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CARDIOVASCULAR CARE (L ROEVER, SECTION EDITOR)

Haemodynamic Assessment in Cardiogenic Shock

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Abstract
Purpose of Review This review will discuss the practical applications based on the physiology that underpins some of these commonly used haemodynamic parameters.
Recent Findings Haemodynamic parameters are integral to the management of cardiogenic shock. Some of these are easily measured and ubiquitous, such as arterial blood pressure and central venous pressure. Others, such as the use of pulmonary artery catheters, continue to be discussed and debated.
Summary The management of cardiogenic shock is challenging. Clinicians employ a range of haemodynamic parameters to diagnose and guide therapeutic interventions in cardiogenic shock. Understanding the physiologic basis for these parameters will aid the interpretation and clinical application in cardiogenic shock.

Keywords Cardiogenic shock · Blood pressure · Cardiac output

Introduction

Circulatory shock is defined by specific clinical and haemodynamic parameters in clinical studies (e.g. systolic blood pressure (BP) > 90mmHg [1] or specific cardiac output levels), which creates the misconception of a binary clinical state. In practice, the clinical condition often evolves subtly before rapid and precipitous decline, as compensatory mechanisms are exhausted. This non-linear and often unpredictable clinical course complicates treatment of circulatory shock and emphasizes the need for monitoring of the cardiopulmonary status, to guide the timing and modality of intervention. There are implicit assumptions that (i) these haemodynamic parameters are sufficiently sensitive to detect the early, subtle deterioration, (ii) can be safely applied repeatedly or continuously with the requisite accuracy and precision, and (iii) the haemodynamic parameters parallel known pathophysiologic processes and intervention based on these parameters can improve outcomes. Unfortunately, such an 'ideal' parameter is elusive, and clinicians rely on a range of directly measured and derived haemodynamic measurements to guide decision-making in clinical practice.

A number of these parameters are easily measured and ubiquitous in the intensive care unit. However, misunderstanding of the physiology that underpins these commonly used parameters may lead to a number of apparent paradoxes, for example, the paradox of cardiogenic shock despite systolic BP > 90 mmHg, the apparent contradiction of concurrent increase in arterial BP and drop in cardiac output, clinical deterioration despite increase in mixed venous saturation, and seemingly incompatible drop in right atrial pressure with a drop in cardiac function. Hence, this review will examine the physiology and clinical application of a number of parameters that are commonly used in cardiogenic shock, namely systemic arterial BP, central venous pressure (CVP), cardiac output, and mixed and central venous oxygen saturation.

Arterial Blood Pressure

Measurement

There are well-established methods of measuring arterial BP non-invasively. In critically ill patients, arterial BP is usually measured from indwelling arterial catheters. Radial arterial pressure may underestimate central arterial pressure in the

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presence of severe peripheral vasoconstriction, and central arterial (e.g. femoral artery) catheterization should be considered. Arterial catheterization allows continuous monitoring of arterial BP and its waveform; the latter has been used to assess fluid responsiveness but will not be elaborated here.

Arterial Blood Pressure—Autoregulation and Perfusion Pressure

Arterial BP is dependent on the relative difference between the input and output of blood volume in the arterial system. The input is the left ventricular stroke volume (or pump flow in the case of ventricular assist device), and the output is a function of the time constant, which is the time it takes for the pressure to drop by 63% from baseline. The time constant is the product of resistance and compliance (i.e. the resistive and viscoelastive properties of the arterial tree). Low vascular resistance and/or compliance will reduce the time constant (rapid diastolic pressure decay), and if coupled with slower heart rates, will result in lower diastolic blood pressure. Hence, heart rate and the resistance and compliance of the arterial system determine the diastolic blood pressure, and the interaction with stroke volume will determine the arterial pulse pressure. The implication is that low diastolic blood pressure particularly if it is accompanied by tachycardia would be indicative of low vascular resistance (vasoplegia).

A relatively high resistance is maintained in the arterial system (compared to the venous system) at the arterioles to maintain a higher BP, which is necessary for autoregulation (intrinsic ability of organs to maintain a constant blood flow despite changes in perfusion pressure). The capacity for autoregulation is dependent on sufficient pressure at the inflow to the organ, such that there is sufficient perfusion pressure to increase blood flow to the organ when vessels vasodilate in response to increasing metabolic demands. The corollary is that blood flow to the organ will not increase even with maximal vasodilatation if the inflow pressure is inadequate. Below this inflow pressure level, blood flow to the organ becomes pressure-dependent. The level of perfusion pressure below which blood flow becomes pressure-dependent defines the lower limit of autoregulation (Fig. 1). The autoregulation range is shifted to the right in patients with chronic hypertension [2].

