatory items, it is useful to separate the macrovascular parameters from the microvascular parameters of tissue oxygenation. Macrovascular parameters commonly used in clinical practice are oxygen uptake or consumption (VO_2), oxygen delivery (DO_2), and oxygen extraction ratio (O_2ER). VO_2 is relatively easy to measure since it is the quantity of oxygen consumed by a given tissue per unit time. It is the difference between the quantity of oxygen that enters and that which leaves a given vascular bed:

$$VO_2 = \text{flow} \times (CaO_2 - CvO_2)$$

where CaO_2 and CvO_2 are the oxygen content of arterial and venous blood, respectively. DO_2 is the quantity of oxygen flowing into a given tissue and is calculated as:

$$DO_2 = \text{flow} \times CaO_2$$

Since only a fraction of DO_2 normally diffuses into cells, the remainder is carried away from the organ in the venous effluent. The fraction of DO_2 that diffuses from capillaries into cells, expressed as per cent of the total, is termed the O_2ER and is calculated as VO_2/DO_2, i.e.,

$$O_2ER = (CaO_2\text{-}CvO_2)/CaO_2.$$

Assuming in most circumstances that the hemoglobin concentration is adequate, such a ratio could be simplified as follows:

$$O_2ER = (SaO_2\text{-}SvO_2)/SvO_2 \text{ in \%}.$$

The use of regional SvO_2 is currently the only parameter that approaches the O_2ER [6]. As for circulation parameters, microcirculation parameters for oxygen utiliza-

tion differ from macrocirculation parameters. Tissue PO_2 provides information on tissue oxygenation, but varies considerably within a given organ. This has led to the use of PO_2 histograms to better characterize tissue oxygenation. The final determinant of mitochondrial oxidative phosphorylation is mitochondrial PO_2. The minimum driving oxygen pressure to support oxidative phosphorylation in mitochondria is less than 0.5 mmHg. It depends both on oxygen convection (DO_2) and diffusion from capillary to cell. Metabolic parameters can be used to estimate the tissue redox state, such as lactate/pyruvate ratio, β-hydroxybutyrate/aceto/acetate ratio, and depend both on macro- and microcirculation parameters. If the concept of the whole body DO_2/VO_2 relationship can be easily manipulated by clinicians, it is not the same at the tissue level. When DO_2 varies over a large range, tissues maintain VO_2 constant, extracting only as much oxygen from the blood as appears needed to maintain vital metabolism. This refers to oxygen supply independency and is thought to signify tissue well-being. When DO_2 declines to a critical threshold value, VO_2 can no longer be maintained constant, because of the oxygen extraction limitation. Below this threshold, VO_2 declines in proportion to DO_2, a phenomenon referred to as oxygen supply dependency. The corresponding O_2ER is approximately 70%. Such a biphasic view of the VO_2/DO_2 relation has been demonstrated in many organs, at least experimentally. This concept has lost importance in clinical ICU practice, because assumptions must be made which are incorrect for some ICU patients:

- Oxygen demand is constant at all DO_2 values
- Whole body measurements accurately reflect oxygenation of all organs
- All DO_2 is equal for all physiologic conditions

Two problems are created by the variations in VO_2 with respect to application of the VO_2/DO_2 model:

- the critical DO_2 varies with the change in VO_2 demand;
- increased VO_2 due to increased oxygen demand is normally supported not by an increase in the O_2ER, but rather by an increase in DO_2.

Thus, when oxygen demand is allowed to vary, the DO_2-VO_2 relation is no longer biphasic but linear. It is not oxygen supply dependency but oxygen demand dependency (Fig.3). In ICU patients, one can admit that the cardiovascular system provides tissues with twice the critical value of DO_2 needed to support an oxygen supply-independent metabolism. When oxygen demand exceeds this capability of the cardiovascular system, then the O_2ER increases to supply oxygen demand.

The most important limitation for clinicians is that the whole body VO_2-DO_2 relationship does not reflect phenomena occurring in individual organs, as illustrated by many examples. Experimentally, it has been shown that critical DO_2 in different organs differs from the whole body value. This is more true in clinical conditions in which ventilation, especially with positive end-expiratory pressure (PEEP), the type of disease, and the pharmacology of the drugs used could alter the distribution of whole body DO_2 among organs. A septic patient treated with PEEP plus pressors may have a reduced liver blood flow due to PEEP, with an increase in cardiac oxygen demand due to inotropes and chronotropes. It is clear that the DO_2-VO_2 relationship of the liver and the heart differ from that of the whole body.

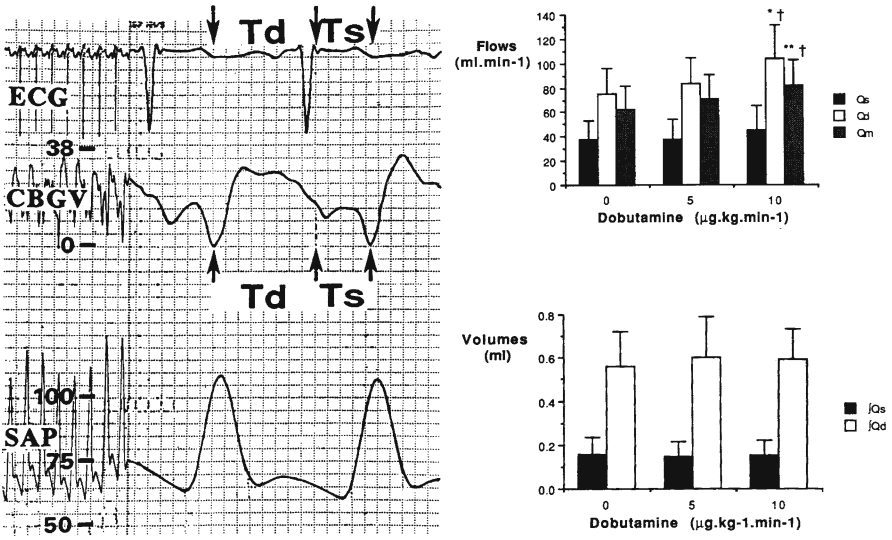

Fig. 3. Left panel: coronary blood flow tracings, with quoting of systole and diastole time (Ts and Td). The right panel shows the impact of dobutamine on phasic coronary bypass flow at three different doses. The lower part shows the oxygenated blood volume entering coronary vessels in relation to dobutamine dose [8].

Another frequent condition in ICU patients limits the applicability of this concept. When an organ is perfused by a stenotic vessel, the poststenotic vascular bed is already maximally dilated. Additional vasodilatation cannot be obtained to increase flow and DO_2. Perfusion in this tissue is then dependent not on whole body and local DO_2, but rather on arterial blood pressure. At the cerebral level, when autoregulation is abolished, cerebral blood flow is dependent on blood pressure, which then becomes the main determinant of cerebral DO_2.

Finally, there is a third mechanism by which the model of DO_2-VO_2 is limited in clinical conditions. It is possible that factors other than macrovascular DO_2 determine tissue oxygen supply. Some clinical ICU conditions are characterized by a maldistribution of whole body DO_2 among organs, with overperfusion of some, and underperfusion of others. Oxygen diffusion between capillaries and mitochondria may differ among organs, because of important interstitial edema, abnormal structural barriers, or abnormal presence of migrating cells from blood (immune cells) within the tissue, trapping oxygen. Practically, in non-septic conditions, the most important determinant of VO_2-limitation is the convective factor DO_2. In septic conditions, if DO_2 remains a major determinant at least at the early phase, other factors interfere such as microvascular alterations (obstruction, or shunt), cellular dysoxia, oxygen radical formation. Finally, when hemoglobin concentration is corrected and arterial oxygen saturation is over 95%, it is more DO_2 than oxygen diffusion that determines tissue perfusion.

Organ Variability of Oxygen Demand In ICU Situations

The liver is a good example of VO_2 variations during acute situations. It is known that liver oxygen demand depends on the concentration of substrates reaching the liver: the more elevated the nutritional substrate supply, the more elevated the liver oxygen demand. As a result of this elevated oxygen demand, liver DO_2 has to increase. In sepsis or in systemic inflammation, the liver shifts the metabolism towards the acute phase response. The net effect of this shift on liver oxygen demand is not known, and may differ patient to patient. Kidney blood flow, like most organs (except brain and heart), varies in direct proportion to cardiac output. A reduction in cardiac output by 50% will produce a similar reduction in renal blood flow. However in contrast to other organs, kidney VO_2 decreases dramatically in parallel with a decrease in kidney DO_2, even in physiological ranges. Since NaCl reabsorption accounts for two thirds of kidney VO_2, the reduced VO_2 implies a decreasing demand to reabsorb NaCL. The use of furosemide provides protection against kidney hypoperfusion, since it decreases oxygen demand by the drug-induced limitation of NaCl reabsorption.

Integration of the Determinants

Two separate conditions have to be considered in the analysis of regional perfusion determinants: first, when systemic blood flow is not the limiting factor, and second, when systemic blood flow is one of the limiting factors. In these two conditions, the consequences for organ perfusion are different as is the impact of therapy. Such differences are amplified by metabolic stimulation. If an organ has an elevated oxygen demand, sudden hypoperfusion will induce more cellular damage and organ dysfunction than in an organ at rest. As an extreme example, a patient having a cardiac arrest when at rest has a better chance of being successfully resuscitated than if the heart is stressed. Few sportsmen having a cardiac arrest have been successfully resuscitated compared to patients experiencing a cardiac arrest when at rest. It should be noted in cardiopulmonary trials that some patients were successfully resuscitated. Among the survivors, those having a good neurologic score had a long delay for cardiopulmonary (CPR) intervention (>10 min) [7]. This confirms the ability of cardiac and brain cells to turn off the metabolism maintaining only essential functions, when in a pre-arrest condition the organ was not being stimulated. The duration of poor organ perfusion is an additional factor to be taken into account. This factor allows vascular or cardiac surgery to be preformed during which every effort is made to reduce oxygen demand, and to limit the duration of absence of organ perfusion: short duration of aortic clamping, cooling of the heart during bypass, use of diuretics and or mannitol to protect the kidney, participate in preventing post procedure organ failure. The tolerance of hypoperfusion varies among organs: 5 to 7 min for brain total ischemia, 15 min for heart, 2 to 3 hours for the liver, 8 hours for skeletal muscle.

Determinants of Regional Perfusion when Systemic Circulation is not the Limiting Factor

When the organ is not ischemic, the situation is close to physiological and the determinants depend on organ characteristics.

Heart perfusion: Myocardial perfusion is provided by coronary vessels. The distribution of flow depends on three major vessels, with frequent efficient anastomoses within territories. The main characteristic of this circulation is that coronary blood flow is the adapting factor to cater for myocardial metabolic demand, since coronary circulation oxygen extraction is physiologically sub-maximal [4]. Any change in myocardial metabolic demand will be immediately followed by an adapted flow. More precisely, the energy consumed during one contraction has to be covered during the next diastole [8]. The greater the cost of one contraction, such as extrasystole, the more elevated should be the flow for the next diastole. It becomes clear why heart rate is the most important determinant of myocardial metabolic demand. Each contraction consumes energy that has to be covered by diastolic perfusion. That explains why β blocking agents are so powerful in reducing the imbalance between myocardial demand and supply. The limited diastolic time during tachycardia may reduce the capacity of the diastolic oxygenated blood volume to cover the metabolic demand [8]. This has to be kept in mind when using inotropes, which are also chronotrope drugs, in ICU patients. Patients with a limited coronary blood flow adaptation related to coronary disease and/or severe anemia, may suffer during inotrope treatment as it can induce myocardial ischemia. In ICU patients, additional arterial hypotension may participate in amplification of myocardial ischemia, in relation to a decrease in diastolic left coronary perfusion pressure. During resuscitation, fluid loading may also participate in myocardial ischemia, since it can increase the end-diastolic ventricular volume and the wall tension. Such effect could in turn change the intra-myocardial pressure, which becomes the back pressure of coronary blood flow. Myocardial tissue pressure seems to be largely higher than coronary vein pressure. It has been shown that the zero flow pressure in the coronary vascular bed is close to 30 to 40 mmHg [9]. Any increase in such a pressure may participate in the deterioration of perfusion pressure, and consequently in a reduction in blood flow, despite a higher demand.

For the right coronary blood flow, since the perfusion is both systolic and diastolic, determinants for perfusion involve the two components [4]. For systolic perfusion, the concepts are grossly the same as those of the left ventricle. It should be mentioned that it is better preserved on the right than on the left, since pressures on the right side are largely lower than on the left. It will then be relatively independent of systemic pressure, but largely dependent on pulmonary hypertension. In presence of chronic pulmonary hypertension, the systolic perfusion pressure is reduced, inducing a flow pattern identical to that observed on the left ventricle. With regard the diastolic perfusion pressure, this is very well maintained since diastolic aortic pressure is largely higher than the end-diastolic right ventricular pressure. We can conclude that without systemic circulatory failure, the right ventricle is particularly well protected from ischemia. The oxygen demand of

the right ventricle is increased by right ventricular afterload. The blood flow has then to increase to cover such an increase in requirements. The vascular tone is reduced and flow increases if perfusion pressure is adequate.

The organ is ischemic: This is a frequent condition in the ICU because of age related co-morbidity such as coronary artery disease. Downstream of the coronary stenosis, the resistance is low, related to the metabolic demand of myocardium. This implies that a further dilatation will be limited if it is required to improve flow supply. This is a major concept in coronary reserve impairment. This reserve can be tested dynamically by inotropes, such as dobutamine. The stress test induces an increase in myocardial demand that has to be covered by flow. The coronary stenosis may limit this flow increase, leading to myocardial ischemia and dysfunction.

The vasodilatation leads to a flow dependency on perfusion pressure. If for any reason, systemic pressure is low, flow decreases in parallel, adding another ischemic factor. Finally, anemia limiting oxygen transport to the myocardium, may also worsen myocardial ischemia.

To summarize, left coronary perfusion depends on perfusion pressure, i.e., mainly diastolic aortic pressure. In some circumstances, the back flow pressure, i.e., the left ventricular pressure, could limit the flow in the presence of diastolic overload, especially if there is low diastolic aortic pressure. The main determinants of myocardial demand are: heart rate, afterload, and inotropism. The presence of a stenosis induces a post stenotic vasodilatation, causing the flow to be pressure dependent. This limited coronary reserve creates a high-risk of ischemia for the left myocardium. Regarding right coronary blood flow, in relation to the territory supplied, the flow is both systolic and diastolic. It is relatively well protected from left side modifications, but depends essentially on the right side pressures: pulmonary arterial pressure, right ventricular end-diastolic pressure. With an abnormal systemic circulation, with hypotension, tachycardia, and anemia, myocardial perfusion can be compromised leading to ischemia and/or necrosis. It is then crucial to evaluate the tolerance to the circulatory conditions and the impact of treatment by dynamic tests such as: fluid loading and/or pressors, or inotropes with careful evaluation of S-T segment, troponin I, or echocardiography to quickly detect myocardial ischemia.

Determinants of Regional Perfusion when The Systemic Circulation is the Limiting Factor

Even when the coronary circulation is intact, there are some critical circumstances during which myocardial perfusion is compromised. In the association of severe hypotension, as during shock, with a reflex and therapeutic tachycardia and anemia, all the conditions are created to induce ischemia. Hemorrhagic shock may induce severe myocardial ischemia in coronary disease patients. Septic shock seems to be less dangerous, since myocardial ischemia has been demonstrated rarely. However, the co-existence of severe coronary stenosis and septic shock may lead to ischemia as assessed by elevated tropinin I. For the right circulation,

frequently challenged in ICU situations, the reasoning is different. The main determinant of right ventricular myocardial demand is the afterload, i.e, the pulmonary pressure. When pulmonary hypertension occurs with systemic hypotension, right ventricular ischemia may be observed. This is mainly important in septic shock, when systolic aortic pressure falls and systolic pulmonary pressure rises, reducing coronary perfusion pressure. The right systolic coronary blood flow decreases limiting the adequate supply for an elevated myocardial demand. This ischemia may induce right ventricular systolic dysfunction. Pulmonary embolism is also a good example. The huge increase in afterload, and consequently in myocardial demand, imposes a large increase in coronary blood flow. If this increase is not sufficient, right myocardial ischemia may occur, precipitating the collapse.

The cerebral circulation: The cerebral blood flow is normally independent of systemic circulatory conditions [10]. The brain conditions determine the cerebral blood flow. The basic principle agreed by neurophysiologists is that the cerebral blood flow is coupled to cerebral oxygen consumption. Each modification of cerebral metabolic demand is followed by modification of cerebral blood flow. This implies that for the clinician to have some indication of brain metabolic state will require specific explorations. Among these, seizure detection is the most obvious. In the absence of any clear modification in brain metabolism, the blood saturation in the jugular vein (SjO_2) can help. If SjO_2 is low (<70%), we can suppose that cerebral blood flow is not adequate for some reason. Multimodal monitoring is then of interest to provide a spectrum of items to diagnose the most probable causal mechanism.

For a given cerebral metabolic rate, brain perfusion depends on several factors: the cerebral perfusion pressure according to the autoregulation concept, the partial pressure of CO_2 (PCO_2), and the tissue oxygenation. Figure 4 shows the flow modifications observed in relation to the cerebral perfusion pressure.

In normal brain conditions, autoregulation works to maintain the flow within a large range of cerebral perfusion pressure values. However, because of peripheral pattern modifications, this regulation can be overcome. For example, acute hypercapnia, a frequent situation in ICU patients, leads to cerebral vasodilatation, increased cerebral blood flow, and increased cerebral blood volume. With normal intracranial pressure (ICP), the consequences are negligible.

When ICP is elevated, in conditions that increase cerebral blood flow and also cerebral blood volume, ICP increases because of lack of space in a rigid box. This situation may induce secondary brain ischemia [10]. That is the reason why, during brain injury, multimodal monitoring allows the diagnosis of brain hypoperfusion and determination of the mechanism of the decrease in cerebral perfusion pressure. If ICP elevation relates to hypercapnia-induced cerebral vasodilatation, it has to be controlled by ventilation. If the perfusion is limited because of anemia despite a significant cerebral blood flow, transfusion is the appropriate treatment. After correcting $PaCO_2$ and hemoglobin level, if ICP remains elevated it is the combination between all the parameters given by monitors that will provide a mechanism:

- pure cerebrospinal fluid (CSF) control problem: CSF derivation has to be performed.

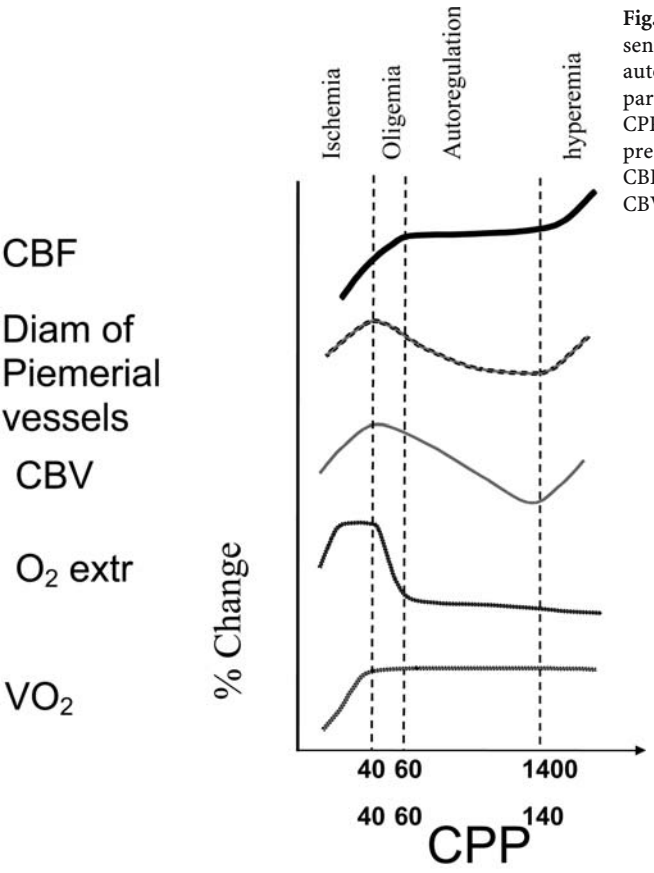

Fig. 4. Schematic representation of cerebral autoregulation on involved parameters.
CPP: cerebral perfussion pressure;
CBF: cerebral blood flow;
CBV: cerebral blood volume

- Brain parenchyma edema: osmotherapy, craniectomy, in rare cases, lumbar puncture
- Elevated cerebral blood volume: several means can be used.
  - Use of autoregulation in the remaining reactive areas by increasing cerebral perfusion pressure with norepinephrine
  - Reduction of cerebral blood flow by acute hypocapnia or $PaCO_2$ decrease
  - Reduction of cerebral oxygen demand by anesthetic drugs that reduce metabolic induced dilatation.

Transcranial Doppler associated with SjO_2 provides perfusion/oxygenation information [6]. Since cerebral blood flow is autoregulated, the phasic cerebral blood flow velocity has a large diastolic component. This diastolic flow velocity depends on parenchymal resistance: high resistance induces low diastolic velocity. The typical example is the brain dead patient, who is characterized by an absence of cerebral blood flow, and a zero diastolic blood flow velocity [11]. When diastolic

blood velocity is reduced with ICP elevation, the perfusion is altered. ICP and mainly cerebral perfusion pressure have to be improved.

In the absence of brain injury, except in dramatic situations, systemic circulation does not influence cerebral perfusion, especially in ICU sedated patients. Little information is available about the relation systemic/brain blood flow in patients with severe systemic inflammation [12, 13]. It is conceivable that systemic inflammation induces changes also in cerebral vessels and in their vascular tone control [13, 14]. Modification of brain perfusion and function might then be observed in severe sepsis [15].

Early aggressive therapy to maintain brain perfusion has a major impact on secondary brain ischemia in brain trauma patients. Maintaining adequate brain perfusion allows the brain lesion to the limited to the primary trauma lesions, with a better outcome.

Kidney perfusion [16]**:** Physiologically, the kidney has a high oxygen consumption due to active transmembrane transport for tubular functions and not due to the tissue cell oxygen demand. It is during the more intense tubular function that perfusion has to be maintained. It is also during this high risk situation that renal perfusion could be impaired due to hypotension and hypovolemia. Kidney blood flow varies in parallel with cardiac output. But importantly a DO_2 reduction is followed by a reduction in VO_2. The maintenance of tubular functions implies an adaptation of the energetic cost of these functions.

The kidney circulation is complex with a cortical and medullary compartment. The perfusion of the cortex containing glomeruli corresponds to 80% of the renal blood flow. This flow is normally autoregulated at a low and normal VO_2. At the medullary level, the flow is low and well maintained even in severely compromised situations.

Renal perfusion is difficult to measure clinically, since renal blood flow techniques are not routinely available [17]. Clinicians can only evaluate renal perfusion by its functional aspects: diuresis, creatinine clearance, urea levels. In ICU patients, resuscitation strategies may modify kidney perfusion. A good example is the impact of positive pressure breathing on kidney perfusion and function [18]; positive pressure breathing has been shown to cause a constant reduction in urinary output, fractional excretion of Na, and with a reduction in renal blood flow [19]. Various mechanisms are involved that integrate both renal blood flow, perfusion pressure, and neuro-hormonal reflexes [19]. Septic shock induces vasoconstriction of the renal vasculature that seems to be related to the sepsis inflammatory stimulation. This renal vasoconstriction does not respond to classic cardiovascular resuscitation. A recent publication suggests a positive effect of vasopressin when used as a vasopressor on systemic and renal circulation [20]. The renal effects of this treatment in septic shock patients were considered positive with an improvement in urinary output and creatinine clearance, and no apparent deleterious effect on renal tissue [20].

In conclusion, kidney perfusion is largely influenced by the systemic circulation, perfusion pressure and more importantly cardiac output. In addition, when renal DO_2 decreases, renal VO_2 decreases in parallel, limiting the renal consequences of

hypoperfusion. Diuretics and/or mannitol could be given to further reduce renal oxygen demand and protect the tissue.

Conclusion

Organ perfusion is a major challenge for clinicians in the ICU. The major difficulty comes from the technical limitations in ICU patients, and hence it is more frequently the functional modifications that guide the intensivists approach.

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Microcirculatory and Mitochondrial Distress Syndrome (MMDS): A New Look at Sepsis

P. E. Spronk, V. S. Kanoore-Edul, and C. Ince

Introduction

Sepsis is a major challenge in medicine and massive resources and considerable effort has been undertaken to understand the pathophysiology of this syndrome and to look for new therapies. Recently an observational study carried out in the US, has highlighted the relevance of this disease by their finding of a national incidence of 3 cases of severe sepsis per 1000 population. This produced a national estimate of 751,000 cases per annum of which 416,700 (55.5%) had underlying co-morbidity and overall 383,000 (51%) of them received ICU care. The overall hospital mortality rate found in this study was 28.6%, which represents 215,000 deaths nationally [1]. Severe sepsis is thus very common and is associated with a high mortality rate equaling the number of deaths after acute myocardial infarction. Furthermore, its incidence is likely to increase substantially as the population ages.

Severe sepsis is often associated with circulatory shock. This condition occurs when oxygen supply cannot meet the needs of the tissue cells, a condition which, if not corrected in time, can result in severe organ dysfunction [2]. The response of regulatory mechanisms of the cardiovascular system to shock and hypoxemia and thus oxygen delivery (DO_2), is to ensure an increase in the oxygen extraction ratio and thus attempt to match oxygen delivery to the demands of the tissue cells (VO_2). When this attempt fails, and oxygen levels are so low that mitochondrial respiration can no longer be sustained, tissue dysoxia is defined [3].

Under conditions in which oxygen supply becomes limited but microvascular regulation is intact, e.g., during hypovolemic or cardiogenic shock where hypoperfusion is caused by a decrease in cardiac output, the correction of global hemodynamic and oxygen-derived variables would be expected to restore tissue oxygenation [4]. Sepsis and septic shock, however, are characterized by the distributive pathological alteration of blood flow, loss of autoregulation and unresponsive hypotension with low vascular systemic resistance and normal or high cardiac output. The complex nature of the pathophysiology of this syndrome has led to considerable controversy regarding patient management. This is partly due to contradictory results in experimental studies in both animals and humans. For instance, the maximization of global hemodynamic parameters of DO_2 has been shown to improve outcome in hemorrhagic shock [5], whereas this strategy seems inadequate or even detrimental in septic shock [6, 7]. Despite an increase in cardiac

output and DO_2 to tissue in septic shock, seemingly paradoxical regional dysoxia is evident, as indicated by high lactate levels, disturbed acid base balance, and enhanced levels of gastric CO_2. This situation is described as a deficit in oxygen extraction ratio by peripheral tissue and has been well documented in different models of septic shock [8–10]. Essentially two conditions can explain this situation: First, pathological flow heterogeneity caused by dysfunctional autoregulatory mechanisms and, second, microcirculatory dysfunction causing hypoxic pockets and/or mitochondrial dysfunction whereby even in the presence of sufficient oxygen oxidative phosphorylation is not sustained. However, whether the oxygen extraction deficit is caused by regional hypoxia due to maldistribution of blood flow or as a result of so-called cytopathic hypoxia due to a defect in mitochondrial function is still a matter of debate [11]. Undoubtedly it will turn out to be a combination of both factors, each requiring a different therapeutic approach.

Two further important points need to be considered when defining the pathogenesis of sepsis in critically ill patients, these are time and the nature of the therapy being applied. It is clear that the element of time is crucial and that the nature of early sepsis is quite different from that of late sepsis. It could be well argued that what starts out as microcirculatory failure in early sepsis develops into mitochondrial dysfunction in late sepsis. A second important issue is the role of the therapy being applied and its relation to the pathogenesis of the syndrome that presents itself. For example, the pathophysiology and, therefore, pathogenesis when treatment includes the administration of corticosteroids will be very different to the pathophysiology and etiology in a septic patient not being given corticosteroids.

The above considerations and the view that the syndrome is defined by dysfunction at the level of the microcirculation and tissue mitochondria has led us to term it the Microcirculatory and Mitochondrial Dysfunction Syndrome (MMDS). In this model of the syndrome, the underling disease of sepsis is augmented by the therapy being administered resulting in sub-types of the syndrome so that the two are inseparably bound to each other when defining the pathogenesis of MMDS and when considering what subsequent therapeutic approach needs to be considered. Now that the behavior of these compartments can be studied in patients, new insights into the pathogenesis and treatment of sepsis are being gained. In this chapter, a brief review is presented of clinical and experimental studies that focus on the pathophysiology of oxygen transport to tissue during sepsis and resuscitation. The concept of MMDS is considered as a model for describing sepsis and resuscitation and its role in the pathogenesis of multiple organ dysfunction syndrome (MODS).

The Microcirculation and Oxygen Transport to the Tissues

The aim of the microcirculatory network is to deliver essential nutrients and oxygen to cells and to remove metabolized products from the tissues. The microcirculation consists of narrowing blood vessels connecting the arterial and venous systems. Arterioles form a diverging network of vessels ranging from first order arterioles through metarterioles to terminal arterioles supplying the capillary bed, the central and smallest portion (diameter 7–12 μm) of the microcirculation.

Blood draining this bed is collected by post capillary venules that ultimately converge into large venules. Through fare channels as well as arterio-venous shunts, together with diffusional shunting can cause pathological shunting of weak microcirculatory units and cause tissue dysoxia [4]. Metabolic and myogenic control of microvessels underlies the autoregulatory mechanisms ensuring the match of oxygen supply to demand. Hence, from a physiological point of view, the entire network should be regarded as a functional unit. Its functional behavior, however, is highly heterogeneous and the microcirculation of each organ differs both in anatomy and function. Besides different capillary densities and receptors present, different types of capillaries are present as well, with interrupted, fenestrated, continuous or discontinuous membranes. These anatomical differences in the capillaries explain the different degree of filtration of the microcirculatory beds in different organ systems. Each organ will of course also have its own oxygen consumption and blood flow depending on regional metabolic demands. The regulation of blood flow to the organs and the distribution of oxygen transport within organs is strictly regulated under physiological conditions, but during critical illness severely disturbed also as a consequence of the compounds and fluids being administered. The heterogeneity between organ systems with respect to oxygen consumption and microvascular properties is depicted in Figure 1.

The classical Krogh model of oxygen transport from the microcirculation to the tissues dictates that oxygen exchange occurs principally in the capillary bed, but

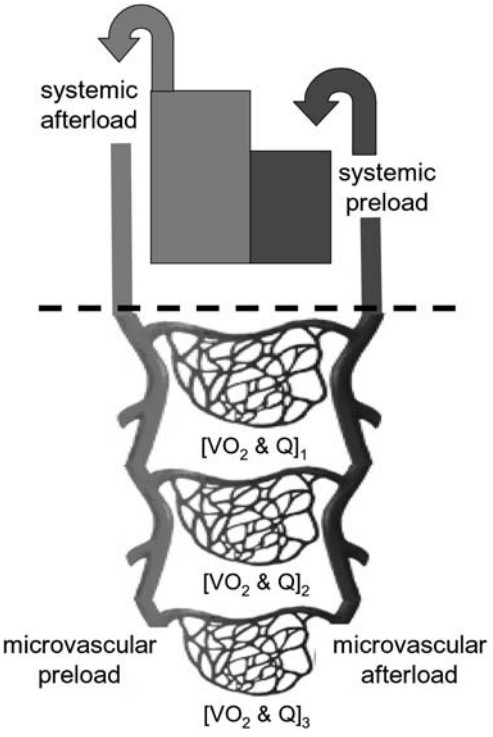

Fig. 1. Schematic depiction of global circulation and microcirculatory blood flow in different organ systems with organ specific oxygen consumption and flow $[VO_2 \& Q]_{1-3}$. Systemic afterload could be interpreted as microvascular preload, while systemic preload could be thought of as microvascular afterload. Specific vasoactive medication can be chosen to modulate microvascular perfusion.

recent data on longitudinal and radial oxygen gradients in the arteriolar blood vessels of most tissues suggests that a significant amount of oxygen is lost from those vessels [12]. Hence, the oxygen being supplied by capillaries to the tissues may be secondary to that supplied by arterioles in some tissues. The fractional oxygen loss in the arteriolar network is thought to depend on the metabolic activity of the organ involved, the arteriolar network being the main site of delivery in tissue with low metabolic activity. Conversely, in tissue with a high rate of metabolic activity and thus high blood flow, the fall in blood oxygen levels appears to occur in the capillary bed [13]. Also, there is some additional loss of oxygen from the venular network. In all these cases however, the mean PO_2 of the distal venules is generally higher than that of the post capillary vessels. This effect is likely to be caused by both convective shunt and a diffusional shunt from arteries to venules. Thus, oxygen transport to the tissues is achieved by a combination of a convective mechanism (blood flow) that is highly heterogeneous and a diffusive mechanism, which together achieve a remarkable homogenous oxygenation of the microcirculation [13]. This shunting becomes more severe in septic than in hemorrhagic shock and is an indication of the shut down of the microcirculation and the onset of tissue distress [4].

The Microcirculation in Sepsis

Sepsis, and its sequels septic shock and MODS, represent progressive stages of the same illness in which a systemic response to an infection mediated by endogenous mediators may lead to a generalized inflammatory reaction in organs distant from the initial insult, eventually leading to organ dysfunction and failure [14]. It is now well accepted that abnormalities in microcirculatory function are a major contributing factor to MODS in sepsis [15, 16]. Data from experimental animal studies and from human studies show that almost each functional component of the microcirculation is affected during sepsis[17].

Oxidative stress in sepsis occurs when the balance is lost between the phagocytic formation of reactive oxygen species (ROS) – predominantly superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxide radicals (HO^-)-, and their removal by endogenous antioxidant pathways [18]. An overwhelming production of ROS is believed to contribute directly to endothelial and tissue injury via membrane lipid peroxidation and cellular DNA damage. A large number of studies are focusing their attention on the role of antioxidant defence systems in order to develop new pharmacological approaches. In septic shock, glutathione, a natural intracellular antioxidant is decreased. This can lead to decreased protection of cell membranes against oxygen radicals. N-acetylcysteine (NAC) serves as a precursor for glutathione and can replenish glutathiones stores. Also, NAC can act as a direct scavenging agent and can produce antioxidant and cytoprotective effects. Furthermore, NAC may improve microvascular blood flow. Rank et al. [19] investigated the influence of NAC on liver blood flow, hepatosplanchnic oxygen transport-related variables, and liver function during early septic shock. Patients were conventionally resuscitated with volume infusion and the use of inotropes if required to obtain a stable condition. They were randomly assigned to receive either a bolus of

150 mg/kg NAC followed by a continuous infusion of 12.5 mg/kg/hr for 90 min, or placebo. After NAC treatment, hepatosplanchnic blood flow and function improved. This increase was related to an increase in cardiac index secondary to a decrease in systemic vascular resistance. However, no statistically significant differences in outcome could be demonstrated between the groups [19]. Recently, NAC was found to have beneficial effects on the activation of nuclear factor-κB (NF-κB). Administration of NAC resulted in decreased NF-κB activation in patients with sepsis, associated with decreases in interleukin-8 (IL-8) [20]. These data suggest that antioxidant therapy with NAC may be useful in blunting the inflammatory response to sepsis, but further studies focusing on an improvement in outcome are warranted.

Local distribution of blood flow in most tissues is mainly determined by the tone of precapillary arterioles. They are under the influence of intrinsic and extrinsic factors where local intrinsic factors play a role in phenomena such as autoregulation. In a septic state, the only vascular bed where intrinsic vasoregulation is preserved is thought to be the cerebral vasculature [17, 21]. Extrinsic factors like neural and humoral factors are also severely affected during clinical and experimental sepsis induced by lipopolysaccharide (LPS). The arteriolar response to vasoconstrictors and vasodilators is attenuated in many organs, resulting in a decrease in peripheral resistance with systemic hypotension because it appears that the hyporesponsiveness of vasoconstrictors predominates. Paradoxically, at the microvascular level, sepsis causes heterogeneous effects on constriction and dilation at different levels of the microcirculation [17].

The venular end of the microcirculation is the primary locus of inflammatory events such as neutrophil adhesion and emigration, and protein and water leakage. Underlying microcirculatory dysfunction is the presence of inflammatory mediators, as well as altered functional states in various cell systems. Endothelial activation for example, is accompanied by up-regulation of adhesion molecules, swelling and pseudopod formation, polymorphonuclear (PMN) cell accumulation in organs, adhesion and emigration, and vascular protein leakage coupled to leukocyte emigration. These events lead to an exaggerated inflammatory response in the venular bed. Besides vascular and tissue cells, red blood cells are also affected by sepsis resulting in altered blood viscosity and other hemorheological parameters [22, 23]. All of the above altered cellular dysfunction will affect microcirculatory distress and ultimately result in organ dysfunction depending on their respective contributions and severity, and the time of onset of the septic state, in addition to the nature of therapy being applied.

In order to obtain direct evidence for tissue hypoxia in patients with sepsis, partial oxygen pressure was measured within skeletal muscle in humans with septic shock. In one of these studies serial intermittent and continuous measurements of skeletal muscle PO_2 was assessed by polarographic needle electrodes in patient with sepsis. The results were compared with patients with cardiogenic shock and patients with limited infection. Mean skeletal muscle PO_2 was increased in patients with sepsis compared with patients with limited infection and with patients with cardiogenic shock. In the same study the authors did serial measurements of the PO_2 distribution during seven consecutive days in another group of patient with sepsis, and the data showed that a more severe degree of sepsis was associated with

an increase in mean skeletal muscle PO_2. They concluded that oxygen utilization within skeletal muscle decreased with deterioration of sepsis, thereby increasing skeletal muscle PO_2 [24].

Recently, Sair et al. conducted a study in septic patients to assess tissue oxygenation and perfusion [25]. They hypothesized that sepsis is accompanied by regional hypoperfusion with inherent impairment of peripheral tissue oxygenation. They employed an amperometric microelectrode technique, laser Doppler flowmetry and strain gauge plethysmography to assess tissue PO_2 (PtO_2) and the relative distribution of perfusion between forearm muscle and subcutaneous tissues in healthy subjects. They compared these results with those obtained in patients with established systemic sepsis and in individuals with a transient inflammatory response related to cardiopulmonary bypass (CBP). They also investigated tissue responses induced by forearm ischemia and reperfusion. They found that baseline muscle PtO_2 was higher in septic patients than in volunteers and post CBP patients, although there were no differences in baseline subcutaneous PtO_2. Subcutaneous and muscle PtO_2 decreased during ischemia in all groups, but this decrease was initially more rapid in septic muscle compared with controls. During forearm ischemia, baseline red cell flux decreased significantly in healthy volunteers, whereas red cell flux was higher at baseline in the septic group. The main findings of this study were that there was an increase in muscle PtO_2 tension in systemic sepsis compared to controls and patients recovering from CBP, and that these changes were specific to muscle. There was a rapid decrease in muscle PtO_2 during stagnant ischemia and the relative increase in muscle PtO_2 was not accompanied by an increase in microvascular flow in this tissue. The authors concluded that tissue PO_2 recovery during reperfusion appears to be intact. These observations do not support the concept of impaired tissue oxygenation or extraction as an underlying cause of organ failure in sepsis. However, it is important to keep in mind the differences between organs regarding microcirculatory properties and how they respond to sepsis. The main limitation of oxygen electrodes is their extremely limited area of measurement, with penetration depths of approximately 15 μm, and their sensitivity to arterial oxygenation [26]. They measure an average PO_2 of tissue cells, capillaries, and larger blood vessels in the vicinity of the electrode and may therefore miss the presence of hidden hypoxic areas because oxygenation is highly heterogeneous at this level. In addition, since laser Doppler flowmetry provides a relative signal of red blood cell flow from an unknown tissue volume, it is unable to discriminate fundamental capillary stopped-flow or flow heterogeneity induced by sepsis. While the exact mechanism of microvascular stasis is still to be determined, it is clear that sepsis causes local regions of ischemia in the tissue by virtue of capillary stopped-flow (27).

Microcirculatory Weak Units and PO_2 Gap

During hypoxemia, oxygenation of the microcirculation can become highly heterogeneous, with well-oxygenated microcirculatory units next to hypoxic units. The properties of such disadvantaged microcirculatory units was studied effectively with the use of NADH fluorescence by Ince et al. in different models. These

microcirculatory units were termed microcirculatory weak units because they are the first to become dysoxic during distress and the last to recover from an episode of ischemia. Pd-porphyrin phosphorescence imaging and embolism by microspheres of different diameters identified these microcirculatory weak units as being composed of capillary vessels and they were found to reside close to the venules, where the well oxygenated units were found next to the arterioles. The presence of such hypoxic microcirculatory weak units suggests that these units are being shunted during hypoxemia. This would be expected to result in microcirculatory PO_2 values becoming lower than venous PO_2 values. In several studies, Pd-porphyrin phosphorescence was used to analyze the behavior of microcirculatory PO_2 during hemorrhagic shock and resuscitation in pig ileum [26, 28]. The results of these studies showed that under normoxic conditions serosal microcirculatory PO_2 was equal to, or slightly higher than venous PO_2. During hemorrhagic shock, however, venous PO_2 decreased to a plateau level, whereas microcirculatory PO_2 continued to decrease in value. This resulted in an increasing disparity between the microcirculatory PO_2 and the venous PO_2. This disparity was termed the PO_2 gap reflecting the consequences of oxygen shunting of the microcirculation. Resuscitation with crystalloid or Hb solutions was able to restore this gap to baseline levels. To study the role of microcirculatory PO_2 during the early phases of sepsis, Pd-porphyrin phosphorescence studies were carried out in pig intestines [29]. At baseline, serosal microcirculatory PO_2 was equal to or slightly higher than venous PO_2. During endotoxemia, microcirculatory PO_2 decreased in value and the PO_2 gap between microcirculatory and venous oxygen levels increased with time. The gap in PO_2 occurred prior to the deterioration of other variables, although gastric tonometry correlated positively with the severity of the PO_2 gap. Microcirculatory PO_2 was equally depressed in both hemorrhagic and septic shock, but the PO_2 gap was more severe in the septic animals. This difference in the PO_2 gap was interpreted as reflecting a larger shunting fraction present during endotoxemia than during hemorrhage. Shunting of oxygen from the microcirculation could explain the condition in sepsis in which signs of regional dysoxia are evident despite apparently sufficient oxygen delivery. The presence of microcirculatory weak units was first identified in the heart and soon microcirculatory weak units were also found in other organs such as the mucosal villi of the intestines and the cortex of the kidney, but not in cat skeletal muscle [30]. These findings suggest that the presence of microcirculatory weak units in different organs and their reaction to hypoxemia and sepsis, is dictated by the specific microcirculatory architecture. Nevertheless, shunted parts of the microcirculatory network should be recruited, for instance by locally acting vaso-active modulators. One of the central players in hemodynamic abnormalities of the microcirculation is nitric oxide (NO), not only due to its role in determining autoregulation but also due to its heterogeneous expression of the inducible NO synthase (NOS), and its effects on hemorheological parameters such as red blood cell deformability (31).

NO has both beneficial and detrimental effects on many organ systems. In the endothelium, NO functions as a regulator of vascular tone, thereby modulating microvascular perfusion, and as an inhibitor of platelet adhesion and aggregation. Release of NO is highly controlled by shear stress of flowing blood acting on the

endothelial cells in all arteries of the body. Bacteremia results in a cytokine-mediated induction of inducible NO synthase (iNOS) in macrophages, hepatocytes, cardiac cells, and especially in vascular smooth muscle cells. After iNOS induction, smooth muscle cells produce large amounts of NO. The resulting inhibition of responsiveness to norepinephrine leads to a loss of vascular tone and the large amounts of NO to loss of auto regulatory capacity. In fact, the pathogenetic role of NO in sepsis and septic shock can encompass both vascular alterations and the direct cellular toxic effects on NO or NO-released compounds. Mice lacking iNOS have been reported to be resistant to endotoxin-induced mortality and vascular hypo contractility [32]. In addition, NO exerts *in vitro* toxic effects including nuclear damage, protein, and membrane phospholipid alterations, and the inhibition of mitochondrial respiration on several cell types [33]. The toxicity of NO itself may be enhanced by the formation of peroxynitrite from the reaction of NO with superoxide. However, the relevance of mitochondrial dysfunction *in vivo* is questionable as administration of SIN-1, an NO donor, in a canine [34] and a pig [35] model of endotoxic shock increased oxygen extraction capabilities. On the other hand, NO may protect cells from oxidative damage by scavenging oxygen free radicals and inhibiting oxygen free radical production. From a shunting point of view, providing additional NO by giving NO donors may be expected to have a beneficial effect on the microcirculation due to its enhancing the driving pressure to the microcirculation because of its vasodilatory effect and thereby opening weak microcirculatory units which otherwise would have been shunted. In addition, other beneficial effects of NO on the microcirculation such as its anti-adhesive effects and improved erythrocyte deformability would be expected to improve perfusion and recruit shunted microcirculatory units. Based on this idea, several NO donors have been tested in relation to sepsis and regional and microcirculatory oxygen transport in experimental animals and recently in humans. The NO donor SIN-1 has been used in endotoxic dogs, where it increased cardiac index and superior mesenteric blood flow without affecting arterial pressure or global oxygen extraction [34].

Nevertheless, it is important to remember that most NO research has been conducted in animal and *in vitro* studies and many of the controversial and contradictory results can arise from the differences in the species studied, the model of sepsis employed, and the timing of measurements [33]. From a hemodynamic point of view, vasodilation is expected to open the microcirculation. Indeed, there is considerable evidence from animal experiments indicating the potential benefit of vasodilators in the presence of sufficient volume [36]. Clinical studies, however, are limited to those involving prostacyclin. Based on our hypotheses that a vasodilator drug with a sufficient amount of volume might improve DO_2 and VO_2 within vulnerable areas by recruitment of weak microcirculatory units at risk, and that correction of microcirculatory shunting may contribute to resuscitation strategies in sepsis [4], we tested the efficacy of the NO donor SIN-1 to resuscitate gut microcirculatory oxygenation in a clinically relevant porcine model of septic shock and resuscitation [35]. Intestinal PCO_2, organ blood flow and microcirculatory PO_2 (μPO_2) of serosa and mucosa of the ileum were measured simultaneously. Microcirculatory PO_2 was measured using the PO_2 dependent quenching of Pd-porphyrin phosphorescence technique. Results showed that LPS injection resulted

in a decrease in mean arterial pressure (MAP), cardiac index (CI), and regional blood flow, while fluid resuscitation restored cardiac output in both groups. MAP remained decreased in both groups but SIN-1 generated significantly higher values of MAP. The systemic vascular resistance (SVR) was depressed following fluid resuscitation and restored to baseline values in the SIN-1 group. DO_2 and VO_2 increased in response to fluid therapy alone and were significantly higher than in the SIN-1 group. Arterial and mesenteric lactate increased. Superior mesenteric artery blood flow decreased together with μPO_2 of the ileal mucosa and serosa. This decrease was accompanied by an increase in the intestinal PCO_2 gap. Administering fluids alone or together with SIN-1 increased flow and mucosal μPO_2 to baseline levels. SIN-1 produced a significantly higher serosal μPO_2 and normalization of the intestinal PCO_2 gap. These findings support the notion that therapy including vasodilators can recruit shunted microcirculatory units and improve tissue oxygenation while maintaining systemic hemodynamic parameters above shock values.

In a recent study in pigs, we found that infusion of the highly selective iNOS inhibitor 1400W, in an endotoxic shock model comparable to the SIN-1 experiment, was also able to restore μPO_2 of the serosal and mucosal side of the ileum [29, 35]. The use of 1400W corrected the intestinal PO_2-gap and thereby the functional shunting of oxygen with normalization of the PCO_2-gap. According to the SIN-1 study cited above, the control group was resuscitated with fluid alone and showed persistent signs of functional shunting. The use of 1400W restored global hemodynamic parameters after endotoxic shock to baseline and corrected the epicardial μPO_2 .In earlier studies we had found that dexamethasone (also an iNOS inhibitor) was able to correct autoregulatory failure in septic rat heart where endotoxin-induced iNOS overproduction underlies heart autoregulatory function (37). These results, in combination with immunohistological studies showing a heterogeneous expression of iNOS during endotoxemia, support the notion that specific iNOS inhibitors could have beneficial effects on correcting pathological heterogeneity in regional flow and restoring autoregulatory function. One could hypothesize that this may be one of the beneficial effects of the clinical administration of corticosteroids in the treatment of sepsis.

Clinical Estimates of Microcirculatory Function

The expedient detection and correction of tissue dysoxia may limit organ dysfunction and improve outcome. However, tissue dysoxia is very difficult to detect at the bedside because there are neither specific clinical signs, nor simple laboratory tests. We are stuck with simple clinical signs of organ dysfunction such as hypotension, oliguria, altered mental status, a disturbed acid-base balance, or high lactate levels. One should however be cautious in interpreting these signs, since many of them may not be present in septic patients, or when they are present, could be very late indicators of organ dysfunction. In fact, it may well be too late for the resuscitation of these patients, since they could already have entered the refractory phase of shock. More invasive methodologies such as the measurement of cardiac output or mixed venous oxygen saturation (SvO_2) levels are also criti-

cized, because these global measures of hemodynamic and oxygen transport parameters including cardiac output, SVR, MAP, and oxygen consumption and extraction provide whole body information on the status of the cardiovascular system but fail to assess the microcirculatory level vital for organ function and in fact the target tissue of sepsis [16].

Lactate levels are thought to reflect anaerobic metabolism associated with tissue dysoxia and might predict a response to therapy and prognosis [38]. The balance between lactate production due to global (shock, hypoxia), local (tissue ischemia), and cellular (mitochondrial dysfunction) factors on the one hand, and lactate clearance depending on metabolic liver function on the other hand, make the interpretation of lactate levels uncertain and difficult [39]. SvO_2 can be measured using a pulmonary artery catheter. The SvO_2 is thought to reflect the average oxygen saturation of all *perfused* microvascular beds. In sepsis, microcirculatory shunting can cause normal SvO_2 while severe local tissue dysoxia is present [4]. Delayed therapy aimed at normalization of SvO_2 failed to demonstrate a survival benefit [6, 7]. Optimization of DO_2 may have been instituted too late in these studies, when irreversible cellular damage was already present. In addition, the high doses of dobutamine needed to reach preset goals of DO_2 may have negatively affected the outcome. Nevertheless, besides ongoing discussions regarding the use of a pulmonary artery catheter in sepsis, the sole use of SvO_2 seems an inadequate parameter as guideline for therapy in the restoration of local tissue oxygenation in septic shock patients. It is still useful to measure SvO_2 because SvO_2 decreases if cardiac output becomes inadequate. Hence SvO_2, if normal or high does not necessarily indicate that everything is alright, while a low SvO_2 should prompt rapid intervention to increase DO_2 to the tissues [40]. If, however, an integrative approach is used in the early stage of treating critically ill patients, states of hypoperfusion might be recognized earlier [41], and, if early treatment is started, may even improve survival [42]. It is likely that the results of the Rivers study are largely due to the prevention of irreversible cellular damage, in contrast to the earlier findings by Hayes and Gattinoni who targeted high oxygen delivery levels during later phases of sepsis [6, 7].

In the last few years, an interesting debate in the critical care arena has centered around the definition of resuscitation end points in the treatment of patients with sepsis. Many attempts have been made to look for specific regional organ monitors. In this context gastric tonometry has appeared to be the only organ specific monitor of tissue dysoxia currently available, since splanchnic hypoperfusion occurs early in shock and may occur before the usual indicators of shock. Although an early clinical trial had suggested that tonometry derived parameters may be useful in guiding therapy [43, 44], these findings were not confirmed recently [45] and its limited sensitivity and specificity has been highlighted. In sepsis, the interpretation of tonometric results is affected by microcirculatory shunting. This complicates the clear establishment of impaired perfusion, since areas with reduced perfusion and CO_2 off-loading are next to hypoxic regions [46]. Intramucosal PCO_2 can increase in the intestinal lumen by two mechanisms: by $HCO3^-$ buffering of protons from the breakdown of high-energy phosphates and metabolic acids generated anaerobically, which would represent dysoxia or in an aerobic state it might be the result of hypoperfusion and decreased washout. In this case oxygen metabolism

could be preserved if the flow were adequate. In an attempt to demonstrate that a rise in PCO_2 could reflect only a decrease in blood flow, Dubin et al. conducted a study in sheep where DO_2 was reduced by decreasing either flow (ischemic hypoxia) or arterial oxygen saturation (hypoxic hypoxia). The PCO_2 increased in the ischemic hypoxia group but remained unchanged in hypoxic hypoxia. These results suggest that a change in PCO_2 may be determined primarily by blood flow [44]. Later, the same group found similar results in a model of endotoxemic sheep where they compared two groups treated with LPS, one of which received hyperresuscitation with fluids; in this group no improvement in PCO_2 could be demonstrated.

To define whether the gastric mucosal–arterial PCO_2 gradient (PCO_2 gap) reliably reflects hepatosplanchnic oxygenation in septic patients, Creteur et al. performed a prospective, observational clinical study, where they measured hepatosplanchnic blood flow by the continuous indocyanine green infusion technique and gastric mucosal PCO_2 by saline tonometry in 36 hemodynamically stable patients with severe sepsis [47]. Suprahepatic venous blood oxygen saturation and PCO_2 also were measured. They determined the mesenteric veno-arterial PCO_2 as the difference between the suprahepatic venous blood PCO_2 and the arterial blood PCO_2. They found significant correlations between the hepatosplanchnic blood flow and the suprahepatic venous blood oxygen saturation, and between the hepatosplanchnic blood flow and the mesenteric veno-arterial PCO_2 gradient. However, there was no statically significant correlation between cardiac index and hepatosplanchnic blood flow, suprahepatic venous blood oxygen saturation, or mesenteric PCO_2 veno-arterial gradient, and between PCO_2 gap and cardiac index, hepatosplanchnic blood flow, the suprahepatic venous blood oxygen saturation, or the mesenteric veno-arterial PCO_2 gradient. In this study, the lack of correlation between CI or SvO_2 and hepatosplanchnic blood flow or suprahepatic venous blood oxygen confirmed that the global assessment of systemic oxygen transport lacks the sensitivity to detect regional gut hypoperfusion. The authors hypothesized that one possibility to explain these data is that the PCO_2 gap reflects merely the perfusion state of the gastric mucosa whereas hepatosplanchnic blood flow, suprahepatic venous blood oxygen saturation and mesenteric veno-arterial PCO_2 gradient are global indices of oxygen supply to the liver and the different layers of the gut (mucosa, muscularis and serosa). In this context, the countercurrent vascular anatomy in the gut villi renders the tip of these villi very vulnerable to hypoxia. The existence of hypoxic arteriovenous shunts at the top of these villi could result in an increased PCO_2 gap from the combination of anaerobic CO_2 production and CO_2 stagnation because of the existence of unperfused mucosal areas. On the other hand, the serosa is extremely sensitive to shunting since oxygen is primarily diverted to the mucosa during fluid resuscitation. Also, there is enhanced iNOS expression in the villi reducing microcirculatory resistance to this compartment. Under such conditions, the luminal CO_2 being measured could also originate from hypoxic serosa. Therefore, the interpretation of PCO_2 gap monitoring is complex and requires further study. Recently, gastric intramucosal PCO_2 values were found to be well correlated with sublingual PCO_2 ($PslCO_2$) values [48]. The baseline difference between $PslCO_2$ and arterial PCO_2 values was a better predictor of survival than the change in lactate or SvO_2 [49]. Further studies should demonstrate

whether this parameter can be used in the clinical management of the patient with septic shock.

We recently introduced [50, 51], validated [52], and clinically applied [15, 53, 54] a new method to observe the microcirculation in patients called orthogonal polarization spectral (OPS) imaging that creates high contrast images without the use of fluorescent dyes. This technique is based on the invention by Slaaf et al. who found that illumination of tissue with green polarized light and filtering reflected by cross polarization resulted in much superior images of the microcirculation when observed under intravital conditions [55]. For OPS imaging a 5× objective (on-screen magnification of 326×) is used during measurements. Data are recorded on a digital videorecorder for later analysis and visualized on a black and white monitor. Because the OPS machine is a small hand held device, it can be used at the bed-side in humans as well as during surgery and a wide variety of clinical scenarios [51] to uniquely visualize on line images of blood cells flowing in the microcirculation in patients. Although nailfold microcirculatory blood flow as established by OPS imaging correlates very well with intravital microscopy microvascular flow when analyzed by specific video-analysis-software [52], this quantitative approach proved unusable with sublingual images due to movement artifacts induced by tongue movements or respiration. Therefore, a semi-quantitative approach was successfully used to analyze changes in microcirculatory flow [15, 56].

Resuscitating the Microcirculation

Resuscitation strategies based on the correction of upstream hemodynamic variables and systemic parameters of DO_2 do not correct downstream indicators of dysoxia. This may in part be explained by the so-called shunting theory of sepsis where microcirculatory units are shunted at the regional level causing patchy hypoxic areas. The therapeutic consequence of this shunting theory implies that procedures aimed at opening and recruiting the microcirculation would be expected to improve regional organ function and tissue distress. Several studies have been performed aimed at recruitment of the tissue microcirculatory flow by use of vasodilators [36]. Radermacher et al. treated septic shock patients with prostacyclin when no further increase in DO_2 could be obtained by volume resuscitation and dobutamine infusion. Gastric intramucosal pH (pHi) improved after starting prostacyclin, suggesting an increase in splanchnic blood flow [57]. Bihari et al. found that, after increasing DO_2 with the vasodilator prostacyclin, all patients survived when the increase in DO_2 did not coincide with an increase in VO_2, whereas all patients died who showed increasing VO_2 [58]. Vasodilation may thus unmask an existing tissue oxygen-debt. By recruitment of the microcirculation, oxygen might have become available to previously hypoxic tissues that were shut down. This concurs with the finding that the glucose oxidation rate improves in septic patients after treatment with prostacyclin [59]. Apparently, the microcirculation in sepsis fails to support adequate tissue oxygenation unless adequately targeted for resuscitation. At the same time, the low peripheral resistance in sepsis cannot be interpreted as a sign of adequate tissue perfusion. Especially in septic

shock, alterations in metabolic pathways called cytopathic hypoxia may lead to additional tissue damage [11].

Oxygen consumption increases with a concurrent increase in DO_2 under nitrate administration [60]. Based on the hypothesis that NO production is increased in sepsis, experiments in septic animal models were performed and indicated that hypotension could be prevented by the inhibition of NOS. This led to clinical studies with several compounds capable of inhibiting NO synthesis. Early promising data showed increasing blood pressures and decreasing doses of vasopressors in septic shock patients treated with NOS inhibitors [61]. However, a subsequent randomized, controlled, multicenter, phase III trial was stopped when interim analysis showed increased mortality in the L-NMMA group compared to placebo [62]. Inhibition of NOS activity seems to result in an apparent improvement in the general hemodynamic situation at the cost, however, of increased mortality [33]. Apparently, completely inhibiting vasodilation is not the proper answer to sepsis. A more specific approach by inhibiting only the inducible form of NOS may be an attractive alternative. Indeed, after application of 1400W (a synthetic iNOS-blocker) in a porcine endotoxemia model, microvascular perfusion was restored due to a redistribution within the gut wall and/or an amelioration of cellular respiration [63].

It seems an appealing thought that the impairment of microcirculatory perfusion results in organ failure and increases the risk of death. Indeed, survival was related to microcirculatory shut-down in rats that were hemorrhaged and subsequently blood volume resuscitated, although whole body hemodynamic parameters were comparable in survivors and non-survivors [64]. Comparable findings were recently reported in humans with septic shock. De Backer et al. reported that sublingual microcirculatory perfusion was more compromised in non-surviving than in surviving septic shock patients [56]. So, is the sublingual microcirculation a mirror of total body microcirculatory dysfunction? We observed normal sublingual microcirculatory perfusion in a septic patient with hepatic failure who received high doses of norepinephrine (Spronk P, unpublished observation). Dubois et al. recently reported a comparable observation in a septic patient treated with vasopressin [65], whereas others observed sublingual microcirculatory shut-down with the use of vasopressin (personal communication). Larger studies should demonstrate why these patients behave differently to apparently the same therapy. Nevertheless, De Backer et al. showed that microcirculatory perfusion improved over time in survivors, whereas the derangement of perfusion in the microvessels of the non-survivors remained [56]. In addition, they showed that sublingual microcirculatory perfusion abnormalities could be corrected by topical application of acetylcholine, thus demonstrating that the local endothelium was still NO responsive, whereas vasoplegia due to ongoing sepsis might be expected. Nitric oxide is an important vasodilator in the microcirculation during sepsis [66]. As mentioned above, we have shown that NO donors in the presence of adequate amounts of volume are highly effective in correcting microcirculatory oxygenation following endotoxemia in a pig model of sepsis, with both mucosal and serosal microvascular PO_2 as well as intraluminal gastric PCO_2 being restored to baseline values [35]. These findings led us to hypothesize that addition of systemic NO to adequately volume resuscitated patients with septic shock would result in an

improvement in microcirculatory perfusion. In a small observational study in septic shock patients, we were indeed able to demonstrate an improvement in sublingual microcirculatory perfusion after the injection of 0.5 mg nitroglycerin [15]. The observation of capillary shutdown next to sustained flow in the larger vessels corroborates the shunting theory of sepsis and indicates the vulnerability of the capillaries also identified by De Backer and co-workers. Upon administration of nitroglycerin, microcirculatory flow increased not only in large, but also in small microvessels showing the efficacy of targeting a resuscitation procedure aimed at the microcirculation. It is important to point out several important issues during the administration of nitroglycerin in our study. All septic patients received a single dose of 1 mg/kg dexamethasone at admission to the ICU as part of standard treatment. This is based on the hypothesis that dexamethasone infusion mitigates the pro-inflammatory mediated induction of iNOS expression. As resuscitation endpoints, we first aimed at a central venous pressure (CVP) of at least 10 mmHg by infusing crystalloids and colloids. If the MAP remained below 60 mmHg, we started dopamine, and if necessary norepinephrine. After these predefined resuscitation endpoints were reached, nitroglycerin was infused, a drip was started (average 2 mg/hr), and microcirculatory observations were made. Although systolic blood pressures dropped temporarily with fast recovery, CVP pressures remained quite stable. In our opinion, this means that venous capacitance was adequately filled in the patients studied. The infusion of nitroglycerin in a constricted venous system would have resulted in a huge drop in both arterial and venous pressures, requiring fast infusion of more fluids to compensate for dilation of the venous reservoir.

All of the patients in this study were discharged from the hospital alive except one who died from late cerebral hemorrhage. This suggests that one can actively open-up the microcirculatory network, and keep it open by volume and vasodilator therapy. Further studies should demonstrate whether this line of thought regarding therapy in sepsis can be guided by microcirculatory flow patterns and may result in a better outcome.

Mitochondrial Dysfunction

Increased tissue PO_2 in some organs of animals and patients with sepsis together with low VO_2 and absence of cell death, lead to the hypothesis that in sepsis oxygen is available but not utilized. Hence, different biochemical mechanisms or mediators have been suggested to account for cellular dysfunction and cytopathic hypoxia *in vitro* and in animal studies, including the inactivation of pyruvate dehydrogenase, the reversible inhibiton of cytochrome oxidase by NO, inhibition of mitochondrial respiratory complexes by peroxinitrite and activation of the nuclear enzyme poly(ADP-ribosyl) polymerase (PARP). Mitochondrial oxidative phosphorylation is responsible for over 90% of the total body oxygen consumption and ATP generation. The respiratory chain includes four individual enzyme complexes which can be inhibited by reactive oxygen and nitrogen species such as NO. This process is facilitated by depletion of the anti oxidative defense systems such as glutathione.

In a recent study, Brealey et al. investigated whether alterations in bioenergetic status in severe sepsis are associated with increased NO production, mitochondrial dysfunction, and antioxidant depletion, and whether these abnormalities relate to organ failure and to outcome [67]. These investigators did skeletal muscle biopsies on 28 critically ill septic patients within 24 h of admission to the ICU and on nine control patients undergoing elective hip surgery. The biopsy samples were analyzed for respiratory-chain activity (complexes I-IV), ATP concentration, reduced glutathione, and nitrite-nitrate concentrations. They found a significant reduction in ATP concentrations in septic patients who died in comparison to surviving septic patients and controls. Also, they found that Complex I activity had a significant inverse correlation with norepinephrine requirements and mortality. There was a significant positive correlation between tissue concentrations of nitrite/nitrate and severity of disease. They concluded that in patients with sepsis there is an association between NO overproduction, antioxidant depletion, mitochondrial dysfunction, and decreased ATP concentrations that relate to organ failure and outcome. These data suggest that bioenergetic failure is an important pathophysiological mechanism that accounts for multiorgan dysfunction in sepsis. However, it is not possible to rule out an alteration in microvascular flow, an early well-known alteration in sepsis from this study. Thus it is not clear whether mitochondrial dysfunction can develop in the presence of sufficient amounts of oxygen. Also, a microcirculatory control defect can result in cytopathic hypoxia.

Microcirculatory and Mitochondrial Dysfunction Syndrome: A New Look at Sepsis

Patients with septic shock show different signs and symptoms depending on the time of presentation and on which therapies have been initiated. In the early stages, septic shock is characterized by a pattern of low cardiac output and high or normal SVR. With fluid resuscitation, both animal and human data have indicated a subsequent switch to a hyperdynamic state, characterized by a low SVR with or without hypotension, a high cardiac output, an increased DO_2, an increased VO_2, and impaired oxygen extraction capacity [68]. In spite of increased oxygen transport, there are signs of tissue dysoxia as expressed by high lactate levels and acid-base disturbances. Whether these disturbances are caused by shunting due to microcirculatory dysfunction and/or impaired mitochondrial function is still a matter of debate.

It is becoming clear that sepsis is a disease of the microcirculation and, in its extension, of the mitochondria, given that systemic hypovolemia has been corrected. Hence, it seems appropriate to define this syndrome as MMDS. In this way the name focuses on the pathophysiology compartment underlying the disease. It is evident from experimental and clinical data that MMDS is a condition poorly reflected by systemic hemodynamic and oxygen derived variables, which explains why in the past such parameters have provided poor resuscitation end-points. It is likely that in the progress of MMDS, microcirculatory dysfunction is followed by mitochondrial failure. As sepsis and its sequelae severe sepsis, septic shock and multi organ failure represent progressive stages of the same illness, so MMDS is

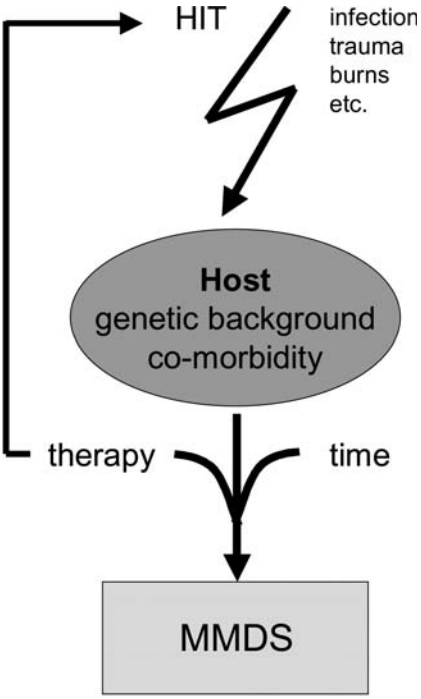

Fig. 2. The development of microcirculatory and mitochondrial dysfunction syndrome (MMDS) depends on the stimulus (HIT), specific host factors, time, and therapy.

also a disease spectrum. In the paragraphs above, we have discussed the evidence indicating that the changes in the microcirculation occur in the early stages of sepsis and that detecting and implementing early therapy directed to recruit the microcirculation could improve outcome. If the disease is not corrected timely, mitochondrial dysfunction could ensue. That is why timing forms an important classification parameter in the definition of MMDS and will define the nature of the pathophysiology of the syndrome as well as the most appropriate therapeutic strategy. In this line of thinking, the different stages and the factors involved in the development of MMDS can be defined (Fig. 2).

A. Time

Stage 1. The patient has systemic inflammatory response syndrome (SIRS) or deterioration of vital organ function. This stage is often difficult to recognize for the untrained eye, since major signs of a deteriorating clinical condition are lacking. One might suspect a problem when peripheral temperature is low, mottled skin is present, or the patient's breathing pattern has changed. If recognized in time, further deterioration might be prevented by the start of adequate therapy. Seventy percent of patients with an in-hospital circulatory arrest show disturbances in basic vital signs in the 6 hour period preceding their arrest [69]. It could be that deterioration of the microcirculation is evident at this stage.

Stage 2. The patient is in severe sepsis or septic shock and resuscitation strategies should be implemented as soon as possible. The recent data by Rivers et al. have convincingly demonstrated that early individualized optimization of global DO_2 results in a better outcome [42]. The problem is of course timing. At presentation, the doctor is frequently unaware of the time that the patient has already been ill, which means that cellular dysfunction and organ failure could already be present. If the patient presents early in the disease process and treatment is started without delay, many potentially life threatening problems might be prevented. If, however, the patient is a sturdy non-complainer and presenting in a critically ill condition, some cellular and organ damage may be difficult to reverse.

B . Microcirculatory Blood Flow

In the first stages of shock, microcirculatory function is used to maintain global circulation by redirecting blood flow to the most vital organ beds like the heart and brain. Microvascular blood flow in compliant vascular beds like the skin and intestine decreases, i.e., these microvascular networks are decruited and shunting phenomena are present. If local DO_2 falls below a critical level, dysoxia occurs present. Organ function seems rather resistant to hypoxic stress, and can restore after a period of dysfunction. Nevertheless, if the period of dysoxia persists for too long organ dysfunction can ensue.

C. Mitochondrial Dysfunction

Secondary to a period of cellular dysoxia, mitochondrial function becomes impaired. It is unclear to what extent such mitochondrial dysfunction is reversible. Preliminary data from animal studies indicate that this process may be reversible [71]. Undoubtedly, however, this reversibility will be time-dependent. Further studies aimed at understanding mitochondrial behavior *in situ* are needed.

D. Therapeutic Modalities

When a state of shock seems present, fluid administration remains the corner stone of treatment [40]. In addition, the right antibiotic should be given. Whenever an adequate arterial pressure and organ perfusion cannot be reached by fluid administration alone, therapy with vasoactive agents should be started. Vasopressor therapy may also be required transiently to sustain life and maintain perfusion in the face of life-threatening hypotension, even if cardiac filling pressures are not elevated [40]. One should also be conscious about global indicators of dysoxia, i.e., mixed venous oxygen ($S(c)vO_2$) and lactate levels. The hematocrit and cardiac output should be optimized, with individual patient characteristics kept in mind, for instance by using vasodilators like ketanserin or nitroglycerin, inodilators like milrinone or calcium sensitizers like levosimendan. The initial treatment with high doses of dexamethasone, known to block the production of iNOS, may also

influence microvascular perfusion by modulation of the NO pathway. If, however, an integrative approach is lacking and for example blood pressure is used as a sole target, derangement of organ perfusion may continue undetected as part of MMDS. In this way, one can imagine that the line of therapy in the septic patient plays an important role in the clinical presentation and definition of the type of MMDS.

Treatment of MMDS

As described above, MMDS comprises a spectrum of symptoms and signs following microcirculatory and mitochondrial dysfunction and manifests itself after resuscitation of the systemic *macro*circulation. Hence, restoration of *micro*circulatory perfusion and function is crucial when considering therapeutic options. But what should be done first? And what tools should we use to monitor therapy in our patients? Recent data have indicated that microcirculatory perfusion might still be deranged after filling pressures and cardiac output are optimized [15]. This underscores the need to direct therapy at the microcirculation *per se* and that correction of systemic parameters are not effective in rescuing the microcirculation *per se*. Microcirculatory derived parameters such as those derived from OPS-imaging and sublingual capnography will be expected to help understand the pathophysiology of MMDS and identify the response to therapeutic interventions. A stepwise approach can be contemplated whereby initially the microcirculation is recruited followed by support to the mitochondria in the form of substrate and mediators such as PARP inhibitors. Application and timing of these therapeutic modalities will depend on the type and phase MMDS is in and will include such factors. Adequate monitoring and appropriate interventions as well a fundamental understanding of the pathophysiology and dynamics of the syndrome may result in improvement of outcome in such critically ill patients.

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'Adequate' Hemodynamics: A Question of Time?

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Introduction

The concept of 'inadequate' hemodynamics is traditionally based on low flow and/or low arterial pressure. However it has been hypothesized that hemodynamics may be 'inadequate' for physiological organ function even if perfusion pressures and cardiac output are within the normal values. This concept was mainly introduced by Shoemaker, who originally observed that critically ill patients who survived major surgery had significantly greater cardiac index and oxygen transport parameters than those who ultimately died [1]. This led many investigators to consider 'supra-normal' hemodynamic values as the essence of 'adequate' hemodynamics in critically ill patients, and hundred of papers have dealt with this issue over the last 25 years. In this brief chapter, we would like to discuss the physiological basis of 'adequate hemodynamics', in the context of cell bioenergetics. Our interpretation, however, does not pretend to preclude or invalidate other views of the problem.

Adequacy of Hemodynamics

Hemodynamics is the physiology concerned with circulatory movements of the blood and the forces involved in the circulation, and its analysis is outside the purpose of this chapter; our focus will be on its adequacy ("good enough") in critically ill patients. However, as hemodynamics is just a servo-mechanism to provide the conditions which maintain a physiological energy charge for cell function, by transporting substrates, oxygen at a given pressure, and clearing the waste products, it is convenient to discuss the 'adequacy of hemodynamics' in the context of cell energy requirements, charge, and consumption. Indeed, the problem is not the definition of a given number for hemodynamic adequacy (pressure and flow) but, instead, the definition of the 'energy failure', which reflects the imbalance between energy supply, production, and consumption. In a simplistic way we have an analogy with a hydroelectric power plant. The falling water (hemodynamics, flow, and pressure), provides the conditions for the generation of electric power through generators (mitochondria), which in turn provide energy (ATP) to 'light the city' (cell functions which consume energy). If the flow is reduced below a critical level, or, anyway, cannot match the energy request, the

light decreases/ceases. However, the same may happen with normal flow if the generator fails. Indeed one problem is to understand which part of the energy failure is due to the hemodynamic impairment, which part is not. Moreover the issue is to understand/quantify the mechanisms through which alternative energy may be supplied and to what extent. It is then worth briefly reviewing the basic concepts of cell/tissue bioenergetics in physiological conditions and in critical illness.

Cell Energy

The energy charge of a cell may be expressed by the following equation:

$$\text{Energy charge} = ([ATP] + \tfrac{1}{2}[ADP]) / ([ATP]+[ADP]+[AMP])$$

It has been known for a long time that the pathways leading to ATP synthesis are inhibited by an elevated energy charge, while the pathways that use ATP are stimulated. The reverse is true for a low energy charge. The physiologic equilibrium is reached when the rate of ATP consumption equals its synthesis, and this 'break even point' is reached at an energy charge of about 0.9. In most cells the energy charge, for the cell to survive, has to be between 0.8 and 0.95.
It is evident that, to maintain a viable energy charge, two conditions have to be met:

1. The supply for ATP synthesis in the mitochondria (oxygen and substrates) and the clearance of waste products, must be sufficient to compensate for the ATP consumed by the cell for mechanical work, active transport of molecules and ions, synthesis of biomolecules.
2. The machinery for ATP synthesis, i.e., the mitochondria, must be structurally and functionally intact.

If one or both of these conditions is not satisfied, energy failure follows. This may lead to cell necrosis or, depending on the degree of failure and its duration, to cell 'adaptation' or apoptosis [2].

Energy Metabolism

The cell gets its energy (ATP) from the combustion of carbohydrates, fats and proteins, using oxygen as a last step of the process (the efficiency is about 40%). The process takes place in well defined cellular compartments, the integrity of which is mandatory for the overall process, and it is strictly regulated by a set of enzymes which are located in the cytoplasm and mitochondria. The transfer of energy from the substrate to ATP occurs in three major steps:

1. Glycolysis, which occurs in the cytoplasm, breaks the glucose down to pyruvate. In normal conditions, the pyruvate enters the mitochondria, while in the absence of oxygen it is reduced to lactate. Of note, in the absence of oxygen:
   a. Only two moles of ATP are produced (5% of the possible energy extractable from the complete glucose oxidation)
   b. No oxygen is consumed and no carbon dioxide (CO_2) is produced

   c. No H^+ are released in the medium
   d. The lactate formation is essential to reconvert the NADH to its oxidized form, NAD+; if not, glycolysis cannot proceed further.
2. The Krebs cycle, which occurs in the mitochondrial matrix, breaks the pyruvate down to CO_2. Most of the energy liberated is saved as electronic energy in NADH and $FADH_2$. Although molecular oxygen does not participate directly in any of the reactions of the cycle, it cannot proceed without oxygen. In fact the NAD^+ and FAD, which accept the electrons and H^+ from the substrate, are regenerated in the mitochondria only if their electrons are transferred to molecular oxygen. Indeed in the absence of oxygen the electron energy cannot be used, the Krebs cycle stops, and no CO_2 is produced.
3. Oxidative phosphorylation occurs in the inner mitochondrial matrix. The energy liberated by the flow of the electrons through the enzymes of the electron transport chain to the final acceptor, molecular oxygen, is used to pump out the protons in the space between the inner and the outer mitochondrial membrane. The electron energy is then transformed, in the intermembrane space, into chemosmotic energy (proton gradient and electrical membrane potential). The protons, following their gradient, are pushed back from the intermembrane space into the matrix through the channel of ATP synthases and their movement produces energy for ATP synthesis and release (30–36 moles of ATP/mole of glucose). The energy of the protons which flow through pores of the inner membrane other than the ATP synthase channel (proton leak) is 'uncoupled' with oxidative phosphorylation and is totally dissipated as heat (about 20% of the total energy is spent in this way [3]).

Molecules, such as nitric oxide (NO), overproduced during sepsis, may cause mitochondrial dysfunction. This may occur both because of reversible binding of NO to the prosthetic groups with a different redox potential [4], or by the reaction of NO with the proteins of the electron transport chain enzymes [5]. If the electronic transfer is impaired, no energy is produced, even in presence of adequate oxygen.

Cell Adaptation to Hypoxia

In hypoxia-tolerant animals, the primary mechanism to maintain the cell energy charge is to decrease the energy demand which results in a regulated metabolic depression [6, 7]. The most important ATP consuming processes in the cell are protein synthesis and ion-motive ATPases, while about 20% of the oxygen consumption (VO_2) may be attributed to the mitochondria proton leak through pores in the inner membrane. The first rapid reaction to anoxia is the inhibition of protein synthesis associated with an increased protein half life [8]. The membrane permeability is decreased (channel arrest) and less energy is required to maintain the ion gradients by the ATPases. The electron transport and proton leak are also decreased [9, 10]. As a general picture, ATP demand is hugely depressed and the cell may survive days and months maintaining a normal electrochemical potential and ATP concentration [11]. These animals, in which the VO_2 decreases with the

oxygen deprivation while maintaining regulated hypometabolism, are 'oxyconformers'.

In men and largely aerobic animals (oxyregulators), metabolism exhibits a high obligatory rate of energy consumption and the forced suppression of metabolism, due to oxygen deprivation, if severe enough, leads to metabolic failure and cell death in minutes to hours. However, some degree of adaptation exists also in mammalian cells and we will focus here on some aspects of 'the hypoxia defense', which may be relevant to our therapeutic approach. In mammals, as oxygen flow decreases, the cellular ATP demand (mostly in the brain and in the heart, less in the muscles) tends to remain constant. This leads to an energy deficit which may only be partially compensated for by the increased anaerobic ATP supply (Pasteur effect). Several mechanisms are implicated.

The hypoxia leads, first, to a systemic response, generated by an increased sympathetic activity [12] leading, together with intrinsic tissue control, to the redistribution of blood flow [13, 14]. Second, the oxygen deprivation is recognized by cells through a variety of oxygen sensors [15], which include proteins with redox groups, such as NADH-reductases, cytochrome-oxidase, etc. These sensors activate a transcriptional ubiquitarian compound: hypoxia inducible factor 1, HIF1 [16]. This is translocated in the nucleus where it binds DNA, promoting a 3–5 fold increase of the enzymes of the glycolytic pathway [17], while downregulating the enzymes of the Krebs cycle [17, 18]. The final result is the maximization of anaerobic ATP and lactate production.

Mammalian cells may also decrease to some extent, in an emergency, their oxygen demands, particularly for protein synthesis, as observed in cardiomyocytes, skeletal muscle cells, and hepatocytes [19–22]. Indeed, the adaptive responses of the critically ill may consist in a modest decrease in oxygen demand due to metabolism shut-down ('oxygen conformance') and in a maximal increase in anaerobic glycolysis. The metabolic depression (decreased VO_2), due to decreased oxygen supply (oxygen conformance) [23], may be seen as part of the 'oxygen supply/dependency relationship', while the increased anaerobic energy production results in increased lactate and acidosis.

It has been suggested that hypercapnic acidosis may have protective effects [24]. In addition, cells appear to be protected by acidosis during severe hypoxia [25–27]. Although the mechanisms are not completely elucidated, some experimental evidence suggests that the pH dependent inhibition of Na^+/H^+ and Na^+/Ca^{++} exchangers [28] leads to a reduction of the energy consuming Na^+/K^+ ATPase activity. The acidosis indeed could decrease ATP demand allowing more time for survival. While the correction of the causes of metabolic acidosis is mandatory, we may wonder if the 'cosmetic' correction of a low pH with bicarbonate is appropriate or instead is a disruption of a natural defense against hypoxia.

It is important to stress that all the mechanisms described cannot sustain a viable cell energy charge for a long time. In fact, anaerobic energy production is very inefficient, the extreme acidosis may inhibit the glycolytic pathway and the decreased protein biosynthesis may lead to structural changes of the mitochondria incompatible with life. It follows that, during energy failure, the timing for corrective intervention is a crucial issue to prevent irreversible mitochondria damage.

Markers of Energy Failure

We will not discuss here extremely important clinical markers of hemodynamic failure, such as the patient's skin alterations, kidney function (urine volume and electrolyte composition), documented low cardiac output, and low perfusion pressures. We will focus instead on markers which rather reflect the energy metabolism failure.

Oxygen Debt Concept

The concept of oxygen debt was introduced by Hill more than 70 years ago, and was refined by Margaria et al. in 1933 [29]. This concept mainly refers to the physiology of intense muscle exercise, performed in a few minutes. During the effort, VO_2 increases from 0.2–0.3 l/min (metabolic baseline at rest) up to 3–5 l/min, and stays at this level until the muscle exercise ends. The VO_2 then declines exponentially but stays higher than the baseline levels, to which it returns within 20 minutes to 2 hours. This 'extra VO_2' was called the 'oxygen debt'. The 'story' of the muscle oxygen debt has been recently reviewed [30]. Here it is enough to remember its physiological basis. The 'oxygen debt' occurs when the ATP consumed by the muscle contraction exceeds the capability of ATP synthesis due to insufficient oxygen supply. At the beginning the energy is in part provided by the creatine phosphate (the alactic oxygen debt). After that, the lactate produced in the muscle, by anaerobic glycolysis, is transferred to the liver, where it is converted to glucose. This, in turn, is transported to the muscle for glycogen resynthesis. Indeed the muscle 'oxygen debt' is paid by the liver.

It is appealing, at first sight, to transfer the concept of 'oxygen debt' to critically ill patients with hemodynamic failure and/or mitochondrial dysfunction. However, important differences must be stressed. First, the oxygen debt, measured as an *increase in* VO_2 in muscle physiology, in critically ill patients is estimated as a *decrease in* VO_2 relative to a hypothetical baseline (which sometimes is difficult to establish, when the patient is already under energy stress). Second, the formation of oxygen debt implies that the cell continues to work at the same energy expenditure as during the 'baseline'. This may apply in acute hemorrhage, as shown experimentally in dogs [31] and pigs [32]. In these conditions the hemorrhage is acute (minutes), the VO_2 decreases, and the markers of oxygen debt are the increase in lactate, decrease in base excess (BE), and the metabolic acidosis. It is more difficult to accept the concept of long lasting (days) oxygen debt. Assuming, as an example, that the energy expenditure to be maintained is 250 mlO_2/min (about 1.25 Kcal/min), an oxygen debt of 10% (0.125 Kcal/min) to be paid by the ATP produced anaerobically would imply the production of 0.017 moles of ATP (1 mole ATP stores 7.3 Kcal). An equal amount of lactate (0.017 moles/minute) would be produced during the process (i.e., 12240 mmol lactate/24 hours). This is unrealistic. To survive, the cell must shut down the energy expenditure, vanishing the concept of oxygen debt.

Indeed, we believe that, with the exception of experimental conditions, such as acute hemorrhage [31, 32], the concept of oxygen debt is hardly applicable and useful in critically ill patients, compared to other markers of energy failure.

Mixed Venous Oxygen Saturation

The venous oxygen saturation (SvO_2) depends on the amount of oxygen supplied to a given region and on the amount of oxygen consumed in that region during that time. According to the Fick equation:

$$SvO_2 = SaO_2 - VO_2/Q \times 1/(1.36 \times Hb)$$

This equation, which may be applied to the whole body (sampling the mixed venous blood, or, as a surrogate, the central venous blood), clearly shows that SvO_2 is a function of several variables, such as flow (hemodynamics, Q), arterial saturation (respiratory function, SaO_2), metabolism (VO_2), and availability of an oxygen carrier (hemoglobin, Hb). Indeed, a change in SvO_2 is a very sensitive, but non-specific, signal.

For a given arterial saturation, the SvO_2 decreases when the ratio of VO_2/Q increases, i.e., when the oxygen supply is insufficient to match the oxygen consumed by the oxidative phosphorylation. This may be due either to an increase in VO_2 or to a decrease in Q, because of hemodynamic failure, as often seen in critically ill patients. In any case when the VO_2/Q ratio increases, the tissue becomes 'hypoxic' relative to the needs. However, for SvO_2 to decrease, the mitochondria have to work and oxygen must be consumed. As a paradox, if in a given region the mitochondria, as the result of a direct insult, cease to function, the SvO_2 of the blood coming out of that region is equal to the SaO_2 of the blood coming into that region. Usually a decreased SvO_2 may be the first signal of a possible hemodynamic inadequacy to match the need, but, as an isolated finding, does not mean, *per se*, that the energy balance of the cell is already in failure. On the other hand, a normal or higher than normal SvO_2, may be associated with cell energy failure when the main impairment is mitochondrial function [33–35], as observed in muscle during sepsis and/or when the microcirculation is shunted [36]. Of note a 'shunted' microcirculation is functionally indistinguishable from mitochondrial dysfunction.

Indeed, while tissue hypoxia should be generally associated with a decreased SvO_2, with or without energy failure, a normal SvO_2 may occur also in presence of energy failure, but without hypoxia. Despite these limitations it is important to stress that the SvO_2, for a given SaO_2 and Hb, is a function of VO_2/Q. Indeed it can be considered as an excellent marker of hemodynamic adequacy as it relates directly to the actual needs (VO_2) and the supply (Q).

Acidosis and Lactate

When oxygen is not sufficiently supplied, or cannot be used, energy production is limited to anaerobic glycolysis, from glucose to lactate. Glycolysis is not an 'alter-

native' source of energy but is the first physiological step of glucose metabolism. When the cell energy charge is low, the glucose influx in the glycolysis pathway is enhanced. However, despite this, the anaerobic energy production is too low to compensate for a normal energy expenditure. Indeed the enhanced glycolytic pathway is a sort of emergency or 'buying time' mechanism instead of a long standing energy source.

From what we have discussed so far, it is quite evident that the real marker of energy failure, whatever its cause, is an increased lactate production although it may also be overproduced in aerobic conditions due to the effect of epinephrine on Na^+/K^+ ATPase activity [37–39]. Its clearance, however, may also be impaired. In a normal man, lactate is mainly produced by active muscle and red blood cells, and it is the main source, together with alanine, for gluconeogenesis. This process converts, mainly in the liver, the lactate into glucose. The energetic cost, however, is very high. In fact, while the conversion of 1 mole of glucose to lactate produces 2 moles of ATP, the conversion of 2 moles of lactate to 1 mole of glucose consumes 6 moles of ATP. Most of the lactate is 'cleared' in the liver either by entering, after transformation into pyruvate, the Krebs cycle, or by conversion into glucose. Both processes require oxygen. The first for a normal functioning of the Krebs cycle, the second for the high ATP requirements, which are provided by oxidative phosphorylation. It is not surprising, indeed, that lactate clearance is also impaired in the critically ill when the whole body, including the liver, may be under energetic stress [40, 41].

As the conversion of glucose to lactate does not produce any H^+, it has been suggested that it is not the lactate but the ATP hydrolysis (i.e., ATP $\rightarrow$ ADP + Pi + H^+) that is the real cause of metabolic acidosis [42]. We have some doubts about this interpretation. In fact lactate is a strong negative ion, almost completely dissociated in blood. The physicochemical approach to acid base equilibrium [43] states that the $[H^+]$ in the medium is not an 'independent' variable (it is impossible to add 'free' H^+ to a solution) but, instead, a variable which is dependent on strong ion difference (SID), the concentration of weak acids (mostly albumin), and PCO_2. The basic principle of the SID approach is that the sum of the negative charges in plasma must be equal to the sum of the positive charges (see Fig. 1). The normal SID is about 42 mEq/l. To maintain electroneutrality, the remaining negative charges are provided by the HCO_3^-, by the dissociated form of weak acids A^-, and by OH^-, which comes from the water dissociation. When a strong ion, such as lactate with its negative charge is added, the sum of HCO_3^-, A^-, and OH^- must decrease, to maintain the electroneutrality. As the product $[OH^-]*[H^+]$ is constant, a decrease in $[OH^-]$ implies an increase in $[H^+]$ (decrease in pH). On the other hand, the sum of $HCO_3^- + A^-$ is nothing else than the 'Buffer Base'. The BE is equal to Actual Buffer Base minus Reference Buffer Base (42 mEq/l), which is exactly the same as Actual SID minus Reference SID (42 mEq/l). Indeed, increased lactate, more negative BE, and decreased SID, in this context, have the same physiological meaning, and are, in our opinion, the more reliable markers of cell energy failure.

