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Functional Hemodynamic Monitoring

With 78 Figures and 35 Tables

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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 functions, 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-

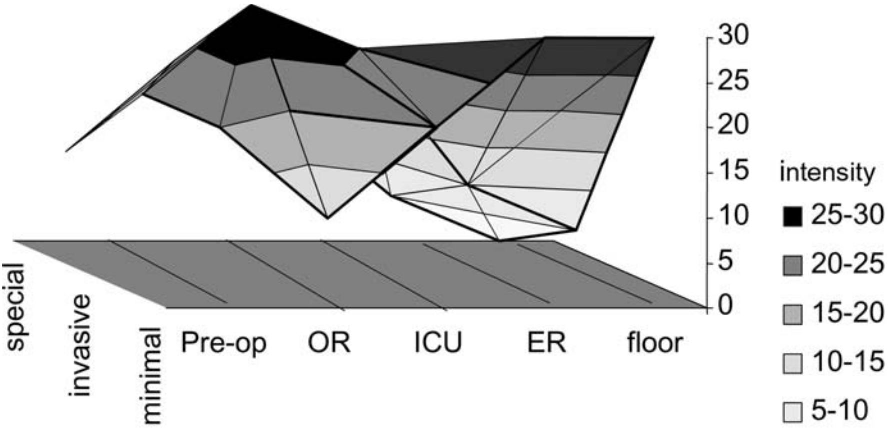

Fig. 1. Schematic representation of the level of intensity of hemodynamic monitoring by place in the health care delivery system and type of monitoring using an arbitrary scoring system from zero to thirty to define level of intensity. Pre-op connotes pre-operative optimization for high risk surgical 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.

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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.

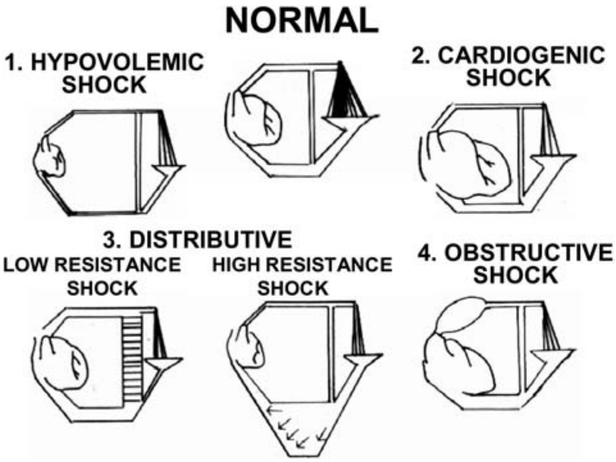

Fig. 1. Diagram representing the hemodynamic features of the four primary etiological shock states. Modified from [15]

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.

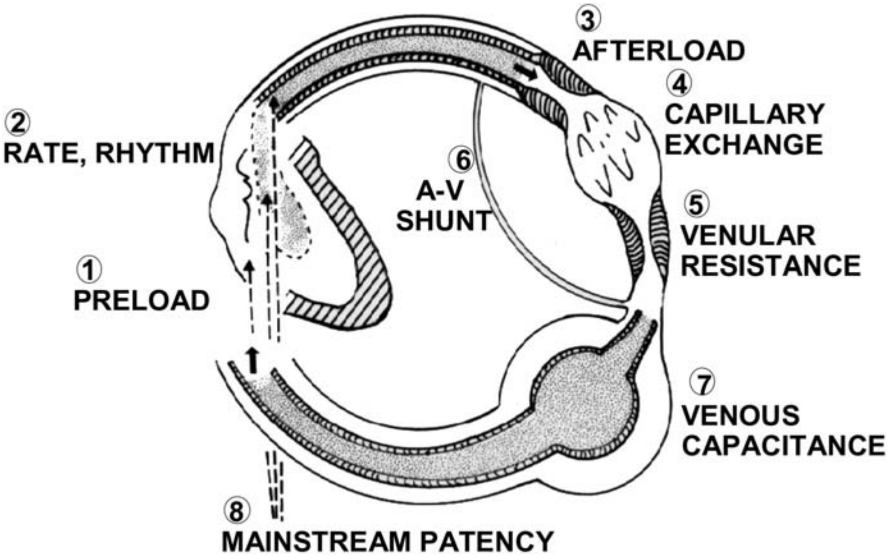

Fig. 2. Hemodynamic loci for identifying mechanisms of perfusion failure. Modified from [15]

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
1	normal	normal	<2	>39	normal 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

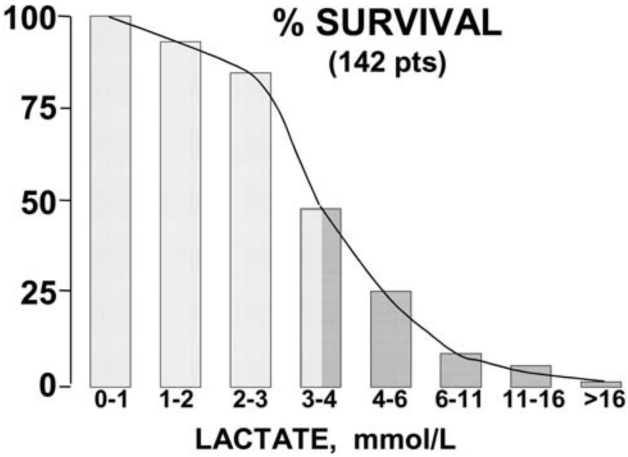

Fig. 3. Prognostic value of arterial blood lactate levels. Modified from [15]

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

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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

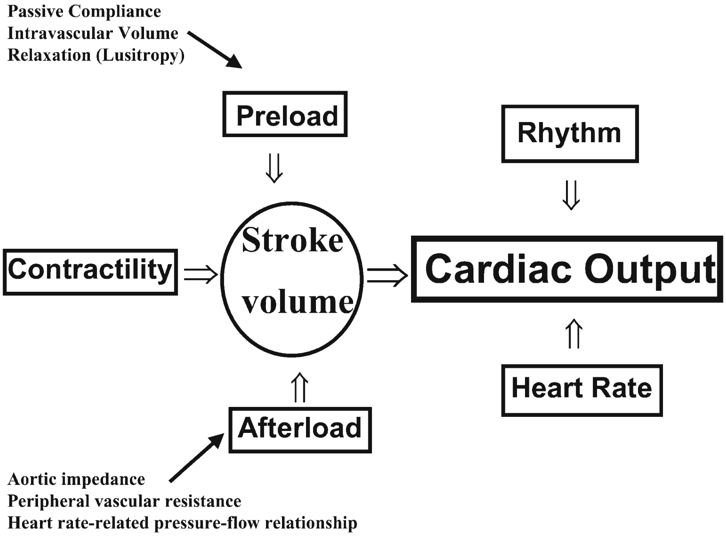

Fig. 1. Determinants of cardiac output

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