Perfusion pressure is defined as the difference between the inflow and outflow pressures. Mean arterial pressure (MAP) is usually used as the organ inflow pressure, but inflow pressure may be lower than MAP due to arterial resistance. There are also significant differences between organs. The heart, for example, is dependent on diastolic BP as the inflow pressure. The CVP is usually assumed to be the outflow pressure, but outflow pressure may be higher than CVP in some cases such as intracranial hypertension or intra-abdominal hypertension. In addition, zero-flow has been shown to occur at a level higher than the CVP—termed the critical closing pressure (Pcc). The demonstration of Pcc implies the presence of a vascular waterfall (Fig. 2), so termed, as flow over the edge of the waterfall is independent on how far the water then drops (i.e. blood flow does not increase with further lowering of CVP).

Pcc is generated by vasomotor tone of arterioles and precapillary sphincters, and decreases towards the outflow pressure with vasodilatation. Pcc is also organ (vascular bed)-specific [3]. In a study of patients undergoing cardiac surgery with the inspiratory hold method, Maas et al. [4•] estimated the Pcc as a lump sum to be about 45 mmHg in normal healthy adults with MAP of about 85 mmHg (i.e. lumped perfusion pressure of 40 mmHg), but Pcc is likely to be much lower in the cerebral and coronary circulations, and in pathological states. Hence, under normal circumstances, perfusion pressure is the difference between inflow pressure and Pcc. However, Pcc approaches mean systemic filling pressure (Pmsf) with the loss of vasomotor tone, and Pmsf is directly related to CVP levels. The CVP is also the main determinant of outflow pressure in some organs (e.g. the heart) [5]. Therefore, the CVP must be considered when setting a MAP target but should not be assumed to be the Pcc. Indeed, the use of CVP instead of Pcc as the outflow pressure would erroneously overestimate systemic vascular resistance (Ohm's law of pressure gradient divided by flow).

Arterial Blood Pressure in Cardiogenic Shock

Hypotension in circulatory shock increases sympathetic nervous activity, and the sympathetic-mediated vasoconstriction overwhelms local metabolic-related vasomotor tone and produces two effects: increase in arterial BP by increasing arteriolar resistance, and redistribution of blood flow to maintain coronary and cerebral circulation at the expense of other tissues or organs. These two effects are mediated by adrenergic receptors. For example, blood flow to cutaneous and skeletal muscles is reduced as high α-adrenergic receptor density in these tissues results in marked vasoconstriction. The heart and cerebral circulation are largely devoid of α-adrenergic receptors. The splanchnic circulation is more complex [6]. The splanchnic and hepatic arteries are well innervated by α- and β2-adrenergic receptors, resulting in vasoconstriction and vasodilatation, respectively. The net effect is dependent on relative receptor density and the specific catecholamines involved (largely α-adrenergic vasoconstrictive effects with norepinephrine). However, the capacitance vessels in the pre-portal organs (intestines) and liver sinusoids are dominated by α-adrenergic receptors, and vasoconstriction expels the splanchnic blood volume into the systemic circulation and increases the stressed volume.

The haemodynamic effects of this increase in stressed volume are dependent on the size of the increase in stressed