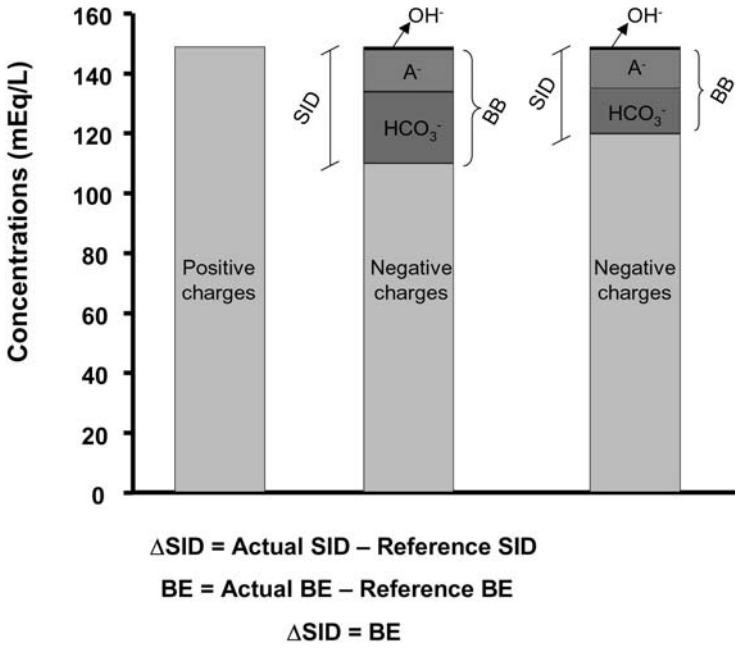

Fig. 1. Right and middle column indicate plasma electroneutrality. The strong ion difference (SID, i.e., the difference between strong positive ions and the strong negative ions) is 'filled' by the sum of HCO_3^-, A^- and OH^- (called also Buffer Base). When the strong ion lactate increases (left column), the space for HCO_3^- and A^- is reduced, as well as for OH^-. Indeed the H+ increases and the pH decreases. The base excess (BE) is equal to the difference between normal SID (middle column) and the actual SID (right column).

Venous/Tissue PCO_2

To understand the physiological meaning of the CO_2 changes during hypoxia/mitochondrial dysfunction, it is convenient to refer first to its content (dissolved CO_2 + HCO_3^- + carbamino compounds) instead of its tension (PCO_2). Rearranging the Fick equation for the CO_2 content it appears that:

$$CvCO_2 = CaCO_2 + VCO_2/Q$$

where $CvCO_2$ is the venous content, the $CaCO_2$ is the arterial content, the VCO_2 is the metabolic CO_2 added to the tissue, and Q is the flow.

If we now rearrange the Fick equation for venous oxygen content:

$$CvO_2 = CaO_2 - VO_2/Q$$

For a metabolic respiratory quotient ($R=VCO_2/VO_2$) equal to 1, the two equations are exactly specular, and their changes are similar also for different R. This means that all the previous discussion on SvO_2 may be equally applied to the $CvCO_2$. In fact, for a given arterial CO_2 content (function of the VA/Q), what changes the venous CO_2 is the ratio between the waste product of *aerobic metabolism* (VCO_2)

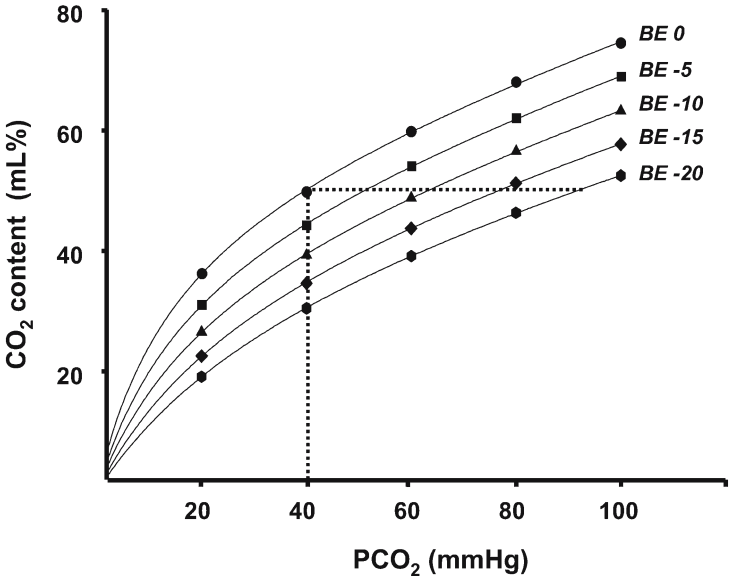

Fig. 2. CO_2 dissociation curve. CO_2 content (ml % of whole blood) vs. CO_2 tension (PCO_2). Each curve is described at constant base excess (BE). As shown, for the same CO_2 content, changing the base excess causes a great change in PCO_2 (see the broken line parallel to axes).

and its clearance by the flow. In an extreme case in which aerobic metabolism is zero, the metabolic production of CO_2 (VCO_2) is also zero, and the venous content equals the arterial content.

However, although 'increased VCO_2' cannot occur in anaerobiosis, there is no doubt that venous PCO_2 (or tissue PCO_2 from gastric tonometry) is increased during energy failure. The meaning of this phenomenon becomes clear if we consider the relationship between the CO_2 content ($CvCO_2$) and the CO_2 tension ($PvCO_2$), also called the CO_2 dissociation curve. This is reasonably linear in the PCO_2 range of 20 to 80 mmHg. However, its position is strongly influenced by the acid base status of the medium (Fig. 2). During the passage into the tissue, in normal conditions the decrease in oxygen saturation is associated with binding of H^+ to hemoglobin. This effect (Haldane) 'buffers' in part the acid-base changes induced by the addition of VCO_2 from the tissue. The overall picture is dramatically changed when a strong ion, such as lactate, is added from the tissue to venous blood. In this case, part of the [H^+] increase due to the increase of the strong ion lactate, is buffered by HCO_3^- which 'liberates' dissolved CO_2 ($PvCO_2$) according to the following reaction:

$$\text{Added } H^+ + HCO_{3V}^- \rightarrow CO_{2V} + H_2O$$

Indeed for a given venous CO_2 content, adding acid sharply increases the $PvCO_2$. The phenomenon is quite clear if we consider the CO_2 dissociation curve, at different BE, as shown in Figure 2. For the same CO_2 content, the change in BE

(i.e., the addition of strong ions such as lactate) results in a great change in PCO_2. Indeed, the large increase in venous PCO_2 during critical hypoxia (or during mitochondrial dysfunction) is not the result of the increased anaerobic VCO_2 production but instead of the acidity change induced (for a given CO_2 content) by the added strong ion. Due to the increased $PvCO_2$, the expired CO_2 may transiently increase, before the new steady state is reached. This transient increase in expired CO_2 must not be confused with the VCO_2 metabolic production. Exhaled CO_2 equals the metabolic CO_2 production only at steady state. The increase in $PvCO_2$ is a very strong signal, and this is a reason why it has been proposed as a 'useful marker' of hypoxia [44, 45]. The distinction between content and tension helps to explain some of the contradictory findings in the theoretical and experimental literature [46].

Hemodynamic Adequacy in the Clinical Scenario

As discussed above, the energy failure due to hemodynamic failure, to mitochondrial dysfunction, or both, implies an adaptive response which consists of increased glycolysis (increased lactate, decreased BE, acidosis, and increased $PvCO_2$) associated with a relative dumping of the energy expenditure (oxygen conformance, i.e., VO_2/DO_2 dependency). The distinction between hemodynamic inadequacy and mitochondrial dysfunction, either due to direct insult (primitive dysfunction) [47–50] or to mitochondrial structural disruption due to prolonged hypoxia (secondary dysfunction), may be clinically relevant. In fact, aggressive hemodynamic treatment is useless and potentially dangerous if the energy failure derives from mitochondrial dysfunction and not from inadequate hemodynamic status.

To roughly discriminate between the two causes of energy failure (beside the baseline S_VO_2, low in hemodynamic failure), two challenge tests are available: the volume load and the dobutamine tests. The first does not imply, *per se*, an increased oxygen consumption [51], and the second may contribute to an increased energy expenditure due to the direct thermogenic effects of dobutamine [52–57]. If the primary cause of the energy failure is tissue hypoxia due to inadequate hemodynamics and the volume infusion or the dobutamine test are able to increase the oxygen transport, the response should be an increased VO_2 (reduction of the adaptive response of oxygen conformity), and a decrease in lactate and its correlates (reduction of the adaptive response of increased anaerobic energy production). Such responses indicate that the mitocondrial function is still adequate. If the challenge test increases the oxygen transport but the VO_2 does not increase, this suggests that the mitochondria are unable to work properly either because of direct insult, as in sepsis, or because the hypoxia was so prolonged that the mitochondria were structurally impaired.

Volume Load Test

This was the subject of two studies conducted by Haupt [58] and Gilbert [59]. The entry criteria (sepsis and circulatory failure), treatment (fluid load), and results were similar. In both studies, some patients were experiencing energy failure (as indicated by increased blood lactate levels). Of these, a subset responded to volume challenge with an increase in DO_2 and VO_2, indicating, from an energy point of view, oxygen supply dependency (oxygen conformance) and still adequate mitochondrial function. On the contrary, other patients with energy failure (high lactate) were unable to increase DO_2 while VO_2 did not significantly change or even decreased. A volume load test alone does not allow the discrimination in these patients between pump failure (cardiac failure) or a primary oxygen machinery defect (mitochondrial failure). To discriminate between these two possible mechanisms of hemodynamic inadequacy, a dobutamine test may be of use.

Dobutamine Test

In patients with energy failure (high lactate), a controlled infusion of dobutamine may reveal cardiac pump failure either when patients are hemodynamically stable [60] or not responsive to volume load [61]. An increased VO_2, following an increased DO_2, suggests that the oxygen machinery (mitochondria) is still functioning adequately.

More complex is the interpretation of the test in septic patients without energy failure (normal lactate). Several studies have included these patients [60, 62–65]. Vallet [63] and Rhodes [65] prospectively tested the dobutamine response, stratifying between patients that were able (responders) or not able (non-responders) to increase VO_2 by more than 15% of the baseline value. They found that responders showed a much greater increase in DO_2 than non-responders, and had a lower mortality. Since the patients were not in energy failure (normal lactate), it is difficult to hypothesize a 'masked oxygen debt', which is just an adaptive response (oxygen conformance) to the energy failure. It is possible that the responders had just a physiological response to the increased metabolic requirements due to the dobutamine. Indeed these patients had adequate hemodynamic response and adequate mitochondrial function. The non-responders, on the contrary, were not able to cope with the increased oxygen demand due to the dobutamine, suggesting both an inadequacy of hemodynamics and/or an inadequacy of mitochondrial function. In fact, considering the dobutamine test as an 'increased energy demand challenge', the non-responders developed energy failure with its typical responses (oxygen conformance and anaerobic metabolism) [63].

'Adequate' Hemodynamics: A Question of Time?

Based on the observation that survivors of high risk operations had significantly higher mean cardiac index, DO_2, and VO_2 than non-survivors [66], and on the results of a prospective trial in which supranormal hemodynamic values used as a

therapeutic goal were associated with improved outcome [1], several studies have been conducted on the so called 'hemodynamic optimization'. After more than 20 years, the matter is still debated. Two recent meta-analyses provided different conclusions [67, 68]. However, a few points must be stressed. First, most studies were targeted to increased DO_2. From what we have discussed so far, it is quite evident that the crucial issue is not a given value of DO_2 but instead an oxygen supply sufficient to match the energy needs. Only two studies [69, 70] investigated a different target, i.e., a 'normal' SvO_2, which more closely reflects the relationship between oxygen demand and supply. These two studies led to different results. Considering all the studies together, the difficulty in comparing them is quite evident. The study populations were different (high risk surgical patients, trauma patients, sepsis patients, etc.). The time of intervention was also not comparable (perioperative, in the emergency room, and in the intensive care unit [ICU]). Moreover, we do not know how many of the treated patients were at risk of energy failure and how many of them were actually in energy failure.

It is beyond the scope of this chapter to attempt any detailed analysis of this controversial matter, however we would like to focus on the timing of interventions. As we discussed above, the adaptive responses to the energy failure (anaerobic energy production and oxygen conformance) are not long-standing mechanisms. It is likely that early interventions may reverse the energy failure more than interventions performed later, when the mitochondria are structurally impaired.

Figure 3 shows, on an ideal time axis, three prototypical randomized controlled trials on hemodynamic treatment. In the study by Shoemaker et al., patients were investigated perioperatively [1]; the study by Rivers et al. was conducted on septic patients very early in the emergency room [69]; while that by Gattinoni et al. was a late study conducted on a general ICU population [70]. The main results are presented trying to focus the attention of the reader on time. As shown from the above mentioned meta-analysis [68], the earlier the intervention and the greater the physiological response to treatment, the better the outcome. If one could imagine a cell under impending energy failure, it becomes obvious that the earlier a clinician can correct a possible underlying hemodynamic failure, the greater the likelihood of the cell not to suffer from hypoxia or any insult originating from mediators.

Therefore, time is the essence. We believe that this is clearly shown by comparing our study of SvO_2 targeted treatment and the study by Rivers et al. The baseline SvO_2 of Rivers' patients in the emergency room was 49% [69]; this strongly suggests that their septic patients had an associated severe hemodynamic impairment. The early correction of the VO_2/DO_2 mismatch (SvO_2 target 70%) was associated with a remarkable decrease in the blood lactate levels, suggesting that the treatment was able to reverse, at least in part, the energy failure. In our study [70], the patients were treated later in the ICU and their SvO_2 at entry was already close to the target (68%, with the target of 70%). Indeed all our hemodynamic manipulations were in the patients in whom most of the possible hemodynamic failure had already been corrected. It is then possible that when we started to treat the patients the game was already 'over'. Of note, however, the tremendous importance of the hemodynamic status in the course of the disease, as shown in Figure 4. The patients who were not able to reach a normal SvO_2 had very high mortality rates.

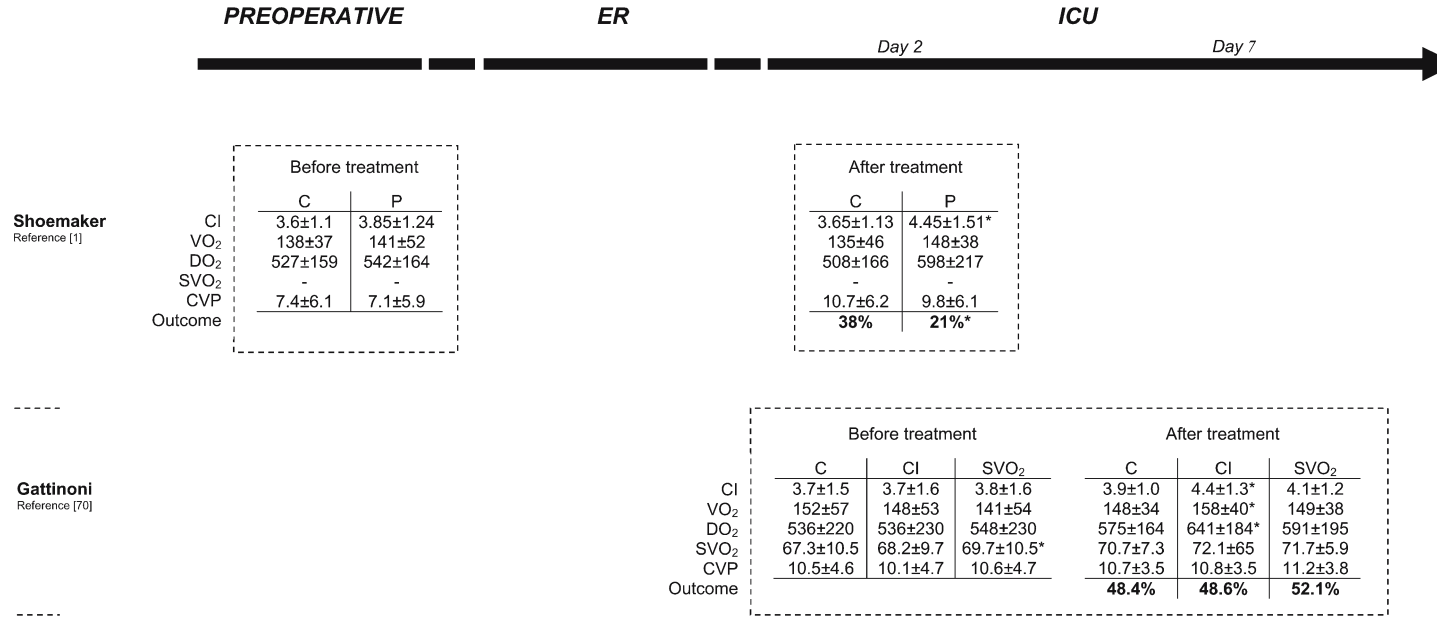

Fig. 3. Results of three prototypical studies on hemodyamic treatment in critically ill patients, synoptically presented under a 'time' frame. ER: emergency room; ICU: intensive care unit; CI: cardiac index (ml/min/m^2); VO_2: oxygen consumption (ml/min/m^2); DO_2: oxygen delivery (ml/min/m^2); SvO_2: venous oxygen saturation (%); CVP: central venous pressure (mmHg); *significant difference between treatments

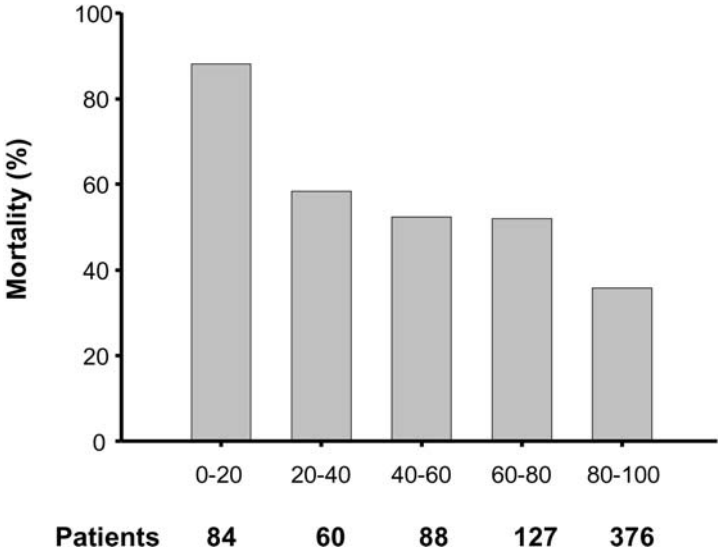

Fig. 4. Sub-analysis of the SvO_2 study [70]. Percent mortality as a function of the percent of time that the patients maintained the target (SvO_2 >= 70%) during the 5-day study. 0% = never on target, i.e., SvO_2 always below 70%, 100% = patients always on target (SvO_2 >= 70%). Note that patients (n=84) who were able to maintain the SvO_2 target for 0–20% of the time had a mortality close to 90%.

Conclusion

Energy failure is a life threatening condition. Energy failure induces two adaptive responses: oxygen conformance (i.e., a decrease in energy expenditure due to partial metabolic shut-down) and increased anaerobic energy production (i.e., increased lactate and acidosis). Energy failure may occur because of primitive mitochondrial impairment or insufficient oxygen supply (inadequate hemodynamics). This condition, if prolonged long enough, unavoidably leads to secondary mitochondrial failure. In patients, the prevalent mechanism of energy failure may be roughly assessed by considering the SvO_2 (low SvO_2 suggests tissue hypoxia with adequate mitochondrial function). A volume load test and dobutamine challenge may also be of value in discriminating these two conditions. Early treatment to correct hemodynamic failure, before secondary irreversible mitochondrial damage occurs, is likely associated with improved survival. Time is essential.

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Limits and Applications of Hemodynamic Monitoring

Arterial Pressure: A Personal View

D. Bennett

Introduction

Three thousand years ago, the Chinese, during the reign of The Yellow Emperor, realized that there was an association between a pulse that was difficult to compress and the subsequent development of stroke. However, it was not until more than 2500 years later that blood pressure was first quantified. In 1731, the Reverend Stephen Hales measured the blood pressure of a horse by inserting a brass tube one sixth of an inch in diameter connected to a glass tube which was nine feet in length into the crural artery. After releasing the ligature, which had previously been tied around the artery, he found that the blood rose in the tube to a height of eight feet above the level of the left ventricle.

Hales made a further series of measurements in animals and calculated that the blood pressure in humans would be about seven feet. Some progress occurred over the next 100 years in developing techniques for measuring blood pressure in patients but it was not until 1876 that Von Basch made a simple sphygmomanometer which allowed him to assess systolic pressure with a fair degree of accuracy and for the first time made it possible to collect data on blood pressure from a large number of patients. Twenty years later, Rocci developed the mercury sphygmomanometer, which has changed little in the last 100 years. Probably the most important development in the measurement of blood pressure was the recognition by Korotkoff that it was possible to define accurately both systolic and diastolic pressure by listening with a stethoscope over the brachial artery below the inflated cuff as the pressure was slowly lowered. It is worth noting that Korotkoff's description was in 1904 so that this year is the 100th anniversary of that event. The principle involved in non-invasive blood pressure has changed little in the last 100 years although several technological developments have occurred during this period.

These developments include the automated auscultatory method that uses a microphone to detect the Korotkoff sounds but this method was sensitive to noise artifact and was found to be inaccurate when measuring in patients with low blood pressure. This technique measures the systolic and diastolic pressures from which the mean pressure is calculated.

In contrast, the oscillatory method, which was devised to overcome the inaccuracies of the auscultatory method, measures the mean pressure from which the systolic and diastolic pressures are calculated, calculations which are prone to error. Other technologies introduced to overcome these problems include infra

sound to detect the very low frequency components of the Krotokoff sounds below 50 Hz, which are inaudible. Ultrasonic technology has been used combined with other technologies to measure blood pressure but these techniques tend to be very operator dependent.

More recently two other techniques have been developed in the hope of overcoming some of the problems that clearly exist with all the existing methods. Impedance plethysmography as its name implies monitors the change in electrical impedance at the measurement site. This changes with local volumetric changes associated with local pulsatile arterial distension occurring with each cardiac cycle.

Arterial tonometry applies a carefully measured compressing pressure to the arterial site The applied pressure is measured by sensors and this allows an arterial waveform to be constructed using an algorithm which is claimed to be very similar to that directly recorded intra-arterially. A recent report using this technique, however, has not shown a good correlation with directly measured pressure [1].

Non-invasive measurement of blood pressure is one of the most widely undertaken procedures in clinical medicine and the data it provides are crucial in monitoring patients with hypertension. However non-invasive techniques are only used in a minority of intensive care unit (ICU) patients and this is for several reasons [2–4].

Accuracy of measurement is of utmost importance in managing critically ill patients particularly when they are cardiovascularly unstable when blood pressure is low. It is vital to know that the mean arterial pressure is 65 mmHg and not 75 mmHg as this is likely to make a fundamental difference to the treatment given [5]. Clinical experience has demonstrated that in these circumstances, particularly if the peripheral circulation is shut down, intra-arterial pressure measurement is much more precise. In addition, it allows continuous monitoring of pressure which none of the invasive techniques can offer. Even in less sick patients with stable circulations, intra-arterial monitoring has the advantage of comfort. Frequently repeated cuff inflations cause significant discomfort and adds to the level of anxiety in an already anxious patient. Finally the presence of an intra-arterial line allows almost unlimited blood sampling mainly for blood gas analysis but also for routine blood tests. Intra-arterial cannulation has therefore become a routine procedure in the vast majority of ICU patients. It is not within the scope of this chapter to discuss the various techniques of arterial cannulation or indeed of the technology behind the measurement of intra- arterial pressure.

Blood pressure is of course determined by the relationship between flow and peripheral resistance and therefore plays a fundamental role in determining perfusion to various organs, particularly the kidneys, heart, and brain. Thus, in situations where global flow may be normal or high, for example in septic shock, a low peripheral resistance must be associated with low mean pressure which inevitably leads to reduced flow to the kidneys once pressure falls below the lower limit of the auto-regulatory mechanism. This lower limit in the typical older patient commonly seen in the ICU, may be relatively high and may be one of the reasons that acute renal failure is a common finding in such patients. The adjustment of the mean pressure to some `optimal' level is vital in trying to minimize the risk of developing acute renal failure although pressure alone is not the only factor leading to the development of renal dysfunction [6].

What level of mean pressure should be targeted is a controversial question about which there is not a clear consensus. Most clinicians aim for a pressure that results in urine production and is associated with the reduction in the metabolic acidosis commonly seen in these circumstances. The majority of clinicians now feel that manipulation of pressure in such patients should only be undertaken with knowledge of cardiac output. This is to prevent vasoconstrictors being administered where pressure is low due to hypovolemia and a low cardiac output. Similarly, careful manipulation of blood pressure plays an essential role in the management of patients with significantly impaired left ventricular function, for example, post infarction or in patients with severe left ventricular failure.

The normal left ventricle is able to maintain a constant cardiac output over a wide range of mean blood pressure. This is not true when left ventricular function is significantly impaired so that as blood pressure rises cardiac output rapidly falls. This is the reason that afterload reduction can be so effective in treating patients with left ventricular failure. Furthermore, as peripheral resistance is a prime determinant of myocardial oxygen consumption its reduction can play an important role in the management of myocardial ischemia. The question then arises again as to what should the target blood pressure be in such patients with significantly impaired left ventricular function with or without evidence of continuing myocardial ischemia This emphasizes why it is so important that when manipulation of blood pressure and cardiac output are to be undertaken, they should be performed with continuous and accurate measurements of both pressure and flow.

Thus, if peripheral vasodilators are used it is very helpful to document that as pressure is lowered, stroke volume and cardiac output increase appropriately. How much pressure should be reduced is dependent on the clinical response of the patient. Peripheral resistance is often very high in these patients because of the low cardiac output and exaggerated sympathetic response resulting in intense peripheral vasoconstriction. As the vascular bed dilates, blood pressure falls, cardiac output increases, and peripheral perfusion improves with improvement in urine flow and correction of metabolic disturbance, usually lactic acidosis. Clearly the pressure that is associated with optimal clinical response should be the target.

It should also be remembered that patients who present acutely with left ventricular failure and high peripheral resistance are often inappropriately treated with diuretics which leads to occult hypovolemia [7]. Peripheral vasodilators are usually given and dilating both the venous and arterial beds the hypovolemia becomes obvious with a sudden severe fall in cardiac output and mean arterial pressure. Apart from the obvious effect on peripheral perfusion, the fall in diastolic arterial pressure can have profound effects on myocardial perfusion exacerbating any underlying ischemic potential. These rapid changes in the physiological status of the patient further confirm the importance of adequate invasive monitoring in such clinical situations.

Blood Pressure and Prognosis in Acute Hypovolemia and Sepsis

Blood pressure has been and is still used as a therapeutic target in the management of acute hypovolemia in the emergency room, particularly in patients with

trauma. Based mainly on anecdotal experience, a systolic pressure of 100 mmHg is the usual target, together with a heart rate not in excess of 120 beats/minute. This is mainly achieved by fluid resuscitation, initially with crystalloid and then blood and colloid depending on the clinical situation.

However, this protocol is not without considerable controversy [8, 9], particularly in the management of penetrating trauma such as gunshot and stab wounds. It is argued that systolic pressure should be maintained between 70 and 80 mmHg by restricting fluid resuscitation to a minimum. The protagonists of this protocol argue that this minimizes the delay in getting the patient to the operating room and more importantly reduces the risk of thrombus that may have formed at the site of the vascular injury from being `blown off' by inappropriate systolic pressure.

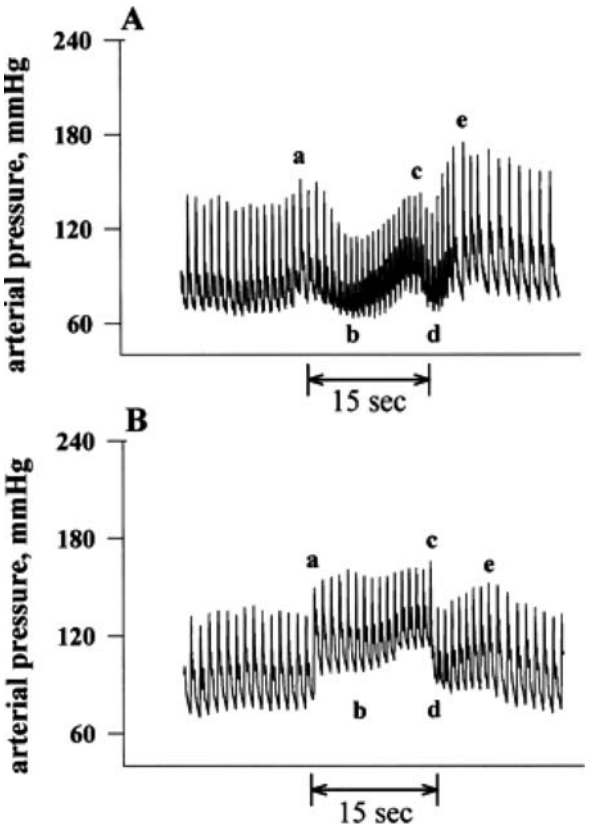
Although the concept of the `golden hour' in which resuscitation should be optimized is widely accepted, there is unfortunately little scientific evidence justifying a systolic pressure of 100 mmHg as a means of achieving this goal. Indeed studies [8] have demonstrated no correlation between pressure and simultaneously measured oxygen delivery. This protocol is usually undertaken by emergency room physicians.

In contrast, patients with septic shock are more likely to be managed within the ICU where the blood pressure target is usually a mean pressure of 65 to 70 mmHg. It is not at all clear why this difference has emerged although it may be related to the fact that measurements of cardiac output are much more likely to be made in the ICU environment. This almost certainly leads to better control of the circulation particularly when markers of perfusion such as lactate, base deficit, and mixed venous oxygen saturation are also monitored.

Although there are several studies demonstrating the prognostic values of base deficit and lactate [10, 11], in trauma patients blood pressure is still considered the most important physiological variable whilst flow is rarely measured in the emergency room. This is perhaps understandable because of the practical difficulties in making such measurements in the acute situation. It is of particular interest, therefore, that Rivers et al. [12] used central venous saturation as a surrogate for cardiac output in severely septic patients admitted to an emergency room and showed that the group where central venous saturation was maintained at 75% had a significantly lower mortality than the control group where saturation was maintained at around 68%. The mean blood pressure was significantly higher in the treatment group at 6 hours as a result of more aggressive fluid resuscitation.

However, there was a subgroup of 63 patients (Rivers, unpublished data, personal communication) who had raised lactate levels and low central venous saturations where the mean arterial blood pressure was greater than 100 mmHg. These were younger and otherwise fitter patients with less comorbidity. The patients assigned to the control group had a 60-day mortality of almost 70%. In very marked contrast, the patients in the treatment group had a 60-day mortality of only 24%. This is an extraordinary difference in outcome even though it is a relatively small number of patients. Indeed the mortality in these control patients was 13% higher than that of the control group from the whole study. How can these differences be explained?

The patients in this study were clearly severely hypovolemic as reflected by the very low central venous saturations of less than 50% on admission to the emergency



Fi.g. 1 Two different arterial pressure profiles during Valsalva maneuvers in 2 normal individuals, both in supine position. A: "typical" response. B: "square" response usually associated with large intrathoracic volumes. a, phase I; b, early phase II; c, late phase II; d, phase III; e, phase IV. [32]

room. As these patients in the subgroup were younger than those in the main body of the study, their cardiovascular reflexes were more likely to be intact resulting in profound arteriolar constriction to maintain mean blood pressure above 100 mmHg. As the authors point out, it is well known that mean blood pressure is well maintained as blood is lost by a proportional increase in systemic vascular resistance until about 18% of the total blood volume has been lost, even though cardiac output will have fallen significantly. It is only then, as peripheral resistance reaches a plateau, that the continuing loss of blood volume is associated with a steep fall in both cardiac output and mean arterial pressure.

These results are similar to the findings in normal subjects [13] where hypovolemia has been produced by prolonged passive 50° head up tilt. This led to a 9% rise in mean arterial pressure, a 37% fall in cardiac output, a rise in peripheral resistance of 41%, and rise in heart rate of 48%. After 30 minutes, the subjects became pre-syncopal and mean arterial pressure fell to 20% below baseline value

and heart rate exactly to base line. Simultaneously measured central venous saturation fell linearly from 75 to 60% during this period. These findings suggest that in the very acute situation with rapid changes in vascular volume, blood pressure probably is not the optimal physiological variable to be monitored and indeed in some circumstances relying on blood pressure alone may result in an increase in mortality. Rivers (unpublished data, personal communication) has suggested that in his study, the subgroup of patients with mean BP above 100 mmHg in the control group received less aggressive volume resuscitation thus prolonging tissue hypoperfusion and hypoxia.

Studies in ICU patients, where the focus has been the maintenance of blood pressure, have not been particularly fruitful. Most intensivists accept that pressure needs to be kept at a level which allows adequate tissue perfusion particularly of the kidneys and heart and that alpha agonists are the most widely used agents to achieve this. More recently there has been increased interest in studying the role of vasopressin [14–16] and its analogs in patients with hypotension due to sepsis. The results of these studies are awaited. Renewed interest in the use of steroids in similar patients has shown small but significant benefit particularly in those patients who have an ablated adrenal response to synacthin [17]. A larger scale study of this approach is being planned.

The hypothesis that the hypotension of sepsis is due to excess production of nitric oxide (NO) resulting from activation of inducible NO synthase in the vascular endothelium led to a large double blind randomized study of NO synthase inhibition using N(G)-monomethyl-L-arginine (L-NMMA) [18]. Unfortunately the treatment group showed no benefit and indeed had a higher mortality than the patients receiving placebo. This was despite the fact that preliminary animal and patient data suggested significant improvement. The result of this study raises important issues of design and appropriate patient recruitment. Were the dosage of L-NMMA and the target blood pressure too high, and was enough attention paid to cardiac output where it was measured?

It might be concluded from the tenor of this chapter thus far that the importance of blood pressure monitoring and its use as a therapeutic target has been downplayed and this is true to a certain extent. As discussed earlier, routine intra-arterial monitoring of blood pressure has become standard for a variety of reasons in the ICU. Until fairly recently this had been done purely for reasons of convenience and patient comfort. For a long time, however a minority of investigators have shown that analysis of the arterial pulse wave contour obtained from an intra-arterial line can provide a great deal of information over and above just the value for arterial pressure [19–21]. This has led to the development of two commercially available technologies for the continuous monitoring of cardiac output obtained by analyzing the pulse wave contour obtained from intra-arterial catheters placed in either the radial or femoral arteries.

Each of these technologies uses rather different protocols for measuring the area under the pressure wave form but both calibrate the area using transpulmonary thermodilution in the case of PiCCO, and lithium dye dilution in the case of LiDCO. These technologies have clearly added a new dimension to arterial pressure monitoring and provide beat-by-beat information on stroke volume and cardiac output [22–25].

Intriguingly, these technologies are being used to determine whether critically ill ventilated patients will respond to volume loading based on a considerable literature [26–28]. A greater than 10 or 12% variability of systolic pressure and/or pulse pressure caused by the positive pressure associated with peak inspiration indicates that the patient is probably hypovolemic and is likely to respond to fluid resuscitation. This is an important technological development because occult hypovolemia is probably not uncommon in critically ill patients and if unrecognized is likely to contribute to an increase in both morbidity and mortality.

Thus, if systolic or pulse pressure variability increases and exceeds 10 to 12% it implies developing hypovolemia and should allow much earlier recognition and treatment with volume replacement being administered more precisely to the point where variability is less than 10%. This approach can only be used in ventilated patients although there are probably a significant number of non-ventilated ICU patients who are relatively hypovolemic, which again is unrecognized.

As a future development, it would be interesting to study such patients using the response of the intra-arterial pressure trace to the Valsalva maneuver as an indicator of fluid status. There is, of course, an extensive literature [29–32] describing various applications of the maneuver but the square wave response in patients with left ventricular failure is probably the best known.

Figure 1a demonstrates the sinusoidal response of a group of normal subjects with the early rise in blood pressure as intra-thoracic pressure rises, followed by the tachycardia and subsequent sharp fall due to a reduction in stroke volume related to the decline in myocardial transmural pressure and ventricular volumes. Following release of breath holding, the over shoot in stroke volume is reflected by the increase in systolic pressure and bradycardia.

In contrast, Figure 1b shows the response to the maneuver in the same subjects who had been made hypervolemic by ingestion of a volume of 0.9% saline equivalent to 2% of their lean body mass. The difference is very obvious with a typical square response, classical of volume overload. Hypovolemia was then produced by administering 30 mg of furosemide. The study also showed that the maximal fall in systolic pressure was greatest in the hypovolemic subjects and least in the volume loaded subjects [32].

Conclusion

Blood pressure is one of the most frequently measured variables in medicine and is obviously of great importance in detecting patients with clinical hypertension and monitoring their subsequent treatment. However, in critically ill unstable patients its use may have been overemphasized. The reliance on systolic pressure in trauma patients may well be cloaking important hypovolemia that can only be detected by direct measurement of flow or surrogates such as central or mixed venous saturation, base deficit, and lactate.

Similarly the reliance on mean pressure in septic patients may be misleading, particularly when it is high and the optimal level at which to maintain pressure in such patients is still unclear. Furthermore, there is still uncertainty about which agent to use to achieve the desired pressure. The notion that so much reliance is

placed on pressure is related to the fact that it has for a very long time been relatively easy to measure and it is only rather more recently that flow measurements have become routine in most ICUs.

It is gratifying, therefore, that with the advent of pulse contour analysis, pressure and flow data can be obtained from a single signal from which the state of volemia can be estimated. It is not the intention of the author to discourage clinicians from measuring blood pressure but to encourage better understanding of the relationship between pressure and flow. The emergence of the new technologies may go a long way to achieving this end.

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Central Venous Pressure: Uses and Limitations

T. Smith, R. M. Grounds, and A. Rhodes

Introduction

A key component of the management of the critically ill patient is the optimization of cardiovascular function, including the provision of an adequate circulating volume and the titration of cardiac preload to improve cardiac output. In spite of the appearance of several newer monitoring technologies, central venous pressure (CVP) monitoring remains in common use [1] as an index of circulatory filling and of cardiac preload. In this chapter we will discuss the uses and limitations of this monitor in the critically ill patient.

Defining Central Venous Pressure

What is the Central Venous Pressure?

Central venous pressure is the intravascular pressure in the great thoracic veins, measured relative to atmospheric pressure. It is conventionally measured at the junction of the superior vena cava and the right atrium and provides an estimate of the right atrial pressure.

The Central Venous Pressure Waveform

The normal CVP exhibits a complex waveform as illustrated in Figure 1. The waveform is described in terms of its components, three ascending 'waves' and two descents. The a-wave corresponds to atrial contraction and the x descent to atrial relaxation. The c wave, which punctuates the x descent, is caused by the closure of the tricuspid valve at the start of ventricular systole and the bulging of its leaflets back into the atrium. The v wave is due to continued venous return in the presence of a closed tricuspid valve. The y descent occurs at the end of ventricular systole when the tricuspid valve opens and blood once again flows from the atrium into the ventricle. This normal CVP waveform may be modified by a number of pathologies.

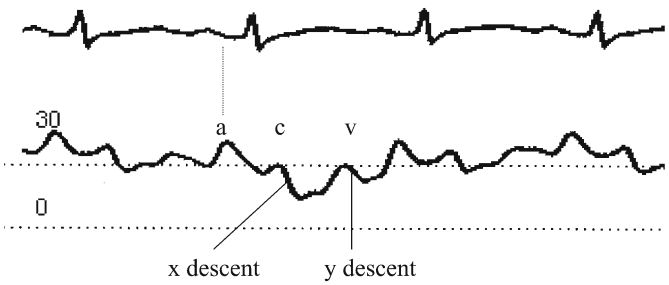

Fig. 1. Central venous pressure waveform from a ventilated patient (bottom) with time synchronized electrocardiograph trace (top). The a-wave represents atrial contraction and occurs immediately after atrial depolarization as represented by the p wave on the EKG. The c-wave represents bulging of the tricuspid valve in early ventricular systole and is followed by the v-wave, caused by atrial filling during ventricular systole.

1. In atrial fibrillation, the a wave is lost and the c wave may become more prominent; if there is coarse fibrillation of the atria, fibrillation waves may be visible in the CVP waveform.
2. In the presence of A-V dissociation or junctional rhythm where atrial contraction may occur during ventricular systole, extremely tall canon a waves occur due to atrial contraction against a closed tricuspid valve.
3. In tricuspid regurgitation, blood is ejected backwards during ventricular systole from the right ventricle into the right atrium. This produces a large fused c-v wave on the CVP trace.
4. In tricuspid stenosis, forward movement of blood from the right atrium into the ventricle occurs against a greater than normal resistance leading to an accentuated a-wave and an attenuated y-descent.
5. Similarly, if right ventricular compliance is decreased by either myocardial or pericardial disease the a-wave will be accentuated.
6. With pericardial constriction, a short steep y-descent will also be seen which allows differentiation from cardiac tamponade where the CVP will be monophasic with a single x-descent.

Determinants of Central Venous Pressure

The CVP must clearly be influenced by the volume of blood in the central venous compartment and the compliance of that compartment. Starling and co-workers demonstrated the relationships between CVP and cardiac output and between the venous return and the CVP [2, 3]. By plotting the two relationships on the same set of axes it can be seen that the 'ventricular function curve' and the 'venous return curve' intersect at only one point, demonstrating that if all other factors remain constant, i.e., if nothing happens to alter the shape of either of the two curves, a given CVP can, at equilibrium, be associated with only one possible cardiac output and, similarly, a given cardiac output (or venous return) will, at equilibrium, be

associated with a specific CVP. Both curves can of course be affected by a number of factors: total blood volume, and the distribution of that blood volume between the different vascular compartments (determined by vascular tone) will affect the venous return curve. The inotropic state of the right ventricle will affect the shape of the ventricular function curve. When any one of these factors is altered there will be an imbalance between cardiac output and venous return, which will persist for a short time until a new equilibrium is reached at a new central venous blood volume and/or an altered central venous vascular tone.

As the superior vena cava, where the CVP is measured, is a thoracic structure pressure changes in the thoracic cavity will affect the measured CVP. This has important practical implications for the measurement of CVP as the intrathoracic pressure changes cyclically with breathing. There are also important implications for the accuracy of CVP measurements in patients with either extrinsically applied or intrinsic positive end expiratory pressure (PEEP) as the intrathoracic pressure will not return to atmospheric pressure at any time during the respiratory cycle.

Additionally, as discussed in the previous section, tricuspid valve disease, myocardial and pericardial disease and cardiac rhythm abnormalities will all affect the CVP waveform.

A summary list of factors affecting the CVP is given in Table 1.

Table 1. Factors affecting the measured CVP

Central venous blood volume	• Venous return/cardiac output • Total blood volume • Regional vascular tone
Compliance of central compartment	• Vascular tone • Right ventricular compliance – Myocardial disease – Pericardial disease – Tamponade
Tricuspid valve disease	• Stenosis • Regurgitation
Cardiac rhythm	• Junctional rhythm • AF • A-V dissociation
Reference level of transducer	• Positioning of patient
Intrathoracic pressure	• Respiration • Intermittent positive pressure ventilation (IPPV) • Positive end-expiratory pressure (PEEP) • Tension pneumothorax

How is the CVP Monitored?

The CVP is commonly measured by means of a fluid filled cannula with its tip in the superior vena cava connected to either a fluid filled manometer or, more commonly in the critical care setting, to an electronic pressure transducer linked to a monitor which will display a continuous pressure wave.

In order to accurately measure CVP, it is important to appropriately set the reference level of the pressure measuring device, whether a fluid filled manometer or electrical transducer, at the level of the right atrium. In the supine patient, this point is best estimated by using the intersection of the fourth intercostal space with the midaxillary line, however, this reference may not be as accurate in patients not in the supine position [4].

If the CVP is to be used as an index of cardiac preload then, theoretically, the most relevant pressure to measure from the CVP trace is the pressure at the onset of the c wave. The c wave marks the closure of the tricuspid valve at the beginning of ventricular systole and immediately before its onset the measured pressure should be equivalent to the right ventricular end diastolic pressure (except in the case of tricuspid stenosis where a pressure gradient will always exist between the two chambers). Where no c wave is clearly visible, it is conventional to take the average pressure during the a-wave. Where no a wave is visible (e.g., in atrial fibrillation) the pressure at the Z-point (that point on the CVP wave which corresponds with the end of the QRS complex on the electrocardiogram [EKG]) should be used. It is worthy of note that many of the commercially available monitoring systems do not measure the CVP in this way but simply generate a mean CVP during the whole cardiac cycle and average this value over a number of cycles.

As can be seen from the above although CVP is used as an index of circulatory filling and preload many factors can affect the CVP waveform and the measured pressure (Table 1).

Potential Uses of the CVP

Utility of CVP to Predict Cardiac Preload

Theoretical objections

In 1895, Otto Frank demonstrated that the pressure generated in an isometrically contracting ventricle was proportional to the end diastolic volume of the chamber [5]. Starling and his co-workers expanded this work to show that the stroke volume of the contracting heart was proportional to the end diastolic volume up to a point where a plateau was reached and increasing volume would no longer increase the stroke volume (Fig. 2). It is a common practice in critical care medicine to maximize the cardiac output by using intravenous fluid administration to increase the preload and, therefore, stroke volume. However, excessive infusion of fluid carries its own problems and is therefore to be avoided; the aim therefore is

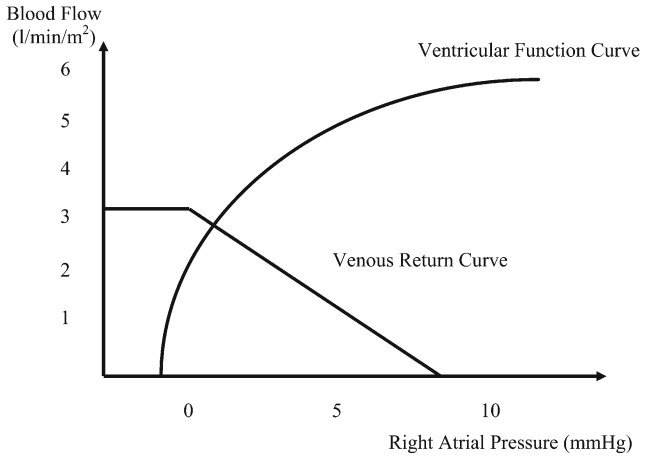

Fig. 2. Ventricular function and venous return curves

to ensure that the preload places the heart at the top of the ascending part of the Starling curve, i.e., the minimum preload to attain maximal stroke volume.

Preload is the length of the cardiac muscle fibers at the end of diastole. The use of CVP as an index of preload therefore relies on two assumptions: that CVP is equivalent to the filling pressure of the heart and that myofibril length is proportional to the cardiac filling pressure.

Unfortunately, the measured CVP often does not truly correspond to the pressure distending the right atrium at the end of diastole. As discussed above the most relevant pressure in this context is the pressure at the onset of the c wave and this is not the pressure displayed by many monitoring systems. Also, the pressure that dilates the ventricle is not the intravascular pressure but the transmural pressure, i.e., the difference between the pressure within the ventricle (intravascular pressure) and the intrathoracic pressure (extravascular pressure). Changes in intrathoracic pressure affect the intravascular pressure, for example the changes in CVP seen during the respiratory cycle, and if changes in intrathoracic pressure were completely transmitted across the vessel wall the transmural pressure would remain constant. However, it is not possible to determine for an individual patient the extent to which these pressure changes are transmitted and so the transmural pressure cannot be accurately determined. One solution would be to manually measure the end-diastolic CVP at the end of expiration and in the absence of PEEP (either intrinsic or extrinsic) when the intrathoracic pressure is equal to atmospheric pressure and the transmural pressure is, therefore, equal to the intravascular pressure. However, this is not possible with all monitors or in all patients. We would suggest that, to maximize the reliability of the measurement, where CVP is to be used to as an index of cardiac preload the end expiratory end diastolic CVP should be manually measured in the same manner that a pulmonary artery occlusion pressure (PAOP) would be measured.

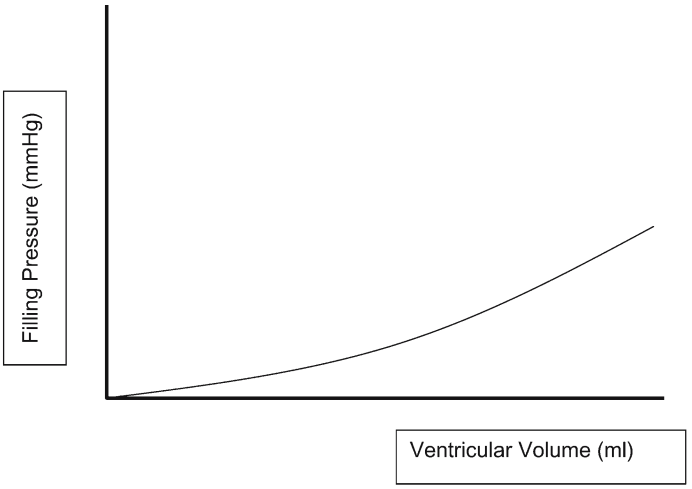

Fig. 3. Ventricular diastolic pressure volume curve

In addition, myofibril length is not linearly related to the pressure distending the ventricle. In fact the diastolic pressure/volume relationship is curvilinear, the gradient of the curve increasing as filling pressure rises (Fig. 3). This curve is not fixed between or even within individuals but will vary with factors that cause changes in ventricular compliance, e.g., inotropic state, myocardial ischemia, myocardial edema.

Clinical evidence

It is clear from the above that the CVP is not likely to provide an ideal index of right ventricular preload. This expectation is borne out in several clinical studies. CVP has been shown to correlate poorly with cardiac index [6]. Also, CVP correlates poorly with stroke volume index [7]. Given the wide intersubject variability one would expect in the ventricular function curves and venous return curves of critically ill patients, the lack of correlation of measured CVP with cardiac output in groups of patients may be considered less than surprising. However, changes in CVP during volume loading also correlate poorly with changes in stroke volume index during the same period [8-10]. In addition, the CVP correlates poorly with other indices of cardiac preload that have been demonstrated to correlate well with cardiac output or cardiac index including the intrathoracic blood volume index and left ventricular end diastolic volume index [11] and right ventricular end diastolic volume index [12, 13].

A clear problem with the use of the CVP to optimize the cardiac preload is that it does not allow optimization of left ventricular function. The left ventricular preload is related to the end diastolic left atrial pressure as the right ventricular preload is related to the end diastolic right arterial pressure. The PAOP is clinically

used as an index of left ventricular preload in much the same way as CVP is used as an index of right ventricular preload. Although in health the CVP and PAOP are closely related, the relationship between the two may be less predictable in disease [14, 15]. However, it may be argued that as the left and right ventricular outputs must be equal, the optimization of cardiac output may be adequately carried out by use of the CVP in certain circumstances as the right ventricle's output will normally stop responding to fluid infusion before the left ventricle and the left ventricle's output will clearly be limited by the right ventricle's maximum output ("no left sided success without right sided success") [16]. In clinical practice, the problem remains that a failing left ventricle may allow the rapid development of pulmonary edema after the infusion of even a small volume of intravenous fluid and this cannot be readily predicted by the use of CVP monitoring.

Utility of CVP to Predict the Volume Responsive Patient

During the optimization of cardiovascular function, an important decision is whether to attempt to increase cardiac output by giving additional fluid or whether to administer inotropic drugs. A desirable characteristic, therefore, of any index of preload is that it should be able to predict whether or not the heart is fluid responsive, i.e., whether a further increase in preload will result in an increase in stroke volume [17]. The majority of studies of the predictive value of CVP for fluid responsiveness have been unable to demonstrate a relationship between the baseline CVP and the response to filling [18-20]; those studies where a relationship between low CVP and fluid responsiveness has been demonstrated [21, 22] found such an overlap of CVP values between the responder and non-responder groups that no threshold value which would discriminate between the two groups could be determined. Use of CVP measurements to assess whether or not a patient's cardiac output will increase significantly in response to an infusion of intravenous fluid cannot therefore be recommended. Currently, the only use of CVP measurement in this process is to ensure that a large enough fluid bolus is given to attempt to increase cardiac output by ensuring that an increase in ventricular filling pressure is achieved.

Dynamic Changes in CVP

Recently there has been interest in using the dynamic changes in CVP with respiration to predict fluid responsiveness. Two studies from the same group [23, 24], both involving spontaneously breathing patients, have shown that an inspiratory fall in CVP by ≥ 1 mmHg is highly predictive of a fluid responsive cardiac index (positive predictive value 77%/84% and negative predictive value 81%/93%).

Although the CVP in the supine patient is a poor index of circulating volume postural changes in CVP may be a more reliable indicator of intravascular volume status [4]. Measurement of postural changes in CVP seems, however, unlikely to

become a widely adopted clinical tool within the context of the acutely or critically ill patient in the ICU.

Utility of CVP as a Measure of Circulatory Filling

Central venous pressure can without doubt be affected by the intravascular volume. Approximately two thirds of the intravascular volume is contained in the venous system and the total intravascular volume will affect the mean venous pressure. Only a proportion of the total intravascular volume exerts any distending force on the vasculature [25] thereby causing a positive pressure within the vasculature; this volume cannot be measured in the intact human and will vary with the vascular tone which is therefore also an important determinant of the CVP. The volume of blood in the central veins will also be affected by the distribution of the venous blood volume through the venous system: peripheral venoconstriction and the effects of the muscle pump will redistribute volume from the peripheral veins to the central veins and so increase CVP whereas peripheral vasodilatation and upright posture will redistribute volume to the peripheral venous compartment and decrease the CVP. Furthermore, the CVP depends not only on the volume of blood in the central venous system but on the compliance of that system. With so many factors other than intravascular volume affecting the CVP one might expect that CVP would be a relatively inexact measure of intravascular volume particularly in the intact organism where feedback mechanisms will compensate for a decreased intravascular volume by stimulating vasoconstriction. This expectation is borne out in clinical studies where not only has CVP been shown to correlate poorly with blood volumes measured by indicator dilution but the change in CVP after fluid resuscitation of shocked patients also correlated poorly with the measured change in blood volume [26, 27]. CVP has also been found to correlate poorly with the volume of fluid administered during ENT surgery in spite of a progressive decrease in hematocrit during surgery suggesting intravascular volume expansion [28].

Clinical Outcomes and CVP monitoring

Considering the paucity of data to support CVP as a useful physiological monitor one would not expect CVP monitoring to have a significant positive effect on outcome. There are relatively few studies that examine this issue particularly in the critically ill, presumably because CVP monitoring has become an almost routine part of ICU care.

Fluid administration targeted by CVP monitoring during hip surgery shortened the time before patients were medically fit for discharge [29]. However, similar results were obtained using Doppler flow monitoring to guide fluid administration and it might be suggested that similar results in both groups could have been achieved by simply giving larger volumes of fluid without additional monitoring. In another study, fluid administration aiming to keep the CVP greater than 5 mmHg during renal transplant surgery resulted in a greater frequency of graft

function within the first three postoperative days than in a control group without CVP monitoring [30]. Whilst these studies probably demonstrate an important use of CVP monitoring in detecting low circulating volumes in surgical patients which when detected can be appropriately managed and thus lead to improved outcome it is doubtful what bearing they have in critically ill patients where more usually the CVP is relatively high and the question is whether fluid or vasoactive drugs should be the next intervention.

In some circumstances CVP monitoring may provide prognostic information. A CVP of > 15 mmHg after cardiac surgery is a significant predictor of poor outcome [31].

Of more relevance to ICU medicine, the decrease in cardiac output in response to an increase in PEEP (from 0 to 30 mmHg) correlates with the initial level of CVP and patients with an initial CVP of ≤ 10 mmHg experience a greater fall in cardiac index than patients with CVP >10 mmHg (–30% +/– 9 vs. –8% +/– 7) [32]. Maintaining a CVP of >10 mmHg may therefore be desirable in the ventilated patient. Surprisingly the inspiratory decrease in CVP appears unable to predict the cardiovascular response to PEEP in a similar way [33].

When considering the utility of CVP monitoring it is appropriate to make the analysis in the context of other possible modalities of monitoring available to measure similar physiological variables. The most common alternative to CVP monitoring as an index of cardiac preload and volume status is pulmonary artery pressure monitoring using a pulmonary artery catheter (PAC). The use of PACs has been associated with greater morbidity and cost than the use of central venous catheters and a number of studies have suggested that in many cases they do not offer any advantages over CVP monitoring, particularly in low risk surgical patients [34] and may in fact worsen outcome increasing both the complication rate and time spent intubated after cardiac surgery [35]. An examination of the utility of PACs as an alternative to central venous catheters is outside the scope of this chapter but it is to be hoped that a clear answer to this question will be given by the large multicenter study currently underway.

Perhaps the most powerful studies indicating the usefulness of CVP monitoring, or lack thereof, in critical care are those involving goal directed therapy. One such study in septic patients showed no difference in outcome between patients with CVP or PAC monitoring where therapy was directed towards achieving normal values of measured variables; however, in those patients where therapy was directed to achieving supraphysiological values for cardiac index and oxygen delivery an improved outcome was seen [36]. Clearly such goal directed therapy requires monitoring other than simple CVP monitoring. Similarly, early goal directed therapy of septic patients in the emergency department resulted in significantly improved outcomes when therapy was directed at improving mixed venous saturations rather than at normalizing the CVP, mean arterial pressure (MAP) and urine output [37].

Conclusion

The two clinical studies on surgical patients [29, 30] confirm the potential utility of CVP monitoring in some patient groups. As a decrease in CVP is a relatively late sign of intravascular volume depletion in a patient with intact vasoconstrictor reflexes it is possible that in the patient groups in these two studies there is a significant risk of severe hypovolemia which would, if not detected by CVP monitoring, remain untreated causing increased morbidity. It may, however, be argued that CVP may be a better measure of volume status in anesthetized patients whose vasoconstrictor reflexes are pharmacologically impaired by the anesthetic drugs.

There is no convincing evidence that CVP monitoring improves outcome in the critically ill patient, particularly when other variables are being assessed. Additionally, it is clear from studies examining goal directed therapy that targeting fluid therapy to normalizing the CVP in a critically ill patient is not an optimal treatment strategy.

There is no doubt that there is a significant morbidity and possibly even mortality associated with obtaining central venous access; central cannulation having a complication rate of up to 6% even when performed by experienced staff [38]. This risk may outweigh the risk of giving large volumes of fluid without central pressure monitoring in the general surgical population. However, the majority of critically ill patients require central venous access for the administration of drugs or potassium and there appears to be some potential advantage in measuring central venous oxygen saturation at least during the early stages of treatment for which central access is also required. If central venous access is to be obtained then it would seem appropriate to monitor the CVP. As long as this variable is considered in the context of the whole clinical picture and other monitored and laboratory variables and the underlying pathophysiology taken into account then it is unlikely that CVP monitoring will lead to a worsened outcome and there are some situations such as a large occult blood loss or extreme vasodilatation where a change in CVP may provide an early warning of the problem.

The role for CVP as a monitor for use in the cardiovascular optimization of critically ill patients remains important largely because most critically ill patients will require central venous access for other reasons and so monitoring the CVP becomes essentially a risk free procedure as the risks are associated with obtaining access rather than the monitoring process itself. However, as a monitor it has significant weaknesses and with the increasing availability of other less invasive and apparently better measures of preload and circulatory filling the importance of CVP monitoring is likely to decline in this context, at least within the critical care setting, although it may be some time before other preload monitors are available on general wards in our hospitals.

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Pulmonary Artery Occlusion Pressure: Measurement, Significance, and Clinical Uses

J. J. Marini and J. W. Leatherman

Introduction

Originally, the primary motivation for the development of the balloon flotation pulmonary artery catheter (PAC) was to measure the pulmonary artery occlusion ('wedge') pressure (PAOP), which estimates the pulmonary venous pressure downstream from the alveolar capillary bed. Now, after more than three decades of continuous use and modification, many added functions of the catheter have alternatives that are less invasive and occasionally more informative (e.g., minimally invasive cardiac output estimation, superior vena cava oxygen saturation, transesophageal ultrasonic imaging). It can reasonably be argued that the primary justification for the placement of the PAC today is once again to monitor the occlusion pressure, a useful measurement that has no practical alternative. Pulmonary venous pressure plays a crucial role in the evolution and treatment of numerous life threatening problems encountered in the practice of intensive care. Not only is pulmonary venous pressure the minimum hydrostatic filtering pressure for pulmonary edema formation, but it approximates the mean intra-cavitary left atrial pressure that influences left ventricular (LV) pre-load. This chapter will review important aspects of the measurement and interpretation of the PAOP, the best estimate of pulmonary venous pressure at the bedside.

Pressure Monitoring System

Essential system components required for pressure monitoring include a fluid-filled catheter and connecting tubing, a transducer to convert the mechanical energy from the pressure wave into an electrical signal, and a signal processing unit that conditions and amplifies this electrical signal for display. Two primary features of the pressure monitoring system determine its dynamic response properties: natural resonant frequency and damping coefficient [1, 2]. Once perturbed, each catheter-transducer system tends to oscillate at a unique (natural resonant) frequency, determined by the elasticity and capacitance of its deformable elements. An un-damped system responds well to the low-frequency components of a complex waveform, but it exaggerates the amplitude of components near the resonant value. Modest damping is desirable for optimal fidelity and for suppression of unwanted high-frequency vibration ('noise'); however, excessive damping

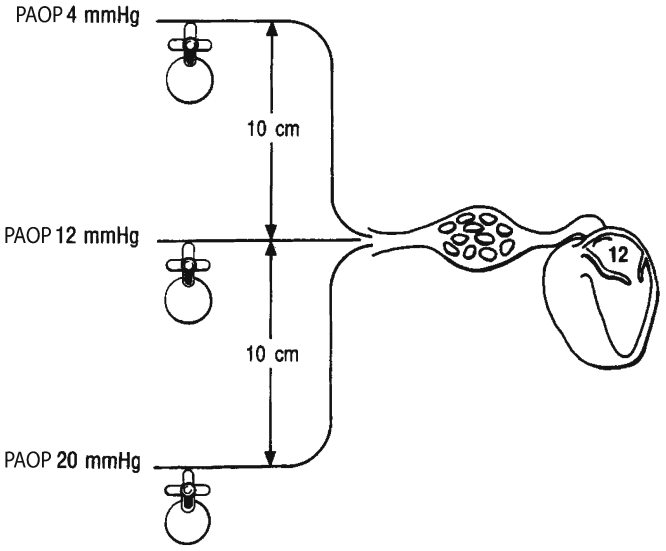

Fig 1. Effect of transducer position on pressure measurement. Once 'zeroed' at the left atrial level, movements of the transducer relative to the patient will influence the recorded value.

smoothes the tracing unnaturally and eliminates important frequency components of the pressure waveform (see below).

For the hydraulic monitoring system to display accurate pressures, it is essential that the system be 'zeroed' (balanced) at the phlebostatic axis (mid-axillary line, fourth intercostal space). Body angle is not crucial, so that one can zero the transducer with the orthopneic patient upright or semi-upright. Once the transducer has been zeroed, however, movement of the transducer relative to the heart will cause the recorded pressure to underestimate or overestimate the true value (Fig. 1). Because the pulmonary circuit is a low-pressure vascular bed, small errors in transducer position may be clinically significant.

The transducer converts mechanical energy from the fluid-filled tubing into an electrical signal that is then amplified and displayed. The disposable transducers currently used in the ICU are sufficiently accurate for routine clinical purposes [3].

Catheter Insertion

The right ventricle (RV) should be entered within 30 cm from the internal jugular or subclavian entry sites. After entering the RV, insertion of an additional 10 to 15 cm of catheter is usually sufficient to reach the pulmonary artery. Entry into the pulmonary artery is reflected by an abrupt rise in diastolic pressure; a dicrotic notch due to pulmonic valve closure may be apparent. The catheter is then gradually advanced until a PAOP is signaled by a transition to an atrial waveform and a fall in mean pressure.

A number of factors may interfere with recognition of characteristic waveforms during catheter insertion. Severe hypovolemia and other causes of decreased stroke volume reduce the pulmonary artery pulse pressure and the difference between mean pulmonary artery pressure and PAOP, potentially creating difficulties in determining whether a valid PAOP tracing has been achieved. With pericardial tamponade or RV infarction, the right ventricular end-diastolic pressure (RVEDP) approaches pulmonary artery diastolic pressure, making the transition from RV to pulmonary artery sufficiently difficult to appreciate that fluoroscopy may be required to confirm catheter position [4]. Large swings in intrathoracic pressure may create major problems for waveform interpretation. If the patient is mechanically ventilated, elimination of large respiratory excursions with sedation (or temporary paralysis) may aid in delineation of the tracing and will enhance reliability of the measurements obtained [5]. Another 'recognition' problem is excessive catheter 'whip' caused by 'shock transients' being transmitted to the catheter during RV contraction in hyperdynamic states. Overdamping occurs when air bubbles, clots, fibrin, or tubing kinks diminish transmission of the pulsatile pressure waveform to the transducer, resulting in a decrease in systolic pressure and an increase in diastolic pressure. An over-damped pulmonary artery pressure tracing may be mistaken for PAOP, leading to unnecessary retraction of a properly positioned catheter. A simple bedside test for overdamping is the 'rapid flush' maneuver [1]. Because of the length and small gauge of the catheter, very high pressures are generated near the transducer when the flush device is opened. An appropriately damped system will show a rapid fall in pressure with a modest 'overshoot' and prompt return to a crisp pulmonary artery tracing upon sudden closure of the flush device. In contrast, an overdamped system will demonstrate a gradual return to the baseline pressure, without an overshoot.

PAC-derived Pressures

The properly positioned PAC provides access to pressures from three sites: right atrium (Pra), pulmonary artery, and pulmonary veins – the 'wedge' pressure (PAOP).

Pulmonary Artery Pressure

The pulmonary artery waveform has a systolic pressure wave and a diastolic trough. A dicrotic notch due to closure of the pulmonic valve may be seen on the terminal portion of the systolic pressure wave, and the pressure at the dicrotic notch closely approximates mean pulmonary artery pressure [6]. Like the right atrial V wave, the pulmonary artery systolic wave typically coincides with the electrical T wave (Fig. 2). The pulmonary artery diastolic pressure is recorded as the pressure just before the beginning of the systolic pressure wave.

Pulmonary artery pressure is determined by the volume of blood ejected into the pulmonary artery during systole, the resistance within the pulmonary vascular bed, and the downstream (left atrial) pressure. Normal values for pulmonary artery

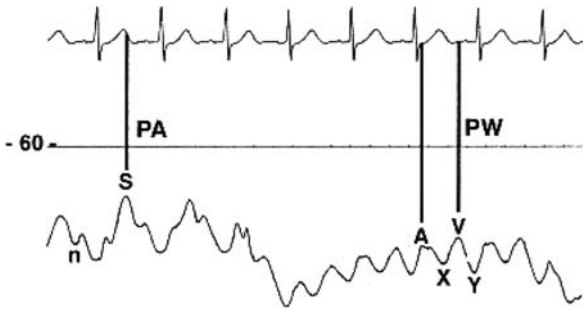

Fig. 2. Pressure waveforms recorded simultaneously with an electrocardiogram. The 'A' wave times most closely with the QRS, while the 'V' wave occurs in the latter portion of the T wave. PA: pulmonary artery pressure; PW: pulmonary artery occlusion pressure

pressure are as follows: systolic, 15 to 30 mmHg; diastolic, 4 to 12 mmHg; and mean, 9 to 18 mmHg [4]. The normal pulmonary vascular network is a low-resistance circuit with enormous reserve, so that large increases in cardiac output do not cause pressure to rise significantly. This large capillary reserve normally offers such slight resistance to runoff during diastole that the difference between the pulmonary artery diastolic pressure and the PAOP (the pulmonary artery diastolic pressure-PAOP gradient) is $\leq$ 5 mmHg. Increased pulmonary vascular resistance (PVR) causes the pulmonary artery diastolic pressure-PAOP gradient to widen, whereas an increase in left atrial pressure results in a proportional rise in the pulmonary artery diastolic pressure and PAOP [7, 8]. Therefore, the pulmonary artery diastolic pressure-PAOP gradient is used to differentiate pulmonary hypertension due to increased PVR from pulmonary venous hypertension.

An increased cardiac output alone will not cause pulmonary hypertension. However, in the setting of increased vascular resistance, the degree to which pulmonary artery pressure increases will be influenced by the cardiac output. Pulmonary hypertension may result from the combination of a modest increase in vascular resistance and a major increase in cardiac output due to sepsis, cirrhosis, agitation, fever or other factors. The relative contributions of blood flow and the pulmonary vasculature to the increase in pulmonary artery pressure can be assessed by measuring cardiac output by thermodilution and calculating PVR:

PVR = [pulmonary artery pressure-PAOP]/cardiac output

It should be appreciated, however, that interpretation of the PVR is confounded by the fact that the pulmonary vascular bed behaves like a Starling (variable) resistor; PVR increases as flow decreases and the calculated PVR must be interpreted with respect to the cardiac output at the time the measurement is made [9]. For example, a fall in cardiac output due to hemorrhage may produce a rise in calculated PVR, even though the pulmonary vascular bed has not been directly affected; the PVR may then 'normalize' once the cardiac output returns to its baseline value. Conversely, calculated PVR may decrease solely due to an increase in cardiac output. The latter may be particularly relevant when assessing the response to vasodilators that affect both the pulmonary and systemic vascular

beds. With decreased cardiac output, a rise in calculated PVR that is accompanied by an increase in driving pressure within the pulmonary circuit (pulmonary artery pressure-PAOP) would clearly indicate active pulmonary vasoconstriction, whereas a reduction in driving pressure at increased cardiac output would provide unequivocal evidence of vasodilation [10].

Pulmonary Artery Occlusion ('Wedge') Pressure (PAOP)

The systolic pressure wave in the pulmonary artery tracing *precedes* the V wave of the PAOP tracing when referenced to the electrocardiogram (EKG). An appreciation of this relationship is needed when tracings are being analyzed to ensure that balloon inflation has resulted in a transition from an arterial (pulmonary artery) to an atrial (PAOP) waveform, and to detect the presence of a 'giant' V wave in the PAOP tracing (see below).

The PAOP is obtained when the inflated catheter obstructs forward flow within a branch of the pulmonary artery, creating a static column of blood between the tip of the catheter and the point (junction, or j point) in the pulmonary venous bed where it intersects with flowing blood. Since the fully inflated catheter impacts in segmental or lobar pulmonary arteries, the j point is usually located in medium-to-large pulmonary veins. If the catheter were to be advanced with the balloon only partially inflated (or uninflated), obstruction to flow will occur in a much smaller artery and the j point will accordingly move upstream to the smaller pulmonary veins. Since there is normally a resistive pressure drop across the small pulmonary veins, the PAOP recorded with a distal uninflated catheter will be slightly higher than the PAOP obtained with a fully inflated catheter [11]. Due to resistance in the small pulmonary veins, the PAOP will underestimate the pressure in the pulmonary capillaries (see below), but the absence of any appreciable resistive pressure drop across the larger pulmonary veins dictates that the PAOP will reliably reflect left atrial pressure.

For the PAOP to accurately represent left atrial pressure it is essential that the tip of the inflated catheter lie free within the vessel lumen, and the inflated balloon must completely interrupt forward flow within the obstructed artery. Obstruction to flow at the catheter tip can lead to 'overwedging', while failure of the balloon to seal the vessel lumen results in a 'partial' or 'incomplete' PAOP. Overwedging is recognized by a progressive rise in pressure during balloon inflation and usually results from balloon trapping the tip against the vessel wall. In such cases the continuous flow from the flush system results in a steady buildup in pressure at the catheter tip, or at least as high as required to cause compensatory leakage from the trapped pocket. If overwedging occurs, the deflated catheter should be retracted before reinflating the balloon to achieve a more suitable PAOP tracing and to prevent possible vessel injury.

An incomplete PAOP tracing occurs when the inflated balloon does not completely interrupt forward flow, resulting in a recorded pressure that is intermediate between mean pulmonary artery pressure and PAOP (Fig. 3). As a result, the measured PAOP will overestimate the true value, potentially leading to serious errors in patient management. In the absence of pulmonic valve insufficiency or

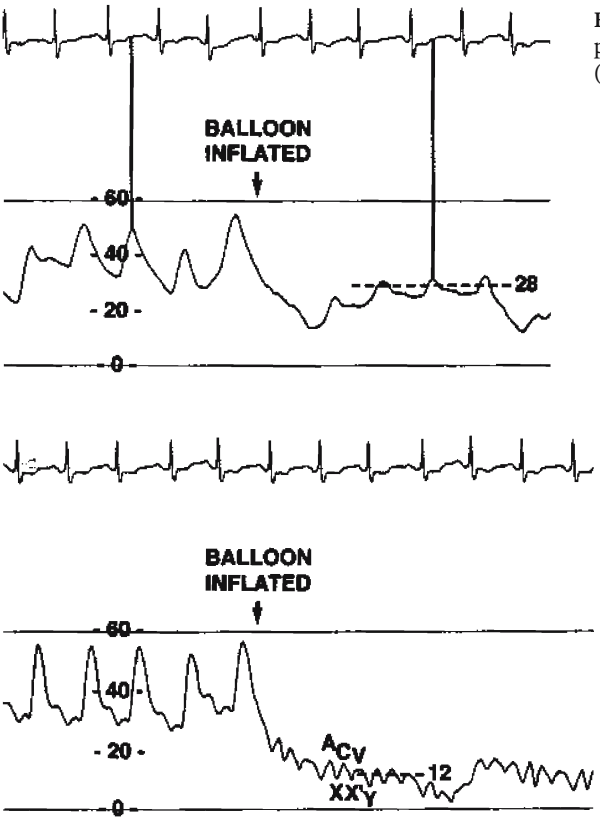

Fig. 3. Comparison of incomplete (top) with complete (bottom) wedge recordings.

prominent A or V waves that increase its mean value, the PAOP should be equal to or less than the pulmonary artery diastolic pressure. Therefore, incomplete wedging should always be suspected if the PAOP exceeds the pulmonary artery diastolic pressure [12]. However, incomplete wedging can also occur despite the presence of a positive pulmonary artery diastolic pressure-PAOP gradient. Incomplete wedging often occurs in patients with pulmonary hypertension whose increased pulmonary vascular resistance results in a marked increase in the pulmonary artery diastolic pressure-PAOP gradient. In this setting, the measured PAOP can increase significantly above the true value due to incomplete wedging, yet still remain less than the pulmonary artery diastolic pressure, giving the impression that a reliable PAOP has been obtained [13]. When this occurs the measured pulmonary artery diastolic pressure-PAOP gradient will decrease in comparison to previous values. With pulmonary hypertension, incomplete wedging should be suspected when the pulmonary artery diastolic pressure-PAOP unexpectedly narrows, or at the time of insertion when a normal pulmonary artery diastolic pressure-PAOP gradient is found when a widened gradient would be suspected (e.g., severe acute respiratory distress syndrome [ARDS]) [13]. Another clue to incomplete wedging is provided by a pressure waveform that is more consistent with pulmonary artery pressure

than PAOP (Fig. 3). Incomplete wedging can result from a catheter that is too proximal, in which case advancement of the inflated catheter may be corrective. Alternatively, a catheter that is too distal, perhaps with its tip at a vascular branch point, can also lead to incomplete wedging. This circumstance is suggested by measuring a lower (but more accurate) PAOP when the balloon is only partially inflated [13]. Note that a smaller balloon volume would ordinarily be expected to lodge in a smaller vessel with correspondingly *higher* (not lower) value for the balloon occlusion pressure. In such cases, retraction of the deflated catheter before full balloon inflation may yield a more accurate PAOP and potentially reduce the risk of vessel injury due to distal catheter placement.

One method that has been suggested to confirm the reliability of the PAOP is aspiration of highly oxygenated blood from the distal lumen of the inflated catheter [14]. However, there are several important considerations when using the PaO_2 of aspirated blood to confirm a wedge position. First, failure to obtain highly oxygenated blood in the PAOP position could occur if the catheter tip is located in a vessel whose capillary bed supplies an area of markedly reduced alveolar ventilation [1,15]. Second, it is recommended that an initial 15 to 20 ml of 'dead space' blood be withdrawn and discarded before the sample for analysis is obtained, to reduce the likelihood of obtaining a false-negative result when the inflated catheter has truly wedged [49]. Finally, a false-positive result (i.e., high oxygen saturation in aspirated blood when the catheter is not wedged) can occur if the sample is aspirated too quickly. It is recommended that the sample be aspirated at a rate no faster than 3 ml/min [15].

Respiratory influences on the PAOP

The PAOP is an *intravascular* pressure, but it is the *transmural* pressure (intravascular minus pleural) that represents the distending pressure for cardiac filling and the hydrostatic component of the Starling forces that govern transcapillary fluid movement. During normal breathing, the lung returns to its relaxed volume at end-expiration, with alveolar pressure being atmospheric and pleural pressure slightly negative. The PAOP should therefore be measured at end-expiration, the point in the respiratory cycle when juxtacardiac (pleural) pressure can be most reliably estimated. Either a strip recording or the cursor method should be used to record the end-expiratory PAOP since digital readouts that average over the respiratory cycle may overestimate or underestimate the PAOP.

Even when strip recordings are used, there may be inaccuracies in identifying the end-expiratory PAOP [16]. In one study, agreement among a group of critical care physicians who interpreted the same pressure recordings was only moderate, and addition of an airway tracing to identify end-expiration was without benefit [17]. A recent study found considerable inter-observer variability among intensive care unit (ICU) nurses and physicians who were asked to record the PAOP from the same strip recordings. The most important factor contributing to inter-observer variability was the presence of a large amount of respiratory variation [18]. Furthermore, a brief educational program did not improve the agreement among observers [19]. These data highlight some of the ongoing educational deficiencies

among ICU physicians and nurses regarding some of the most basic aspects of hemodynamic monitoring, and support the need for more intensive instruction, as proposed in the recent report by the Pulmonary Artery Consensus Conference Organization (PACCO) [20].

A frequent error in identifying end-expiration is the false assumption that during mechanical ventilation the lowest point in the PAOP tracing reflects end-expiration. While this may be true during controlled ventilation, inspiratory efforts that trigger mechanical breaths will produce a nadir in the PAOP tracing immediately after end-expiration [21]. Identification of end-expiration in the PAOP tracing is aided by the knowledge that expiration is usually longer than inspiration, two exceptions being tachypnea and inverse ratio ventilation. In reality, identification of end-expiration in the PAOP tracing should not be difficult as long as the respiratory influences on the PAOP are interpreted in relationship to the patient's ventilatory pattern. When confusion occurs, a simultaneous airway pressure tracing can precisely time the end of expiratory airflow.

Even when the PAOP is reliably recorded at end-expiration, the measured value will overestimate the transmural pressure if intrathoracic pressure is positive at that point in the cycle. Positive juxtacardiac pressure at end-expiration may result from the increase in lung volume that results from applied positive end-expiratory pressure (PEEP) or auto-PEEP, or from increased intraabdominal pressure due to active expiration or the abdominal compartment syndrome. In the latter two circumstances, lung volume is not increased. Whatever the cause, however, increased juxtacardiac (pleural) pressure must be recognized and taken into account when PAOP is used in clinical decision making.

Applied PEEP and auto-PEEP

PEEP may influence the PAOP in one of two ways. First, the positive alveolar pressure could conceivably compress the pulmonary microvasculature sufficiently so that there is no longer a continuous column of blood between the catheter tip and left atrium, resulting in a 'PAOP' that reflects *alveolar* rather than pulmonary venous pressure. Second, even when PEEP does not interfere with the reliability of the PAOP as an indicator of pulmonary venous pressure, it may nonetheless result in increased juxta-cardiac pressure so that the measured PAOP overestimates transmural pressure (left atrial pressure-pleural pressure).

In theory, the lung can be divided into three physiologic 'zones' based on the relationship of pressures in the pulmonary artery, alveolus, and pulmonary vein [1]. This model would predict that the catheter tip must be in Zone 3 (pulmonary vein pressure > alveolar pressure) at end-expiration for the PAOP to provide a reliable estimate of left atrial pressure, and this would not be the case if PEEP was greater than the left atrial pressure. However, in the great majority of instances the PAOP will reliably reflect left atrial pressure even when PEEP exceeds the latter [22–25]. Several factors may help explain this apparent paradox. Regardless of the values of PEEP and left atrial pressure, as long as there is a patent vascular channel between the catheter tip and the left atrium, the PAOP should reflect left atrial pressure. Since flow-directed catheters often place themselves below the level of

the left atrium, local pulmonary venous pressure will be higher than left atrial pressure, encouraging vascular patency [26]. Even when the catheter tip lies at or above the atrial level, there may still be a branch of the occluded artery extending below the left atrium that prevents the wedged catheter from recording alveolar pressure [27]. In addition, extra-alveolar vessels could preserve vascular continuity between the catheter tip and left atrium, regardless of the level of PEEP [25]. Finally, damaged lungs may not transmit alveolar pressure as fully to the capillary bed as normal lungs. In a dog model of unilateral lung injury, agreement between PAOP and left atrial pressure in the injured lung was excellent up to a PEEP of 20 cmH_2O, while PAOP overestimated left atrial pressure in the uninjured lung at a PEEP above 10 cmH_2O [22]. A clinical study involving patients with ARDS found good agreement between the PAOP and left ventricular end-diastolic pressure (LVEDP), even at a PEEP of 20 cmH_2O [23]. Since high levels of applied PEEP are generally restricted to patients with ARDS, the PAOP is likely to reliably reflect left atrial pressure even when high level PEEP is required.

Although uncommon, non-Zone 3 conditions should be considered when the PAOP tracing does not possess characteristics of an atrial waveform and the end-expiratory PAOP approximates PEEP. In this circumstance, a simple bedside method of ensuring a Zone 3 condition may be useful [24]. This technique involves a comparison of the change in pulmonary artery systolic pressure and change in PAOP (ΔPAOP) during a controlled ventilator breath. Since the former reflects the increment in pleural pressure during a positive-pressure breath, a ratio of change in pulmonary artery systolic pressure/ΔPAOP close to unity would indicate that the ventilator-induced rise in PAOP also results from change in pleural pressure, thereby insuring Zone 3. In contrast, ΔPAOP will exceed change in pulmonary artery systolic pressure if the PAOP tracing tracks the larger pressure change within the alveoli, in which case Zone 3 may not be present [24]. Over 90% of patients with ARDS have a change in pulmonary artery systolic pressure/ΔPAOP close to unity (0.7 to 1.2), even at PEEP of 20 cmH_2O [24]. Even in those few instances when PAOP tracks alveolar pressure during inspiration, a Zone 3 condition could still be present *at end expiration*, when alveolar pressures are least. In brief, data from several sources strongly indicate that the end-expiratory PAOP will nearly always represent the downstream vascular pressure (pulmonary vein pressure, left atrial pressure) in ARDS, even when high levels of PEEP are required. Concern that the PAOP may instead be representing alveolar pressure should be limited to those rare instances in which the PAOP tracing has an unnaturally smooth appearance that is uncharacteristic of an atrial waveform, the end-expiratory PAOP is close to 80% of the applied PEEP (because mmHg ~ 0.8 x cmH_2O), and the ΔPAOP is significantly greater than change in pulmonary artery systolic pressure during a controlled ventilator breath.

Even though PEEP seldom interferes with the reliability of the PAOP as a measure of left atrial pressure, it does cause the PAOP to overestimate the actual *transmural* pressure by increasing pleural pressure at end-expiration. The effect of PEEP on pleural pressure is determined by two factors: the PEEP-induced increase in lung volume and the chest wall compliance. The degree to which lung volume increases in response to PEEP relates inversely to lung compliance [1, 28]. Decreased chest wall compliance (e.g., increased intraabdominal pressure or morbid

obesity) enhances the fraction of PEEP transmitted to the pleural space, whereas reduced lung compliance (e.g., ARDS) may blunt PEEP transmission. One study found that the percentage of PEEP transmitted to the pleural space (as estimated with an esophageal balloon) in ARDS varied from 24 to 37% [29]. However, changes in esophageal pressure may underestimate the actual changes of juxtacardiac pressure when the heart and lungs are both expanded [30, 31]. Thus, in individual patients it may be difficult to reliably estimate the actual juxtacardiac pressure, and hence the transmural pressure (PAOP-pleural pressure), with PEEP.

Two methods for estimating transmural pressure on PEEP have been described for use in patients who are breathing passively. The first employs a brief ventilator disconnection, during which time the PAOP falls rapidly to a nadir, then subsequently rises due to altered ventricular loading conditions. It has been suggested that the nadir PAOP after PEEP removal, however, occurs beforehand and therefore closely estimates the transmural pressure while on PEEP [32]. Although this technique potentially yields a more accurate estimate of transmural pressure, it encourages alveolar derecruitment and hypoxemia in patients with severe ARDS (a post-measurement recruitment maneuver may then be advisable). In addition, the nadir method will not be reliable in patients with auto-PEEP due to airflow obstruction, since intrathoracic pressure falls very slowly after ventilator disconnection. The second technique, which neither requires ventilator disconnection nor is invalidated in patients with airflow obstruction, uses the ratio of ΔPAOP/change in pulmonary alveolar pressure during a controlled ventilator breath to calculate the percent of alveolar pressure that is transmitted to the pleural space [33]; in Zone 3, ΔPAOP should reflect the change in pleural pressure and change in alveolar pressure is defined as plateau pressure-PEEP. The effect of PEEP on pleural pressure is then estimated by multiplying PEEP by the transmission ratio. This allows calculation of the adjusted PAOP at end-expiration as (PAOP-change in pleural pressure) [33]. In one study, estimates of adjusted 'transmural' pressure using the latter technique were virtually identical to those obtained by the nadir method in patients on PEEP who did not have dynamic hyperinflation [33]. As noted above, the nadir method is unreliable for estimating transmural pressure in patients with airflow obstruction and auto-PEEP, whereas the alternative technique involving calculation of the transmission ratio retains its validity in this patient population [33]. Even though these techniques may provide valid estimates of transmural pressure, it is unclear whether they contribute positively to patient management. In clinical decision making, use of the PAOP should not focus excessively on its absolute value. Rather, *changes* in the PAOP with therapeutic interventions and their correlation with relevant endpoints (e.g., blood pressure, PaO_2, cardiac output, urine output) are of greater importance, and such changes can be assessed without correcting the measured PAOP for the effects of PEEP.

Auto-PEEP may create greater difficulties in use of the PAOP than applied PEEP, for several reasons. First, hemodynamically significant auto-PEEP may be occult. Second, because auto-PEEP usually occurs in the setting of chronic obstructive pulmonary disease (COPD) with normal or increased lung compliance, a larger component of the alveolar pressure may be transmitted to the juxtacardiac space. Third, the absence of parenchymal lung promotes non-Zone 3 conditions. As noted earlier, estimates of transmural pressure based upon the ΔPAOP/change in alveolar

pressure ratio are more reliable than the nadir PAOP technique in patients with auto-PEEP due to airflow obstruction. From a practical standpoint, the potential hemodynamic significance of auto-PEEP can be easily determined by assessing whether a 30- to 45-second interruption of positive-pressure ventilation leads to an increase in blood pressure and cardiac output [34]. Although this maneuver usually also results in a lower PAOP, an unchanged PAOP does not exclude the presence of hemodynamically significant auto-PEEP, because a large increase in venous return could offset the reduction in juxtacardiac pressure.

Active expiration

When the abdominal expiratory muscles remain active throughout expiration, the resultant increase in juxtacardiac pressure causes the end-expiratory PAOP to overestimate transmural pressure (Fig. 4). Although initially described in spontaneously breathing patients with COPD, this problem also occurs in the absence of obstructive lung disease and in mechanically ventilated patients [35]. Since the pressure generated by the abdominal expiratory muscles is transmitted directly to the pleural space and is not 'buffered' by the lungs, active exhalation typically causes the end-expiratory PAOP to overestimate transmural pressure to a much greater extent than does the application of PEEP [36]. With active exhalation, it is common for the end-expiratory PAOP to overestimate transmural pressure by more than 10 mmHg [5, 36]. Failure to appreciate the effect of active exhalation on

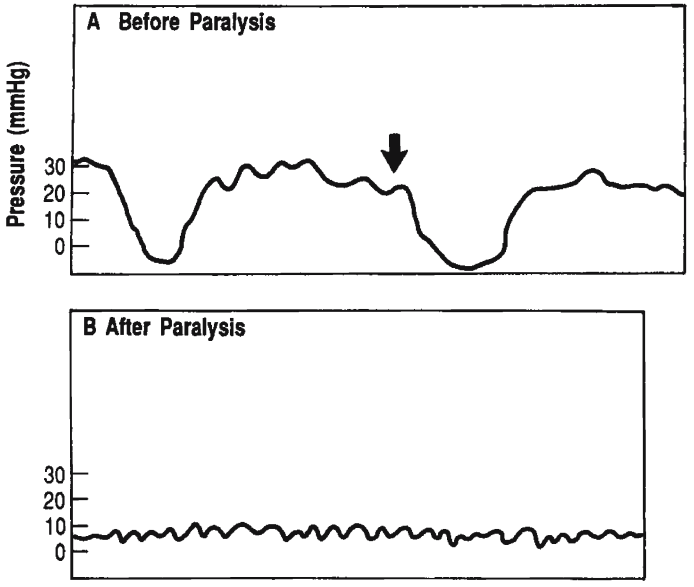

Fig. 4. Effect of vigorous respiratory muscle activity on end-expiratory wedge pressure (arrow).

the measured PAOP may result in inappropriate treatment of hypovolemic patients with diuretics or vasopressors on the basis of a misleadingly elevated PAOP.

When respiratory excursions in the PAOP tracing are due entirely to inspiratory muscle activity, the end-expiratory PAOP will remain unaffected. However, respiratory excursions that exceed 10–15 mmHg increase the likelihood of active expiration [5]. Inspection of the PAOP tracing may provide a clue to active expiration if pressure progressive rises during exhalation. However, an end-expiratory plateau in the PAOP tracing does not exclude positive intrathoracic pressure due to tonic expiratory muscle activity [36,37]. Abdominal palpation may be useful in detecting muscle activity that persists throughout expiration. In mechanically ventilated patients, use of sedation (or even paralysis) may be used to reduce or eliminate expiratory muscle activity [5, 36]. In the nonintubated patient, recording the PAOP while the patient sips water through a straw sometimes helps eliminate large respiratory fluctuations. An esophageal balloon can also be used to provide a better estimate of transmural pressure [35]. In those circumstances where prominent respiratory muscle activity cannot be eliminated and esophageal pressure is unavailable, transmural pressure is often better estimated by the PAOP measured midway between end-inspiration and end-expiration [36]. However, the latter is not true in all instances [36], and it may be most appropriate to simply recognize that an accurate estimate of transmural pressure may not be possible in this situation.