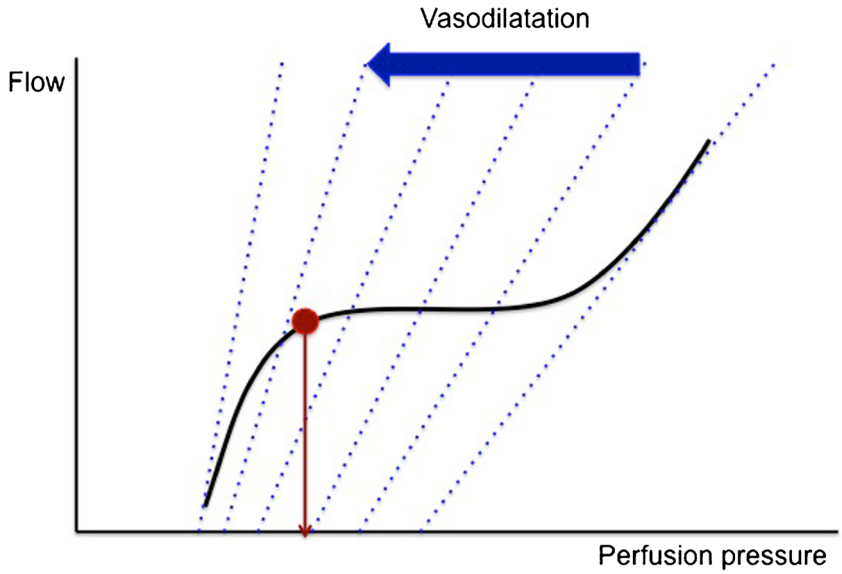

Fig. 1 Autoregulation. Vasodilatation shifts the pressure-flow relation leftwards. The inflexion point (dot) indicates the lower limit of autoregulation, i.e. flow drops as perfusion pressure drops below this level of perfusion pressure. The zone of autoregulation is organ-specific and very narrow in the liver and kidney

volume relative to the increase in resistance to venous return due to venoconstriction and the preload responsiveness of the heart [7]. Venous return (and ventricular preload) is increased if the increase in stressed volume overcomes the α-mediated increase in venoconstriction (resistance in venous return). However, in hypovolaemia and poor cardiac function (e.g. post-cardiac surgery), the recruitable unstressed volume may be limited and the venoconstrictive effects of α-agonists would dominate and reduce venous return and further jeopardize splanchnic blood flow. Hence, the use of isolated α-agonists should be avoided in hypovolaemia.

Pulmonary venous pressure frequently increases in cardiogenic shock due to depressed left ventricular contractile function, as right ventricular output is not matched by left ventricular output [8]. The increase in venous return from splanchnic vasoconstriction may not result in an increase in stroke volume (and BP) if the impaired left ventricle is not preload responsive and the splanchnic blood volume is simply redistributed to the pulmonary circulation, which would compound the already elevated pulmonary venous pressure and worsen cardiogenic pulmonary congestion. Thus, hypotension in the presence of left ventricular dysfunction and pulmonary congestion implies that the left ventricle is no longer preload responsive and the arterial BP cannot be corrected by fluid administration.

Exogenous catecholamines, α-agonists, angiotensin II and vasopressin (or the more V1 receptor selective terlipressin) are often used to increase arterial BP by increasing arteriolar vasoconstriction. However, these drugs exacerbate and alter this regional redistribution of blood flow. In the setting of cardiogenic shock, blood flow to the splanchnic circulation is already reduced by the reduction in cardiac output and α-adrenergic-mediated regional vasoconstriction. Vasopressin and α-agonists can induce further vasoconstriction and critically compromise the splanchnic circulation. Furthermore, venoconstriction with α-agonists reduces venous return and further reduces cardiac output. Indeed, α-agonists may increase MAP, myocardial oxygen consumption from pressure

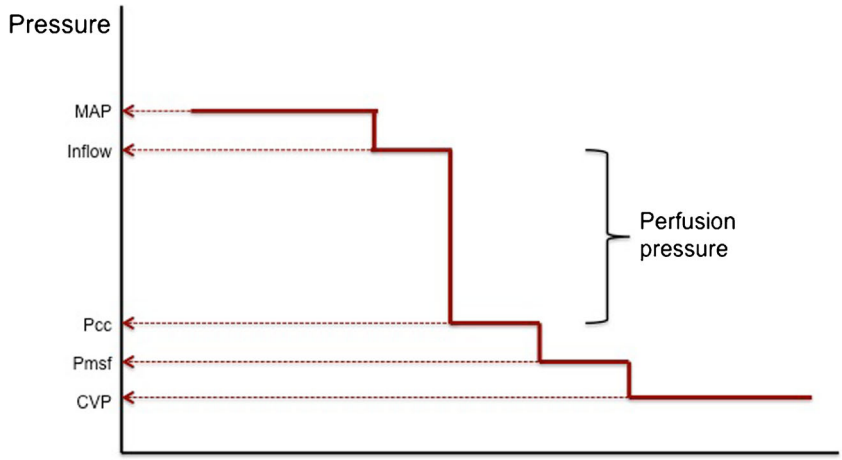

Fig. 2 Perfusion pressure is the difference between the organ inflow and outflow pressures. The inflow pressure may be lower than MAP due to arterial resistance. The Pcc is the zero-flow pressure and is the outflow pressure. Hence, perfusion pressure is the difference between inflow pressure and Pcc. Pcc is organ-specific and drops with vasodilatation and in pathological states. The gradient between mean systemic filling pressure (Pmsf) and CVP maintains the gradient for venous return

work, but reduces cardiac output due to increase in resistance to venous return. Isolated α-agonists have not been shown to increase blood flow to any organ systems in circulatory shock despite the MAP increase [9].

Progression of cardiogenic shock is associated with a change in the clinical phenotype to one that is analogous to septic shock, characterized by microcirculatory abnormalities, vasoplegia due to the loss of adrenergic receptors and inflammatory mediator-induced release of vasoactive agents (e.g. nitric oxide) [10]. The combination of impaired autoregulation due to systemic hypotension, microcirculatory abnormalities and vasoplegia impairs the normal redistribution of blood flow to vital organs in cardiogenic shock and accelerates the downward spiral towards death from multi-organ failure [11].

In summary, in cardiogenic shock:

1. Low diastolic blood pressure, particularly in the presence of tachycardia, is indicative of concomitant low vascular resistance.
2. A MAP of 65 mmHg has been recommended in circulatory shock [12•], but a higher MAP may be indicated in patients with chronic hypertension due to the rightward shift of the autoregulation range.
3. A higher MAP is also indicated in the face of high CVP, especially in right heart failure, as CVP is the key determinant of outflow and perfusion pressure in the heart.
4. Low arterial BP in the presence of left ventricular dysfunction and pulmonary congestion is very unlikely to be fluid responsive.
5. Isolated α-agonists should be avoided, particularly in the presence of hypovolaemia and/or persistently low cardiac output.
6. Increasing vasopressor use that is not accompanied by improvement in cardiac output and organ perfusion should prompt alternative strategies, such as mechanical circulatory support.

Central Venous (Right Atrial) Pressure

Measurement of Central Venous Pressure

The CVP has three positive waves: the 'a', 'c', and 'v' waves and two negative waves: the 'x' and 'y' descents. The a wave is produced by atrial contraction, which is followed by x descent due to the fall in atrial pressure during atrial relaxation. Atrial contraction and relaxation is followed by ventricular systole, producing the c wave by backward 'bulging' of the tricuspid valve at the onset of ventricular systole. The subsequent v wave is due to atrial filling during diastole before tricuspid valve opening. Atrial pressure drops when the tricuspid valve opens, producing early ventricular filling and the y descent.

Due to the low ranges of CVP measurements, the effects of slight 'errors' from levelling and variable points of measurement can be significant. It is recommended that CVP measurement be made at the level of 5 cm below the sternal angle (location of the right atrium) at end-expiration when pleural pressure is close to zero [13]. Computer-generated mean CVP measurements are often used for monitoring, but these measurements tend to over-estimate the CVP. Measuring the CVP at the z point, which is at the leading edge of the c wave, has been recommended, as this is the final pressure in the ventricle just before ventricular contraction (end-diastolic pressure) [14], but the c wave is often not visible and the z point not easy to identify. Hence, the CVP measurement at the base of the a wave should be used [15].

Physiology of Central Venous Pressure

Central venous pressure is a function of cardiac function and venous return, expressed graphically as the point of intersection between the cardiac function and venous return curves. The cardiac function curve shifts based on contractility and afterload. The venous return function is dependent on vascular (stressed) volume, venous compliance, resistance to venous return and the venous waterfall (the venous pressure that defines that maximal cardiac output). An increase in stressed volume will shift the venous return curve to the right in parallel, and assuming unchanged contractile function will result in higher CVP. However, CVP may be relatively unchanged with fluid administration if there is concomitant increase in contractility (Fig. 3).

The slope of the venous return function is inversely related to the resistance in venous return. Hence, venoconstriction reduces the slope and reduces the CVP and cardiac output even if cardiac function is unchanged. Indeed, it is worth noting that increasing the resistance in venous return may have a larger effect on venous return and cardiac output than increasing arterial resistance [16]. Based on the physiological determinants, it is clear that the diagnostic value of CVP is limited in the absence of corresponding cardiac output.