Clinical Use of Pressure Measurements

There are three principal uses of PAC-derived pressures in the ICU:
- diagnosis of cardiovascular disorders by waveform analysis
- diagnosis and management of pulmonary edema, and
- evaluation of preload.

Abnormal Waveforms in Cardiac Disorders

Unfortunately, physicians and nurses sometimes focus solely on the numbers generated by the pressure monitoring system, without carefully assessing the pressure waveforms. Analysis of pressure waveforms may prove valuable in the diagnosis of certain cardiovascular disorders, including mitral regurgitation, tricuspid regurgitation, RV infarction, pericardial tamponade, and limitation of cardiac filling due to constrictive pericarditis or restrictive cardiomyopathy.

Acute mitral regurgitation is most often due to papillary muscle ischemia or rupture. When the mitral valve suddenly becomes incompetent, an unaccomodated left atrium accepts blood from the left ventricle during systole, producing a prominent 'V' wave (Fig. 5). A large V wave gives the pulmonary artery pressure tracing a bifid appearance, owing to the presence of both a pulmonary artery systolic wave and the V wave. When the balloon is inflated, the tracing becomes monophasic as the pulmonary artery systolic wave disappears (Fig.5). A giant V wave is most reliably confirmed with the aid of a simultaneous recording of the

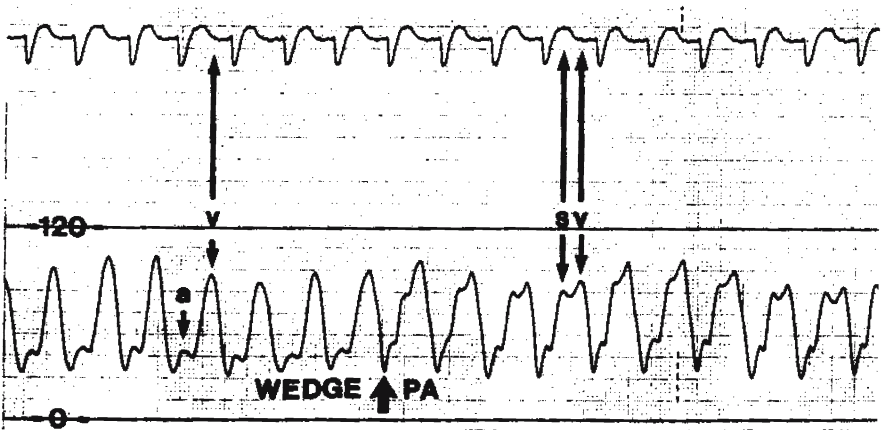

Fig. 5. Acute mitral regurgitation. Note that the waveform changes from monophasic during balloon occlusion (left) to bifid after occlusion is released. The regurgitant V wave is observed even during the wedge phase.

EKG during balloon inflation. Although the pulmonary artery systolic wave and the left atrial V wave are generated almost at the same time, the latter must travel back through the pulmonary vasculature to the catheter tip. Therefore, when the pressure tracing is referenced to the EKG, the V wave will be seen later in the cardiac cycle than the pulmonary artery systolic wave. In the presence of a giant V wave, the pulmonary artery diastolic pressure is lower than the mean PAOP, and the mean pressure may change only minimally upon transition from pulmonary artery pressure to PAOP, giving the impression that the catheter has failed to wedge. This impression may lead to the insertion of excess catheter, favoring distal placement that could lead to pulmonary infarction, or to rupture of the artery upon balloon inflation.

A large V wave leads to an increase in pulmonary capillary pressure, often with resulting pulmonary edema. When mitral insufficiency is due to intermittent ischemia of the papillary muscle, giant V waves may be quite transient. Failure to appreciate these intermittent giant V waves may lead to a mistaken diagnosis of noncardiogenic pulmonary edema, because the PAOP will be normal between periods of ischemia.

Large V waves do not always indicate mitral insufficiency. The size of the V wave depends on both the volume of blood entering the atrium during ventricular systole and left atrial compliance [38, 39]. Decreased left atrial compliance may result in a prominent V wave in the absence of mitral regurgitation. Conversely, when the left atrium is markedly dilated, severe valvular regurgitation may give rise to a trivial V wave, especially when there is coexisting hypovolemia [39]. The important effect of left atrial compliance on the size of the V wave was demonstrated by a study that simultaneously evaluated the height of the V wave and the degree of regurgitation as determined by ventriculography [39]. One-third of patients who had large V

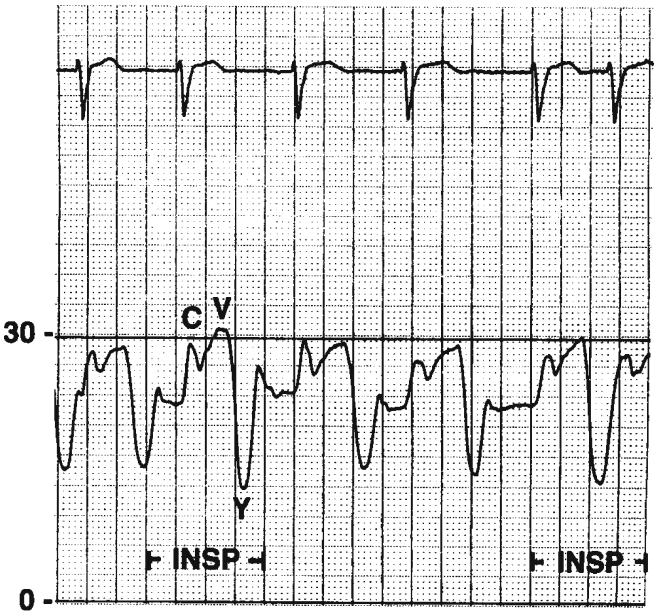

Fig. 6. Tricuspid regurgitation. Note broad 'cv' wave and inspiratory variation of the prominent 'Y descent'.

waves (> 10 mm Hg) had no valvular regurgitation, and a similar percentage of patients with severe valvular regurgitation had trivial V waves [39].

Hypervolemia is a common cause of a prominent V wave. When the left atrium is overdistended, it operates on the steep portion of its compliance curve; i.e., small changes in volume produce large changes in pressure. As a result, passive filling from the pulmonary veins can lead to a prominent V wave, and the latter may be quite large if cardiac output is increased. With hypervolemia or intrinsic reduction in left atrial compliance, the A wave may also be prominent, provided that the underlying rhythm is not atrial fibrillaton. Following diuresis, the A and V waves become less pronounced. Another cause of a large V wave is an acute ventricular septal defect, because the increased pulmonary blood flow enhances filling of the left atrium during ventricular systole. Thus, both papillary muscle rupture (or dysfunction) and acute ventricular septal defect (VSD) can be associated with prominent V waves, and these two complications of myocardial infarction must usually be differentiated by other means.

Tricuspid regurgitation is most often due to chronic pulmonary hypertension with dilation of the right ventricle. With tricuspid regurgitation, there is often a characteristically broad V (or "C-V") wave in the central venous (right atrial) tracing (Fig. 6). The V wave of tricuspid regurgitation is generally less prominent than the V wave of mitral regurgitation, probably because the systemic veins have a much greater capacitance than do the pulmonary veins. One of the most consistent findings in the right atrial pressure tracing of patients with tricuspid regurgi-

tation is a steep Y descent. The latter often becomes more pronounced with inspiration (Fig. 6). Kussmaul's sign, an increase in right atrial pressure with inspiration, is also commonly observed in patients with severe tricuspid regurgitation.

Right ventricular injury may complicate an inferior-posterior myocardial infarction. Common findings include hypotension with clear lung fields, Kussmaul's sign, positive hepatojugular reflux, and a right atrial pressure that equals, or even exceeds, the PAOP. The right atrial pressure tracing in RV infarction often reveals prominent X and Y descents, and these deepen with inspiration or volume loading [4]. With right ventricular infarction, the RV and pulmonary artery pulse pressures narrow, and with RV failure, the RVEDP may approximate the pulmonary artery diastolic pressure. This, together with the frequent presence of tricuspid regurgitation, may lead to difficulties in bedside insertion of the PAC, and fluoroscopy may be required [4]. In the setting of a patent foramen ovale, patients with RV infarction may develop significant hypoxemia due to a right-to-left atrial shunt. Profound hypoxemia with a clear chest radiograph and refractory hypotension would also be consistent with major pulmonary embolus. The hemodynamic profile of these two disorders is different, however, in that massive pulmonary embolism is characterized by a significant increase in the pulmonary artery diastolic pressure-PAOP gradient while the latter is unaffected by RV infarction [7].

Pericardial tamponade is characterized by an increase in intrapericardial pressure that limits cardiac filling in diastole. With advanced tamponade, intrapericardial pressure becomes the key determinant of cardiac diastolic pressures, resulting in the characteristic 'equalization' of the right atrial pressure and PAOP. Intrapericardial pressure is a function of the amount of pericardial fluid, pericardial compliance, and total cardiac volume. The X descent is preserved in tamponade, because it occurs in early systole when blood is being ejected from the heart, thereby permitting a fall in pericardial fluid pressure. In contrast, the Y descent occurs during diastole when blood is being transferred from the atria to the ventricles, during which time total cardiac volume (and intrapericardial pressure) are unchanged. As a result, there is little (if any) change in right atrial pressure during diastole, accounting for the characteristically blunted Y descent of pericardial tamponade [40]. Attention to the Y descent may prove to be quite useful in the differential diagnosis of a low cardiac output with near-equalization of pressures. An absent Y descent dictates that echocardiography be performed to evaluate for possible pericardial tamponade, while a well-preserved Y descent argues against this diagnosis.

Constrictive pericarditis and restrictive cardiomyopathy have similar hemodynamic findings. Both disorders may be associated with striking increases in right atrial pressure and PAOP due to limitation of cardiac filling. In restrictive cardiomyopathy, the PAOP is usually greater than the right atrial pressure, while in constrictive pericarditis, the right and left atria exhibit similar pressures. In contrast to pericardial tamponade, the Y descent is prominent and is often deeper than the X descent. The prominent Y descent is due to rapid ventricular filling during early diastole, with sharp curtailment of further filling during the later portion of diastole.

Diagnosis and Management of Pulmonary Edema

The PAOP is commonly used to aid in the differentiation of cardiogenic and noncardiogenic pulmonary edema. For uninjured lungs, the expected PAOP threshold for hydrostatic pulmonary edema is approximately 22 to 25 mmHg; a higher threshold is common if the PAOP has been chronically elevated. When capillary permeability is increased, however, pulmonary edema occurs at a much lower PAOP. Indeed, one generally accepted criterion for ARDS has been a PAOP < 18 mmHg. It is important to appreciate, however, that an isolated PAOP reading does not reliably predict whether pulmonary edema occurred on the basis of increased pulmonary capillary pressure alone or on the basis of altered permeability, especially when recorded after a therapeutic intervention. Acute hydrostatic pulmonary edema frequently occurs despite normal intravascular volume on the basis of an acute decrease in LV compliance resulting from ischemia or accelerated hypertension. By the time a PAC is placed, the acute process has often resolved, resulting in a normal or even reduced PAOP, depending in part on what type of therapy (diuretics, vasodilators) has been given. In this circumstance, maintaining the PAOP ≤ 18 mmHg over the next 24 hours should lead to marked clinical and roentgenographic improvement if pulmonary edema had been due to elevated pulmonary capillary pressure prior to catheter insertion. Conversely, lack of improvement or worsening would suggest altered permeability as the etiology of pulmonary edema. One must be careful, however, when hydrostatic pulmonary edema is due to intermittent elevations in PAOP due to myocardial ischemia. Transient ischemia-related elevations in PAOP may be missed by intermittently recording PAOP, potentially leading to an erroneous diagnosis of ARDS. Some bedside monitors store pressure data from the previous 12 to 24 hours, and inspection of a graphic display of the stored data may be useful in detecting transient elevations in pulmonary artery pressure that occur during periods of intermittent ischemia. Just as patients with hydrostatic pulmonary edema may have a normal PAOP, patients whose pulmonary edema is due primarily to increased permeabililty may have an increased PAOP due to volume expansion [41]. In brief, the pathogenesis of pulmonary edema formation should not be based solely on PAOP, and clarification of the underlying mechanism may require a period of careful clinical and radiologic observation.

PAOP, the pressure in a large pulmonary vein, represents a very low-end estimate of the average pressure across the fluid-permeable vascular bed. Normally, about 40% of the resistance across the pulmonary vascular bed resides in the small veins (Fig. 7) [42]. When pulmonary arterial and venous resistances are normally distributed, the Gaar equation predicts pulmonary capillary pressure by the formula:

Pulmonary capillary pressure = PAOP + 0.4 x (pulmonary artery pressure-PAOP) [42].

Since the driving pressure (pulmonary artery pressure-PAOP) across the vascular bed is normally very low, pulmonary capillary pressure will be only a few mm Hg above PAOP. However, a significant pressure drop from pulmonary capillary pressure to PAOP could occur under conditions of increased venous resistance, increased cardiac output, or both. For example, the markedly increased venous

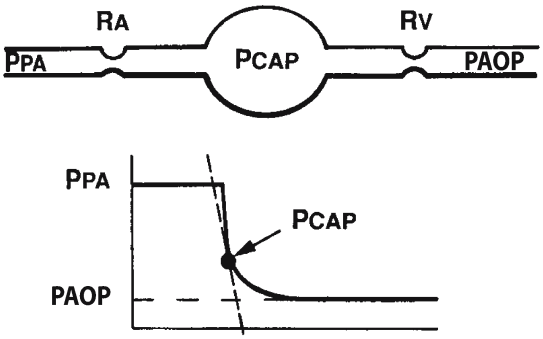

Fig. 7. Relationship of wedge pressure (PAOP) to capillary pressure. When there is a wide separation of mean pulmonary artery pressure (P_{PA}) and PAOP, the effective filtration pressure may be considerably higher than indicated by the wedge. Pcap: pulmonary capillary pressure

resistance of pulmonary veno-occlusive disease results in clinical evidence of increased pulmonary capillary pressure (pulmonary edema, Kerley B lines) despite a normal PAOP [43]. Other clinical conditions that selectively increase venous resistance are not well-defined.

A variety of techniques for determining pulmonary capillary pressure have been described [44–46]. The transition from a pulmonary artery pressure to a PAOP waveform after balloon occlusion includes an initial rapid decay and a subsequent slower decay (Fig.7). In experimental animals, the inflection point between the rapid and slow components has been shown to represent pulmonary capillary pressure as measured by isogravimetric or simultaneous double occlusion (arterial and venous) techniques [44]. Estimates of pulmonary capillary pressure from visual inspection of pressure tracings after balloon occlusion has been used in humans [45, 46]. One study concluded that pulmonary capillary pressure was on average 7 mmHg higher than the measured PAOP in patients with ARDS [45]. In this study, the estimated pulmonary capillary pressure and the calculated pulmonary capillary pressure by the Gaar equation were highly correlated, implying that arterial and venous resistances are increased equally in ARDS [45]. It should be appreciated, however, that it may be difficult to confidently determine the pulmonary capillary pressure by inspection of the pressure tracing following balloon occlusion [47]. Furthermore, even if an accurate estimate of pulmonary capillary pressure can be obtained, it is unclear how this would have any practical advantage over the PAOP in guiding fluid management, as non-capillary micro-vessels are also fluid permeable. The important point is that PAOP is a low-range estimate of pulmonary capillary pressure; the true value of the latter lies somewhere between pulmonary artery pressure and PAOP. It follows that increases in the driving pressure across the microvasculature caused by increases of cardiac output have the potential to exacerbate edema formation.

Downward manipulation of PAOP by diuresis or ultrafiltration will reduce pulmonary capillary pressure and may markedly benefit gas exchange in patients with ARDS. There is no minimum value for PAOP below which removal of intravas-

cular volume is contraindicated, provided that cardiac output is adequate. If the clinical problem is severely impaired gas exchange requiring high inspired oxygen fraction (FiO_2) or high PEEP, then a trial of PAOP reduction is reasonable, so long as cardiac output and blood pressure remain within acceptable limits. As with all therapeutic manipulations, clinically relevant end points (e.g., PaO_2, blood pressure, cardiac output) should be assessed before and after PAOP reduction.

Assessment of Preload

When afterload and intrinsic contractility are held constant, the forcefulness of ventricular contraction is determined by end-diastolic fiber length (preload) [48]. The most commonly used indicators of preload adequacy are PAOP and right atrial pressure [49]. Indeed, one of the principal reasons for developing the PAC was to have a bedside method of assessing LV preload [50]. However, in order to reliably assess preload, the PAOP must accurately reflect LVEDP, and LVEDP must correlate well with left ventricular end-diastolic volume (LVEDV). Under most circumstances, the PAOP provides a close approximation of LVEDP. Exceptions include an overestimation of LVEDP by the mean PAOP with mitral stenosis or mitral regurgitation with very large V wave, and underestimation of LVEDP by the mean PAOP when diastolic dysfunction or hypervolemia causes the LVEDP to increase markedly with atrial systole ('atrial kick') [1]. With a large V wave, LVEDP is best estimated by the pressure just before the onset of the V wave; with a prominent A wave, LVEDP is best estimated by the pressure at the 'z point', just after the peak of the A wave [48]. Unfortunately, even though the mean PAOP is usually equivalent to LVEDP, factors that alter LV compliance (hypertrophy, ischemia) or change juxtacardiac pressure (PEEP, active exhalation) may profoundly influence the relationship between LVEDP and LVEDV. It is not surprising, therefore, that among different patients an equivalent LVEDV may be associated with widely varying PAOP [51].

Despite its theoretical appeal, the absolute value of the PAOP is subject to a number of modifying influences that complicate its interpretation and render the unmodified number an unreliable guide to preload accuracy. The optimal PAOP (for preload) can be defined as the PAOP above which there is minimal increase in stroke volume. In normal individuals, optimal PAOP is often 10–12 mmHg [52]. During resuscitation from hypovolemic or septic shock the optimal PAOP is usually $\leq$ 14 mmHg [53], while in acute myocardial infarction it is often between 14–18 mmHg [54]. However, these target values are certainly not valid in all cases. By measuring stroke volume at different PAOP values, a cardiac function curve can be constructed, thereby defining optimal PAOP for an individual patient. This may be particularly useful in patients who also have established or incipient ARDS, because a PAOP above the optimal value will increase the risk of worsening oxygenation without offering any benefit with regard to cardiac output. It should be appreciated, however, that the relationship between PAOP and cardiac output may change as a consequence of alterations in LV compliance, myocardial contractility, or juxtacardiac pressure, and may therefore need to be redefined if clinical status changes.

The most clinically relevant test of the PAOP as an indicator of preload is its ability to predict the hemodynamic response to a fluid challenge when hypotension, oliguria, or tachycardia leads to uncertainty about the adequacy of preload. Studies that have examined the utility of the PAOP in predicting fluid responsiveness have been recently reviewed [55]. Seven of nine studies found that the PAOP was no different in fluid responders and non-responders, and analysis by receiver-operating curves in two studies indicated that the PAOP was not particularly useful as predictor of fluid responsiveness [56, 57]. One study did find a significant inverse relationship between PAOP and fluid-induced change in stroke volume, but the degree of correlation was only moderate [58]. Although these data suggest a major limitation of the PAOP as an indicator of preload, it is clear that there must be a PAOP above which volume expansion would almost always be futile, and a PAOP below which a positive response to fluid is virtually certain. To confidently define these cut-off PAOP values, however, would require a large study in which individual values for PAOP and fluid-induced change in stroke volume are reported for each patient, with a wide range of PAOP values being examined. The influence of pleural pressure and ventricular compliance would also need to be considered. Individual values for PAOP and fluid-induced change in stroke volume have been reported in two studies [58, 59]. Although no patient with a PAOP > 18 mmHg had a positive response to fluid and all patients with a PAOP <8 mm Hg were fluid responders, the number of patients within these PAOP domains was too small to draw any firm conclusions about the usefulness of these cut-off values [58, 59]. Furthermore, in the great majority of patients who had a PAOP between 8–18 mmHg there was no apparent relationship between PAOP and fluid response. In brief, while the PAOP is often used in clinical practice as an indicator of the adequacy of preload, most of the evidence to date would suggest that it has limited utility in predicting fluid responsiveness, at least over the range of values most often encountered in the ICU.

Of the above-mentioned nine studies that assessed PAOP and fluid responsiveness, five also examined the right atrial pressure [55]. Overall, the data for right atrial pressure were quite similar to those described for the PAOP, in that three of five studies found no difference between the right atrial pressure of responders and non-responders [55], and there was only a modest inverse correlation between right atrial pressure and the fluid-induced change in stroke volume [58]. There did not appear to be an appreciable difference in the predictive value of the right atrial pressure and the PAOP with regard to fluid response. It might be anticipated, however, that the right atrial pressure would be inferior to the PAOP in a population of patients with severe isolated LV dysfunction related to acute myocardial infarction or other causes [60]. Conversely, in patients with severe RV dysfunction and preserved LV function, the right atrial pressure may be more relevant than the PAOP [61].

Although PAOP and right atrial pressure are used most widely in guiding fluid therapy in the ICU [49, 55], measurements of cardiac volumes have also been used to predict fluid responsiveness [58, 62–64]. A modified PAC with a rapid-response thermistor permits simultaneous measurement of RV ejection fraction (RVEF) and stroke volume, from which RV end-diastolic volume (RVEDV) can be calculated. Several studies have compared the PAOP and RVEDV as predictors of fluid responsiveness [58, 62, 63]. One study found the RVEDV to be superior to the

PAOP, and suggested that either a positive or negative response to fluid could be reliably predicted when the RVEDV index was < 90 or > 138 ml/m^2, respectively [63]. However, a subsequent study found that that these threshold values for RVEDV index were unreliable, and both the PAOP and right atrial pressure predicted the response to fluid better than the RVEDV [58]. It is not clear that the RVEDV is any better than the PAOP (or right atrial pressure) at predicting fluid responsiveness.

In contrast to the static indicators of preload mentioned above, methods that rely upon the dynamic response to respiratory changes in intrathoracic pressure have performed somewhat better at predicting fluid response. One method is based upon the presence or absence of a reduction in right atrial pressure during a spontaneous breath [65]. When right atrial pressure decreased with inspiration, a positive response to fluid was likely (though not inevitable). Conversely, when a spontaneous breath did not produce a fall in right atrial pressure, cardiac output remained unchanged or decreased after a fluid challenge [65]. In this study, neither the PAOP nor the right atrial pressure discriminated responders and non-responders [65]. A follow-up study confirmed that patients with an inspiratory decrease in right atrial pressure had a much greater probability of responding to fluid than did patients whose right atrial pressure did not change with inspiration [66]. A second method is based on the change in arterial pressure from inspiration to expiration during controlled positive pressure ventilation [54]. In a study involving septic patients with circulatory failure, the respiratory variation in arterial pulse pressure was much greater in responders than in non-responders, and a threshold value was found that discriminated these two groups with a high degree of accuracy [54, 56, 57]. A second study that used a slight modification of this technique also found the respiratory variation in arterial pressure to predict the response to fluid much better than the PAOP or LV end-diastolic area (LVEDA) in patients with sepsis [53, 54, 56]. Although more investigations are needed to confirm these studies, methods that rely on the dynamic response to respiratory changes in intrathoracic pressure may ultimately prove to be better indicators of the adequacy of preload than static indicators such as the PAOP, right atrial pressure, RVEDV, and LVEDA [55].

Vascular Resistance Estimation

Combining thermodilution cardiac output with measurements of systemic and pulmonary pressures allows calculation of vascular resistances:

systemic vascular resistance (SVR) = (arterial pressure-right atrial pressure)/cardiac output

PVR = (pulmonary artery pressure-PAOP)/cardiac output

To assess the appropriateness of cardiac output to body mass, thermodilution cardiac output is divided by body surface area (BSA) to calculate cardiac index. Unlike flow (cardiac output), pulmonary and systemic pressures are not body size dependent. Therefore, to avoid misinterpretation due to variation in body mass, it

is also appropriate to compute indices of SVR and PVR by using cardiac index rather than cardiac output in the resistance calculations.

Assessment of thermodilution cardiac output and SVR may be particularly helpful in the assessment of hypotension, oliguria, and unexplained lactic acidosis. Measurement of thermodilution cardiac output is of particular value in the management of septic shock and ARDS. Septic hypotension is often due primarily to excessive arterial vasodilation, but decreased venous return and myocardial dysfunction may contribute to the hemodynamic derangement. By assessing the relative contribution of cardiac output and SVR to systemic hypotension, the clinician may be able to more rationally apply fluid, vasopressor, and inotropic therapy. In ARDS, a fall in blood pressure could result from hypovolemia, left ventricular dysfunction, pneumothorax, pulmonary emboli, increasing PVR from ARDS, a change in applied PEEP, or dynamic hyperinflation, all of which produce hypotension through a decrease in cardiac output. Evaluation would consist of measurement of intravascular and airway pressures, perhaps along with obtaining a chest x-ray, EKG, or echocardiogram. On the other hand, these conditions would be of little concern if it were known that cardiac output remained unchanged, indicating that the fall in blood pressure was due entirely to a reduction in SVR.

Sepsis is the most common cause of hypotension with a low SVR, but other conditions may produce a similar hemodynamic profile. Severe hypotension resulting from excessive arterial vasodilation can occur as a result of acute adrenal insufficiency [67], thiamine deficiency (beri-beri), severe pancreatitis, or poisoning with a variety of drugs or toxins (e.g., nitrates, calcium channel blockers, aspirin, tricyclic antidepressants). Systemic arteriovenous fistulae, as occur with cirrhosis, also lead to a high cardiac output-low SVR hemodynamic profile, albeit usually with normal blood pressure. Failure to include non-infectious processes in the differential diagnosis of a high cardiac output/low SVR state may result in misdiagnosis of life-threatening, treatable conditions [68].

Conclusion

Controversy continues as to the clinical worth of the PAC. In large part, the value of this device is determined by the skill of the practitioner in the use of the data it provides. The PAOP, perhaps the catheter's signature measurement, is a potentially useful number on which important management decisions regarding fluids and vasopressors often depend. The acquisition and interpretation of the wedge, however, requires a high level understanding of its technical and physiologic determinants and an appreciation of the potential for error.

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Cardiac Output by Thermodilution and Arterial Pulse Contour Techniques

J. R. C. Jansen and P. C. M. van den Berg

Introduction

A reliable method of cardiac output monitoring is particularly desirable in patients in the intensive care unit (ICU) and in patients undergoing cardiac, thoracic, or vascular interventions. As the patient's hemodynamic status may change rapidly, continuous monitoring of cardiac output will provide information allowing rapid adjustment of therapy.

Over the years, there has been a continuing development of new methods and devices to measure cardiac output, but none of these methods has gained unrestricted acceptance. Only the conventional thermodilution method has been generally accepted and is currently the clinical standard to which all other methods are compared. However, this method can only provide mean cardiac output if three or more single estimates are averaged, because individual thermodilution estimates show substantial scatter [1–4]. Also, the 'recent breakthrough' [5–9] of the 'old' transpulmonary thermodilution [10–13], as an alternative to the pulmonary artery catheter (PAC), needs three measurements to be averaged to reach sufficient precision. Three measurements with this system consume approximately 3 minutes. Therefore, these two thermodilution methods lack the ability to monitor cardiac output continuously.

There are eight desirable characteristics for cardiac output monitoring techniques [14]: accuracy, reproducibility or precision, fast response time, operator independency, ease of use, continuous use, cost effectiveness, and no increased mortality and morbidity. Unfortunately, a technique which combines these eight characteristics has not become available yet. Consequently, in clinical practice the cardiac output measurement technique used varies depending on the preference of the treating physician and the available equipment.

How to Evaluate these Techniques?

In an editorial, Gardner [15] proposed to establish objective criteria to judge the accuracy and reproducibility of cardiac output measurement methods. Critchley and Critchley [16], in an effort to establish such objective criteria, state that: "if a 'new' method is to replace an older, accepted method, the new method should itself have errors not greater than the older method". Therefore, knowledge and

an accurate application of the older method are essential for a good evaluation of a new technique. Otherwise, the difference between the evaluated method and the reference method can be determined mainly by the reference method. Single estimates of cardiac output show substantial scatter (SD=15%) [1–4]. The averaged value of a triplicate, randomly injected series of thermodilution measurements has an error of 10% [2–4]. But, the best technique is to do three or four thermodilution measurements automatically with a power injector and to perform the injections at moments equally spread over the ventilatory cycle [4]. Under hemodynamically stable conditions, highly repeatable estimates of mean cardiac output (SD=3.5%) were obtained with this technique. Despite this reduction in errors (from 15% to 3.5%), the variation between different techniques of measuring cardiac output can be best evaluated by computing the average of both techniques as well as bias and precision statistics. Bland and Altman [17] proposed that bias or accuracy (the mean difference between the techniques) is an appropriate indication of agreement between techniques. Precision (the standard deviation of the differences, SD) indicates the random error. The limits of agreement (bias ± 2SD) indicate whether a change in cardiac output may be accepted as significant, based on the results of the two techniques. Thus, the limits of agreement involve the combination of errors of each measurement technique.

Review of the current literature on continuous cardiac output techniques revealed a lack of consistency in the presentation of results. Often the method under study is compared to thermodilution by linear regression analysis, also known as calibration statistic (Fig. 1), presenting the regression coefficients of the line together with the correlation r^2. Bland and Altman [18, 19] in their statistical notes pointed out that it could be highly misleading to analyze data pairs by combining repeated observations from several patients and then calculating standard regressions and r^2 as indicated in Figure 1.

Criteria as to whether a newer technique could replace an older technique (the bolus thermodilution technique) are often missing. Two methods of measurements can generally be considered interchangeable if the bias between the methods is close to zero and if the precision or limits of agreement for repeated measurements of each technique are comparable. If the results of both methods are statistically independent and we have the precision of the comparison (dif) and an estimate of the precision of the reference method (ref) then the precision of the new method (new) can be computed with Pythagoras' law:

$$\text{new} = \sqrt{(\text{dif}^2 - \text{ref}^2)}$$ [16].

For example, having found a precision of the difference between methods of 20% and using a reference method with 10% precision (i.e., the averaged result of triplicate randomly injected thermodilution measurement) the precision of the new method is calculated as $17.3\% = \sqrt{(20^2 - 10^2)}$. It should be concluded that the new method cannot replace the reference method (10% versus 17%).

In this chapter, we restrict the description and the discussion to two groups of continuous cardiac output measurements: First the continuous thermodilution method and second different pulse contour methods.

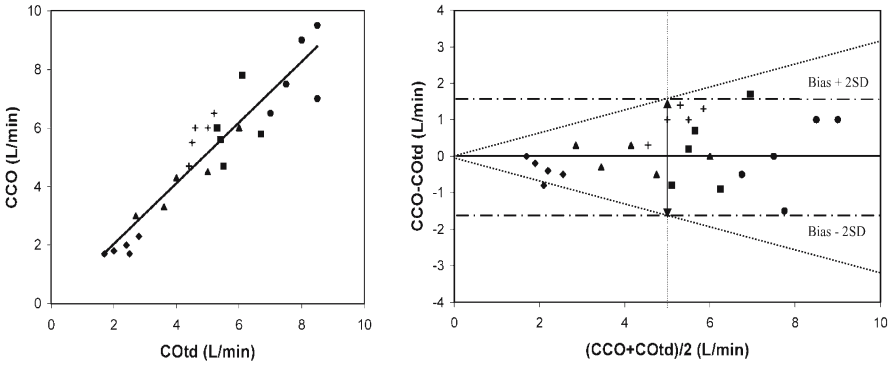

Fig. 1. Regression analysis comparing continuous cardiac output (CCO) with conventional thermodilution cardiac output (Cotd, simulated data, 5 patients each plotted with a different symbol and 5 measurements per patient). Least square regression of the pooled data gave y=1.04x – 0.04; R^2=0.87. Although the results of the pooled data seem impressive, clearly there is no equality of slope for the different patients and the variance within most patients is small compared to the variance between the patients. Therefore the figure mainly describes the difference between the patients instead of describing the relation between CCO and COtd. Bland-Altman plot of the difference between CCO and COtd. Averaged COtd = 5.0 l/min; averaged CCO = 5.02 l/min; bias, 0.01 l/min, SD=0.8 l/min (18%); limits of agreement from –1.6 (–36%) to 1.6 (36%) l/min. The arrow indicates the limits of agreement at mean of all data i.e., COtd and CCO.

Continuous Thermodilution methods

Ten years ago, two continuous cardiac output methods by thermodilution became available, which attempt to convert an irregular intermittent process to an automatic technique that does not require the injection of fluid into the patient. These methods are based on the delivery of electrically generated heat to the blood near the right atrium and ventricle and measurement of the resulting temperature change in the pulmonary artery.

Vigilance system, Edwards

The first method combines the use of indicator dilution principles (the injection of heat as indicator) with stochastic system identification to measure blood flow [20, 21]. Stochastic system identification can be used to measure system parameters in a noisy environment. For thermodilution, small amounts of thermal energy (heat-indicator) are transported directly into the blood in a pseudo random on-off pattern to form the input signal. The resulting blood temperature changes are detected with a thermistor in the pulmonary artery. This signal is small in proportion to the resident pulmonary artery thermal noise. To overcome this problem, a cross correlation is carried out on the input signal and the temperature data measured in the pulmonary artery, resulting in a thermodilution curve, as would

have been found after a bolus injection. From this dilution curve, cardiac output is computed using the classical Stewart-Hamilton equation. The entire process is automated, requiring no user intervention. A detailed explanation of the technique is given by Yelderman et al. [20, 21].

Several authors [21–32] showed that the 'continuous' cardiac output method compares with reasonable accuracy and precision to the conventional thermodilution in the ICU and operating room (OR) (Table 1). However, the results show larger variations in the OR shortly after coronary artery bypass [26, 28, 30]. This may be explained by periods of large pulmonary blood flow modulation and cyclic baseline temperature fluctuations due to mechanical ventilation, and pulmonary temperature baseline drift. During these periods, the immunity to thermal noise and the ability to average-out effects of temperature baseline drift, respiratory artefacts, and cardiac irregularities seem insufficient.

The 'continuous' cardiac output measurement has an averaging technique built-in; therefore, the displayed cardiac output number represents the averaged value of the previous 3 to 6 minutes [20, 21]. Under extreme clinical situations this delay can run up to 12 minutes [33]. This property of the technique makes it difficult to accept it as a 'continuous' cardiac output monitoring system.

Opti-Q, Abbott

The second method employing a PAC similar to the Vigilance system, periodically applies 20 s of a 40 s cycle time heat to the blood in the right atrium and right ventricle. Cardiac output is calculated by the classical Stewart-Hamilton equation from measurement of the applied input heat power and the resulting temperature change measured by a thermistor situated in the pulmonary artery. The displayed continuous cardiac output reflects either the averaged results of the previous 3 min ('fast mode') or of the previous 80–120 s ('urgent mode'). The results of different studies [34–37] are summarized in Table 1.

Concerns with the Continuous Thermodilution Technique

Recently, the use of both continuous thermodilution cardiac output methods has been under discussion. Many physicians believe that the PAC, due to its multipurpose role, is useful for the diagnosis, treatment, and assessment of volume status in critically ill patients. However, this has not been confirmed by studies. In contrast, different investigators have raised doubts about the effectiveness and safety of the PAC [38–40]. Indeed, most recent studies do not show a difference in morbidity and mortality between patients with and without a PAC [38, 39]. On the other hand, in these trials the introduction of the PAC was not associated with a significant increase in morbidity and mortality. The inability to demonstrate the merit of the PAC in predicting outcome does not necessarily mean that our monitors using the PAC are not functioning [38]. It may also indicate a persisting lack of correct and consistent interpretation of PAC-derived data among physicians [41] or ineffectiveness of our current therapeutic options in reversing criti-

Table 1. Agreement between continuous thermodilution cardiac output and conventional thermodilution cardiac output.

site	ref.	number		(CO_x – COpa)		Limits of agreement	
		pat.	obs.	bias l/min	SD l/min	lower l/min	upper l/min
Vigilance system, Edwards							
ICU	21	54	222	0.02	0.55	–1.03	1.07
OR – ICU	22	20	231	0.31	1.01	–1.7	2.3
ICU	23	14	163	0.35	1.01	–1.67	2.37
ICU	24	35	404	0.03	0.52	–1.01	1.06
OR	25	25	61	0.41	0.82	–1.23	2.05
ICU	26	22	286	0.05	0.56	–1.08	1.12
OR	27	30	540	–0.02	0.59	–1.20	1.16
OR Liver	28	12	192	–0.24	1.78	–2.80	2.32
ICU	29	56	56	0.15	0.81	–1.47	1.77
OR+ICU	30	25	380	–0.40	1.25	–2.90	2.10
OR Liver	31	34	186	0.02	0.74	–1.46	1.50
OR Lung	32	58	318	0.15	0.69	–1.24	1.54
Opti-Q, Abbott							
OR	34	26	312	0.09	0.74	–1.39	1.56
ICU	35	15	87	0.00	0.74	–1.48	1.48
ICU	36	47	327	0.12	0.84	–1.56	1.80
ICU	37	20	240	0.52	1.29	–2.06	4.00

cal disease states. Thus, further investigation into the role of the PAC is feasible, likely safe, and should proceed forthwith [40].

Pulse Contour Methods

The estimation of cardiac output via pulse contour analysis is an indirect method, since cardiac output is not measured directly, as with an electromagnetic flow probe, but is computed from a pressure pulsation on basis of a criterion or model. The origin of the pulse contour method for estimation of beat-to-beat stroke volume goes back to the classic Windkessel model described by Otto Frank in 1899 [42]. Most pulse contour methods are, explicitly or implicitly based on this model. They relate an arterial pressure or pressure difference to a flow or volume change.

Wesseling's Cz Method

Trending cardiac output by arterial pulse contour by Wesseling's Cz method involves measuring the area under the systolic portion of the arterial pressure wave (A_{sys}) from the end of diastole to the end of the ejection phase. Dividing A_{sys} by aortic impedance (Z_{ao}) provides a measure of stroke volume:

$$V_Z = A_{sys} / Z_{ao}$$

Obviously, this model for the human circulation is much too simple. Therefore, this approach has been extended: mean arterial pressure is used for the correction of pressure dependent non-linear changes in cross sectional area of the aorta, and heart rate is used to correct for reflections from the periphery. These corrections for pressure (Pmean) and heart rate (HR) are furthermore age (Age) dependent. Wesseling's extended approach incorporated these corrections. A detailed description of this Cz method can be found elsewhere [43, 44]. Briefly, the computation can be written as:

$$V_{Cz} = V_Z \ [0.66 + 0.005HR - 0.01Age(0.014Pmean - 0.8)]$$
$$CO_{Cz} = \text{cal} * HR * V_{CzCz}$$

is pulse contour cardiac output. The calibration factor, cal= CO_{Cz}/CO_{ref}, is determined at least once for each patient by comparing pulse contour cardiac output with an absolute cardiac output estimate determined by thermodilution (CO_{ref}). Because the equation corrects for reflections from the periphery, peripheral pressure from the radial artery can be used instead of central aortic pressure.

The pulse contour Cz investigations in patients undergoing coronary artery bypass graft (CABG) surgery showed a good agreement with the simultaneous estimates of thermodilution. The results of different authors [43–47] are summarized in Table 2. The data of Jansen and colleagues [43] suggest that the precision of the difference between the two methods is related to mean flow. This is advantageous in clinical situations, in which a low flow state requires an accurate estimate for appropriate intervention.

The work of Weismann and colleagues [45] also demonstrated that in patients under surgery for arteriovenous malformations in the brain, Wesseling's Cz pulse contour method was able to reflect cardiac output accurately during induced hypotension with esmolol and during restoration of blood pressure with phenylephrine (Table 2). Also, Irlbeck and colleagues [46] showed the applicability of the pulse contour method during intensive care treatment. They concluded that recalibration of the method may be necessary after extreme hemodynamic changes due to sepsis or cooling. Alteration of vascular tone by clinically used dosages of vasoactive drugs, however, had no destabilizing effect on Wesseling's Cz pulse contour method.

Modelflow Method

Ten years ago Wesseling and co-workers [44] discovered that even a simple extension of the classical Windkessel model could be adequate to improve pulse

Table 2. Agreement of pulse contour cardiac output and conventional or transpulmonary thermodilution cardiac output.

site	ref.	number		(CO_x – COpa)		Limits of agreement		
		pat.	obs.	bias L/min	SD L/min	lower L/min	upper L/min	
Wesseling's Cz method								
OR	43	7	64	0.1	0.5	–1.0	1.1	
OR	44	8	68	0.28	0.54	–0.80	1.36	
OR	45	11	119	0.06	0.58	–1.10	1.22	
ICU	46	20	165	0.09	0.85	–1.61	1.79	
ICU (recal)	„	„	„	0.00	0.56	–1.12	1.12	
OR	47	127	94	0.02	0.55	–1.08	1.12	
Modelflow method								
OR	44	8	68	0.09	0.36	–0.6	0.8	
OR	49	54	436	–0.13	0.47	–1.05	0.79	
ICU	50	32	137	–0.1	0.74	–1.58	1.38	
healthy sub!	52	9	155	0.28	0.66	–1.04	1.60	
non invasive, Modelflow-finapres method								
ICU no cal	51	29	175	0.68	1.32	–1.94	3.32	
healthy sub!	52	9	155	–0.04	0.52	–1.08	1.00	
PulseCO system, LidCO)								
OR*	53	9	142	–0.14	0.67	–1.48	1.20	COpa
ICU*	54	20	100	0.05	0.62	–1.2 0	1.25	COpa
ICU	55	35	35	0.25	0.85	–2.0	1.40	COlidco
ICU	56	24	24	–0.54	0.95	–2.43	1.35	COpa
PiCCO system, version 1.x, Pulsion								
OR+IC	30	25	380	–0.14	1.16	–2.46	2.18	1xrecal. COpa
OR	34	26	312	0.15	1.14	–2.07	2.51	2–3x recal. COpa
ICU	57	24	204	0.07	0.70	–1.34	1.47	auto-recal? COpa, COao
OR	58	20	192	–0.1	0.42	–0.94	0.74	auto-recal? COpa, COao
ICU	59	29	9x29	0.11	0.60	–1.09	1.31	auto-recal? COpa, Coao
ICU	60	24	517	0.08	1.81	–3.54	3.70	auto-recal?, COao
PiCCO system, version 4.x, Pulsion								
ICU	60	24	517	–0.2	1.2	–2.50	2.10	auto-recal? COao
OR Liver	31	62	186	0.04	0.85	–1.65	1.73	auto-recal? COpa, COao,
OR Lungs	32	58	318	0.08	0.72	–1.35	–1.52	auto-recal? COpa, COao

pat, number of patients; obs, number of observations; CO_x , cardiac output estimated with the method under study; COpa, cardiac output estimated by conventional thermodilution; COao, transpulmonary thermodilution cardiac output; auto-recal?, read text; COlidco, cardiac output from LidCO system, ICU, intensive care unit; OR, operating room; *, recalculated from data in publication.

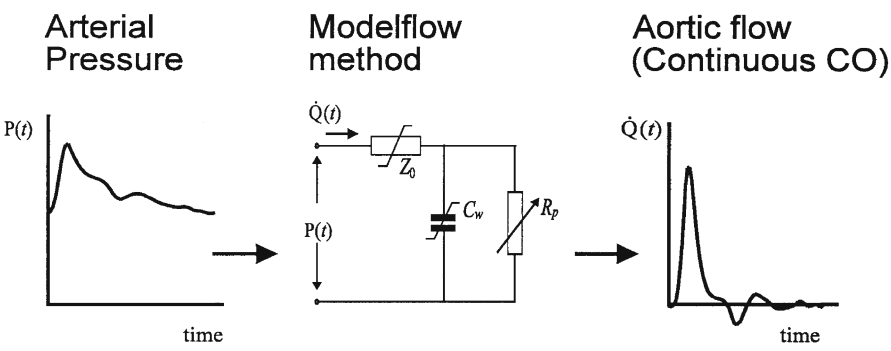

Fig. 2. Schematic diagram of the three-element non-linear, self-adapting model (middle) with and input pressure (right) and simulated flow pulse (left). Arterial pressure (P(t)) is applied to the model input. Z_0, characteristic impedance of the proximal aorta; C_w, arterial Windkessel compliance; R_p, total systemic peripheral resistance. The non-linear properties of Z_0 and C_w are indicated by a stylized S symbol. R_p has an arrow indicating that it adapts to changes in systemic resistance. The result of the model simulation is a flow curve (Q' (t)). Integrated per beat (the area under the curve) it yields stroke volume. Figure adapted from [49].

contour analysis. Left ventricular contraction causes inflow of blood into the arterial system, but this inflow is opposed by arterial counter pressure and aortic and peripheral systemic input impedance. The Modelflow method simulates this behavior. A hemodynamic model of arterial input impedance is used, known in physiological literature for its realistic properties in computing stroke volume (Fig. 2). The model includes the three principal components of opposition: characteristic impedance, which represents the opposition of the aorta to pulsatile inflow; Windkessel compliance which represents the opposition of the aorta to volume increases; and peripheral resistance which represents the opposition of the vascular beds to the drainage of blood. These components are not constant but impedance and compliance depend on pressure itself [48]. Systemic peripheral resistance depends on many factors including circulatory filling, metabolism, sympathetic tone, and presence of vasoactive drugs.

Aortic compliance decreases substantially when pressure increases (Fig. 3). This non-linear behavior of the aorta would be a major source of error if not taken into account. The aortic characteristic impedance, in contrast to compliance, increases only moderately with pressure. These non-linear relationships were studied *in vitro* by Langewouters et al. [48] and described as mathematical functions whose properties regress tightly on patient age and gender, and depend slightly on height and weight. These authors found that arteriosclerosis does not affect the aortic compliance, since the increased aortic wall stiffness, resulting from sclerosis, is compensated for by a larger cross sectional area (Fig. 3).

A patient's aortic cross sectional area is, however, not accurately known and true values in individual patients may deviate about 30% from Langewouter's study population average. This results in an uncertainty in computed cardiac output of also 30%. Therefore, the absolute value of the computed cardiac output is uncertain unless calibration against another cardiac output method such as thermodilution

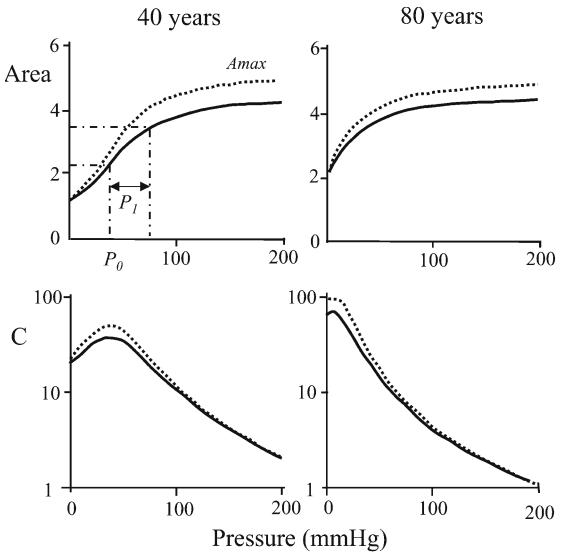

Fig. 3. *Top panel.* Pressure-area curves for human aortas with moderate atherosclerosis (solid line) and severe atherosclerosis (dotted line) at the ages of 40 and 80 years respectively. Area, aortic cross-sectional area (cm^2); Pressure, arterial pressure (mmHg); Amax, maximal cross-sectional area at high pressure; P_0, position of the inflection point on the pressure axis; P_1, steepness of the curve. *Bottom panel.* The matching compliance curve on a semi-logarithmic scale. C, aortic compliance ($10^{-3}.cm^2.mmHg^{-1}$). Compliance decreases when pressure increases because an aorta can expand elastically because an increasing amount of collagen fibers in its wall are fully stretched. Modified from [50] with permission.

is performed once. The tracking of changes in cardiac output, however, does not deteriorate due to this uncertainty in aortic cross sectional area [44, 49].

A first test of Modelflow was done in a group of eight patients undergoing coronary artery bypass surgery [44]. This test was done off-line. For results see Table 2. A second test was undertaken to evaluate Modelflow on-line in three academic clinical centers, (US, Belgium, and the Netherlands) and to increase the number of comparisons [49]. Thermodilution and Modelflow results correlated well (Fig. 4). No significant differences in bias and SD for the difference between thermodilution and Modelflow were found for the different clinical settings. This was true in spite of the fact that different surgical and anesthetic protocols were followed by the different hospitals. These differences had no influence on the accuracy of the methods. The results of Jellema et al. [50] showed that once calibrated by thermodilution, Modelflow cardiac output agreed well with thermodilution cardiac output even after 48 hours of monitoring in ICU patients.

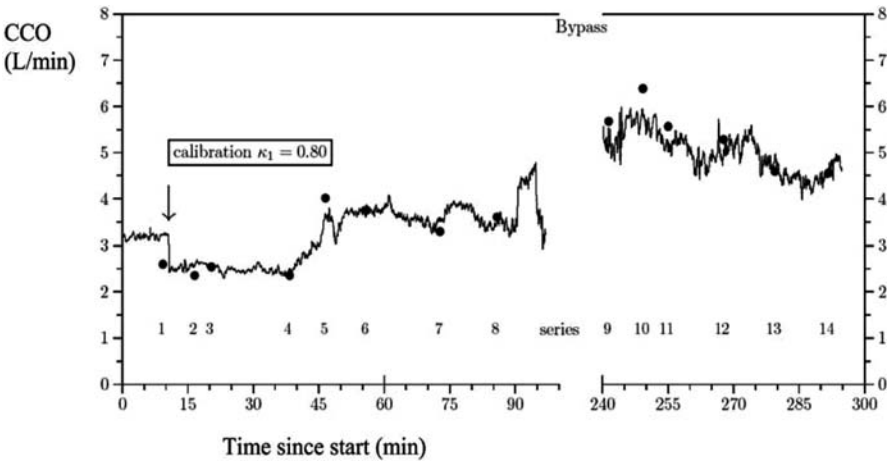

Fig. 4. Trend plot of an individual patient. The mean of a series of four thermodilutions is plotted (dots) together with a 16 beat average of Modelflow pulse contour cardiac output (line). The pulse contour method is calibrated with the first series of thermodilution.

Non-invasive Modelflow-finapres Method

Invasiveness is another aspect to be considered. Clearly, the Modelflow method as described above, requires an invasively obtained signal: radial artery pressure. Thus, although as a method it does not add invasiveness, it is not non-invasive. In a remarkable study, however, Hirschl et al. [51] used non-invasive finger arterial pressure as input to Modelflow in critically ill patients in an emergency department. Expressed as cardiac index, their results are quite similar to the results before calibration described by others [44, 49, 50].

In another non-invasive study in young adult healthy volunteers who underwent a laboratory tilt table protocol, Modelflow stroke volume with non-invasive finger arterial pressure as input was shown to track changes in thermodilution to within 10% error during head-up tilt. Head-up tilt and standing induce blood volume shifts in the body with 50% and 30%, respectively, reductions in stroke volume on average [52]. Although not obtained in critically ill patients we tend to see these results as a further confirmation that non-invasive tracking of changes in cardiac output may prove itself in the future.

PulseCO System, LidCO

The PulseCO monitor of LidCO calculates continuous cardiac output by analysis of the arterial blood pressure trace. A detailed description of this method is given on the web site of LidCO [www.lidco.com]. An accurate relationship between blood volume and pressure within the arterial circulation can be thought to serve as an accurate way of determining the change in blood volume in the arterial tree

during diastole. Furthermore, assuming diastole to have a fixed time relation to the whole heart cycle time, a relatively simple scaling of this volume change would give stroke volume. The relationship between blood volume and pressure would be straightforward if the compliance (i. e., pressure change per unit volume change) were constant. However, arterial compliance changes as arterial pressure changes (see Fig. 3). A stiffening of the vasculature occurs as pressure and volume increase such that, at higher pressures, a given increase in pressure expands the arterial tree by a smaller volume. Nevertheless, the form of this curvilinear relationship can be derived from the data given by Langewouters et al. [48] given patient's age and sex. Using this curvilinear relationship, nominal changes in arterial volume within every cardiac cycle can be calculated from the pressure waveform. The maximal change in volume can be thought of as the nominal stroke volume. Nominal cardiac output is equal to the product of nominal stroke volume and heart rate. These nominal values are converted to actual values by multiplying the nominal stroke volume or nominal cardiac output by a calibration factor. This patient-specific calibration (COreference/COnominal) is derived from an independently measured cardiac output, such as the averaged cardiac output value of three or more single conventional thermodilution measurements or the cardiac output value obtained from the transpulmonary lithium indicator dilution curve (LidCO).

The experiences with the LidCO-PulsCO system are from very recent studies [53–56]. The number of patients studied and the number of observations are low compared to that of the other pulse contour methods. Linton and Linton [53] demonstrated that the pulse contour cardiac output did not differ from thermodilution cardiac output over a larger range of systemic vascular resistances (SVR) changed by phenylephrine. Hamilton and colleagues [54] showed that the calibration factor for the pulse contour did not change within an 8 hour observation period.

PiCCO Pulse Contour System, Pulsion

The first software version 1.x: According to the manufacturer (Pulsion Medical System, Munich, Germany), this software version contains the original Wesseling algorithm [Manual]. Clearly, however, it deviates from Wesseling's Cz method. No age related corrections for pressure dependent nonlinear changes in cross sectional area of the aorta can be entered into the PiCCO device. For a description see the Wesseling Cz method above. Many comparisons have been done with this software version [30, 34, 57–60] (Table 2).

The second software version 4.x: This new pulse-contour algorithm is a more sophisticated formula that analyzes the actual shape of the pressure waveform in addition to the area under the systolic portion of the pressure wave. Furthermore, the software takes into account the individual aortic compliance and SVR based on the following considerations. During systole, more blood is ejected from the left ventricle into the aorta than blood that actually leaves the aorta. During the subsequent diastole, the volume remaining in the aorta flows into the arterial

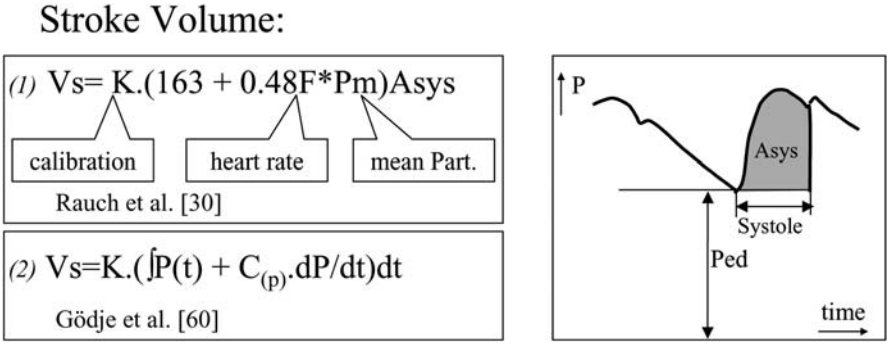

Fig. 5. Schematic representation of the PiCCO pulse contour algorithm (version 1 and 2). Equations derived from references [30, 60]. Vs, stroke volume; K, calibration factor; F, heart rate; P, arterial pressure; Asys or P(t)dt, area under the systolic part of the pressure curve as indicated in figure, C, pressure dependent arterial compliance; Ped, end diastolic pressure.

network at a rate determined by the aortic compliance (C), systemic vascular resistance (R), and the blood pressure (Windkessel effect). The shape of the arterial pressure curve (exponential decay time = R x C) after the dicrotic notch is representative for this passive emptying of the aorta. The systemic vascular resistance, R, is determined by the quotient of mean arterial pressure (MAP) divided by cardiac output measured by the reference method (R=MAP/CO). As the decay time and R are known, compliance, C, can be computed. As is the case with the original Wesseling algorithm, there still is need for a patient-specific calibration, which is determined by three transpulmonary artery thermodilution measurements (COao). The new algorithm is shown in detail in Figure 5.

In an impressive recent study, Della Rocca et al [31] compared the results of two intermittent methods (pulmonary thermodilution [COpa] and transpulmonary thermodilution [COao]), with the results of two continuous cardiac output methods PCCO (PiCCO) and CCO (Edwards) (Tables 1 and 2). Tzenkov and Perez Peña in a letter to the editor questioned, correctly, the method of automatic re-calibration of the PiCCO system used by Della Rocca and colleagues [31] as well as of other authors. Because of this automatic recalibration of the PiCCO system, the value of PCCO after recalibration is in principle equal to thermodilution COao. We also found this automatic recalibration misleading (non published comparative pilot study, PiCCO software version 4.1.1). When carrying out a comparative study it is likely that one first carries out the necessary practical operations before recording the results of COao and PCCO instead of first putting down the PCCO results and then performing three or more thermodilution measurements and finally putting down the results. To prevent automatic recalibration the results of each transpulmonary thermodilution measurement must be deleted immediately.

In their answer to Tzenkov and Perez Peña, Della Rocca and colleagues stated: “As previously reported by Rödig et al [34], Gödje [58,59] and Bottiger [27] we measured PCCO immediately before and after the series of intermittent COao measurements, and the mean of these data pairs was recorded”. If we correctly

understand this statement, the difference found between PCCO and COao must be multiplied by two, because PCCO after performing the measurement of COao (re-calibration) is equal to COao? (Difference= COao- (PCCObefore+PCCOafter)/2, as PCCOafter=COao it follows that the computed Difference=(COao-CCObefore)/2). To prevent such uncertainty about the presented data, authors should explicitly mention how they have performed their study. In addition, the manufacturer should adapt the software in such a way that the user gets the simultaneously collected values of PCCO and COao as well as the possibility whether to calibrate or not. After reading the study of Rödig et al. [34], a remarkable difference in study setup compared to Della Rocca et al. is apparent. Rödig et al. [34] as well as Rauch et al. [30] explicitly mentioned that they used the transpulmonary thermodilution technique (COao) only to calibrate PCCO at two or three instants (at start and after transfer to the ICU). Furthermore, comparisons were made with the conventional thermodilution (COpa) instead of the COao method to prevent a sequential automatic recalibration of PCCO.

Major Concerns About Pulse Contour Methods

Patient related concerns. The performance of all pulse contour methods is compromised in patients with aortic valve regurgitation, with aortic aneurysms, with an intra aortic balloon pump, during cardiopulmonary bypass (CPB), and during aortic clamping. The properties of the aorta may also change with a patient's position. In young volunteers, the change from supine to standing position had no effect on the difference between Modelflow and thermodilution cardiac output [52]. However, no data are available regarding whether this holds for obese patients nor are data available from subjects where position changed from supine to prone position.

Quality control of the arterial pressure waveform. The pressure required for pulse contour analysis is proximal aortic pressure, which is not routinely available. Radial artery pressure is usually reliable because the pressure transfer function from aorta to radial artery is assumed to be constant. However, it is well known that this assumption has been occasionally violated, for instance shortly after CPB [49]. Radial artery pressure is usually measured with fluid filled catheter-transducer systems. The catheter lines are routinely kept open with continuous flush devices. In view of pulse contour analysis any decrease in the quality of the pressure recorded with the catheter-transducer system might have an impact on the pulse contour derived cardiac output as illustrated in Figure 6. Therefore, detection of damped waveforms is needed and should be built into pulse contour systems. At present, only the Modelflow method provides such an alarm.

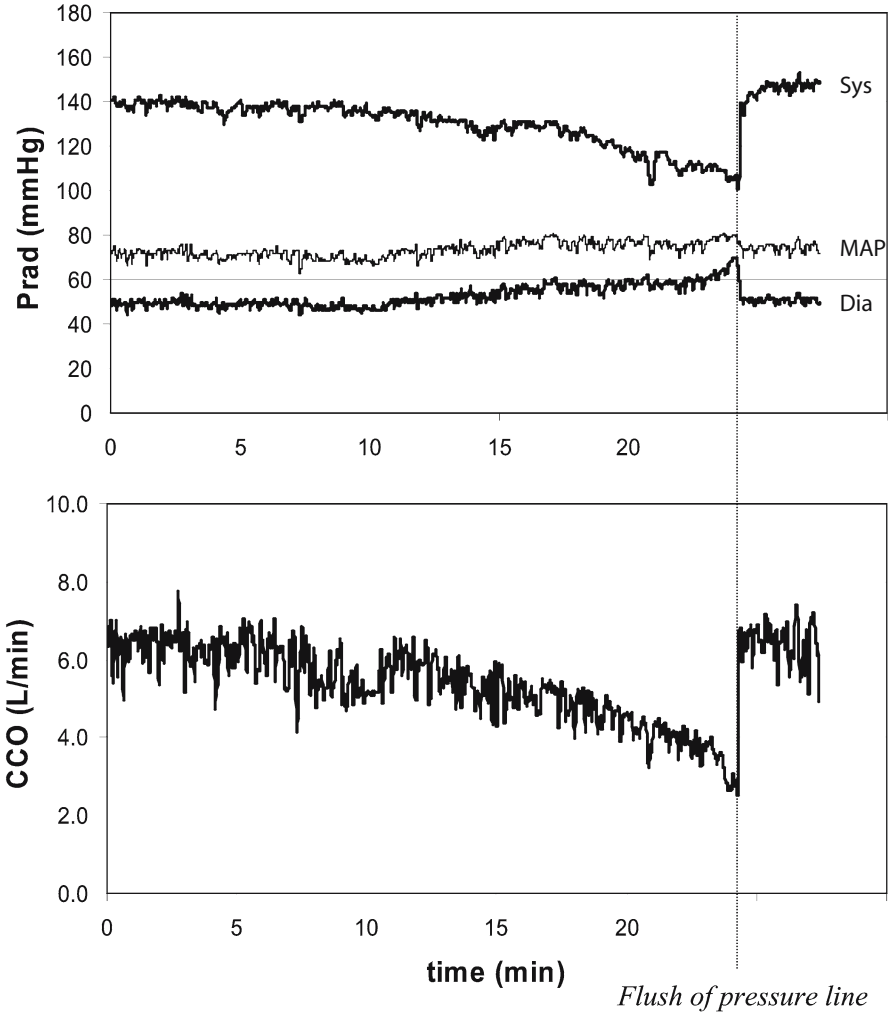

Fig. 6. Effects of damped radial artery pressure on LidCO pulse contour output of an individual patient. Upper panel systolic (Sys), diastolic (Dia) and mean (MAP) radial artery pressure (Prad). Bottom panel cardiac output by PulseCO (CCO).

Can the Continuous Thermodilution Methods and Pulse Contour Methods Replace Conventional Thermodilution?

The averaged precision for the difference between the different techniques and conventional thermodilution is given in Table 3. The averaged precision of the method under study is calculated from the averaged difference between the method under study and bolus thermodilution assuming two levels of precision for the bolus thermodilution, i.e., 10% and 5%. Ten percent represents the preci-

Table 3. Precision (SD of bias) of continuous cardiac output techniques, compared to the bolus thermodilution method (COpa) calculated at two levels of precision for this technique, i.e. 10% and 5%.

Technique	N pat	N obs	Difference with COpa bias L/min	bias %	precision L/min	precision %	Calculated precision with COpa10% %	COpa5% %
Continious Thermodilution								
Vigilance, Edwards	385	3039	0.01	0.21	0.88	16.9	12.6	15.3
Opti-Q, Abbott	108	966	0.20	3.62	0.94	16.55	13.8	16.3
Pulse contour after one calibration								
Wesseling Cz	193	675	0.07	1.33	0.64	11.57	5.8	10.4
Modelflow	103	796	–0.03	–0.48	0.56	9.89	1.6	8.8
LidCO	88	301	–0.02	–0.37	0.65	12.84	6.2	10.7
PiCCO-old	148	1866	0.03	0.57	1.23	20.58	20.1	21.8
PiCCO-new	144	1021	–0.07	–1.26	1.01	17.4	15.4	17.7

sion of the averaged value of three randomly applied thermodilution measurements and 5% represents the averaged result of three measurements equally spread over the ventilatory cycle. None of the methods can replace the thermodilution technique with three measurements equally spread over the ventilatory cycle, except perhaps, the Modelflow techniques. Most of the techniques can replace the thermodilution method with three measurements randomly applied.

Conclusion

None of the studied techniques fulfills all eight criteria mentioned in the introduction. The continuous thermodilution methods, for instance, do not have a fast response, need skilled physicians to introduce the PAC, and are invasive. The pulse contour techniques are, for instance, sensitive to decreased quality of the pressure signal and need a reliable invasive calibration. With respect to accuracy and precision, most methods may replace the thermodilution method with a precision of 10% for the averaged result of three randomly performed measurements. The Modelflow technique might replace thermodilution estimates based on the averaged result of three measurements equally spread over the ventilatory cycle. The lower precision of the continuous cardiac output techniques may, in clinical settings, be outweighed by the advantages of automatic and continuous monitoring. Under research conditions, the use of the conventional thermodilu-

tion method with three or four measurements equally spread over the ventilatory cycle remains the method of choice.

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Clinical Value of Intrathoracic Volumes from Transpulmonary Indicator Dilution

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Introduction

Hemodynamic monitoring of the critically ill aims at early identification and treatment of critical changes in hemodynamic variables that threaten tissue oxygen delivery [1]. Traditionally, the pulmonary artery catheter (PAC) has been used to monitor patients with circulatory disturbance, not responding to initial measures, when clinical signs fail to indicate the volume and cardiac status of the patient [2, 3]. Nevertheless, the usefulness of the catheter has been questioned, either because insertion and use is associated with increased risks, or the data obtained by the catheter are in error and are poorly interpreted by intensive care unit (ICU) staff [3]. Additionally, hemodynamic goals associated with survival and the manner to achieve them, in a number of critical conditions, are controversial or difficult to reach in practice [1].

Indeed, clinical signs are poor indicators of volume status and heart function in the critically ill [2]. Classical clinical signs of (cardiac) hypovolemia such as a low central venous (CVP) or right atrial pressure or pulmonary artery occlusion (capillary wedge) pressure (PAOP), may not predict a rise in cardiac output upon fluid challenge, i.e., fluid responsiveness [2, 4]. This may relate to their poor reflection of circulating volume and cardiac preload [2, 4], which is better represented by end-diastolic volumes than by pressure, among others caused by the difficulty to estimate transmural pressures in mechanically ventilated patients on positive end-expiratory pressure (PEEP), by interindividual differences in ventricular compliance, by changes in compliance during fluid loading, etc [4]. Indeed, the flat portion of the ventricular compliance curve, relating end-diastolic pressures to volumes implies greater changes in volumes than in pressures during changes in preload. Finally, the end-diastolic wall stress actually indicating preload, is determined by diameter, wall thickness, and shape.

Fluid therapy is the mainstay of treatment in hypovolemia and shock and the therapeutic endpoint most often described and aimed for is an 'optimal' cardiac index, as defined by a cardiac index that does not further increase upon fluid challenges and that corresponds to the peak of the ventricular performance curve relating stroke volume or work to preload [1, 4]. Fluid responsiveness is also often used to diagnose hypovolemia, since a rise in stroke volume upon a fluid challenge would denote a suboptimal cardiac index and central hypovolemia. In the absence of any predictor, one has to give fluids empirically, with the associated risk of

overfilling the intra- and eventually the extra-vascular compartment, when hypovolemia is absent and cardiac index does not increase. Indeed, pulmonary and peripheral edema may be deleterious, so that avoiding overhydration is important.

A variety of volume versus pressure estimates of cardiac filling have been proposed and used to help establish the (central or cardiac) volume status of the patient, the occurrence of (cardiac) hypovolemia, and to predict fluid responsiveness [4]. Nuclear angiography has been performed in the past [5] to evaluate cardiac dimensions amd predict fluid responsivenss, but this method is laborious and non-continuous. Indeed, a high right ventricular end-diastolic volume index (RVEDVI) and CVP in (a minority of) patients with septic shock precluded a rise in cardiac index during fluid loading [5]. Echocardiography can be done to evaluate cardiac dimensions and help in predicting preload and fluid responsiveness [4, 6, 7]. This can be performed transthoracically or transesophageally, but the expertise is not widely available among intensivists and again is of a non-continuous nature.

Intermittent or continuous PAC and thermodilution-based right ventricular volume assessment can be done, and authors have shown that RVEDVI does not correlate well to end-diastolic pressure (CVP) and that the former predicted fluid responsiveness better than the latter, although this is a controversial issue [4, 8-10]. Indeed, Wagner et al. [10] observed that the PAOP was a better predictor of fluid responsiveness than the RVEDVI (bolus thermodilution technique). Utilizing a rapid response right ventricular ejection fraction (RVEF) catheter (Edwards Laboratories), the technique is evolving from bolus to semi-continuous thermal dilution, but the method is still based on a PAC with its potential risks and drawbacks. The intermittent bolus technique for assessing right ventricular volumes also carries the disadvantage, at least in mechanically ventilated patients, of high dependency on the ventilatory cycle, so that inspiration increases volumes and decreases RVEF, and expiration decreases volumes and increases RVEF [11]. On the other hand, the semi-continuous method for assessing right ventricular volumes, that averages, over some time, the volumes determined by the thermal indicator, may be too slow to assess rapid changes during fluid loading or catecholamine dosing.

At this stage in the development of hemodynamic monitoring, a new technique has become available for assessment of cardiac preload, output, and function. The transpulmonary technique referred to here, does not involve a PAC and its associated risks [3], and additionally yields intrathoracic distribution volumes, including intrathoracic and global end-diastolic blood volumes, pulmonary blood volume and extravascular lung water (EVLW), the latter two as indices of pulmonary congestion, permeability, and edema. In combination with a PAC, left and right heart loading conditions can be evaluated separately (Table 1), although the clinical applicability has been limited so far.

This chapter will elaborate on the role of intrathoracic blood volumes determined by transpulmonary dilution (without a PAC), in the monitoring of critically ill patients, with respect to assessing volume status and heart function, and response to fluids in the treatment of hypovolemia and shock. Obviously, the monitoring of these volumes instead of pressures still necessitates a central venous catheter. Nevertheless, transpulmonary volumetric monitoring may constitute a useful alternative to PAC pressure monitoring.

Table 1. Volumetric assessment and normal values

Based on mean transit time (MTT) for thermal (therm) and dye dilution curves:

Intrathoracic blood volume index (ITBVI, normal 850–1000 mL/m^2) = MTT_{dye} x cardiac index $(CI)_{therm}$

Intrathoracic thermal volume (ITTV) = MTT_{therm} x CO_{therm}

Extravascular thermal volume (ETV) and extravascular lung water (EVLW, normal 3–7 mL/kg)
EVLW = ITTV-ITBV

With pulmonary artery (pa) catheter:

Right heart end-diastolic volume index
RHEDVI (normal 325–425 mL/m^2) = $MTT_{thermpa}$ x $CI_{thermpa}$

Based on downslope time (DST) of dilution curves:

Pulmonary blood volume index (PBVI) (normal 150–250 mL/min/m^2)= DST_{dye} x CI_{dye}
Pulmonary thermal volume (PTV) = DST_{therm} x CO_{therm}

EVLW[1] = PTV-PBV (PBV can also be estimated from single thermodilution 1.25 x GEDV – 28.4 – GEDV)

With pulmonary artery (pa) catheter

Right ventricular end-diastolic volume index,
RVEDVI (normal 90–125 mL/m^2) = $DST_{thermpa}$ x $CI_{thermpa}$

Combined:

Global end-diastolic volume index, GEDVI (normal 680–800 mL/m^2) = ITTV- PTV

Left heart end-diastolic volume index, LHEDVI (normal 275–375 mL/m^2)= GEDVI-RHEDVI

Total ICG plasma curve (up to 2–3 min):

Total blood volume index, TBVI (normal 2600–3200 mL/m_2)

Plasma disappearance rate, PDR (normal 18–25 %/h)

[1]Alternative EVLW estimates based on double thermal-dye or single thermal dilution.

Technique of Transpulmonary Intrathoracic Volume Measurements

The thermal-dye (indocyanine green, ICG) method of assessing intrathoracic blood volumes was revived by a German company (Pulsion Medical Systems, Munich, Germany), in the early 1990s [12, 13]. The method involves a 4F fibreoptic-thermistor catheter introduced via the femoral artery into the aorta. The procedure is relatively harmless but should be weighed against the risks of pulmonary artery catheterization when the former is preferred over the latter. A central venous injection of a cold bolus of ICG – i.e., a diffusible tracer and a nondiffusible dye – serves to detect dilution curves, after transpulmonary passage, in the aorta

and calculation of cardiac index and associated volumes (Fig. 1 and Table 1, [13]). Indeed, the mean transit time multiplied by cardiac output of the thermal dilution curve yields the intrathoracic thermal volume, consisting of extravascular thermal volume, as a measure of EVLW, and the intrathoracic blood volume index (ITBVI). The latter comprises the pulmonary blood volume and the global end-diastolic volume index (GEDVI) of the heart. The double indicator thermal-dye dilution technique has evolved into a single thermal indicator dilution technique (PiCCO, Pulsion Medical Systems). The single thermodilution technique assumes a constant relationship between GEDVI and ITBVI, so that ITBVI* = 1.25 x GEDV – 28.4 ml (see Fig. 2, [14–16]). This relationship has thus been validated in a large number of patients, even though the coefficients in this relation slightly differ from study to study without a major impact on the single thermodilution estimate of ITBVI and, as a preload parameter, its relation to cardiac index (14–17). Whereas ITBVI is thus slightly larger than GEDVI, ITBVI is about 33% of total blood volume index (TBVI) [13]. If the stroke volume index is multiplied by 4 and divided by GEDVI, the result is a rough indicator of the ejection fraction, which may be useful to characterize cardiac function. The global cardiac function index is calculated from cardiac index divided by GEDVI, another index of cardiac function, of which the clinical significance in the critically ill is relatively unknown also. The intrathoracic and total blood volumes may better relate to functional hemodynamics than the EVLW, so that the following discussion is limited to the value of the former volumes in assessing preload and predicting fluid responsiveness. This is not to annihilate the importance of monitoring EVLW in preventing or monitoring pulmonary edema, as described before [18, 19]. In fact, (fluid) resuscitation of critically ill patients on the basis of the EVLW rather than on the basis of PAC-derived PAOP, may decrease ventilator and ICU days [18].

Validity

The error of the transpulmonary measurements is within 10%, at maximum [9, 13]. Moreover, pulmonary arterial and transpulmonary thermodilution methods yield cardiac indexes that are roughly similar and highly correlated [9, 13, 17, 20–25]. Of note, the former, and not the latter, is highly affected by the phase of the ventilatory cycle in mechanically ventilated patients, in which the thermal bolus is injected [11]. However, an obstruction of pulmonary vessels afterloading the right ventricle may not be detected by the ITBVI/GEDVI measurements, when pulmonary blood volume decreases and right ventricular dilatation is partially offset by left ventricular underfilling, so that ITBVI/GEDVI may remain unchanged [26]. Hence, the transpulmonary method may not be useful in evaluating and monitoring right ventricular dilatation in the course of obstructive shock caused by pulmonary emboli. In this case, however, a PAC can still be used, if the emboli do not preclude advancement into the pulmonary artery and a correct assessment of right ventricular volumes is required in combination with the transpulmonary technique [9, 13, 25, 26]. On the other hand, authors have described that the ITBVI follows the volume status and inotropic state of the heart better in pigs and humans than the RVEDV (bolus thermodilution), because it includes the status of

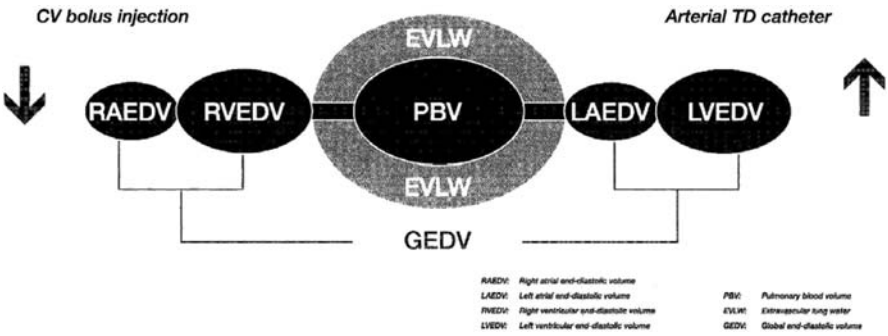

Fig. 1. Intrathoracic volumes as assessed from indicator (thermal-dye or single thermal) dilution after central venous injection and detection via femoral artery catheter. Global end-diastolic volume (GEDV) consists of right atrial end ventricular combined with left atrial and ventricular end-diastolic volume. Intrathoracic thermal volume consists of GEDV plus extravascular lung water (EVLW) plus pulmonary blood volume (PBV), equaling intrathoracic blood volume (ITBV). Pulmonary thermal volume (PTV) consists of EVLW and PBV. Subtracting ITBV from intrathoracic thermal volume gives the EVLW (see Table). Figure modified from Pulsion Medical Systems, with permission.

both ventricles [9, 27]. Using mechanically ventilated sheep with lung injury and computer tomographic assessment of left ventricular dimensions, however, ITBVI and REDVI correlated equally well with LVEDV, and the computer tomography and transpulmonary cardiac output correlated highly too [25].

Assessing both ITBVI/GEDVI and cardiac index from the same curves could lead to mathematical rather than physiological coupling [27, 28]. Bleeding indeed lowers both ITBVI and cardiac index [29]. However, diminishing the inotropic state of the heart by beta-blockade in cardiac surgery patients increased the ITBVI and did not change the cardiac index, indicating flattening of the cardiac function curve rather than a major effect of mathematical coupling of ITBVI and cardiac index, at least when the double thermal-dye indicator technique was used [28]. Conversely, increasing the inotropic state in pigs and critically ill (septic) patients by administering dobutamine increased cardiac index and hardly changed ITBVI, indicating improved myocardial function [27, 30, 31]. ITBVI (single transpulmonary thermal dilution) correlated better to PAC-based cardiac index and stroke volume index determinations than CVP and PAOP in liver transplantation patients, again arguing against a major effect of mathematical coupling of ITBVI and cardiac index when both are derived from the same set of curves [23]. Indeed, single thermal dilution ITBVI correlates well with thermal-dye dilution ITBVI with little bias and fair precision [16].

Finally, ITBVI/GEDVI has been compared to computer tomography or echocardiographic determinations of LV end-diastolic dimensions to assess the similarity and magnitude of responses to changes in volume, in experimental animals and humans [16, 25, 32–34]. Increasing airway pressure [25], leg raising [34], changing from supine to sitting position [33], cardiac surgery [32], and fluid

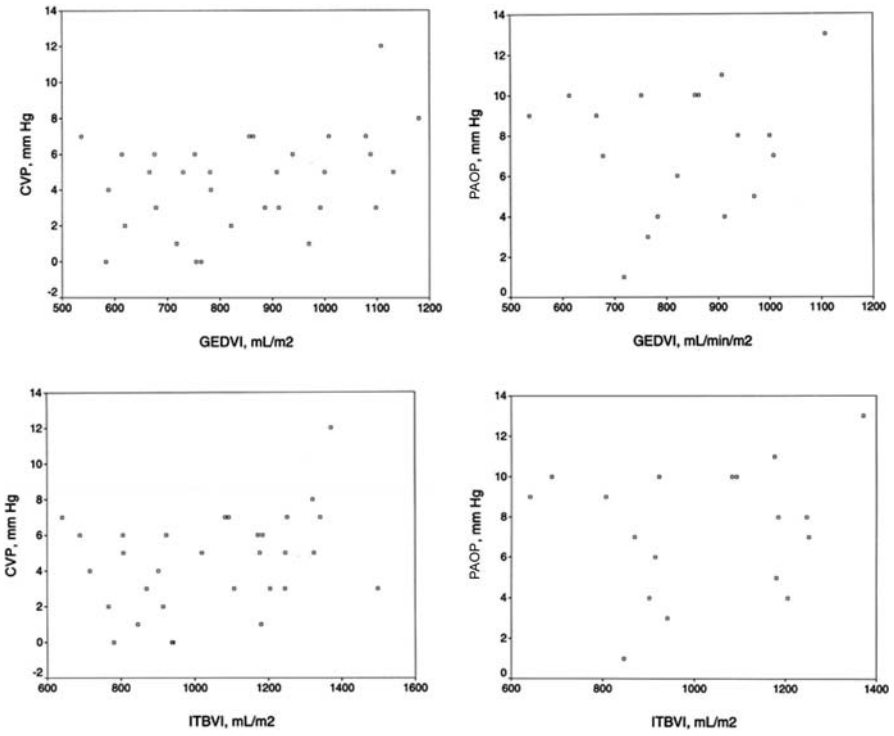

Fig. 2. Left upper: relation between transpulmonary (thermal-dye dilution) global end-diastolic volume (GEDVI) and central venous pressure (CVP, r=0.36, p<0.05) in 32 clinically hypovolemic post cardiac surgery patients. Right upper: relation between transpulmonary GEDVI and pulmonary artery occlusion pressure (PAOP, r=0.15, p=0.55) in 18 of the 32 post cardiac surgery patients. Left lower: relation between transpulmonary intrathoracic blood volume (ITBVI) and CVP (r=0.32, p=0.08) in 32 post cardiac surgery patients. Right lower: relation between transpulmonary ITBVI and PCWP (r=0.18, p=0.47) in 18 post-cardiac surgery patients. The correlation at baseline between CI and CVP and PAOP was not significant, while CI and GEDVI and ITBVI correlated (r=0.49, p<0.004 for GEDVI and r=0.56, p<0.001 for ITBVI). ITBVI was 1.19 x GEDVI -35.4 ml (r=0.96, p<0.0001). The data imply that filling pressures are poor indicators of cardiac preload assessed from GEDV and ITBV indices. (Unpublished observations by J Verhey and ABJ Groeneveld)

loading [16] indeed caused directionally similar changes in these two unrelated cardiac volume estimates, arguing in favor of the validity of the virtual ITBVI/GEDVI. Total blood volume determined with ICG and the fiberoptic technique have been compared with other methods and the technique proved reliable [35]. TBVI decreases during hypovolemia and increases during hypervolemia [36]. ICG-derived TBVI estimations could be confounded by severely increased capillary permeability, since the albumin-bound dye would rapidly disappear into the interstitium.

Clinical Application

Preload assessment. The transpulmonary indicator dilution method is increasingly used to assess preload and predict fluid responsiveness in critical illness. Whereas the thermal-dye method (Edwards, densitometer) has been used in the past mainly to assess EVLW from extravascular thermal volume after transpulmonary passage, the current thermal (-dye) technique has been used in addition to assess intrathoracic blood volumes. As has been suggested for the bolus thermodilution RVEDVI [4, 8, 10], the intrathoracic volumes are considered as better preload indicators than filling pressures, such as CVP or PAOP, as determined with help of a PAC. Indeed, the correlation between filling pressures and volumes and between changes in the former versus the latter are poor, suggesting wide interindividual differences and changes in ventricular compliance in the course of treatment [9, 12, 23, 24, 32, 33, 37, 38]. In contrast, ITBVI/GEDVI (changes) have been shown to better relate to stroke volume and cardiac index (changes) than filling pressures (changes), including the PAOP, under a number of clinical circumstances [12, 21, 23, 24, 31, 33, 38, 39]. Hence, fluid loading increases ITBVI/GEDVI and thus cardiac index in parallel, while changes in pressures do not well correlate to changes in the variables [16, 31, 36, 38, 40]. The poor value of filling pressures may relate in part to the common (end-expiratory) assessment of intrathoracic intravascular pressures versus atmospheric pressure, even in mechanically ventilated patients on PEEP. In the latter case, transmural pressures should better reflect filling pressures, but transmission of airway pressure is difficult to establish and only rarely taken into account [8]. In patients with impaired cardiac function, however, continuous fluid administration increased filling pressures (CVP/PAOP) more than ITBVI/GEDVI, even at unchanged cardiac index and a slightly increased stroke volume [38]. Hence, in the steep portion of the diastolic compliance curve, pressures increased more than volumes upon increases in volume, so that a pressure response to volume loading seemed to follow a rise in stroke volume better than did a volume response [38].

In cardiac surgery patients, we (Fig. 2–3) and others [9, 32, 36, 37, 40] have noted that ITBVI/GEDVI, as determined by the thermal-dye method, better relates to cardiac index and changes therein than the filling pressures, even at constant airway pressure, again confirming the idea that preload is better assessed via volume than via pressure measurements and that correct assessment may help to predict fluid responsiveness. Other circumstances for which volumetric assessment could be useful include major liver or lung surgery/transplantation [23, 24, 41], heart transplantation [21], sepsis [31, 39, 42], burns, mechanical ventilation for acute respiratory failure [12] and others, e.g., conditions in which it is often difficult to decide at the bedside if a patient needs fluids or inotropes to improve cardiac index, arterial blood pressure, diuresis and so on. How volume monitoring compares to dynamic measures such as stroke volume variation or pressure variation in assessing preload and predicting fluid responsiveness, is still open for study [4, 29, 40]. The clinical value of applying the TBVI as determined from the ICG dilution curve is less certain, even though the plasma disappearance rate of ICG has some prognostic impact [43]. Since ICG is taken up by the liver, the plasma

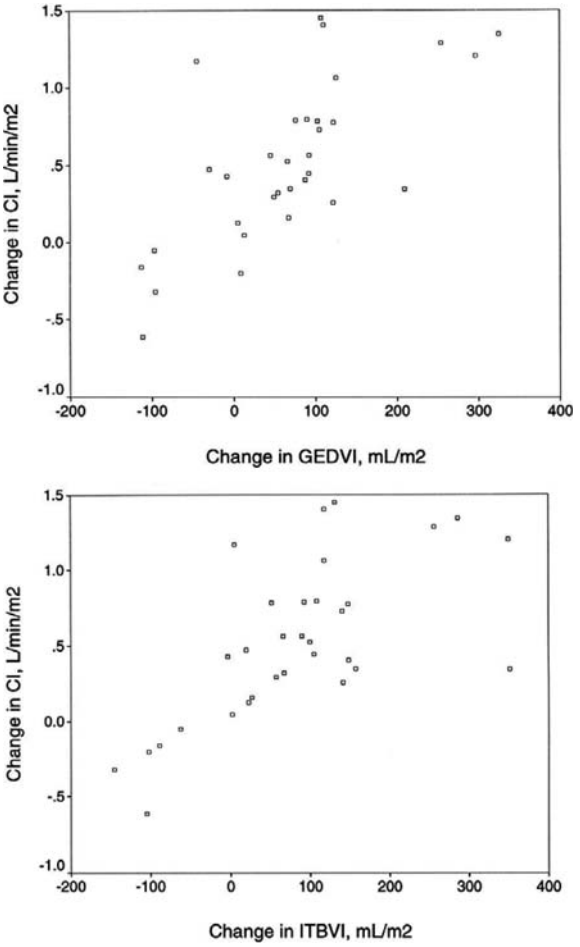

Fig. 3. Relation between changes in transpulmonary cardiac index (CI) upon 90 min fluid loading (about 1600 ml) in 32 clinically hypovolemic post-cardiac surgery patients, and global end-diastolic volume (GEDVI, upper, n=32) and intrathoracic blood volume (ITBVI, lower, n=32), determined by thermal-dye dilution: the r was 0.70, $p<0.001$ for GEDVI and r=0.67, $p<0.001$ for ITBVI, while the r for CI changes versus CVP (n=38) or PAOP (n=24) changes was r=0.30, p=0.06 and r=0.27, p=0.20, respectively. The data imply that filling pressures are poor and volumes are good indicators of a CI response to fluid loading. (Unpublished observations by J Verhey and ABJ Groeneveld)

disappearance rate can be considered as a rough measure of hepatic perfusion and function [43].

Fluid responsiveness. Of great importance, is the prediction, from hemodynamic measurements, that a patient will benefit from fluid resuscitation, i.e., has a low cardiac index related to underfilling of the heart, responsive to fluid loading with an increase in stroke volume and cardiac index. Indeed, the static CVP (right atrial pressure) and PAOP are poor predictors of such response [4]. Both high and low filling pressures have been associated with a positive response to fluid loading [5, 7]. A low baseline ITBVI/GEDVI may be better able to predict such response than filling pressures, so that low *a priori* volumes are associated with a greater rise in cardiac index upon fluid loading than high *a priori* volumes, associated with cardiac dilatation caused by overfilling or cardiac dysfunction. Indeed, Michard et al. observed that a GEDVI of 900 ml/m^2 or greater, precluded a rise in GEDVI during

fluid loading, at least in septic patients [31]. Obviously, more information is needed to establish optimum cutoff values for intrathoracic blood volumes which are associated with a low likelihood of a favorable response to fluid challenges, in a variety of conditions. Another pitfall for a high ITBVI/GEDVI, that does not preclude fluid responsiveness, includes a thoracic or aortic aneurysm, that increases the mean transit time of the indicator. A positive response to fluid loading might be predicted by the response to passive leg raising, the Trendelenburg position, or by changing from supine to sitting position, even though the ITBVI/GEDVI responses to these maneuvers and to fluids have not been compared yet. In fact, if the legs are raised, filling pressures may rise substantially, but ITBVI and thus cardiac index may only slightly increase [34]. In anesthetized patients, changing from supine to sitting position decreases ITBVI and thus stroke volume and cardiac index [33].

Conclusion

Functional hemodynamic monitoring of intrathoracic volumes with double or single (thermal) indicator dilution may be a useful tool to assess preload and fluid responsiveness in critically ill patients. The method obviates the use of a PAC, but a formal prospective comparison of transpulmonary and pulmonary artery catheterization considering the effect of volume (rather than pressure) monitoring on morbidity and mortality of critically ill patients is lacking.

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Methodology and Value of Assessing Extravascular Lung Water

A. B. J. Groeneveld and J. Verheij

Introduction

Impaired gas exchange, reduced pulmonary compliance, and pulmonary consolidations on chest radiography are, either alone or together, poor indicators of the amount and course of pulmonary edema, of various etiologies [1, 2]. The value of the bedside chest radiograph, which is often routinely obtained on a daily basis in critically ill patients, in estimating edema is indeed somewhat controversial [3]. Even though authors have shown that changes in chest radiographic consolidations may not perfectly parallel changes in extravasuclar lung water (EVLW) as determined by a thermal-dye double indicator technique [1, 2, 4], the cardiothoracic ratio, vascular pedicle width, and scored radiographic abnormalities consistent with edema may fairly parallel pulmonary hydrostatic forces, fluid balance, and gas exchange abnormalities in patients [5–7]. Assessing radiographic criteria for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), however, is prone to interobserver variability and may therefore not be very helpful in estimating lung injury nor edema [8]. Indeed, the differentiation between cardiogenic/hydrostatic and permeability pulmonary edema (ALI/ARDS) on chest radiographs is difficult and highly controversial [3, 5]. Nevertheless, a changing distribution of consolidation on chest radiography upon changes in posture is consistent with edema of a hydrostatic rather than of an inflammatory/permeability nature.

Therefore, investigators have searched for decades for a method to directly quantify pulmonary edema. Ideally, the method should be applicable at the bedside, reliable and accurate, should be repeatable and have a short response time. Obviously, computer tomography (CT) scanning, positron emission tomography (PET) and magnetic resonance imaging (MRI) may be useful to indirectly assess pulmonary edema [3], but for the purpose of this discussion these techniques are omitted because they are not applicable at the bedside. Radionuclide techniques include the pulmonary leak index (PLI) method for assessing pulmonary vascular permeability to intravenously injected and radiolabeled transferrin, and the transpulmonary indicator dilution of diffusible versus nondiffusible radiolabeled substances [9]. The diffusible compounds include ^{3}H- or ^{2}H-water, but these methods require multiple femoral artery blood samples and elaborate *ex vivo* equipment, before a result can be obtained [10–13]. The difference in mean transit time of the diffusible versus the nondiffusible tracer, multiplied by cardiac output,

is a measure of extravascular water in the thorax, i.e., lung water. Alternatively, a probe or gammacamera for precordial recordings of time-radioactivity curves has also been applied to calculate mean transit times for the first passage of intravenously injected diffusible and nondiffusible (protein-bound) tracers. The methods have been shown to be of some value but have mainly been applied as a research tool and have never attained routine clinical application. Other radionuclide methods include the transmission attenuation of radioactive cobalt through the thorax [14], which is linearly related to the amount of EVLW if pulmonary blood volume remains constant. The latter can be ascertained by concomitant red cell labeling and blood pool monitoring by a gammacamera or probe. External detection of equilibrium kinetics of ^{123}I-albumin and ^{123}I-Na has been used to assess respective distribution volumes of intra- and extravascular (edema) spaces in the lungs, after correction for chest wall radioactivity and attenuation [15]. Finally, transthoracic impedance tomography has been evaluated as a tool to indirectly assess pulmonary edema [16].

Transpulmonary Thermal-dye Dilution

The bedside method to directly assess the amount of EVLW as a measure of pulmonary edema in the critically ill that has been applied most often is the assessment of extravascular thermal volume (ETV) with help of the transpulmonary double indicator dilution technique, involving a dye and cold, central venous bolus injection and detection of the respective dilution curves in the aorta via a femoral artery catheter [2]. Indeed, heat may be more readily diffusible than water-soluble substances [12]. The differences in dilution curves between the intravascular dye and the cold, of which some dissipates into the pulmonary structures, dependent on their hydration status, yields a thermal distribution volume as a rough indicator of EVLW – pulmonary edema. The technique (Edwards Laboratories, Ca, USA) employed in the past utilizes the femoral artery catheter to withdraw blood at a constant rate for *ex vivo* determination of dye density with a densitometer. The blood can be returned via a central vein. The thermal signal is detected intravascularly. Using a lung water computer, dye and thermal dilution curves are compared, at a similar starting point. The difference in mean transit time multiplied by cardiac output yields the ETV in the thorax, as a measure of EVLW. The thermal-dye EVLW densitometer method never gained routine application, partially because of its laborious and invasive nature.

The technique was revived in the 1990s by a German company, utilizing a similar approach with a fiberoptic and thermistor-equiped 4F femoral artery catheter and thermal-dye dilution, to assess the EVLW [17–22]. The technique involves the intravascular determination of both the dye and the thermal signal (COLD machine Z-021 [17], Pulsion Medical Systems, München, Germany), after central venous injection of the indicators [18, 20–22]. The mean transit time of the dye (detected in the aorta via a fiberoptic equipped femoral artery catheter) multiplied by cardiac output yields the intrathoracic blood volume, while the mean transit time of the thermal signal (detected by a thermistor mounted on the femoral artery catheter) multiplied by cardiac output yields the intrathoracic thermal volume. Subtracting

the volumes, gives the ETV as a measure of EVLW (in ml/kg, upper normal values about 7 ml/kg [18, 20–23]). The transpulmonary technique not only allows for assessment of EVLW but also of intrathoracic blood volumes and cardiac output, without the use a pulmonary artery catheter (PAC). The reproducibility of this thermal-dye EVLW is within 10% [21].

A modification of the transpulmonary technique with detection in the femoral artery recently marketed (PiCCO, Pulsion Medical Systems, München, Germany), is the single thermodilution technique for EVLW estimation. This system utilizes a constant relation between global end-diastolic volume (GEDV), estimated from the difference of intrathoracic thermal volume and the pulmonary thermal volume, calculated from the thermal dilution downslope time multiplied by cardiac output, and the intrathoracic blood volume, so that intrathoracic blood volume equals 1.25 times GEDV-28.4 ml, at least in humans [24, 25]. The difference between the intrathoracic thermal volume, estimated from the mean transit time of the thermal signal multiplied by cardiac output, and the intrathoracic blood volume estimated above is the ETV or EVLW* [25]. The latter technique might simplify that using the thermal-dye, and suffice to judge the EVLW for clinical purposes [24, 25]. This certainly needs further evaluation, however, even though first evaluations suggest a good correlation between single thermal and thermal-dye dilutional EVLW [24, 25].

Another evolving parameter is the permeability index, the ratio of EVLW to pulmonary blood volume [26, 27] (Fig. 1). Pulmonary blood volume is determined from the difference between pulmonary thermal volume (intrathoracic thermal volume minus GEDV) and EVLW. Indeed, congestive heart failure leading to a rise in pulmonary blood volume and edema is expected to increase the ratio less than an increase in permeability in the course of ALI/ARDS. Definite human data confirming this concept are still lacking [28]. When combined with pulmonary blood volume, assessment of EVLW could nevertheless also help to differentiate between edema types, i.e., mainly hydrostatic versus predominant permeability edema. The utility of this concept also needs further evaluation.

Validation and Pitfalls in Animal Studies

When creating pulmonary edema in swine by inflating a left atrial balloon, authors observed that doubling (>11.4 ml/kg) of the thermal-dye ELVW (densitometer technique) and beyond was associated with progressive alveolar flooding and deterioration of gas exchange [29]. Intermediate, but supranormal levels of EVLW resulted in perivascular cuffing only. Hence, the method may be more sensitive than radiographic techniques to estimate edema formation. Resorption of alveolar edema, as measured by the technique, is relatively independent of hydrostatic and colloid osmotic forces, since this is an active alveolar process [19].

Despite its potential, there are some drawbacks of the thermal-dye dilution method inherent to the technique, and some questions remain as to the effect of cardiac output and hypoperfusion of edematous areas on the measurement. Indeed, a change in cardiac output itself should not alter pulmonary edema, even during permeability edema, since the edema is mainly governed by transcapillary

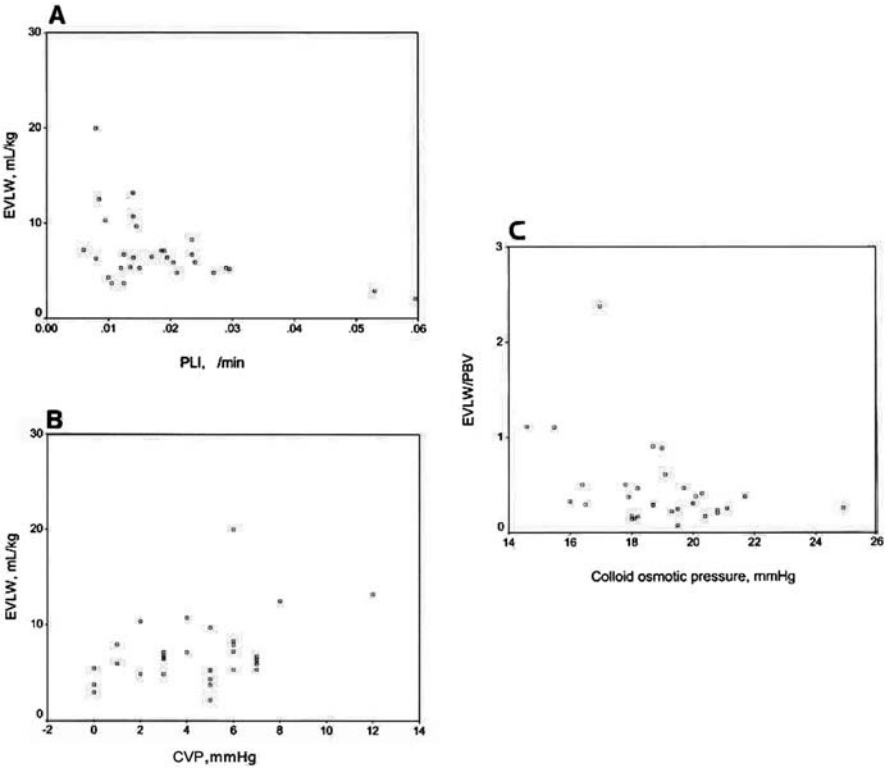

Fig. 1. A. Relation between extravascular lung water (thermal-dye EVLW, normal below 7 ml/kg) and pulmonary leak index (PLI, normal below 15 $x10^{-3}$/min) to radiolabeled transferrin, in 30 patients directly after cardiac surgery ($r=-0.47$, $p<0.01$). B. Relation between EVLW and central venous pressure (CVP, mmHg) in 30 patients after cardiac surgery ($r=0.39$, $p<0.05$). EVLW did not relate to intrathoracic blood volume nor cardiac output. C. Relation between ratio of EVLW and pulmonary blood volume (PBV) to measured plasma colloid osmotic pressure (mm Hg) in 30 patients after cardiac surgery ($r=-0.40$, $P<0.05$) (unpublished observations J. Verheij and ABJ Groeneveld). The data suggest that the postoperative EVLW increase is largely governed by hydrostatic and colloid osmotic forces, rather than by pulmonary blood volume or protein permeability.

pulmonary pressures, interstitial compliance, and alveolar resorption. The thermal-dye method may not pick up the distribution volume of the temperature indicator in areas that are underperfused, so that EVLW becomes directly dependent on cardiac output. Obstructing pulmonary arteries in a pig model, mimicking pulmonary arterial embolization, indeed lowered thermal-dye EVLW [30]. Using the Edwards densitometer technique, Mihm et al. and others, however, noted that the EVLW (ETV) may overestimate gravimetric EVLW at a post mortem examination, the gold standard, in dogs and human organ donors, regardless of the cause

of edema, i.e., hydrostatic forces or increased permeability, and this may also apply to the fiberoptic technique [12, 17, 31, 32]. Nevertheless, the correlation of EVLW obtained by gravimetric and thermal-dye techniques was high over a wide range of volumes [17, 31, 32]. Underestimations have been reported as well, even for the fiberoptic technique [33]. A high cardiac output may lead to underestimating EVLW, by impairing time for thermal diffusion, and positive end-expiratory pressure (PEEP) may increase the distribution of the thermal indicator and increase EVLW, although this is controversial and opposite observations have been made, depending on the technique used [18, 31, 34, 35]. Indeed, the fiberoptic technique may be less prone to (technical) errors inducing (direct and inverse) cardiac output-dependency of EVLW than the densitometer technique, but more prone to errors than the ^{2}H-water indicator dilution technique [12, 18]. Thermal loss may affect both cardiac output, when determined from the thermodilution curve, and the ETV [12, 26, 31].

The effect of airway pressures, i.e., PEEP, on EVLW (thermal-dye technique) is controversial, and may depend on, among others, the type of lung injury, the mechanical ventilation protocol used, the level of recruitment, and the degree of ventilator-induced lung injury (VILI) [17]. Nevertheless, incremental PEEP may decrease pulmonary edema, as measured by thermal-dye EVLW (fiberoptic method), one hour after the PEEP increment, in a surfactant washout model of ALI in sheep [36]. The decrease in EVLW was directly associated with a decrease in non-aerated and an increase in aerated lung volume, estimated from CT scans. The EVLW could well reflect recruitment (and thus reperfusion) rather than the severity of lung injury, as suggested earlier [34, 35]. Within an observation period of 6 hours, PEEP and low tidal volumes decreased gravimetric and thermal-dye EVLW (fiberoptic method) to a similar extent, in oleic acid-induced pulmonary edema in pigs [33].

Edema that is poorly perfused is poorly reflected by the thermal-dye technique, so that some types of edema, as has been demonstrated in prior animal studies, are less well reflected by EVLW measurements than others [21, 34, 35, 37]. Carlile et al. [34, 35, 37], using the densitometer technique, noted that hydrochloric acid aspiration in dogs increased gravimetric pulmonary edema more than the thermal-dye EVLW, so that ETV underestimated edema. Unilateral hydrochloric acid injury, in particular, increased gravimetric more than thermal-dye ELVW [35, 37]. In spite of underestimation, hydrochloric acid instillation into the airway still increased thermal-dye EVLW in other studies [38]. Alloxan, oleic acid, or α-naphthylthiourea (ANTU)-induced pulmonary edema, mimicking endogenous ALI/ARDS in man, increased both thermal-dye and gravimetric EVLW to a similar extent [17, 26, 33, 34, 37].

Clinical Studies

Authors have addressed the issue of cardiac output dependency in man. Boldt et al., observed that altering cardiac output after cardiac surgery in humans did not affect the thermal-dye EVLW (densitometer technique) [39]. Nevertheless, the thermal-dye method is expected to better reflect the degree of edema during

ALI/ARDS, caused by indirect injury, including sepsis, than caused by direct/inhalational injury, in man. Indeed, Holm et al. observed no EVLW elevation in man suffering from burn inhalation injury and resuscitated with crystalloid solutions [27]. However, the chest radiograph did not show evidence for pulmonary edema in most cases, so that the normal EVLW may have been correct.

In cardiogenic pulmonary edema, EVLW is elevated [2, 28, 40], to return, within 24 h, to normal values upon successful treatment. EVLW may also transiently increase after cardiac surgery [20]. Authors have shown [1, 2, 40, 41], that EVLW is increased in ARDS, and more so when ARDS is severe. The degree of pulmonary edema may be even greater than during cardiogenic pulmonary edema [2, 40]. Survivors may have less EVLW than non-survivors [41]. A recent paper utilizing the new fiberoptic technique confirmed the prognostically unfavorable effect of a high EVLW, regardless of the type of severity of underlying disease, in the critically ill, having sepsis, ARDS, or other conditions [22]. Hence, EVLW may constitute a measure of pulmonary vascular injury and its prognosis.

Determinants of EVLW have been evaluated, showing that changes in EVLW (densitometer technique) correlated to changes in pulmonary artery occlusion pressure (PAOP) in cardiogenic and permeability types of pulmonary edema [40]. Intrathoracic volumes correlated better with EVLW in patients with cardiogenic or permeability edema than pressures, including the PAOP, in some studies [4, 28, 41–42]. However, there is no consistent positive relation of EVLW to intrathoracic blood volume [27, 28, 42], thereby arguing against a major confounding effect of mathematical coupling between intrathoracic blood volume and EVLW, partly derived from the same dilution curves. Our preliminary observations suggest that, after cardiac surgery, a rise in EVLW (thermal-dye) may better relate to Starling forces than to increased permeability, cardiac output or intrathoracic blood volume (Fig. 1), in line with previous observations in cardiogenic and in permeability edema [40]. During ALI/ARDS, EVLW may only poorly correlate with oxygenation, i.e., the PO_2/FiO_2 ratio or venous admixture, suggesting that edema does not, or only partially, contribute to gas exchange abnormalities [4, 20, 27, 41, 43].

There are some limited clinical data that EVLW monitoring affects treatment also. The thermal-dye EVLW measurement has been compared with PAC-based pressure monitoring for the treatment of patients with ALI. Indeed, (fluid) therapy based on this EVLW (densitometer technique) rather than on a PAOP after pulmonary artery catheterization was associated, in critically ill patients with ALI and pulmonary edema, with an increase in ventilator-free days and decreased morbidity, since the EVLW-monitored group received less fluids [23]. However, there are no new diagnostic therapeutic studies utilizing the fiberoptic technique, aimed at preventing or ameliorating an increase in EVLW and subsequent morbidity and mortality, thereby confirming and extending the Mitchell et al. study [23, 44]. Pressure support ventilation for weaning proved more effective when EVLW was relatively low (<11 ml/kg) than when it was high [43].

The time constant for changes in EVLW upon changes in hemodynamics and treatment, the value in decision making, morbidity, and mortality of the critically ill remain unresolved issues, in spite of some information on time and treatment effects in prior animal models [17, 19, 25, 31, 33–35]). Potential areas of clinical evaluation of EVLW measurements include drug treatment for ARDS and resorp-

tion of pulmonary edema, ventilatory strategies to prevent VILI, and monitoring of fluid resuscitation and fluid balance manipulation. The determinants of EVLW in man clearly deserve further study, and clarification of mechanisms could help to define new treatments during which EVLW monitoring could be helpful [45].

Conclusion

The thermal(-dye) technique for assessing extravascular thermal volume in the thorax as a bedside measure of EVLW is a promising technique to evaluate the severity and course of both permeability and hydrostatic/cardiogenic pulmonary edema, and may serve as a semicontinuous guide to judge effect of treatment. The method has been currently integrated with the transpulmonary assessment of global hemodynamics, allowing concomitant assessment of preload and fluid responsiveness and thereby further help in (fluid) therapy decisions at the bedside.

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Arterial Pulse Contour Analysis: Applicability to Clinical Routine

D. A. Reuter and A. E. Goetz

„Es ist vielleicht nicht ohne Interesse, dass man aus der Grundschwingung des arteriellen Systems unter gewissen Annahmen für das Zustandekommen der Wellenreflexion das von dem Herzen aufgeworfene Volumen berechnen kann, wenn die Druckänderung des Pulses bekannt ist."

"It might be of interest that one can calculate the blood volume, which is ejected by the heart by analyzing the basic oscillation of the arterial system under specific assumptions of the origin of wave reflections, if the change in pulse pressure is known."

Otto Frank, 1930

Introduction

The aim of the hemodynamic management of critically ill patients is to secure adequate organ perfusion. This is essential for an adequate tissue oxygenation in order to prevent organ failure or to restore organ function. The driving force of blood flow and hence of perfusion is the function of the heart. Therefore, of course, monitoring of the adequacy of cardiac function is the focus of the classical hemodynamic monitoring concept. Further, if cardiac function, and hence systemic perfusion, is inadequate, hemodynamic monitoring allows the reason(s) for this inadequacy, i.e. a lack of cardiac preload, myocardial contractility, or cardiac afterload to be determined. Historically, hemodynamic monitoring has been founded mostly on the measurement of blood pressures: arterial pressure monitoring serves as a surrogate for cardiac output function, afterload, and systemic perfusion, whereas central venous and wedge pressure monitoring have been used to estimate cardiac preload. Within the last few years, continuous and relatively simple techniques of assessing systemic blood flow instead of pressure have found their way into the clinical routine. One of these techniques is arterial pulse contour analysis to monitor stroke volume and cardiac output continuously. Integrating such a monitoring tool into the existing and accepted concepts such as pressure- and volume-monitoring seems to be a promising way for new, physiology-directed therapeutic strategies.

Monitoring the Adequacy of Cardiac Function: Blood Pressure vs. Blood Flow

Continuous measurement of arterial blood pressure is an unquestioned part of the hemodynamic monitoring of critically ill patients in the intensive care unit (ICU). However, not only blood pressure but more importantly blood flow, i.e., cardiac output, determines organ perfusion. Thus, it is a logical rationale to implement techniques that allow measurement of cardiac output in the ICU setting. The most commonly used technique for cardiac output monitoring within the past 30 years has been the thermodilution technique using a pulmonary artery catheter (PAC). For many years, the PAC has been the only clinically available tool to measure cardiac output; hence, it has influenced and shaped more than one generation of critical care physicians. However, besides, of course, measuring another physiologic entity (flow vs. pressure), the thermodilution technique differs decisively in another two points from invasive pressure monitoring: It is neither a *continuous* nor an *automated* technique. This sounds profane; however it has an important impact regarding the clinical relevance of measuring cardiac output: The blood pressure waveform as well as the pressure values are always displayed automatically, continuously, and in real-time on the monitor; and, if not, placing an arterial line is one of the very first interventions in a patient who becomes hemodynamically instable. Thus, blood pressure, which is in fact only a very limited surrogate for organ perfusion becomes automatically the first-line therapeutic target. Therefore, the implementation of a technique to measure cardiac output in a comparably automated and continuous way with a comparably low risk profile might be of great benefit in the treatment of critically ill patients.

Two completely different techniques to measure cardiac output in such a continuous and automated fashion have gained increasing interest within the last years, namely ultrasound Doppler techniques, which are discussed in another chapter of this book, and arterial pulse contour analysis.

The concept of arterial pulse contour analysis for monitoring stroke volume and cardiac output actually is not a really novel development of the past years. As cited above, the first scientific work on arterial pulse contour analysis dates from 1930, with its theoretical background already published in 1899 by Otto Frank from the Physiologic Institute of the University of Munich, Germany [1, 2]. Franks' original intention was to develop a simple method to measure the blood flow produced by the heart and modified by the aortic Windkessel basically for laboratory work. The basic assumption of this method is the existence of a direct relation between the arterial pressure and its course over time to arterial blood flow and the course of this blood flow over time. However, this theoretical model has clearly found its way out of the laboratory and has become the basis of all pulse contour methods that are implemented in commercially available monitoring devices today.

Continuous Cardiac Output Monitoring by Pulse Contour Analysis

Several groups followed the concept of Frank to calculate stroke volume and cardiac output of the left heart by analyzing the aortic pulse contour. An impor-

tant step forward towards its clinical applicability was the development of the Cz method by Wesseling and colleagues [3, 4]. Briefly, this method involves the calculation of the area under the systolic portion of the arterial pressure waveform, which, divided by aortic impedance, allows the estimation of the left ventricular stroke volume. Further refinements were achieved by incorporating corrections of pressure dependent non-linear changes in the cross-sectional area of the aorta and reflections from the periphery, both age-dependent. Once calibrated with a reference technique that enables the determination of an absolute cardiac output value, as for example thermodilution, this methodology enabled accurate and, most importantly, continuous tracking of cardiac output in cardiac surgery and intensive care patients [4, 5].

A further mathematical extension of the Windkessel model was the introduction of the Modelflow method, again by Wesseling and colleagues. A detailed description of this mathematical model can be found elsewhere [6]. Several studies pointed towards the usefulness and the robustness of this technique for continuous cardiac output monitoring [7].

Various different monitoring devices are commercially available at the moment using arterial pulse contour analysis for continuous cardiac output monitoring, for example, the PiCCO© or the PulseCO©. Although both systems use different proprietary pulse contour algorithms, the basic concept of these monitors regarding continuous cardiac output monitoring is the same: Initially, absolute cardiac output is measured by an indicator dilution technique (transcardiopulmonary thermodilution (PiCCO©) vs. lithium dilution (PulseCO©). This value of dilution cardiac output is used to calibrate arterial pulse contour analysis cardiac output, which is then measured continuously in an automated fashion [8, 9]. In numerous studies, pulse contour cardiac output measurements have been compared against the clinical gold standard, the thermodilution technique, in different groups of patients. By far most of these studies were performed with the PiCCO© system, so that it must be concluded that at least this device reliably allows the continuous measurement of cardiac output by arterial pulse contour analysis in clinical circumstances in adult patients [10–13]. Thus, the method of arterial pulse contour analysis seems to be indeed a useful carrier to transfer clinically relevant, direct information on systemic blood flow in an automated and continuous mode, and most importantly without any time delay at the patient's bed side.

Preload Monitoring and the Estimation of Fluid Responsiveness in Mechanically Ventilated Patients

Hemodynamic instability with low cardiac output in critically ill patients is often caused by hypovolemia. However, determining the level of preload and most importantly fluid responsiveness, i.e., predicting whether fluid loading will increase a patient's cardiac output or not, still is a very difficult decision at the patient's bedside. Numerous studies published within the last 15 years have clearly demonstrated that volumetric parameters such as the global end-diastolic volume index (GEDVI), the intrathoracic blood volume index (ITBVI) (both by transcardiopulmonary thermodilution), or the left ventricular end-diastolic area

(LVEDA) by transesophageal echocardiography (TEE) allow the assessment of cardiac preload as well as the monitoring of changes in preload under fluid therapy in critically ill patients much more reliably than the cardiac filling pressures, central venous pressure (CVP) or pulmonary artery occlusion pressure (PAOP) [14–18]. Based on these findings, volumetric parameters are increasingly implemented in clinical routine and decision making. However, as summarized in recent reviews, those volumetric parameters, although slightly better than the cardiac filling pressures CVP and PAOP, do not reliably allow the assessment of fluid responsiveness [19, 20]. This means that all these static parameters do not allow the prediction, prior to fluid loading, of whether the intervention in question will increase the patient's cardiac output or not. Fluid loading is one of the most frequent therapeutic steps in the ICU in hypotensive patients, although in around 50% of the patients fluid loading actually fails to increase cardiac output [21]. Many patients therefore receive unnecessary and potentially harmful fluid loading, whereas in other patients, in whom fluid administration would actually be beneficial, this intervention is not performed. Within the last few years, there has been renewed interest into the specific interactions of the lungs and the cardiovascular system caused by mechanical ventilation [22]. So called dynamic parameters, such as the systolic pressure variation (SPV), the pulse pressure variation (PPV), and the stroke volume variation (SVV), all based on ventilation-induced changes in the interactions of heart and lungs have been evaluated by different groups to improve the assessment of fluid responsiveness, and by that to optimize fluid therapy in mechanically ventilated patients [23–29]; the results have been promising. The rationale behind the parameters SVV and PPV, but also changes in aortic peak flow velocity assessed by TEE is similar; the alternating intrathoracic pressure during each mechanical breath induces transient but distinct changes – predominantly in cardiac preload – which, according to the Frank-Starling mechanism, lead to undulations in left ventricular stroke volume. Thus, each mechanical breath serves as a small endogenous volume loading and un-loading maneuver. The degree of undulation depends on where the patient's left ventricle is operating on the Starling curve. The Starling (or ventricular function) curve describes the relation between preload and stroke volume [30]. A steep slope of the Starling curve is associated with large SVV, whereas a shallow slope results in only small SVV. Thus, high SVV indicates volume responsiveness, or in other words, that stroke volume and cardiac output can be improved by fluid loading. Conversely, a low SVV in a hypotensive patient will support the decision to use catecholamines. Arterial pulse contour analysis now seems to be a useful method to measure, again continuously and in an automated fashion, those variations of stroke volume causative for SPV and PPV. Indeed, in different groups of patients (healthy patients undergoing neurosurgery, cardiac surgery patients, as well as septic patients), SVV tracked by arterial pulse contour analysis allowed fluid responsiveness to be correctly predicted [27–29, 31]. In contrast, a recently published study in cardiac surgery patients did not find a significant correlation between SVV measured by arterial pulse contour analysis at baseline and the increase in cardiac output following fluid loading [32]. However, this finding appears to conflict with the close correlation the authors found in the same study between baseline values of SVV and the relative changes in SVV they induced by

volume loading. Further, as already stated by the authors, the SVV data were not compared to other parameters quantifying heart-lung interactions during mechanical ventilation, such as SPV, PPV, or Doppler-derived changes in aortic peak-flow velocity. This would have excluded any potential methodological or technical errors in their measurements. However, these data quickened concerns regarding the ability of arterial pulse contour analysis to truly detect the changes in left ventricular stroke volume during the ventilatory cycle [33]. And indeed, an experimental validation against a real gold standard is desirable to truly determine `the limits of arterial pulse contour analysis' under extreme hemodynamic conditions. However, the close correlation between arterial pulse contour analysis SVV with both SPV and PPV in clinical circumstances strengthens the view that arterial pulse contour analysis can indeed serve as a clinically reliable tool to transfer this functional and essential information on heart-lung interactions in an automated and continuous fashion to the bedside [27, 34, 35].

Integrated Approach to Hemodynamic Management in Critically Ill Patients

Monitoring cardiocirculatory function, and the assessment of dysfunction such as hypovolemia as the reason for hemodynamic instability and low perfusion, is complex in critically ill patients, in particular in those who require mechanical ventilation. Within the last few years, increasing consensus has been achieved that the measurement of blood pressure alone does not fulfill the demands that are required for differentiated hemodynamic monitoring and goal directed guiding of therapy. The introduction of new techniques into ICU hemodynamic monitoring, such as 2-D TEE, Doppler and volumetric measurements by thermodilution (GEDV, ITBV, EVLW), as well as the re-establishment and refinement of techniques such as the arterial pulse contour analysis have widened the visual angle of hemodynamic assessment. In particular the increased understanding of heart-lung interactions under mechanical ventilation have led to a clinically more distinguished interpretation of preload monitoring, i.e., the clinical differentiation between preload as a volumetric measure and fluid responsiveness. Thus, hemodynamic monitoring now also incorporates into clinical decision making the ventilator settings and the automated hemodynamic challenge to the circulation that is performed by the ventilator during each breath. Arterial pulse contour analysis with its parameters `continuous cardiac output', `continuous stroke volume', and `continuous SVV' therefore represents one carrier of important information that seems to be clinically applicable and reliable in the context of an integrated approach to hemodynamic management.

Conclusion

Functional hemodynamic monitoring, which allows more detailed insights into cardiovascular physiology and disease, might help to improve the detection and the understanding of pathological cardiocirculatory situations. Functional

hemodynamic monitoring thus has the theoretical potential to improve the therapeutic management of critically patients and, thereby, outcome. Arterial pulse contour analysis represents a method that can contribute to this development in two ways: First, this method can transfer information on cardiac output and hence on blood flow quasi on-line to the physician at the bedside in an automated and continuous mode; so this information is permanently available. Second, it enables the direct interactions between the lungs and the cardiovascular system to be tracked continuously both under spontaneous respiration and mechanical ventilation. Initial approaches to analyze these interactions by means of SPV, PPV, and SVV have opened up novel ways of preload monitoring in mechanically ventilated patients. In fact, these concepts have already been transferred from the laboratory to the patient's bedside, and, most importantly, seem to be useful in daily practice. However, this aspect of functional preload monitoring might only be the very first step in understanding and utilizing heart-lung interactions for the hemodynamic management of critically ill patients.

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Arterial Pulse Power Analysis: The LiDCO^{TM}plus System

A. Rhodes and R. Sunderland

Introduction

The aims of hemodynamic monitoring are to provide a comprehensive overview of a patient's circulatory status in order to inform and direct clinicians as to diagnostic state, treatment strategies, and prognosis. The monitoring, therefore, needs to provide useful information at an appropriate time and with limited complications that could be directly attributed to the individual technique. Measurement of cardiac output or stroke volume has been regarded as a necessary facet of caring for critically ill patients, however until recently has been only possible with the use of the pulmonary artery catheter (PAC). With the current controversies regarding the use of the PAC, several new less invasive technologies have become available to provide similar information. This chapter focuses on the use of arterial pulse contour and power analysis as a technique to measure and monitor cardiac output or stroke volume and focuses on the technology introduced by the LiDCO company with their LiDCO^{TM}*plus* monitor.

Arterial Pulse Contour Analysis

Arterial pulse contour analysis is a technique of measuring and monitoring stroke volume on a beat-to-beat basis from the arterial pulse pressure waveform. This has several advantages over existing technologies, as the majority of critically ill patients already have arterial pressure traces transduced making the technique virtually non-invasive and able to monitor changes in stroke volume and cardiac output on an almost continuous basis.

History of Arterial Pulse Contour Analysis (Table 1)

The first direct measurement of arterial blood pressure was by the Reverend Stephen Hales in 1733. As early as 1899, the concept of using the blood pressure waveform to measure blood flow changes was first suggested by Otto Frank [2].

Otto Frank described the circulation in terms of a Windkessel model (Windkessel is the German word for air-chamber). The Windkessel model described the loads faced by the heart in pumping blood through the pulmonary or systemic

Table 1. History of pressure waveform analysis

1. Windkessel model of the circulation – Otto Frank, 1899 [1, 2]
2. First pulse pressure method – Erlanger and Hooker, 1904 – suggested that stroke volume is proportional to the pulse pressure (systolic – diastolic) [3]
3. Requirement for calibration of pulse pressure by an independent cardiac output measure was suggested by Wezler and Bogler in 1904 [21]
4. Pulse pressure simply corrected for arterial compliance was investigated by Liljestrand and Zander, 1927
5. Compliance of the human aorta documented first by Remington et al., 1948 [4]
6. Aortic systolic area based pulse contour method, Kouchoukos et al., 1970 [5]
7. Systolic area with correction factors (3 element Windkessel model), Wesseling and Jansen, 1993 [6, 7]
8. Compliance corrected pressure waveform 'net' pulse power approach – Band et al, 1996 [22]

circulations and the relationship between blood pressure and flow in the aorta or pulmonary arteries. This model likens the heart and systemic arterial system to a closed hydraulic circuit comprised of a water pump connected to a chamber. The circuit is filled with water except for a pocket of air in the chamber. As water is pumped into the chamber, the water both compresses the air in the pocket and pushes water back out of the chamber, back to the pump. The compressibility of air in the pocket simulates the elasticity and extensibility of the major arteries, as blood is pumped through them from the heart. This is commonly referred to as arterial compliance. The resistance that the water encounters whilst leaving the Windkessel and flowing back to the pump equates to the resistance to flow that blood encounters on its passage through the arterial tree. This is commonly referred to as peripheral resistance. This somewhat simplistic view of the circulation was referred to as the '2-element Windkessel model' and has helped us to understand the underlying physiology and, by solving the individual components of the model, to calculate flow. Frank's objective was to derive cardiac output from the aortic pressure. By measuring the pulse wave velocity over the aorta (carotid to femoral) the compliance could be estimated. Knowing the time constant from the diastolic aortic pressure decay and compliance, the peripheral resistance could then be derived. From mean pressure and resistance, using Ohm's law, mean flow could be calculated. This technique has been further refined in recent years to develop a 3 and 4 element Windkessel model. This has been used to define the systolic area under the pulse contour curve and thus help to estimate stroke volume.

In 1904, Erlanger and Hooker stated "Upon the amount of blood that is thrown out by the heart during systole then, does the magnitude of the pulse-pressure in the aorta depend" [3]. Although this is an intuitive statement, the translation of these observations into a robust system of measuring cardiac output has had to overcome a number of confounding problems that has led to the introduction of this technique only in the last few years.

Table 2. Lithium dilution cardiac output (CO) measurement validation studies

Author	Species	Validation	Mean	Range CO	Bias of CO	2 x SD	%Error of bias
Kurita [9]	Swine	PAC, EMF	1.5	0.2–2.8	0.1	0.36	24
Mason [10]	Dogs	PAC	3	1–13	0.1	0.9	30
Linton [11]	Horse	PAC	20*	12–42	–0.9	2.8	14
Corley [12]	Foals	PAC	13*	4–22	0.05	3.0	13
Garcia-Rodriguez [13]	Human	PAC	6*	3.5–9.5	–0.5	1.2	20
Linton [14]	Human	TPTD	2	0.4–6	–0.1	0.6	30
Linton [15]	Human	PAC	5 *	2.4–10.2	–0.2	0.9	18

PAC: pulmonary artery catheter; EMF: electromagnetic flow probes; TPTD: transpulmonary thermodilution; * is where the data for mean cardiac output are not readily available from the papers and have had to be estimated from the original data.

Following Otto Frank, attention turned to using the aortic /arterial pulse pressure to estimate the stroke volume. The concept centered around the theory that fluctuations in blood pressure (pulse height) around a mean value are caused by the volume of blood (the stroke volume) forced into the arterial conduit by each systole. However, a number of complicating factors were identified – first the requirement for calibration via an indicator dilution measurement. At that time this was by no means a trivial problem and remained so until the recent advent of transpulmonary indicator dilution techniques – such as the LiDCO lithium method. Second, and of equal importance is the correction of pulse pressure necessary due to the non-linear compliance of the arterial wall. Effectively this means that when stretched (through the input of a further volume of blood) at a higher blood pressure, the compliance of the aorta is less than at low blood pressures. It was not until 1948 [4], that there were accurate enough data from human aortas to attempt compliance correction of blood pressure data. So by the 1970s both compliance correction (to linearize the blood pressure data) and calibration via indicator dilution (green dye and thermal indicators) was possible. This led to the suggestion that one could move away from simplistic pulse pressure approaches to actually measuring the systolic area (to closure of the aortic valve) of the calibrated and compliance corrected waveform [5]. In essence, this approach is one based on integrating the area of the systolic part of the linear pressure/volume waveform. These approaches are generically referred to as Pulse Contour Methods [5–7].

Pulse Pressure Relationship to Stroke Volume

The fluctuations of blood pressure around a mean value are caused by the volume of blood (the stroke volume) forced into the arterial conduit by each systole. The magnitude of this change in pressure – known as the pulse pressure – is a function of the magnitude of the stroke volume. The translation of these concepts into a workable system has been complicated by a number of factors that make this relationship between pulse pressure and stroke volume more difficult:

1. The compliance of the aorta is not a linear relationship between pressure and volume. This non-linearity prevents any simple approach to estimate volumes from the pressure change. There needs to be correction for this non-linearity for any individual patient.
2. Wave reflection. The pulse pressure measured from an arterial trace is actually the combination of an incident pressure wave ejected from the heart and a reflected pressure wave from the periphery. In order to calculate the stroke volume, these two waves have to be recognized and separated. This is further complicated by the fact that the reflected waves change in size dependent on the proximity of the sampling site to the heart and also the patients age.
3. Damping. As the change in pressure around a mean value describes the stroke volume, accurate pressure measurements are imperative. Unfortunately pressure transducer systems used in routine clinical practice often suffer from either being under or over damped, leading to imperfect waveforms and measurements.
4. Aortic flow during systole. Although the filling of the aorta is on an intermittent pulsatile basis, the outflow tends to be more continuous.

Ideal Algorithm for Arterial Pulse Contour Analysis

Taking these problems discussed above into account, the ideal algorithm for arterial pulse contour analysis would contain the following features:

1. The algorithm would work independent of the artery the blood pressure is monitored from – despite the fact that the arterial pressure waveform shape and pressure is changed by its transmission through the arterial tree to the periphery.
2. It would correct for aortic non linearity and may be calibrated to take account of individual variations in aortic characteristics and therefore give absolute stroke volume.
3. It would be minimally or even not affected by changes in systemic vascular resistance causing changes in reflected wave augmentation of the arterial pressure.
4. It would not rely on identifying details of wave morphology.
5. It would be only minimally affected by the damping often seen in arterial lines.

The LiDCO^{TM}plus Method of Pulse Power Analysis

The algorithm utilized for the LiDCO^{TM}*plus* technique of arterial pulse power analysis has a number of features that gets around the problems discussed above. This approach is non morphology based, i.e., is not a pulse contour method. Rather it is based on the assumption that the net power change in a heartbeat is the balance between the input of a mass (stroke volume) of blood minus the blood mass lost to the periphery during the beat. It is based on simple physics, i.e., conservation of mass/power and an assumption that following correction for compliance and calibration there is a linear relationship between net power and net flow. Autocorrelation is used to both define the beat period and the net power change across the whole beat. In taking the whole beat, and not a portion of the beat, the method is independent of the position of the reflected wave. Autocorrelation is a time based method and thereby avoids using a frequency approach to measuring power (such as Fourier transforms) and thus the effects of arterial damping (which change frequency response) are limited.

These can be summarized as follows:

1. The algorithm compliance corrects any arterial pressure signal to a standardized volume waveform (volume in arbitrary units) through the equation

   $$\Delta V/\Delta bp = \text{calibration} \times 250 \times e^{-k.bp}$$

   where V is volume, bp is blood pressure and k is the curve coefficient. The number 250 represents the saturation value in mls, i.e., maximum additional volume above the starting volume at atmospheric pressure that the aorta/arterial tree can fill to.
2. Autocorrelation of the now standardized volume waveform – derives both the period of the beat plus a net effective beat 'power factor (R.M.S – root mean square) which is proportional to the 'nominal stroke volume ejected into the aorta.
3. This 'nominal' stroke volume can be scaled to an actual stroke volume by an independent indicator dilution measurement, e.g., lithium dilution cardiac output from the LiDCO^{TM} system.
4. The scaling/calibration factor corrects for the arterial tree compliance for a given blood pressure and corrects for variations between individuals.
5. The scaling/calibration factor changes the saturation value (maximum volume of the aorta/arterial tree) used for the compliance correcting equation – rather than the curve coefficient (k). Thus any potential drift/change in the calibration factor is limited to the extent that the aortic/arterial tree maximum volume can change over the short term (hours).

Theoretical benefits of the Pulse Power Approach to Pulse Contour Analysis

In theory, the features of the pulse power algorithm enable the LiDCO^{TM}*plus* to have several advantages over the pulse contour/systolic area analysis approach. These advantages include:

1. Any arterial site can be used for blood pressure measurement, not just a central artery. As the algorithm looks at the power of the whole pulse contour and not just the systolic area, morphology is not as important. The net power from the input of stroke volume – outflow during the beat is calculated, thus negating the effect of reflected waves.
2. The effect of damping on the transducer system will be similarly reduced. Within reasonable limits the power of the waveform will remain the same, whether the system is over or under damped and thus the changes in stroke volume will remain accurate [15].
3. This system can be calibrated with any form of measurement of cardiac output, so long as the error coefficient of the calibrating technique is less than the error of the LiDCO^{TM}*plus* system. The lithium dilution cardiac output system that is incorporated in this technology (see later) enables a relatively non-invasive and highly accurate mechanism of calibration.

Lithium Dilution Cardiac Output Measurement: The LiDCO^{TM} system

The technique of lithium dilution cardiac output measurement was described by Linton in 1993. A bolus of isotonic lithium chloride (0.002–0.004 mmol/kg) is injected using either central or peripheral venous access. The subsequent concentration of lithium in the circulation is then measured by a lithium ion-selective electrode situated in an appropriate arterial line. This information is used to generate a concentration time curve and the cardiac output can then be calculated from the known amount of lithium and the area under the curve after the first peak, representing the cardiac output before recirculation. Lithium, long established in psychiatric practice as a treatment for mania, has several advantages when used as the indicator in a dilution technique; it does not naturally occur in plasma and therefore can generate a high signal to noise ratio when using an ion selective electrode to measure changes in plasma concentration thus allowing small doses of lithium to be used. At these levels lithium is pharmacologically inert and safe, toxic levels would only be achieved if the maximum recommended dose were greatly exceeded. Rapid redistribution and no significant first pass loss from the circulation add to the suitability of lithium for this technique [8].

The lithium ion selective electrode is central to the LiDCO system and is housed in a flow-through cell attached to the manometer tubing of an arterial cannula. A peristaltic pump is used to control the rate of blood flow through the sensor at 4 ml/min and the eccentric inlet insures mixing of the sample as it passes the membrane selectively permeable to lithium. The Nernst equation relates the plasma lithium concentration to the voltage across the membrane, after the appli-

cation of a correction for plasma sodium, the main determinant of baseline voltage in the absence of lithium. An isolated amplifier is used to measure the voltage that is then digitalized prior to analysis online. The sensor must be primed before use with heparinized saline in order to make an electrical connection between the reference electrode and the blood sample at the electrode tip.

Validation Studies – LiDCO calibration

Calibration precision is very important for arterial pressure waveform analysis systems – the minimum specification is that calibration has to be at least as accurate as green dye or averaged triplicate bolus pulmonary artery thermodilution. Inaccuracy beyond these standards will result in confusion between changes in patient hemodynamic status and scatter in the measurement itself. Lithium dilution has been validated against several methods including electromagnetic flow probes and pulmonary artery thermodilution and has proven to be a very robust and accurate mechanism for measuring cardiac output in both adults, children and animals (Table 2) [9–15].

Linton et al. [15] demonstrated good overall agreement between thermodilution and the LiDCO in 40 patients from a high dependency post operative unit and intensive care unit (ICU). Thirty-four had undergone cardiac surgery requiring cardiopulmonary bypass (CPB) within the previous two days, the other diagnoses were two recent myocardial infarcts, two septicemias, one acute respiratory distress syndrome (ARDS), and one pericardectomy. Cardiac output was measured five times in each patient using lithium dilution (single measurement) and bolus thermodilution (series of three to six measurements according to standard clinical practice and taking the average of the closest three). Linear regression analysis ($r^2 = 0.94$) for lithium dilution vs. thermodilution demonstrated that lithium dilution was at least as accurate as bolus thermodilution.

Kurita et al. [9] compared cardiac output measurements in their sample group of ten pigs undergoing general anesthesia; they used LiDCO, thermodilution, and electromagnetic flowmetry. This necessitated a PAC, femoral artery catheter and an electromagnetic flowmeter placed around the ascending aorta. Baseline measurements for all three techniques were compared to hyper- and hypodynamic states induced by dobutamine and propranolol, respectively. Over a range of cardiac outputs from 0.2 to 2.8 l/min, the correlation between LiDCO and electromagnetic flowmetry ($r^2 = 0.95$) was higher than that between thermodilution and electromagnetic flowmetry ($r^2 = 0.87$) suggesting that the LiDCO was more reliable than conventional thermodilution.

In all the studies validating the LiDCO to date, acceptable levels of bias and precision have been found (Table 2). This suggests that the LiDCO system is at least as accurate and effective as standard thermodilution. Several other studies have also assessed the necessity for the lithium injection to be made via the central venous route [13,16–17]. All of these studies concluded that a peripheral venous injection was just as accurate.

Table 3. Validation studies of the pulse power algorithm in the Lidco^{tm}*plus* System

Author	Species	Validation	Mean CO	Range of CO	Bias	2 x SD of bias	%Error
Hamilton [18]	Post cardiac surgery (8hrs)	LiDCO	5.5*	3.3–8.5	0.1	1.2	22
Jonas [20]	ICU	LiDCO	8.2	5.3–17.1	0.3	1.7	21
Pittman [19]	ICU for 24 hours	LiDCO	6	3.5–10.5	0.15	1.3	22
Heller [23]	Intra op. 2.5–8.5 hours	LiDCO	5*	2.7–21.3	0	1.0	20

* is where the data for mean cardiac output (CO) are not readily available from the papers and have had to be estimated from the original data.

Validation Studies – Pulse Power Analysis with LiDCO^{TM}plus System (Table 3)

The pulse power approach has been validated in a number of clinical settings [18–20]. A number of these studies have now been published and a number presented at International meetings and are awaiting publication. Although the evidence is accumulating to demonstrate the accuracy of this technique, the validation set is not yet complete and future studies are awaited.

The accuracy of the pulse power technique has been assessed in comparison to lithium dilution as well as PAC techniques. The validation has been performed in surgical as well as ICU settings for up to eight hours between calibration intervals. The data suggest that the pulse power approach remains accurate for long time periods with minimal drift. The data remain accurate despite changes in peripheral resistance although users would be advised to make a recalibration prior to a major therapeutic shift if a calibration had not been made in the recent past. The data also remains accurate despite suboptimal arterial line damping characteristics [19].

Limitations

The main limitations to this technology revolve around the use of the lithium. As the technique requires a large difference between the signal and background noise to get a reliable indicator dilution curve, it can be difficult to get reliable readings in patients already on therapeutic lithium. Other drugs that can cross react with the lithium sensor are high peak doses of muscle relaxants and these can cause the sensor to drift. If this system is to be used intra-operatively, then the lithium

calibration needs to be performed either prior to the use of muscle relaxation or after the initial peak has had time to subside.

Conclusion

The LiDCO^{TM}*plus* system of cardiac output measurement and monitoring appears to be a safe and effective method of tracking flow. It is minimally invasive and easy to use under the majority of clinical conditions likely to be encountered.

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Esophageal Doppler monitoring

M. Singer

Introduction: History

The Doppler effect states that the shift in frequency emitted by, or reflected off, a moving object is proportional to the relative velocity between object and observer. A formula was derived, relating frequency shift to velocity, and encompassing other variables including the angulation of the point of observation to the path of the moving object, and the speed of sound (Fig. 1). Proportionality between changes in frequency shift and velocity are maintained if these variables are kept constant.

First described by Christian Doppler in 1842, the first application of the Doppler effect was an early sonar technique developed during the First World War by Ernest Rutherford for detecting enemy submarines. It has since been applied to many other areas including radar speed traps and radio-astronomy. Its earliest medical application was in obstetric practice in the 1950s. In the following decade, Light [1] reported measurement of aortic blood flow by directing a percutaneous probe towards the aortic arch and descending aorta. This probe was initially placed over the second left intercostal space and, subsequently, in the suprasternal notch. Huntsman et al [2] also used a suprasternal probe, albeit directed at the ascending aorta. His group performed the first correlation against a comparator technique for measuring cardiac output (thermodilution), describing good agreement between the two techniques [3].

Though rapid, safe, painless and totally non-invasive, the suprasternal Doppler technique carries several disadvantages (Table 1). Alternative approaches include

$$V = \frac{c\ f_d}{2f_T \cos\theta}$$

v = flow velocity
c = speed of sound (in body tissue = 1540 m/sec)
fd = frequency shift (HZ)
cos θ = cosine angle between sound beam axis & velocity vector
ft = frequecy of transmitte ultrasound (Hz)

Fig. 1.
Doppler equation

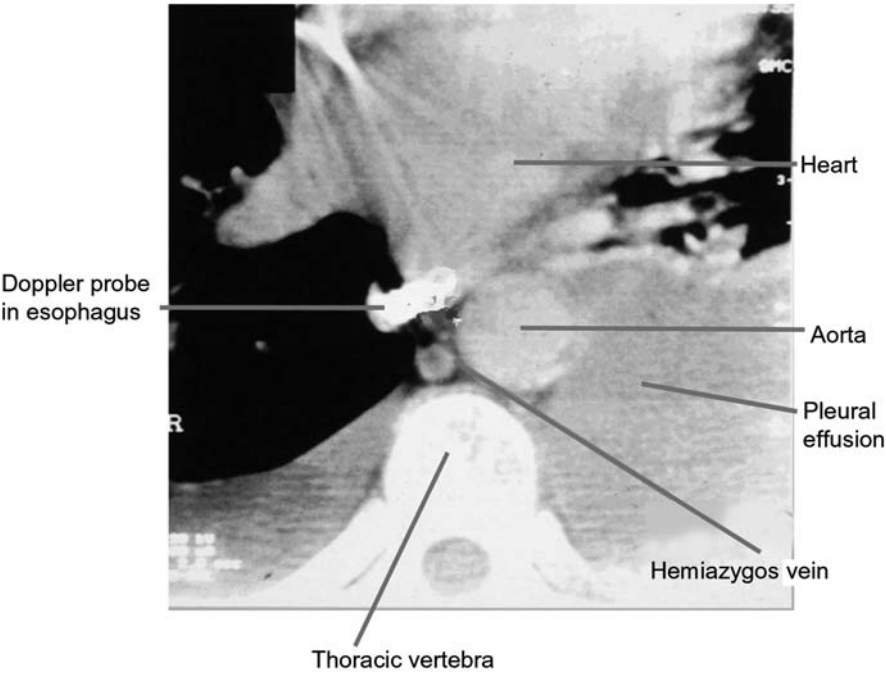

Fig. 2. CT scan indicating thoracic anatomy and proximity of esophageal Doppler probe to descending thoracic aorta

Table 1. Disadvantages of suprasternal technique

• need for adequate training to find and identify an optimal aortic flow signal
• loss of signal in patients with large `air windows' (e.g., emphysema) through which sound waves travel poorly
• turbulent flow generated by aortic valve deformities which invalidates flow measurement in the ascending or arch portions of the aorta
• failure to fix the probe in correct position to enable continuous monitoring

esophageal (Fig. 2) and transtracheal routes. The latter technique [4], incorporated into an endotracheal tube, had a short commercial existence, due in no small part to its lack of adequate validation prior to launch and shall not be discussed further.

The esophageal route has been incorporated into both stand-alone Doppler and combined echocardiographic-Doppler devices (transesophageal echocardiography [TEE]). This article will concentrate only on those techniques directed solely toward measuring blood flow velocity in the descending thoracic aorta, and from which a variety of parameters describing hemodynamic status can be obtained.

In 1971, Side and Gosling, using a 1 cm diameter esophageal probe emitting and receiving 5 MHz continuous wave Doppler ultrasound, recorded velocity waveforms of blood flow in the aortic arch [5]. Although they did not publish further, with prescient foresight they suggested possible applications such as the detection of aortic valve disease and to aid perioperative hemodynamic management - "beat-to-beat changes in the flow pattern and peak velocity and acceleration can be of considerable value to the surgeon by giving immediate warning of deteriorating cardiac efficiency."

Olson and Cooke reported their design of a combined esophageal Doppler and pulse-echo system in 1974. Continuous measurement of flow velocity could be combined with aortic diameter to provide a volumetric measure [6]. Though the paper concentrated on canine studies, they did describe five human subjects instrumented with good results. Importantly, they demonstrated in their animal work that aortic diameter only increased from 16.9 to 17.8 mm over the cardiac cycle, with most of this change occurring in early systole. Thus, most of the forward flow in systole passes through an aorta of constant diameter. In the same year, Duck et al. described their prototype esophageal probe with the first detailed account of insertion, focusing, and difficulties encountered in human subjects [7]. Their 5.5 mm diameter transducer emitted 8 MHz continuous wave Doppler ultrasound at an angle of 45°, assuming parallel axes of descending aorta and esophagus. Fifteen anesthetized adults had the transducer passed 30-40 cm beyond their lips. High quality, low signal-to-noise ratio signals were found within ten minutes, any delay being ascribed to either the initial presence of air and/or the build-up of a mucus coating over the probe head that acted as a good coupling agent. Directional orientation was achieved by probe rotation using the maximal pitch of an audible signal. Incorrect probe positioning gave characteristically different Doppler signals from other flows, e.g., intracardiac or hemiazygos venous.

In 1975, Daigle et al. [8] described a 7.5 MHz pulsed wave esophageal Doppler probe with an echo-ranging system that measured aortic diameter. Flow measurements were validated against electromagnetic flowmetry and pulsed Doppler flow cuffs placed around the aorta of beagles at the level of the diaphragm. A blunt velocity profile was demonstrated during forward flow in the descending thoracic aorta. They too observed small fluctuations in aortic diameter over the cardiac cycle, mainly occurring in early systole, reaching 1.2 mm at the level of the aortic arch and 0.6 mm near the diaphragm. They concluded that..."the simplicity of the esophageal probe technique and its ability to obtain hemodynamic information non-traumatically are important assets which should lead to increasing use of such probes in numerous measurement applications" [8].

Lavandier and colleagues developed a similar device which was 6.8 mm in diameter and combined a 5 MHz continuous wave Doppler ultrasound system angled at 40° with an A-scan echo transducer to measure aortic diameter [9, 10]. A latex balloon surrounded the distal end of the tube which, when inflated, was claimed to maintain probe position and provide good transducer coupling. A probe inserted to a depth of 35 cm from the lips would be at the level of the 5th-6th thoracic vertebrae, at which point the esophagus runs parallel with the descending aorta. Reproducibility between two observers was very close with a maximum difference of 1.9% in 11 patients. Doppler cardiac output was compared with thermodilution

in 21 patients. Although the correlation coefficient was 0.98 (standard error of 0.54 l/min), the Doppler values (6.67±2.3 l/min) under-estimated thermodilution values (7.88±2.6 l/min). The authors attributed this variation to numerous factors inherent in their device yet did not consider the imperfect gold standard provided by thermodilution. This device became commercially available as the Dynemo 3000 (Sometec, France), and is now marketed by Arrow as the Hemosonic 100. It measures descending aortic blood flow though an integral correction factor assuming that a fixed proportion of upper:lower blood flow will provide an estimation of total blood flow if required. Though trend following is likely to be reasonable, it will be affected by inaccuracies generated through aortic diameter measurement; these differ by as much as 30% against echocardiographic-derived data [11].

Another commercial Doppler device, the Ultracom, was launched by Lawrence Medical Systems (USA) in the mid-1980s. A later reincarnation, the Accucom, was subsequently marketed by Datascope (Parasmus, New Jersey, USA). The Ultracom had a 6 mm continuous-wave esophageal Doppler transducer with two additional inputs to provide a volumetric measure of total body cardiac output, namely a suprasternal Doppler probe to calibrate descending aortic blood flow to total body blood flow; and pulsed A-mode echocardiography to measure ascending aortic diameter. The signal was optimized by an audio signal and a signal level seen on a digital LED display. This manipulation required 2-10 minutes and the suprasternal calibration a further 2-10 minutes. Mark et al. compared Doppler cardiac output against simultaneous thermodilution in 16 patients undergoing surgery [12]. Echocardiographic estimation of aortic diameter was compared with direct intra-operative measurement in 23 patients. For each individual patient there was a fairly constant calibration error between Doppler and thermodilution cardiac output measurement, which accounted for much of the variability. In particular, aortic diameter measurements showed poor overall correlation. After excluding patients in whom there was difficulty in obtaining a clear echo image, only 71% were within 3 mm of one another (approximately 10% of aortic diameter dimensions). Nevertheless, trend-following of cardiac output was satisfactory. The authors concluded that significant errors were introduced by the calibration steps of measuring aortic diameter and ascending aortic flow, and suggested that further investigations should address the need for absolute cardiac output values and that trends alone may be sufficient to aid management in many instances. The Accucom did away with the echocardiographic technique by utilizing a nomogram that calculated ascending aortic diameter; however the calibration step using a suprasternal Doppler probe remained. A number of studies assessing the Accucom found reasonable correlation against thermodilution, but rather variable absolute values of cardiac output [13, 14]. As the Accucom was not particularly user-friendly, it failed to achieve acceptance by the clinical community, and was discontinued.

Singer and colleagues described a continuous wave esophageal Doppler system that, in various stages of evolution, has been called ODM-1 and ODM-2 (EDM in US) (Doptek, Chichester, UK) and, latterly, Cardio-Q (Deltex, Chichester, UK). This device incorporates only Doppler flow velocity measurement and no diameter-measuring device. Initially used to compare trends between descending aortic blood flow and total cardiac output measured by thermodilution [15], Singer found the proportionality between thermodilution-measured right heart output and

esophageal Doppler-measured descending aortic blood flow was maintained across a wide range of flows and pressures. He subsequently developed a nomogram (incorporating the patient's age, height and weight) that translated the descending aortic Doppler values into an estimate of total left ventricular cardiac output without the need for other measurements. This obviates the requirement to measure aortic diameter, thus removing a potentially large source of error, which is magnified two-fold as the square of the radius is used in the calculation of aortic cross-sectional area. A 2 mm error in measuring a 25 mm aortic diameter would introduce a 16% error in aortic cross-sectional area. This would appear to explain the physiologically surprising finding reported by Cariou et al. [11] of a variation in ascending:descending aortic blood flow ranging from 44 to 90% based on concurrent total cardiac output (thermodilution) and descending aortic flow (Doppler) measurements.

Comparative Validation Studies

Numerous studies using several comparator techniques including thermodilution, echocardiography, and dye dilution have generally shown high agreement across a wide variety of conditions in perioperative and intensive care unit (ICU) patients [15-29]. The correlation in cardiac output measurements with other techniques lends strong support to the fact that blood flowing down the descending thoracic aorta remains, in most circumstances, in a fairly fixed proportion of total left ventricular cardiac output, despite large changes in blood pressure, cardiac output and body temperature [29]. Changes in posture have not been formally examined.

There have been some published studies that do not find close agreement with absolute values of cardiac output measured by thermodilution, although most do report good trend-following [30-34]; this discrepancy may be related to specific conditions such as advanced pregnancy [30] and epidural anesthesia [31] which affect the proportionality between upper and lower body flow. Operator dependency has also been cited as affecting accuracy [32] while issues pertaining to this particular machine's accuracy in measuring aortic diameter have been discussed earlier. Experience and the quality of training may be relevant, as highlighted by Lefrant et al. [20]. Finally, the exactitude of the comparator technique should be queried; for example, Roeck et al. [34] utilized eight different operators and reported a single-operator coefficient of variation for thermodilution averaging 7.5%, but greater than 10% in an unspecified number of patients.

Though reported use is limited, an esophageal Doppler nomogram has also been developed specifically for pediatric patients, and subsequently validated [35]. A recent systematic review of the use in children of various Doppler techniques for measuring cardiac output found acceptable reproducibility [36].

Waveform Characteristics

Most esophageal Doppler devices display a velocity-time waveform in real time (Fig. 3). The area of the waveform (the velocity-time integral or `stroke distance') is proportional to blood flow traveling down the descending thoracic aorta assuming, as stated above, an aortic diameter that changes little during systole. Assuming proportionality between upper and lower blood flow, as validated in the studies described above, this waveform area is also proportional to left ventricular stroke volume.

Other than waveform size, further information regarding hemodynamic status can be derived from the waveform shape (Fig. 4). The peak velocity declines by approximately 1% per annum of adult life with normal values of 90-120 cm/sec in a resting 20 year old to 50-70 cm/sec in a resting 70 year old. Values falling outside the age-expected normal ranges are indicative of a hypo- or hyperdynamic circulation. The former is clearly seen in left ventricular failure while the latter is observed in conditions as diverse as sepsis and pregnancy. Peak velocity and acceleration both provide information on left ventricular contractility; for example, a positive inotrope will increase both variables while the converse is seen with myocardial depression resulting from cardiodepressant drugs or ischemia. These variables provide similar information to dP/dT data obtained from intraventricular pressure transducers. It should be stressed that neither dP/dT, peak velocity, or acceleration are `pure' measures of contractility; inotropic changes cannot occur in isolation *in vivo* due to compensatory changes in afterload and preload.

The flow time – the base of the waveform – is affected by heart rate. Systolic and diastolic time intervals are reduced with tachycardia and lengthened during bradycardia. Using a derivation of Bazett's equation, which corrects the electrocardiographic (EKG) QT interval to a heart rate of 60 bpm, the flow time can be similarly corrected by dividing it by the square root of the cycle time. Thus, for a heart rate

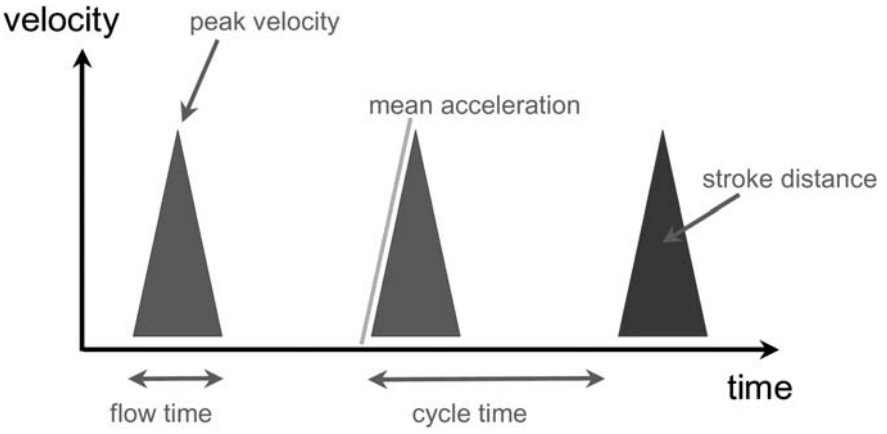

Fig. 3. Doppler velocity-time waveform

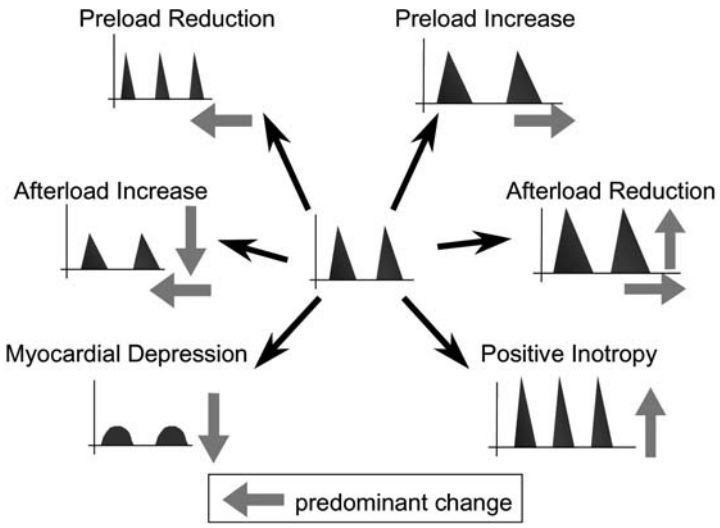

Fig. 4. Changes in waveform shape with hemodynamic maneuvers

of 60 bpm, the cycle time will be one second and the systolic flow time will be approximately a third of this. The `corrected flow time' (FTc) has a range of 0.33–0.36 sec in the normal individual. The FTc is inversely related to systemic vascular resistance; thus, in vasoconstricted states such as hypovolemia, excess vasopressor therapy or hypothermia, the FTc narrows, while in low resistance conditions such as sepsis, the FTc widens [37]. The FTc has been found to be superior to wedge pressure measurement in optimizing preload and cardiac output in several studies [24, 27, 38].

The above characteristics of the waveform can be used both diagnostically and therapeutically. Diagnostic information is provided by the height of the waveform, and the slope of the upstroke, which give an indication of contractile status, while the width (corrected for heart rate) describes the degree of constriction or dilatation within the circulation [37, 38]. Moderate or severe aortic regurgitation is denoted by a reverse blood flow component occurring throughout diastole. The flow equivalent of `pulsus paradoxus' or `respiratory swing' is clearly seen in conditions such as severe asthma or pericardial tamponade. A narrow, reduced-size waveform in conjunction with a raised central venous pressure (CVP) suggests a major obstruction within the heart or pulmonary tree, for example pulmonary embolus, tension pneumothorax, right ventricular infarction, or pericardial tamponade. The monitor also provides on–line support for clinical management as the cardiovascular effects of a maneuver can be immediately appreciated. For example, a Starling-type ventricular function curve can be constructed by viewing the response to fluid challenges (Fig. 5). Optimal filling is reached at the point where no further improvement occurs in stroke volume [38]. If evidence of organ perfusion persists, alternative therapies should be sought, for example vasodilators or inotropes. Subsequent re-challenge with fluid may then be necessary. Similarly,

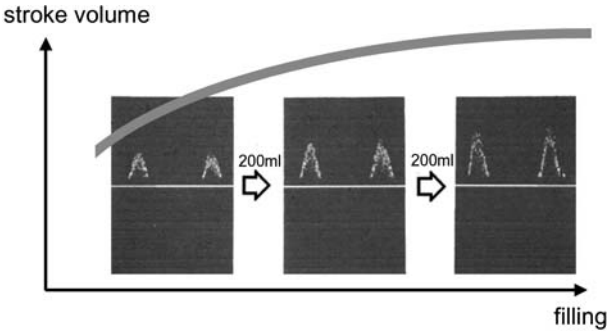

Fig. 5. Starling-type ventricular function curve to repeated 200 ml fluid challenges

other challenges can be attempted, such as altering the level of positive and-expiratory pressure (PEEP) [39] or other ventilator settings. Any improvement (or deterioration) can be immediately viewed.

Perioperative Outcome Studies

To my knowledge, the esophageal Doppler technique is unique among `non-invasive' cardiac output monitoring technologies in that it is the only device successfully utilized in prospective, randomized controlled perioperative trials to guide hemodynamic management and demonstrate an improvement in outcome. The CardioQ (or its ODM/EDM forerunner) has been used intraoperatively in cardiac surgical [40], femoral neck repair [41, 42] and abdominal surgical patients [43, 44], and postoperatively after cardiac surgery [45], with the control group in each study randomized to standard practice either with [40, 42–45] or without [41] a central venous catheter. All used a Starling-challenge type regimen to optimize fluid loading using the Doppler probe, giving an average 500–800 ml of additional colloid over the study period. This was sufficient to reduce postoperative complications in all of the studies, and significantly reduce hospital stay in five of them (Table 2). Importantly, the postoperative cardiac surgical study [45] was conducted by nurses following a treatment algorithm.

Other Reported Applications

The ease of use of the device has led to a number of reported applications in the operative room, ICU, and emergency room. Perioperative hemodynamic monitoring has been performed during laparoscopy [46, 47], aortic aneursym repair [16], and off-pump cardiac bypass [48]. In the ICU, a series of case studies has been reported, as has the hemodynamic monitoring of PEEP optimization [39]), manual hyperinflation during physiotherapy [49], and lung recruitment maneuvers [50]. An observational study by Poeze et al in cardiac surgical patients [51]

Table 2. Perioperative outcome studies

Surgical group	Ref	n	Hospital stay (median unless stated)		p value	% reduction in stay
			Control	Doppler-guided		
Cardiac surgery	[40]	60	10.1	6.4	<0.05	37
Femoral neck repair	[41]	40	20	12	<0.05	39
Femoral neck repair	[42]	59	16.7 (*)	12.5 (*)	<0.05	25
Abdominal surgery	[43]	100	7 (*)	5 (*)	0.03	29
Abdominal surgery	[44]	57				
Post-operative cardiac surgery	[45]	173	9	7	0.02	22

*= mean

revealed that a low stroke index immediately upon admission to the ICU was the best indicator of a poor outcome, and that specificity and sensitivity was even higher at 4 hours in those patients whose stroke index had fallen. Studies in the ICU [28] and emergency room [52] have highlighted the inaccuracy of clinician estimates of cardiac output and volume status using clinical signs alone.

Conclusion

Esophageal Doppler monitoring of aortic blood flow is a quick and simple technique that, with a relatively short period of training, takes minutes to insert and perform. Correct signal acquisition is easy to achieve and recognize and, from both the size and shape of the waveform, decisions on fluid therapy, inotrope, pressor and dilator usage, and ventilator settings are facilitated. In many ICUs this is now being undertaken by nurses, thus obviating the need for clinician availability and expertise. This will hopefully aid identification and prompt correction of any hemodynamic deterioration. The perioperative studies show that Doppler-guided optimization of fluid loading – a simple and cheap intervention – will significantly impact upon outcome and hospital stay in the high-risk surgical patient, presumably via reduction of any tissue oxygen debt, cytokine and sympathetic activation.

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Splanchnic Blood Flow

J. Creteur

Introduction

The splanchnic region may be at a higher risk of ischemia than other parts of the body. When cardiac output decreases, adaptive mechanisms favor blood flow redistribution to the brain and heart so that splanchnic blood flow may be the first to decrease and the last to recover during resuscitation. Furthermore, ischemia may occur in the splanchnic area not only when splanchnic blood flow is reduced, but also when hepatosplanchnic metabolism is markedly increased, potentially leading to a mismatch between oxygen demand and oxygen supply in this region [1]. This situation is typically found in sepsis. Periods of gut ischemia may cause the release of inflammatory cytokines and bacterial translocation, thereby causing damage in remote organs [2–5]. Gut hypoperfusion is often suspected in critically ill patients but identifying it can be difficult. The usual diagnostic tools, such as echography or computed tomography (CT) scan, are not sensitive enough and can only detect extreme situations. Global hemodynamic measurements are commonly performed in critically ill patients and provide essential information, but lack the sensitivity to detect gut hypoperfusion. Since the crucial role of splanchnic ischemia in the pathogenesis of multiple organ failure has been promoted [6], medical literature relating to critically ill patients emphasizes the need for a monitoring tool able to detect gut ischemia. Such a system may help minimize or prevent episodes of splanchnic ischemia, by identifying earlier and more accurately those patients at high risk of ischemic organ failure and death, especially when conventional indicators are normal. Such a monitor should then also be able to guide therapy and, thereby, improve the outcome of critically ill patients.

Measurements of Splanchnic Blood Flow and Oxygen Transport

Human studies concerning total hepatosplanchnic blood flow are relatively scarce, owing to methodological difficulties of quantitative measurement. Direct measurement of blood flow in this region is virtually impossible without surgery for obvious anatomical reasons: there are multiple sites of influx and efflux, and portal venous and hepatic arterial blood are mixed within the liver. Therefore,

such measurements are presently used exclusively for clinical research. However, the following techniques are available:

Pulsed Doppler Ultrasound Flowmetry

This technique allows the quantification of portal venous and/or hepatic arterial blood flow, either non-invasively [7] or via implanted Doppler probes [8]. In contrast to laser Doppler flowmetry, the ultrasound technique yields absolute flow values in ml/min. Nevertheless, important limitations have to be noted. First, the calculation of regional blood flow crucially depends on the correct measurement of the blood vessel diameter. In addition, this technique can only estimate blood flow, and, hence, does not allow the assessment of oxygen transport parameters.

Mucosal Laser Doppler Flowmetry

The intestinal mucosal blood flow can be assessed by laser Doppler flowmetry [9]. The magnitude of the Doppler shift in the illuminated tissue depends on the product of the number of moving red blood cells and their velocity. This well-known effect can be applied to a laser-produced monochromatic beam in order to measure blood flow within the gut mucosa. The optical probe employed normally has a spatial resolution of 1 mm, and therefore the measurements theoretically only reflect surface (i.e., mucosal) blood flow. The laser Doppler probe can be placed in the stomach using an endoscopic tube [10]. Although this method is probably not useful for providing absolute tissue blood flow, it is reliable for assessing relative changes in gastric or gut mucosal perfusion [9, 11].

The drawbacks of this method need to be addressed. Due to its small spatial resolution, this technique cannot take into account spatial heterogenity of perfusion described, for example, in sepsis. Spatial variation can only be taken into account if measurements are recorded at various mucosal sites. Additional technical problems include the uncertainty of the volume of tissue in which local blood flow is measured as well as the difficulty in calibrating the laser mucosal blood flow meter in absolute units and the manual problem of maintaining gentle contact between the optical probe and the tissue without excess pressure which could *per se* influence mucosal perfusion [9, 10].

Estimation of Hepatosplanchnic Blood Flow Using the Fick Principle and Measurement of Hepatic Venous Oxygen Saturation

Total hepatosplanchnic blood flow can be estimated from the hepatic uptake of substances exclusively metabolized by the liver and distributed in the plasma [12]. Indocyanine green (ICG) seems to be preferable to bromosulphthalein since it has fewer adverse effects and undergoes less removal by extrahepatic tissues. The steady-state infusion technique based on the Fick principle has been refined for application in intensive care by Uusaro et al [12]. After an intravenous bolus ICG

infusion of 12 mg, a continuous infusion of 1 mg/min is administered for 30 min. After 20, 25, and 30 min of ICG infusion, arterial and hepatic venous blood samples are taken simultaneously. The plasma ICG levels are measured by spectrophotometry and determined using a stamping curve obtained by dilution of a known ICG quantity in a control serum. According to Uusaro et al [12], the measurement of hepatosplanchnic blood flow by this technique has a variation coefficient of 7 ± 1%. According to the Fick principle, the hepatosplanchnic blood flow (HBF) can then be calculated as:

$$\text{HBF (ml/min)} = \text{ICG administration rate (mg/min)} / (Ca - Chv) \times (1 - Hct)$$

where Ca and Chv are the systemic arterial and suprahepatic venous ICG blood concentration (mg/ml), respectively, and Hct the hematocrit of the blood sample.

An alternative approach to this method for the estimation of hepatosplanchnic blood flow is the bolus ICG dye clearance technique [13]. Nevertheless, when compared to the former, it should be noted that the bolus technique seems to yield less valid results [12]. Hepatic venous catheterization is mandatory for both techniques: first, the hepatic ICG extraction may vary widely in individual patients since hepatic ICG extractions between 15 and 95% have been reported in disease states [12]; second, ICG extraction is influenced by therapeutic interventions such as infusion of dobutamine or other vasoactive compounds resulting in changes of up to 50% in either direction [12]; finally, ICG extraction must always exceed the limit of 10%, which is necessary for the valid application of this method [12].

For clinical reasons due to its easier applicability, ICG clearance without hepatic venous catheterization, can be used as a bedside parameter of hepatic function and perfusion. In principle, after a bolus injection, arterial ICG concentrations will fall in a monoexponential manner. By logarithmic transformation of the typical indicator dilution curve, the decay of concentration is characterized by a line with negative slope, which permits the determination of the ICG concentration at baseline by backward extrapolation of the line. For simplification of this approach, the initial ICG concentration is normalized to 100% and the negative slope of this line is expressed as percentage change per time. The slope of the line is called the ICG plasma disappearance rate (PDR) which is expressed in %/min. Normal values for ICG clearance and ICG-PDR are considered to be higher than 700 ml/min.m² or 18%/min, respectively. Since serial blood sampling for extracorporeal ICG concentration analysis is expensive and time consuming, bedside assessment of ICG-PDR has become available with the use of a transcutaneous densitometric device. Sakka et al. [14] have analyzed the agreement between invasive arterial (fiberoptic based) and transcutaneous (pulse densitometric) assessment of ICG-PDR in critically ill patients. They concluded that non-invasive assessment was a reliable alternative [14].

Hepatic venous catheterization with the measurement of hepatic venous hemoglobin oxygen saturation (ShO_2) alone may assume particular importance for the monitoring of the hepatosplanchnic region in the critically ill. The gradient (DSO_2) between mixed-venous oxygen saturation (SvO_2) and ShO_2 may more specifically reflect splanchnic ischemia than ShO_2 alone, since, in some cases, changes in ShO_2 can simply parallel changes in SvO_2.

The measurement of ShO_2 may be useful to evaluate the adequacy of splanchnic blood flow [15]. Several studies [16–18] have documented that DSO_2 is commonly increased in septic patients. In addition, an elevated gradient between SvO_2 and ShO_2 is suggestive of hepatosplanchnic VO_2/DO_2 dependency [17].

The monitoring of ShO_2 is invasive, involving the insertion of a hepatic catheter. In addition to problems associated with vessel puncture and catheter-related infections, hepatic vein catheterization could be associated, theoretically, with complications, including ventricular arrhythmia due to catheter mobilization, hepatic vein thrombosis, or rupture. There are, however, no data reporting such complications with the use of these catheters in patients with various medical conditions (e.g., bleeding varices, sepsis, pulmonary embolism) or surgical conditions (e.g., cardiac surgery, liver surgery, including transplantation). In a series of >100 hepatic vein catheterizations, Uusaro et al. [12] did not report any adverse event. We have also inserted >100 catheters in patients with severe sepsis and have not observed any complications (unpublished data). Hence, it appears that, under strict medical supervision, the use of these catheters is safe.

Catheters are generally placed using fluoroscopic guidance but irradiation is limited, since the catheter is usually rapidly inserted. However, not all centers have access to this facility at the bedside. Ultrasound techniques (usually using echocardiographic equipment), which are safe and available in almost every intensive care unit (ICU) or operating room, can be used as an alternative but require relevant technical skills.

Several studies [17–19] have suggested that this technique can help identify a subset of patients with distinct regional hemodynamic patterns. Ruokonen et al. [19] observed in patients with acute pancreatitis that the response of splanchnic blood flow during a dobutamine infusion could not be predicted by changes in cardiac output. We [17] also observed that hepatosplanchnic oxygen uptake and oxygen supply covariance occurred only in patients with severe sepsis who had a DSO_2 of >10%, although changes in whole body DO_2 and VO_2 were similar in all patients.

The use of ShO_2 monitoring to identify patients with an adverse outcome is still a matter of debate. In some specific patient populations, ShO_2 may be related to outcome. After extended hepatectomy, Kainuma et al. [15] observed that the magnitude and the duration of decrease in ShO_2 were correlated with postoperative liver dysfunction and mortality rate. Takano et al. [20] and Matsuda et al. [21] also observed that ShO_2 monitoring was useful to predict outcome after the Fontan operation was performed during cardiac surgery in patients particularly at risk for developing right ventricular failure. In a study involving a small group of patients with sepsis, Trager et al. [22] reported that ShO_2 was lower in nonsurvivors than in survivors. However, in our experience, only the few patients with a markedly reduced ShO_2 have a higher mortality rate [18]. Hence, the prognostic value of ShO_2 in critically ill patients remains to be demonstrated.

While the benefit of `normalization' of ShO_2 remains questionable, it seems reasonable to try to avoid further deterioration of hepatosplanchnic oxygenation. Measurements of ShO_2 have identified the deleterious effects of some catecholamines [16, 23–26] and of the application of positive end-expiratory pressure (PEEP) [22] on hepatosplanchnic oxygenation. Epinephrine decreased fractional splanch-

nic blood flow and ShO_2 compared with norepinephrine alone or combined with dobutamine [24]. Although the effects of adrenergic agents are variable and often unpredictable, dobutamine usually increases hepatosplanchnic blood flow and ShO_2 [16, 25, 26]. In addition, measurement of oxygenation parameters enables us to assess the effects of these agents not only on hepatosplanchnic blood flow but also on cellular metabolism. While moderate levels of PEEP do not affect ShO_2, PEEP levels of >10 cmH_2O can decrease ShO_2 [22]. Hence, ShO_2 monitoring could help to guide fluid infusion, adrenergic support, or PEEP administration. Continuous monitoring of the ShO_2 with a fiberoptic catheter may yield valuable on-line information for the evaluation of therapeutic interventions.

Unfortunately, this measurement reflects total hepatosplanchnic blood flow, including not only portal, but also hepatic arterial blood flow. Hence, gut hypoperfusion as assessed by gastric tonometry can still occur even when ShO_2 is maintained [27]. Ideally portal blood should be sampled, but this is not feasible in clinical practice. Hepatic vein lactate measurements [28] can also be used to detect splanchnic hypoxia, but similar limitations apply to these measurements. In addition, lactate measurements can be influenced by other factors than tissue hypoxia [29].

Nevertheless the limitations of this method must not be underestimated: several studies have shown that due to the particular role of the liver, the metabolic activity of the hepatosplanchnic area cannot be inferred from oxygen uptake/supply relationships [25, 30].

Gastric Tonometry

Because the stomach is a relatively easy organ to access, gastric tonometry is a minimally invasive means to determine perfusion to the stomach and may provide crucial information about perfusion to the rest of the splanchnic bed. Gastric tonometry attempts to determine the perfusion of the gastric mucosa using measurements of local PCO_2 [31]. CO_2 diffuses from the mucosa into the lumen of the stomach and subsequently into the silicone balloon of the tonometer. After an equilibration period, the PCO_2 within the balloon is supposed to be equal to the gastric mucosal CO_2 ($PgCO_2$) and can be measured by one of two means: (1) saline tonometry, where saline solution is anaerobically injected into the balloon, sampled after an equilibration period and measured using a blood gas analyzer; or (2) air tonometry, where air is pumped through the balloon and the PCO_2 is determined automatically by an infrared detector on a semi-continuous basis. By assuming that arterial bicarbonate equals mucosal bicarbonate, intramucosal pH (pHi) can be calculated using the Henderson-Hasselbalch equation. Unfortunately, this last assumption is incorrect. Simulations of mesenteric ischemia indicate that use of the arterial bicarbonate will result in errors in the determination of gastric pHi [32]. In addition, acute respiratory acid/base disturbances will introduce errors in the calculation of pHi [33]. Metabolic acidosis (and its subsequent decrease in arterial bicarbonate), as found in renal failure, can lead to the calculation of a low pHi value in the absence of any gut hypoperfusion. Consequently, pHi has been replaced by the PCO_2 gap (the difference between gastric mucosal

and arterial PCO_2) as a better way to determine the adequacy of the perfusion to the stomach [34, 35].

There are a number of factors that may cause errors in the determination of gastric PCO_2 ($PgCO_2$), and these must be taken into account. If saline tonometry is used, some blood gas analyzers will consistently and dramatically underestimate the PCO_2 in the saline solution [36]. Use of buffered saline solutions will improve the accuracy of the PCO_2 determination, but the time for a steady state to be reached in the tonometer is increased [37]. Gastric acid secretion may also increase CO_2 production by titration of luminal acid with bicarbonate in the gastric mucus or refluxed duodenal contents, thereby introducing additional errors into determination of the PCO_2 gap. Use of H_2-blockers will reduce this error in healthy volunteers [38], but not in critically ill patients [39]. Sucralfate does not appear to interfere with determination of gastric pHi [40]. Gastric but not duodenal feedings will cause a false reduction in gastric pHi (or increase in $PgCO_2$) [41, 42]. Practically, in view of these methodological problems, the use of saline tonometry should be abandoned, and the use of automated gas tonometry encouraged. The controversy persists on the usefulness of H_2-blocker administration during gastric tonometry monitoring, but the main limitation for the routine continuous use of such a technique is the impossibility of insuring the reliability of $PgCO_2$ values when patients are fed through conventional naso-gastric tubes.

Interpretation of the PCO_2gap

According to the Fick Equation, the determinants of the PCO_2gap are mucosal blood flow and mucosal CO_2 production (VCO_2), so that PCO_2gap represents a good marker of the adequacy between local blood flow and metabolism. In healthy volunteers, a PCO_2gap of 8 mmHg seems to represent an adequate balance between mucosal CO_2 production and regional perfusion [43]. For a constant VCO_2, the decrease in gastric mucosal blood flow will lead to a decrease in the mucosal CO_2 washout and a subsequent increase in $PgCO_2$. When oxygen delivery to the mucosa is reduced below metabolic demand, acidosis ensues. Under anaerobic conditions, H+ ions are generated by two mechanisms: 1) excessive production of lactic acid related to the accelerated anaerobic glycolysis, since pyruvate can no longer be cleared by the Krebs cycle; 2) hydrolysis of adenosine triphosphate (ATP) and adenosine diphosphate (ADP). The protons generated will then be buffered by HCO_3^- ions into the cell so that CO_2 will be generated.

Low Cardiac Output States (Ischemic Hypoxia)

In contrast to sepsis, systemic low flow states cause splanchnic hypoperfusion with no initial change in splanchnic oxygen consumption, regardless of whether the etiology is cardiac or acute hypovolemia. By diverting blood supply mediated by sympathetic adrenergic stimulation [44], both the liver (which can redistribute an additional 1 l of blood to the systemic circulation under cardiovascular stress)

and the gut are an efficient means of ensuring that vital organs are perfused during acute hypovolemia [45, 46].

Guzman et al. [47] studied the effects on $PgCO_2$ of a reduction in oxygen delivery induced by a progressive hemorrhage in dogs. They reported a marked increase in $PgCO_2$ well before the systemic critical oxygen delivery value was reached. In this situation, increase in $PgCO_2$ could be used as an early index of hemodynamic instability.

Gastric tonometry during induced short-term hypovolemia in healthy volunteers showed a reduced gastric pHi and this resolved with resuscitation [48]. Interestingly, this was the only significant clinical indicator of hypovolemia, with heart rate, blood pressure and peripheral perfusion showing no change after a 20–25% blood volume venesection. Moreover, simulated [49] and actual [45] hypovolemia in healthy human volunteers showed that splanchnic vasoconstriction exists beyond the period of restoration of normal systemic hemodynamics after apparently adequate fluid resuscitation.

Using a canine model of cardiac tamponade, Schlichtig and Bowles [50] demonstrated that the production of CO_2 from anaerobic pathways is difficult to detect in ischemic hypoxic tissue without the use of direct or indirect measurements of tissue PCO_2 (such as gastric tonometry). Veno-arterial CO_2 gradients as global parameters could not detect localized ischemic hypoxia because the efferent venous blood flow can be high enough to wash out the CO_2 produced from the always perfused tissues and, because of the marked fall in CO_2 production from the anaerobic pathway that should occur in these circumstances, total CO_2 production can be markedly decreased [51]. Therefore, tissue to arterial PCO_2 gradients are thought to be more reliable markers of tissue hypoxia than veno-arterial CO_2 gradients [50].

One of the problems that has plagued gastric tonometry is that the value for pHi or PCO_2 where hypoxia occurs is unknown. In a canine model of cardiac tamponade, Schlichtig and Bowles [50] measured intestinal oxygen delivery and tonometric CO_2 in the jejunum and ileum. They determined that hypoxia occurred around a PCO_2gap of 25 to 35 mmHg. Therefore, between 8 and 25 mmHg, any value of PCO_2gap must be interpreted as the reflection of moderate hypoperfusion without hypoxia.

As already mentioned, during the development of low flow state, PCO_2gap increases early before the occurrence of systemic hemodynamic alterations. This property can be used to detect occult hypovolemia in an apparently hemodynamically stabilized patient. The susceptibility of the gut mucosa to any decrease in systemic blood flow can be explained by at least two mechanisms. First, splanchnic blood flow is reduced early during even minor cardiovascular alterations in an attempt to preserve blood supply to more vital organs, namely the heart and the brain. Second, the tip of the gut villus may be particularly susceptible to a reduction in blood flow, in view of the local countercurrent mechanism supplying oxygen, responsible for the presence of a PO_2 gradient between the base and the top of the villi [52].

Hypoxic and Anemic Hypoxia

Several investigators have questioned the ability of gastric mucosal PCO_2 to detect tissue hypoxia. Neviere et al. [53] reported that the increase in PCO_2gap in pigs was less pronounced in hypoxic hypoxia (decrease in PaO_2) than in ischemic hypoxia (decrease in blood flow). Similarly, the increase in PCO_2gap was blunted in anemic hypoxia in sheep [54]. This suggests that maintenance of flow limits the increase in PCO_2gap. These experimental studies demonstrate well that the principal determinant for the PCO_2gap is the blood flow. When mucosal blood flow is maintained, and despite evidence of mucosal hypoxia, PCO_2gap does not increase [53]. Therefore in this condition, a normal PCO_2gap cannot exclude severe hypoxia. Nevertheless, such severe hypoxic or anemic hypoxia is very uncommon in clinical practice.

Severe Sepsis/septic Shock

The interpretation of the PCO_2gap in sepsis is more complex. Indeed, this syndrome may be associated with coexistence of a normal or high cardiac output, inter and intra-organ blood flow redistribution, altered microcirculation and oxygen extraction capabilities. These alterations are particularly marked in the splanchnic regions and they can all interfere theoretically with the gut tissue CO_2 production and elimination.

Some argue that in the presence of high flows, the increase in PCO_2gap found in sepsis reflects metabolic alteration (endotoxin-mediated cell mitochondrial toxicity, the so-called cytopathic hypoxia [55]) more than hypoperfusion. This hypothesis was initially strengthened by experimental studies [56, 57] which reported that mucosal acidosis may occur in sepsis despite preserved or increased mucosal blood flow [56, 57] and mucosal oxygenation [56]. VanderMeer et al. [56] demonstrated in pigs that endotoxin infusion resulted in a significant increase in intramucosal hydrogen ion concentration, while mucosal perfusion, assessed by laser-Doppler flowmetry, did not change significantly, and mucosal PO_2, assessed by microelectrodes, increased significantly [56]. In a similar porcine model of endotoxic shock, Revelly et al. [57] showed that pHi was inversely correlated with mucosal blood flow suggesting that the decrease in pHi during endotoxic shock may be due to direct metabolic alterations induced by endotoxin rather than to mucosal hypoperfusion. Kellum et al. [58] did not find any correlation between PCO_2gap and portal venous blood flow or the gut lactate production during endotoxic shock in dogs.