Central Venous Pressure in Cardiogenic Shock

The CVP is widely used as a guide to fluid therapy. Fluid responsiveness refers to the likelihood of an increase in stroke volume with fluid administration. Stroke volume response to fluid administration is dependent on ventricular preload, contractility and afterload. Ventricular volume is the main determinant of preload, and the relationship between ventricular volume and CVP (or right atrial pressure) is dependent on the pressure-volume relation, i.e. compliance of the chamber. The pressure-volume relationship in the heart or vessel is non-

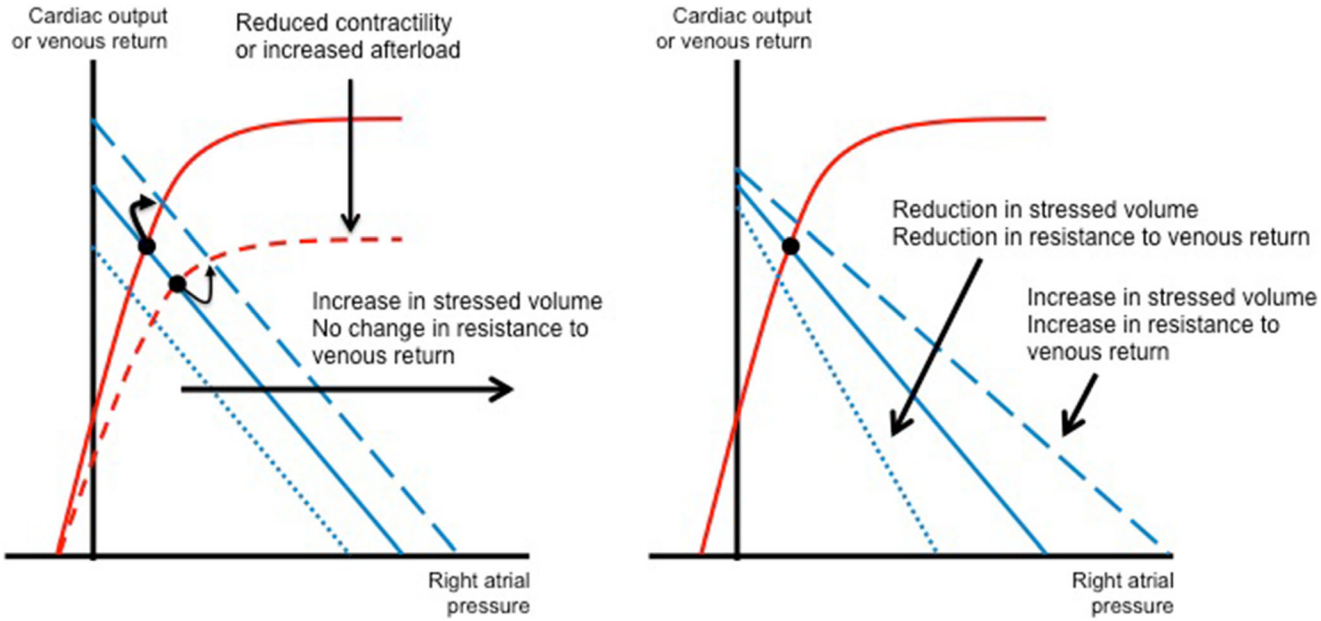

Fig. 3 Cardiac output and CVP are determined by the point of the intersection between the cardiac function and venous return curves. The cardiac function curve is shifted downwards in the face of increased afterload or reduced contractility. The venous return curve is right shifted in parallel with volume expansion, but the slope is inversely related to resistance to venous return. The intercept of the venous return curve on the *x*- and *y*-axes defines the Pmsf and the vascular waterfall (also known as the Starling resistor—the pressure below which no further increase in flow can be achieved), respectively. With normal contractile function and venous return function (solid line, left figure), fluid administration shifts the venous return curve rightwards (dashed) with increase in cardiac output (thick curved arrow). However, fluid administration results in little increase in cardiac output (thin curved arrow) if cardiac function is impaired

linear, with the filling pressure increasing exponentially at higher volumes per unit change in volume (Fig. 4). Stiffness is also altered in pericardial and myocardial diseases (e.g. restrictive cardiomyopathy) and positive pressure ventilation (increased juxta-pericardial pressure), resulting in high CVP despite normal right ventricular volumes (low preload). As a result, CVP becomes an unreliable surrogate of ventricular preload in pathological states. In addition, ventricular contractility and afterload cannot be inferred from CVP. Although as a group, patients are more likely to be fluid responsive when the CVP is low, up to 25% of patients with CVP < 10 mmHg do not respond to fluid therapy, and fluid responsiveness is unlikely when CVP > 13 mmHg [17]. Unsurprisingly, CVP has been shown to be a poor guide for fluid responsiveness [18]. Other measures of fluid responsiveness such as arterial pulse pressure variation have been reviewed elsewhere [19].