Clinical data also cast doubt on the idea that gastric tonometry can be used as a reliable marker of hepatosplanchnic perfusion in septic patients. We [27] measured gastric PCO_2 gap, hepatosplanchnic blood flow (via ICG infusion), ShO_2, and hepatic venoarterial PCO_2 gradient in 36 patients with severe sepsis and found that the gastric PCO_2 did not correlate with the other indexes of hepatosplanchnic oxygenation. Similar findings have been found in cardiac surgery patients treated with dobutamine [59, 60].

Nevertheless, despite these conflicting results, strong evidence argues for the predominant role of a decrease in mucosal blood flow in the increase in PCO_2gap found in sepsis. Experimentally, sepsis or endotoxemia have been associated with alterations in gut mucosal oxygenation measured by PO_2 electrodes or laser-Doppler in pigs [61, 62] or in dogs [63], even when global perfusion was maintained [63]. In different models of normotensive sepsis, microcirculatory alterations at the level of the gut villi (decrease in the capillary density and/or in the number of well perfused capillaries) have been reported in rats [64–66] and in dogs [67]. Tugtekin et al. [68] demonstrated, in septic pigs, that the increased PCO_2gap was related to the heterogeneity of gut mucosal blood flow (assessed with the Orthogonal Polarization Spectral imaging technique) even though cardiac output and mesenteric blood flow were maintained.

In addition to many animal investigations, support for the notion that gastric pHi assesses local mucosal perfusion comes from a study of 17 patients receiving mechanical ventilation [69] A low gastric pHi in these patients was associated with a lower mucosal blood flow as determined by laser Doppler flowmetry compared to patients with a normal pHi. Nevière et al. [11] demonstrated in septic patients that the increase in gastric mucosal blood flow induced by a dobutamine infusion was followed by a decrease in $PgCO_2$. In hemodynamically septic patients, we [70] reported that the decrease in PCO_2gap during a dobutamine infusion occurred only in patients with inadequate hepatosplanchnic blood flow (i. e., low fractional splanchnic blood flow, suprahepatic venous oxygen desaturation). While splanchnic blood flow increased in all patients, splanchnic oxygen consumption increased only in patients presenting a dobutamine induced-decrease in PCO_2gap, which could be explained by a blood flow redistribution to the initially hypoperfused gut mucosa.

Microciculatory alterations are ubiquitous in sepsis and thus take place in all parts of the body. We have evaluated the relations between sublingual PCO_2 ($PslCO_2$) and sublingual microcirculatory alterations (assessed by the Orthogonal Polarization Spectral imaging technique [Cytoscan^R, Cytometrics, Philadelphia, PA, USA]) during resuscitation of patients with septic shock. Resuscitation maneuvers (mainly, increase in blood flow with fluid challenge and dobutamine infusion) decreased $PslCO_2$gap progressively from 40 ± 18 to 15 ± 9 mmHg (Fig. 1) and, simultaneously, increased the percentage of well perfused capillaries (%WPC) from 46 ± 13 to 62 ± 8% (both: $p < 0.05$) (Fig. 2). At baseline, there was a correlation between $PslCO_2$ and the %WPC ($r^2 = 0.80$) (Fig. 3). Even if cytopathic hypoxia occurs, the main determinant of the tissue PCO_2 seems to be microcirculatory blood flow since, first, we found at baseline a correlation between tissue PCO_2 and the %WPC, and second, the improvement in microcirculation was followed by a decrease in tissue PCO_2. Finally, it seems difficult to imagine that the increase in tissue PCO_2 found in sepsis is due only to cytopathic hypoxia in the presence of maintained tissue perfusion. First, this maintained flow should be able to clear a great part of the produced CO_2. Second, in view of the curvilinearity of the relationship between tissue PCO_2 and blood flow, changes in blood flow in normal or high values ranges should have almost no effect on $PgCO_2$, which is not the case in the majority of experimental and clinical studies.

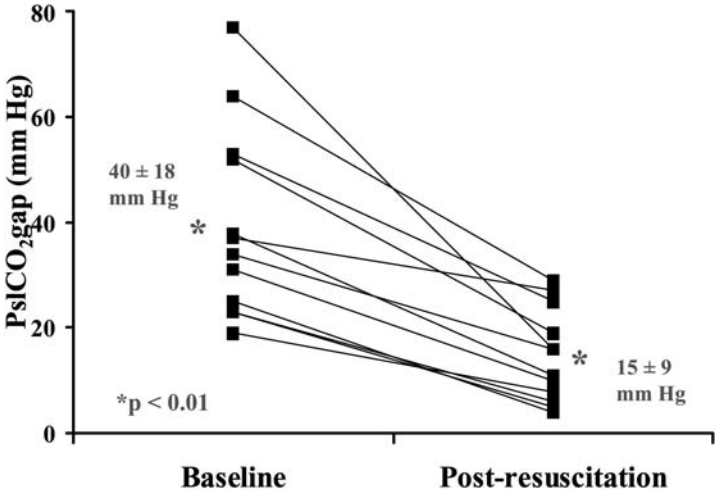

Fig. 1. Individual effect of resuscitation maneuvers on sublingual-arterial PCO_2 gradient (PslCO2gap) in 12 patients with septic shock.

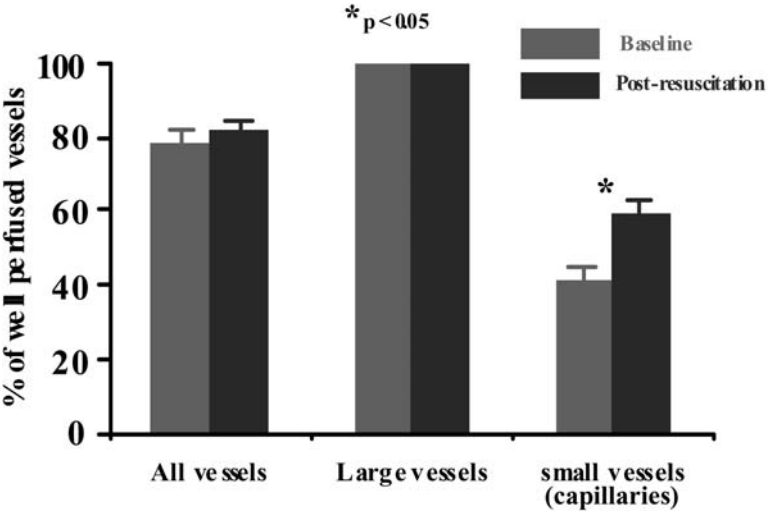

Fig. 2. Effect of resuscitation maneuvers on sublingual microcirculation (percentage of well perfused vessels) assessed by the Orthogonal Polarization Spectral imaging technique in 12 patients with septic shock.

Several studies have demonstrated that an increase in gastric mucosal PCO_2 is associated with a poor outcome in critically ill patients, including patients with septic shock [71] and postoperative patients [72]. Increased PCO_2gap, which is independent of systemic acidosis and hypercarbia, is also associated with a worse outcome in septic patients [73].

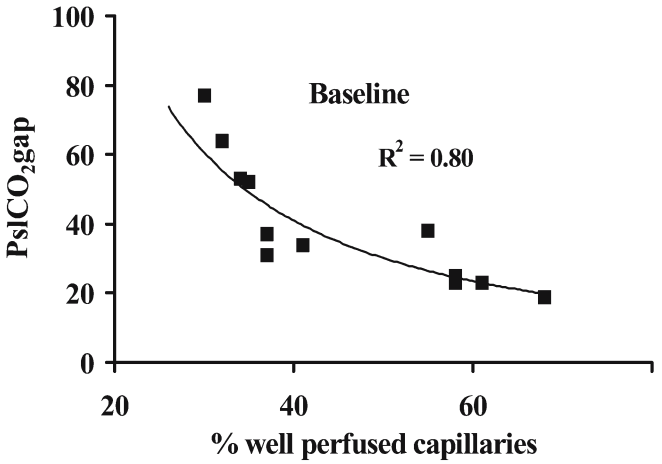

Fig. 3. Correlation between sublingual PCO_2 ($PslCO_2$) and the percentage of well-perfused capillaries at baseline.

Although gastric tonometry does not reflect global hepatosplanchnic perfusion in sepsis, it remains a valuable monitoring tool. On the one hand, if mucosal gastric acidosis in sepsis is primarily due to mucosal hypoperfusion, and if gastric tonometry, by detecting mucosal hypoperfusion, can lead to therapeutic interventions which could decrease the development of multiple organ failure, then the lack of correlation between PCO_2gap and the systemic and even the regional hemodynamic and/or oxygenation parameters argues for the use of gastric tonometry as the only method available to detect gastric mucosal hypoperfusion. On the other hand, if gastric intramucosal acidosis in sepsis is primarily due to direct metabolic cellular alterations mediated by endotoxin, gastric tonometry can provide a valuable assessment of metabolic alterations. Either scenario can account for the prognostic value of gastric tonometry that has been shown in a number of studies [71, 73–76).

Should Measurements be Confined to the Stomach?

Having established that the measurement of gastrointestinal luminal PCO_2 should be of clinical significance, the stomach has become the natural choice for the performance of gastrointestinal tonometry because of its ease of access. It is not, however, without potential sources of artifact, in particular, the production of CO_2 from the reaction of gastric acid and refluxed duodenal contents. The mid-gut or sigmoid may provide useful information [77]. The former is difficult to access and the latter technically more challenging than gastric tonometry and not without potential artifact e.g., bacterial production of CO_2. Knuesel et al. [78] specifically addressed the problem of the potential redistribution of blood flow within the splanchnic bed during an acute decrease in splanchnic blood flow, and its impact

on regional CO_2 measurements. The authors designed a complex surgical model in pigs in which a shunt between the proximal and the distal abdominal aorta generated a specific decrease in splanchnic blood flow with minor changes in cardiac output or arterial pressure. Tonometry catheters were inserted in the jejunum and in the stomach. They [78] first observed that regional redistribution between the various splanchnic organs did not occur. Accordingly, jejunal and gastric tonometric values increased similarly. This is of particular importance as some authors have reported that gastric tonometry may be less sensitive than jejunal tonometry [79]. The physiological basis for this limitation would be the hepatic arterial buffer response, which would favor celiac trunk vasodilatation and, hence, preservation of gastric perfusion. However, this compensatory response cannot be maintained and is lost in sepsis. Hence, differences between gastric and jejunal PCO_2 are probably more related to specific technical problems, such as gastroesophageal reflux, than to blood flow redistribution inside the splanchnic area.

Haldane Effect

The effect of oxygen saturation on the relationship between carbon dioxide content and PCO_2 is known as the Haldane effect: at a given CO_2 content, venous or mucosal PCO_2 increases with increasing venous or mucosal oxygen saturation. Calculating CO_2 content, Jakob et al. [79] suggested that the Haldane effect may explain the paradoxical increase in PCO_2gap together with an increase in splanchnic blood flow in patients after cardiac surgery. They effectively reported that patients increasing their PCO_2gap had a greater increase in DSO_2, which was a condition in which the Haldane effect is more likely to occur. Nevertheless, a number of methodological problems were identified [80]: the use of saline tonometry and its potential methodological drawbacks, the changes in PCO_2gap that were within the range of error, and the temperature which was not taken into account in the simplified formulas used to calculated the CO_2 content, despite the fact that patients experienced major changes in temperature. All these remarks led us [80] to conclude that the Haldane effect could not be involved in the increase in PCO_2gap that was observed in some of these patients. Knuesel et al. [78] tried to evaluate the role of the Haldane effect on PCO_2 gradients in an animal model of acute hepatosplanchnic hypoperfusion. They observed that the Haldane effect played a minor role in their results as, in most cases, PCO_2 gradients and CO_2 content differences evolved similarly.

Conclusion

Enthusiasm in new technologies has pushed clinical researchers to conduct large studies evaluating the effect of gut resuscitation on critically ill patients; perhaps these studies were conducted too early, before sufficient knowledge of the physiologic meaning of the values provided by these new technologies had been gathered. Monitoring hepatosplanchnic oxygenation might prove to be useful if one

believes that gut ischemia contributes to the development of multiple organ failure. Further studies will be necessary to determine first, the hypoxia threshold values provided by these different monitoring techniques and second, the efficacy of different treatments to correct these variables. If resuscitation guided by gut monitoring improves patient outcome, the pathophysiological link between splanchnic ischemia and multiple organ dysfunction will be established.

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Measurement of Oxygen Derived Variables and Cardiac Performance

Microcirculatory Blood Flow: Videomicroscopy

D. De Backer

Introduction

In the classical view of hemodynamic monitoring, it is usually considered that organ blood flow should be preserved as long as arterial pressure, representative of perfusion pressure of the organs, and cardiac output are maintained. Several studies have reported that alterations in regional blood flow and metabolism can also occur, especially in sepsis [1, 2]. Accordingly, the splanchnic region can be monitored via gastric tonometry, hepatic vein oxygen saturation and indocyanine green disappearance. Curiously, the microcirculation is often neglected, even though the microcirculation is the place where most of the exchanges in oxygen and nutrients between the blood and the tissues occur. The study of the microcirculation has long been difficult as it required the use of large microscopes applied on fixed tissue preparations. Recent technical developments have allowed the direct visualization of the microcirculation in critically ill patients opening the door of monitoring of the microcirculation. In this chapter we will discuss the rationale for future bedside monitoring of the microcirculation.

Specificity of the Microcirculation

The microcirculation differs from the systemic circulation by many aspects. First, capillary PO_2 is much lower than arterial PO_2, due to direct diffusion of oxygen from arteriole crossing a venule but also by consumption at the endothelial level. Second, the local hematocrit differs from the systemic hematocrit and is heterogeneous, as a consequence of the Farheus effect and of the interposition of an obligatory plasma layer in vessels of varying diameter and non-linear hematocrit distribution at asymmetric capillary branch points. Third, the control of microvascular blood flow is complex and depends both on local metabolic control and on systemic, humoral, controls. Finally, the architecture of the microvessels differs among organs, hence some organs may be more vulnerable to a decrease in global blood flow.

Evidence for Microcirculatory Alterations in Experimental Studies

Numerous experimental studies have reported that microvascular blood flow is altered in various conditions, including hemorrhagic shock [3], ischemia/reperfusion injury [4], and sepsis [5–11]. Whatever the type of injury, these alterations include a decrease in capillary density and an increased heterogeneity of blood flow. Interestingly, these alterations are more severe in septic than in other insults [12,13].

Endotoxin administration induces severe microcirculatory alterations, including severe arteriolar and venular vasocostriction in rats [6], and a decreased capillary density in dogs [14]. Severe microcirculatory alterations were also observed in normodynamic models of sepsis obtained by cecal ligation and perforation. These alterations included a decrease in the perfused capillary density and an increase in the number of stopped-flow capillaries and in heterogeneity of spatial distribution of perfused capillaries [7, 10, 15]. Of note, these microcirculatory alterations clearly differ from macrocirculatory hemodynamic alterations in sepsis, with vasoconstriction in the microcirculation in opposition to the vasodilatory state with high cardiac output.

Several mechanisms can be evoked to explain these microvascular alterations. In view of the severe vasoconstriction observed in some vessels, it seems very likely that inflammatory and vasoactive mediators such as tumor necrosis factor (TNF) [16] and endothelin [17] that can cause microvascular vasoconstriction are involved. In contrast, nitric oxide (NO) seems to have a protective role [18]. In addition, blood flow in capillaries may be impaired by the formation of microthrombi [19, 20], by the impairment of leukocyte [21] and erythrocyte [22] deformability [23], and by the adhesion of leukocytes to endothelial cells [23, 24]. It is likely that many of these mechanisms contribute to the microvascular alterations.

Implications of Microcirculatory Alterations

Microvascular alterations can have major physiopathological implications. First, the juxtaposition of well perfused and non-perfused capillaries leads to a marked heterogeneity in blood flow which may be responsible for the decrease in oxygen extraction capabilities that is observed in sepsis [14, 25, 26]. Second, microvascular alterations are associated with zones of tissue hypoxia, as suggested by the decreased intravascular PO_2 [27, 28]. Finally, the transient flow observed in some capillaries may lead to focal areas with ischemia/reperfusion injury.

One major question is whether these microvascular blood flow alterations are the initial mechanism, leading to alterations in tissue metabolism or are these alterations secondary, with flow matching direct heterogenous metabolic alterations? It is difficult to separate these two contradictory alternatives. Several arguments nevertheless suggest that microcirculatory alterations may be the triggering event. First, in a pivotal study, Ellis et al. [15] reported in a model of peritonitis induced by cecal ligation that heterogeneity of microvascular blood flow increased

with an increased number of stopped flow capillaries (from 10 to 38%) and an increase in the proportion of fast-flow to normal-flow capillaries. In addition, in the well perfused capillaries, oxygen extraction was increased, not decreased, and the VO_2 of this segment was also increased. These results argue strongly against a sepsis-induced mitochondrial dysfunction, at least in the early phase of sepsis. Indeed a primary mitochondrial dysfunction would have been accompanied by a decreased VO_2 and oxygen extraction in this segment. Similarly, Ince et al. [27] reported that microvascular PO_2 is decreased in sepsis, which is incompatible with primary metabolic alterations. This suggests that the decrease in extraction capabilities that is observed in sepsis is related to blood flow heterogeneity but not to impaired capacities of the tissues to use oxygen. Second, we observed that the severity of alteration in the sublingual microcirculation was inversely related to sublingual PCO_2 and that both alterations can be reversed [29]. If flow matched metabolism, PCO_2 would not have been increased in these patients. Altogether these observations suggest that microcirculatory alterations are involved in the pathophysiology of sepsis-induced organ dysfunction and do not match metabolic alterations, at least in the early phases of sepsis.

Methods to Investigate the Microcirculation in Critically Ill Patients

Most of the experimental studies were performed using intravital microscopy, the gold standard technique for studying the microcirculation. Unfortunately, this technique cannot be used in humans, as large microscopes are generally applied on a fixed tissue preparation while fluorescent dyes are infused. Alternative methods have been used in humans, including phlethysmography, videomicroscopy of the nailfold area, and laser Doppler techniques. An extensive review of the available techniques can be found elsewhere [30]. Nailfold videomicroscopy uses microscopes applied on a finger that is fixed under its focus. Unfortunately, the nailfold area is probably not the best area to study in critically ill patients. This area is very sensitive to changes in temperature. Ambient temperature can be controlled but not body temperature. In addition, peripheral vasoconstriction can also occur during chills and acute circulatory failure and can even be promoted by the use of vasopressor agents. Hence, this area is of limited interest in critically ill patients. Laser Doppler techniques have been used frequently in critically ill patients. The advantage of this technique is that it can be applied on various tissues and can even be inserted in the upper digestive tract through a nasogastric tube. Laser Doppler provides measurements of blood flow in relative units (mV), accordingly only relative changes to baseline can be assessed. However, the major limitation of this technique is that it does not take into account the heterogeneity of microvascular blood flow, the measured parameter representing the average of the velocities in all the vessels included in the investigated volume (~1 mm^3). Phlethysmographic techniques have similar limitations.

Orthogonal Polarization Spectral (OPS) imaging is a non-invasive technique that allows the direct visualization of the microcirculation [31]. The device is composed of a small camera and a few lenses, is small and can be used easily at the

bedside. Polarized light illuminates the area of interest, the light is scattered by the tissue and collected by the objective lens. A polarization filter (analyzer), oriented orthogonal to the initial plane of the illumination light, is placed in front of the imaging camera and eliminates the reflected light scattered at or near the surface of the tissue that retains its original polarization. Depolarized light scattered deeper within the tissues passes through the analyzer. High contrast images of the microcirculation are formed by absorbing structures (e.g., blood vessels) close to the surface that are illuminated by the depolarized light coming from deeper structures. Due to its specific characteristics, this device can be used to visualize the microcirculation in tissues protected by a thin epithelial layer, such as mucosal surface. In critically ill patients, the sublingual area is the most easily investigated mucosal surfaces. Other mucosal surfaces include rectal and vaginal surfaces, which are of limited accessibility, and ileal or colic mucosa in patients with enterostomies. Images can also be generated in eyelids and in the nailfold [32].

The use of OPS imaging techniques to visualize the microcirculation has been validated against standard techniques. In various animal models, vessel diameters, functional capillary density, and vessel blood flow were similar with OPS imaging and standard intravital fluorescence videomicroscopy [31, 33–35]. In human healthy volunteers, the agreement in the measurement of capillary density and red blood cell velocity in the nailfold area was excellent between OPS imaging and capillaroscopy [32]. Unfortunately, a quantitative approach cannot be used for observations of the sublingual microcirculation in critically ill patients, due to small movements (especially respiratory movements). Hence, we [36] developed a semi-quantitative method to determine capillary density and the proportion of perfused capillaries. The investigation of the sublingual microcirculation requires a collaborative or sedated patient, and the absence of bloody secretions in the mouth.

Microvascular Blood Flow is Altered in Critically Ill Patients

Using videomicroscopy of the nailfold area, Freedlander et al. [37] reported in 1922 that capillary stasis occurred. However, these observations are quite old, and the definition of shock state, although lethal, may be questioned in the absence of cardiovascular and respiratory support. More recently, various investigators [23, 38] used laser Doppler to investigate skin and muscle microvascular blood flow and observed that basal blood flow may be decreased or increased compared to healthy volunteers. These studies are nevertheless difficult to compare as skin microvascular blood flow differs according to the site investigated [39]. More importantly, the increase in microvascular blood flow was blunted after partial occlusion [40].

Using the OPS technique in the sublingual area of patients in circulatory failure, we [36, 41] observed that microcirculatory alterations are frequent in shock states. We investigated 50 patients with severe sepsis (n = 8) and septic shock (n = 42) within 48 hours of the onset of sepsis. Compared to young healthy volunteers and age matched controls (patients before cardiac surgery), septic patients presented a decrease in capillary density (4.5 [4.2 – 5.2] n/mm vs 5.4 [5.4 – 6.3] n/mm in controls, $p<0.05$) and a decrease in the proportion of the perfused capillaries

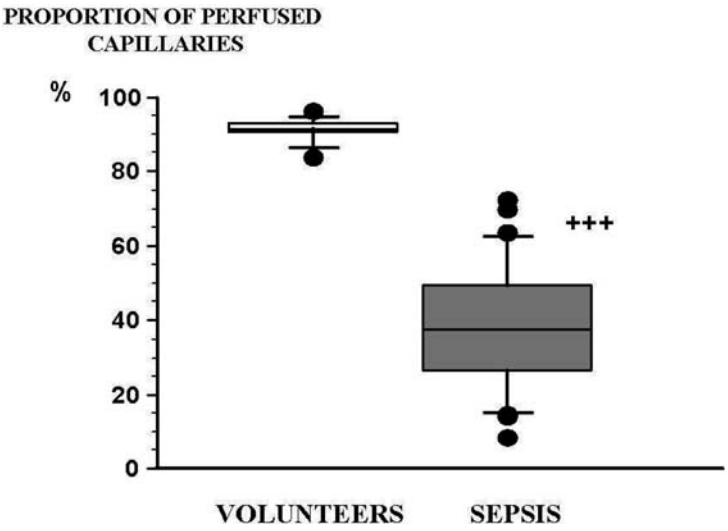

Fig. 1. Proportion of perfused capillaries in patients with sepsis. +++p<0.001 vs volunteers Modified from [36] with permission

(Fig. 1). An increase in the number of capillaries with stagnant flow and in the number of capillaries with intermittent flow equally contributed to the decrease in capillary perfusion (32 [27–39]% and 32 [22–37]%, respectively, in septic patients vs 4 [3–5]% and 5 [4–6]% in controls). Interestingly, these alterations were fully reversible: after topical application of a high dose of acetylcholine the proportion of perfused capillaries increased from 44 [24–60]% to 94 [77–96]%, p<0.01). This suggests that these alterations are not fixed and that the microcirculation can be manipulated. Current studies are ongoing to determine the effects of various interventions on the microcirculation in humans. Vasodilators may also be of value [42]. Recently, Spronk et al. [43] reported that nitroglycerin improved the sublingual microcirculation; unfortunately it also induced a marked hypotension. In addition the potential cytotoxic effects of NO donors should not be neglected so that further studies are needed before this intervention can be translated into clinical practice.

Microcirculatory alterations can also be observed in other conditions than sepsis. We [41] observed that the proportion of perfused capillaries was also decreased in patients with severe heart failure and cardiogenic shock (Fig. 2). These alterations were also fully reversed by the topical application of acetylcholine. Microvascular blood flow can also be altered after cardiac surgery. In 28 patients submitted to cardiac surgery, we observed that the proportion of perfused capillaries decreased after cardiopulmonary bypass (from 88 [87–88] to 54 [51–56], p<0.05), and remained altered during the first hours of admission in the intensive care unit (ICU), and almost normalized the day after surgery [44]. However, these alterations were far less pronounced than in patients with septic or cardiogenic shock.

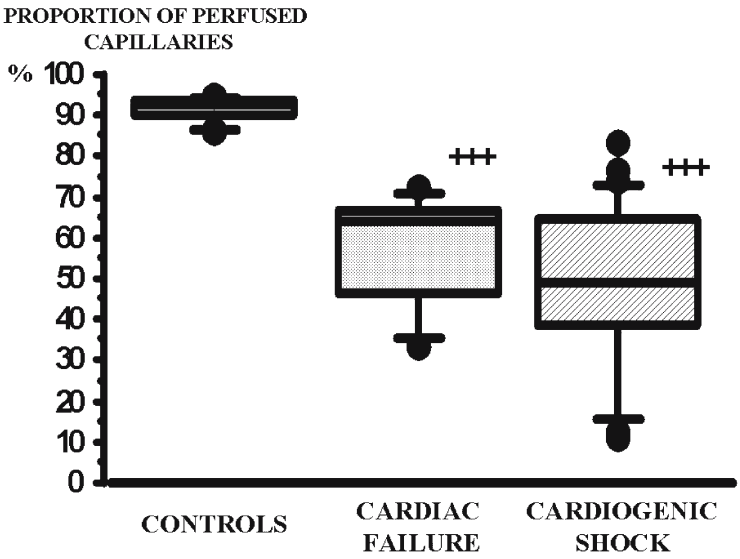

Fig. 2. Proportion of perfused capillaries in patients with severe heart failure and cardiogenic shock. +++p<0.001 vs controls. Modified from [41] with permission

Influence of Systemic Factors?

One major question is whether these microvascular blood flow alterations are influenced by systemic factors. If yes, monitoring the microcirculation may be useless, as these alterations may be inferred from more easily applicable monitoring techniques.

As microcirculatory and macrocirculatory alterations usually coexist, it is quite difficult to separate the influence of both factors. Experimental studies suggest that microcirculatory alterations can occur even when blood flow or perfusion pressure are maintained [12, 13, 45]. In a hyperdynamic model of endotoxic shock, Tugtekin et al. [45] observed that the number of unperfused and heterogeneously perfused gut villi was increased. Similarly, Nakajima et al. [13] reported that endotoxin decreased the density of perfused villi and red blood cell velocity in perfused villi, independent of the effects on arterial pressure.

Data in patients are scarcer. Using laser Doppler in patients with septic shock, LeDoux et al. [46] reported that skin blood flow was not affected when mean arterial pressure was increased from 65 to 85 mmHg with norepinephrine. Using the OPS technique on the sublingual microcirculation in 96 patients with severe sepsis and septic shock, we observed that the severity of microcirculatory alterations was not related to arterial pressure, the use of vasopressors, or cardiac index [47].

Remaining Questions

One important question is whether the microcirculatory alterations are similar and if they occur simultaneously and at the same degree of severity in the various microvascular beds. Animal models have clearly shown that similar alterations occur in striated muscles [7, 15], small bowel mucosa [10], liver [48], pancreas [49], and skinfold [4]. However, none of these models simultaneously investigated different organs, hence the severity and the time course of these lesions may vary between the different organs. This may be of particular importance for the bedside monitoring of the human microcirculation, especially as the sites accessible are limited. Preliminary data in humans nevertheless suggest that similar microvascular alterations can be observed in the sublingual area and on ileostomies and colostomies [50].

Link Between Microcirculatory Alterations and Outcome

The alterations in microvascular blood flow can have important implications. In rats submitted to 60 min of severe hemorrhage with subsequent restoration of blood volume, Zhao et al. [3] observed that microvascular alterations were more severe in rats that subsequently died compared to survivors, despite similar whole-body hemodynamics. Similarly, Kerger et al. [51] reported that functional capillary density and interstitial PO_2 in the hamster skinfold were lower in non-survivors during hemorrhage and after resuscitation. Hence, in animal models microcirculatory alterations have been related to outcome.

In our recent study in patients with severe sepsis [36], we observed that the severity of microcirculatory alterations was more pronounced in non-survivors than in survivors. We further [52] daily investigated the sublingual microcirculation in a cohort of 49 patients with septic shock up to shock resolution or death, and we observed that microvascular blood flow rapidly resolved in survivors but remained altered in non survivors, whether these patients died in shock or from multiple organ failure after shock was resolved. In survivors, microcirculatory alterations improved even though these patients were still on vasopressors for several days. In addition, the observation that microvascular alterations improved by more than 7.5% within the first 24 hours of observation was an excellent predictor of outcome (71% survival rate above this cut-off value versus only 19% below it). These data suggest that microvascular blood flow alterations are implicated in the pathophysiological process involved in the development of multiple organ failure and death in septic patients.

Conclusion

The microcirculation is a key element in tissue oxygenation, as it is the place where most oxygen and nutrient exchange take place. Multiple experimental studies have demonstrated that microvascular blood flow is altered in hemorrhage, ischemia-reperfusion injury and especially in sepsis. These alterations can

be observed in various organs and are characterized by an increased number of absent or intermittently perfused capillaries and heterogeneity in blood flow. The study of the microcirculation in humans has long been difficult. Laser Doppler or phlethysmography techniques do not take into account heterogeneity of blood flow, and hence are not able to detect these alterations. The development of OPS imaging techniques has allowed the direct visualization of the human microcirculation. Using OPS techniques we demonstrated that the sublingual microcirculation of patients with acute circulatory failure is markedly altered and that these alterations are related to outcome. These alterations are not influenced by arterial pressure or vasopressor agents and cannot be detected by the classical monitoring devices. Monitoring the microcirculation of patients with acute circulatory failure may help to detect patients in whom further interventions may be required.

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Mixed Venous Oxygen Saturation (SvO_2)

J. B. Hall

Introduction

Physiologic parameters should not be monitored in critically ill patients simply because they can be monitored, but when monitoring the parameter meets the following criteria:

1) there is a sound pathophysiologic rationale for perturbations in the given measurement in the course of illness;
2) the parameter can be reliably measured under typical conditions;
3) the monitored variable offers information not available from more routine monitoring and interventions exist which can influence the monitored variable; and
4) titrating therapy in accord with this monitored variable has a salutary effect on outcome.

This chapter will evaluate the evidence for the utility of monitoring mixed venous oxygen saturation (SvO_2) in critically ill patients with regard to each of these criteria. Comment will be made on the relationship of superior venal caval oxygen saturation ($ScvO_2$) to SvO_2, since this has been used as a surrogate measure for SvO_2 in the most definitive trials linking monitoring to cardiovascular intervention.

Sound Physiologic Rationale?

A model for conditions of reduced oxygen delivery (DO_2) in critical illness and the response of peripheral tissues to such reductions is shown in Figure 1 [1]. As DO_2 is reduced – in critical illness by hypoxemia (hypoxic hypoxia), anemia (anemic hypoxia), decreased cardiac output (stagnant hypoxia), or any combination thereof – oxygen consumption (VO_2) is maintained by virtue of peripheral tissues taking up a greater fraction of the oxygen delivered. At a sufficiently low level of delivery, approximately 7 ml/kg/min in this example – VO_2 becomes dependent on DO_2 and further reductions in DO_2 are associated with a fall in VO_2. This delivery-dependent limb of the VO_2-DO_2 relationship is characterized by lactic acidosis, organ dysfunction, physiologic instability, and death.

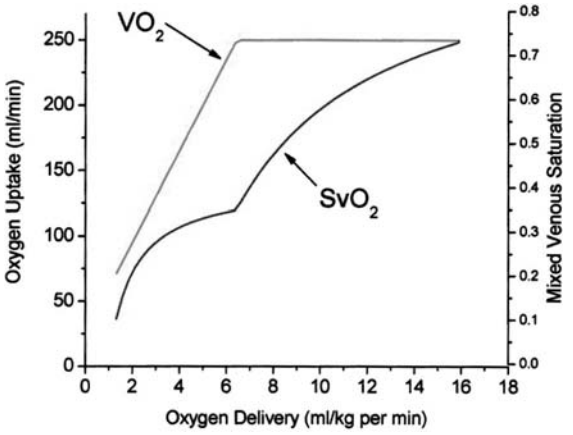

Fig. 1. The relationship of oxygen delivery (DO_2) to oxygen uptake (VO_2). Note that as DO_2 is reduced, as for example in a patient with a falling cardiac output, VO_2 is maintained. This is achieved by tissues taking up a greater fraction of the oxygen available to them, and is signaled by a fall in mixed venous oxygen saturation (SvO_2)

As is shown in this figure, SvO_2 falls as DO_2 is diminished, reflecting tissue uptake being maintained, extraction fraction (VO_2/DO_2) rising, and arterio-venous content difference widening. $_{SvO2}$ decreases because oxygen extraction increases. Importantly, this model predicts an early fall in SvO_2 as DO_2 begins to fall, suggesting that SvO_2 could provide an early signal to determine the adequacy of delivery. Oxygen extraction fraction is not maximal at the critical delivery point – it continues to increase as DO_2 falls below the critical point. However, the increase in extraction fraction is not sufficient to maintain VO_2, which becomes DO_2 supply-dependent. These data are generated from a simple model of oxygen delivery and uptake, based upon the following assumptions:

a) critical DO_2 = 6.6 ml/min per kg
b) critical extraction ratio ~ 0.63, and
c) the decrease in DO_2 reflects a progressive decrease in cardiac output while arterial oxygen content remains normal at 15.9 ml/dl (i.e., stagnant hypoxia).

While these data are theoretical, numerous animal and human investigations confirm similar behavior – including reduction in flow to peripheral tissues during cardiopulmonary bypass and observation of patients during withdrawal of life support. By way of example, when neonates undergoing repair of a hypoplastic left ventricle are profiled and cardiac output is related to anaerobic state (as judged by incremental lactic acid increase) and SvO_2, an SvO_2 level of 30% was a threshold below which anaerobic metabolism occurred, similar to the results predicted by the model shown [2].

While there appears to be a sound rationale for a low SvO_2 signaling inadequate DO_2 in anemic, hypoxic, and stagnant models of hypoxia, this is less clear in pathophysiologic processes associated with high output hypotension – sepsis, liver failure, pancreatitis, and other conditions marked by a systemic inflammatory response syndrome. In these conditions, once fluid resuscitation has taken place, the circulation is characterized by high flow, low systemic arterial pressure, and a high SvO_2 despite an elevated oxygen consumption. It is also arguable that tissue

hypoxia does not exist under these conditions, or at least is not the primary determinant of lactic acidosis. Nonetheless, it has been argued that while a high SvO_2 may not guarantee absence of lactic acidosis or a risk for progression of organ failures, a low SvO_2 signals inadequate resuscitation and has in fact been used as an endpoint for outcome studies assessing benefit from specific algorithms titrating therapy to this endpoint.

Interestingly, some data in critically ill patients indicate that SvO_2 may be a monitored variable that identifies patients with cardiac performance inadequate to permit withdrawal of life support measures such as mechanical ventilation. In one study comparing patients who failed and passed spontaneous breathing trials, the failed patients exhibited an inability to increase cardiac index during their breathing trial, associated with a marked fall in SvO_2, a pattern distinctly different than that seen in patients successfully liberated from mechanical ventilation, who increased cardiac index and maintained their SvO_2 constant [3].

Reliable Measurement under Clinical Conditions?

SvO_2 is routinely measured by withdrawing a sample of blood from the distal port of the unwedged pulmonary artery catheter (PAC), or continuously with a fiberoptic catheter that measures oxygen saturation by reflectance oximetry [4]. Accuracy during intermittent sampling is enhanced by discarding the initial 3 ml of blood, then withdrawing a sample very slowly so as to avoid contamination with capillary blood. The SvO_2 should be measured by co-oximetry, because the steep slope of the oxygen dissociation curve in the venous range means that small errors in measurement of PvO_2 may result in substantial errors in calculation of SvO_2.

Ordinarily, the oxygen saturation is lower in the superior vena cava than in the inferior vena cava, but the reverse is true in shock due to redistribution of blood flow away from splanchnic, renal, and mesenteric beds [5, 6]. Thus, the oxygen saturation of blood obtained from a central venous catheter in the superior vena cava (ScvO2) will overestimate SvO_2 in shock. Although the absolute values of SvO_2 and $ScvO_2$ may differ, they tend to track together with changing hemodynamic conditions. Furthermore, it has been argued that a low $ScvO_2$ in the setting of shock may be clinically relevant because it implies an even lower SvO_2. Because $ScvO_2$ can be measured employing only a central venous catheter and does not require right heart catheterization, some have recommended its routine use and it has been employed in recent trials assessing resuscitation strategies (vide infra).

Studies with comparisons of $ScvO_2$ and SvO_2 are summarized in Table 1.

The Monitored Variable Offers Unique Information and also Directs Therapeutic Interventions?

Monitoring of SvO_2 has had wide application in the peri-operative and intensive care unit (ICU) settings. In the aggregate, these studies have shown that decrements in SvO_2 often precede vital sign abnormalities, signal other events such as myocardial ischemia, shock, and arrhythmias, and that interventions that either

Table 1. Studies with comparisons of $ScvO_2$ and SvO_2

Study [Ref]	r Correlation	Setting
Goldman [7]	Not given	27 MI pts in CCU
Goldman [8]	Not given	31 MI pts in CCU
Reinhart [9]	0.96	Canine study under hypoxia, hypovolemia, hyperoxia, resuscitation
Berridge [10]	0.93	51 ICU pts
Scheinman [11]	0.86	24 CCU pts; Correlation only acceptable in stable pts
Lee [5]	0.88	43 CCU pts; correlation not good in pts in shock
Martin [12]	0.48	7 ICU pts, correlation poor over course of interventions
Faber [13]	0.75	24 septic ICU pts
Davies [14]	0.94	Pig model of shock and lung injury
Shah [15]	Not given	Hemorrhagic shock rat model
Schou [16]	0.97	Hemodilution pig model
Baquero-Cano [17]	0.88	Neonatal pig sepsis
Scalea [18]	0.95	Hemorrhagic canine model
Herrera [19]	Differences less than 5% for all pts	Cardiothoracic pts undergoing surgery (n=23)
Edwards [20]	Poor correlation	Severe shock shortly after ICU admission
Kong [21]	Not given	Good correlation in pts with end-stage renal disease
Wendt [22]	0.90	ICU pts
Emerman [23]	0.93 for PO_2	Canine cardiac arrest model
Tahvanainen [24]	Not given	Use of ScvO2 for calculation of intrapulmonary shunt in ICU patients
Ladakis [25]	0.95	61 mechanically ventilated pts

CCU: coronary care unit; MI: myocardial infarction

decrease VO_2 (anesthesia, sedation and reduced work of breathing with positive pressure ventilation, hypothermia) or increase DO_2 (increased PaO_2, hemoglobin, or cardiac output (fluids, vasoactive drugs)) can restore a more favorable balance between oxygen utilization and delivery which is heralded by increments in SvO_2.

Several studies have indicated that resuscitation of patients guided by vital signs and intravascular pressure measurements may not achieve an adequate circulation and that additional goals of therapy are identified by SvO_2. Anders and colleagues [26] reported a series of patients presenting with severe congestive heart failure with ejection fractions < 30% who underwent initial therapy based upon central venous pressure, heart rate, and blood pressure guidelines. When the patients were then divided into a group with persisting lactic acidosis and those without, the patients with this marker of tissue hypoxia exhibited significantly lower SvO_2 levels (26 to 34%) despite normal vital signs. Additional therapy with inotropes, afterload reduction, and revascularization had a tendency to increase SvO_2 and resolve lactic acidosis.

Similarly, Rady and colleagues [27] reported a group of patients with diverse forms of shock including hypovolemia and sepsis who underwent routine resuscitative measures directed at target levels of central venous pressure and blood pressure. Despite achieving these goals, a significant fraction of patients continued to exhibit high lactate levels which correlated with low SvO_2.

Studies Have Confirmed Improved Patient Outcome When Therapy is Titrated Against the Measured Variable?

Three large prospective, randomized controlled trials have been conducted which have linked a specific strategy of resuscitation of the circulation to the monitored SvO_2. Gattinoni and colleagues [28] enrolled patients who had been admitted to the ICU with a heterogenous group of underlying disorders to be randomized to one of three strategies based on hemodynamic targets – normal values of cardiac index (CI), supranormal values of CI (> 4.5 l/min/m2), or to SvO_2 > 70% or an arteriovenous content difference < 20%. No differences were noted in survival or other outcome measures.

Interpretation of these results has often included the observation that enrollment after a period of time spent in arriving in the ICU and being initially stabilized may have allowed loss of a window of opportunity to intervene in a way that would ultimately yield improved outcomes. Accordingly two other studies have focused upon resuscitation and monitoring of patients closer to the inception of their illness – specifically in the emergency department – or during the course of surgery. Rivers et al. [29] enrolled patients admitted to the emergency department with severe sepsis and septic shock, randomizing them to routine therapy or early goal-directed therapy (EGDT), which in addition to targeting routine ranges of right atrial and arterial blood pressure included a target of $ScvO_2 > 70\%$. This EGDT was conducted for the first six hours of management, after which all patients were treated equivalently. EGDT resulted in greater fluid and vasoactive drug therapy in the first six hours, but less of such therapy in the ensuing days. Survival in-hospital and at 28 and 60 days was improved in the EGDT group, and among survivors the duration of hospital stay and mechanical ventilation were reduced in the EGDT group.

Polonen and colleagues [30] studied patients undergoing cardiac surgery, randomizing them to control or protocol care. Protocolized care had, as goals of therapy, maintenance of $SvO_2 > 70\%$ and lactate concentration less than 2 mmol/l

during the initial 8 hours of postoperative care in the ICU. The median hospital stay was shorter in the protocol group and morbidity was less frequent at the time of hospital discharge in the protocol group (1.1 vs 6.1%, p<.01).

Conclusion

While the use and interpretation of mixed venous and central venous oxygen saturation is based upon traditional principles of physiology with much confirmation in the bench and clinical literature, a large gap only partially filled in exists between measurement of this parameter and our ability to offer interventions based on its measurement that will have a salutary effects on patient outcomes. Within this divide between first principles and treatment, the following conclusions can be offered:

1) the rationale that extremely low venous oxygen saturation levels signal at least a risk for, if not actual, tissue hypoxia is strong. Normal or high levels measured at a whole body level do not guarantee the existence of significant regional tissue hypoxia or in the setting of sepsis, progressive tissue dysfunction and organ failure in the absence of hypoxia.
2) Under many circumstances central $ScvO_2$ is a reasonable surrogate measure for SvO_2 and in most settings of shock tends to slightly over-estimate SvO_2.
3) Clinical data support the utility of venous oxygen saturation levels to predict patients at risk for organ dysfunction and poor outcome.
4) At least one well conducted prospective randomized control trial in patients with severe sepsis has demonstrated that therapy titrated to the $ScvO_2$ can improve survival.

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Central Venous Oxygen Saturation ($ScvO_2$)

K. Reinhart and F. Bloos

Introduction

About 100 years ago, the German physiologist Pflüger stated that the cardiorespiratory system fulfills its physiological task by guaranteeing cellular oxygen supply and removing waste products of cellular metabolism. In his opinion, everything else was of secondary importance: 'arterial oxygen content, arterial pressures, blood flow velocity, mode of cardiac work, and mode of respiration, all are incidental and subordinate; they all combine their actions only in service to the cells' [1]. Despite the modern technology of the 21st century, we are only able to monitor what Pflüger called 'incidental and subordinate'.

Continuous measurement of the systemic blood pressure and heart rate are routinely obtained in critically ill patients. It is a very basic question to what extent the routinely measured cardiorespiratory parameters provide information about the adequacy of oxygen transport and, more importantly, on the quality of tissue oxygenation. Recognition, prevention, and treatment of tissue hypoxia play a key role in intensive care medicine. The aim of cardiovascular monitoring is the early recognition of impending tissue hypoxia. In some situations, tissue hypoxia may exist despite normal values obtained by conventional hemodynamic monitoring such as arterial blood pressure, central venous pressure (CVP), heart rate, and urine output.

Measurement of mixed venous oxygen saturation (SvO_2) from the pulmonary artery has for some time been advocated as an indirect index of tissue oxygenation. In myocardial infarction, decreased SvO_2 was found to be indicative of current or imminent cardiac failure [2]. In several diseases such as cardiopulmonary disease, septic shock, cardiogenic shock, and in patients after cardiovascular surgery, a low SvO_2 has been associated with a poor prognosis [3–7]. Based on these findings, fiberoptic pulmonary artery catheters (PACs) for continuous SvO_2 measurement have been developed.

However, pulmonary artery catheterization is costly and includes inherent risks. Furthermore, its usefulness in various clinical conditions remains under debate due to lack of convincing data [8–10]. In comparison, central venous catheterization via the superior vena cava is part of standard care for critically ill patients and is easier and safer to perform. Similar to SvO_2, the measurement of central venous oxygen saturation ($ScvO_2$), has been advocated as a simple method to assess changes in the adequacy of global oxygen supply in various clinical setting [2, 9,

10]. However, whether this parameter exactly mirrors the SvO_2 has been questioned, especially in critically ill patients. For example, shock increases the difference between SvO_2 and $ScvO_2$ since oxygen extraction is increased in the hepatosplanchnic region but not in the brain [11, 12].

Furthermore, Rivers and coworkers demonstrated in a recent prospective randomized study in patients with severe sepsis and septic shock that, in addition to maintaining CVP above 8–12 mmHg, mean arterial pressure (MAP) above 65 mmHg, and urine output above 0.5 ml/kg/h, the maintenance of a $ScvO_2$ above 70% resulted in an absolute reduction of mortality by 15% [13]. These findings refueled the interest in the measurement of $ScvO_2$ in critically ill patients. The purpose of this review is to discuss the differences and the similarities between mixed and central venous oxygen saturation.

Physiological Differences between SvO_2 and $ScvO_2$

The SvO_2 is measured in the pulmonary artery and reflects the venous oxygen saturation of the whole body. According to the Fick principle, mixed venous oxygen content (CvO_2) can be expressed by:

$$CvO_2 = CaO_2 - \frac{VO_2}{CO}$$

Thus, CvO_2 reflects the relationship between whole body oxygen need and cardiac output under conditions of a constant CaO_2. SvO_2 is the most important factor in determining CvO_2 since physically dissolved oxygen reflected by PvO_2 can be neglected and hemoglobin should be constant over a certain period of time in most clinical settings. Due to this relationship, SvO_2 has been propagated as a parameter describing the adequacy of tissue oxygenation [4, 5].

SvO_2 measurement always necessitates the insertion of a PAC, which is a costly and an invasive procedure. Already in 1969, Scheinman and coworkers investigated whether $ScvO_2$ could reflect changes in SvO_2 [14].

As depicted in Figure 1, venous oxygen saturations differ between organ systems since they extract different amounts of oxygen. It is therefore reasonable that a venous oxygen saturation depends on the site of measurement. In healthy humans, the oxygen saturation in the inferior vena cava is somewhat higher than in the superior vena cava10 [15]. Since the pulmonary artery contains a mixture of blood from both the superior as well as the inferior vena cava, SvO_2 is greater than the oxygen saturation in the superior vena cava. Most commonly, central venous catheters are inserted via a jugular vein or subclavian vein. Thus, central venous blood sampling should reflect the venous blood of the upper body only. However, the tip of the catheter may not only be located in the superior vena cava but also at the superior vena caval/atrial junction or inside the right atrium [16]. Ten to thirty percent of central venous catheters are inserted into the right atrium [17]. It might be possible, therefore, that blood drawn from a central venous catheter also to some degree contains blood from the inferior vena cava. Furthermore, the catheter tip may move depending on the position of the patient. When a patient is moved from

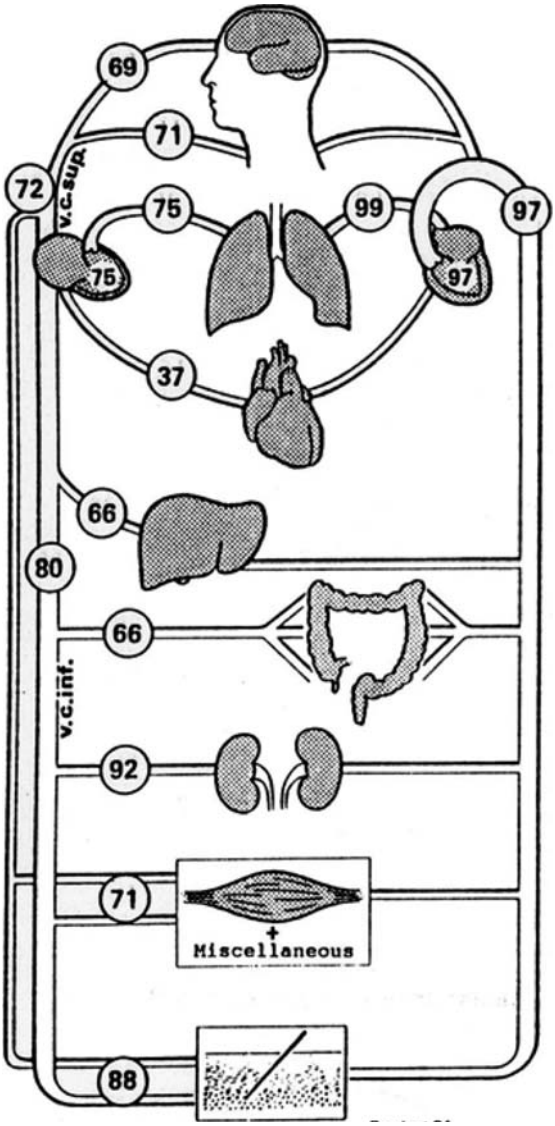

Fig. 1. Schematic figure of arterial and venous oxygen saturations in various regions of the human circulation. v. c. sup.: superior vena cava; v. c. inf.: inferior vena cave [18].

a supine to an upright position, the catheter moves upwards away from the right atrium due to lengthening of mediastinal structures and *vice versa* [16].

Factors that may Impact on the Difference between SvO_2 and $ScvO_2$

The physiological difference between $ScvO_2$ and SvO_2 is not constant and may be affected by several conditions. These conditions include: (i) general anesthesia,

(ii) severe head injury, (iii) redistribution of blood flow as occurs in shock, and (iv) microcirculatory shunting or cell death.

During anesthesia, $ScvO_2$ may exceed SvO_2 by up to 6% [19, 20]. This observation may be explained by the effect that inhalational anesthetics have on increasing cerebral blood flow while decreasing cerebral metabolism and therefore reducing cerebral oxygen extraction. This leads to a higher oxygen saturation in the superior vena cava. A similar effect can be observed in patients with elevated intracranial pressures where cerebral trauma and barbiturate coma may decrease cerebral metabolism. Patients with elevated intracranial pressures revealed the highest difference between SvO_2 and $ScvO_2$ [21].

The reversal of the physiological difference between $ScvO_2$ and SvO_2 can also be observed in the state of cardiocirculatory shock. During hemodynamic deterioration, mesenteric and renal blood flow decreases followed by an increase in oxygen extraction in these organs [22, 23]. Naturally, this goes along with venous desaturation in the lower body. On the other hand, cerebral blood flow is maintained over some period in shock causing a delayed drop of $ScvO_2$ in comparison to SvO_2 [24]. This effect has been demonstrated in several types of shock such as hemorrhagic, septic, and neurogenic shock as well as during heart failure [11, 14, 21].

Theoretically, the physiological difference between SvO_2 and $ScvO_2$ may also be altered if the regional oxygen extraction of a certain organ decreases. This may be due to increased shunting in the microcirculation. The oxygen saturation in shunt capillaries stays at nearly arterial level causing an increase of the oxygen saturation in the venous effluent [25]. Progressive cell death would also decrease oxygen extraction in the affected organ.

Parallel Tracking of SvO_2 and $ScvO_2$

Several animal studies have been performed to prove the reliability of $ScvO_2$ as a substitute for SvO_2. High correlation coefficients have been reported between $ScvO_2$ and SvO_2 under various conditions [26–29]. Only during cardiopulmonary resuscitation did $ScvO_2$ not sufficiently reflect SvO_2 [30]. As in the experimental setting, a good correlation between $ScvO_2$ and SvO_2 can be found in critically ill patients [2, 19, 31, 32]. This relationship holds true over a wide range of cardiac output values [33]. It was therefore concluded that $ScvO_2$ yields adequate information about SvO_2. However, several conditions such as shock or general anesthesia (see above) affect the physiological difference between SvO_2 and $ScvO_2$. This has resulted in some authors stating that the correlation between $ScvO_2$ and SvO_2 is clinically unacceptable in critically ill patients [34, 35].

According to the physiological properties of $ScvO_2$, it is reasonable that a precise determination of SvO_2 by the measurement of $ScvO_2$ is not possible. However, more important than the precise prediction of SvO_2 is the question whether changes in SvO_2 indicating a hemodynamic derangement or a treatment effect are mirrored by changes in the $ScvO_2$. In a dog model, various clinical conditions, such as hypoxia and hemorrhagic shock, were investigated regarding their effects on these parameters [36]. This study confirmed that $ScvO_2$ differs from SvO_2 but changes in SvO_2 were accompanied by parallel changes in $ScvO_2$ (Fig. 2).

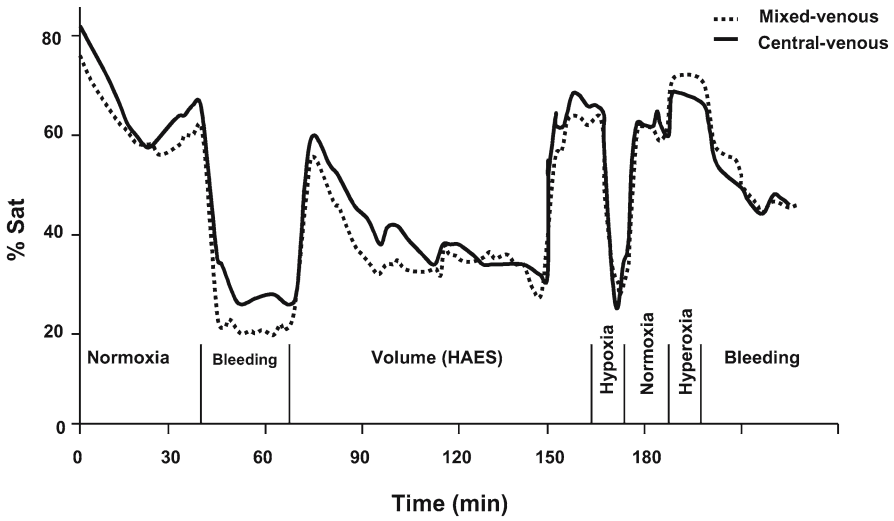

Fig. 2. Changes of $ScvO_2$ and SvO_2 caused by several experimental manipulations in a dog [36].

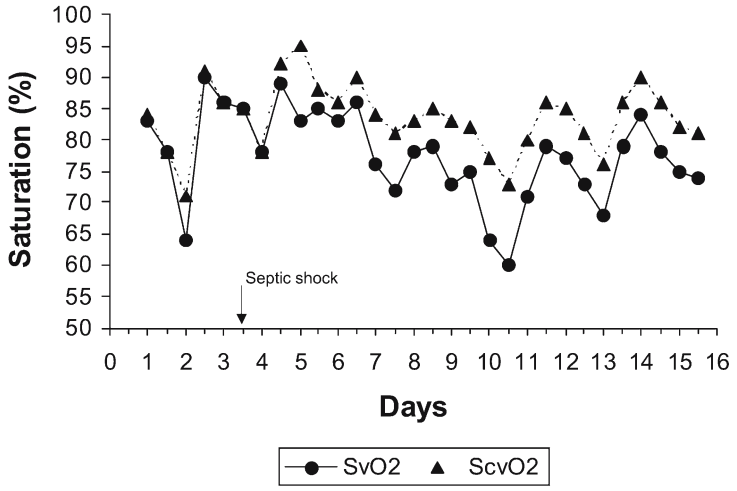

Fig. 3. Course of mixed venous (SvO_2) and central venous ($ScvO_2$) oxygen saturations over several days in a septic patient who developed septic shock on day 3. Modified from [18]

These findings could also be demonstrated in the clinical setting where 32 critically ill surgical patients were monitored for a total of 1097 hours. A good agreement between SvO_2 and $ScvO_2$ was demonstrated [21]. The authors concluded that the continuous measurement of $ScvO_2$ might be a reliable and convenient tool to monitor the adequacy of the oxygen supply/demand ratio. Fig. 3 shows an example of a septic patient who developed septic shock on day 3. Although the

difference between SvO_2 and $ScvO_2$ increases after onset of septic shock, the curves of both parameters change in parallel.

Clinical Application of $ScvO_2$

Severe Sepsis and Septic Shock

Severe sepsis and septic shock are frequently complicated by the development of the multiple organ dysfunction syndrome (MODS). Tissue hypoxia is believed to be one of the most important mechanisms for the onset of MODS. However, treatment concepts favoring the achievement of a maximum oxygen delivery (DO_2) proved to be of no benefit to these patients [37]. Furthermore, it is very difficult to define goals for cardiovascular resuscitation in these patients. In this context, Rivers and coworkers demonstrated, in patients with severe sepsis or septic shock, that an early and aggressive resuscitation guided by the $ScvO_2$ additionally to CVP and MAP reduced the 28 day mortality rate from 46.5 to 30.5% ($p=0.009$) [13]. Compared to the conventionally treated group, the $ScvO_2$ group received more fluids, more frequently received dobutamine, and were given more blood transfusion during the first 6 hours. This resulted in a faster and better improvement in organ functions in the $ScvO_2$ group.

Severe Trauma and Hemorrhagic Shock

The treatment of severely traumatized patients is defined by early and aggressive resuscitation followed by early surgical intervention. Since it was demonstrated in animal experiments that $ScvO_2$ decreases linearly with the amount of blood loss [28], it would be reasonable to investigate this parameter in patients after severe trauma. In 50% of patients with shock, who had been hemodynamically stabilized according to vital signs such as heart rate, blood pressure, and CVP, $ScvO_2$ was insufficient [38]. These patients with a $ScvO_2$ <65% were in need of further interventions and demonstrated prolonged cardiac dysfunction and elevated lactate levels. Although there has been no study that investigated the validity of $ScvO_2$ to guide hemodynamic stabilization in polytrauma patients, there is good evidence from patients with severe sepsis or septic shock that the $ScvO_2$ is a good parameter in the resuscitation of hemodynamically unstable patients [13].

In initially hemodynamically stable patients after trauma, a $ScvO_2$ below 65% was able to detect those patients who suffered from blood loss and were in need of blood transfusion [39]. However, in a similar study, only lactate concentrations and arterial base deficit, but not $ScvO_2$, was able to distinguish patients with delayed blood loss from patients without bleeding prior to surgery [40].

Heart Failure and Cardiac Arrest

Heart failure is characterized by a limited cardiac output. Therefore, such patients are unable to sufficiently increase cardiac output during a rise in oxygen needs. Changes in oxygen need can therefore only be covered by changes in oxygen extraction [41]. In these patients, SvO_2 is tightly correlated with cardiac output and a drop in SvO_2 is a good and early marker of cardiac deterioration [42, 43]. Correlation between SvO_2 and $ScvO_2$ was insufficient in patients with heart failure [14] but was reported to be accurate in patients with myocardial infarction [44]. Nevertheless, patients with congestive heart failure who present high serum lactate levels and a low $ScvO_2$, require a more aggressive management in the emergency department than patients with normal $ScvO_2$ and normal lactate levels [45]. Patients with a $ScvO_2$ below 60% were in cardiogenic shock [44].

During cardiac arrest, cardiopulmonary resuscitation (CPR) is applied to the patient with the goal of reestablishing circulation by the use of standardized procedures. In this setting, continuous $ScvO_2$ measurement can be helpful. Venous blood is massively desaturated during cardiac arrest due to maximum oxygen extraction resulting in a $ScvO_2$ <20%. Successful chest compression leads to an immediate increase in $ScvO_2$ above 40% [46]. In all patients who reached a $ScvO_2$ >72% during CPR, a return of spontaneous circulation was observed [47]. Furthermore, central venous PO2 ($PcvO_2$) during CPR was a predictor for outcome. All patients who did not reach a $PcvO_2$ >31 mmHg during CPR, died [48]. On the other hand, a very high $ScvO_2$ (>80%) in the presence of a very low DO_2 after successful CPR is also an unfavorable predictor of outcome. It has been argued that a very high $ScvO_2$ is indicative of an impairment in tissue oxygen utilization probably due to a prolonged cardiac arrest [49].

Conclusion

Measurement of $ScvO_2$ is simple and does not necessitate additional invasive techniques. There is a good correlation between $ScvO_2$ and SvO_2 under non-shock conditions. During the state of circulatory shock, however, $ScvO_2$ does not always exactly mirror SvO_2. However, changes of both parameters occur in a parallel manner. Furthermore, changes in SvO_2 due to therapeutic interventions are well reflected in changes of $ScvO_2$. This holds true especially in patients with severe sepsis/septic shock and patients with cardiac arrest. In critically ill patients, $ScvO_2$ is greater than SvO_2. This implies that a pathological $ScvO_2$ indicates an even lower SvO_2. $ScvO_2$ should not be used as the only measure in the assessment of the cardiocirculatory system but be combined with standard vital parameters (heart rate, blood pressure, CVP), lactate measurement and parameters of organ function (urine output). The addition of $ScvO_2$ measurement to standard hemodynamic monitoring in patients at high risk or with manifest tissue hypoxia is likely to be helpful for early detection and improved treatment of this dangerous clinical condition.

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DO_2/VO_2 relationships

J. L. Vincent

Introduction

Most cellular activities require oxygen, primarily obtained from the degradation of adenosine triphosphate (ATP) and other high-energy compounds. Oxygen must, therefore, be present in the mitochondria in sufficient amounts to maintain effective concentrations of ATP by the electron transport system. Cells must perform various activities in order to survive, including membrane transport, growth, cellular repair, and maintenance processes. They often also have facultative functions, such as contractility, electrolyte or protein transport, motility, or various biosynthetic activities. If oxygen availability is limited, cellular oxygen consumption may fall, and become supply-dependent. Facultative functions are the first to be affected, leading to cellular and, ultimately, organ dysfunction. If the situation becomes more serious, obligatory functions can no longer be maintained, and irreversible alterations may occur resulting in cell death. Maintaining sufficient oxygen availability to the cell is thus fundamental for cell survival: the hypoxic cell is doomed to become malfunctional and to die.

Oxygen delivery vs oxygen availability

The amount of oxygen available in the cell is determined by a number of central and peripheral factors. The central factors depend on the adequacy of cardiorespiratory function (cardiac index and PaO_2) and the hemoglobin concentration, according to the formulas given in Table 1. Peripheral factors depend on the distribution of cardiac output to the various organs, and the regulation of the microcirculation, which is determined by the autonomic control of vascular tone, local microvascular responses, and the degree of affinity of the hemoglobin molecule for oxygen.

Among the central factors, cardiac output is a more important determinant of oxygen delivery (DO_2) than the arterial oxygen content (Table 1), as a fall in hemoglobin or SaO_2 can be compensated by an increase in cardiac output, whereas the opposite is not true. If cardiac output falls, SaO_2 cannot rise above 100% and hemoglobin concentration cannot increase acutely. Furthermore, an increase in red blood cell mass does not efficiently increase DO_2, because cardiac output usually decreases as a result of the associated increase in blood viscosity. Hence,

Table 1. The determinants of oxygen delivery, oxygen consumption, and oxygen extraction

Oxygen delivery (DO_2) = CO x Hb x SaO_2 x C x 10
Oxygen consumption (VO_2) = CO x (CaO_2 CvO_2) x 10 (Neglecting the dissolved oxygen) = CO x Hb x (SaO2-SvO2) x C
Oxygen extraction (O_2ER) = VO_2/DO_2 = (CaO_2-CvO_2)/CaO_2
or neglecting the dissolved oxygen = (SaO_2-SvO_2)/SaO_2
where CO represents the cardiac output, Hb the hemoglobin concentration, SaO_2 and SvO_2 the arterial and the mixed venous oxygen saturations, respectively, and C the constant value representing the amount of oxygen bound to 1 g of Hb (this value is usually 1.34 or 1.39).

cardiac output is the most important factor in the constant adaptation of the body's oxygen needs in physiological conditions.

The peripheral factors can change substantially in inflammatory conditions (including sepsis), when local control of the vascular tone may be altered, the formation of microthrombi may shut down some capillaries, and edema may develop. Changes in hemoglobin oxygen affinity can also influence the peripheral delivery of oxygen.

Basic concepts: The Relationship between VO_2 and DO_2 and the concept of VO_2/DO_2 Dependency

A number of animal experiments using different models [1–4] have shown that oxygen uptake (VO_2) remains independent of DO_2 over a wide range of values, because oxygen extraction (O_2ER, which is the ratio of VO_2 over DO_2) can readily adapt to the changes in DO_2. When cardiac output is acutely reduced by acute blood withdrawal, tamponade, anemia, or hypoxemia, O_2ER increases (SvO_2 decreases) and VO_2 remains quite stable, until DO_2 falls below a critically low threshold (DO_2crit), when VO_2 starts to fall. An abrupt increase in blood lactate concentrations then occurs, indicating the development of anaerobic metabolism (Fig. 1). In the presence of sepsis mediators, as after the administration of endotoxin or live bacteria [5, 6], oxygen extraction capabilities are altered so that the DO_2crit is higher and the critical O_2ER is typically lower than in control conditions. In these conditions, VO_2 can become dependent on DO_2 even when DO_2 is normal or elevated. Altogether, these observations help to characterize the four principal types of circulatory shock (Fig. 2).

Although such studies performed in anesthetized animals can hardly be reproduced in humans, an acute reduction in DO_2 can be observed in the intensive care unit (ICU) during withdrawal of life support [7]. In these dying patients, VO_2 remained relatively constant until DO_2 fell below very low values.

A number of studies have correlated the VO_2/DO_2 dependency phenomenon to profound circulatory alterations. Bihari et al. [8] showed that an increase in VO_2 during a prostacyclin infusion was a characteristic of non-survivors. A number of

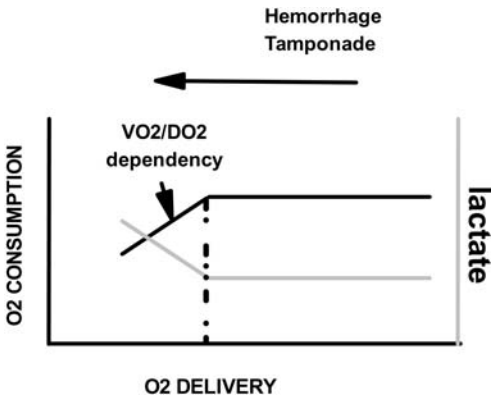

Fig. 1. Relationship between oxygen uptake (VO_2) and oxygen delivery (DO_2) when DO2 is acutely reduced by tamponade or hemorrhage in anesthetized animals. Note that blood lactate levels increase as soon as DO_2 falls below DO_2crit.

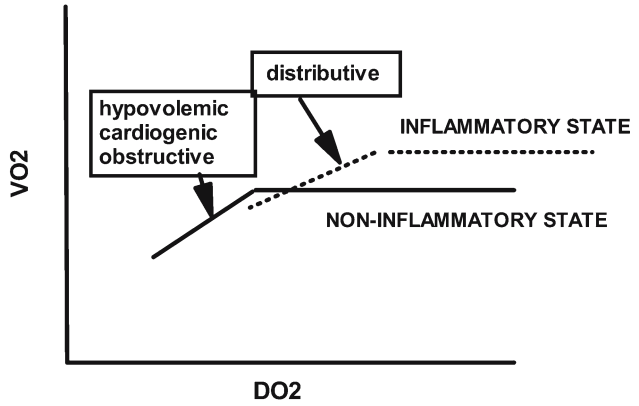

Fig. 2. The four types of acute circulatory failure.

investigators have also reported that patients with acute circulatory failure with increased blood lactate concentrations demonstrate an increase in VO_2 when DO_2 is acutely increased by fluid infusion [9], blood transfusions or dobutamine administration [10]. Such a phenomenon has not been observed in stable patients with normal lactate concentrations [9–12].

Others have challenged these observations, arguing that the VO_2 was usually determined from the Fick principle rather than determined independently from expired gas analysis. Hence, VO_2 and DO_2 were calculated from the same variables, i.e., cardiac output, hemoglobin concentrations, and SaO_2, resulting in mathematical coupling of data.

Indirect calorimetry also has its limitations and sources of error, and becomes very imprecise when high FiO_2 are delivered. Incidentally, many authors have argued that VO_2 is *calculated* using the Fick equation, but *measured* when obtained by indirect calorimetry. This is clearly wrong: With both techniques, VO_2 results from a calculation of the product of flow (blood flow or gas flow) and oxygen content differences (between arterial and venous blood or between inspired and

Table 2. Calculation of oxygen uptake by indirect calorimetry

$$VO2 = \frac{FiO_2 \times (1 - FeO_2 - FeCO_2)}{(1 - FiO_2 - FeO_2)} \times VE$$

where FeCO2 is the expired CO2 fraction, FiO2 and FeO2 the inspired and expired oxygen fraction, respectively, and VE the expiratory flow rate

expired gases). In fact, the formula used to calculate VO_2 by indirect calorimetry is quite complex (Table 2).

In addition, this reasoning can itself be criticized. First, the effect of mathematical coupling of data does not seem to be major if the changes in DO_2 are of sufficient magntitude [13]. Second, this limitation cannot explain how the changes in VO_2 can be observed in some individuals and not in others. It is important to note that all studies using indirect calorimetry to determine VO_2 included only stabilized patients: this is largely due to the time needed to install the material used for VO_2 determinations. The same applies to the studies arguing that changes in VO_2 can be observed only in patients with high lactate concentrations: these studies included stabilized patients in whom signs of shock had already resolved. Admittedly, the interpretation of elevated blood lactate concentrations is not always straightforward, as hyperlactatemia can be influenced by decreased lactate clearance. Also, in sepsis, hyperlactatemia does not necessarily reflect anaerobic metabolism secondary to cellular hypoxia, but other mechanisms, like increased glycolysis or abnormal pyruvate metabolism [14]. Hence, hyperlactatemia should complement the clinical evaluation of circulatory shock, including arterial hypotension and signs of altered tissue perfusion like altered sensorium, altered cutaneous perfusion, and decreased urine output.

Altogether, these studies indicate that the VO_2/DO_2 dependency phenomenon can be observed but only in patients who are clearly unstable, during shock resuscitation; it is a hallmark of acute circulatory failure (shock) [15].

A more important limitation is that the global VO_2/DO_2 assessment is not precise enough to be useful clinically and, more specifically, to guide therapy. Furthermore, VO_2/DO_2 dependency may occur regionally, especially in the hepatosplanchnic region [16] (Fig. 3). Comparisons of VO_2 and DO_2 are useless, because obtaining these derived variables is hard to interpret and the plot of VO_2 vs DO_2 is limited by the problem of mathematical coupling of data. However, evaluation of the relationship between cardiac output and oxygen extraction may be very useful to evaluate the adequacy of the cardiac output response [17]. Such a CI/O_2ER relationship has no problem of mathematical coupling of data (Fig. 4). Increased lactate concentrations remain a reliable prognostic indicator, actually superior to DO_2 and VO_2 values [18]; increasing DO_2 to higher values when blood lactate levels are normal has not been shown to be beneficial.

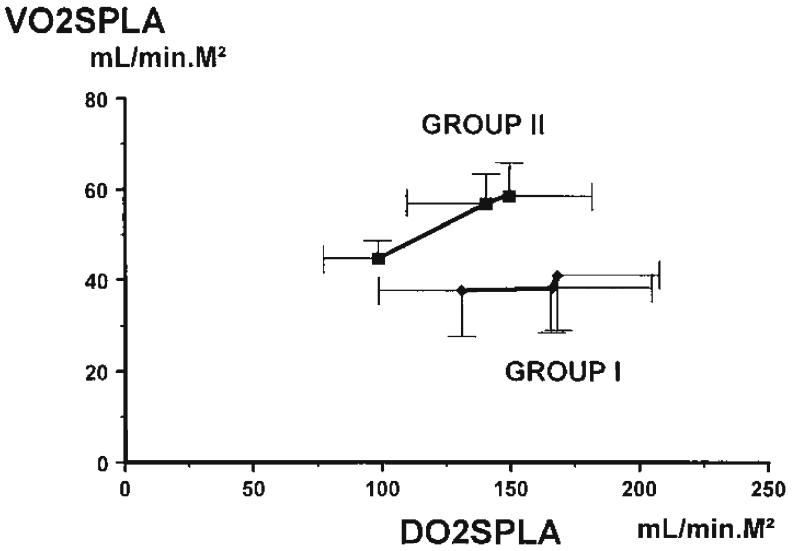

Fig. 3. Regional VO_2/DO_2 relationship in the splanchnic circulation in patients with severe sepsis. Group I: patients with gradient between mixed venous and hepatic venous oxygen saturation lower than or equal to 10%. Group II: patients with gradient between mixed venous and hepatic venous oxygen saturation higher than 10%. Data are presented as mean ± SEM. (From [16] with permission)

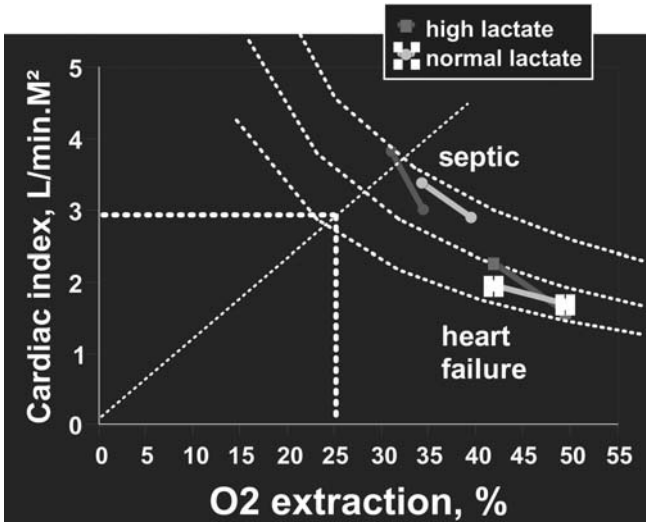

Fig. 4. Cardiac index/O_2ER diagram during a short term dobutamine infusion indicating VO_2/DO_2 dependency in patients with increased lactate levels but not in those with normal lactate levels (data from [10]).

Clinical implications

The Supranormal DO_2 Approach

William Shoemaker and his colleagues proposed that DO_2 should be maintained at supranormal values (at least 600 ml/min.M²) in all patients at risk of complications, to ensure sufficient oxygen availability to the cells [19]. This proposal was based on the observation that survivors from sepsis or trauma usually generate higher DO_2 than non-survivors [20]. Although this approach may have merits in some populations [21, 22], it is limited by two important aspects. One is that patients with higher DO_2 are more likely to survive, simply because they have a better physiological reserve, allowing them to generate a higher cardiac output. The second is that increasing DO_2 to supranormal values in all patients 'at risk' may be beneficial to some, still underresuscitated, but harmful to others, already well resuscitated, who would thus receive too much fluid and adrenergic agents like dobutamine.

This concept is an oversimplification of a complex phenomenon. When applied to a mixed group of critically ill patients, such strategies have been shown to be ineffective [23] and may even be harmful, especially if high doses of dobutamine are administered [24].

The Titrated Approach

It is more meaningful to have a titrated approach, individualized according to results of a careful clinical evaluation and some paraclinical tests including measurements of cardiac index, SvO_2, blood lactate concentrations, and perhaps regional PCO_2. This requires a complete understanding of the pathophysiologic alterations

As mentioned above, the relationship between CI and SvO_2 does not have the problem of mathematical coupling of data associated with the evaluation of the relationship between VO_2 and DO_2 when both are obtained from the same values of cardiac output, hemoglobin concentrations, SaO_2, and SvO_2. The study of such variables also avoids cumbersome calculations, as cardiac index is a primary variable and O_2ER is very simply calculated (Table 1). In most cases, the relationship between CI and SvO_2 or even central venous oxygen saturation ($ScvO_2$) alone may suffice. There are, however, two reasons why the relationship between CI and O_2ER would be better (Fig. 4.). One is that the relationship between CI and SvO_2 is curvilinear, rendering the data interpretation more difficult. The second, is that even when hypoxemia is avoided, SaO_2 can still vary between about 90 and 99% in the acutely ill patient, i.e., a 10% variation in the variable. Nevertheless, SvO_2, or maybe even $ScvO_2$ alone, may be used in an algorithm for resuscitation. Rivers et al. [25] showed that monitoring $ScvO_2$ could result in a significantly lower mortality rate in patients with severe sepsis and septic shock. Likewise, Polonen et al. [26]found, in cardiac surgery patients, that maintaining SvO_2 at normal or high levels shortens hospital stay and lowers the degree of organ dysfunction at time of discharge from hospital. Nevertheless, lactate concentrations remain valuable in

shock states. Although one may argue that lactate concentrations reflect other cellular abnormalities than anerobic metabolism secondary to hypoxia, persistently raised lactate levels should represent an alarm signal. Hence, in addition to clinical evaluation, repeated measurements of SvO_2 and blood lactate may be helpful.

Conclusion

Maintenance of adequate DO_2 is essential to preserve organ function, as a low DO_2 is a straightforward path to organ failure and death, and treatment must be titrated to the individual based on the integration of several factors including clinical examination and available oxygenation and hemodynamic parameters. The relationship between VO_2/DO_2 remains an important concept, even though its simple application to guide therapy may be too simplistic. The relationship between cardiac index and O_2ER (or its simplification SvO_2) can be helpful.

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Cardiac Preload Evaluation Using Echocardiographic Techniques

M. Slama

Introduction

For many decades, central venous (CVP) pulmonary artery occlusion pressures (PAOP), assumed to reflect of right and left filling pressures, respectively, have been used to assess right and left cardiac preload. Although they are obtained from invasive catheterization, they are still used by a lot of physicians in their fluid infusion decision making process [1]. Many approaches have been proposed to assess preload using non-invasive techniques. Echocardiography and cardiac Doppler have been extensively used in the cardiologic field but have taken time to be widely used in the intensive care unit (ICU). However, echocardiography is now considered by most European ICU physicians as the first line method to evaluate cardiac function in patients with hemodynamic instability, not only in terms of diagnosis but also in terms of the therapeutic decision making process [2–3]. Regarding cardiac preload and cardiac preload reserve, cardiac echo-Doppler can provide important information.

Echocardiographic Indices

Vena Cava Size and Size Changes

The inferior vena cava is a highly compliant vessel that changes its size with changes in CVP. The inferior vena cava can be visualized using transthoracic echocardiography. Short axis or long axis views from a sub costal view are used to measure the diameter or the area of this vessel [4]. For a long time, attempts were made to estimate CVP from measurements of inferior vena caval dimensions. Because of the complex relationship between CVP, right heart function, blood volume, and intrathoracic pressures, divergent results were reported depending on the disease category of patients, the timing in measurement in the respiratory cycle, the presence of significant tricuspid regurgitation, etc. While Mintz et al. [5] found a good positive correlation ($r = 0.72$) between the end diastolic inferior vena cava diameter normalized for body surface area and the right atrial pressure, others found poor correlations between absolute values of inferior vena cava diameters and right atrial pressure [4, 6, 7]. In patients receiving mechanical ventilation, three studies have evaluated the correlation between inferior vena

cava size and right atrial pressure [7–9]; Lichtenstein et al. found a good correlation whereas Nagueh et al. and Jue et al. observed unsatisfactory correlation. This may be due to different techniques used to measure the diameter of the inferior vena cava [10]. When inferior vena cava size is measured using a two-dimensional method, correlation with right atrial pressure is poor. Using M-mode measurements, correlation was demonstrated to be good. To summarize all these findings, a small inferior vena cava size corresponds to normal right atrial pressure. An inferior vena cava diameter equal or inferior to 12 mm seems to predict a right atrial pressure of 10 mmHg or less 100% of the time. In contrast, an increased inferior vena cava size may correspond either to a normal or increased right atrial pressure. Importantly, inferior vena cava size depends on end-expiratory pressure in mechanically ventilated patients [11]. Therefore, inferior vena cava diameter increases when end-expiratory pressure increases. So, in patients with a high end-expiratory pressure, an increased inferior vena cava size may be present in patients with a low or normal right atrial pressure.

In the same way, the transverse diameter of the left hepatic vein was measured to assess right atrial pressure. Luca et al. demonstrated a good correlation between expiratory or inspiratory diameters and right atrial pressure. Moreover, percentage increments of left hepatic vein diameter correlated well with percent changes of mean right atrial pressure during the rapid infusion of 250–5000 ml of saline [12].

Right atrial pressure was also assessed by recording inferior vena caval flow using pulsed Doppler and analyzing tricuspid annulus movement using Doppler tissue imaging (DTI).

More interestingly, in spontaneously breathing patients, the collapsibility index, defined as the inspiratory percent decrease in inferior vena cava diameter was demonstrated to be well correlated with the value of right atrial pressure [4, 6, 7]. In spontaneously breathing patients, a collapsibility index > 50% would indicate a right atrial pressure < 10 mmHg with a good predictive accuracy [6] in terms of sensitivity and specificity. Nevertheless, although respiratory variation of inferior vena cava diameter can indicate the level of right atrial pressure, the knowledge of right atrial pressure is of little value for managing patients with cardiovascular compromise, first, because by nature, filling pressures do not fully reflect preload and second, because a given value of filling pressure does not provide relevant information on volume responsiveness in a given patient. In patients receiving mechanical ventilation, while the collapsibility index was reported to fail to reflect CVP [7], the respiratory changes of the inferior vena cava diameter were shown to be highly correlated with the percent increase in cardiac output induced by a 500 ml fluid infusion (Feissel M, unpublished data).

The superior vena cava (SVC) was also analyzed. Vieillard-Baron et al. demonstrated a collapse of this vessel during insufflations in mechanically ventilated patients. A collapsibility index > 60% was described as an excellent predictor of a positive hemodynamic response to fluid challenge (unpublished data).

Interatrial Septal Shape and Movement

The shape and movements of the interatrial septum depend on pressure as well as the size and contraction of left and right atrium during apnea. As with pressure variations, the temporal sequence of right and left atrial contraction is different over a cardiac cycle [13]. Therefore, the interatrial septum has cyclic oscillations depending on the pressure gradient between the left and right atrium. During atrial contraction, the septum bulges into the left atrium. In contrast, during systole the interatrial septum moves into the right atrium and at end-systole into the left atrium. During diastole, the septum bows toward the right atrium (Fig. 1). The amplitude of these movements is less than 1 cm in normovolemia and may be more than 1.5 cm in hypovolemia.

In spontaneously breathing patients, the interatrial septum moves during inspiratory and expiratory phases. During the inspiratory phase, right preload increases and the septum moves toward the left atrium. During mechanical ventilation, movement of the interatrial septum is also observed. Insufflations decrease right preload and increase left prelaod and as a consequence, the interatrial septum is curved towards the right atrium. During the end-expiratory phase, left preload decreases and interatrial septal reverse (right to left) movement is observed [14]. In the same way, pulmonary arterial hypertension changes these movements by increasing right atrial pressure.

PAOP may be assessed using transthoracic echocardiography or transesophageal echocardiography (TEE) by observing curvature and movement of the interatrial septum. The interatrial septum is usually curved toward the right atrium when PAOP > 14–15 mmHg. Mid-systolic reversal (right to left) was demonstrated

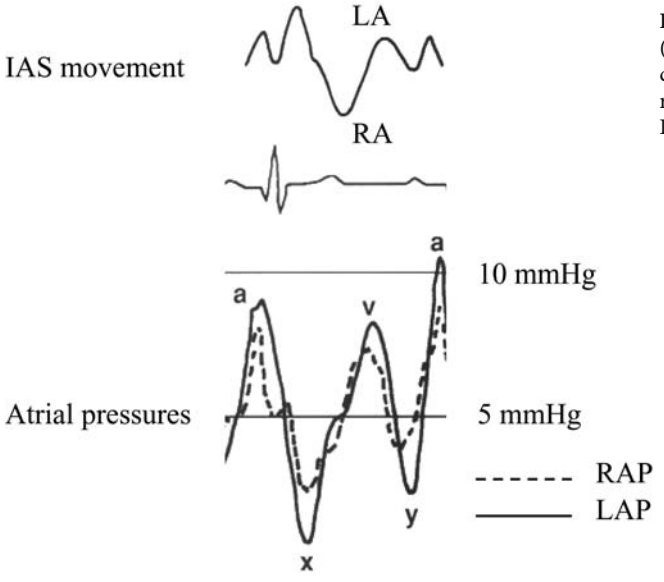

Fig. 1. Interatrial septal (IAS) movement over a cardiac cycle. RAP: right atrial pressure; LAP: left atrial pressure.

when PAOP << 14–15 mmHg. This movement was minimal when PAOP was between 12–14 mmHg and buckling of the septum was noted when PAOP was < 10 mmHg [15].

Therefore, movements of the interatrial septum are complex with variations throughout the cardiac and ventilation cycles. Nevertheless, these movements give information concerning left and right atrial pressures, but should be interpreted with caution particularly in mechanically ventilated patients.

Left Ventricular Dimensions

The end-diastolic size of the left ventricle (LV) determines the strain of myocardial fiber before systolic contraction, which represents the LV preload. In many studies, LV diameter, area, or volumes have been demonstrated to be good indicators of preload. In experimental and clinical studies the LV size has been demonstrated to decrease during provoked volume depletion and to increase after blood restitution [16–19]. Moreover, during provoked hypovolemia induced by stepwise blood withdrawal, the LV size was found to correlate with the amount of blood withdrawn [19]. In many clinical situations, volume depletion is associated with a decreased LV size, particularly during general anesthesia. The best way to quantify the LV size in ICU patients, is to measure the LV area using TEE. From a transgastric view, the LV end-diastolic area (LVEDA) can be measured at the papillary muscle level. Values of 5.2–18.8 cm^2 have been found in a normal population [20]. A good correlation was found between LV area obtained from echocardiography and LV volume obtained from angiography [21]. Cheung et al. [18] demonstrated that TEE was sensitive enough to assess changes in cardiac preload, since in this study, 5% of the blood volume change could be detected using TEE measurement of LVEDA. In another study performed in a pediatric department, TEE was able to detect 2.5% of blood volume changes. In contrast, others found a low sensitivity of TEE in tracking changes in volume status [18]. In a non-published study, we measured LV size using transthoracic echocardiography before and after hemodialysis. After 2 liters of ultrafiltration – which represents a blood volume loss of 250–300 ml – the LV size did not change; this was confirmed by others [22]. Technical problems including low reproducibility of LV measurements in ICU patients could explain these findings. Therefore, in our opinion, LVEDA seems to have a low sensitivity to detect blood volume changes in critically ill patients. Moreover, the LV size has never been described as a predictive index of a positive hemodynamic effect after fluid expansion in patients with shock. Because the LV size is a highly variable parameter, the individual 'optimal' size to obtain the best preload to eject the highest stroke volume is unknown. Patients with LV systolic dysfunction, dilated left ventricle, and a normal or high LV diastolic pressure experience a high preload but may be in hypovolemic shock because their preload may be insufficient to eject the best stroke volume. After a small fluid challenge, such patients may increase LV size and stroke volume without a marked increase in end-diastolic pressure. Thus, the 'optimal' LV size to obtain the optimal stroke volume in such patients cannot be comparable with the optimal LV size in patients without LV systolic dysfunction and dilated cardiomyopathy. It has to be noted

that knowledge of LVEDA has been demonstrated to be of little value in predicting an increase in cardiac output in response to fluid infusion in patients with cardiovascular instability [1]. In patients with sepsis-induced hypotension, responders and non-responders to fluid could not be clearly discriminated before fluid infusion by using baseline values of LVEDA measured using echocardiography. Moreover, considerable overlap of baseline individual values of LVEDA was observed between responders and non-responders supporting the interpretation that a given LVEDA value cannot reliably predict fluid responsiveness in an individual patient [1, 23].

Left Diastolic Pressure Assessment Using Doppler Techniques

Wedge, left atrial, or LV mean or end-diastolic pressures have been proposed to reflect LV preload. Many studies have tried to assess these pressures, using cardiac Doppler.

Mitral Flow

From a 4-apical view, mitral flow may be recorded using pulsed Doppler. This flow is composed by an early (E wave) and late wave (A wave). Several indices have been found to correlate with diastolic pressures: ratio of E to A maximal velocity (E/A), deceleration time of E (DTE) wave, and deceleration time of A wave (DTA). A small E wave, E/A <1, DTE>150 ms [24], DTA >60 ms [25] are usually associated with low LV diastolic pressures [26]. Unfortunately, the mitral flow depends on numerous factors, such as LV relaxation and compliance, heart rate, etc. To this extent, 'normal' mitral flow may be recorded in the presence of high LV pressure in patients with diastolic dysfunction. Recently, it has been proposed that the velocity of the E wave (which is very dependent on diastolic function) should be 'normalized' by a preload-independent Doppler parameter. Maximal early diastolic velocity of the mitral annulus (Em) recorded using DTI and early diastolic mitral flow propagation velocity (Vp) using M-mode color Doppler have been proposed to assess the LV end-diastolic pressure (LVEDP). Values of E/Em <8 [27, 28] and E/Vp <2.5 [29] were found to be usually associated with low LVEDP. Finally, it must be stressed that in the presence of tachycardia (> 120 beats/min) or arrhythmias, little information can be drawn from transmitral flow recordings in terms of assessment of filling pressures.

Venous Pulmonary Flow

Venous pulmonary flow can be used to assess LVEDP. Kucherer et al. [30] were the first authors to report a relationship between the systolic fraction (ratio between velocity time integral [VTI] of the systolic wave and the sum of the VTI of diastolic and systolic waves) and the left atrial diastolic pressure. The systolic fraction (SF) < 55% was described as a sensitive parameter to detect a high left

atrial pressure (>15 mmHg). This flow is also influenced by LV diastolic function and hence should be used with caution in patients with LV diastolic dysfunction.

Combination of Mitral and Venous Pulmonary Flows

During atrial contraction, the blood is ejected into the LV (A wave on mitral flow) and into the pulmonary veins (reverse a wave on venous pulmonary flow). In the presence of high LV diastolic pressure, duration of the A wave shortens and the ratio between the duration of the A and a waves becomes less than 1. Therefore, normal or low LV diastolic pressures are usually associated with an A/a ratio > 1 (31, 32).

This approach of assessing left diastolic pressures has many limitations. First these pressures are different from each other, in particular with mitral valve disease or reduced LV compliance. Second, the relationship between LV diastolic volume and pressure is not linear but curvilinear and depends on the LV compliance such that, for a given LV volume, filling pressures are higher in patients with a reduced LV compliance than in those with normal LV compliance and a change in volume results in more marked changes in pressures in the former group of patients. Third, these indices have never been evaluated in terms of prediction of fluid responsiveness.

Cardiac Output

The cardiac output can be measured easily using echocardiography and Doppler [33]. Many methods using either transthoracic and/or transesophageal approaches have been described and validated in ICU patients [34–36]. Measuring cardiac output at the level of the aortic annulus represents the best technique. Using the transthoracic method, the diameter of the aortic annulus should be measured from a long axis view of the LV at the level of insertion of the aortic valve while aortic blood flow must be recorded using continuous wave Doppler from an apical 5-chamber view. Using the transesophageal approach, the aortic area can be measured directly and aortic flow can be obtained either from a transgastric 5-chamber view or from a transgastric proximal view with an angle of 110–130°. In terms of diagnosis of volume depletion, the information provided by the sole measurement of cardiac output is non specific, since hypovolemic conditions are associated with low cardiac output values as are cardiac failure conditions. However, since echocardiography also gives information on cardiac function, cardiac chamber dimensions, and mitral and pulmonary vein flow patterns, combined measurements of several variables may help to diagnose low volume status. For example, in a patient with no history of cardiac disease, the association of a low cardiac output with a normal ejection fraction should most often lead to the diagnosis of hypovolemia, even if more sophisticated indices are not recorded. Obviously, in the case of prior cardiac dysfunction, the diagnosis of volume depletion could be more difficult to make from such static cardiac echo-Doppler measurements.

Evaluation of Preload Dependence using Doppler Parameters

In patients receiving mechanical ventilation, the magnitude of stroke volume variation over a respiratory cycle has been proposed to provide relevant information on volume status [37]. Indeed, by reducing the pressure gradient for venous return, mechanical insufflation decreases right ventricular (RV) filling and consequently the RV stroke volume, if the RV is sensitive to changes in preload. In this condition, the following decrease in LV filling will also induce a significant decrease in LV stroke volume if the LV is sensitive to changes in preload. Therefore, the magnitude of the respiratory changes in LV stroke volume, that reflects the sensitivity of the heart to changes in preload induced by mechanical insufflation, has been proposed as a predictor of fluid responsiveness [38]. Because the arterial pulse pressure is directly proportional to LV stroke volume, the respiratory changes in LV stroke volume have been shown to be reflected by changes in pulse pressure [39]. Accordingly, the respiratory changes in pulse pressure have been demonstrated to accurately predict fluid responsiveness in mechanically ventilated patients with septic shock [40]. The magnitude of the respiratory changes in systolic pressure has also been proposed to assess fluid responsiveness in patients with acute circulatory failure related to sepsis [41]. Using cardiac echo-Doppler, LV stroke volume can be obtained by calculating the product of aortic VTI and aortic area, measured at the level of the aortic annulus. Because aortic area is assumed to be unchanged over the respiratory cycle, respiratory variation in stroke volume can be estimated by respiratory variation in VTI. Using this hypothesis, we have shown, in a recent experimental study, that the magnitude of the respiratory changes in VTI (recorded by transthoracic echocardiography at the level of aortic annulus) was a highly sensitive indicator of blood withdrawal and blood restitution in rabbits receiving mechanical ventilation [42]. Moreover, this dynamic parameter was able to predict fluid responsiveness more reliably than conventional static markers of cardiac preload measured by echocardiography [42]. The superiority of such dynamic parameters over static ventricular preload parameters to predict fluid responsiveness in critically ill patients has been emphasized recently [1]. In this way, Feissel et al. [23] using TEE, demonstrated that the magnitude of respiratory variation of the peak value of blood velocity recorded at the level of the aortic annulus (Vpeak), was better than static measurement of LVEDA for predicting the hemodynamic effects of volume expansion in septic shock patients receiving mechanical ventilation. In this study, Feissel et al demonstrated that when patients with septic shock experienced a value of Vpeak > 12%, 500 ml fluid infusion increased stroke volume and cardiac output by more than 15% while decreasing Vpeak proportionally [23].

It must be stressed that the use of dynamic parameters such as respiratory variation of surrogates of stroke volume to assess volemic status, must be applied only in patients who receive mechanical ventilation with a perfect adaptation to their ventilator and who do not experience cardiac arrhythmias.

Conclusion

In summary, using echocardiographic and Doppler parameters, low volume status is often characterized by a small inferior vena cava size and large diameter respiratory changes, large respiratory movements of the interatrial septum, small LV size, E/A ratio < 1, DTE > 150 ms, TDA > 60 ms, A/a > 1, SF > 55 %, E/Em < 8 and E/Vp < 2.5, low cardiac output and large respiratory variations of aortic flow or stroke volume.

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Right Ventricular End-Diastolic Volume

J. Boldt

"Since during critical illness maintenance of the cardiac output may depend upon right ventricular function, the clinician needs to be able to discern the presence of right ventricular dysfunction ..." (William Hurford, Intensive Care Medicine, 1988)

Introduction

Improvements in surgical techniques and perioperative anesthetic management have led to surgery and intensive care therapy for patients who would have never been acceptable candidates before. Accurate assessment of hemodynamic status is a 'conditio sine qua non' when managing the critically ill. There has been a tremendous increase in the availability of monitoring devices over the last years. Ongoing developments in monitoring techniques have shed new light on our knowledge of pathophysiologic processes associated with critical illness and have influenced our therapeutic approaches.

The interest in hemodynamic monitoring is focused mostly on the 'dominant' left side of the heart. The tendency to 'overlook' the right ventricle as an important part of the circulatory system is due to the fact that it has traditionally been regarded as a passive conduit, responsible for accepting venous blood and pumping it through the pulmonary circulation to the left ventricle [1]. Maintenance of normal circulatory homeostasis, however, depends on an adequate function of both ventricles. Changes in dimension and performance of one ventricle influence the geometry of the other (Fig. 1). There is growing interest in the importance of the neglected right side of the heart, particularly in patients suffering from sepsis, trauma, acute respiratory distress syndrome (ARDS), and in heart transplanted patients [2].

Why May A Closer Look at Right Ventricular Volumes be of Interest?

Ventricular interdependence is a complex interplay of interactions mediated by the common myocardial fiber bundles, the interventricular septum, the constraining influence of the pericardium, and the pulmonary circulation (Fig. 2). Thus alterations in right ventricular (RV) function may have detrimental consequences on the function of the left side of the heart (Fig. 3). The consequences on altered

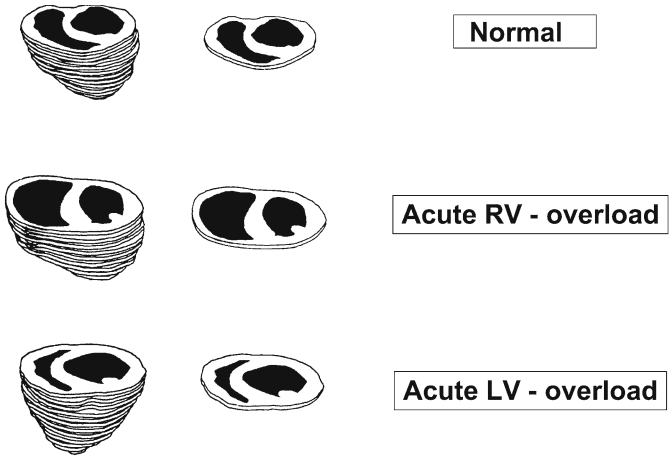

Fig. 1. Geometry of the right ventricle (RV) in combination with changes of the shape of the left ventricle (LV)

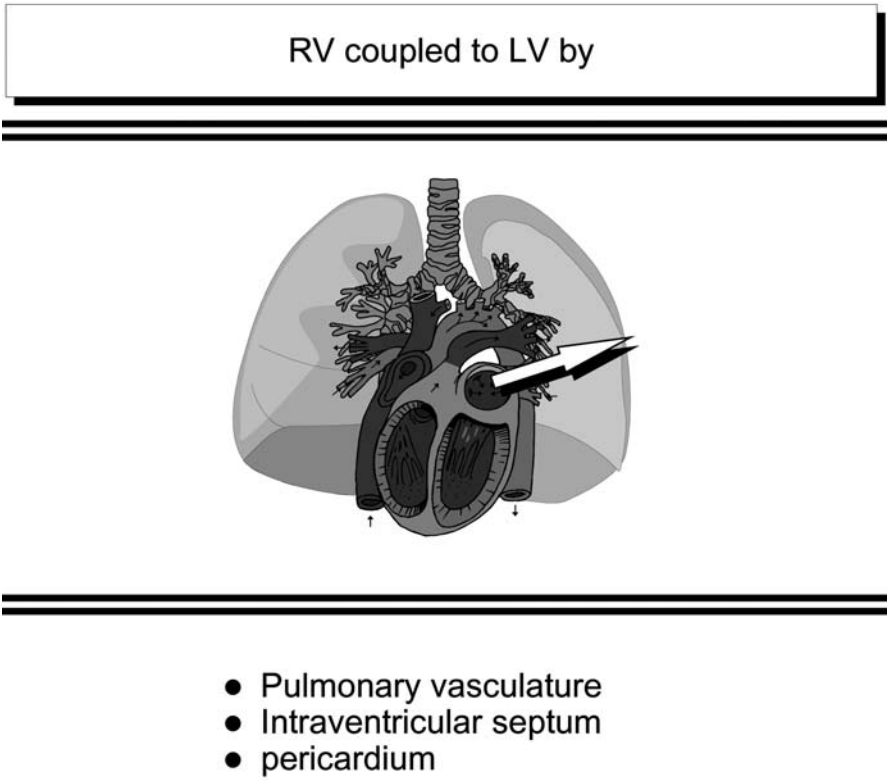

Fig. 2. Coupling of the right ventricle (RV) with the left ventricle (LV)

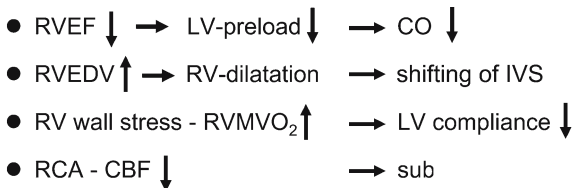

Fig. 3. Influence of changes in right ventricluar (RV) hemodynamics on the left ventricle. CO: cardiac output; RVEF: right ventricular ejection fraction; RVEDV: right ventricular end–diastolic volume; IVS: interventricular septum; RCA: right coronary artery; CBF: coronary blood flow

loading (e.g., increased preload) and unloading (e.g., increased afterload) conditions differs widely between the two ventricles (Fig. 4). Another important aspect for understanding the (patho-) physiology of RV performance is represented by the compliance, that describes the relationship between end-diastolic volume and end-diastolic pressure of the ventricle.

How to Assess Preload Conditions?

RV preload is often assessed by measuring filling pressures such as central venous pressure (CVP) or right atrial pressure. Both, however, do not correlate with RV end-diastolic volume (RVEDV) [3, 4]. For several years, pulmonary capillary wedge pressure – better named pulmonary artery occlusion pressure (PAOP) – has been used as the primary surrogate for left ventricular (LV) preload. It has been demonstrated that monitoring of RVEDV is easier and more accurate than PAOP, especially in patients with high levels of positive end-expiratory pressure (PEEP) or other ventilatory support that may raise intrathoracic pressure [5].

Monitoring of Right Ventricular Volumes by Thermodilution

With conventional pressure monitoring, assessment of RV preload is not accurately possible. Hoffman et al. [4] demonstrated no significant correlation between CVP and RVEDV and emphasized that the preload factor in the original Frank-Starling hypothesis had nothing to do with pressure but volume.

RV loading and performance are difficult to measure by conventional monitoring techniques because of the functional anatomy and complex geometry of the right ventricle [6]. Bing et al. [7] were the first to propose the principle of indicator dilution measurement to quantify RV volumes. Although the response time of conventional thermistors was sufficient to measure thermodilution cardiac output, they were, however, not rapid enough to accurately measure beat-to-beat step changes in temperature required to calculate ventricular volumes. Mounting fast-response thermistors on conventional thermodilution pulmonary artery catheters (PACs) allows rapid detection of changes in pulmonary artery temperature.

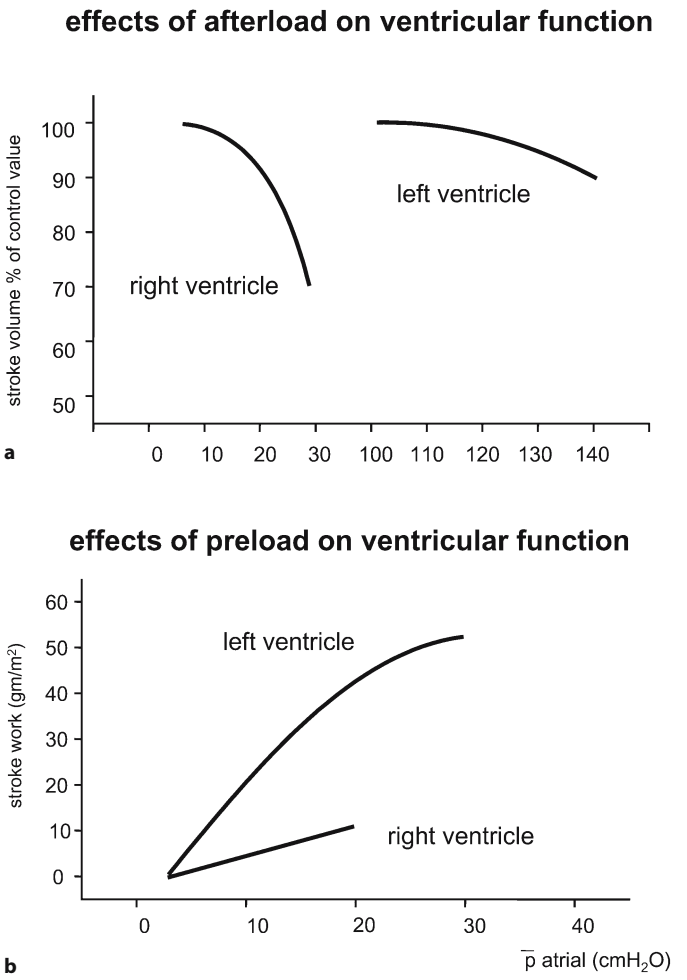

Fig. 4. Effects of changes in afterload (a) and preload (b) on right and left ventricular performance

Measurement of RV volumes (RVEDV, RV end-systolic volume [RVESV]) and RV ejection fraction (RVEF) by thermodilution is an easy to perform technique with no accumulation of toxic indicators based on the use of a fast-response thermistor. This enables accurate detection of rapid step changes in the staircase curve of the downstream temperature change (Fig. 5). The catheter is equipped with a fast-response thermistor and electrodes for intracardiac electrocardiographic (EKG) recording. The typical downslope thermodilution washout curve follows an exponential decay, interrupted by the diastolic plateaus (Fig. 5). The ratio between the temperature change of two successive diastolic plateaus represents the fraction of blood remaining in the right ventricle (=residual fraction

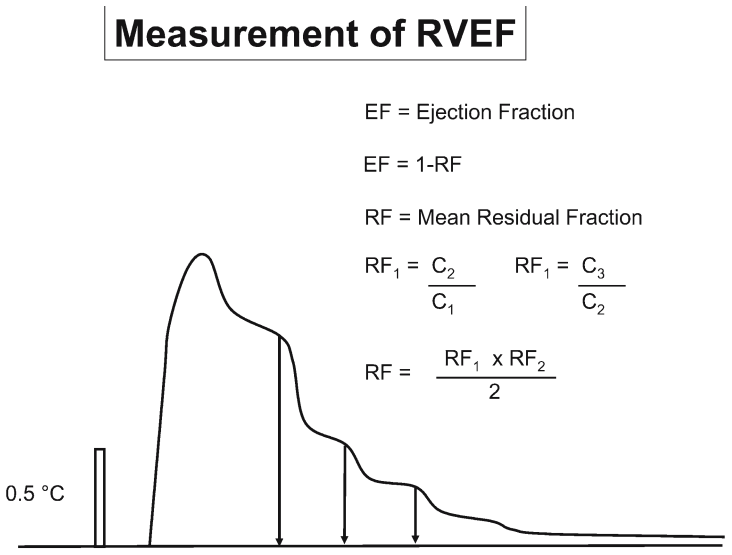

Fig. 5. Principle of measuring right ventricular volumes and ejection fraction

[RF]). RVEF is calculated from EF=1-RF. The thermistor of the thermodilation volumetric catheter is able to measure beat-to-beat temperature variations of the downstream temperature changes after injection of an (ice-cold) indicator (e.g., dextrose) or – nowadays – (almost) continuously by using heating filaments mounted on the catheter by which energy is transmitted to the circulating blood. As cardiac output and stroke volume are calculated by the microprocessor, RVEDV can be derived from stroke volume/RVEF and RVESV=RVEDV-stroke volume.

The accuracy and validity of this technique have been shown by using radionuclear methods in humans as well as in the animal model and it has been proved to be valid and accurate for measuring RV volumes (and RVEF) in comparison to radiographic, radionuclide, and echocardiographic methods [8–12]. Measurement of RV volume by thermodilution shows reproducible results (coefficient of variation of near 7%) [13]. Moreover, measuring RVEDV by thermodilution is unaffected by arbitrary and often poorly reproducible zero points for pressure transducers that are necessary to measure filling pressures (e.g. CVP, PAOP).

Problems With Measuring Right Ventricular Volumes

All monitoring devices have their pros and cons. While close monitoring of RV volumes (and RVEF) using thermodilution technique was assessed as a useful monitor [14], others stated good reproducibility, but less certain accuracy [15].

The major problems associated with RV volumetric catheters are:

- injection technique
- irregular heart rate (arrhythmias, atrial fibrillation)

- intracardiac shunt
- tricuspid regurgitation
- place of injection of cold indicator
- mathematical coupling
- higher costs

Injection Technique

The accuracy of the intermittent thermodilution technique is reported to range from ±3% to ±30% [16]. Its accuracy depends on several factors including constant injection, technique (=homogeneity) of injection, temperature of the injectate bolus, timing of the indicator injection within the respiratory cycle, and others [17–19]. The question concerning the optimal technique for measuring cardiac output by intermittent bolus thermodilution is still controversial. One of the major problems appears to be the timing of the thermal injection. Both end-expiratory and end-inspiratory points on the ventilatory cycle are used for measurement of cardiac output. Others have suggested averaging three thermal injections distributed equally over the ventilatory cycle or to calculate four to five thermal injections carried out at random relative to the ventilatory cycle [19]. Recently it has been demonstrated, in a study in critically ill patients on mechanical ventilation, that for correct measurement of RVEDV using the thermodilution technique, multiple determinations at equally spaced intervals, or at least eight at random injections in the ventilator cycle are necessary due to ventilatory modulation of RV volumes and interindividual differences therein [20].

Arrhythmias

When using the thermodilution technique to assess RV volumes, accurate sensing of R-waves is a prerequisite to calculate residual temperature. When the R-R-interval is irregular (e.g., secondary to atrial fibrillation) volumes (and ejection fraction) cannot correctly be determined. Aside from irregular heart rate, RV monitoring using RV volumetric catheters may become less reliable at higher heart rates (e.g., tachycardia >150 beats/min), because the R-R-interval is too short to identify ejection fraction [21, 22].

Place of Injection

Conventional thermodilution measurements involve positioning of the catheter injectate port in the right atrium – in immediate proximity to the tricuspid valve. In an animal study in pigs, the effects of catheter position on thermodilution RVEF measurements were studied. A RV thermodilution catheter was placed in the pulmonary artery, an injectate catheter in the right atrium, an atrial pacing electrode, and a systemic arterial catheter [23]. RVEF measurements were determined using thermodilution with incremental increases in pulmonary valve to

thermistor distance and with incremental increases in injectate port to tricuspid valve distance. Measurements were obtained at a paced rate of 102 beats/min and repeated with pacing-induced tachycardia (140 beats/min). There were no significant differences in thermodilution RVEF measurements with the thermistor positioned 0 to 10 cm from the pulmonary valve at either heart rate. A significant reduction in RVEF occurred with the injection port located 5 to 7 cm proximal to the tricuspid valve, with this decrease becoming more pronounced during tachycardia. The authors concluded that thermodilution RVEF measurements (and RVEDV) appear to be independent of thermistor position within the pulmonary artery. However, large distances from the injectate port to the tricuspid valve reduced RVEF measurements.

Mathematical Coupling

Another concern regarding RV volumetric catheters is based on possible mathematical coupling [15]: measurement of cardiac output and RVEDV both use the thermodilution principle. Since the RVEDV is calculated by dividing the stroke volume by the ejection fraction, it appears that the relationship between cardiac index (CI) and stroke volume causes the statistical correlation. Chang et al. [24] measured cardiac output by the Fick principle and RVEDV by thermodilution and thus removed the possible effect of mathematical coupling. Others have also argued that the better correlation of RVEDV with CI versus PAOP and CI is not due to coupling *per se* [25]: Durham et al [5] showed that RVEDV correlated more closely with CI than PAOP in 38 critically ill patients, even after correction for mathematical coupling. Nelson et al. [26] measured RVEF and cardiac output by the intermittent bolus thermodilution method and continuous cardiac output by a pulsed thermal energy technique. RVEDV calculated from thermodilution correlated well with both the thermodilution-derived cardiac output and the independently measured continuous cardiac output. Because random measurement errors of the two techniques differ, mathematical coupling alone does not explain the correlation between RVEDV estimates of preload and cardiac output.

Cost Considerations

RV volumetric monitoring adds considerable costs to conventional PAC monitoring, especially when using (near) continuous measurement techniques. Nelson [22] reported an addition of +20% to the costs of the traditional PAC. These are only estimated data, because costs vary widely between different countries. Moreover, hardware costs (another bed-sided computer system) have to be added.

Is Monitoring of RVEDV useful from a Clinical Point of View?

RV decompensation may result from several insults and may have various negative sequelae (Fig. 6). Introduction of RV volumetric measurement into a PAC has

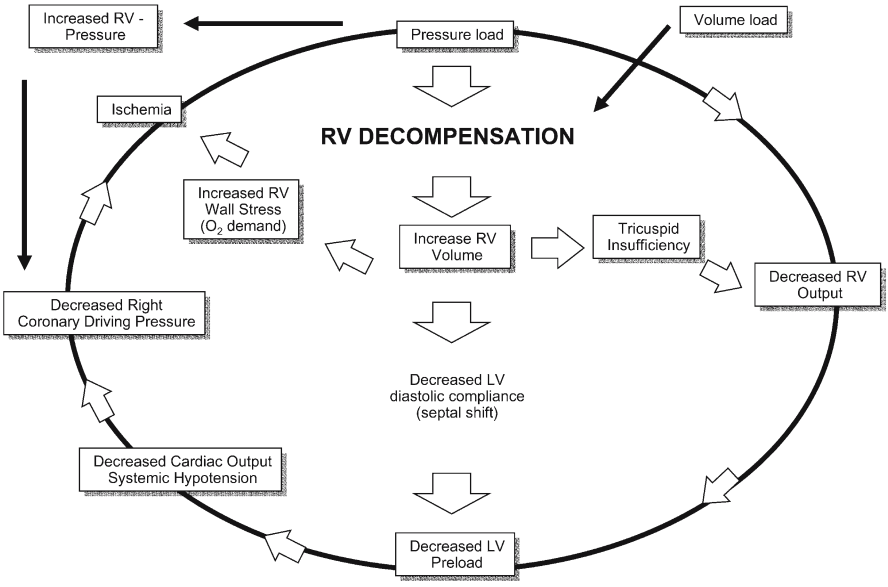

Fig. 6. Reasons for right ventricular (RV) decompensation and its consequences

broadened the overall assessment of cardiac function in the critically ill (27). Enlarging our monitoring armamentarium by measuring RV volumes has several advantages:

- bedside monitoring system
- no risk of indicator accumulation (repeated measurements)
- no more invasive than a standard PAC
- additional information besides pulmonary artery pressure, PAOP, and cardiac output
- less expensive than other techniques for assessing RV function
- (near) continuous RV hemodynamic monitoring possible

RVEDV correlates well with CI. This correlation between RV preload and LV function appears to be of particular value when considering volume challenge in patients with inadequate cardiac output [22]. Cardiac preload is often assessed by monitoring PAOP. However, there is increasing evidence that PAOP appears to be poor predictor of the preload status. In the critically ill, the assumption that PAOP reflects left atrial pressure and thus LV end-diastolic pressure (LVEDP) is often incorrect most likely due to changes in ventricular compliance. Mechanical ventilation and use of PEEP are reasons for the dissociation of PAOP and preload status. In mechanically ventilated trauma patients, PAOP was not able to reflect preload, whereas RVEDV was a reliable indicator of preload [28, 29]. Several other studies in the critically ill have demonstrated that RVEDV is a much better predictor of preload than PAOP:

- RVEDV was reported to be a better predictor of preload-recruitable stroke volume by a fluid challenge than filling pressure, so that a high volume may preclude a further rise in cardiac output with fluids, independent of filling pressures [3, 20].
- In patients undergoing aortic reconstruction, monitoring of RVEDV using a thermodilution technique provided a better means of evaluating the cause of decreased cardiac output during surgery and led to direct appropriate interventions [30]. Additionally, changes in CI with aortic cross-clamping correlated with the degree of coronary artery disease and were not reflected by PAOP.
- Intra-abdominal hypertension and abdominal compartment syndrome cause significant morbidity and mortality in surgical and trauma patients. Maintenance of intravascular preload and use of open abdomen techniques are essential. Multiple regression analysis demonstrated that RVEDV is superior to PAOP and CVP as an estimate of preload status in patients with an open abdomen [31].
- Sepsis may be associated with complex changes in RV function related to multiple factors both directly and indirectly altering diastolic and systolic ventricular function [10, 32, 33]. In this situation, RVEDV and RVESV vary independently of changes in right atrial pressure and ejection pressure most likely due to the fact that the RV is a highly compliant chamber during filling and thus changes in RVEDV do not alter RV wall stress (preload) or ejection efficiency (RVEF). The slope of the RVESV/RVEDV relation should be inversely proportional to ejection efficiency [10].

An increasing number of cases of RV ischemia and RV failure after coronary bypass grafting have been reported [34]. Because of the relatively hazardous RV preservation during cardiopulmonary bypass (CPB), postoperative RV function may be impaired by myocardial areas that remain ischemic [35]. Increased end-diastolic volume (and decreased RV contractility index) may occur already prior to CPB – especially in patients with reduced LV function or in elderly cardiac surgery patient (Figs. 7 and 8) [36, 37]. In 30 consecutive patients with reduced LV function (LV ejection fraction [LVEF]) undergoing myocardial revascularization, RV hemodynamics were studied from the beginning of anesthesia until the end of the operation [36]. The data were compared with 30 consecutive patients with almost normal LVEF. RVEF was significantly lower in the patients with a LVEF below 30% and RVEDV was significantly higher (Fig. 7). These patients may be unable to make the adaptations required. Acute volume loading may lead to further deterioration of myocardial function due to RV failure, a condition that cannot be diagnosed readily at the bedside with conventional monitoring techniques. As ischemia of the RV myocardium seems to be the limiting factor in the response to pressure load, reduced RV function already preoperatively may have disastrous consequences for RV performance during and after weaning from bypass. More attention should be focused upon the right ventricle in these patients, which can be monitored by rapid response thermodilution. Knowledge of the complex interaction between both sides of the heart may enable us to optimize patient management during the perioperative period (e.g., volume versus inotropes).

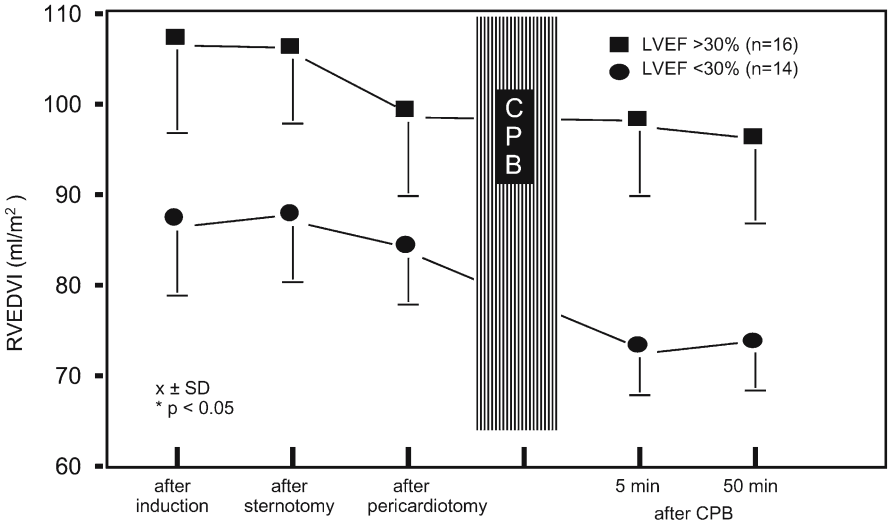

Fig. 7. Right ventricular end-diastolic volume index (RVEDVI) in patients undergoing cardiac surgery showing almost normal left ventricular function (ejection fraction >30%) in contrast to patients with markedly reduced left ventricular function (ejection fraction <30%). CPB: cardiopulmonary bypass – modified from [37] with permission

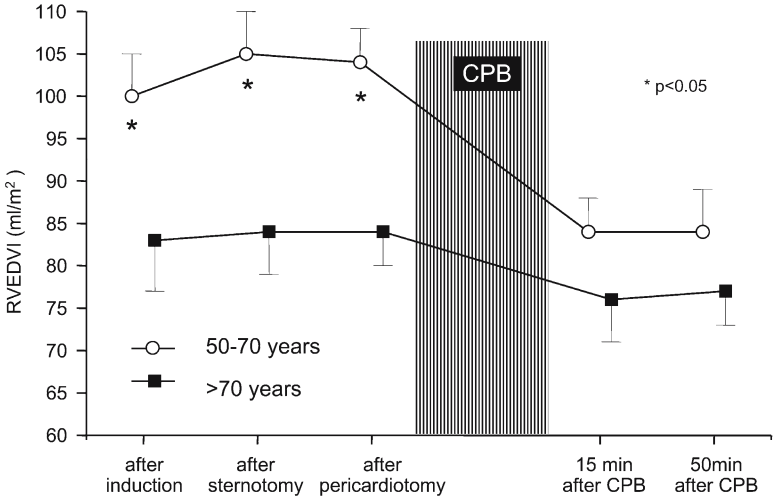

Fig. 8. Right ventricular end-diastolic volume index (RVEDVI) in patients undergoing cardiac surgery aged either >70 years or aged 50–70 years. CPB: cardiopulmonary bypass – modified from [36] with permission

Impact of RV Monitoring on Outcome

One of the most urgent questions is whether RV volumetric monitoring may help to improve 'outcome'. It is dubious whether a specific monitoring system is actually able to improve 'outcome' (i.e., to reduce lethality). However, it is certain that monitoring of RV volumes by a PAC yields additional beneficial information. In a small sample of surgical patients with sepsis, ARDS, and hemorrhagic shock (n=13), the additional information derived from RVEDV index (RVEDVI) did not change treatment in 43 of 46 instances [38]. However, patients with increased intra-abdominal pressures may show misleadingly high PAOP despite low preload. These patients clearly benefited from the additional information derived from ventricular volume measurements. Additionally, clinicians who are reluctant to take off-PEEP PAOP may also find this catheter useful [38]. Others demonstrated that monitoring RVEF by using RV volumetric catheters is a predictor of survival in trauma patients [39] and in patients with congestive heart failure associated with coronary artery disease [40]. Thus monitoring of RV data may contribute to the evaluation of the patient's prognosis [2]. However, no large clinical trials are available showing a beneficial impact of RV volume monitoring on patient outcome. By using this sophisticated monitoring device, additional data are available that may be associated with the danger that the untrained and uncritical physician is confused and misled by such a mass of information.

Conclusion

RV dysfunction is recognized as an important factor in modulating hemodynamics in critical illness. Various factors can contribute to an abnormal RV performance including perioperative RV infarction, insufficient revascularization of the right coronary artery, RV overdistension, inadequate (hypothermic) protection of the right ventricle, or pulmonary injury (=increasing RV afterload).

With the help of conventional pressure monitoring, accurate assessment of RV performance is not possible: The assessment of ventricular function is based upon the measurement of both volumes and pressures. Commonly monitored parameters such as CVP, right atrial pressure, or RV pressure have been demonstrated to be invalid for judging RV loading conditions. Further development of computer techniques allows intermittent or (near) continuous monitoring of RV hemodynamics.

Measurement of RVEDV using the fast-response thermodilution technique provides a more accurate estimation of (true) fiber preload. The results on the value of monitoring RVEDV are, however, far from being uniform. The discrepancy in the benefits of RVEDV monitoring as a surrogate of cardiac preload is most likely due to the diverse patient populations studied [25]. It is important to stress that it is not the absolute values of RVEDV (RVESV or RVEF) that are of interest, but the intraindividual changes (e.g., after volume therapy, inotropes, or vasodilators).

Whether enlarging our monitoring armamentarium by using thermodilution RV volume measurements may help to improve patient outcome remains to be elucidated. There is no doubt that the use of monitoring devices may yield addi-

tional information, and there is no doubt that some information may be useful. But there can also be no doubt that the malfunctioning monitor device and the inadequately-trained, misinterpreting physician may be a great risk for the patient – "A fool with a tool is still a fool".

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Assessment of Fluid Responsiveness

Fluid Therapy of Tissue Hypoperfusion

R. P. Dellinger

Introduction

Acute circulatory shock comes in many forms. Despite the etiology, fluid therapy is considered the initial intervention in the overwhelming majority of cases. The most common cause of shock is an adequacy of intravascular volume such as may occur due to acute blood loss (trauma or gastrointestinal hemorrhage) or fluid and electrolyte loss (vomiting or diarrhea). In hypovolemic shock, a 30% to 40% loss of circulating blood volume leads to marked hypotension and organ hypoperfusion. Trauma life support protocols teach that the initial management of the trauma patient is the placement of two wide bore 16 to 18 gauge cannulas followed by administration of 2 liters of warm Ringers lactate. This is now essentially a universal postulate for the initial treatment for traumatic induced hypovolemia. The second most common cause of acute circulatory failure is likely cardiac, and fluid challenge is less likely to be appropriate therapy. Septic shock and severe sepsis-associated organ hypoperfusion is the third important and frequently seen cause of acute circulatory failure, and again fluid challenge is the highest priority for treatment. Less commonly seen, but equally important, etiologies include pulmonary embolism, pericardial tamponade, anaphylaxis, and neurogenic. Of these, only pulmonary embolism would not be expected to benefit from fluid challenge.

Clear cut initial targets for resuscitation are mean arterial pressure (MAP) > 60–65 mm Hg as the primary indicator of adequate tissue perfusion. Markers of adequate perfusion such as lactate, venous oxygen saturation, mentation, and urine output are also important [1].

Persistent Tissue Hypoperfusion

Following initial resuscitation evidence of tissue hypoperfusion may persist in the critically ill patient. Signs of tissue hypoperfusion may also wax and wane in the intensive care unit (ICU) patient and be considerably more subtle than the patient presenting with acute hypotension and fluid evidence of tissue hypoperfusion. In that circumstance, a ‘fluid challenge’ is administered followed by careful observation for evidence of physiologic benefit or even harm.

Importance of the Venous System

The venous system contains 60 to 75% of the blood volume, with the great majority of that in the small veins and venules [2, 3]. The venous blood volume of the bat wing is estimated to contain 84% of the total vascular volume [4]. The most important venous bed in the human body is the splanchnic region, which is richly innervated, highly compliant and holds approximately 25% of the total blood volume [2, 4], whereas the skeletal muscle capacitance vessels are poorly innervated and not significantly involved in the carotid sinus reflex [5, 6]. The venous system as the primary capacitance region in the body, has great influence on venous return and cardiac output. It is important not to confuse venous tone with venous return. Venous return is the rate of return of blood to the heart and must be equivalent to the cardiac output in a steady state condition. Determinants of body venomotor tone include mean circulatory filling pressure, venous compliance, venous resistance, and blood volume. In contrast, venous return or cardiac output is controlled by cardiac as well as vascular factors, including arterial and venous resistances, arterial and venous compliances, cardiac contractility, heart rate, and blood volume. Assessments of total body venous tone are demonstrated in Table 1.

The importance of the venous system in the pathophysiology of shock and in decisions on volume loading cannot be overemphasized. Adaptive venous system mechanisms in fish have long been enigmatic; since fish live in a gravity-free environment and have no venous valves, venous return in fish has been attributed to cardiac aspiration. However, the ability of the blue fish to withstand head-up tilting when out of water and the rapid posthemorrhagic restoration of arterial blood pressure in the trout points to the importance of venous tone in shock or shock-like conditions, even in this low level vertebrate [7–9]. The increase in vascular tone that accompanies hypovolemia is targeted to increase upstream pressure in the venous reservoirs and increase venous return to the heart.

Measurement of Vascular Compliance

Shock patients require rapid infusion of iso-osmotic and iso-oncotic fluids and research quantitation of vascular compliance is difficult. In order to obtain reli-

Table 1. Venous tone components [2]

• Venous compliance
• Venous capacitance function
• Venous resistance
• Mean capillary filling pressure (MCFP)
• Pressure gradient of venous return (MCFP – right atrial pressure)

able data, the investigation must be performed in the shortest time possible, and under conditions of stable systemic blood pressure, not frequently present in shock. In addition, the effect of mechanical ventilation on mechanical vessels is important, and needs to be distinguished from the disease producing the shock [10].

Response to Volume Expansion

Normal reaction to volume expansion includes a decrease in systemic and pulmonary vascular resistance due to counter regulation by baro- and volume receptors [11]. Arterial compliance often remains unchanged [12]. Neurohormonal reaction to volume expansion is associated with a reduction in the activity of the renin-angiotensin-aldosterone system, with a decrease in plasma renin activity [13, 14]. Plasma catecholamine levels decrease or remain unchanged, depending on baseline systemic nervous system activity. Changes in circulating vasopressin level are influenced by the combined effect of changes in plasma osmolality and sympathetic nervous system activity [15]. Thus, a hypo-osmotic fluid expansion would likely produce a significant decrease in circulating vasopressin [15]. Vascular and neurohumoral responses to volume expansion vary in expression based on type of fluids used (water, saline, hypertonic saline, oncotic fluid, and red blood cells/blood) [11].

The expected result of volume expansion in hypoperfusion states is an increase in left ventricular volume and cardiac output. It must be remembered, however, that the relationship between ventricular preload and stroke volume, as described by Frank and Starling is not linear, but curvilinear. An increase in ventricular preload produces an increased stroke volume only in circumstances where the ventricle is operating on the ascending portion of the Starling curve. If the ventricle is operating on the flat portion of the Starling curve, increase in preload produces no significant change in stroke volume (preload independent) [16]. An individual in a hypoperfused state will 'respond' to fluid challenge only if both ventricles are operating on the ascending portion of the Starling curve, i.e., both exhibiting preload dependence (Fig. 1). The increase in stroke volume as a result of fluid challenge depends not only on the increase in end-diastolic volume, but also on ventricular function since a decrease in ventricular contractility decreases the slope of the relationship between end-diastolic volume and stroke volume [17]. Fluid challenge in normal individuals almost always produces an increase in stroke volume. However, in patients with acute circulatory failure, the rate of response to fluid challenge markedly decreases to approximately 50%. Since increase in stroke volume is not the rule in acute circulatory failure, and since overly aggressive volume expansion may produce deleterious effects, variables that would predict response to fluid challenge would be important for clinical decision-making. However, many patients with acute circulatory failure lack clinical and laboratory indicators of hypovolemia, yet respond to fluid challenge. More precise bedside indicators of right and left ventricular preload might allow bedside decision-making to be optimized.

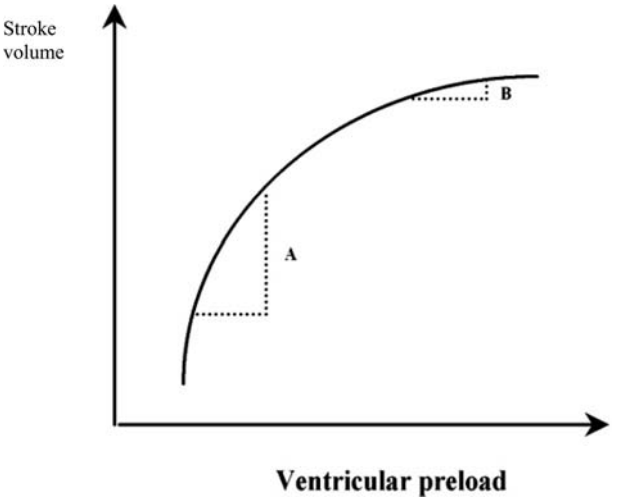

Fig. 1. The same increase in preload produces a significantly greater increase in stroke volume on the steep ascending portion of the Frank-Starling Curve. From [16] with permission

Table 2. Criteria for initiating a fluid challenge in adults with tissue hypoperfusion

- Systolic BP < 90 mm Hg
- Mean arterial pressure < 65 mm Hg
- Oliguria (urine output) consistently less than 30 mL/h
- Tachycardia > 100/min
- Lactic acidosis
- Cool extremities
- CVP < 8 mm Hg
- PAOP < 18 mm Hg
- Requirement for vasopressors to maintain blood pressure
- Drop in systolic blood pressure > 40 mm Hg

CVP: central venous pressure; PAOP: pulmonary artery occlusion pressure

Triggers for fluid challenge in a patient with acute circulatory failure are shown in Table 2.

Responses to Hypovolemia

Human responses to hypovolemia could be utilized as targets to reverse as indicative of successful of volume resuscitation. Table 3 lists the anticipated body responses to hypovolemia.

Table 3. Anticipated body responses to hypovolemia

- Decrease in blood pressure
- Increase in pulse pressure
- Increase in sympathetic nervous system activity
- Tachycardia
- Diversion of blood from skin and viscera to muscles and vital organs
- Reflex veno constriction
- Fluid shift from intracellular to extracellular space
- Increased afterload from sympathetic vasoconstriction and humoral factors
- Activation of renin-angiotensin system
- Increased lactate

Ventricular Preload Indicators of Fluid Challenge Response

Predicting response to fluid challenge based on ventricular preload may be problematic [18, 19]. Most frequently used hemodynamic markers of preload are central venous pressure (CVP, right atrial pressure) and pulmonary artery occlusion pressure (PAOP) [16], pressure estimates of right and left ventricle filling respectively. Many studies show that the initial CVP or PAOP value does not predict response to fluid challenge, and a consistent threshold value cannot be found to indicate whether a patient will be a responder or nonresponder to fluid challenge [20–22]. Right atrial pressure and PAOP may overestimate transmural pressures in patients with external or intrinsic positive end-expiratory pressure (PEEP). PAOP is highly dependent on left ventricular compliance, frequently decreased in critically ill patients. Therefore, it is not surprising that since end-diastolic volumes are determined by chamber compliance and transmural pressures, estimates of intracavitary pressures such as right atrial pressure and PAOP are often poor indicators of left ventricular preload. Volume expansion is expected to increase right ventricular end-diastolic volume (RVEDV) as well as left ventricular end-diastolic volume (LVEDV). This increase in right and left ventricular end diastolic volume depends on how the fluid is partitioned into the different cardiovascular compliance areas. RVEDV is calculated from the measurement of right ventricular ejection fraction and cardiac output by using a fast-response thermistor pulmonary artery catheter (PAC) [20, 23]. The calculation of right ventricular ejection fraction using the fast-response thermistor plus the knowledge of cardiac output and heart rate allows RVEDV to be calculated by the following formula:

$$\text{RVEDV} = \frac{(\text{Cardiac output/heart rate}}{\text{Right ventricular ejection fraction}}$$

RVEDV may be a better indicator of ventricular filling than PAOP, but may be influenced by tricuspid regurgitation.

Left ventricular end-diastolic area (LVEDA) as a measurement of LVEDV can be measured by either transesophageal or jugular notch echocardiography [19, 24]. The latter uses the transgastric short axis view of the left ventricle. LVEDA is an area and may not correlate well with diastolic volume measurement. In addition, in the presence of right ventricular dysfunction a beneficial hemodynamic effect of volume expansion cannot be expected even in the presence of low estimates of left ventricular preload. In order to truly predict the effect of fluid challenge in patients with known end-diastolic volume, one would also ideally need to know: (a) diastolic chamber compliance, (b) juxtacardiac pressure, (c) ventricular function curve, and (d) how the fluid will be partitioned in the series of vascular compartments leading up to the ventricle. It is important to recognize that response to a fluid challenge depends not only upon the volume status of the ventricle, but also on venous compliance, ventricular compliance, and ventricular function. Since ICU patients frequently have alterations in venous capacitance, ventricular compliance, and contractility, it is not surprising that bedside indicators of ventricular volume may be poorly predictive rof esponse to fluid challenge.

In the ICU, plasma volume expansion is considered at an end point when thermodilution derived measures of left ventricular blood flow or left ventricular stroke work fail to improve after fluid challenges. Conventionally in the emergency department measurement of blood pressure, pulse rate, and capillary refill have been used to assess circulatory status and need for fluid challenge. The use of Doppler ultrasound allows a velocity profile of blood flow in the thoracic aorta to be measured. This can be done either by supersternal (noninvasive approach) or esophageally (minimally invasive). Using a portable suprasternal Doppler ultrasound device, patients presenting to the emergency department with acute circulatory failure were identified as fluid responders utilizing measurement of stroke distance [24]. A time interval of a measured velocity profile is calculated and is called stroke distance and has been shown to be a proxy for left ventricular stroke volume. The product of stroke distance and MAP is called linear stroke work and is a reasonable estimate of left ventricular stroke work. Finally, the product of stroke distance and heart rate, called minute distance, is used as an estimate of cardiac output. In this study performed in the emergency department, 3.5 ml/kg boluses of colloid were infused intravenously over 10 minutes with stroke distance increases of at least 10% from previous value judged to indicate reasonable surrogates of volume responsiveness [25–28].

Although the assessment of preload may be a poor predictor of response to fluid challenge [16], response of respiratory changes in pressures and volumes following fluid challenge are more reliable indicators of hemodynamic improvement [29, 30] (Table 4).

Table 4. Respiratory change parameters for predicting fluid challenge responsiveness

- Right atrial pressure and spontaneously breathing patients
- LV stroke volume and mechanically ventilated patients
- Systolic pressure
- Pulse pressure

Central Venous Pressure as a Marker of Volume Responsiveness

To insure accurate placement of a CVP catheter it can be advanced into the right ventricle, then withdrawn until the right ventricular tracing is lost, and then withdrawn another 3–5 cm to assure a location in the superior vena cava [31]. Normal CVP ranges from 2 to 8 mmHg. The CVP is not a direct indicator of hypovolemia. After massive blood or fluid loss levels exceeding 11 cmH_2O have been reported. Mechanisms for this include onset of cardiac dysfunction with decreased coronary perfusion or veno constriction. CVP does not reflect vascular volume directly, but rather indicates the relationship between the volume that enters the heart and the effectiveness with which the heart ejects that volume [32]. Initially measured CVP exceeding 15 mmHg supports congestive heart failure, pulmonary embolism, or pericardial tamponade as the cause of acute circulatory failure. Initial CVP < 9 mmHg indicates a clearcut need for fluid challenge. When the initial CVP is found to be in the range of 9 to 15 mmHg the need for volume resuscitation to correct circulatory shock may be ascertained by observing changes in venous pressure during infusion of fluid boluses. A reference pressure value is established during an initial 10-minute period of observation in a patient with acute circulatory shock. A fluid challenge is then delivered. If the CVP increases by more than 5 mmHg during this interval, the infusion is discontinued. If the CVP does not increase by more than 5 mmHg over the 10-minute period, the process is repeated. Serial CVPs every 5 minutes following 100 ml challenges of isotonic saline are administered. If the CVP pressure rises no more than 4 mmHg and returns to within 2 mmHg of the initial level within 15 minutes after infusion, additional fluid challenges are likely to be beneficial.

Failure to show a significant increase in MAP after rapid bolus infusion of crystalloid, despite an increase in right atrial pressure, indicates the need to begin combined inotrope/vasopressor therapy. An adequate fluid challenge is defined as one in which either blood pressure or cardiac output increases.

Peripheral Venous Pressure

Studies attempting to utilize peripheral venous pressure as a more easily obtained marker of venous filling have demonstrated its unreliability. Under normal situations, peripheral venous pressure is higher than CVP since this is the gradient of

Table 5. Etiologies of uncontrolled hemorrhagic shock. From [33] with permission.

• Ruptured abdominal aortic aneurysm
• Penetrating truncal injury
• Traumatic aortic rupture
• Major hemothroax
• Major hemoperitoneum
• Severe pelvic fracture
• Gastrointestimal hemorrhage
• Ectopic pregnancy
• Antepartum hemorrhage
• Postpartum hemorrhage

blood return from periphery to the heart; however, in shock conditions this relationship is not reliable.

Volume Resuscitation of Hemorrhagic Shock: Minimal Volume Resuscitation

The concept of minimal volume resuscitation is now practiced by many clinicians who treat the list of etiologies of uncontrolled hemorrhagic shock in Table 5. The rationale for minimal volume resuscitation is that increased flow and pressure may lead to increased hemorrhage and loss of hemostasis [33]. Sudden increases in blood flow have the potential to precipitate rebleeding in sites that have obtained hemostasis. In general, fluid resuscitation has a negative influence on hemostasis, due not only to the increase in blood pressure and flow, but also to the reduced blood viscosity and dilution of clotting factors. Furthermore, some noncrystalloid volume solutions have direct anti-hemostasis properties. The concept of minimal volume resuscitation centers around using mini boluses of fluid to maintain a palpable radial pulse in absence of ability to measure blood pressure or a systolic blood pressure between 80 and 90 mmHg. The concept of minimal volume resuscitation is not new, in fact reports of possible benefit of this strategy date back to 1915 and were published in 1918 [34]. Near fatal models of uncontrolled hemorrhagic shock show that both no fluid and high fluid options produce very high mortality rates. Animal studies also demonstrate that a MAP of 40 mmHg offers the best balance of maintaining critical perfusion and hemostasis and is associated with optimum outcome [35]. Vascular surgeons were one of the first groups to promote minimal fluid resuscitation in patients with leaking abdominal aortic aneurysm [36, 37]. Several investigations support benefits of minimal fluid resuscitation in patients with severe truncal penetrating trauma [38, 39].

For leaking abdominal aortic aneurysm the optimum systolic blood pressure is thought to be 60–80 mmHg [37].

Choice of Fluids

Meta-analyses suggest that crystalloid and colloid fluids are equivalent for fluid challenges [40–42]. The use of Ringers lactate solution as the fluid of choice is most prominent in burns. It offers some buffering capacity, but carries a theoretical risk of iatrogenically increasing lactate acidosis in large doses in patients with liver failure. Unlike normal saline, it will not produce a hyperchloremic metabolic acidosis. In patients with severe hemorrhagic shock, type-specific group compatible blood given early compliments crystalloid resuscitation.

Amount and Rate of Fluid Administration

Initial Resuscitation

When fluid is administered as part of the initial resuscitation of profound tissue hypoperfusion (hypotension, lactic acidosis) an aggressive approach is taken. The recent recommendation from the Surviving Sepsis Campaign as to amount and rate of fluid resuscitation is:

"Fluid challenge in patients with suspected hypovolemia (suspected inadequate arterial circulation) may be given at a rate of 500–1000 ml of crystalloids or 300–500 ml of colloids over 30 mins and repeated based on response (increase in blood pressure and urine output) and tolerance (evidence of intravascular volume overload) [43]."

Fluid challenge must be separated from increasing maintenance fluid administration. Fluid challenge is used to describe the initial volume expansion period in which the response of the patient to fluid administration is carefully evaluated. During this process, large amounts of fluid may be administered over a short period of time under close monitoring to evaluate the patient's response and avoid the development of pulmonary edema. With venodilation and ongoing capillary leak, most patients require continuing aggressive fluid resuscitation during the first 24 hrs of management. Input is typically much greater than output, and input/output ratio is of no utility to judge fluid resuscitation needs during this time period [43].

Fluid Challenge

When fluid is administered to a more stable patient with the purpose of testing the response of the intravascular system and in such a situation where the benefit (or even detriment) of fluid administration is not clear, a smaller volume of fluid is chosen. This volume is typically in the range of 100–200 ml of crystalloid or 50–100 ml of colloid.

Table 6. Changes in normals and cirrhotics following plasma volume expansion

	Normals	**Cirrhotics**
Cardiac output	↑	↑
Blood pressure	↑	–
Systemic vascular resistance	↓	↓
Arterial compliance	– ↓	– ↑
Central blood volume	↑	– ↑
Interstitial space	↑	↑

Adapted from [44] with permission

Volume Expansion in Cirrhotics

Response to fluid challenge in patients with cirrhosis is different than in those without (Table 6) [44, 45]. An understanding of this difference is important in decision-making concerning fluid challenges in suspected tissue hypoperfusion in cirrhotic patients.

Primary and Secondary Periods of Shock Resuscitation

Primary and secondary periods of shock resuscitation have been described [46]. The primary period represents the first round of resuscitation and encompasses restoration of production of cardiac rhythm and forward blood flow and attainment of adequate MAP. The secondary period of resuscitation represents goals of establishing adequate organ perfusion pressure for all organs as well as oxygen transport to the metabolically active tissues.

Fluid challenge in Sepsis-Induced Hypoperfusion

General loss of vascular tone is a hallmark of sepsis and affects both arteries and veins. Fluid administration compensates for the increase in venous capacitance and maintains or even produces an increased cardiac output. In one animal study, fluid resuscitation blunted some of the neurohumoral mechanisms that are associated with more rapid deterioration, including severe decrease in cardiac function [47].

Both passive and active mechanisms produce alterations of veins in severe sepsis and rapid volume expansion produces arteriolar vasodilatation [48, 49]. In severe sepsis this change may be enhanced. In addition, although drug therapy utilized in the management of severe sepsis may not significantly influence the total blood

volume (TBV)/CVP, neurohumoral factors may modify vein properties [49, 50]. Whether this change is a primary defect or an adaptive mechanism is not clear [51]. Few changes in vascular compliance have been described during the early phase of experimental septic shock. The TBV/CVP ratio is more markedly reduced in the presence of severe disease. Distinguishing the direct effects of sepsis on venous compliance vessels from the reflex effects of hypotension is difficult [52]. Fall in blood pressure would be expected to elicit increases in sympathetic nervous system tone, which would then decrease venous compliance even in the absence of sepsis. In severe sepsis and septic shock, the effect of circulating blood volume and venous return is increased and appears to be a compensatory mechanism. Strong interactions appear to exist between reduced effective venous vascular compliance, degree of systemic hypotension, and severity of sepsis. Knowledge of total effective vascular compliance would be a very useful guide for fluid infusion and evaluation of cardiac function. Despite varying degrees of fluid loading in septic patients, mean blood pressure appears to remain constantly lower than in mechanically ventilated non-septic patients [53].

In patients with acute circulatory failure, alterations in arterial and venous compliance and filling are frequently accompanied by alterations in ventricular contractility. This complex relationship makes effects of therapy very unpredictable. In septic shock, initial measurement of left ventricular ejection fraction was a poor predictor of outcome with left ventricular ejection fraction actually lower in patients who recovered. The explanation for this paradox is the fact that left ventricular ejection fraction may not be a reliable indicator of left ventricular systolic function in a septic patient with a left ventricle that is unloaded by the low systemic vascular resistance (SVR). Left ventricular ejection fraction indicates the status of the SVR in addition to inherent contractile function. A significantly smaller LVEDV has been shown to exist in non-survivors versus survivors [54]. In those patients with the poorer prognosis, left ventricular size continued to decrease despite fluid challenge, perhaps indicative of persistent fluid leak.

A recent study of early goal-directed therapy in recent onset septic shock supports fluid challenge targeted toward a CVP of 8–12 mmHg and a central venous oxygen saturation of 70% [55].

Conclusion

Despite sophisticated bedside methods for judging response to fluid challenges, the gold standard of beneficial response remains objective changes in circulation such as increase in blood pressure, increased mental alertness, and increased urine flow.

The importance of early resuscitation of acute circulatory failure is supported by success of early goal directed therapy targeting the first 6 hours of hospitalization therapy with distinct goals of therapy [55]. When the patient is mechanically ventilated, this target should be higher due to the effects of increased intrathoracic pressure on transmural filling pressure.

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The Use of Central Venous Pressure in Critically Ill Patients

S. Magder

Introduction

The assessment of the central venous pressure (CVP) is one of the basic elements of a standard physical exam. This is done at the bedside by measuring the vertical height of the distension of the jugular veins above the sternal angle, which is where the second rib meets the sternum. The sternal angle is used because it is fortuitously approximately 5 cm above the mid-point of the right atrium whether the patient is lying down or whether the patient is sitting upright at a 60° angle. This works because the right atrium is a relatively anterior structure and sits just below the sternal angle. Differences in heart size only add a small difference to the measurement, and this standard reference point allows comparisons over time and by different operators. The midpoint of the right atrium is used as the standard reference point because it represents the lowest pressure for the blood returning to the heart, and the starting point from which the heart raises the pressure. The value is in cmH_2O, which can be converted to mmHg by dividing the value in centimeters by 1.36, which accounts for the density of mercury and the conversion from cmH_2O to mmHg. A major reason given for assessing the CVP is that it gives an indication of a person's volume status, but before the usefulness of this measure can be assessed, it is important to appreciate the factors that determine CVP and right atrial pressure [1]. In this chapter, I will use CVP and right atrial pressure interchangeably because there is normally only a negligible resistance between the pressure in the large veins and the right heart and the pressures are essentially the same.

What determines the CVP?

The cardiac output and right atrial pressure are determined by the interaction of the function of the heart and the function of the circuit that returns blood to the heart (Fig. 1) [2]. Cardiac function is typically represented by a 'Starling Curve', in which cardiac output is plotted as a function of the preload as estimated by the right atrial pressure. The cardiac function curve shifts upward with an increase in cardiac contractility or heart rate or a decrease in ventricular afterload and downward by the opposite. In other words, when cardiac function increases, there is an increase in cardiac output at a given right atrial pressure. The return function is

determined by the stressed vascular volume (i.e., the portion of total vascular volume that creates pressure in vessels), vascular compliance, the resistance to venous return, and the right atrial pressure. The right atrial pressure is thus common to both the cardiac function and return function and right atrial pressure (or CVP) is determined by how these two functions interact.

When examining the interaction of cardiac function and return function, it is important to appreciate that these two functions have limits (Fig. 1). The return function is limited when the right atrial pressure is less than atmospheric pressure or less than pleural pressure when the pleural pressure is greater than zero. When the return function is limited, increasing cardiac function does not increase cardiac output. On a venous return curve this is seen as a plateau.

The cardiac function is limited when cardiac filling is limited and therefore there cannot be an increase in cardiac output by the Starling mechanism despite increases in right atrial pressure. This is represented by the plateau of the cardiac function curve. Importantly, when cardiac function is limited, an increase in return function, as would occur with an increase in blood volume, does not increase cardiac output and can potentially do harm. The high venous pressure distends the right heart and pushes the septum to the left, which can then interfere with left heart function. High right ventricular pressures can impede coronary flow and myocardial perfusion, which can contribute to myocardial dysfunction. A high venous pressure also can compromise renal and hepatic function and lead to peripheral edema. Also of note, in the plateau phase of the cardiac function curve, decreases in right atrial pressure can occur without a decrease in cardiac output. The preload (defined as the pressure which gives the ventricular stretch before ventricular contraction) in this phase is effectively 'wasted preload'. It is thus clinically useful to know the right atrial pressure at which cardiac output becomes limited.

Unfortunately, the right atrial pressure at which the cardiac function curve reaches a plateau is very variable and exact guidelines are not possible. As an approximation, the probability of a response is low at CVPs greater than 12 mmHg [3] but, as has often been noted [4–6], the actual value of the CVP is not as useful as the dynamic response to fluids or another treatment. Importantly, it is the

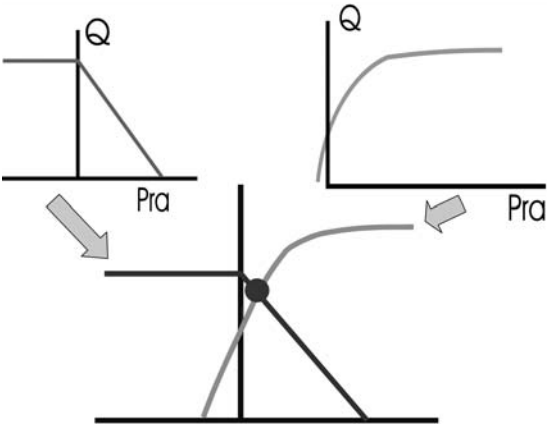

Fig.1. Right atrial pressure (and CVP) is determined by interaction of return function (upper left) and cardiac function (upper right). The abscissa is right atrial pressure (Pra) and the ordinate is flow (Q). Because the axes are the same they can be plotted together (bottom) and this gives *the* cardiac output and *the* right atrial pressure of the patient.

relationship of CVP to cardiac output that is critical. An analogous situation is the clinical interpretation of PCO2 on a blood gas. To make sense of the clinical significance of a value of PCO2 requires a simultaneous assessment of the pH, for only then can one determine if the process is acute or chronic and whether the person has adapted or not.

What does the CVP not tell you?

It is important to appreciate what the CVP does not tell you. The CVP by itself does not tell you the person's volume status or give an estimate of the mean circulatory filling pressure which is the mean pressure that distends the elastic vascular structure [2, 7]. Since the magnitude of the CVP is determined by the intersection of the pump function and circuit function, it is possible to have a very dynamic heart in association with a large blood volume and a low CVP. A simple example is exercise. During exercise, the CVP in a normal subject is only in the range of 2–4 mmHg and yet this is associated with very high cardiac outputs, and blood volume that is maximal [8, 9]. A high CVP also does not mean volume excess, for if there is a decrease in pump function or a restrictive process in the heart, the CVP could be elevated without the blood volume being increased.

The volume that is important for the determination of cardiac output is the stressed volume, for this is the volume which creates the mean circulatory filling pressure, which is the driving force for the return of blood to the heart [7]. Under resting conditions, approximately 70% of blood volume is unstressed and 30% is stressed [10]. However, sympathetic stimulation can recruit unstressed volume into stressed volume and maintain a normal mean circulatory filling pressure [11]. Thus, the unstressed volume provides an internal reservoir that can maintain an adequate mean circulatory filling pressure. This means that a patient can have a reduced total blood volume and yet have a normal CVP, mean circulatory filling pressure, cardiac output, and blood pressure, because the stressed volume is maintained by contraction of capacitant veins and only the unstressed volume is decreased. However, the significance of the reduced volume and decreased capacitance (i.e., decreased total volume for the pressure) will become very apparent if sympathetic tone is decreased by sedation or if an increase in mean circulatory filling pressure is required to compensate for a physical stress such as that produced by an increase in intrathoracic pressure [12]. Furthermore, infused volume may not remain as stressed volume. An increase in cardiac output and arterial pressure could result in reflex adjustments through the baroreceptors which will result in dilation of capacitance vessels and conversion of some of the increase in stressed volume into unstressed volume [11]. The magnitude of this effect will depend upon the overall balance of the system and is not readily predictable.

Technical Issues for the Measurement of CVP

Before one can consider using the CVP diagnostically, it is essential to understand the technical factors involved in the measurement. The range of CVP at which

most changes in cardiac output occur is from approximately 0 to 10 mmHg. For a normal cardiac output of 5 l/min, this means that, as an approximation, for constant cardiac function (i.e., constant heart rate, contractility, and afterload), a 1 mmHg change in right atrial pressure will result in a change of about 500 ml/min. Therefore small differences in the measurement of CVP due to differences in leveling, where the measurements are made with respect to the 'a' and 'v' waves and the assessment of the effects of respiratory efforts, can have significant impact on clinical conclusions. These issues will be discussed in this section. The most important point is that common principles are developed for this essential to allow trending of the measurements over time by the same person, repeated measurements by other health care workers, and comparison of results among different investigators.

All vascular pressures with fluid filled catheters are made relative to a reference level that is arbitrarily chosen. It is generally agreed that the mid-point of the right atrium is the appropriate standard reference point for hemodyamic measurements. This is the lowest pressure for the blood returning to the heart, and the pressure from which the heart re-circulates the blood. As noted in the introduction, the relation of the CVP to the right atrium is assessed on physical exam by making measurement of venous distension relative to the sternal angle which is a vertical distance of approximately 5 cm above the mid-point of the right atrium, whether the subject is lying down or sitting upright at a 60°. This reference position is used in some intensive care units (ICUs), including my own, for leveling measuring devices, but more often the mid-axillary (mid-thoracic) position is used because it does not require a leveling device to set the transducer. It is important to appreciate that CVP measurements that use the mid-axillary position give values that are 2 mmHg greater than those that use 5 cm below the sternal angle as the reference point. Furthermore, measurements made with the mid-axillary position must be made with the subject lying supine, whereas those made relative to the sternal angle can be made in any position up to 60° as long as the transducer is re-leveled [13].

When measuring the CVP one could choose the peak of the 'a' or 'v' wave, the mean pressure or the base of the waves (Fig. 2). The difference between the peak and the base of these waves can be as much as 8–10 mmHg and occasionally even higher, and therefore the choice can have a significant effect on the measurement. Since a major reason for measuring the CVP is for the assessment of cardiac preload, the measurement should reflect this value. Therefore, it has been recommended that the 'z' point or base of the 'c' wave be used for the measurement for this gives the final pressure in the ventricle before the onset of systole, and therefore is the closest approximation of the preload (Fig. 2). The 'c' wave is produced by buckling of the atrio-ventricular valves back into the ventricle and the base of the 'c' wave is just at the onset of systole. However, the 'c' wave is often hard to see and the base of the 'a' wave gives a good approximation of this value. If the electrocardiogram (EKG) signal is synchronized with the hemodynamic tracings on the monitor, the onset of the QRS wave can be used to identify the appropriate point on the CVP tracing after taking into account the delay of around .08 sec of the pressure signal from the fluid filled catheter measurement compared to the electrical signal.

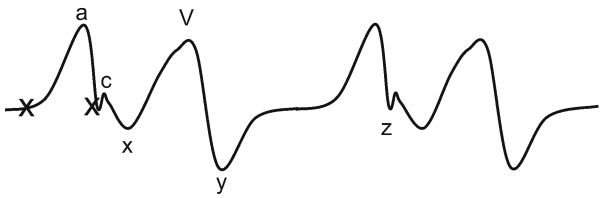

Fig. 2. Example of right atrial pressure tracing over two cardiac cycles. The X marks the appropriate place to make the measurement.

It needs to be appreciated that although the base of the 'a' wave is used for the measurement, this does not mean that there is no significance to the peaks or troughs of the other waves of the CVP. For example, if the base of the 'a' wave is 10 mmHg, but there is a 'v' wave with a peak of 20 mmHg, it is the value of 20 mmHg that affects the liver and kidney and can have very significant pathological consequences. Therefore, one must distinguish the measured pressure as recorded in the standard manner for reproducibility and as a measure of cardiac preload from the actual pressure that occurs during the cardiac cycle, which may have other consequences.

A major factor affecting the value of the CVP is the variation in pleural pressure for it is pleural pressure that surrounds the heart. Hemodynamic pressures are measured relative to atmosphere for this is the value that surrounds the measuring devices, and is therefore the value for zeroing measuring devices, whether the device is a column of mercury or water or a transducer. However, it is the transmural pressure, which is the difference in pressure between inside and outside the elastic structure, that determines the distension of the structure. This is not a problem when the right atrial pressure is analyzed as the backpressure for the return function, for the veins and venules that return blood to the heart are effectively surrounded by atmospheric pressure. However, the use of right atrial pressure measurements zeroed relative to atmosphere creates a problem for the measurement of pressures inside the thorax, for changes in pleural pressure relative to atmosphere effectively change the environment of intrathoracic structures relative to atmosphere and create changes in cardiac pressure which do not reflect the transmural pressure (Fig. 3). Thus, an increase in intrathoracic pressure can result in an increase is right heart pressure relative to atmosphere, even though right heart volume decreases and visa versa. This is because the distending pressure is the pressure inside the heart relative to outside the heart, but we unfortunately have to zero transducers to atmospheric pressure, which is outside the thorax, rather than pleural pressure, which is the true pressure outside the wall of the heart. To try to avoid the artifact produced by changes in pleural pressure, hemodynamic measurements are made at end-expiration, whether the subject is breathing spontaneously or whether the subject is ventilated with positive pressure, for at end-expiration the pleural pressure is closest to atmospheric pressure.

In patients who have positive end-expiratory pressure (PEEP), there is still an added positive pressure at end-expiration that creates an error in the measurement. However, even at a PEEP of 10 cmH_2O, which is less than 8 mmHg, and considering

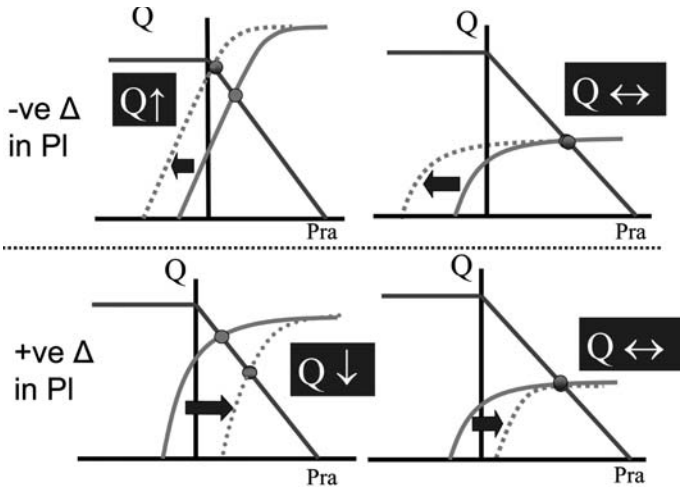

Fig. 3. The effect of changes in pleural pressure on the relationship of cardiac function and return function. The top panel shows a fall in pleural pressure as occurs with a spontaneous breath. On the left, the return function intersects the ascending part of the cardiac function curve and a fall in pleural pressure (Pl) decreases right atrial pressure (Pra) relative to atmosphere and increases right heart output (flow, Q). Patients with this status should have an increase in cardiac output with volume. On the right, the return function intersects the plateau of the function curve and right atrial pressure and cardiac output do not decrease with a decrease in pleural pressure. Patients with this condition should not respond to volume. The bottom part of the figure shows a rise in pleural pressure. When the return function intersects the ascending part of the function curve (left side), an increase in pleural pressure would be expected to decrease cardiac output. When the return function intersects the plateau of the function curve (right side), an increase in pleural pressure should not decrease cardiac output until the cardiac function curve shifts enough so that the return curve intersect the ascending part of the function curve.

that less than half the PEEP is transmitted to the pleural space, and even less than that in the pathological conditions that usually require PEEP, the error is only in the range of 2–3 mmHg. Above a PEEP of 10 cmH_2O, however, the pleural pressure at end-expiration can become clinically significant.

An important condition where changes in pleural pressure can have a marked effect on the measurement of CVP is during forced expiration. This is a very common phenomenon in critically ill patients, whether ventilated or breathing spontaneously. The forced expiration elevates pleural pressure during expiration and thus artificially elevates the CVP. There are two patterns. In one, there is a prolonged expiratory phase; in these patients, the CVP should be measured in the longest breaths and it should be appreciated that this still may be an over-estimate. In the second pattern, there is a progressive rise in CVP during expiration and in these patients, the measurement should not be made at end-expiration and a rough approximation can be made at the start of expiration before they start to bear down.

The respiratory alteration in the pulmonary artery occlusion pressure (PAOP) can give a reasonable estimate of the respiratory changes in pleural pressure [14],

however, respiratory variations in CVP do not. This is because the right atrium is connected to the large venous capacitance, which is outside the thorax. Thus the pressure source for the right atrium is not affected by the change in pleural pressure, whereas the outflow, i.e., the right atrium is directly affected. This means that the gradient for venous return is directly affected by changes in pleural pressure, which will consequently change the filling of the right atrium. In contrast, during a change in pleural pressure, the pressure in the pulmonary venous capacitance relative to atmospheric pressure changes directly with the change in left atrial pressure, so that the gradient for filling of the left heart is not affected by this mechanism. However, it is eventually affected by the serial transmission of the changes that occurred in right heart output.

How to use the CVP

The CVP measurement is most commonly used to give an assessment of the adequacy of a patient's blood volume and the preload for the right heart. However, it has been widely documented that the actual value of the CVP is a poor predictor of volume status. In reported series [4], patients with CVP of as low as 2 mmHg failed to respond to a volume infusion that increased the CVP, whereas a patient with a CVP of 16 mmHg responded (Fig. 4). In a recent series, we found that 35% of patients with a CVP of ≤ 10 mmHg failed to respond to a fluid challenge [3]. Thus, it is not possible to give specific numbers for the best value of the CVP. On the other-hand, in the same series we found that few patients had an increase in cardiac output with volume loading when the CVP > 12 mmHg. Thus, as an approximation, volume loading is unlikely to increase cardiac output in patients with CVP > 12 mmHg unless they have something to explain the higher values such as an increase in intrathoracic pressure or a decrease in right ventricular compliance.

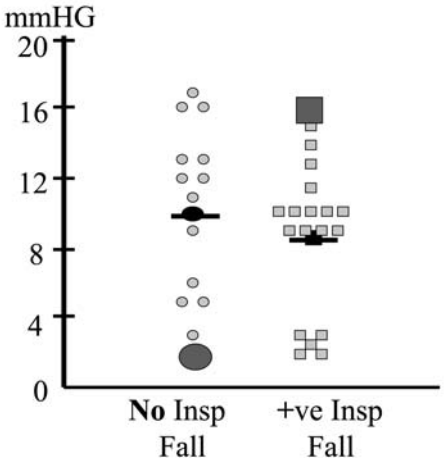

Fig. 4. Initial right atrial pressures in patients first classified as having or not having a respiratory variation in right atrial pressure with a spontaneous inspiratory effort (adapted from [4] with permission). Although the response to fluids was very different in the two groups, the initial right atrial pressure did not predict the fluid response. The large circle marks a patient with a right atrial pressure of 2 mmHg who did not respond to fluids and the large box marks a patient with a right atrial pressure of 16 mmHg who responded to fluids.

The most specific way to determine the clinical significance of a value of CVP is to perform a dynamic test. The gold standard is to give an infusion of fluid that increases the CVP by at least 2 mmHg and then assess the change in cardiac output. The value of 2 mmHg is suggested so that one can be certain that the CVP truly increased and that there was an adequate test of Starling's law. The cardiac function curve is steep, so that a 2 mmHg rise in CVP should result in a significant rise in cardiac output (i.e., >250 ml/min) if the heart is functioning on the steep part of the curve. If there is no rise in cardiac output with a rise of CVP of 2 mmHg, then it is highly unlikely that fluid infusion will increase cardiac output and an inotropic agent is needed to increase cardiac output. When performing a fluid challenge the rise in CVP, and not the volume given, is the important criterion for determining if the test was adequate. With the Starling mechanism, the stroke volume goes up on the contraction following an increase in end-diastolic volume. Thus, if one is concerned about the consequences of giving fluids to someone who may not have an increase in cardiac output, the amount of test fluid can be minimized by rapidly infusing the fluid and assessing the cardiac output as soon as the CVP increases by an adequate amount. With a rapid infusion, the type of fluid should also not matter, and the faster the fluid is given the less that has to be given. It is also important to appreciate that blood pressure is not a good guide as to whether the cardiac output rose with the fluid infusion. In the series discussed above [3], we found that almost three fourths of patients who had an increase in cardiac output did not have an increase in blood pressure. It is thus very difficult to determine the role of fluids without a measure of cardiac output or a surrogate.

Another dynamic test, involves the use of the change in CVP that occurs with an inspiratory fall in pleural pressure (Figs. 4 and 5) [4] and is based on the change in position of the cardiac function curve relative to the position of the return curve in a Guyton cardiac function-venous return plot (Fig. 3) [15]. A decrease in pleural pressure makes the pressures in the heart more negative relative to atmosphere and the rest of the body, whereas the venous return curve is unaffected because the veins are surrounded by atmosphere. When the heart functions on the ascending part of the cardiac function curve, this results in a fall in right atrial pressure relative to atmosphere and an increase in the gradient for venous return and an increase in right heart output. Under this condition, a volume infusion should increase cardiac output. However, when the heart is functioning on the flat part of the cardiac function curve, the fall in pleural pressure does not produce a change in right atrial pressure and therefore the gradient for venous return does not change nor does cardiac output. Under this condition a volume infusion should not increase cardiac output.

We tested this concept in 33 ICU patients (Fig. 5). A key first step was to ensure that the patients had an adequate inspiratory effort. We did this by using the respiratory variation in PAOP as an indicator of the fall in pleural pressure. A decrease of 2 mmHg with inspiration was considered to represent an adequate change in pleural pressure to test the response of the right atrium. We included ventilated patients as long as they had at least some triggered breaths, which demonstrated an adequate decrease in pleural pressure as indicated by the fall in PAOP. An inspiratory fall in right atrial pressure, measured at the base of the 'a' wave, of ≥ 1 mmHg was considered a respiratory response. These patients were

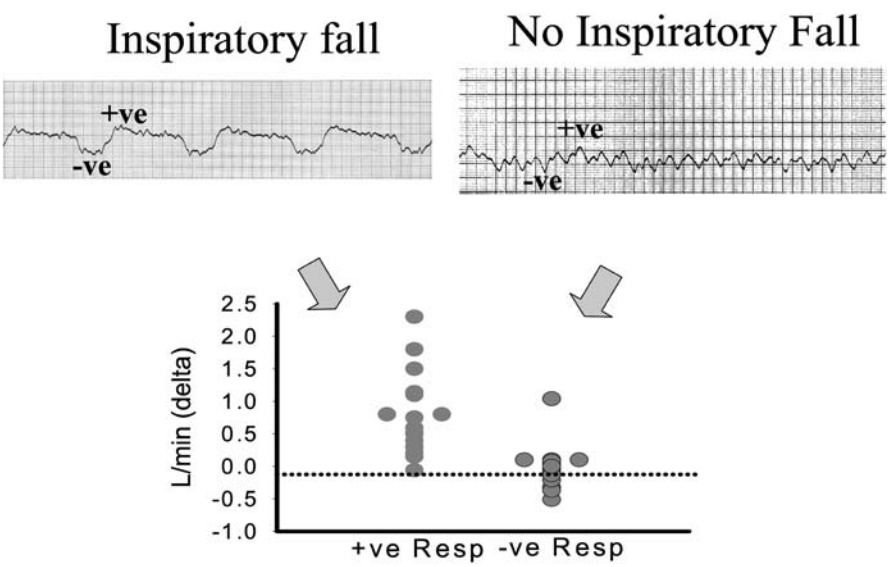

Fig. 5. The use of respiratory variation in right atrial pressure to predict the response to a fluid challenge (adapted from [4] with permission). The top shows examples of a respiratory fall in right atrial pressure (left) or no response (right). On the bottom, as predicted most of those with a inspiratory fall in right atrial pressure had a rise in cardiac output whereas only one of those with no inspiratory fall had a rise in right atrial pressure.

expected to respond to fluids; there were 19 in this category, and 16 of the 19 had a rise in cardiac output of ≥ 250 ml/min with the volume infusion. It is not surprising that they did not all have an increase, because some could have started from a value of right atrial pressure that was close to the plateau. An inspiratory fall in right atrial pressure of < 1 mmHg was considered a negative response and these patients were not expected to respond to fluids; there were 14 patients in this category and of these, only 1 had an increase in cardiac output of ≥ 250 ml/min. In retrospect, the inspiratory effort in that patient was likely not large enough to produce a fall in right atrial pressure to properly classify the patient. The test thus is most useful in the negative. That is, patients who have no fall in right atrial pressure with an inspiratory effort, are very unlikely to have an increase in cardiac output with a volume infusion. Of importance, the initial right atrial pressure (Fig. 4), PAOP, cardiac output, and blood pressure, did not predict the response to fluids as observed in other studies [6].

We also reasoned that this test should predict which patients would have a fall in cardiac output when PEEP is applied [16]. The reasoning was as follows. As discussed above, in patients who have a fall in CVP with a spontaneous inspiration the heart should be functioning on the ascending part of the cardiac function curve. PEEP shifts the cardiac function curve to the right of the venous return curve (Fig. 3). Thus the venous return curve will intersect the cardiac function at a higher right atrial pressure but a lower value of cardiac output, and cardiac output thus should

fall. On the other hand, in patients who have no fall in CVP with a spontaneous inspiration, the heart should be functioning on the plateau of the cardiac function curve, and these patients should have a range of increases in PEEP in which there is no decrease in cardiac output. However, when the increase in PEEP is large enough so that the ascending part of the cardiac function curve intersects the venous return curve, there will be a fall in cardiac output. We tested this in 18 ICU patients [16]. As in the study in which we tested the potential to predict the response to a fluid challenge, we separated the patients into those who had an inspiratory fall in CVP of ≥ 1 mmHg and those who did not and assessed the adequacy of the inspiratory effort from the inspiratory fall in PAOP. The overall pattern was consistent with the hypothetical predictions, but there was much more variability than in the volume study. Of the seven patients who had an inspiratory fall in CVP, and therefore should have had a fall in cardiac output when PEEP was applied, the average cardiac output fell by 0.7 ± 0.8 l/min ($p < 0.05$), but the cardiac output did not always fall. Of the 11 patients with no inspiratory fall in CVP who therefore should not have had a fall in cardiac output, the average cardiac output did not change (change of -.04 ± 1.5 l/min), but the individual responses were highly variable. Thus, the overall concept was supported, but the predictions in individual patients were poor. The likely reason why this study failed to provide as strong a prediction as in the fluid challenge study, is that reflex adjustments in vascular capacitance occur when PEEP is applied, and these can maintain cardiac output in the face of increased intrathoracic pressue by shifting the venous return curve to the right [17]. The potential for this mechanism to maintain cardiac output depends on the reserves in the venous capacitance and sympathetic response, which are highly variable in critically ill patients and cannot be assessed in patients. Thus this test fails to provide an accurate predictor of the cardiac output response to PEEP but indicates the variability of the cardiac output response to PEEP. Jellinek et al. performed a similar study in which they examined the usefulness of the initial right atrial pressure, PAOP, and right ventricular volume for predicting a hemodynamic response to increases in airway pressure [18]. They found that a right atrial pressure < 10 mmHg best predicted a decrease in cardiac output. Based on our study on respiratory variation and the response to PEEP, this would indicate that they were on the ascending part of the cardiac function curve. However, although in that series 10 mmHg provided a clear cut off, I would not expect this to be true in all patients. From our prospective series [3], some patients with CVP as low as 2–4 mmHg failed to respond to fluids indicating that they were on the flat part of the function curve and therefore should not initially have a fall in cardiac output with PEEP. Second, if the PEEP is raised sufficiently, there will be a fall in cardiac output in all patients for eventually the cardiac function curve will shift to the right sufficiently so that the ascending part of the cardiac function curve intersects the venous return curve. Finally, it should be appreciated that the transducers were referenced to the mid-thorax so that the value would have been approximately 8 mmHg if the transducers were referenced to 5 cm below the sternal angle.

A useful 'dynamic' approach to the assessment of the significance of a value of the CVP involves the use of passive leg raising to transiently increase the CVP and to then determine if this is associated with a change in cardiac output. This was used successfully by Boulain and co-workers who showed that patients who had a

rise in cardiac output with leg raising also had an increase with a volume load [19]. Furthermore, an increase in the pulse pressure also correlated with an increase in stroke volume and therefore provided a potential non-invasive indication of the cardiac output response to volume loading.

In the dynamic test that used the respiratory variation in the CVP to predict the response to a fluid challenge, the patient had to have an inspiratory effort, but many patients have no spontaneous efforts. Another indicator that can be of use in these patients is the magnitude of the 'y' descent. In a small series of patients, we found that patients that had a 'y' descent of > 4 mmHg did not respond to fluids [20]. The rationale is that this represents a 'restrictive' state, which is what occurs on the plateau of the cardiac function curve. That is not to say that the patient has restrictive heart disease, but rather restrictive hemodynamics. The series was small so the specificity of this test is not well established, but it does provide a simple non-invasive guide. Another useful clinical point is that the loss of a 'y' descent in a patient with an elevated CVP, is very suggestive of cardiac tamponade.

When assessing fluid responsiveness, it is also essential to keep in mind that just because the cardiac output increases with a fluid infusion, does not mean that the person needs the fluid. In the healthy state, the heart usually functions on the ascending part of the cardiac function curve so that a volume infusion will almost always increase cardiac output, but a volume infusion is obviously not indicated. Outcome data on the role of fluids in the management of critically ill patients is lacking, and thus the decision to use fluids, even in patients who respond to volume loading, remains very subjective.

There has been discussion about whether to use the PAOP or the right atrial pressure for the assessment of the response to a fluid challenge and the preload of the heart. First of all, for both of these measures, it is not the absolute value that is important but rather the change in cardiac output that is associated with the change in their value. That having been said, I believe that the right atrial pressure is always the value that should be used when trying to optimize cardiac output by giving fluids or drugs. That is because the right atrial pressure gives the result of the interaction of the cardiac function and return function and a volume infusion acts by changing the return function. Furthermore, the right and left hearts are in series and the only way a left sided event can affect cardiac output is by altering the right atrial pressure. Thus, even in a patient with a ruptured mitral valve or an occlusion of a circumflex coronary artery, cardiac output will only decrease when the right atrial pressure rises. Alternatively, a patient who has an underfilled left ventricle as indicated by a low PAOP, can only have an increase in cardiac output with a volume infusion if the right heart output can increase, so that if the right heart function curve has plateaued there will not be a rise in cardiac output with volume infusion. The motto is 'no left-sided success without right-sided success'. What the PAOP gives is diagnostic information. For example if the PAOP is elevated but the right atrial pressure is not, then the primary pathological process is in the left heart and diagnostic possibilities are limited to severe hypertension, mitral or aortic valve disease, or coronary artery disease, all of which can be easily assessed clinically. Equal increases in PAOP and right atrial pressure indicate a biventricular process and a right atrial pressure greater than the PAOP indicates a primary right-sided problem.

For hemodynamic management of hypotension, I begin with an assessment of the cardiac output. If the cardiac output is normal or elevated, then the hypotension is due to a low systemic vascular resistance and the primary therapy should be directed at correcting the vascular resistance. If the blood pressure fell with a fall in cardiac output, the next question is what happened to the right atrial pressure. If the right atrial pressure rose, then the primary problem is pump function and therapy should be aimed at increasing pump function. If the cardiac output fell with a fall in right atrial pressure, then the primary problem is a decrease in the return function (usually a loss of volume) and volume therapy is the likely solution.

Conclusion

In summary, CVP by itself does not indicate cardiac function or vascular volume, but rather it gives an indication of the interaction of pump function and return function. As such, a high CVP can be due to an increase in blood volume, a decrease in pump function or both, for they often go together. It is important to appreciate that the cardiac function curve has a plateau, and once the plateau is reached, further increases in vascular volume and right atrial pressure will not result in an increase in cardiac output. There is no universal value that can be given for the right atrial pressure at which the plateau of the function curve occurs, but in general the probability of the cardiac output increasing with a CVP > 12 mmHg (leveled 5 cm below the sternal angle) is low, unless the patient has had a chronic increase in pulmonary pressures which altered right heart compliance or has increased pleural pressure which alters the assessment of the transmural pressure. The significance of a particular value of CVP is best assessed by a dynamic test in which the change in CVP is related to a change in cardiac output or a surrogate such as a change in pulse pressure or Doppler flows. The major clinical point is that it is not the actual CVP that counts, but the hemodynamic consequences of a change in CVP.

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Arterial Pressure Variation during Positive-pressure Ventilation

A. Perel, S. Preisman, and H. Berkenstadt

Introduction

The hemodynamic status of critically ill patients may include the whole spectrum of volume states and myocardial performance. Accurate diagnosis of this cardiovascular status is therefore mandatory for the achievement of optimal preload conditions and optimal cardiac performance. However, the hemodynamic parameters that are most often used in clinical practice to assess preload, namely the central venous pressure (CVP) and the pulmonary artery occlusion pressure (PAOP), are far from perfect. A recent literature analysis has clearly demonstrated that the CVP and the PAOP are poor predictors of the response of the cardiac output to fluid loading and cannot differentiate between patients that respond to volume loading (responders) and patients that do not (non-responders) [1]. This inadequacy of filling pressures is due to the fact that, besides being determined by the end-diastolic volume of the heart chambers, they are also directly affected by ventricular compliance, which can be quite variable. Hence pressures are limited in their ability to reflect volumes. However, `volumes' themselves are often mediocre predictors of fluid-responsiveness, namely the degree by which the cardiac output responds to a volume load, since their relationship to the stroke volume depends on ventricular contractility, which can be extremely variable and cannot be directly measured in clinical practice. This is why even more accurate measures of preload, like the global end-diastolic volume or the left ventricular (LV) end-diastolic area (LVEDA), have a limited capability of predicting fluid responsiveness.

Traditionally fluid responsiveness is assessed by a time-consuming and invasive graded volume loading, which includes repetitive measurements of cardiac output and filling pressures and the construction of actual Frank-Starling LV function curves. However, although fluid loading is one of the most common therapeutic steps taken in the intensive care unit (ICU), it fails to increase the cardiac output in about 50% of the patients [2]. The resulting unnecessary fluid administration may be harmful especially in patients with respiratory, renal, and/or cardiac failure. Overzealous fluid administration may indeed be an underestimated occult source of mortality in the ICU, since the excess fluid may increase interstitial edema in various organs, increase lung water content, postpone weaning, and increase the risk of sepsis. Part of this excess fluid administration may also stem from the fact that the end-point of fluid resuscitation is frequently unclear. Hence the impor-

tance of an accurate assessment of fluid responsiveness lies not only in the detection of latent hypovolemia or a meticulous 'prophylactic optimization', but also in the withholding of fluids when their administration may not be of benefit.