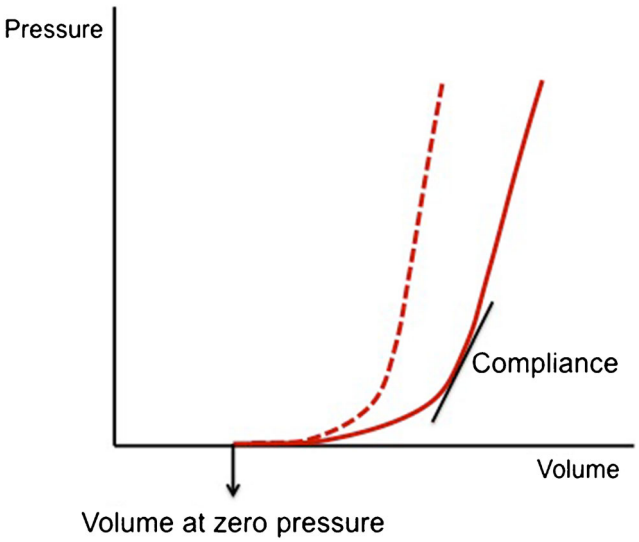

Fig. 4 Non-linear pressure-volume relation applicable to the cardiac chamber, pericardium or the wall of the blood vessel. This relationship defines the stiffness of the vessel. A stiffer vessel will have a left-shifted pressure-volume relation (dashed line) which indicates a higher pressure at the same or lower distending pressure. Regardless of the stiffness of the vessel, the pressure increases exponentially as volume increases, indicating lower compliance at higher volume

The CVP waveform and dynamic changes with respiration should be considered in guiding fluid therapy. The y descent, which corresponds to early diastolic filling, is affected by the relative filling pressure of the atria and ventricles at the start of diastole, the compliance of the chambers, and the pressure outside the heart. The steep y descent suggests that the atrial volume lies on the steep part of the diastolic pressure–volume curve (a small reduction in atrial volume results in large drop in pressure) and the ventricle is relatively non-compliant (ventricular filling pressure rises rapidly with filling, resulting in abrupt termination of filling). On this basis, fluid infusion is unlikely to elicit an increase in stroke volume in the presence of steep y descent (y descent is greater than 4 mmHg [20]).

The CVP normally falls during inspiration when spontaneously breathing, due to the negative intra-thoracic pressure.

Kussmaul sign refers to an inspiratory rise (or absence of the normal inspiratory fall) in CVP. Kussmaul sign is probably related to the poor right atrial/ventricular compliance, which are unable to accommodate the increase in venous return during inspiration (venous return increases during inspiration due to diaphragmatic descent which increases intra-abdominal pressure and simultaneous drop in intra-thoracic pressure) without significant increase in pressure. Hence, the lack of inspiratory fall in CVP is associated with poor response to volume loading.

Some patients may be fluid responsive even in the presence of an elevated CVP. However, the potential benefits of fluid administration in these cases must be balanced against the risks of venous congestion. Upstream organs such as the liver will face the high backpressure, and the injury from venous congestion may outweigh the benefit of modest increase in stroke volume with fluid administration. Of note, severe tricuspid regurgitation, which produces large systolic waves (often from onset of c wave extending to the v wave) even at modestly elevated CVP measurement (at the base of the a wave), can result in significant venous congestion.

In summary, CVP:

1. Is a function of venous return and cardiac function, and not simply a measure of 'filling status'
2. Is a poor guide of fluid responsiveness, although the waveforms and changes with respiration may be helpful in some cases
3. Is a measure of systemic venous congestion
4. Should be interpreted with concurrent cardiac output measurements and assessment of the right ventricular dimensions

Pulmonary Artery Catheterization

The pulmonary artery catheter (PAC) has been used in the clinical management of the critically ill patient since 1970. Randomized trials do not support routine use of PAC, but do not exclude potential benefit in selected cases, not least as these trials required clinical equipoise and would have excluded patients who the clinicians felt may benefit from PAC-guided therapy [21]. Indeed, improvement in clinical outcomes with PAC is unlikely in routine low-risk cases, or very high-risk cases, as treatment may be futile in the latter. In addition, the PAC is a monitoring device and must be coupled to appropriate therapy of proven benefit. The use of PAC is unlikely to be beneficial if measurement and interpretation of the data are erroneous, leading to inappropriate and potentially harmful interventions, and/or there is no effective therapeutic intervention irrespective of the measured data. The lack of specific protocols to define the therapeutic strategy and goals may have confounded the results of the trials [22].