In mechanically ventilated patients, the hemodynamic effects of the increase in intrathoracic pressure offer dynamic information about fluid responsiveness. This direct clinical application of the physiological principles of heart-lung interaction during mechanical ventilation is gaining ever-growing interest and has been the topic of many reviews and editorials, most of which are quite recent [2–14]. In this chapter, we will describe the basic physiological principles of this monitoring approach, review the various parameters that have been developed and delineate the usefulness as well as the limitations of this technique.

The Hemodynamic Effects of the Mechanical Breath

The main hemodynamic effect of the increase in the intrathoracic pressure during positive-pressure ventilation is normally a decrease in right ventricular (RV) filling due to a decreased venous return. This decrease in RV filling has been shown to be about 20% in calves with artificial hearts [15], and to result in a decrease in RV stroke output of about 20% as well in patients ventilated with tidal volumes of 10–15 ml/kg [16]. The inspiratory decrease in RV outflow may be much more significant (about 70%) in the presence of hypovolemia, and is then associated with a high degree of inspiratory collapse of the superior vena cava [17]. The inspiratory decrease in RV outflow can be normalized (to about 25%) once the vena caval 'zone 2' conditions are corrected by volume expansion [17]. The reduction in venous return during the mechanical breath may be so significant that large tidal volumes were shown to decrease the LV end-diastolic volume (LVEDV) only slightly less than with the inferior vena cava occlusion maneuver [18].

The effect of the mechanical breath on venous return may be more complicated in the presence of hypervolemia or congestive heart failure. In these conditions the inspiratory diaphragmatic descent and the associated increase in abdominal pressure may cause squeezing of the abdominal venous compartment and the congested liver (which are under 'zone 3' conditions), causing an increase in the venous return during the mechanical breath [19]. This mechanism may be responsible in part for the lack of the decrease in cardiac output when positive end-expiratory pressure (PEEP) is applied to hypervolemic patients. In patients with ARDS, the inspiratory decrease in RV stroke output may occur also because of an increase in RV outflow impedance [20].

The transient inspiratory decrease in RV output leads to a decrease in the LV stroke output after a few beats. However, the first and immediate effect of the rise in intrathoracic pressure on the LV is normally an augmentation of the LV stroke volume [15, 16, 21–24]. This augmentation is due to the inspiratory squeezing of the pulmonary blood volume, an increase in pulmonary venous flow [23] (Fig. 1), significant increases in left atrial and LV dimensions, and increased LV stroke volume [16, 21–24]. This effect is more pronounced in the presence of congested ('zone 3') lungs, but when the lungs are in zone 2 conditions the opposite occurs, namely pulmonary venous flow decreases during inspiration [24].

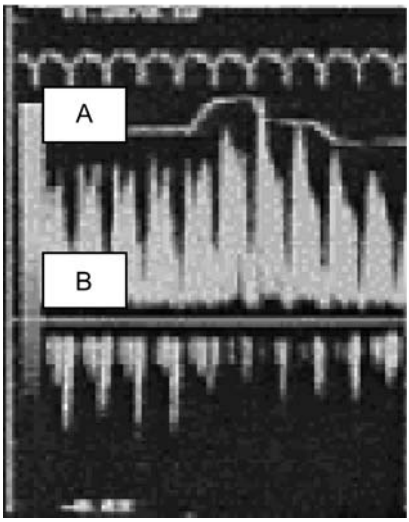

Fig. 1. A. Airway pressure. **B.** Pulmonary venous flow. Doppler pulmonary venous flow velocity during the respiratory cycle. The transient inspiratory increase is associated with increased left atrial and LV dimensions, transient increase in LV stroke output and a prominent ΔUp (see later). Adapted from [23] with permission

Another suggested mechanism for the early inspiratory increase in LV stroke volume is a decrease in the transmural aortic pressure reflecting an effective decrease in LV afterload [22]. However, Vieillard-Baron et al. found recently that LV systolic wall stress, an index of LV afterload, significantly increased during tidal ventilation [23]. In addition, these authors found it difficult to imagine that the small increase in pleural pressures during lung inflation in their patients would have any measurable effect on LV ejection pressure. The conclusion therefore of this excellent study is that the inspiratory augmentation of LV stroke volume is due first and foremost due to increased LV preload and not a decrease in afterload [23]. Magder, on the contrary, has suggested even more recently that the inspiratory increase in LV stroke volume is not due to increase in LV preload but rather due to the aortic valve opening earlier and staying open longer during the inspiratory increase in pleural pressure [14]. Other hypothetical mechanisms that have been mentioned as being able to contribute to the early inspiratory increase in LV stroke volume include a higher external pressure exerted on the LV by the increased lung volume, better LV contractility due to the decreased size of the RV, and lung inflation-induced adrenergic discharge. The potential clinical implications of the inspiratory augmentation of the stroke volume have been repeatedly explored, since using the mechanical breath as a form of LV assist device is both sound physiologically and appealing clinically. However, to date there is no clinically accepted method that takes advantage of this phenomenon.

The second phase of the response of the LV to the mechanical breath is normally a decrease in LV stroke output, which is the result of the earlier decrease in RV stroke output. In summary, the mechanical breath induces cyclic changes in the output of the right and left ventricles. These normally include an early increase in LV stroke output and a simultaneous decrease in RV output. The expiratory phase is normally associated with an increased RV output and a decrease in LV output.

Under normal conditions, the output of both ventricles evens out at end-expiration [16].

Basic Principles of Arterial Pressure Waveform Analysis (SPV, ΔUp, ΔDown)

The previously described respiratory fluctuations in the LV stroke output are reflected in the arterial pressure waveform. The early inspiratory augmentation of the LV stroke output is reflected as an increase in the systolic blood pressure termed delta up (dUp, ΔUp), while the later decrease in LV stroke output is reflected in a decrease in the systolic blood pressure termed delta down (dDown, ΔDown) [26] (Fig. 2). The ΔUp is measured as the difference between the maximal value of the systolic blood pressure and the systolic blood pressure during a long end-expiratory pause or a short (5 seconds) apnea, while the ΔDown is measured as the difference between the reference end-expiratory systolic blood pressure and the minimal systolic blood pressure value. The sum of the ΔUp and the ΔDown, which is the difference between the maximal and the minimal systolic blood pressure values during one mechanical breath, is termed the systolic pressure variation (SPV) [26].

It is important to note again that the ΔUp and the ΔDown represent two different hemodynamic events. The ΔDown is due to the decrease in venous return during the mechanical breath, and its magnitude reflects *fluid responsiveness*, namely, the degree by which LV stroke output decreases in response to a transiently decreased preload. The ΔUp, on the other hand, reflects the early inspiratory augmentation of the LV stroke output, and has been originally described as 'reversed pulsus paradoxus' [21]. Theoretically the ΔUp can be influenced by some partial transmission of the airway pressure to the LV and aorta during the mechanical breath and thus not be necessarily representative of augmented LV stroke volume [26–28]. The actual degree of this transmission seems however to be minimal [14, 23], which is not surprising in view of the close correlation of the SPV to the variations in the pulse pressure [27, 28] and in the stroke volume itself [29, 30]. However, in a study that was designed to test the hypothesis that changes in the systolic blood pressure

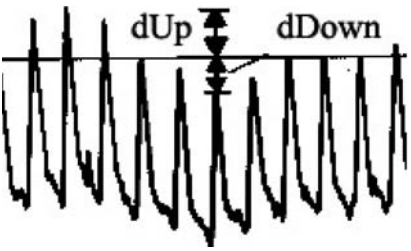

Fig. 2. The normal changes in the arterial pressure during a mechanical breath. The difference between the maximal and minimal values of the systolic BP is the systolic pressure variation (SPV). The systolic BP value during a short apnea is used as the reference pressure to measure the ΔUp (delta up) and the ΔDown (delta down), which are the two components of the SPV.

are induced solely by in-phase changes in intrathoracic pressure, and which was done in patients with relatively small systolic blood pressure values in both closed and open chest conditions, Denault et al did not find a consistent relationship between the changes in the systolic blood pressure and the LVEDA as determined by an automated border detection software [26]. They therefore claimed that "changes in systolic arterial pressure reflect changes in airway pressure better than they reflect concomitant changes in LV hemodynamics", and that the ΔDown is not related to a decrease in preload [26]. However, besides a long list of self-admitted study limitations, the recorded analog signals that accompany this publication are suggestive of a possible problem of synchronicity between the arterial pressure and the LV area recordings, since the recorded transient decrease in LV area seems to be associated with a simultaneous increase in arterial *pulse pressure* and hence with an increase in LV stroke volume (see figure 2 in ref [26]).

In contrast with the results of Denault et al. [26], many others have found, using a variety of techniques, that indeed the changes in the arterial pressure do correspond to real changes in the LV stroke volume. The SPV and ΔDown were repeatedly found to either very significantly correlate with, or to behave in exactly the same way as, changes in stroke volume measured or estimated by aortic velocity-time integral [31–33], by Doppler echocardiography [16, 23], by the arterial pulse pressure [27, 28], and by the pulse contour method [29, 30]. A recent study using conductance volumetry has also shown that the arterial pressure and the LV volume change simultaneously during a mechanical breath [18]. For all practical purposes, therefore, the SPV, ΔDown and ΔUp should be perceived as representing true changes in the LV stroke output during the mechanical breath.

The SPV and ΔDown Reflect Volume Status and Predict Fluid Responsiveness

The respiratory changes in the systolic blood pressure were first quantified by Coyle et al. in 1983 [34]. Since then many experimental [25, 29, 35–41] and clinical [28, 30, 31, 42–47] reports have repeatedly shown that the SPV and the ΔDown are sensitive indicators of changes in blood volume. The first experimental report was done in an animal model of graded hemorrhage and retransfusion [25]. The rate of the hemorrhage in this model was relatively slow so that arterial blood pressure and heart rate remained practically unchanged even when the animals were exanguinated by 30% of their estimated blood volume and when the cardiac output was significantly reduced [25]. In addition, a vest was inflated around the dogs' chest so as to bring their normally elevated chest-wall compliance to more human-like values. This work was the first to clearly demonstrate the ability of the SPV and the ΔDown to detect occult hypovolemia, as well as their very significant correlation with the degree of hemorrhage and with the changes in cardiac output. Other animal studies of graded hemorrhage have produced the same results, namely that the ΔDown increases gradually with each step in the hemorrhage, that during hypovolemia it is the main component of the SPV, and that it decreases back to normal values following restitution of intravascular volume. In one study, where pigs were exsanguinated to a mean arterial pressure (MAP) of 30 mmHg, the

Table 1. Immediate effects of passive leg raising (PLR) in18 patients following induction of anesthesia for cardiac surgery.

	Baseline	PLR*	Change (%)
Cardiac output (l/min)	4.5 ± 1.1[#]	5.7 ± 1.1	23
PAOP (mmHg)	12.9 ± 4.5	14.1 ± 4.8	10
SPV (mmHg)	11.3 ± 5.1	5.9 ± 2.4	48
ΔDown (mmHg)	7.5 ± 3.7	3.3 ± 2.0	56

*All PLR values significantly different than baseline. [#]Mean ± SD

ΔDown was not considered to reflect the degree of hemorrhage better than the MAP and other hemodynamic parameters [40]. However, when the blood pressure is changing rapidly or when it is very low, it is highly recommended that the SPV and the ΔDown are expressed as percentages of the systolic pressure value during end-expiration, namely as %SPV and %ΔDown [3,6]. If in the above mentioned study [40] the %ΔDown had been used rather than the ΔDown in absolute mmHg, then it would have changed much more significantly during the hypotensive period and would have become more significant.

In another experimental study, Pizov et al found that the application of PEEP in normovolemic dogs caused a significant reduction in cardiac output that was associated with significant increases in the SPV and ΔDown [38]. The same level of PEEP, however, did not affect cardiac output in hypervolemic dogs with induced myocardial depression, nor did it change the SPV and the ΔDown. Hence the presence of a significant ΔDown should prevent the augmentation of PEEP without prior fluid loading or without the application of more advanced hemodynamic monitoring, while the absence of the ΔDown means that the expected hemodynamic effects of PEEP will most probably be negligible. In critically ill patients the pulse pressure variation (PPV) values prior to PEEP application were shown to significantly correlate with the PEEP-induced changes in cardiac output, which also correlated with the changes in PPV following PEEP [27].

The sensitivity of the SPV and the ΔDown to changes in intravascular volume can also be seen from their response to passive leg raising. In patients with acute circulatory failure the changes in the respiratory-induced PPV during passive leg raising were significantly correlated with changes in stroke volume during passive leg raising and following rapid fluid expansion [47]. Our own data on the effects of passive leg raising on the SPV and ΔDown in patients following induction of anesthesia for cardiac surgery are shown in Table 1. It is important to note that the SPV and ΔDown change much more significantly compared to other parameters denoting their surprising sensitivity to changes in effective blood volume.

The SPV and the ΔDown have also been found to correlate with other parameters that reflect the volume status, like the intrathoracic blood volume (ITBV) [39], the echocardiographic LVEDA [41, 42], and even the PAOP [48]. However, the main

value of the SPV and ΔDown lies in their accuracy as *predictors* of fluid responsiveness. A number of clinical studies have shown that these parameters have much better correlation to the change in the cardiac output following volume loading, than the CVP and the PAOP [28,42,45,50]. Moreover, an excellent study done by Tavernier et al. in a group of septic patients, found that the ΔDown was more sensitive and more specific than both filling pressures and the LVEDA [44]. A ΔDown component of more than 5 mmHg indicated that the stroke volume index would increase in response to a subsequent fluid challenge with positive and negative predictive values of 95% and 93% respectively [44]. One study only, done recently in patients undergoing cardiac surgery, found that the PAOP predicted the response to a fluid bolus better than the SPV and ΔDown, while echocardiographic-derived values had no predictive value at all [50]. However most of the volume-loading steps were done in the presence of very low SPV (3–5 mmHg) and ΔDown (1–2.6 mmHg) values, denoting reduced baseline fluid responsiveness. Baseline values of SPV and ΔDown were however significantly higher in those patients in whom the cardiac output increased following fluid expansion [50].

In humans the reported values for the SPV vary between 7–16 mmHg and between 2–11 mmHg for the ΔDown [23, 28, 30, 31, 42–46, 49–50]. This large spectrum of 'normal' values is due to a variety of filling conditions and the tidal volumes employed. However, human studies that examined the effects of hemorrhage on the SPV and ΔDown found that a decrease of 500 ml (or 10%) in the blood volume resulted in an increase of about 5 mmHg in the SPV and ΔDown [43, 45, 46]. Varying degrees of fluid expansion in humans have always shown the SPV to decrease significantly by anywhere from 2.5–10 mmHg [28, 30, 31, 42, 44], while experimental data have repeatedly shown that hypervolemia and/or congestive heart failure were associated with a relatively small SPV value and a practically non-existent ΔDown segment [25,36–38]. One has to note that in cases of severe right ventricular failure the lack of ΔDown may be due to the RV, and not the LV, being non-responsive to volume loading. Rarely, severe RV failure may be associated with a ΔDown, though with no fluid responsiveness. This may be due to further loading of the RV during inspiration, as well as a possible leftward septal shift.

The Inspiratory Increase in Arterial Pressure – ΔUp (Delta Up, DUp)

We have earlier described the ΔUp as representing an inspiratory augmentation of the LV stroke volume. In experimental studies the ΔUp has been repeatedly shown to increase during hypervolemia and/or congestive heart failure [25, 36, 37, 41]. In addition we have observed that the retransfusion stage that follows significant blood loss was associated with deterioration in LV function, as well as elevated ΔUp [41]. We have previously shown that experimental pharmacological induction of myocardial depression together with volume loading caused the SPV to decrease from 9 to 3 mmHg and the ΔUp to increase from 0.6 to 2.7 mmHg, with the ΔUp becoming responsible for practically all of the SPV [36]. In critically ill patients the ΔUp has been shown to be a frequent, and at times the main, component of the SPV [23, 44]. A recent study has found that among the 31 septic patients studied, 23 had a ΔUp (3.8 ± 1.8 mmHg), isolated in 7 cases, and associ-

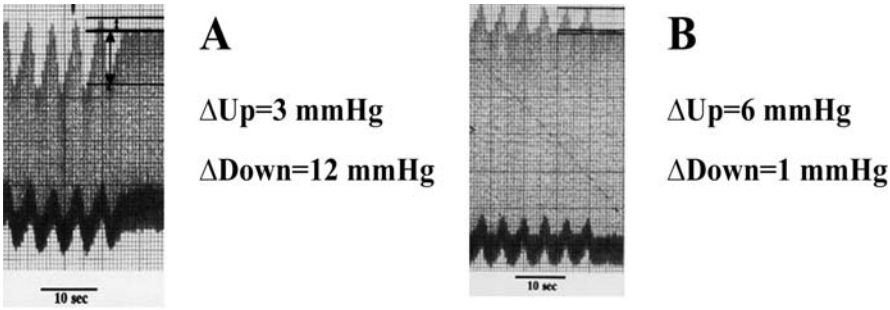

Fig. 3. A. Left panel depicts SPV of 15 mmHg in a critically ill patient, most of it being due to a ΔDown. **B.** Right panel depicts same patient after the administration of 1000 ml of plasma expander. The ΔUp increased to 6 mmHg comprising nearly all the SPV. From [46] with permission

ated with ΔDown in 16 cases. Twenty-four patients had a ΔDown (8.6± 7.2 mm Hg), isolated in eight cases and associated with a ΔUp in 16 cases [23]. According to this study the presence of the ΔUp was associated with increased inspiratory pulmonary venous flow, and its absence associated with no change in pulmonary venous flow during inspiration [23].

The fact that fluid administration causes the ΔUp to increase may be explained by more lung regions being converted from zone 2 to zone 3 conditions, causing a higher inspiratory increase in pulmonary venous flow [23, 24]. This is nicely demonstrated by the following case (Fig. 3), where fluid expansion had eliminated the ΔDown and caused the ΔUp to significantly increase [44]. The fact that all these changes occurred without any concomitant change in the airway pressure, and the observation that the ΔUp is associated with a significant increase in pulmonary venous flow during lung inflation, does not support the argument that the ΔUp is mainly due to a transmitted airway pressure [26–28]. In addition to the lungs containing more blood, external pressure on the heart by the inflating lungs and a possible contribution of the decrease in afterload should also be considered as contributing to the ΔUp in these conditions. It is of interest to note that in complete open-chest conditions there is normally a small ΔUp that is most probably due to squeezing of pulmonary blood volume as well. It may well be that under these conditions the ΔUp is indicative of the LV being fluid-responsive, but this has to be studied further.

The fact that the ΔUp does not normally reflect fluid responsiveness and yet can be so significant has some very important implications. The first is that simple eyeballing of the arterial pressure fluctuations during mechanical ventilation without relating them to some reference pressure may be misleading. Second, a patient presenting with a prominent ΔUp should be considered as being either hypervolemic or as having compromised LV function. The mechanical breath serves as a repetitive ‘assist device’ to the LV in such conditions. Weaning the patient from ventilatory support at this time without improving their cardiovascular function (e.g., diuretics, inotropes or afterload reduction) is probably not advisable. The last

and not least implication of the presence of a prominent ΔUp is that the interpretation of the SPV, stroke volume variation (SVV), and PPV as parameters of fluid responsiveness should be done with caution, as these parameters include a component (ΔUp) that is not directly related to fluid responsiveness.

The Pulse Pressure Variation and the Stroke Volume Variation

The PPV is the difference between the maximal and minimal pulse pressures during the mechanical breath cycle divided by the mean of these two values [27, 28]. The rationale of using the PPV rather than the SPV as a parameter of fluid responsiveness is that the pulse pressure is directly related to LV stroke volume and that it is not influenced by any transmission of pleural pressure since such transmission would affect the systolic and diastolic pressure to the same degree. The PPV has indeed been shown to be an excellent predictor of fluid responsiveness during the application of PEEP [27] and in septic patients [28]. The application of PEEP increased PPV from 9±7% to 16±13% [27] while fluid loading in septic patients caused it to decrease from 14±10% to 7±5% [28]. A PPV value of 13% allowed discrimination between responders (increase in cardiac index [CI]=15%) and non-responders with a sensitivity of 94% and a specificity of 96%, which was somewhat better than that of the SPV, but much better than that of the PAOP and the CVP [28]. It is interesting to note that in another study, a similar threshold value of 12% in the respiratory variability of the aortic flow allowed discrimination between responders and non-responders with a sensitivity of 100% and a specificity of 89%, while the LVEDA index was not significantly different between the two groups [32]. Another recent study, examining the respiratory variations in the preejection period, has shown the PPV to correlate better with the change of stroke volume following fluid load than the SPV and even the ΔDown [49]. Theoretically, the performance of the PPV may be improved even further, especially in the presence of a significant isolated ΔDown, if the difference between the maximal and minimal pulse pressure values would be related not to the mean of these two values, but rather to the pulse pressure during end- expiration or apnea. In the presence of a large ΔUp, the PPV, like the SPV and SVV, will be less effective in predicting fluid responsiveness. In rare cases of severe RV failure, a considerable pulse pressure may be associated with lack of fluid responsiveness, as noted earlier.

Measuring the respiratory variation of the stroke volume itself rather than that of surrogate parameters has become possible with the renewed introduction of pulse contour analysis in the PiCCO monitor (Pulsion Medical Systems, Munich, Germany). The SVV is the difference between the maximal and minimal stroke volume during one mechanical breath, divided by the mean stroke volume value. The SVV has been shown to be a sensitive indicator of fluid responsiveness in anesthetized patients and to correlate well with the changes in cardiac output following volume loading [30, 51–54]. In healthy patients undergoing neurosurgery, a SVV value of 9.5% was found to predict a positive (=5%) increase in cardiac output in response to only 100 ml of plasma expander with 79% sensitivity and 93% specificity [51]. In patients with normal and impaired cardiac function undergoing

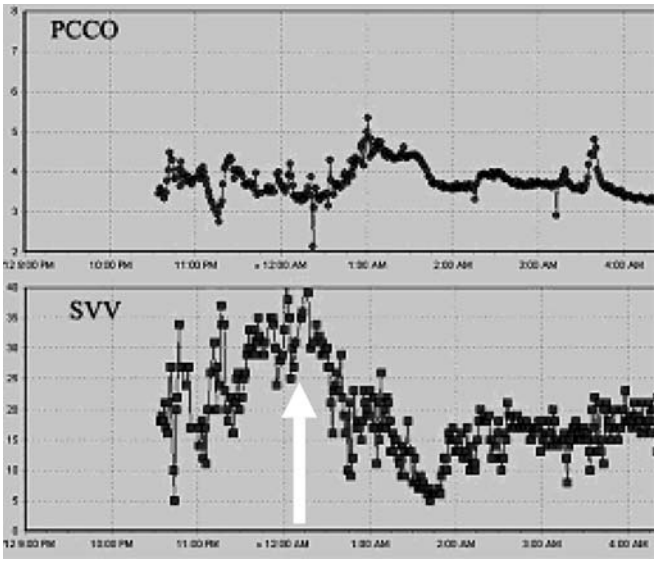

Fig. 4. Fluid loading (arrow) causing immediate increase in the continuous CO (PCCO, upper panel) and a simultaneous decrease in SVV (lower panel). Trended PiCCO parameters recorded on the **MV**ICU patient data management system (*i***MD***soft*, Israel). Courtesy of Dr Eran Segal, Sheba Medical Center, Tel Aviv, Israel.

cardiac surgery, the same SVV value of 9.5% was found to predict a positive (=5%) increase in cardiac output in response to a much larger fluid load with a sensitivity of 71–79% and a specificity of 80–85% [53]. It is important to note that in this study the SVV was a better predictor of fluid responsiveness in patients with normal cardiac function than in patients with a low preoperative ejection fraction and higher intraoperative LV end-diastolic dimensions [53]. The most probable explanation for this difference is that the patients with impaired cardiac function may have had a characteristically higher ΔUp, and that the prominence of the ΔUp had resulted in a lesser predictive ability of the SVV, as mentioned earlier, since the ΔUp is not directly related to fluid responsiveness.

Another study in cardiac patients has found no significant relationship between baseline SVV values and the percentage of change in the cardiac output following volume loading [55]. These results are indeed surprising in view of the fact that there was a very significant correlation between baseline SVV values and the change in SVV after volume loading [55]. In an accompanying editorial [11], and in another [9] that accompanied the studies by Reuter et al [52], Pinsky has repeatedly claimed that the use of the SVV for clinical decision-making cannot be recommended. As correctly pointed out by Pinsky, the SVV measured by the pulse contour method has not been validated on a beat-by-beat basis against a 'gold-standard' measurement of stroke volume. However, the SVV has been shown in the meantime to correlate extremely well with the SPV [29,30], attesting to the robustness of the algorithm used in the PiCCO monitor. The clinical results that have been published

so far, and our own clinical experience (Fig. 4), justify the clinical use of this parameter within its limitations.

The respiratory variations of other pulsatile parameters have been suggested to reflect fluid responsiveness in the same manner as the SPV, PPV, and SVV. These include the ventilation-induced changes in the pulse oximeter's plethysmographic waveform [46], in the collapsibility of the superior vena cava [17], in the aortic blood flow velocity [31, 32] and the aortic velocity-time integral [33], and in the preejection period [49]. All these parameters were shown to reflect the status of fluid responsiveness better than existing 'preload' parameters.

Systolic Pressure Variations during Programmed Positive-Pressure Ventilation

The change in arterial pressure following a mechanical breath is dependent not only on the status of fluid responsiveness but also on the magnitude of the tidal volume itself [37, 54], since larger increases in intrathoracic pressure will reduce venous return to a greater extent. In view of this fact and of the limitations of current functional hemodynamic monitoring (see below), we have developed the Respiratory Systolic Variation Test (RSVT) which is a ventilatory maneuver that is composed of three consecutive incremental pressure-controlled (10, 20, and 30 cmH_2O) breaths (Fig. 5) [56–58]. This maneuver would normally produce respec-

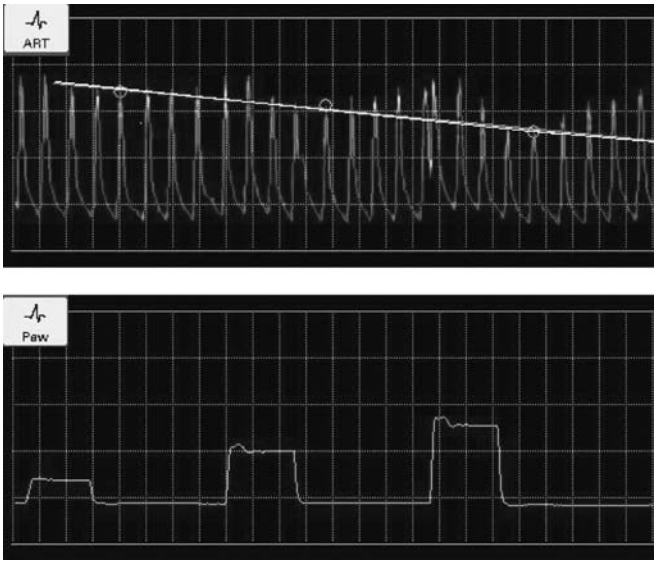

Fig. 5. Upper panel shows the slope (line of best fit) connecting the three respective lowest systolic pressures following each of the three consecutive incremental breaths (10, 20, 30 cmH_2O) of the RSVT maneuver (lower panel). Upper panel – arterial pressure Lower panel – airway pressure

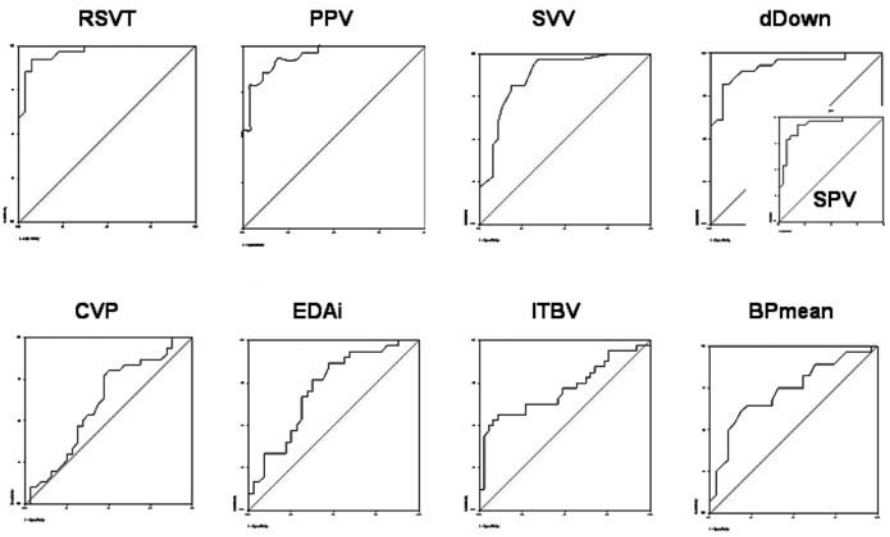

Fig. 6. Receiver-operating characteristics curves comparing various functional hemodynamic and preload parameters in patients undergoing cardiac surgery. The respiratory systolic variation test (RSVT) slope is in the left upper corner. (Preisman et al., unpublished data) PPV: pulse pressure variation; SVV: stroke volume variation; CVP: central venous pressure; ITBV: intrathoracic blood volume; BP: blood pressure; EDAI: end-diastolic area index

tive incremental decreases in the venous return and hence in the LV stroke volume and in the systolic arterial pressure. Plotting the respective three lowest systolic pressure values (one after each breath respectively) against their respective airway pressure produces a slope that reflects fluid responsiveness and that is termed the RSVT slope.

In dogs subjected to graded hemorrhage, the RSVT slope increased significantly from 0.12±0.09 to 0.79±0.62 mmHg/cmH_2O after 30% removal of blood volume, and showed an overall significant correlation (r = -.81) to the stroke volume index [56]. In 14 patients who underwent vascular surgery, a baseline RSVT slope of 0.30 ± 0.18 decreased to 0.10 ± 0.09 mmHg/cmH_2O ($p<.001$) after volume loading, and correlated significantly with the LVEDA (r = -0.817) and with the changes in stroke volume index following volume loading (r = 0.8492) [57]. An RSVT value of ≥0.24 mmHg/cmH_2O predicted a change of 15% in CI with a sensitivity of 87.5% and a specificity of 83%, while a value ≥0.34 mmHg/cmH_2O predicted a change of CI of 20% with a sensitivity of 83% and a specificity of 75% (Perel A et al, unpublished data). In another study in dogs with induced LV failure, the RSVT slopes correlated significantly (r = 0.7154) with the slopes of actual LV function curves [58]. In patients undergoing cardiac surgery, the RSVT slope compared favorably with other functional hemodynamic parameters, which as a group performed better than 'preload' indices (Fig. 6, Preisman et al, unpublished data).

The RSVT has the potential to become the preferred parameter of fluid responsiveness since it is highly standardized, it is not influenced by the ΔUp and hence reflects fluid responsiveness only, it is potentially less influenced by changing compliance, and it produces a slope that correlates with the slope of the LV function curve, which is often mentioned but only rarely measured. Further studies are needed to establish the effectiveness of this parameter that is produced by a true automated linkage of the ventilator and the monitor.

Limitations of Functional Hemodynamic Parameters

The main limitation of functional hemodynamic parameters is that their use is limited to patients who are on fully controlled mechanical ventilation. In patients who are breathing spontaneously or on partial ventilatory support, quantification of the respiratory changes in pulsatile parameters may be inaccurate and difficult to interpret. Other potential inaccuracies may be due to the lack of standardization of the magnitude of the tidal volume employed, an exaggerated variation in the presence of large tidal volumes and too little variation when low tidal volumes are being used [59]. Exaggerated variations can also be seen in the presence of air-trapping or reduced chest wall compliance [6, 14]. Decreased lung compliance by itself should not affect the usefulness of the SPV and its derivatives if the tidal volume is unchanged, since the effects of increased airway pressure and its reduced transmission may cancel each other out. In fact some of the major clinical studies on functional hemodynamic parameters have been done in patients who were in respiratory failure [23, 27, 28, 44].

Since functional hemodynamic parameters rely on individually measured beats, any arrhythmias may cause significant inaccuracies. Nodal rhythm, however, may increase the SPV by effectively decreasing preload due to the loss of the 'atrial kick'. As mentioned before, the SPV, SVV, and PPV include the ΔUp, a component that is unrelated to fluid-responsiveness and that may reduce their ability to accurately reflect fluid responsiveness. This may occur especially when they are in mid-range, since an SPV of 5–6 mmHg may be composed of only a ΔUp, only a ΔDown or a combination of both. The ΔDown has therefore a theoretical advantage in that it is a parameter of fluid responsiveness only. The measurement of the ΔDown (and the ΔUp) necessitates however a long end-expiratory pause or the introduction of a short apnea followed by a careful analysis of the effects of the succeeding (or preceding) mechanical breath on the arterial pressure waveform. The apnea should preferably be achieved without disconnecting the patient from the ventilator, so as not to lose the prevailing PEEP or auto-PEEP. Some attempts have been made to automate the measurement of the SPV and even define automatically the reference systolic blood pressure measured at end-expiration for the automatic measurement of ΔUp and ΔDown [60–62], but the automated measurement of these parameters is still unavailable in commercial monitors. The SVV and PPV are however measured automatically in the PiCCO and the LidCo monitors.

Conclusion

We are often confronted with a variety of static parameters that do not provide a conclusive picture. Challenging the system with a standardized stimulus may provide new insights about the function of the whole system. The normal effects of this stimulus have to be well known, so that interpretation of the response to this stimulus is clear and preferably immediate. Confounding factors may decrease the usability of this approach.

These are general guidelines for the use of any diagnostic or therapeutic functional test, and directly apply to the use of the increase in intrathoracic pressure as a repetitive challenge of the circulation. In order to be used and interpreted correctly one must have a basic knowledge of the normal physiology of heart-lung interaction during mechanical ventilation. The resulting functional hemodynamics parameters can be of great value in the monitoring of ventilated patients, in which hemodynamic uncertainty and potential instability are often present. Since the main hemodynamic effect of the mechanical breath is normally a decrease in venous return, the hemodynamic response to the transient decrease in preload (the ΔDown) reflects the degree of fluid-responsiveness. For the SPV, PPV, and SVV parameters, values above 10–13% indicate, with very high sensitivity and specificity, that fluid loading will cause an increase in cardiac output. Since all these parameters are affected by the early inspiratory augmentation of LV stroke volume, their performance can be further standardized and improved by automated respiratory maneuvers in which fluid responsiveness alone is being analyzed, like the RSVT. Besides supplying an immediate estimation of fluid responsiveness, these parameters are extremely sensitive to changes in preload, and therefore are useful in following the response to fluid loading.

Since the normal healthy heart is fluid responsive, the presence of fluid responsiveness is not an indication by itself to administer fluids. In addition functional hemodynamic parameters do not offer an answer to the dilemma of cardiovascular 'optimization'. However, by being able to detect occult hypovolemia, identify the presence of fluid responsiveness or its absence in low-flow states, and reflect the response to changes in effective blood volume, these parameters offer immediate, dynamic, and essential information about the cardiovascular function.

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Arterial Pulse Pressure Variation During Positive Pressure Ventilation and Passive Leg Raising

J.-L. Teboul, X. Monnet, and C. Richard

Introduction

Inadequate cardiac preload can play a major role in the development of acute circulatory failure or its aggravation in critically ill patients. However, its detection is difficult at the bedside because of the unreliability of clinical signs of cardiac function in the intensive care unit (ICU) setting. Recently, renewed interest in the cardiovascular significance of heart-lung interactions has emerged. In this chapter, we focus on the magnitude of the respiratory variation in arterial pulse pressure and on the hemodynamic response to a passive leg raising maneuver as simple tools to detect preload responsiveness in critically ill patients.

Arterial Pulse Pressure Respiratory Variation

Respiratory Changes in Stroke Volume

Mechanical ventilation-induced cyclic changes in cardiac loading conditions

- Mechanical insufflation decreases the preload of the right ventricle (RV) [1, 2]. The RV preload reduction is due to the decrease in the venous return related to the inspiratory increase in pleural pressure [1]. However, the degree of inspiratory reduction in systemic venous return and thus of the filling of the right heart depends on the volume status. Indeed, in hypovolemic patients, the reduction of systemic venous return during mechanical insufflation is expected to be more marked than in patients with hypervolemic conditions. In support of this hypothesis, the positive end-expiratory pressure (PEEP)-induced decrease in cardiac output was found to be more marked when patients were hypovolemic [2] and to be attenuated by volume infusion [3, 4]. This phenomenon could be explained by at least three mechanisms. The first is a greater increase in right atrial pressure (i.e., in the backpressure to venous return) during mechanical insufflation in hypovolemic patients. This greater increase in right atrial pressure could be due to the higher transmission of intrathoracic pressure inside the right atrium when the right atrium is underfilled than when it is overfilled [5]. The second mechanism refers to the collapsible nature of the great systemic veins and to the possible occurrence of a venous waterfall phenomenon between

the extrathoracic inferior vena cava and the right atrium. Collapse of the inferior vena cava as it enters the thorax has been advocated to explain the flow limitation and pulsus paradoxus during stressed spontaneous breathing conditions and pulsus paradoxus was demonstrated to decrease after volume loading in acute asthma [6]. In dogs, by inducing a focal compression of the intrathoracic inferior vena cava, PEEP was showed to create conditions of a waterfall in the intrathoracic inferior vena cava, in cases of low right atrial pressure [7]. In some mechanically ventilated patients, using transesophageal echocardiography (TEE), Vieillard-Baron et al. [8] showed a collapse of the superior vena cava that decreased after fluid infusion. The third mechanism that could explain the greater mechanical insufflation-induced decrease in systemic venous return in hypovolemic patients is that the increase in RV impedance produced by lung inflation [9, 10] is amplified by a waterfall effect due to the collapse of poorly filled alveolar vessels (zone 2) [11]. However, the insufflation-induced fall in vena caval flow occurring before the fall in RV output [12] suggests that this mechanism does not play a major role. Obviously, all these mechanisms may play an additive role in the fact that the decrease in systemic venous return during mechanical insufflation is more marked in hypovolemic conditions.

- Mechanical insufflation increases the RV afterload in relation to the inspiratory increase in transpulmonary pressure (alveolar minus pleural pressure) [13].
- The mechanical insufflation-induced decrease in RV preload and increase in RV afterload both lead to a decrease in RV stroke volume which is minimum at the end of the inspiratory period. As discussed above, the inspiratory impairment of venous return is assumed to be the main mechanism of the inspiratory RV ejection reduction [12].
- The inspiratory reduction of RV ejection leads to a decrease in left ventricular (LV) filling after a phase lag of 2–3 heart beats because of the long blood pulmonary transit time [14]. Thus, the LV preload reduction may induce a decrease in LV stroke volume, which is minimum during the expiratory period.
- Two other mechanisms may also occur: First, mechanical insufflation may induce a squeezing of blood out of alveolar vessels and thus transiently increase LV preload [15, 16]. Second, the inspiratory increase in pleural pressure may decrease LV afterload and thus enhance LV ejection [17]. The first mechanism in hypervolemic patients and the second mechanism in patients with severe LV systolic dysfunction may induce a slight increase in LV stroke volume during the inspiratory period. However, both experimental and clinical data suggest that these two mechanisms are only minor determinants of the respiratory changes in LV stroke volume, even in the case of LV dysfunction [18–20].

Therefore, intermittent positive pressure ventilation induces cyclic changes in LV stroke volume (maximum during the inspiratory period and minimum during the expiratory period) which are mainly related to the expiratory decrease in LV preload due to the inspiratory decrease in RV output.

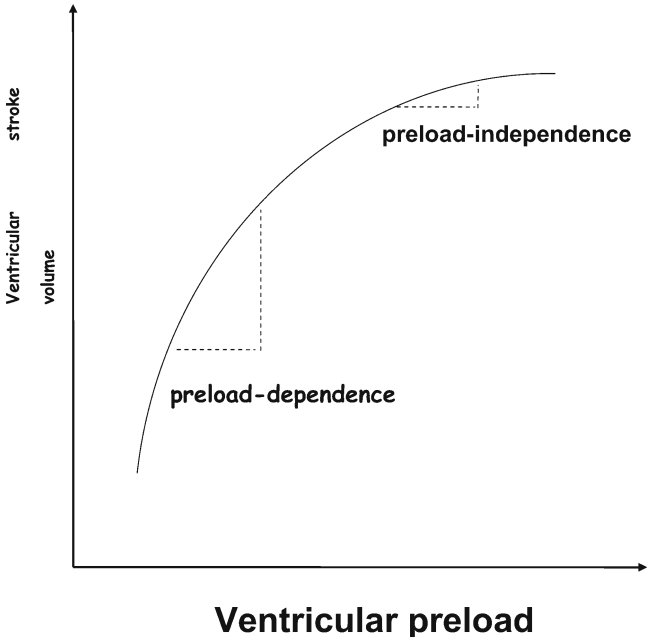

Fig. 1. Schematic representation of the Frank-Starling relationship between ventricular preload and ventricular stroke volume. A given change in preload induces a larger change in stroke volume when the ventricle operates on the ascending portion of the relationship (condition of preload-dependence) than when it operates on the flat portion of the curve (condition of preload independence).

Interpretation of the magnitude of respiratory changes in left ventricular stroke volume

The magnitude of the respiratory changes in LV stroke volume depends on the volume status (see above) and on the position of both ventricles on the Frank-Starling relationship [21, 22] (Fig. 1). When the ventricle operates on the ascending portion of the curve, a change in its preload induces a large change in its stroke volume (condition of " preload-dependence"). In contrast, when the ventricle operates on the flat portion of the relationship, a similar change in its preload induces only a small change in its stroke volume (condition of "preload-independence").

Consequently:

- the presence of large respiratory changes in LV stroke volume would mean that both ventricles are preload-dependent.
- the presence of small respiratory changes in LV stroke volume would mean either that at least one of the ventricles is preload-independent or in a lesser extent that ventricles are still preload-dependent but hypervolemic conditions are present.

Respiratory Changes in Arterial Pulse Pressure

The arterial pulse pressure (defined as the difference between the systolic and the diastolic pressure) is directly proportional to LV stroke volume and inversely related to arterial compliance [21]. The pulse pressure is not directly influenced by the cyclic changes in pleural pressure since the increase in pleural pressure induced by mechanical insufflation affects both diastolic and systolic pressure. In this regard, the respiratory changes in LV stroke volume have been shown to be reflected by changes in peripheral pulse pressure during the respiratory cycle [14]. Thus, in mechanically ventilated patients, the pulse pressure is maximum at the end of the inspiratory period (maximal values of LV preload and stroke volume) and minimum 2–3 heart beats later, i.e., during the expiratory period (Fig. 2).

It has to be noted that respiratory changes in systolic pressure result both from changes in diastolic pressure (reflecting mainly changes in pleural pressure) and pulse pressure (reflecting changes in LV stroke volume). Thus, systolic pressure is also maximum at the end of the inspiratory period and minimum during the expiratory period (Fig. 2).

Since the respiratory changes in arterial pulse pressure reflect the changes in left ventricular stroke volume, they should be a marker of biventricular preload-dependence.

Pulse Pressure Variation for Detecting Volume Responsiveness

Because of the positive relationship between ventricular preload and stroke volume, the expected hemodynamic response to volume infusion is an increase in LV stroke volume and hence in cardiac output. However, since the relationship between ventricular preload and stroke volume is not linear but curvilinear, a vol-

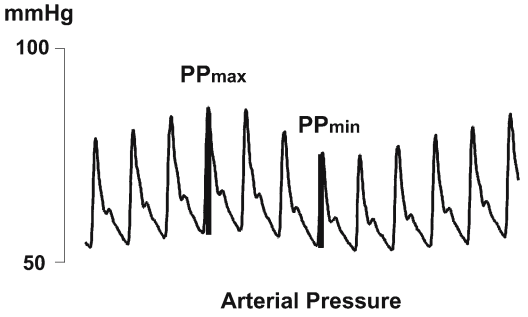

Fig. 2. Respiratory changes in arterial pressure in a mechanically ventilated patient. The pulse pressure (systolic minus diastolic pressure) is maximal (PPmax) at the end of the inspiratory period and minimal (PPmin) three heart beats later, i.e., during the expiratory period. The respiratory changes in pulse pressure (PPV) can be calculated as the difference between PPmax and PPmin, divided by the mean of the two values, and expressed as a percentage:
PPV (%) = 100 x (PPmax – PPmin) / [(PPmax = PPmin) / 2]

ume-expansion-induced increase in RV preload results in a significant increase in RV stroke volume only if the right ventricle operates on the ascending portion of its preload/stroke volume relationship (RV preload-dependence). In this condition, the resulting increase in LV preload induces a significant increase in LV stroke volume only if the left ventricle is preload-dependent. Therefore, a patient is a responder to volume expansion only if both ventricles are preload-dependent. Because respiratory changes in stroke volume also occur in biventricular preload-dependent conditions, it has been logically postulated that the magnitude of respiratory changes in stroke volume can give useful information on the degree of volume responsiveness [23]. As a reflection of LV stroke volume respiratory variation, arterial pulse pressure respiratory variation has been proposed to detect volume responsiveness in mechanically ventilated patients [24]. It has to be noted that the magnitude of systolic pressure variation has also been proposed to detect volume responsiveness in mechanically ventilated patients [20, 25]. However, the respiratory changes in systolic pressure depend not only on the changes in LV stroke volume but also directly on the changes in pleural pressure [26]. Consequently, respiratory changes in systolic pressure could be observed in patients whose LV stroke volume remains unchanged over the respiratory cycle. In contrast, the respiratory changes in pulse pressure are not directly affected by the pleural pressure changes. Indeed, the inspiratory increase in extramural aortic pressure may increase both diastolic and systolic pressure, such that pulse pressure is not significantly influenced by this phenomenon. Thus, the respiratory changes in pulse pressure should be more specific of the changes in LV stroke volume than changes in systolic pressure.

Recent clinical studies have emphasized the usefulness of arterial pulse pressure variation to detect volume responsiveness in mechanically ventilated patients [27, 28]. The arterial pulse pressure respiratory variation (PPV) is usually calculated as the difference between the maximal (PPmax) and the minimal (PPmin) value of pulse pressure over a single respiratory cycle (Fig. 2), divided by the average of the two values, and expressed as a percentage:

$$PPV\ (\%) = (PPmax - PPmin) / [(PPmax + PPmin) / 2] \times 100.$$

In 40 patients with acute circulatory failure related to sepsis, Michard et al. [27] demonstrated that:

- PPV accurately predicted the hemodynamic effects of volume expansion: a threshold value of 13% allowed discrimination between responder (defined as patients who experienced an increase in cardiac index = 15 % in response to volume expansion) and non-responder patients with a sensitivity and a specificity of 94 and 96%, respectively
- the baseline value of PPV was closely correlated (r^2= 0.85) with the percent increase in cardiac index in response to volume expansion: the higher PPV before volume expansion, the greater the increase in cardiac index
- although systolic pressure variation also predicted the hemodynamic response to fluid, it was a less reliable indicator of fluid responsiveness than PPV in terms of sensitivity and specificity

- the decrease in PPV induced by volume expansion was correlated with the increase in cardiac index such that changes in PPV could be used not only to predict but also to assess the hemodynamic effects of volume expansion
- neither baseline right atrial pressure nor pulmonary artery occlusion pressure (PAOP) predicted the hemodynamic response to volume infusion.

Bendjelid et al. [28] also reported a close positive correlation ($r^2 = 0.83$) between PPV at baseline and the percent increase in cardiac output induced by volume infusion in cardiac surgery patients. In that study, the correlation between systolic pressure variation and the percent increase in cardiac output induced by volume infusion was also significant but weak ($r^2 = 0.52$) while no relation was found between volume-induced increase in cardiac output and right atrial pressure or PAOP [27].

These two studies [27, 28] confirm the superiority of dynamic indices such as PPV over static markers of cardiac preload such as cardiac filling pressures and also over systolic pressure variation to detect volume responsiveness in mechanically ventilated patients as has been emphasized in two recent reviews of the literature addressing the issue of prediction of fluid responsiveness in mechanically ventilated patients [29, 30]. In this regard, it must be remembered that markers of preload are poorly correlated with indicators of preload responsiveness (or preload-dependence) [31] mostly because the slope of the Frank-Starling curve (indicating preload responsiveness) is highly dependent on cardiac contractility, such that the same preload can be associated with preload responsiveness in the case of normal cardiac contractility or with the absence of preload responsiveness in the case of reduced cardiac contractility [23].

In summary,

- the presence of large respiratory changes in arterial pulse pressure reflecting a biventricular preload-dependence, means that the cardiac output would increase with fluid therapy
- the absence of respiratory changes in arterial pulse pressure means that the cardiac output would not increase with fluid therapy.

Pulse Pressure Variation for Predicting and Assessing the Hemodynamic Effects of PEEP

In ventilated patients with acute lung injury (ALI), PEEP may improve pulmonary gas exchange. However, it may also decrease cardiac output and thus offset the expected benefits in terms of oxygen delivery. The adverse hemodynamic effects of PEEP are not easily predictable in clinical practice, although they were shown to be more likely to occur in patients with low left ventricular filling pressures [2, 32].

It was recently hypothesized that the respiratory changes in arterial pulse pressure could predict the effects of PEEP on cardiac output. Indeed, the PEEP-induced decrease in cardiac output and the decrease in RV output induced by mechanical insufflation share the same mechanisms, i.e., the negative effects of increased pleural pressure on RV filling and of increased transpulmonary pressure

on RV ejection. Thus, it was assumed that the PEEP-induced decrease in cardiac output would correlate with the magnitude of the inspiratory decrease in RV stroke volume and of the expiratory decrease in LV stroke volume. In 14 ventilated patients with ALI, a very close relationship ($r^2 = 0.83$) was found between PPV prior to the application of PEEP and the PEEP-induced decrease in cardiac index [4]. This finding strongly suggested that PPV before applying PEEP could predict the hemodynamic effects of PEEP. Moreover, PEEP increased PPV such that the PEEP-induced decrease in cardiac index also correlated with the PEEP-induced increase in PPV [4]. Thus, the comparison of PPV prior to and after the application of PEEP may help to assess the hemodynamic effects of PEEP.

In a study in cardiac surgery patients, a significant negative correlation was also found between PEEP-induced changes in cardiac output and PPV before PEEP application ($r^2 = 0.63$) [28].

Limitations of Using Pulse Pressure Variation

It has to be stressed that temporal analysis of the respiratory changes in arterial pressure is not possible in patients with cardiac arrhythmias. Moreover, to ensure that the observed fluctuations in arterial pressure reflect only the effects of intermittent positive ventilation and not the effects of patient respiratory efforts, perfect sedation is required. In fact, this is not a real limitation in mechanically ventilated patients with ALI or septic shock, in whom sedation is frequently used. By increasing alveolar and pleural pressure, a rise in tidal volume may influence the magnitude of the respiratory changes in arterial pressure. Szold et al. [18] previously showed in ventilated dogs that the higher the tidal volume, the more marked were the respiratory changes in systolic arterial pressure. The magnitude of stroke volume variation measured using PiCCO technology has been also been demonstrated to depend on the tidal volume delivered by the ventilator [33]. Obviously, increasing tidal volume does not change the whole blood volume but may modify fluid responsiveness. Indeed, by increasing the mean pleural pressure, an increase in tidal volume may reduce the venous return pressure gradient, RV filling, and thus induce a leftward shift on the Frank-Starling curve. Therefore, the RV stroke volume becomes more sensitive to a preload reduction (the preload-dependence is more marked). If the LV is also preload-dependent, this will result in increased respiratory changes in arterial pressure. Therefore, it is important to note that the arterial pressure respiratory variation is not an indicator of total blood volume but a marker of fluid responsiveness, which is more useful in clinical practice. Thus, the potential influence of tidal volume on the respiratory changes in arterial pressure is not too great a limitation for its use as an indicator of fluid responsiveness [34]. However, when the tidal volume is extremely low, the inspiratory increase in pleural pressure may not be sufficient to induce significant arterial pressure respiratory variation even in the presence of biventricular preload-dependence conditions. However, low tidal volumes are generally used in patients with acute respiratory distress syndrome (ARDS) who exhibit large changes in alveolar pressure, such that changes in intrathoracic pressure over the respiratory cycle are not necessarily small in the presence of low tidal volumes.

Furthermore, it is not definitively established that using low tidal volume (6 ml/kg) ventilation in patients with ARDS is better than using normal tidal volumes (8–10 ml/kg) [35].

Even if the detection of fluid responsiveness is of particular use in the decision making process concerning volume expansion in patients with circulatory shock, two important points must be kept in mind. First, since both ventricles of healthy subjects operate on the steep portion of the preload/stroke volume relationship, volume responsiveness is a physiological phenomenon related to a normal preload reserve. Therefore, detecting volume responsiveness must not systematically lead to the decision to infuse fluid. Such a decision must be based on the presence of signs of cardiovascular compromise and must be balanced with the potential risk of pulmonary edema formation and worsening gas exchange. Second, it is reasonable to postulate that volume loading should be more beneficial in a hypotensive patient with low cardiac output and volume responsiveness than in a hypotensive patient with a relatively high cardiac output and some degree of volume responsiveness in whom early administration of a vasopressive agent should be more logical. This emphasizes the great interest of new commercially available devices that monitor and automatically display both cardiac output and indices of volume responsiveness such as PPV from beat-to-beat analysis of the arterial pressure waveform.

Passive Leg Raising

Passive leg raising is a maneuver that transiently and reversibly increases venous return by shifting venous blood from the legs to the intrathoracic compartment [36, 37]. The passive leg raising (45° elevation) results in an increase in right [38] and left [39, 40] ventricular preload. In this extent, passive leg raising can mimic the effects of fluid loading and has been proposed for a long time as a first line therapy of hypovolemic shock ("autotransfusion" effect). The way in which passive leg raising can alter preload is probably by an increase in the mean systemic pressure, the driving force for venous return [41], due to the gravitational shift of venous blood from unstressed to stressed volume. This mechanism is probably of major importance during passive leg raising in patients receiving mechanical ventilation because the volume of blood enclosed by the thoracic and splanchnic beds is already stressed by positive airway pressure and these vascular compartments are less compliant than when mechanical ventilation is not used [42]. In these conditions, the increase in mean systemic pressure with passive leg raising is expected to be higher in mechanically ventilated patients than in non mechanically ventilated patients. However, the effects of passive leg raising on cardiac output are variable [38, 43–45], probably dependent on the degree of leg elevation and on the existence of cardiac preload-dependence. In this regard, Boulain et al. [46] found in critically ill patients receiving mechanical ventilation that the increase in stroke volume induced by passive leg raising occurred only in patients who increase their stroke volume in response to 300 ml volume infusion. In those patients who were non-responders to fluids, passive leg raising did not change stroke volume despite increases in right atrial pressure and PAOP. Thus, passive

leg raising which was able to increase cardiac preload in all the studied patients, increased stroke volume only in those with cardiac preload-dependence. In this regard, passive leg raising has been proposed to serve as a test detecting biventricular-dependence and thus fluid responsiveness in critically patients, particularly in those receiving mechanical ventilation [46]. It is interesting to note that in the above-mentioned clinical study, the changes in PAOP induced by passive leg raising were immediately and fully reversible when the patients' legs were laid down. This finding suggests that passive leg raising may help in predicting individual fluid responsiveness while avoiding the hazards of unnecessary fluid loading.

Theoretically, the best marker of the hemodynamic response to passive leg raising as a predictor of the hemodynamic response to fluid loading would be a significant increase in stroke volume. Because arterial pulse pressure is directly proportional to LV stroke volume and assuming that arterial compliance is not altered by passive leg raising, an increase in pulse pressure during passive leg raising should indicate an increase in stroke volume during passive leg raising and thus a positive response to fluid infusion. In this regard, Boulain et al. [46] showed that the increase in radial artery pulse pressure was a good predictor of volume responsiveness in critically ill patients receiving mechanical ventilation, although the correlation between passive leg raising-induced changes in radial pulse pressure and fluid loading-induced changes in stroke volume was good ($r= 0.74$) but not excellent. This finding was probably because changes in radial pulse pressure may not reflect changes in aortic pulse pressure owing to the potential occurrence of complex changes in pressure wave propagation and reflection during change in blood flow induced by passive leg raising. In addition, a given change in stroke volume in different patients with different aortic compliance may be reflected by different changes in aortic pulse pressure. For these reasons, the direct measurement of stroke volume during passive leg raising should be more appropriate to detect volume responsiveness. Because of the short period of this test (within 1 minute), the thermodilution method is not appropriate even in its automatic and semi-continuous mode. Indeed, this method takes at least 10 minutes to completely detect a given change in cardiac output [47]. A beat-to-beat basis for measuring stroke volume or cardiac output would be a better approach for tracking rapid changes of stroke volume induced by passive leg raising. Technologies using pulse contour analysis, such as the PiCCO system, would be appropriate. However, to our knowledge, no data have been published yet on the effects of passive leg raising on PiCCO stroke volume as predicting fluid responsiveness. Maybe the location of the thermodilution catheter in the femoral artery could represent a limitation to performing easily the passive leg raising maneuver. An alternative beat-to-beat based monitoring method is esophageal Doppler which allows continuous measurement of blood flow in the descending aorta. This could be the ideal method to detect volume responsiveness using passive leg raising as it is non-invasive and easy to learn and to perform. Recent technologic developments allow continuous measurement of both the aortic blood velocity (Doppler method) and the diameter of the descending aorta (time-motion echographic transducer). Therefore, it is now possible to monitor blood flow in the descending aorta. To our knowledge, there is no published study that has examined the effects of passive leg raising on aortic

blood flow as a test to detect fluid responsiveness in critically ill patients. We have recently performed two studies not yet published, on that issue. The first study enrolled 36 mechanically ventilated and fully sedated patients monitored using a transesophageal Doppler (Hemosonic 100 Arrow) which allows continuous measurement of blood flow in the descending aorta (ABF). In all patients, for whom the decision of volume resuscitation was taken by the attending physician, we performed a passive leg raising maneuver before giving fluid. Patients who increased their mean ABF by more than 15% after fluid administration (500 ml) were considered as volume-responders. In the 18 responders, ABF increased by 32±24% ($p < 0.05$) after passive leg raising and by 42±24% after volume infusion. In the 18 non-responders, ABF did not change with passive leg raising. Considering all patients, the increase in ABF induced by passive leg raising correlated with that induced by volume infusion ($r = 0.82$, $p < 0.001$). An increase in ABF of more than 8% induced by passive leg raising predicted the response to volume infusion with a sensitivity of 94% and a specificity of 89%. Therefore, this method (passive leg raising) has been considered as reliable in the detection of fluid responsiveness in mechanically ventilated patients. The other study enrolled 22 patients receiving mechanical ventilation but with the persistence of spontaneous breathing activity which prevents the use of dynamic indices that use heart-lung interactions namely, arterial pressure variation, etc. We asked whether passive leg raising remains a reliable test to detect volume responsiveness under conditions where valuable indices of volume responsiveness are lacking. In the 10 responders to volume expansion, the ABF increased by 21±13% ($p < 0.05$) after passive leg raising and by 42±20% after volume infusion. In the 12 non responders, ABF did not change significantly, either with passive leg raising or after volume infusion. Considering all patients, the increase in ABF induced by passive leg raising correlated well with that induced by volume infusion ($r = 0.78$, $p < 0.001$). An increase in ABF induced by passive leg raising = ≥8% predicted the response to volume infusion with a sensitivity of 92% and a specificity of 91%. Therefore, transesohageal Doppler monitoring seems a reliable method to evaluate the effect of passive leg raising for predicting fluid responsiveness even in mechanically ventilated patients with persistent spontaneous breathing activity.

Conclusion

The quantification of the respiratory changes in arterial pulse pressure is a reliable tool to detect volume responsiveness and to predict the hemodynamic response to PEEP in mechanically ventilated patients without spontaneous breathing activity or arrhythmias. In those with persistent spontaneous breathing activity, a reversible test, such as passive leg raising can be helpful to predict volume responsiveness. A significant increase in arterial pulse pressure or in aortic blood flow measured with transesophageal Doppler during passive leg raising would indicate a positive hemodynamic response to volume infusion.

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Development of Treatment Algorithms

Standardization of Care by Defining Endpoints of Resuscitation

M. Mythen, H. Meeran, and M. Grocott

Introduction

The risk of mortality or major morbidity from critical illness remains high. Mortality ranges from 5% or more for some major surgical procedures to over 40% for septic shock [1, 2]. Treatment strategies that can reduce this mortality are of obvious importance to patients, health professionals, and resource managers. Hemodynamic optimization in the form of standardized goal-directed care protocols has shown some promising reductions in morbidity and mortality.

The Development of Goal-Directed Therapy

Mortality risk for an individual patient depends on interacting factors. First, on the severity of the acute illness, for example type of surgery, trauma or organ failure score. Second, on the patient's physiological reserve determined by the presence of pre-existing disease. Critical illness results in a rise in metabolic demand. The ability of the cardiovascular system to meet this demand and avoid tissue hypoxia correlates with survival. Observational studies of critically ill patients demonstrated higher indexes of cardiac output, oxygen delivery (DO_2), and oxygen consumption in survivors compared with non-survivors [3–6]. In addition, variables that reflect blood flow and oxygen flux are better predictors of mortality than those more commonly measured such as heart rate, blood pressure, central venous pressure (CVP), and hemoglobin [7]. These supranormal values of cardiac output and oxygen transport exhibited by survivors were then suggested as treatment goals [8]. A prospective trial tested this hypothesis and showed a reduction in mortality when supranormal oxygen transport values were used as endpoints for resuscitation of surgical patients [9]. A large number of subsequent studies have been conducted on the theme of supranormal oxygen transport goals or hemodynamic optimization with inconsistent results.

Why is Standardized Hemodynamic Optimization not always Beneficial?

The lack of benefit demonstrated by some studies may have been due to the inclusion of different patient groups, the application of inappropriate treatment

goals or treatment protocols. Previous reviews have been supportive of hemodynamic optimization although pooled results of trials fail to show a significant reduction in mortality [10–14].

The terms 'goal-directed therapy', 'pre-optimization', or 'hemodynamic optimization' lack a precise definition. The effectiveness of this treatment strategy is still controversial. However, there is sufficient evidence to suggest a framework on which to develop current treatment guidelines and future research into hemodynamic resuscitation of the critically ill patient.

Advantages of Standardized Care

The application of evidence-based guidelines to clinical practice has increased in recent years. There are obvious potential advantages of introducing decision-making that is rational and based on evidence. Clinical care can be simplified by the use of treatment algorithms. Standardized algorithms can facilitate cooperation between different healthcare professionals. Patients should benefit from the adoption of treatments based on evidence, whereas useless treatments can be discarded. It has been hoped that this approach may also reduce costs for healthcare purchasers [15].

Potential Problems with Standardized Care

Unfortunately standardization of care by the use of guidelines and protocols may not necessarily be a success. There are no certainties in clinical care and individual patients may have needs that fall outside standard guidelines. The rigid application of protocols cannot replace clinical judgment.

For standardized care to be successful either clinically, or in the setting of a research study, it must first be based on sound evidence. Treatment goals must be rational and achievable, validated by their association with improved outcome in previous studies. Standardized treatment algorithms must be previously validated. In other words, it must have been demonstrated that the treatment is successful in achieving the prescribed goals for all patients, or at least the majority. Research studies must have comparable intervention and control groups and adequate power to show a difference, this is often a problem in critical care based work. A summary of randomized trials of hemodynamic optimization and how they compare with this ideal is shown in Table 1a. Clinicians may be cautious in translating the benefits of treatment shown in research studies into everyday practice. Merely taking part in a study tends to result in some improvement in outcome for patients [16]. Implementation of standardized care guidelines requires a process of education and audit to prove their effectiveness. Finally, powerful social forces and organizational culture may have to be overcome [17, 18].

Endpoints of Resuscitation

A variety of endpoints have been studied in trials of hemodynamic optimization. These can be divided into indexes of oxygen transport derived from pulmonary artery catheter (PAC) measurements, measurements of flow in response to circulating volume optimization, and markers of tissue perfusion. Table 1b summarizes trials with different endpoints and study populations so that they may be compared more easily. This table can be cross-referenced with the more detailed Tables 2a–4b. The intention of these is also to emphasize features of trial design and conduct that are associated with positive outcome.

Oxygen Transport Goals

DO_2, oxygen consumption (VO_2), and cardiac index (CI) are logical indices to measure because they have been shown to predict survival [7]. The median values for these variables were DO_2 600 mls/min/m^2, VO_2 170 mls/min/m^2, and CI >4.5 l/min/m^2 in survivors. When these supranormal values have been used as treatment goals in randomized controlled trials they have been associated with improvements in important outcomes such as mortality, complications, and length of intensive care unit (ICU) stay [9, 19–27]. Tables 2a and 2b compare the demographic features and results of studies that use indices of oxygen transport as resuscitation endpoints.

Optimization of Circulatory Volume

Fluid optimization as an endpoint of resuscitation has been shown to reduce length of hospital stay and important complications in patients undergoing a variety of major surgical procedures [28–32]. This is usually achieved with an esophageal Doppler monitor to evaluate changes in flow in response to fluid challenges. The principle this approach shares with PAC-based studies is that hemodynamic resuscitation begins with volume optimization. However, the application of pre-defined hemodynamic values as goals is avoided, so that the maximum cardiac output achieved by each patient depends upon their own physiology. The endpoint of resuscitation is therefore achievable in all patients. The treatment strategy follows a simple, standard fluid challenge algorithm. Patients in the treatment group of these studies have significantly higher cardiac output values, thus demonstrating that the treatment algorithm is effective. Tables 3a and 3b compare these studies in detail.

Surrogate Markers of End-Organ Perfusion

Markers of tissue perfusion have also been used as endpoints for resuscitation. These include mixed venous oxygen saturation (SvO_2), lactate, base excess, and gut mucosal pH using gastric tonometry. The use of these endpoints is attractive,

Table 1a. An at-a-glance summary of studies of hemodynamic optimization.

	Study population[a]	Treatment goals clearly defined for both groups	Intervention group received more treatment than controls	Intervention group achieved higher goal values than controls	Standardized environment for treatment and control groups	Intention to treat analysis: outcome favors treatment
Berlauk et al 1991 [40]	S		•		•	•
Bishop et al 1995 [27]	T	•	•	•	•	•
Boyd et al 1993 [21]	S	•	•	•	•	•
Conway et al 2002 [32]	S		•	•	•	•
Gan et al 2002 [31]	S		•	•		•
Lobo et al 2000 [22]	S	•	•		•	•
Mythen et al 1995 [28]	S		•	•	•	•
Polonen et al 2000 [33]	S	•	•	•	•	•
Rivers et al 2001 [35]	C	•	•	•	•	•
Schultz et al 1985 [41]	S					•
Shoemaker et al 1988 [9]	S	•		•	•	•
Sinclair et al 1997 [29]	S		•	•	•	
Ueno et al 1998 [19]	S	•	•	•	•	•
Venn et al 2002 [30]	S		•	•	•	•
Wilson et al 1999 [20]	S		•			•
Yu et al 1998 [23]	C	•	•	•	•	•
Alia et al 1999 [45]	C	•			•	

Table 1a. *Continued*

	Study population[a]	Treatment goals clearly defined for both groups	Intervention group received more treatment than controls	Intervention group achieved higher goal values than controls	Standardized environment for treatment and control groups	Intention to treat analysis: outcome favors treatment
Bender et al 1997 [39]	S		•			
Durham et al 1996 [50]	C	•			•	
Fleming et al 1992 [26]	T	•	•	•	•	
Gattinoni et al 1995 [44]	C	•	•	•	•	
Hayes et al 1994 [49]	C	•	•	•	•	
Ivatury et al 1995 [37]	T	•			•	
Pargger et al 1998 [36]	S		•		•	
Sandham et al 2003 [43]	S		•		•	
Tuchschmidt et al 1992 [25]	C	•	•	•	•	
Valentine et al 1998 [38]	S		•			
Velmahos et al 2000 [47]	T	•			•	
Yu et al 1993 [46]	C	•	•		•	
Yu et al 1995 [48]	C	•	•	•	•	
Ziegler et al 1997 [34]	S		•		•	

(•) Indicates the presence of features important in determining the likelihood of producing a positive outcome. Studies with a positive outcome are presented first. [a] S=surgical, T=trauma, C=mixed critical illness

Table 1b. Summary of randomized studies of standardized hemodynamic resuscitation with various treatment goals.

Study	Study population	Intervention group goals	Treatment	Intervention group received more treatment than control	Intervention group achieved higher goal values	Main outcome variable	Outcome favors intervention
Berlauk et al 1991 [40]	Vascular surgery	CI≥2.8 l/min/m^2	Fluids +/– inotropes	Yes	Not known	Morbidity	Yes $p<<0.05$
Bishop et al 1995 [27]	Trauma	CI≥4.5 l/min/m^2, DO_2I≥670 l/min/m^2, VO_2I≥166 ml/min/m^2	Fluids +/– inotropes	Yes	Yes	Mortality	Yes $p=0.02$
Boyd et al 1993 [11]	General surgery	DO_2I>600 ml/min/m^2	Fluids +/– inotropes	Yes	Yes	Mortality	Yes $p=0.015$
Conway et al 2002 [32]	General surgery	SV and FTc	Fluid	Yes	Yes	Morbidity	Yes $p=0.02$
Gan et al 2002 [31]	General surgery	FTc and SV	Fluid	Yes	Yes	Length of hospital stay	Yes $p=0.03$
Lobo et al 2000 [22]	General surgery	DO_2I>600 ml/min/m^2	Fluids +/– inotropes	Yes	Yes	Mortality	Yes $p<<0.05$
Muller et al 1999 [42]	General surgery	No clear goals	Inotropes	Yes	No clear goals	Splanchnic oxygenation	Yes $p<<0.05$
Mythen et al 1995 [28]	Cardiac surgery	SV	Fluid	Yes	Yes	Morbidity	Yes $p=0.01$
Polonen et al 2000 [33]	Cardiac surgery	SvO_2>70%, lactate ≤2.0 mmol/l	Fluids +/– inotropes	Yes	Yes	Length of hospital stay	Yes $p<<0.05$
Rivers et al 2001 [35]	Sepsis	SvO_2>70%	Fluids +/– inotropes	Yes	Yes	Mortality	Yes $p=0.009$

Table 1b. *Continued*

Study	Study population	Intervention group goals	Treatment	Intervention group received more treatment than control	Intervention group achieved higher goal values	Main outcome variable	Outcome favors intervention
Scalea et al 1990 [24]	Trauma	CI >4.0 l/min/m^2, VO_2I>170 ml/min/m^2 (early vs late intervention not a randomized controlled trial)	Fluids +/– inotropes	No	Yes	Mortality	Yes p<<0.001
Schultz et al 1985 [41]	Hip surgery	Normalization of physiological profile from PAC studies. Values not specified.	Fluids +/– inotropes	Not known	Not known	Mortality	2.9 vs 29% no p value given.
Shoemaker et al 1988 [9]	General surgery	CI 3.5–4.5 l/min/m^2, DO_2I>600 ml/min/m^2, VO_2I>170 ml/min/m^2	Fluids +/– s inotrope	Not known	Yes	Mortality	Yes p<<0.01
Sinclair et al 1997 [29]	Hip surgery	SV and FTc	Fluid	Yes	Yes	Length of hospital stay	Yes p<0.05
Ueno et al 1998 [19]	Hepatic surgery	CI 3.5–4.5 l/min/m^2, DO_2I>600 ml/min/m^2, VO_2I>170 ml/min/m^2	Fluids +/– inotropes	Yes	Yes	Liver function	Yes p<0.05
Venn et al 2002 [30]	Hip surgery	SV, FTc, CVP	Fluid	Yes	Yes	Time to fitness for discharge	Yes p=0.008
Wilson et al 1999 [20]	General surgery	DO_2I>600 ml/min/m^2	Fluids +/– inotropes	Yes	Yes	Mortality	Yes p=0.007

Table 1b. *Continued*

Study	Study population	Intervention group goals	Treatment	Intervention group received more treatment than control	Intervention group achieved higher goal values	Main outcome variable	Outcome favors intervention
Yu et al 1998 [23]	Mixed critical illness ≥50 years old	$DO_2I \geq 600$ l/min/m^2	Fluids +/– inotropes	Yes	Yes	Mortality	Yes p=0.01
Alia et al 1999 [45]	Sepsis	$DO_2I > 600$ ml/min/m^2	Fluids +/– inotropes	Yes	No	Mortality	No
Bender et al 1997 [39]	Vascular surgery	$CI \geq 2.8$ l/min/m^2	Fluids +/– inotropes	Yes	Not known	Mortality	No
Durham et al 1996 [50]	Mixed critical illness	$DO_2I > 600$ ml/min/m^2, $VO_2I > 170$ ml/min/m^2	Fluids +/– inotropes	Not known	No	Mortality	No
Fleming et al 1992 [26]	Trauma	$CI \geq 4.52$ l/min/m^2, $DO_2I \geq 670$ l/min/m^2, $VO_2I \geq 166$ ml/min/m^2	Fluids +/– inotropes	Yes	Yes	Mortality	No
Gattinoni et al 1995 [44]	Mixed critical illness	$CI \geq 4.5$ l/min/m^2 or $SvO_2 \geq 70\%$	Fluids +/– inotropes	Yes	Only in CI group	Mortality	No
Hayes et al 1994 [49]	Mixed critical illness	$CI \geq 4.5$ l/min/m^2, $DO_2I \geq 600$ l/min/m^2, $VO_2I \geq 170$ ml/min/m^2	Fluids +/– inotropes	Yes	Yes	Mortality	No
Ivatury et al 1995 [37]	Trauma	pHi≥7.30 or $DO_2I \geq 600$ l/min/m^2 and $VO_2I \geq 150$ ml/min/m^2	Fluids +/– inotropes	Not known	Yes	Morbidity	No
Pargger et al 1998 [36]	Vascular surgery	pHi≥7.32	Fluids +/– inotropes	Yes	No	Morbidity	No

Table 1b. *Continued*

Study	Study population	Intervention group goals	Treatment	Intervention group received more treatment than control	Intervention group achieved higher goal values	Main outcome variable	Outcome favors intervention
Sandham et al 2003 [43]	General surgery	DO_2I 550–600 ml/min/m^2 CI 3.5–4.5 l/min/m^2	Fluids +/– inotropes	Yes	Not known	Mortality	No
Tuchschmidt et al 1992 [25]	Sepsis	CI≥6.0 l/min/m^2	Fluids +/– inotropes	Yes	Yes	Mortality	No
Valentine et al 1998 [38]	Vascular surgery	CI≥2.8 l/min/m^2	Fluids +/– inotropes	Yes	Not known	Morbidity	No
Velmahos et al 2000 [47]	Trauma	CI ≥4.5 l/min/m^2, DO_2I>600 ml/min/m^2, VO_2I>170 ml/min/m^2	Fluids +/– inotropes	No	Not known	Mortality	No
Yu et al 1993 [46]	Mixed critical illness	DO_2I≥600 l/min/m^2	Fluids +/– inotropes	Yes	No	Mortality	No
Yu et al 1995 [48]	Mixed critical illness	DO_2I≥600 l/min/m^2	Fluids +/– inotropes	Yes	No	Mortality	No
Ziegler et al 1997 [34]	Vascular surgery	SvO_2≥65%	Fluids +/– inotropes	Yes	Yes	Morbidity	No

Studies with positive outcomes are presented first. Abbreviations: CI=cardiac index, DO_2I=oxygen delivery index, VO_2I=oxygen consumption index, SV=stroke volume, FTc=corrected flow time, pHi=gastric mucosal pH, SvO_2=mixed venous oxygen saturation, PAC=pulmonary artery catheter, vs=versus.

Table 2a. Demographic features of studies using oxygen transport values as endpoints of resuscitation.

Study	Inclusion criteria	Timing of intervention	Study monitor Intervention group	Study monitor control group	Treatment goals intervention	Treatment goals control	Treatments	Environment treatment group	Environment control group
Alia et al 1999 [45]	Established critical illness: Severe sepsis or septic shock	Within 6hrs of study entry until 96hrs	PAC	PAC	DO_2I>600 ml/min/m^2	DO_2I>130 ml/min/m^2	Crystalloid, dopamine, norepinephrine, dobutamine	ICU	ICU
Bender et al 1997 [39]	Infrarenal aortic or lower limb elective vascular surgery	Preoperatively until 16hrs after surgery	PAC	CVP	PAOP 8–15 mmHg, CI≥l/min/m2, SVR<1100 dyne-s/cm^5	Not specified	Crystalloid, dopamine, blood, nitrates.	ICU before and after surgery	ICU before and after surgery
Berlauk et al 1991 [40]	Lower limb vascular surgery	3hrs preoperatively until end of surgery	PAC	CVP	PAOP CI≥2.8 l/min/m^2, SVR<1100 dyne-s/cm^5	Not specified	Fluid, dopamine, dobutamine, nitrates.	ICU before and after surgery	ICU before and after surgery
Bishop et al 1995 [27]	Trauma excluding head injury	6hrs after surgery or 12hrs after admission until 48hrs	PAC	CVP	CI≥4.5 l/min /m^2, DO_2I≥ 670l/min/m^2, VO_2I≥166 ml/min/m^2	CVP 8-12, SAP>120 mmHg, HR<110/min, urine 30–50 ml/hr	Fluid, blood, dobutamine	ICU	ICU

Table 2a. *Continued*

Study	Inclusion criteria	Timing of intervention	Study monitor Intervention group	Study monitor control group	Treatment goals intervention	Treatment goals control	Treatments	Environment treatment group	Environment control group
Boyd et al 1993 [11]	High risk surgery by Shoemaker criteria	Preoperatively until 24hrs after surgery	PAC	PAC	DO_2I>600 ml/min/m^2	PAOP 12–14 mmHg, Hb≥12g/dl	Gelofusine, blood, dopexamine	ICU	ICU
Durham et al 1996 [50]	Established critical illness: Trauma, sepsis, shock, renal failure, respiratory failure	Study entry until PAC no longer required	PAC	PAC	DO_2I>600 ml/min/m^2, VO_2I>170 ml/min/m^2	Optimal CI (minimum 3.5) using PAOP up to 18 mmHg, Hb 11 g/dl	Fluid, blood, dobutamine, dopamine, nitrates	ICU	ICU
Fleming et al 1992 [26]	Trauma	Within 6hrs of admission or surgery for 48hrs	PAC	CVP	CI≥4.52 l/min/m^2, DO_2I≥670 l/min/m^2, VO_2I≥166 ml/min/m^2	SAP120 mmHg, Hb≥10 g/dl, CVP 8–12 mmHg	Fluid, blood, dobutamine	ICU	ICU
Gattinoni et al 1995 [44]	High risk surgery by Shoemaker criteria, sepsis, respiratory failure or trauma	Within 48hrs of admission for 5 days	PAC	PAC	CI≥4.5 l/min/m^2 or Sv≥$O_2$70%	CI≥2.5–3.5 l/min/m^2	Fluid, blood, dobutamine, dopamine, norepinephrine, epinephrine, nitrates	ICU	ICU

Table 2a. *Continued*

Study	Inclusion criteria	Timing of intervention	Study monitor Intervention group	Study monitor control group	Treatment goals intervention	Treatment goals control	Treatments	Environment treatment group	Environment control group
Hayes et al 1994 [49]	Established critical illness: High-risk surgery by Shoemaker criteria, sepsis, trauma, respiratory failure. With failure to meet goals with volume alone	Within 24hrs of ICU admission, (except two patients). Length of treatment unspecified.	PAC	PAC	CI≥4.5 l/min/m^2, DO_2I≥ 600 l/min/m^2, VO_2I≥170 ml/min/m^2	CI>2.8 l/min/m^2	Fluid, blood, dopamine dobutamine, norepinephrine .	ICU	ICU
Lobo et al 2000 [22]	High risk elective surgery	Preoperative until 24hrs after operation	PAC	PAC	DO_2I>600 ml/min/m^2	DO_2I 520–600 ml/min/m^2	Fluid, blood, dobutamine, dopamine, nitrates	ICU	ICU
Sandham et al 2003 [43]	ASA III or IV major surgery	Started before operation, but length of treatment unclear	PAC	Not specified	DO_2I 550–600 ml/min/m^2, CI 3.5–4.5l /min/m^2	Not specified	Fluid, inotropes, blood	ICU	ICU

Table 2a. *Continued*

Study	Inclusion criteria	Timing of intervention	Study monitor Intervention group	Study monitor control group	Treatment goals intervention	Treatment goals control	Treatments	Environment treatment group	Environment control group
Schultz et al 1985 [41]	Hip fracture surgery	Before operation until 1–2 days after operation	PAC	CVP	Normal values derived from PAC. Values not stated	No goals	Fluid and inotropes	Not specified	Not specified
Shoemaker et al 1988 [9]	High risk surgery according to predefined criteria	Started before operation, but length of treatment unclear	PAC	PAC or CVP	CI 3.5–4.5 l/min/m^2, DO_2I>600 ml/min/m^2, VO_2I>170 ml/min/m^2	PAOP or CVP 4–12 mmHg, CI 2.8–3.5 l/min/m^2, DO_2I 400–550 ml/min/m^2, VO_2I 120–140 ml/min/m^2	Fluid, blood, dopamine, dobutamine, norepinephrine nitrates	ICU	ICU
Tuchschmidt et al 1992 [25]	Established critical illness: Septic shock	Within 4hrs of diagnosis for 72hrs	PAC	PAC	CI≥6.0 l/min/m^2, SAP≥90 mmHg	CI≥3.0 l/min/m^2, SAP≥90 mmHg	Albumin, blood, dopamine	ICU	ICU
Ueno et al 1998 [19]	Elective hepatectomy surgery	First 12hrs after surgery	PAC	PAC	CI≥4.5 l/min/m^2, DO_2I>600 ml/min/m^2, VO_2I>170 ml/min/m^2	CI≥2.8–4.0 l/min/m^2	Fluid, blood, dopamine, dobutamine	ICU	ICU

Table 2a. *Continued*

Study	Inclusion criteria	Timing of intervention	Study monitor Intervention group	Study monitor control group	Treatment goals intervention	Treatment goals control	Treatments	Environment treatment group	Environment control group
Valentine et al 1998 [38]	Elective aortic surgery	14hrs preoperatively until surgery	PAC	Not specified	PAOP 8–15 mmHg, CI≥2.8 l/min/m^2, SVR<1100 dyne-s/cm^5	No goals	Fluid, nitrates, dopamine	ICU	Ward
Velmahos et al 2000 [47]	Trauma with shock	Within 30mins of admission for 24hrs	Bioimpedance cardiac output then PAC	Bioimpedance cardiac output, PAC if indicated	CI≥4.5 l/min/m^2, DO_2I>600 ml/min/m^2, VO_2I>170 ml/min/m^2	DO_2I>450 ml/min/m^2, VO_2I>130 ml/min/m^2	Fluid, blood, dopamine, dobutamine, epinephrine, norepinephrine	ICU	ICU
Wilson et al 1999 [20]	High risk major elective surgery	4hrs preoperatively to 12–24hrs after surgery	PAC	Not specified	DO_2I>600 ml/min/m^2	No goals epinephrine or dopexamine	Fluid, blood,	ICU	Ward, HDU or ICU
Yu et al 1993 [46]	Established critical illness: SIRS. Sepsis, severe sepsis, septic shock	From admission to PAC removal or disease improvement	PAC	PAC	DO_2I>600 ml/min/m^2	DO_2I 450–550 ml/min/m^2	Fluid, blood, dopamine, dobutamine, epinephrine, norepinephrine	ICU	ICU

Table 2a. *Continued*

Study	Inclusion criteria	Timing of intervention	Study monitor Intervention group	Study monitor control group	Treatment goals intervention	Treatment goals control	Treatments	Environment treatment group	Environment control group
Yu et al 1995 [48]	Established critical illness: SIRS. Sepsis, severe sepsis, septic shock, requiring inotropes to achieve DO_2I> 600 ml/min/m^2	From admission to PAC removal or disease improvement	PAC	PAC	DO_2I>600 ml/min/m^2	DO_2I 450–550 ml/min/m^2	Fluid, blood, dopamine, dobutamine, epinephrine, norepinephrine	ICU	ICU
Yu et al 1998 [23]	Established critical illness: SIRS. Sepsis, severe sepsis, septic shock ≥50yrs and >75yr old groups	Within 24hrs of diagnosis to removal of PAC or disease improvement	PAC	PAC	DO_2I>600 ml/min/m^2	DO_2I 450–550 ml/min/m^2	Fluid, blood, dopamine, dobutamine	ICU	ICU

Abbreviations: CI=cardiac index, DO_2I=oxygen delivery index, VO_2I=oxygen consumption index, PAC=pulmonary artery catheter, vs=versus, CVP=central venous pressure, ICU= intensive care unit, PAOP=pulmonary artery occlusion pressure, Hb=hemoglobin, SAP=systolic arterial blood pressure, HR=heart rate, CI=cardiac index, SVR=systemic vascular resistance, SIRS=systemic inflammatory response syndrome.

Table 2b. Summary of results of studies using oxygen transport values as endpoints of resuscitation.

Study	DO_2I (ml/min/m^2) Intervention group	DO_2I (ml/min/m^2) Control group	VO_2I (ml/min/m^2) Intervention group	VO_2I (ml/min/m^2) Control group	Excess treatment for intervention group vs control group	Morbidity (intervention vs control group)	Mortality (intervention vs control group)
Alia et al 1999 [45]	Over 96hr period: 520	439 n/s p=0.2	Over 96hr period: 142	126 n/s p=0.07	N/s difference: Mean dobutamine 10.3 vs 7.9 mcg/kg/min p=0.21	Bacteremia 13% vs 34% of controls p=0.04	N/s
Bender et al 1997 [39]	Not measured. All intervention group reached goal of CI 2.8l/min/m^2	Not known. PAC not necessarily inserted	Not measured	Not measured	Crystalloid 5137 vs 3789 ml p<0.003	N/s	N/s
Berlauk et al 1991 [40]	Not measured. All but one in intervention groups reached goal of CI 2.8l/min/m^2	Not known. PAC not necessarily inserted	Not measured	Not measured	Preoperative fluids and vasoactive drugs in treatment groups	Fewer intraoperative and post operative complications p<0.05	1.5% in treatment groups, 9.5% in control group p=0.08
Bishop et al 1995 [27]	12–24hrs: 720±19 24–48hrs 759±14	567±23 p<0.01 24–48 hrs 577±13 p<0.01	12–24hrs: 158±3 24–48 hrs 149±3	138±4 p<0.01 24–48hrs 137±3 p<0.01	Net fluid intake in ICU 1768±263 vs 925±163 ml p=0.005	0.74±0.28 vs 1.62±0.28 organ failures per patient p<0.05 ICU stay 6±1 vs 11±2 days p<0.05	18 vs 37% p=0.03

Table 2b. *Continued*

Study	DO_2I ($ml/min/m^2$) Intervention group	DO_2I ($ml/min/m^2$) Control group	VO_2I ($ml/min/m^2$) Intervention group	VO_2I ($ml/min/m^2$) Control group	Excess treatment for intervention group vs control group	Morbidity (intervention vs control group)	Mortality (intervention vs control group)
Boyd et al 1993 [11]	Median values: 597 preoperative 537 24hrs postoperative	 399 p<0.001 448 p<0.001	Median values: 134 preoperative 121 24hrs postoperative	 126 n/s 26 n/s	Median preoperative fluid volume 633 vs 450 ml p=0.007	Mean complication rate 0.68 vs 1.35 per patient p=0.008	5.7% vs 22.2% p=0.015
Durham et al 1996 [50]	At 24hrs: 738	 682 p=0.23	At 24hrs: 152	 164 p=0.33	Treatment differences not given	Organ failure in 67% vs 73% p=0.58	N/s. 11% vs 10% p=0.85
Fleming et al 1992 [26]	16hrs: 717±24 24hrs: 737±27 48hrs: 760±17	579±40 p<0.01 653±52 n/s 583±16 p<0.01	16hrs: 161±4 24hrs: 155±4 48hrs: 145±3	152±9 n/s 136±6 p<0.05 133±4 p<0.05	Dobutamine used in 67% of protocol patients. Not used in controls	Organ failures 0.79 vs 1.74 per patient p<0.05, ICU stay 5 vs 12 days p<0.05	N/s. 24 vs 44% p=0.08
Gattinoni et al 1995 [44]	CI group: 641±184 SvO_2 group: 591±165	 575±164 p<0.01 n/s	CI group: 158±40 SvO_2 group: 149±38	 148±34 p<0.01 n/s	CI vs SvO_2 vs controls: Fluid 66.8 vs 60.7 vs 55.2% p=0.027 Dobutamine 65.6 vs 50.6 vs 46.0% p<0.001	Organ dysfunction and length of ICU stay n/s	ICU and six month mortality n/s

Table 2b. *Continued*

Study	DO_2I ($ml/min/m^2$) Intervention group	DO_2I ($ml/min/m^2$) Control group	VO_2I ($ml/min/m^2$) Intervention group	VO_2I ($ml/min/m^2$) Control group	Excess treatment for intervention group vs control group	Morbidity (intervention vs control group)	Mortality (intervention vs control group)
Hayes et al 1994 [49]	Values not given but >600 at 24hrs and area under 48hr DO_2/time curve significantly greater than control group	<600 at 24hrs For 48hr area under curve p=0.0012	Values not given but area under 48hr VO_2/time curve not significantly different	For 48hr area under curve P=0.12	median maximal doses: norepinephrine 1.2 vs 0.23 mcg/kg/min p=0.029, dobutamine 25 vs 10 mcg/kg/min p<0.001	ICU stay, hospital stay n/s	N/s. 54 vs 34% in hospital p=0.04
Lobo et al 2000 [22]	At 24hrs: 658±142	589±116 n/s	At 24hrs: 159±36	149±51	Dobutamine used in 89.5% vs 55% of controls	Complications 32% vs 67% p<0.05	28 day n/s. 60 day mortality 15.7 vs 50% p<0.05
Sandham et al 2003[43]	Unclear but median value >550 post operatively	Not measured	Not measured	Not measured	48.9 vs 32.8% inotropes p<0.001 vasodilators 8.5 vs 3.9% p<0.001, blood 56.6 vs 47% p<0.001 colloid 54.8 vs 47.7% p<0.001	Higher incidence of pulmonary emboli in protocol group 0.8 vs 0% p=0.004	In hospital 7.7 vs 7.8% p=0.93

Table 2b. *Continued*

Study	DO_2I (ml/min/m^2) Intervention group	DO_2I (ml/min/m^2) Control group	VO_2I (ml/min/m^2) Intervention group	VO_2I (ml/min/m^2) Control group	Excess treatment for intervention group vs control group	Morbidity (intervention vs control group)	Mortality (intervention vs control group)
Schultz et al 1985 [41]	Not known	Not measured	Not known	Not measured	Not known	10 vs 11% no p value given	2.9 vs 29% no p value given
Shoemaker et al 1988 [9]	Mean values for first four post operative days: 663±232	561±190 p<0.01	Mean values first four post op days: 136±44	118±43 p<0.01	Not known	Complication rate 1.3 vs 0.39 per patient p<0.05	4 vs 33% p<0.01
Tuchschmidt et al 1992 [25]	First 72hrs post-resuscitation: DO_2 18.8±0.4mls/kg	14.0±0.3 ml/kg p<0.01	VO_2 3.7±0.1ml/kg	3.7±0.6 ml/kg n/s	Colloid 775±25 ml vs 938±33 ml for controls. Dobutamine 30±1 vs 12±1 mcg/kg/min p<0.01	ICU stay 5.3±0.2 vs 8.9±0.6 days p<0.05	N/s. 50 vs 72% p=0.14
Ueno et al 1998 [19]	At 12hrs after surgery: 827±170	523±86 p<0.05	At 12hrs after surgery: 167±35 24hrs: 184±43	110±26 p<0.05 24hrs: 142±34 p<0.05	Dobutamine 69 vs 0% controls Fluid 12–24hrs 34±19 ml/kg vs 32±6 ml/kg p<0.05	Postoperative hyper-bilirubinemia 0 vs 18 patients p<0.05	N/s
Valentine et al 1998 [38]	All patients met endpoint of CI≥2.8l/min/m2 DO_2 not measured	Not measured	Not measured	Not measured	Crystalloid 2620±150 vs 1010±50 ml p<0.001 greater use of vasoactive drugs	Complications and hospital stay n/s	N/s. 5% treatment group vs 2% controls

Table 2b. *Continued*

Study	DO_2I ($ml/min/m^2$) Intervention group	DO_2I ($ml/min/m^2$) Control group	VO_2I ($ml/min/m^2$) Intervention group	VO_2I ($ml/min/m^2$) Control group	Excess treatment for intervention group vs control group	Morbidity (intervention vs control group)	Mortality (intervention vs control group)
Velmahos et al 2000 [47]	Not routinely measured	Not routinely measured	Not routinely measured	Not routinely measured	Inotropes 32% vs 17% n/s	Organ failures 38% vs 57% n/s	N/s. 15% vs 11% for controls
Wilson et al 1999 [20]	Preoperative median values: 721 epinephrine group	Not measured	Not known	Not measured	Mean 1500 ml extra 665 dopexamine group fluid preoperatively epinephrine or dopexamine given to treatment groups	Reduced morbidity 30% vs 61% and length of hospital stay in dopexamine group p=0.009	3 vs 17% p=0.007
Yu et al 1993 [46]	At 24hrs: 617±202	604±169 n/s	At 24hrs: 126+–31	126±38 n/s	Inotropes used in 69 vs 53%	N/s	N/s except subgroup analysis achievers vs non achievers 14% vs 53–60% p=0.01
Yu et al 1995 [48]	At 24hrs in subgroup of achievers: 661±98	524±103 p=0.001	At 24hrs in subgroup of subgroup of 130±36	125±33 n/s	Inotropes given in 100 vs 67% p=0.004	N/s	N/s except on subgroup analysis of achievers in treatment group vs controls 14% vs 21% p=0.005
Yu et al 1998 [23]	At 24hrs 50–75yr group: 594±111 >75yr group: 584±162	534±95 p=0.03 468±84 p=0.01	At 24hrs 50–75yr group: 116±28 >75yr group: 93±13	116±23 n/s 95±21 n/s	50–75yrs inotropes 39 vs 12% p<0.01. >75yrs inotropes 0 vs 10% p<0.012	50–75yrs less pulmonary dysfunction 9 vs 14% p<0.01	N/s. 50–75yrs 9 vs 12% p<0.01 >75yrs 12 vs 11%

Values are mean ± standard deviation unless otherwise specified. N/s=no significant difference (p>0.05), vs=versus, DO_2I=oxygen delivery index, VO_2I=oxygen consumption index, CI=cardiac index, ICU=intensive care unit.

Table 3a. A summary of demographic features of studies using volume optimization as the endpoint of resuscitation.

Study	Inclusion criteria	Timing of intervention	Study monitor Intervention group	Study monitor control group	Treatment goals intervention group	Treatment goals control group	Treatments	Environment treatment group	Environment control group
Conway et al 2002 [32]	Elective major bowel surgery	Anesthesia induction to end of surgery	EDM	EDM	Optimal SV and FTc, algorithm from Sinclair et al.	Conventional fluid therapy as judged by anesthetist	HES fluid challenges	OR and ward or ICU	OR and ward or ICU
Gan et al 2002 [31]	Elective major general, urologic or gynecologic surgery	Anesthesia induction to end of surgery	EDM	HR, blood pressure, CVP, urine. With EDM concealed	Optimal SV and FTc, algorithm from Sinclair et al.	HR<110/min, SAP and CVP within 20% baseline, urine 0.5 ml/kg/hr	HES, blood and crystalloid fluid challenges	OR, postoperative environment unspecified	Theatre, postoperative environment unspecified
Mythen et al 1995 [28]	Elective first time coronary or single valve heart surgery	Anesthesia induction to end of surgery	EDM, CVP monitor and gastric tonometer	Conventional invasive hemodynamic monitoring including CVP. EDM and tonometer concealed	Optimal SV and CVP	No clear goals. Clinical judgement of anesthetist	HES, blood and crystalloid fluid challenges	OR and ICU	OR and ICU
Sinclair et al 1997 [29]	Hip fracture surgery over 55 yrs	Anesthesia induction to end of surgery	EDM	HR, SAP. With EDM concealed	Optimal SV and FTc according to treatment algorithm	No clear goals. Clinical judgement of anesthetist	HES, blood and crystalloid fluid challenges	OR and orthopedic ward	OR and orthopedic ward

Table 3a. *Continued*

Study	Inclusion criteria	Timing of intervention	Study monitor Intervention group	Study monitor control group	Treatment goals intervention group	Treatment goals control group	Treatments	Environment treatment group	Environment control group
Venn et al 2002 [30]	Hip fracture surgery over 65 yrs	Anesthesia induction to end of surgery	EDM	CVP	Optimal SV and Ftc, algorithm from Sinclair et al	Optimal CVP algorithm or conventional therapy	Gelofusine fluid challenges	OR and orthopedic ward	OR and orthopedic ward

Abbreviations: EDM=esophageal Doppler monitor, SV=stroke volume, FTc=corrected flow time, HES=hydroxyethyl starch, HR=heart rate, SAP=systolic arterial blood pressure, CVP=central venous pressure, ICU=intensive care unit, OR=operating room

Table 3b. Summary of results of studies using volume optimization as the endpoint of hemodynamic resuscitation.

Study	Hemodynamic values Intervention group	Hemodynamic values Control group	Excess treatment for intervention group	Morbidity	Mortality
Conway et al 2002 [32]	Final measurements, mean and SD: FTc 0.383±0.03s SV 82.9±24.4mls CO 6.1±1.9l/min	 FTc 0.354±0.045s p<0.05 SV 67.8±18.7 ml p<0.05 CO 5.0±1.4 l/min p<0.05	28.0 vs 19.4 ml/kg colloid p=0.02	Reduced critical care admission 5 vs 0 patients p=0.02	Not analyzed
Gan et al 2002 [31]	Final measurements, mean and SD: FTc .40±0.03s SV 76±19mls CO 5.8±1.6 l/min	 FTc 0.37±0.04s p<0.05 SV 67±17 ml p<0.05 CO 5.1±1.4 l/min p<0.05	847±373 vs 282±470 ml colloid p<0.01	Hospital stay 5±3 vs 7±3 days p=0.03, oral solids 3±0.5 vs 4.7±0.5 days p=0.01	Not analyzed
Mythen et al 1995 [28]	Values not given, but increased SV and CO p<0.01	No change in SV	Colloid 800 to 2400 ml vs 0 to 1800 ml p<0.001	Reduced complications p=0.01, reduced hospital stay p=0.011, reduced ICU stay p=0.023 pHi reduced in controls p<0.001	N/s
Sinclair et al 1997 [29]	Median increases: FTc +38.5ms SV +13mls CO +1.0l/min	 24.0ms p<0.05 –6mls p<0.001 –0.25 l/min p<0.05	Median colloid volume 750 vs 0ml p<0.001	Median time to fitness for discharge 10 vs 15 days p<0.05	Not analyzed
Venn et al 2002 [30]	EDM group median increases: FTc +49.4ms SV +13.5mls CO +0.9l/min CVP group mean increase: CVP +5 mmHg	No EDM used. Mean CVP unchanged p<0.0001	Mean (confidence intervals) colloid volume: EDM 1207(1077–1336) ml, CVP 1123 (921–1324) ml Control 448 (319–576) ml p<0.0001	fitness to discharge time: control 14 days vsCVP 10 days p=0.008 EDM 8 days p=0.023	N/s

Abbreviations: SD=standard deviation, CO=cardiac output, EDM=esophageal Doppler monitor, SV=stroke volume, FTc=corrected flow time, CVP=central venous pressure, ICU=intensive care unit, n/s=not significant (p>0.05), vs=versus.

because ensuring optimal blood flow to the vital organs is the ultimate aim of hemodynamic resuscitation. In a trial of standard treatment versus goals of SvO_2>70% and lactate concentration <2.0 mmol/l in cardiac surgical patients, there was a shorter hospital stay and lower morbidity in the treatment group [33]. No benefit was demonstrated when a lower SvO_2 goal of 65% was used in vascular surgery patients [34]. Mixed venous samples taken from a central line rather than a PAC have also been used to guide hemodynamic resuscitation. Aiming for a central venous oxygen saturation of >70% resulted in a reduction in mortality in patients with sepsis [35].

Gastric mucosal pH (pHi) as an endpoint of resuscitation is based on the observation that the gut is prone to decreased perfusion during hypovolemia and low pHi is a sensitive predictor of poor outcome. Protocolized volume resuscitation can produce an improvement in pHi and reduce morbidity [28]. The use of normal pHi as an endpoint of resuscitation has been shown to improve mortality in a small, randomized study. A standardized treatment algorithm was used, and all but one patient achieved the target pHi of 7.3. No benefit from using pHi>7.32 as a resuscitation endpoint was found in a study of vascular patients. This may be because goal-directed treatment was only started postoperatively and failed to produce a significant difference in pHi between groups. Low pHi was found to be a predictor of major complications [36]. Interestingly, pHi has also been found to be a better predictor of outcome than DO_2 [37]. See Tables 4a and 4b to compare these studies.

Standardized Care Protocols Require a Valid Endpoint

If the correct endpoint of resuscitation is not chosen then a standardized care protocol will not be successful in clinical practice. The same applies to research studies that attempt to contribute to the development of hemodynamic optimization. Studies that have used normal, rather than supranormal oxygen transport values as resuscitation goals, usually show no significant benefit [38–40]. This supports the hypothesis that in order to survive critical illness, patients must generate a higher than normal DO_2 in order to meet an increased metabolic demand. The use of normal hemodynamic values as treatment goals may be beneficial in patients with hip fractures. However, control group patients did not receive equivalent monitoring and had unspecified treatment goals making accurate comparison of the two groups impossible [41]. The exact increase in DO_2 required to survive critical illness must vary according to interacting patient and disease factors. It therefore follows that pre-defined values as goals cannot necessarily be applied to both surgical and medical patients and will be unnecessarily high or too low for some individuals.

If a study uses no target endpoint to guide treatment then although some interesting observations may be made, they contribute little to the development of hemodynamic resuscitation. For example, a trial of the effect of dopexamine on pHi during abdominal surgery demonstrated an improvement in serosal PO_2. Unfortunately this study used a fixed dose of dopexamine, rather than a goal

Table 4a. Demographic features of studies using indices of end-organ perfusion as endpoints of resuscitation.

Study	Inclusion criteria	Timing of intervention	Study monitor intervention group	Study monitor control group	Treatment goals intervention	Treatment goals control	Treatments	Environment treatment group	Environment control group
Gattinoni et al 1995 [44]	High risk surgery by Shoemaker criteria, sepsis, respiratory failure or trauma	Within 48hrs of admission for 5 days	PAC	PAC	CI≥4.5 l/min/m^2 or SvO_2≥70%	CI≥2.5-3.5 l/min/m^2	Fluid, blood, dobutamine, dopamine, norepinephrine, epinephrine, nitroprusside	ICU	ICU
Pargger et al 1998 [36]	Elective infrarenal aortic aneurysm repair	Post operative ICU admission until extubation	Gastric tonometer	Gastric tonometer (values concealed)	pHi>7.32	No clear goals. Clinical judgement	Fluid, blood, dopamine, epinephrine, norepinephrine	ICU	ICU
Polonen et al 2000 [33]	Elective cardiac surgery	Postoperative first 8hrs	PAC	PAC	SvO_2>70% serum lactate ≤2.0mmol/l	CI≥2.5 l/min/m^2, PAOP 12–18 mmHg, MAP 60–90 mmHg	Fluid, blood dobutamine, dopamine	ICU	ICU
Ivatury et al [37] 1995	Trauma	ICU admission until death or invasive monitor not required	PAC and gastric tonometer	PAC and gastric tonometer	pHi>7.3	DO_2I≥600 ml/min/m^2, VO^2I≥150 ml/min/m^2	Fluid, blood, dobutamine, dopamine	ICU	ICU

Table 4a. *Continued*

Study	Inclusion criteria	Timing of intervention	Study monitor intervention group	Study monitor control group	Treatment goals intervention	Treatment goals control	Treatments	Environment treatment group	Environment control group
Rivers et al 2001 [35]	Severe sepsis and septic shock	Emergency department presentation to ICU admission: 6hrs	CVP plus central venous oxygen analysis	CVP	SvO_2 (central) >70%, CVP 8–12 mmHg, MAP ≥ 65 mmHg, Hct≥30%	CVP 8–12 mmHg, MAP ≥ 65 mmHg, Hct≥30%	Fluid, blood, dobutamine, vasopressors, vasodilators	Emergency room then ICU	Emergency room then ICU
Ziegler et al 1997 [34]	Elective aortic or lower limb vascular surgery	12hrs before to 24hrs after operation	PAC	PAC	SvO_2≥65%, PAOP ≥12 mmHg, Hb≥10g/dl	No goals	Crystalloid, blood, dobutamine, nitroprusside	ICU	ICU

Abbreviations: PAC=pulmonary artery catheter, ICU=intensive care unit, pHi=gastric mucosal pH, SvO_2=mixed venous oxygen saturation, Hb=hemoglobin concentration, CVP=central venous pressure, MAP=mean arterial blood pressure, DO_2I=oxygen delivery index, VO_2I=oxygen consumption index, PAOP=pulmonary artery occlusion pressure, Hct=hematocrit.

Table 4b. Summary of the results of studies using indices of end-organ perfusion as endpoints of resuscitation.

Study	DO_2I (ml/min/m^2) Intervention group	DO_2 I (ml/min/m^2) Control group	VO_2 I (ml/min/m^2) Intervention group	VO_2 I (ml/min/m^2) control group	Excess treatment for intervention group	Morbidity	Mortality
Gattinoni et al 1995 [44]	Values over 5 day period: CI group 641±184 SvO_2 group 591±165	575±164 p<0.01 n/s	Values over 5 day period: CI group 158±40 SvO_2 group 149±38	148±34 p<0.01 n/s	SvO_2 group vs control: 60.7 vs 55.2% volume therapy p=0.027, 50.6 vs 46.0% dobutamine p<0.001	N/s	N/s
Ivatury et al 1995 [37]	At 24hrs: 741.7±149.5 (pHi group)	687.1±171.8 (DO_2 group) n/s	At 24hrs: 181.8±40.7 (pHi group) n/s	166.9±35.7 (DO_2 group)	Not known	N/s	N/s
Pargger et al 1998 [36]	Not measured, but difference in pHi n/s between groups	Not measured	Not measured	Not measured	Vasoactive drugs on day 1 69 vs 38% p<0.05	Length of ICU stay and complications n/s	N/s
Polonen et al 2000 [33]	At 8 hrs: 508±106	465 ±94 p<0.001	At 8hrs: 131 ±22	128±22 p<0.05	2271±1523 vs 1970±1219 ml crystalloid p<0.05, 922±431 vs 802±408 ml colloid p<0.01 20.4 vs 7.6% inotropes	Median hospital stay 6 vs 7 days p<0.05. Number with >1 organ dysfunction at discharge 2 vs 11 p<0.01	N/s

Table 4b. *Continued*

Study	DO_2I (ml/min/m^2) Intervention group	DO_2 I (ml/min/m^2) Control group	VO_2 I (ml/min/m^2) Intervention group	VO_2 I (ml/min/m^2) control group	Excess treatment for intervention group	Morbidity	Mortality
Rivers et al 2001 [35]	Not measured, but SvO_2 significantly higher in treatment group p<0.02	Not measured	Not measured	Not measured	(0–6hrs). Fluid: 4981±2984 vs 3499±2438 ml p<0.001. Red cells 64.1 vs 18.5% p<0.001. Dobutamine 13.7 vs 0.8% p<0.001	APACHE II, SAPS II and MODS scores all lower in intervention group at 72hrs p<0.001 for all three	In hospital: 38 vs 59% p=0.009 28 day: 40 vs 61% p=0.01 60 day: 50 vs 70% p=0.03
Ziegler et al 1997 [34]	Mean at 24hrs: 498	422 n/s	Mean at 24hrs: 134	109 n/s	3.6 vs 1.2 ml/kg/hr fluid	N/s	N/s

Values are mean ± standard deviation unless otherwise specified. Abbreviations: ICU=intensive care unit, pHi=gastric mucosal pH, SvO_2=mixed venous oxygen saturation, DO_2I=oxygen delivery index, VO_2I=oxygen consumption index, APACHE II=acute physiology, age and chronic health evaluation version II, SAPS II=simplified acute physiology score version II, MODS= multiple organ dysfunction score, n/s=not significant (p>0.05), vs=versus.

directed treatment algorithm, producing no difference in pHi or global oxygen transport values between groups [42].

Treatment Algorithms May Be Ineffective

The treatment used in standardized hemodynamic resuscitation should follow a simple algorithm. The exact nature of this depends upon the chosen endpoint, but it will be a combination of volume therapy and vasoactive drugs. It is vital that the algorithm, when applied correctly, results in achievement of the endpoint. In studies of supranormal oxygen transport a large proportion of subjects often fail to achieve treatment endpoints. A recent, large, multicenter trial of the use of supranormal goals versus standard therapy guided by CVP showed no difference between the two groups [43]. However, only 62.9% of patients in the treatment group achieved the primary goal of DO_2 index (DO_2I) 550–600mls/min/m^2. It is not possible to conclude that goal directed hemodynamic optimization is of no benefit from this study. The treatment given did not result in achievement of the endpoint in a significant proportion of patients. The absence of cardiac output monitoring in the standard group also precluded the demonstration of a difference in oxygen transport values between the two groups. Another large trial that included normal SvO_2 and supranormal CI groups of critically ill patients demonstrated no reduction in morbidity or mortality. Arguably, this is also due to failure to achieve treatment goals [44]. A smaller study of supranormal DO_2 values in patients with sepsis failed to demonstrate a significant difference in DO_2 between the treatment and control groups [45]. There was also no significant excess treatment received compared to the control group. Thus, it may well be the treatment algorithm or the amount of treatment given, rather than the endpoint that is invalid. Physiological limitations resulting from acute and chronic illness also will prevent many patients from achieving target endpoints.

The Interaction Between Patient Physiology and Treatment

It is often observed in studies of hemodynamic optimization that patients in the control group spontaneously achieve hemodynamic targets used in the treatment group. Conversely, a proportion of patients in the treatment group are unable to achieve the target endpoint despite more aggressive therapy. Those patients who spontaneously achieve target hemodynamics fall into a low mortality group and unsurprisingly, those who are non-achievers despite treatment have a high mortality. These differences must be due to the underlying fitness of patients [46, 47]. A third category of patients do not achieve hemodynamic goals with first line treatment, such as volume therapy, but do with the addition of vasoactive drugs. These patients are potentially moved into a better prognostic group. If this is the case, then this group will derive the most benefit from intensive hemodynamic optimization. How to identify patients who will benefit from hemodynamic augmentation with vasoactive agents is not clear. Some studies indicate that there are patients who respond favorably to treatment with inotropes such as dobutamine

or dopexamine after optimization with fluid [21, 22, 48]. These are usually studies of surgical patients. A beneficial effect tends to be more difficult to demonstrate in studies of more heterogeneous groups of critically ill patients [44, 49, 50]. In some patients, failure to achieve targeted hemodynamic values after volume therapy may be a prognostic indicator, rather than a problem amenable to treatment. One proposed method of identifying patients who might benefit most from hemodynamic resuscitation is cardiopulmonary exercise testing. Patients with a preoperative oxygen consumption of less than 11 ml/kg/min at anerobic threshold were found to have a high mortality risk after major surgery [51]. A low anderobic threshold identifies patients who would be expected to have a poor ability to increase their DO_2 postoperatively. In a subsequent study, these high-risk patients were selected for preoperative intensive care admission and optimization, whereas patients with an anerobic threshold >11 ml/kg/min could be managed on a general ward. This strategy was shown to be successful in allocating intensive care resources to those patients most in need [52].

The Interaction between Pathophysiology and Treatment

Oxygen transport values as endpoints of resuscitation were first developed in studies of surgical patients. Following the success of these studies, the same values were applied to other groups of critically ill patients. Some trials have demonstrated reduced mortality in patients with sepsis and trauma [23, 26, 27, 35]. Others have failed to show any benefit [44, 49, 50].

Endpoints previously validated in a select group of critically ill patients are not necessarily applicable to patients with different diagnoses. It is likely that the cardiac output and DO_2 required for survival varies depending on the type and severity of critical illness. Surgical patients have the advantage of being available for treatment and research studies prior to, or very early on, in the course of their illness. The predominance of surgical studies amongst those with positive results is illustrated by Table 1a. Patients with established critical illness may have irreversible organ damage by the time they receive optimal care. Thus the benefits of standardized hemodynamic resuscitation will be more difficult to demonstrate in non-surgical patients.

Conclusion

Standardized hemodynamic resuscitation results in important improvements in morbidity and mortality for critically ill patients when applied correctly. Key requirements must be fulfilled in the design of treatment protocols. Target endpoints must be previously validated, ideally in a similar patient group. Supranormal oxygen transport values, flow-guided volume optimization, and indices of end-organ perfusion can all be used as endpoints. However, it should be emphasized that volume optimization is an essential part of any hemodynamic resuscitation. Treatment algorithms that demonstrate failure to achieve the endpoint in a significant number of patients must be redesigned. Many issues remain unclear,

particularly regarding different groups of non-surgical critically ill patients. Adequately powered and well-designed randomized trials must be conducted to improve our understanding.

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Protocolized Cardiovascular Management Based on Ventricular-arterial Coupling

M. R. Pinsky

Introduction

Central to the management of any hemodynamically unstable patient is the rapid assessment of the determinants of the cardiovascular insufficiency, followed rapidly by appropriate specific therapies aimed at both stabilizing cardiovascular status and reversing the initiating processes. Within this context, the goal of cardiovascular therapy is to create a physiological condition wherein blood flow and oxygen delivery to the tissues is adequate to meet the varying metabolic demands of the tissues without inducing untoward cardiorespiratory complications. Cardiovascular insufficiency is often referred to a circulatory shock and is often the most overt manifestation of critical illness. Relevant to the immediate and aggressive management of circulatory shock is the use of appropriate therapies. Previously, we had simplified the treatment approach into the asking of three functional performance-based questions [1]:

1. Will blood flow to the body increase (or decrease) if the patient's intravascular volume is increased (or decreased), and if so, by how much?
2. Is any decreased in arterial pressure due to loss of vascular tone or merely due to inadequate blood flow?
3. Is the heart capable of maintaining an effective blood flow with an acceptable perfusion pressure without going into failure?

These immediate questions are functional and physiological in their language but reflect very practical concerns and define very concrete treatments. Presently, however, neither the interpretation of specific hemodynamic subsets to define disease processes nor their specific management of patients with defined hemodynamic alterations is standardized or universally accepted. In fact, marked confusion exists as to the interpretation of specific constellations of hemodynamic variables [2]. This lack of a systematic and universally accepted approach to both diagnosis and management of critically ill patients has serious consequences for the outcome from critical illness. Furthermore, if inappropriate treatment approaches based on flawed interpretation of measured physiological variables is applied to all patients with critical illness, regardless of the etiology of the disease process and independent of their functional status, mortality may actually increase [3, 4]. And if derived hemodynamic data, as may be acquired from a pulmonary artery catheter (PAC), are not used in a prescribed fashion to titrate

care, survival will be no better than if these invasive monitoring devices are not used [5].

Furthermore, data from numerous clinical trials have documented repeatedly that neither right atrial pressure or pulmonary artery occlusion pressure (PAOP) predict well the subsequent response of the subject to an intravascular fluid challenge [6]. Furthermore, measures of absolute left ventricular volumes are only slightly better at predicting preload-responsiveness. Clearly, subjects with small left ventricular end-diastolic volumes (LVEDV) can have a limited response to a volume challenge if their filling is limited either by tamponade, cor pulmonale, or diastolic stiffening. Finally, ventilation and ventilatory therapies, such as the use of positive end-expiratory pressure (PEEP) often complicate this analysis by dissociating filling pressures from measured intrathoracic vascular pressure because of both increasing intrathoracic pressure and cardiac compression by lung expansion [7]. However, ventilation, by phasically altering right atrial pressure also serves as a sine wave forcing function on venous return and can be used to define cardiovascular performance. Several groups have applied this concept to assess preload-responsiveness. The importance of these applications to bedside monitoring is finally being understood and is the basis of at least two of the chapters in this book.

Unfortunately, present diagnostic and treatment protocols lack generalized acceptance and do not directly address the three fundamental questions asked above. Furthermore, existing complex and poorly validated monitoring systems of hemodynamic profile analysis belie the simple fact that most treatments for hemodynamically unstable patients can be resolved by answering these three specific questions. Thus, the stage is set for a more functional method of assessing cardiovascular performance using hemodynamic monitoring.

Measures of Preload do not Predict Preload-responsiveness

Measures of preload have traditionally been used to assess volume status with the assumption that if intracardiac volume were reduced, the patient's cardiac output would increase in response to intravascular volume expansion. Accordingly, several measures of preload have been used to drive both clinical practice and standardize resuscitative management. Such estimates of preload include right atrial pressure, PAOP, RVEDV index (RVEDVI), and left ventricular end-diastolic area (LVEDA). Regrettably, none of these measures consistently predicts preload responsiveness, although minimal values of each may identify those subjects whose cardiac output will decrease in response to a stress known to decrease cardiac output, such as the addition of supplemental PEEP.

Regrettably, right atrial pressure values are of minimal value in predicting preload-responsiveness [6], although a right atrial pressure <10 mmHg is usually associated with a greater likelihood of cardiac decompensation when the subject is exposed to increasing amounts of PEEP [8]. Furthermore, Magder et al. [9] saw that, in their series of hemodynamically unstable subjects treated with volume expansion, the lowest right atrial pressure in a non-responder was 2 mmHg and the highest right atrial pressure in a responder was 18 mmHg. Similar poorly

predictive values for both right atrial pressure and PAOP were seen in a study of septic ventilator-dependent patients reported by Michard et al. [10, 11].

Since measures of filling pressures may not accurately reflect ventricular volumes, increased interest has arisen in the measure of RVEDVI, LVEDA, global end-diastolic volume (GEDV), and total intrathoracic blood volume (TIBV). Although patients with RVEDI values > 120 ml/m^2 are less likely to increase their cardiac output in response to fluid loading, the predictive value of this measure is poor [12]. LVEDA, perhaps the closest measure of left ventricular preload does not predict increased cardiac output in response to volume expansion [13]. Total thoracic blood volume is slightly better than both right atrial pressure and PAOP in predicting an increase in cardiac output in response to volume expansion [6], but again as many as one-third of patients with a low total thoracic blood volume did not increase their cardiac output by > 15%. Finally, GEDV values negatively correlated with the subsequent change in cardiac output in response to volume expansion; however, no specific values could be used to predict response [14]. Thus, in all cases, measures of preload do not reliable predict preload-responsiveness. One is left with the undeniable fact that preload does not equate to preload-responsiveness. Although the majority of subjects who are hypovolemic and responsive to volume expansion with an increase in cardiac output will have reduced cardiac filling pressures and volumes, many patients with low filling pressures or absolute cardiac volumes may not be preload-responsive, whereas many other patients with high filling pressure and expanded cardiac volumes may be preload-responsive. Thus, the reasons why measures of cardiac filling pressures are such poor predictors of preload responsiveness are that they are inaccurate measures of left ventricular preload which itself does not reflect preload responsiveness.

Functional Measures of 'Preload Responsiveness'

Since the gold standard for preload-responsiveness is an increase in cardiac output in response to volume expansion, one may use 'physiologic volume expansion' trials to ascertain preload-responsiveness. Using this approach, the obligatory small changes in ventricular filling induced by spontaneous or positive-pressure ventilation as well as the small increases in venous return induced by leg raising can be examined to define if a subsequent volume expansion trial will increase cardiac output. Although one may not use static measures of filling pressures or cardiac volumes to predict preload responsiveness, one may use their dynamic changes to reflect physiological volume expansion trials. In that regard, changes in right atrial pressure, arterial pressure, and aortic flow have been used to predict preload responsiveness.

Right atrial pressure is not only a component of right ventricular filling pressure but is also the backpressure to systemic venous return. During spontaneous inspiration, pleural pressure decreases decreasing the pressure within all intrathoracic vascular spaces. Right atrial pressure should decrease during spontaneous inspiration, transiently increasing venous return and subsequently cardiac output. If, however, the right ventricle is unable to dilate further, then right atrial pressure will not decrease during inspiration even though intrathoracic pressure decreases.

At the extreme, spontaneous inspiration-associated increases in right atrial pressure might reflect severe right ventricular failure and are referred to as Kussmaul's sign. Since right ventricular failure is a major cause of lack of preload-responsiveness in the hemodynamically unstable patient and since further volume expansion in a patient with acute cor pulmonale may be life taking, identifying those subjects with right ventricular decompensation prior to volume expansion is important. Magder et al. used the fall in right atrial pressure to predict which patients would increase their cardiac outputs in response to a defined fluid challenge [9]. They found that if right atrial pressure decreased by > 2 mmHg during a spontaneous breath then cardiac output increased in 16 of 19 patients in response to volume expansion. If right atrial pressure did not decrease, then cardiac output increased in only one of 14 patients. They also showed that this approach can also be used to predict subsequent changes in cardiac output in response to increasing levels of PEEP in mechanically ventilated subjects [15]. However, these studies rely on right ventricular performance as the signal transducer for blood flow. They do not address the issue of left ventricular performance.

Other studies focused on the effects of positive-pressure ventilation on left ventricular output. Positive-pressure ventilation induces phasic changes in left ventricular stroke volume though similar cyclic changes in venous return, right ventricular output and pulmonary venous blood flow. The magnitude of these changes in left ventricular stroke volume are a function of the size of the tidal breath, the subsequent increase in intrathoracic pressure and the extent that changes in left ventricular output are determined by changes in left ventricular filling pressure. Beat-to-beat changes in left ventricular stroke volume can be easily monitored as beat-to-beat changes in arterial pulse pressure variations, since the only other determinants of pulse pressure, arterial resistance and compliance, cannot change enough to alter pulse pressure during a single breath. To simplify this analysis, Perel et al. examined the systolic pressure variation (SPV) induced by a defined positive-pressure breath in both animals made hypovolemic and in heart failure and humans, demonstrating that the SPV, as specifically the decrease in systolic pressure from an apneic baseline, referred to as ΔDown, identified hemorrhage and was minimized by fluid resuscitation [16, 17]. Tavernier et al. validated these findings [18]. The concept of SPV assumes that all the changes in systolic pressure can be explained by parallel changes in left ventricular stroke volume. Unfortunately, Denault et al. [19] could not demonstrate any relation between left ventricular stroke volume, estimated by transesophageal echocardiographic (TEE) analysis, and SPV, suggesting that factors other than left ventricular stroke volume contribute to SPV. Michard et al. [10, 11] studied the arterial pulse pressure variation (PPV) rather than SPV, reasoning that it would better reflect changes in left ventricular stroke volume because arterial PPV is not influenced by the intrathoracic pressure-induced changes in both systolic and diastolic arterial pressure. They compared SPV with PPV as predictors of the subsequent increase in cardiac output in response to either the addition of PEEP in patients with acute lung injury (ALI) or fluid loading in septic ventilator-dependent patients. They showed that both PPV and SPV of 15% were better than either right atrial pressure or PAOP in predicting preload responsiveness.

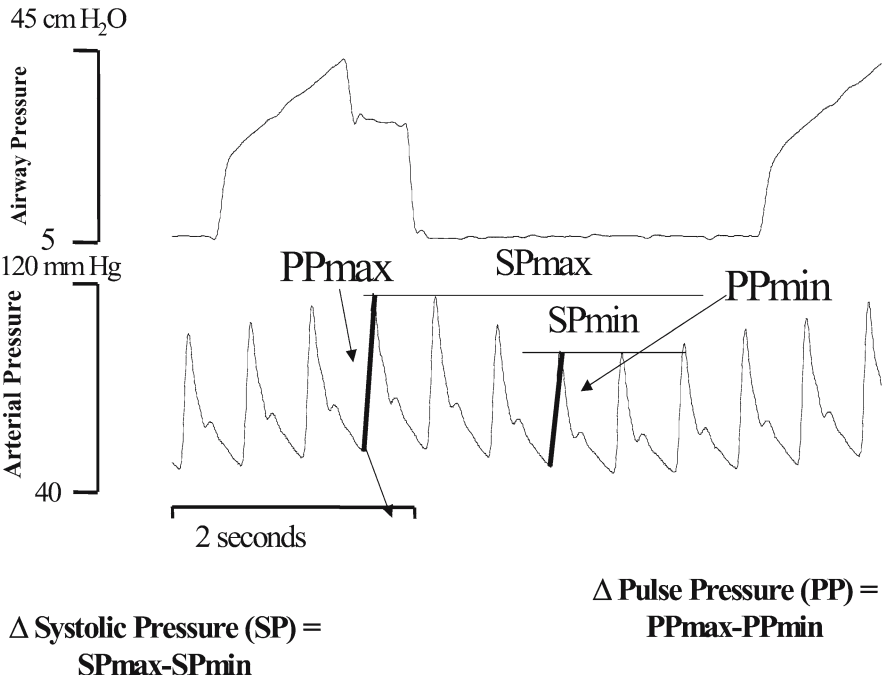

Fig. 1. Strip chart recording of airway pressure and arterial pressure for a subject during positive pressure ventilation, illustrating the technique of calculating both Δ systolic pressure (SP) and Δ pulse pressure (PP).

In patients with acute respiratory distress syndrome (ARDS) requiring artificial ventilation, the degree of PPV during a breath was quantitatively related to the subsequent decrease in cardiac output in response to the addition of increasing amounts of airway pressure [10]. Furthermore, in ventilator-dependent patients with severe sepsis, PPV predicted the amount of increase of the cardiac output in response to intravascular fluid loading [11]. Arterial pulse pressure is the difference between the systolic arterial pressure and diastolic arterial pressure (Fig. 1). For example, if a patient's blood pressure were 120/80 then their pulse pressure would be 120 minus 80, or 40 mmHg. During breathing, the actual pulse pressure will vary slightly. If PPV >15% of the baseline pulse pressure (e.g., 6 mmHg for a mean pulse pressure of 40 mm Hg) for a normal tidal breath (<6 ml/kg), then that patient will increase their cardiac output in response to intravascular volume challenges. Furthermore, this PPV changes inversely as cardiac output changes. Thus, PPV will decrease as cardiac output increases with intravascular fluid loading.

Coming full circle, Feissel et al. [20] demonstrated that measures of left ventricular stroke volume variation (SVV), measured by 2D TEE pulsed Doppler of the aortic outflow tract also predicted preload-responsiveness. SVV can be estimated by the arterial pulse contour method. Arterial pulse contour analysis is not a new technology but one described in the early 1940s. The calculation of left ventricular

stroke volume from the arterial pressure profile is based on the principle that the magnitude of the arterial pulse pressure and pressure decay profile describe a unique stroke volume for a given arterial input impedance. However, how pressure profile is analyzed, the strength given to spectral power analysis, the weight given to resistive versus compliant elements and mean arterial pressure (MAP) varies among published algorithms. Numerous modifications of the original construct are continuously being proposed to address the fundamental weakness of this computational approach [21]. Not surprisingly, the algorithms used to calculate stroke volume by the industry are proprietary, thus making any direct analysis of their ability to track actual stroke volume as arterial circuit conditions very difficult, if not impossible. This is not a minor point of scientific interest, but lies at the center of the Achilles' Heel of the technique. If changes in arterial tone occur, then the primary assumptions about the interaction between stroke volume and pressure also change, and the validity of a specific algorithm may be either retained or degraded. The determinants of arterial input impedance are complex because they reflect a lumped parameter of the entire circulation, whereas actual vascular conductance among different arterial beds may vary significantly and rapidly in disease states [22]. Accordingly, if either global arterial tone or blood flow distribution among vascular beds were to vary, then the relation between the arterial pressure profile and stroke volume may also vary. Since the weight to which specific aspects of the vascular conductivity used in constructing each algorithm is different, knowing that one method of pulse contour analysis is accurate under a given set of conditions does not mean that another method will also be accurate. Furthermore, arterial contour analyses have only been validated under steady-state conditions against indirect measures of cardiac output, such as the thermodilution or dye dilution techniques [23]. Accordingly, the arterial pulse contour technique has not been validated to monitor rapid changes in stroke volume, as may occur over a single breath. Moreover, it is these estimates of stroke volume change over a breath that are used to calculate SVV by the pulse contour technique. Potentially, rapid changes in stroke volume could induce non-steady-state changes in arterial vascular loading. However, the extent to which ventilation may alter the determinants of arterial input impedance used to calculate stroke volume is not known. As previously suggested, if this derived parameter actually reflects true SVV then it should closely parallel changes in PPV, since the two are coupled. Regrettably, although several clinical studies using PiCCO-derived SVV have appeared in the literature over the past three years, none either simultaneously measured PPV or directly measured SVV using echocardiographic techniques [24–26]. The lack of scientific rigor is unfortunate. Hopefully, some clinical trial will actually use a gold standard measure to define the validity of arterial pulse contour-derived SVV, so that its usefulness and limitations in a specific clinical setting can be defined.

Recently, increased interest in esophageal Doppler measures of descending aortic flow as estimates of left ventricular SVV has arisen. Descending aortic flow is not cardiac output but beat-to-beat changes in descending aortic flow should parallel beat-to-bear changes in left ventricular stroke volume. Thus, this measure should provide accurate measures of SVV. Preliminary studies suggest that esophageal Doppler estimates of left ventricular SVV accurately reflect left ventricular

SVV in animal model and humans; however, these data only exist at present in abstract form.

Using any measure of ventilation-induced changes in left ventricular stroke volume, whether SPV, PPV, or SVV to identify preload-responsiveness has two very important limitations. First, for there to be any variation on output the physiological input must be great enough to cause a change in left ventricular filling without co-existent right ventricular failure. Clearly, if the positive-pressure breath is not of large enough magnitude to increase intrathoracic pressure or change intrathoracic vascular capacitance, then no change in left ventricular stroke volume will occur even in preload-responsive patients. Prior studies used tidal volumes greater than 6 ml/kg and most used tidal volumes of 8-12 ml/kg in their studies. Thus, in the setting of pressure-limited ventilation, if the tidal volumes are too small, this measure will become insensitive to preload-responsiveness. Second, spontaneous inspiration increases venous return, increasing right ventricular volumes and decreasing left ventricular diastolic compliance [27]. And this ventricular interdependence is accentuated in the setting of right ventricular failure. Importantly, left ventricular stroke volume decreases during inspiration and right atrial pressure either remains constant or actually increases. Thus, one cannot reliably use left ventricular SVV, SPV, or PPV to identify subjects who are preload responsive during spontaneous ventilation. If right ventricular failure is co-existent however, the combined SVV measures plus loss of right atrial pressure decreases will identify cor pulmonale. Third, in severe heart failure with volume overload, increases in intrathoracic pressure will decrease left ventricular afterload and augment left ventricular ejection [28]. This will give rise to an inspiratory increase in arterial pulse pressure, the so-called reverse pulsus paradoxus [29]. Although occasionally seen, even patients with heart failure need an effective filling pressure. Thus, if they become relatively hypovolemic then they too will develop a PPV. Thus, subjects with severe heart failure may manifest PPV early if hypovolemic and again late if hypervolemic. Thus, in this specific patient population, the blind use of PPV and SVV to define preload-responsiveness is not recommended. Finally, just because a subject displays a SVV or PPV of >15% does not mean that they need fluid resuscitation. It means only that they are preload responsive. Normal healthy subjects requiring mechanical ventilatory support for other reasons will display this degree of flow variation and do not require volume expansion. Thus, the presence of positive-pressure-induced flow variation or its surrogates (SPV, PPV) identifies those subjects whose cardiac output will increase in response to volume expansion, not those subject who would benefit from such therapy. The decision to resuscitate a patient should be made on clinical grounds or based on other independent estimates of organ perfusion, not the presence of flow variation.

Functional Measures of 'Arterial Tone'

The body defends central arterial pressure so as to maintain coronary and cerebral perfusion constant despite a widely varying cardiac output. With marked decreases in cardiac output, as occur with hemorrhagic shock, arterial tone increases, whereas with marked increases in cardiac output, as occur with exercise

and fluid-resuscitated sepsis, arterial tone decreases. From this construct two important concepts evolve. First, systemic hypotension is always pathological, and second, normotension does not imply a stable cardiovascular state. Accordingly, arterial pressure and vasomotor tone can be evaluated in two steps: first determining the actual perfusion pressure, and second determining arterial tone.

Clinically, if MAP decreases below 65 mmHg in a previously health individual, hypoperfusion of some vascular beds occurs, whereas maintaining a MAP greater than 65 mmHg is not associated with increased survival [30]. Hypotension for any reason causes a decrease in brain, heart, gut and kidney blood flow. If sustained, hypotension results in end-organ failure and death. However, even if cardiac output is supranormal, if systemic hypotension co-exists, then blood flow regulation and pressure-dependent flow to all organs may still be impaired. Systemic hypotension is always a medical emergency. Thus, independent of knowing if a patient will increase their cardiac output in response to volume loading, knowing the level of vasomotor tone and its change in response to changes in cardiac output and vasoactive therapy is relevant in deciding on specific therapies and their titration. Thus, a reasonable minimal MAP that one should tolerate in a hemodynamically unstable patient is 65 mm Hg. Importantly, relationship between arterial pressure and regional blood flow is both non-linear and different among vascular beds. Thus, no minimal perfusion pressure can be assumed to guarantee adequate perfusion of all vascular beds, and a change in arterial pressure may induce blood flow redistribution and/or frank ischemia in specific vascular beds [31].

Arterial tone and its changes in response to time and therapy can be readily assessed at the bedside using measures of perfusion pressure relative to blood flow. The resultant ratio is referred to as arterial elastance, because it is the phasic relation between stroke volume and developed pressure rather than the sustained effect of a constant flow on a resistance circuit. Since blood flow is phasic and not constant, elastance is a more accurate measure of arterial tone than is arterial resistance. If MAP and total systemic blood flow are measured then the resultant estimation of arterial tone will quantify global arterial tone. These points are described graphically in Figure 2. Similarly, if only regional blood flow is measured, such as ultrasonic estimates of renal blood flow or cerebral blood flow, then estimates of renal or cerebral vasomotor tone, respectively, can also be estimated.

If one measured left ventricular stroke volume or its surrogate simultaneously with measures of MAP, then their ratio is defined by arterial tone. Any process that increases tone will make MAP increase for the same stroke volume and any process that decreases arterial tone will make MAP decrease for the same left ventricular stroke volume. If, instead of MAP one uses arterial pulse pressure, then one can estimate the SVV to PPV ratio as a direct measure of large vessel arterial tone. Importantly, since both SVV and PPV are unitless numbers, their ratio will be as well. A perfectly coupled arterial flow circuit would have a PPV to SVV ratio close to one. However, the systemic arterial circuit usually varies flow more than pressure, giving the normal central arterial circuit a ventriculo-arterial coupling ratio of about 0.5. Importantly, changes in this ratio of > 20% would reflect real directional similar changes in arterial tone. Recall that arterial tone naturally changes in response to change in flow, to keep perfusion pressure constant. Unfortunately, the coupling ratio for normal subjects is also age-specific, thus defining arterial

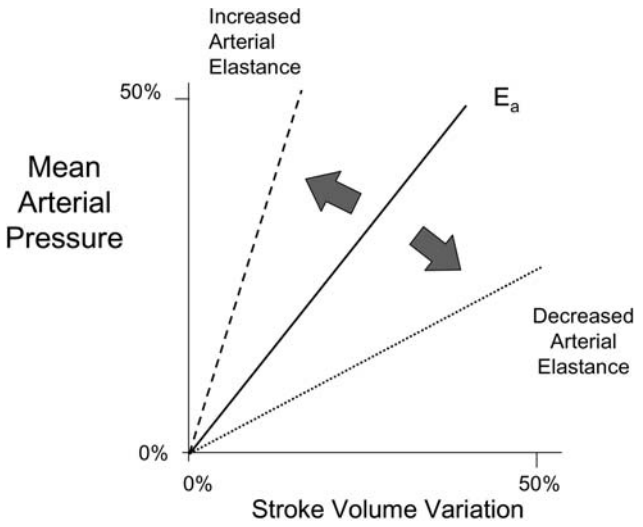

Fig. 2. Effect of changes in arterial vasomotor tone on the relation between arterial pulse pressure and stroke volume.

tone only by the ratio of change in MAP to stroke volume needs to be age-corrected and compared to similar subjects with increased or decreased arterial tone. These studies have not yet been done.

The advantage of comparing the instantaneous relation between PPV and SVV is that they can be acquired simultaneously during positive-pressure ventilation, thus allowing for an instantaneous and continuous on-line assessment of arterial tone and preload-responsiveness. However, even if the determinants of preload-responsiveness are in doubt because of co-existing cor pulmonale or severe left ventricular failure, the relation between arterial pressure to flow is still valid. This is because the cause of the pulse pressure in the first place is the interaction of the ejected left ventricular stroke volume with the arterial impedance circuit. As the blood is rapidly ejected it causes the arterial pressure to rise. The degree to which MAP rises generating the arterial pulse pressure is a function of both left ventricular stroke volume and arterial tone [32]. Increasing left ventricular stroke volume, all else being equal, increases MAP by a proportional amount. Thus, if left ventricular stroke volume were to increase 20% from one beat to the next, MAP would also increase by 20%.

The primary limitation to the bedside application of arterial elastance analysis is not its scientific validity. It is the inherent difficulty in measuring left ventricular stroke volume at the bedside from beat-to-beat. Prior to the advent of esophageal pulsed Doppler techniques and robust arterial pulse contour techniques [21], the routine measure of left ventricular stroke volume on a beat-to-beat basis over prolonged time intervals was not realistic. Although TEE measures of aortic outflow tract flow, using pulsed Doppler techniques is accurate and has been applied in this manner [20], it is limited to specific centers with the expertise and equipment and

also cannot be used continually over prolonged intervals to assess changes in left ventricular stroke volume. Now we have the advantage of assessing these two variables simultaneously and in real time. Even the issues of arterial pulse contour drift from changes in central aortic compliance can be addressed if arterial pressure is used to monitor changes in aortic diameter.

Functional Hemodynamic Monitoring: Treatment-specific Monitoring

Prior studies of the validity of invasive monitoring techniques have been greatly limited by the lack of a defined management protocol based on sound physiological concepts. For example, titrating fluid management to a PAOP value is not logical because PAOP does consistently reflect either left ventricular preload or preload responsiveness. However, PAOP is a very important variable to watch in the acute volume resuscitation of a subject with acute lung injury because iatrogenic elevations in PAOP, independent of left ventricular preload or cardiac output will worsen transvascular fluid flux in the pulmonary circulation, worsening pulmonary edema and gas exchange. Similarly, PAOP is an excellent parameter to monitor when treating severe left ventricular failure patients with afterload reduction therapy, because the end-point of this resuscitation is usually a balance between arterial hypotension and decreases in PAOP. Thus, it is not surprising that only one study to date has documented any improvement in outcome from critical illness using invasive hemodynamic monitoring. The Rivers et al. study titrated cardiovascular management to physiological end-points of arterial pressure and venous blood oxygen saturation [33]. Other studies merely examined the effect of having one form of invasive monitoring present or not on the outcome [3, 5]. Accordingly, we propose using a physiological approach to the hemodynamic management based on the above logic. If one assumes that a PPV or SVV > 15 on positive-pressure ventilation (tidal volume 6–10 ml/kg) reflects preload-responsiveness and a change in arterial elastance of >20% reflects a real directional change, while any MAP above 65 mmHg is not hypotension, then one can develop a very simple but robust treatment algorithm. We developed such a treatment algorithm, called Functional Hemodynamic Monitoring based on the principals of Ventriculo-arterial coupling.

Functional Hemodynamic Monitoring Treatment Algorithm

Assuming one knows if a given subject is preload-responsive and whether their arterial tone is increased, decreased or normal, then several specific treatment algorithms can be developed that follow logically from this knowledge. However, two specific things need to be defined first. First, clearly one needs to know if tissue hypoperfusion exists. And, second, one needs to define an acceptable minimal level of arterial pressure associated with adequate organ perfusion pressure. The second question was addressed above. An adequate MAP in an otherwise

healthy individual can be assumed to be any MAP of >65 mmHg. Clearly, in subjects with pre-existent systemic hypertension, pulmonary hypertension, intracranial hypertension, tense ascities and/or atherosclerotic peripheral vascular disease, the minimal MAP level may be higher than this minimal level defined for otherwise healthy subjects. Identifying tissue hypoperfusion is a much more difficult task. Clearly, in subjects with tachycardia (heart rate > 110 beats/min), systemic hypotension (MAP <65 mmHg), oliguria, hyperlactatemia, altered mental status, and diaphoresis, the diagnosis of circulatory shock comes easily. However, it is much more difficult to identify when to stop aggressive resuscitation or when occult tissue hypoperfusion exists in a compensated shock patient. The study of Rivers et al. [33] demonstrated nicely that some patients who were otherwise stable with normal blood pressures and mentation had decreased superior venal caval oxygen saturation and/or lactic acidosis, consistent with occult tissue hypoperfusion and, more importantly, decreased their in-hospital mortality when given further resuscitation despite no measurable change in these output variables. Thus, one needs to define tissue hypoperfusion before attempting to apply any resuscitation algorithm, because otherwise normal subjects are preload-responsive but will not show improved outcome with resuscitation.

The Functional Hemodynamic Monitoring treatment algorithm is divided into two sequential treatment arms and one contingent treatment arm based on MAP, PPV, and SVV data. The algorithm is put into operation only if the patient develops signs and symptoms of cardiovascular compromise because preload-responsiveness is also a characteristic of normal stable subjects.

Criteria for the diagnosis of hemodynamic instability are readily available and may include:

a. MAP <65 mm Hg, a decrease in MAP of > 20 mm Hg in a previously hypertensive patient and one of the two (b and c below)
b. Evidence of end-organ hypoperfusion: a decrease in urine output to <20 ml/hr, confusion, new onset tachycardia, lactic acidosis, ileus
c. Symptoms of increased sympathetic tone: agitation, confusion, restlessness
d. Evidence of regional tissue hypoperfusion from increased tissue PCO_2, as measured by gastric tonometry, sublingual capnography or other metabolic parameters of oxidative phosphorylation (tissue NAD/NADH, blood lactate/pyruvate, etc.)

If hemodynamic instability were present then one would proceed with the treatment algorithm. Central to the measures of PPV and SVV are changes in venous return. Transient changes in venous return can be assessed by examining the changes in both PPV and SVV during positive-pressure ventilation, if the patient is not making spontaneous respiratory efforts and if the heart rate is regular. Presently, this requires that the subject be on controlled mechanical ventilation receiving a tidal volume of 6–12 ml/kg over a frequency of 10–20 breaths/minute. Alternatively, one may induce a non-invasive physiological preload challenge by leg raising in a supine subject that causes between 300–500 ml of increased venous return. With this type of challenge one measures MAP or stroke volume over approximately 30 seconds prior to leg raising and then compares these measures to the same mean measures taken two minutes after elevating the legs over the

head. Clearly, one could also perform a traditional fluid challenge and compare the pulse pressure and stroke volume measures pre and post-volume expansion, however, the goal of the functional hemodynamic monitoring protocol is to avoid unnecessary and ineffective treatments in order to determine effective ones.

The approach asks three sequential questions before giving any treatment. The first question is: "Is the patient hemodynamically unstable?" Meaning: is tissue hypoperfusion present? If the answer to this first question is no, then no specific treatment needs to be given. If the answer is yes, however, then one proceeds to the next two questions.

The second question is: "Is the patient preload-responsive?" We define preload-responsiveness as a PPV or SVV of > 13%. Clearly, this threshold will be highly dependent on the means by which venous return is varied. Small tidal volume ventilation may need a threshold of 10% and large tidal volume or leg raising maneuvers may require a threshold of 15%. Furthermore, PPV and SVV are not equally affected by changes in arterial tone. If tone were to decrease then for the same degree of preload-responsiveness, SVV would be greater, and with increasing tone, PPV would be greater. Thus, defining the specific threshold value for either PPV or SVV will need further investigation. Preliminary data suggest, however, that threshold values of PPV and SVV are quite similar and it is only the pressure to flow ratio that changes markedly with changes in arterial tone. The answer to this question is either yes or no.

The third question is: "Is arterial tone decreased?" If one is measuring the ratio of PPV to SVV, then a balanced ventriculo-arterial systemic circuit will have a coupling ratio of 0.8 to 1.2, whereas the normal coupling ratio of the systemic arterial circuit using changes in MAP to SVV would have a coupling ratio of 0.4–0.6 [21]. Coupling values below these thresholds would define decreased arterial tone. Thus, the answer to this final question will again be yes or no.

The treatment algorithm, as summarized in Figure 3, creates two major groupings: normal and unstable patients. Treatment is given to unstable patients only. The unstable patients are then separated into four uneven groups based on their responses to the two questions.

Fluid resuscitation: Subjects who are preload-responsive but do not display decreased vasomotor tone require only volume expansion. This scenario exists with classic hypovolemic shock, as may be seen with hemorrhage or severe dehydration. The amount of volume expansion is not defined but can be inferred from the amount of PPV or SVV present. Clearly, the greater the PPV or SVV displayed the greater the volume deficient and the greater the increase in cardiac output in response to volume expansion. One may stratify the volume of each volume expansion bolus or the time to reassess functional status depending on the level of either PPV or SVV.

Vasopressor and fluid resuscitation. Subjects who are both preload-responsive and have decreased vasomotor tone will not increase their MAP with volume expansion alone. Thus, tissue hypoperfusion will persist with isolated volume expansion. This scenario exists with classic septic shock or other forms of vasomotor shock, such as spinal cord injury, adrenal cortical insufficiency and high spinal

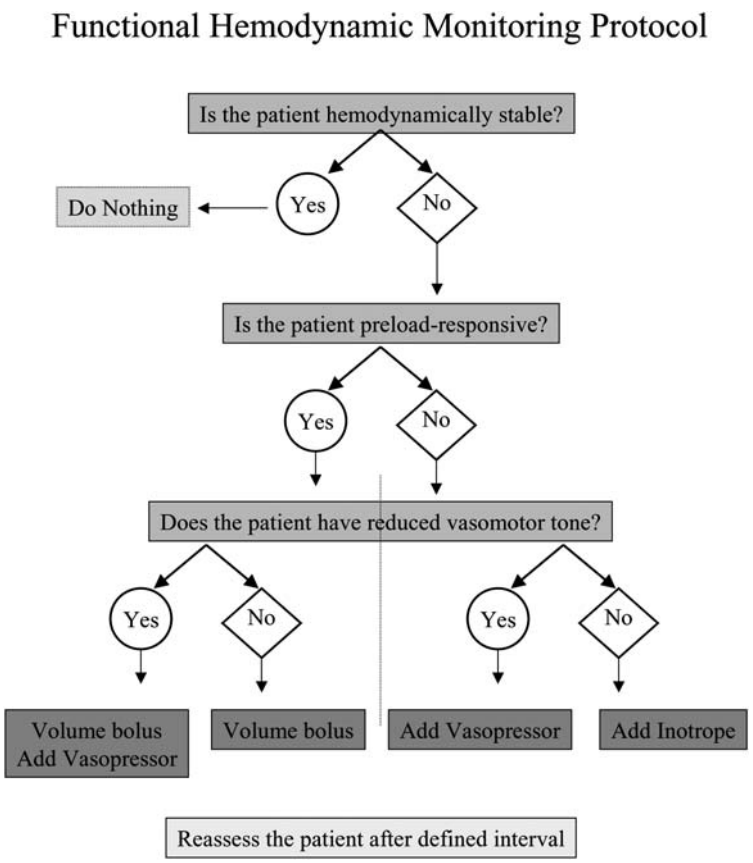

Fig. 3. Schematic flow chart for the decision tree in the cardiovascular management of patients who are hemodynamically unstable using Functional Hemodynamic Monitoring protocols. This protocol application is part of a patented treatment algorithm co-owned by the University of Pittsburgh and Michael R. Pinsky, MD.

anesthesia. These patients need combined volume expansion and vasopressor therapy to restore tissue perfusion. If MAP is ≥65 mmHg and there is no co-existent evidence of tissue hypoperfusion, then vasopressor therapy can be withheld even if vasomotor tone is decreased.

Vasopressor resuscitation. Subjects who are not preload-responsive but have reduced vasomotor tone need only vasopressor therapy to sustain organ perfusion pressure. This scenario exists with classic neurogenic shock following volume expansion, but can be a sustaining quality of volume expansion in septic shock.

Inotropic resuscitation. If the subject is neither preload-responsive nor has reduced vasomotor tone, then the problem is the heart. This functional analysis does

not allow one to define the specific etiology of cardiogenic shock. Massive pulmonary embolism, tamponade, mitral regurgitation, and massive myocardial ischemia/infarction all represent disease processes that are not optimally treated by increased inotropic therapy alone. Although one usually initially starts inotropic therapy, these subjects require further diagnostic and potential therapeutic monitoring. Echocardiographic and pulmonary arterial catheterization for specific monitoring and treatment approaches may be indicated in this group. Importantly, by limiting such limited and/or risky procedures to this group alone, limited and important resources can be focused in a more cost-effective manner suing more traditionally defined management principals.

Acknowledgement. The work was supported in part by NIH grants HL67181–02A1 and HL07820–06

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Cost Effectiveness of Monitoring Techniques

J. Wendon

Introduction

In comparison with pharmacological interventions or operative interventions for various disease processes, little has been published in the field of cost effectiveness of the expanding numbers of monitoring techniques that may be utilized to measure cardiac output, flow, and fluid responsiveness in the intensive care arena. To truly determine the efficacy or misuse of hemodynamic monitoring tools, we require randomized clinical trials with controlled evidence of measurable improvement in relevant clinical outcomes. The relative dearth of such trials, (appreciating that they would require large numbers of patients to be enrolled), has resulted in the fact that most hemodynamic monitoring has been assessed on the effects that interventions, such as vaso-active agents or volume loading, have on physiological measures. It is sadly however, something of a leap of faith to suggest that a given intervention, which results in a perceived improvement in a physiological variable as measured by a given monitor will translate into decreased morbidity and improved outcome.

There are a variety of tools available to us in order to undertake monitoring, these may be simple or complex but regardless there is a requirement that the clinician at the bedside is able to interpret and then initiate appropriate subsequent management plans. This requires appropriate expertise and experience, and is a cost and function that is frequently not examined when a given piece of monitoring is rolled out to general practice. All such equipment has inherent costs. These usually can be considered as: a) the hardware or box that will undertake the monitoring, be it a transducer or a "black box" undertaking a variety of analyses; b) the costs that apply to consumables and maintenance of equipment; and c) the costs required in maintenance and training of individuals. Ideally any piece of monitoring should equate seamlessly to focused, patient-centered care with a resultant decreased morbidity, decreased hospital stay, and improved quality of life.

In all monitoring it is essential to realize that the staff who are going to come into contact with the monitoring and the patient require appropriate training and regular updates. This requires the institution to have a regular program of educational benefit to its doctors, nurses, and technical staff in order to ensure that individuals who work with such equipment are both trained in the trouble shooting, utilization, and interpretation of the physiological data that the monitoring

equipment produces. This is a cost, which is rarely considered in assessment in new physiological monitoring tools, but is probably one of the most pivotal determinants of improving outcome.

Hemodynamic monitoring may be considered non-invasive or invasive. The vast majority of monitoring within the intensive care unit (ICU) environment is of the invasive modality, though non-invasive techniques are growing in number and potential applicability. Examples of the latter are echocardiography, electrical bio-impedance giving a measure of cardiac output and thoracic fluid content, and partial CO_2 re-breathing where frequent cardiac output measurements can be updated every 3 minutes and in addition provides information on respiratory variables, such as end tidal CO_2, airway pressures, respiratory volumes, dynamic compliance, and CO_2 elimination. More commonly utilized methods of hemodynamic monitoring fall within the invasive category. These include, at their most simplistic, peripheral or central arterial puncture and cannulation allowing measurement of blood pressure, and central venous catheterization allowing measurement of central venous saturations, central venous and pulmonary artery pressure. Techniques have been developed to measure cardiac output with thermodilution techniques and arterial pulse contour analysis. Cardiac output can also be measured at the bedside using esophageal Doppler. Many monitoring modalities now provide continuous or semi-continuous measures of cardiac output. In addition several systems provide dynamic, in addition to static, variables, which may give an indication as to the fluid responsiveness of the patient. The evolution of measures that allow an assessment of fluid responsiveness may be of great potential benefit to patients, avoiding hypovolemia and preventing excessive fluid loading.

Arterial Cannulation

Arterial lines are frequently inserted in order to monitor blood pressure – systolic, diastolic, and mean. The arterial line and its transduced pressure can be "eyeballed" with respect to the swing on the arterial line with the respiratory cycle (a simplified systolic pulse pressure variation) and experienced clinicians may gain data from simple observation of changes in waveform in individual patients following interventions. The site of arterial access should be determined by the patient's clinical condition state. Some data suggest that in hemodynamically compromised patients who require pressor agents, femoral artery cannulation should be the preferred option to that of peripheral arterial cannulation; similar data has been obtained for patients in the early stages of bypass [1, 2]. Arterial lines can thus be viewed as being of low cost and moderately effective, though have not been shown to decrease hospital length of stay or improve outcome.

Central Venous Cannulation and Saturation Monitoring

Central venous cannulation is frequently also undertaken in patients who are critically unwell. The site of venous access is again determined by the patient's clinical status, hemodynamic variables, and experience of the practitioner. The

commonest sites of access would be jugular vein, sub-clavian vein, or femoral vein. There are data in the literature suggesting that femoral venous cannulation may be associated with increased risk of infectious complications whilst the data in terms of complications are similar for both jugular and sub-clavian routes. The choice of a standard line or an antimicrobial line will be determined by the infection rate within the environment in which the patient is being cared for [3].

Central venous lines can be utilized to administer drugs to the circulation in a safe and timely fashion, though fluids can be administered as efficiently through wide bore peripheral access as through central access. There is a considerable body of evidence demonstrating that central venous pressure (CVP) measurements do not correlate well with the volume status of the patient nor the likely response to a volume load [4–7]. The time course of CVP following a volume load may however be more informative in this regard. In general however, central venous lines, although relatively cheap and efficacious in terms of access to the central circulation should not be considered effective in terms of assessment of the volume status of the patient nor to the response to volume loading. The lack of correlation between pressure and volume from these lines is similar to those seen for pulmonary artery pressure and pulmonary artery occlusion pressure (PAOP) in that they are significantly affected by ventricular compliance and intra-abdominal pressure and particularly intra-thoracic pressures [4–7].

Increasingly, in recent times there has been enthusiasm for determining venous saturation on blood aspirated from the central venous cannulae. This enthusiasm has been generated in considerable part from the data of Rivers et al. [8], who examined the role of goal directed therapy or standard of care in the emergency room before admission to the ICU. Two hundred and sixty three patients with sepsis were enrolled in the study and the in-hospital mortality was 30.5% in the group assigned early goal directed therapy as compared to 46.5% in the group that was assigned to standard therapy. The early goal directed therapy group was shown to have higher mean central venous saturations, lower lactate concentrations, lower base deficit, and a higher pH. These data would suggest that central venous saturation monitoring as part of goal directed therapy in a cohort of patients presenting to the emergency room with severe sepsis and septic shock showed significant benefit with respect to outcome.

Although this study did show benefit for central venous monitoring and as a component of goal directed therapy in this cohort of patients, it is of importance to note that in patients with sepsis within the ICU, the use of mixed venous oxygen saturation (SvO_2) as part of pulmonary artery monitoring has not been demonstrated to be of such significant benefit. This may relate to the presence of a pulmonary artery catheter (PAC) vs the central venous catheter and the associated risks and benefits, or may relate to the patients within the ICU environment being in the later stages of sepsis. By this time, a hyperdynamic circulation has been realized and in this setting central venous saturation may suggest adequate flow and volume status due to the finding of `normal' SvO_2. The apparently normal SvO_2 may however, be achieved by virtue of significant arterio-venous shunting and there may still exist both tissue dysoxia and fluid responsiveness. The cost effectiveness of such monitoring in the ICU will require further investigation in terms of outcome and morbidity.

Monitoring of central venous saturation can be achieved either utilizing a fiber optic catheter or by undertaking multiple venous sampling. It is likely that the former would be proven to be more cost effective though no recent studies have been undertaken in this regard. The latter mode of monitoring would require multiple samplings from the central line incorporating significant use of nursing or technical time. In addition, the costs of multiple laboratory assays would be required and the risk in terms of multiple disruption of the central line in terms of infection would have to be considered.

Pulmonary Artery Catheterization

The PAC has for many years been considered as the `gold standard' in terms of cardiovascular monitoring. It was first introduced into clinical practice by Swann and colleagues in 1970 and provides a measure of pulmonary artery pressure, PAOP and cardiac index by virtue of thermodilution. Although in recent years much literature has been published in regard to the benefit or otherwise of the PAC, it remains the standard in terms of cardiac output estimation that new technologies are most often compared with. Thermodilution cardiac output undertaken through the PAC was validated by comparison with both the Fick and dye-dilution measures of measuring cardiac output. These, like electromagnetic measurements from the aortic route, require considerable time and expertise. Thus it is the thermodilution technique that is used as the usual comparator. There are limitations to this technology; in particular, there are inaccuracies in the presence of cardiac shunts, tricuspid regurgitation, marked blood stream temperature variations, and also beat-to-beat variations throughout the respiratory cycle. The PAC has been modified in recent years, particularly by virtue of incorporation of a thermal coil in the right ventricular portion providing a method to semi-continuously monitor cardiac output. Pulmonary artery catheterization provides, therefore, a semi-continuous method of accurately measuring cardiac output but it requires by definition central venous cannulation and there is an increased risk of infection with such lines if they remain *in situ* for prolonged periods of time.

The PAC, however, provides other measurements than cardiac output; specifically pulmonary artery pressure and the PAOP. Measurement of pulmonary artery pressures may be of considerable import to the clinician managing an individual with pulmonary hypertension and associated right ventricular dysfunction where therapeutic modalities may be aimed at decreasing pulmonary artery pressure and improving right ventricular function. This has been seen in patient prognosis with regard to the effect of an intervention such as sidenafil or nebulized epoprostenol in the setting of right heart failure and pulmonary hypertension [9–13]. Pulmonary artery pressure and right ventricular function may however equally be measured using echocardiography. This modality has the advantage of being non-invasive and without risk of potentiating arrhythmias or central line related complications. The level of experience required in the operator is however reasonable and only intermittent measurements are obtained.

It has, however, now been recognized in several studies that the pulmonary artery pressure, and more particularly the PAOP, are not good reflectors of the volume status of the patient, their degree of fluid resuscitation, nor their likely response to fluid loading [4–7]. This situation may be further exacerbated in the setting of intra-abdominal hypertension [14]. In order to address this concern the PAC has been further developed to the volumetric PAC. This catheter has a rapid response thermo slur and intra-cardiac electrocardiogram (EKG) electrode, which allows calculation of the right ventricular ejection fraction (RVEF) and when combined with stroke volume the right ventricular end diastolic volume (RVEDV). These have been well validated and it is suggested that RVEDV index (RVEDVI) is a better indicator of pre-load in the critically ill patient than the PAOP [12, 13]. Furthermore, many PACs have continuous fiberoptic estimation of SvO_2 offering another useful modality in patients in whom physiological manipulations may be undertaken to improve oxygen carrying capacity and cardiac output with a view to normalizing SvO_2 and tissue perfusion [9, 15]. It has been suggested that SvO_2 can indicate changes in cardiac output with normal values for SvO_2 ranging between 70–75%. A correlation can be demonstrated between cardiac output and SvO_2 but this correlation is not linear but curvilinear and only holds if oxygen consumption and arterial oxygen content do not change. In addition SvO_2 only reflects overall oxygen reserve and does not account for impaired oxygen supply to individual organs nor arterial venous shunting. As to whether such interventions are cost effective in the intensive care population as compared to a population in the emergency department or in the pre-operative and operative periods of care has yet to be established.

It would seem, therefore, that the PAC has well defined clinical uses in providing data on response to therapy and stratifying risk. Is this costeffective? There are no definitive studies, however, it may be proposed that such risk stratification may be beneficial in terms of allocation of resources. In addition there is a considerable body of evidence to suggest that optimization of hemodynamic and oxygen transport variables in pre and perioperative high risk patients is beneficial in regard to outcome. Work by Kern and Shoemaker [16] demonstrated that achieving pre determined hemodynamic and oxygen transport goals resulted in improved outcome. These goals were achieved with fluids and vasoactive drugs from data obtained from the PAC. This work has now been replicated by several other groups in a variety of surgical settings, albeit utilizing in some series a PAC and in others an esophageal Doppler to drive fluid and vasoactive drug therapies. In general hemodynamic management strategies have been shown to be successful in improving outcome in planned major surgery, but this effect is not translated to the ICU patient. Boyd et al., utilizing a PAC, demonstrated a significant decrease in mortality (75%, 5.7 vs 22%) and a decreased rate of complications [17]. Similar work from Wilson et al. [18] randomizing patients to PAC, fluid, and vasoactive therapies, versus standard of care also demonstrated improved outcome in the optimized groups (3 vs 17%). A compounding feature of this study was, however, the fact that only the active limb patients were routinely admitted to a critical care area post operatively and this may also, therefore, have impacted on outcome. By contrast to these studies suggesting significant benefit in terms of pre-optimization is the study of Sandham et al. [19]. High-risk surgical patients were randomized to receive

either a PAC and goal directed therapy or standard of care management. All patients were deemed high risk and were scheduled for urgent or elective surgery; 1,994 patients underwent randomization. Hospital mortality was similar at 7.7% for the standard of care group and 7.8% in the PAC group. There was a higher incidence of pulmonary embolism in the catheter group however (p=0.004). Survival rates at 6 months were 88.1 and 87.4% and at 12 months 83.9 and 83% for PAC versus standard of care. The median hospital stay was 10 days in each group. Thus there was no observed benefit for the cohort randomized to therapy directed by PAC over standard care in this elderly high-risk surgical population.

The concept of extrapolating goal directed therapy to the ICU environment was therefore adopted. Unlike the perioperative scenario the data in this field are much less clear as to benefit and cost effectiveness. A study of surgical patients admitted to the ICU following the development of organ failure [20], and the work by Hayes et al. [21] utilizing goal directed therapy in general ICU patients with multiple organ failure failed to show any benefit in the treatment limb. The meta analysis of Heyland et al. [22] also failed to demonstrate improved outcome in patients in whom therapeutic strategy was the targeting of super-physiological end points. A more recent meta analysis by Boyd and Bennett demonstrated that outcome was not improved when therapies attempted to improve tissue perfusion in patients in whom multiple organ failure was already established, compared to when PAC guided management was undertaken in patients prior to an insult, (the majority of the studies here being major surgery) where a significant improvement in outcome could be realized [23].

The importance of not just the monitoring modality but which therapies are driven by it is perhaps exemplified in the paper of Sandison et al. [24]. Outcome for emergency and urgent infra-renal abdominal aortic aneurysm surgery was compared in two hospitals, one of whom used PAC directed therapy. The surgery was undertaken by the same surgical team in both hospitals. Mortality was higher in the "PAC" hospital (28 vs 9%) despite there being no difference in pre-operative morbidity or risk factors between the patient groups. Similarly, there was no difference in operating time, blood loss, or base excess at the end of surgery. The hospital with the higher mortality placed PACs in 96% of patients vs 18% in the hospital with the lower mortality. Patients who received a PAC received more crystalloid, more colloid, and more inotropes and had a higher incidence of acute renal failure despite passing similar volumes of urine. ICU length of stay in the patients who underwent pulmonary artery catheterization was higher at 3 vs 2 days as was overall hospital length of stay (median 17.5 vs 12 days).

The controversy as to whether to use a PAC to drive therapeutic modalities in a variety of clinical settings has been longstanding but culminated with the publication by Connors et al. [25] in 1996 where a higher mortality rate was attributed to patients in whom a PAC had been inserted, with higher resource use. This study was, however, retrospective and not randomized. A more recent Medline review by Ivanof et al. [26] by contrast suggested a decreased morbidity when a PAC-guided therapeutic strategy was utilized. This ongoing debate has resulted in further studies being undertaken to examine the potential benefit or otherwise of pulmonary artery catheterization in the critical care setting.

It terms of utilization of invasive monitoring and support, data have recently been published [27] examining gender related differences in intensive care. In this study, nearly 26,000 patients were examined, hospitality mortality rate was slightly higher in women than men but severity of illness adjusted mortality rates were not different. Men received overall increased level of care and had a higher probability of receiving invasive procedures such as ventilation, vasoactive medications, fluids, central venous catheter, peripheral arterial catheter, PAC, renal replacement therapy, and intra-cranial pressure monitoring. Despite a higher severity of illness in women, men received increased levels of intervention with more invasive procedures but this did not translate into improved outcomes. Similarly, work from the Support investigators [28] examining resource utilization and survival of patients with congestive heart failure requiring hospitalization found a 42.9% increased cost in patients hospitalized under a cardiologist than those hospitalized under a generalist even after adjustment for socio-demographic characteristics and severity of illness. Patients of cardiologists were more likely to have undergone right heart catheterization or cardiac catheterization and had a higher risk of being transferred to an ICU. It is of note that adjusted survival did not significantly differ between the 2 groups at 30 days, despite increased resource utilization and cost factors in the cardiologist group.

Yu et al. [29] recently published on the variation in resource and therapeutic modality use among academic centers in managing patients with severe sepsis. There was considerable variation across centers in the use of PACs (overall 19.4%) and albumin infusion (14.4%); even when adjustments had been made for age, sex, co-morbidity score and organ dysfunction; the odds for using the therapeutic modality still varied significantly. No relationship was seen between therapeutic modality utilization and outcome [29]. The same investigators examined the relationship of PAC to mortality and resource utilization in a cohort of greater than 100 patients with severe sepsis. PAC placement was not associated with any change in mortality rate or in any differences in resource utilization. Similarly no significant differences were found for total hospital charges comparing the PAC group with the non-PAC group [30]. Another recent publication similarly addressed the early use of PAC and outcome in patients with shock and acute respiratory distress syndrome (ARDS) [31]. This multicenter randomized study of 676 patients, who fulfilled criteria for shock, ARDS or both; was conducted in 36 ICUs in France. Patients were randomized to receive either a PAC or not and the subsequent treatment was left to the discretion of the individual clinician. The two groups were similar at baseline and no significant differences in mortality were observed in either group at day 14 (49.9 vs 51.3%), day 28 (59.4 vs 61%), or at day 90 (70.7 vs 72%). There was no difference in the mean number of days free of organ system failure, renal support or vaso-active agents when these parameters were compared at day 14. Nor was there any difference in number of days within the ICU or use of mechanical ventilation at day 28. Thus in both of the above studies, although pulmonary artery catheterization appeared safe, it did not impact on outcome or morbidity. It would appear equally, however, not to relate to an increased cost in the paper of Yu et al.

Thus, PAC-directed therapy may be considered cost effective in patients prior to major surgery but its role in a patient with established organ failure has not been demonstrated in terms of decreased morbidity or improved outcome.

LiDCO

Lithium indicated dilution cardiac output (LiDCO) measurement has been developed using miniaturized ion selective electrodes. Utilizing this method, cardiac output can be measured by indicator dilution of lithium from either a central or peripheral injection with pick up of indicator from a peripheral arterial line. The LiDCO method agrees well with standard thermodilution and electro-magnetic flow techniques [32–24]. The indicator dose is very low and should have no physiological consequences. Accurate sodium and hemoglobin values are needed to correctly calculate the cardiac output and the technology cannot be utilized in patients on lithium therapy and those who have just received bolus of neuromuscular blocking drugs. The intermittent technique of measuring cardiac output can be incorporated with pulse contour analysis and in the case of LiDCO may be undertaken with a peripheral arterial cannula. Following lithium calibration, beat-to-beat information relating to cardiac output, stroke volume and systolic blood pressure variation can be obtained. As such, it has the potential to provide static and dynamic variables that will indicate presence or absence of fluid responsiveness [35]. This system requires little in the way of new monitoring to be inserted into the patient and the costs are derived from the monitoring system, lithium electrodes, and dose of lithium for calibration purposes. As yet there are few data on outcome or decreased morbidity or mortality but it is likely to have a potential to decrease morbidity and hospital stay when utilized in a similar manner to that of the esophageal Doppler or, in some circumstances, PAC in determining optimal fluid or vasoactive therapies particularly in patients prior to and during major surgical intervention.

PiCCO

Pulse contour analysis is also utilized with the PiCCO monitoring technique. The calibration indicator in this system is that of either a bolus of ice cold or room temperature saline into a central vein, the thermistor in a central arterial catheter (normally femoral or axillary) being utilized to detect temperature change and hence flow. Excellent correlation is found in comparison with standard thermodilution techniques [36, 37]. In addition to providing data on cardiac output and stroke volume, preload variables are provided. These variables, intra-thoracic blood volume and end-diastolic blood volume correlate significantly with changes in cardiac output and stroke volume as compared to traditional markers of preload such as CVP or PAOP [4–7]. Global end diastolic volume, as provided by this mode of monitoring, has been shown to increase with fluid loading but not with dobutamine therapy [5]. In addition to these static variables, the PiCCO system provides dynamic data in the form of stroke volume variation (SVV) and pulse

pressure variation (PPV) allowing prediction of volume responsiveness. Similar to systolic pressure variation (SPV), PPV and SVV have been shown to predict fluid responsiveness [38–43]. Such dynamic data, (SVV, PPV, or SPV) are only applicable in patients who are ventilated, not breathing spontaneously, and in sinus rhythm. Increasingly, monitoring techniques recognize that to assess merely the effects of a fluid challenge is perhaps to risk, in some patient cohorts, infusing excessive amounts of fluid and increasing morbidity [24]. The development and utilization of dynamic variables of cardiovascular status are thus to be encouraged and it is hoped that future studies will demonstrate that fluid therapy and vasoactive therapies that are guided by such modalities will result in improved outcome.

From mean transit time, the exponential down slope time of the transpulmonary thermodilution measurement, and cardiac output, the intra-thoracic thermal volume and pulmonary thermal volume are calculated; made up of the intra-thoracic blood volume, pulmonary blood volume, and the extra-vascular lung water index (EVLWI). The EVLWI is the difference between the intrathoracic thermal and the intrathoracic blood volume and is obtained along with preload volume values with each fluid calibration. EVLWI undertaken using a single cold indicator technique has been recently validated against double indicator technique and a reference gravimetric method [44, 45]. A monitor with the technique to provide a measure of EVLW and hence pulmonary vascular permeability in association with volume status of the patient has the potential to impact significantly on the management of patients with hypotension, hypoxemia, and especially those with acute lung injury (ALI) and ARDS, in determining optimum fluid management and vasopressor therapy. Sakka et al. have demonstrated increased EVLWI in patients who do not survive [46]. The work of Mitchell examined a EVLWI based treatment algorithm in patients admitted to the ICU who required a PAC [47]. Pulmonary artery catheterization was undertaken in all patients; 52 had an EVLWI management protocol with EVLWI measured at the bedside with the indicator-dilution technique. The standard of care patients, 49, had their fluid therapy guided by PAOP measurements. The EVLWI patients had significantly lower cumulative fluid balance and this was associated with a decrease in ventilated days and decreased ICU stay. Although further studies are required to confirm this effect, it is likely that utilization of EVLWI in the management of patients with hypoxia and lung injury in dictating fluid therapies will be cost effective.

In terms of cost, a specific femoral artery cannula is needed to utilize this monitoring technique, whilst central venous catheterization would normally have been undertaken routinely in such patients. Some clinicians have concerns in regard to central arterial catheterization (axillary lung brachial or femoral), although there are data to suggest that central arterial cannulation is preferable to peripheral arterial cannulation in patients receiving pressor agents [1, 2]. There are no data on increased morbidity in relation to central arterial cannulation utilizing this technology.

Esophageal Doppler

Esophageal Doppler is a technique that has been examined in some detail in patients in whom optimization strategies have been undertaken prior to major surgery in addition to those in the critical care environment. Utilizing this technique, an ultrasound transducer on an esophageal probe interrogates the ascending aortic blood flow to determine the flow velocity. Stroke volume is then derived from the average flow velocity, ejection time, and cross sectional area of the aorta. Utilizing this technique, cardiac output and stroke volume measurement is provided continuously. The blood flow velocity is measured in the descending aorta and therefore represents a fixed fraction of the total cardiac output usually around 70%. Optimal location of the probe is identified by visual and audible signals. Excellent correlation has been demonstrated by cardiac output measured using this technique and thermodilution and Fick methods [48, 49].

In terms of pre-optimization, this technique has been shown to be highly valuable, although is not universally adopted [50]. Sinclair and colleagues [51] randomized patients proceeding to surgery for hip fracture to conventional fluid management or fluid management guided by esophageal Doppler. Fluid therapy in the Doppler group was designed to maintain maximal stroke volume. Post-operative recovery time was faster in the protocol group with a 39% decrease in hospital stay. Venn and colleagues [52] have also investigated fluid challenge versus conventional care in patients undergoing hip fracture and femoral fracture repair. Ninty patients were randomized to standard care, fluid therapy dictated by central venous catheter, or esophageal Doppler probe. There was less hypotension in the Doppler and central venous catheter group and these patients had shorter post-operative recovery times compared to the conventional therapy group. The data therefore, in the pre and peri-operative group of patients, appear to support the use of pre-optimization of cardiac output and stroke volume [53].

Esophageal Doppler technology has been limited to intubated patients and generally utilized in the operating room setting. The development of smaller trans-nasal tubes allows use in non-ventilated patients. A significant advantage of the esophageal Doppler probe is the speed at which physiological data can be obtained in the clinical setting. In addition to cardiac output, data can be obtained on pre-load and contractility and these factors prove useful in terms of ventricular performance having a better relationship to left ventricular end diastolic volume (LVEDV) than traditional PAOP, and hence can be used to predict fluid responsiveness. The cost of the Doppler probe is comparable with other techniques. The technique is however dependent on appropriate pattern recognition of the Doppler signal and re-positioning of the probe should the signal deteriorate. Small changes in position can have a significant impact on the data generated, thus operator training is paramount.

The role of this monitoring technique in improving outcome in patients with established organ dysfunction has not been investigated; however the stroke volume data generated in patients post cardiac surgery on admission to the ICU has been shown to be predictive of complications [54]. Whether a therapeutic strategy

initiated on admission can limit these complications and improve outcome is less clear.

Echocardiography

Cardiac echocardiography has now been included as a routine monitoring modality within the ICU. It allows assessment of global and regional ventricular function, either using transthoracic echocardiography or transesophageal techniques. Most data suggest that transesophageal echocardiography (TEE) provides more accurate information in regards to cardiac parameters though the use of contrast when using transcutaneous techniques improves modality yield [55].

Echocardiography allows assessment of structural abnormalities, aortic dissection, endocarditis, pulmonary embolism, and ventricular wall motion abnormalities, data which are not available from other monitoring modalities. In addition, hypovolemia, left ventricular dysfunction, global systolic function, and ventricular size can also be assessed. It has a unique advantage over other monitoring techniques in that it has the potential to provide diagnostic data in addition to physiological data within the ICU environment [56].

Echocardiography is a highly accurate method of assessing cardiac performance and fluid responsiveness, though requires an appropriate echocardiography machine to be located within the ICU environment and to have staff available 24 hours a day who are proficient in its use. It has the disadvantage that it is not a continuous modality of monitoring and is thus best used in conjunction with other monitoring modalities. It has the advantage, in patients who are not ventilated or undergoing other invasive monitoring, of being able to assess cardiac output and cardiac function in a non-invasive manner [57]. LVEDV, in some studies, is predictive of fluid responsiveness but the accuracy of this parameter is not clear. Inferior vena caval collapsibility index may also prove to be a predictor of preload. The magnitude of respiratory variation of peak blood velocity over the aortic annulus may also be predictive of fluid responsiveness [58–60].

Other techniques

Other non-invasive modalities to measure cardiac output are those of thoracic electrical bio-impedance and partial CO_2 re-breathing. Both of these are attractive in that they require no invasive manipulation of the patient and although potentially highly applicable in the ward/high dependency environment or in the preoperative assessment arena they are not in routine clinical use. Their cost effectiveness in an ICU environment has not been assessed.

Organ perfusion

Other monitoring techniques that require consideration in terms of cost effectiveness are those that might give us further information as to organ perfusion and

microcirculation. The modalities discussed above give assessment as to global cardiac flow and global measures of whole body oxygen utilization by virtue of mixed venous or central venous saturations. The potential limitations of central saturations in patients with hyperdynamic state, has been discussed previously. Of the aforementioned monitoring modalities, the PiCCO system is unique in its ability to provide information regarding an individual organ, specifically that of extra-vascular lung water, in terms of leak index in association with volume status.

Other potential parameters to assess organ perfusion and micro-circulation are those of blood lactate. The presence of elevated blood lactate levels has been shown to be a poor prognostic marker in patients on admission to general ICUs. Smith et al. [61] showed, in an observational study, that a base excess on admission of -4 and a corresponding lactate of 1.5 mmol/l is associated with an 80% sensitivity and 58.7% specificity for mortality. McNelis et al. [62] examined blood lactate in patients admitted to a surgical ICU. Patients were stratified by lactate normalization time; those who did not achieve normal lactate sustained 100% mortality, those obtaining normalization of lactate between 48 and 96 hours had a 42.5% mortality, whilst those who normalized their lactate within 24–48 hours had a 13.3% mortality and those that normalized lactate in hours had a mortality rate of only 3.9%. What is not clear is whether any of the monitoring techniques discussed above can be incorporated along with delta blood lactate to facilitate improved therapeutic modalities and cost effectiveness. It is of note that in a similar cohort of patients, Cusack et al. could not demonstrate a significant difference between strong ion gap comparing survivors and non-survivors [63].

Monitoring of the hepato-splanchnic circulation and function may also be potentially useful and cost effective in attempts to decrease morbidity and improve outcome. It has not, however, been subject to a controlled trial to allow any statements as to cost effectiveness. It has, however, been recognized that significant flow dependency may exist within the splanchnic bed in patients with sepsis and organ dysfunction [64–67]. This can be considered along with the work of Sakka et al. demonstrating that indocyanine green clearance within the first 24 hours of admission had a similar area under the receiver operating curve to that of APACHE scoring in predicting outcome [68]. If one suggests that this may be related to inadequate flow to the hepato-splanchnic bed, then further manipulation of hemodynamics in addition to that obtained from global monitoring may have a potential to improve outcome. As to whether this would be cost effective is yet to be determined by further studies.

Another potential monitoring modality is gastric tonometry. Abnormalities of gastric CO_2 gap have been seen despite normal systemic hemodynamic and metabolic parameters. Increased CO_2 gap and gastric intramucosal pH (pHi) have been shown to be sensitive though not specific predictors of outcome in critically ill patients [69, 70]. As to whether manipulations can be undertaken to improve gastric tonometry with subsequent improved outcome and hence be cost effective has not been examined.

Tissue oxygen tension and tissue micro-dialysis are monitoring techniques that are now becoming clinically available and have undergone provisional studies. They have the potential to provide increasing physiological data and under-

standing of the abnormalities of critical illness at a local level but their full clinical applicability in the critical care environment is yet to be assessed.

Conclusion

There are many monitoring modalites available to those working within the critical care environment. The number of techniques by which data can be obtained has mushroomed, as has the nature of those data [71]. We have available to us continuous venous saturations, pressure and volume measurements, cardiac output and stroke volume values. In addition we are able now to obtain data that allow us to predict fluid responsiveness and to examine individual organ function. It is unlikely that any particular monitoring technique provides totality of clinical need. We should now be in a position, as critical care clinicians, to provide multi-medullatory monitoring, which can be tailored to individual patient requirements. The majority of work examining cost effectiveness has been undertaken in the field of the PAC and newer monitoring technologies have not yet been subjected to such rigorous cost effectiveness assessment.

We must, when considering the potential benefit or detrimental effect of any monitoring tool address not only the data provided, but how easy it is to interpret the data, make clinical decisions based on the data, and trouble shoot the system. Paramount in all of this, is the often forgotten fact that, without question, a monitor is only as good as the clinical team that interpret the data in an educated and informed manner, undertaking further measurement and assessment after every therapeutic intervention in order to truly optimize patient care. No monitor in isolation can be expected to change outcome for the better; it is inherent upon us as clinicians within the field of critical care to ensure that we utilize monitoring to optimal capacity.

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Subject Index

Printing: Mercedes-Druck, Berlin
Binding: Stein+Lehmann, Berlin