Nonetheless, PAC may be of benefit in selected patients with circulatory shock, particularly if:

1. Initial therapy fails to produce the expected results
2. Escalating doses of inotropes or vasopressors are required
3. Assessment of haemodynamics and perfusion is required for drug titration or volume management
4. Assessment of pulmonary haemodynamics and right ventricular function prior to cardiac transplantation or left ventricular assist device therapy

A range of parameters can be derived from PAC measurements (Table 1). Only cardiac output and oxygen delivery will be discussed in this review.

Cardiac Output

The two most commonly used techniques for determining cardiac output (CO) are the thermodilution and Fick methods. Thermodilution measurements involve injecting a fluid bolus at a known temperature into the proximal port of the PAC, and recording the change in temperature at the distal end of the catheter with a thermistor. The change in temperature recorded at the pulmonary site after the injection of cold saline produces a curve that rises to a maximum quickly and then decline with mono-exponential kinetics. CO is calculated from this curve based on the temperature and specific gravity of blood, and the temperature, specific gravity and volume of injected fluid:

$$CO = (Vi \times (Tb - Ti) \times 60 \times 1.08)/A$$

where Vi = volume of injectate (ml), Tb = blood temperature, Ti = injectate temperature, 1.08 = correction factor and A = area under the curve.

The area under the temperature–time curve is integrated and is inversely proportional to the CO.

The measurement of CO by thermodilution is inherently variable, due to a number of factors including (i) the inevitable noise from respiratory fluctuation in temperature (about 0.05 °C), although this is relatively minor compared to the mean change in temperature of about 0.5 °C with the thermodilution technique; (ii) transfer of heat from blood into the fluid in the catheter; and (iii) variability in the volume of the injectate. Using larger volume of cold injectate may reduce some of the variability, but the large volume may not be clinically appropriate. In general, 10 ml of cold injectate is typically used for CO studies. Rapid (within 2 s) injection of colder injectate reduces the variability of CO measurements [23].

Table 1 Measured and derived haemodynamic parameters

Measurement	Formula
Cardiac output (L/min)	O_2 consumption/[($SaO_2 - MvO_2$) × 1.36 × Hb × 10]
Cardiac index (L/min/m^2)	Cardiac output/BSA
Stroke volume (ml)	Cardiac output/HR × 1000
Stroke volume index (ml/m^2)	Stroke volume/BSA
Transpulmonary gradient (mmHg)	Mean PA pressure − mean PAOP
Diastolic pressure gradient (mmHg)	PA diastolic pressure − mean PAOP
Pulmonary vascular resistance (WU)	Transpulmonary gradient/cardiac output
Pulmonary capacitance (ml/mmHg)	Stroke volume/pulmonary artery pulse pressure
Systemic vascular resistance (WU)	(Mean arterial BP − mean RA pressure)/cardiac output
RV stroke work (g/beat)	Stroke volume × (Mean PA pressure − mean RA pressure) × 0.0136
Cardiac power output (W)	(mean arterial − right atrial pressure) × CO ÷ 451
Pulmonary blood flow, Qp	O2 consumption/($PVO_2 - PAO_2$)
Systemic blood flow, Qs	O2 consumption/($SaO_2 - MvO_2$)
Intracardiac shunt, Qp/Qs	Pulmonary blood flow/systemic blood flow = ($SaO_2 - MvO_2$)/($PVO_2 - PAO_2$)

Multiply Wood units by 80 to convert to dynes/s/cm^5 . MvO2 is mixed venous oxygen saturation (sampled from the PA) but can be calculated in the presence of a left-to-right shunt as ($3 \times SVCO_2 + IVCO_2$)/4. Note the use of CVP as the outflow pressure to calculate systemic vascular resistance (Ohm's law of pressure gradient divided by flow) overestimates systemic vascular resistance

Hb haemoglobin, *SaO_2* arterial oxygen saturation, *BSA* body surface area, *HR* heart rate, *PAOP* pulmonary artery occlusion pressure, *WU* Wood units

The standard deviation between repeat measurements is about 7% [24]. The standard error of the mean of 3 measurements varied from 2 to 5%, suggesting that this technique may detect changes of 6–15% [25], under steady-state conditions. Finally, there must be no additional blood leaving or entering the circulation beyond the site of mixing and before the site of detection, rendering thermodilution unsuitable in the presence of an intracardiac shunt or drainage of blood from the right atrium/ventricle in an extracorporeal circulation.

Cardiac output can be estimated by the Fick equation:

$$CO = VO_2/[Hb \times 1.36 \times (SaO_2 - SvO_2)]$$

where VO_2 = oxygen consumption, CO = cardiac output, Hb = haemoglobin, SaO_2 = arterial oxygen saturation and SvO_2 = mixed venous oxygen saturation.

Therefore, the Fick method requires measurement of oxygen consumption (e.g. using a rebreathing bag), which may be impractical in clinical practice. Oxygen consumption is thus often assumed based on age, sex and body surface area. Resting VO_2 is dependent on age, gender, height and weight, and basal metabolism, which is mostly due to digestion and body temperature. A normal meal usually increases the metabolic rate by 4–10%, and each degree change in temperature over or under 37 °C alters VO_2 by 13%. Drugs such as catecholamines [26] and dobutamine [27, 28] also have well-documented thermogenic effects and may increase VO_2 by over 8%, particularly at higher doses. VO_2 may be reduced by anti-pyretics, sedation and neuromuscular blockage. Increase in VO_2 triggers neurohormonal responses to increase oxygen delivery.

Studies have demonstrated a reasonable correlation between thermodilution and Fick methods for the estimation of CO, although there may be significant variation in individual patients [29]. Thermodilution tends to overestimate CO in low output states, and it is also inaccurate in patients with significant tricuspid regurgitation (both under- and over-estimate CO by variable degrees). However, the reliance of Fick CO calculation on an assumed oxygen consumption is a major limitation, particularly in the critically ill.

Cardiac output measurements complement cardiac imaging modalities such as echocardiography in determining the aetiology of circulatory shock, assess the severity, and guide and assess response to interventions. However, cardiac output is dependent on heart rate and stroke volume, and the latter is dependent on preload, contractility and afterload. Hence, cardiac output:

1. Is related to but not a marker of cardiac function per se. The corollary is that cardiac output should be interpreted in the context of loading conditions and adequacy of tissue perfusion.
2. Therapeutic interventions should not target an arbitrary range of cardiac output but should be aimed at restoring tissue perfusion.

Mixed Venous Oxygen Saturations

Mixed venous saturation (SvO_2) is a key component in the Fick equation and is measured from the pulmonary artery,

where there is complete mixing of venous blood from both vena cava and coronary sinus. Like thermodilution, Fick calculation of CO is not applicable in the presence of intracardiac shunts. There is no regulatory loop for maintaining the mixed venous oxygen partial pressure or SvO_2 within a specific normal range, unlike blood pressure (baroreceptors and sympathetic/ neuro-hormonal modulation) and haemoglobin (iron mobilization [30], erythropoietin production by the kidneys [31] and the release of red blood cells [32]). Instead, SvO_2 is directly related to the balance between oxygen delivery ($DO_2 = CO \times Hb \times 1.36 \times SaO_2$) and oxygen consumption as follows:

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

Hence, low SvO_2 may be a result of reduced cardiac output, anaemia, low arterial blood oxygen saturation and/or high VO_2 (Fig. 5). The relationship between SvO_2 and cardiac output is non-linear. In low output states, relatively small drops in CO may be accompanied by significant reduction in SvO_2. Parenthetically, the non-linear relationship also illustrates the limitation of CO measurements in estimating adequacy of tissue oxygenation in low CO conditions (small errors in CO measurements lead to significant variation in SvO_2).

This balance between oxygen delivery and oxygen consumption can also be expressed as the oxygen extraction ratio (ERO_2):

$$ERO_2 = VO_2/DO_2,$$

Hence,

$$SvO_2 = SaO_2 \times (1 - ERO_2)$$

An acute fall in DO_2 (e.g. falling cardiac output, bleeding or hypoxaemia) relative to VO_2 results in an increase in oxygen extraction (increase ERO_2). Oxygen consumption is normally independent of DO_2, but an ERO_2 that exceeds a critical threshold is associated with tissue hypoxia and anaerobic metabolism, and VO_2 drops with DO_2—so-called supply dependence (Fig. 6). This critical ERO_2 threshold is approximately 0.7 in normal healthy whole animals [33, 34] and may be similar regionally in skeletal muscle [35], the intestines [36], the heart [37] and the brain [38]. This ERO_2 of 0.7 corresponds to SvO_2 of about 30%. However, this critical ERO_2 is not constant. The critical ERO_2 may be lowered by impaired oxygen extraction due to heterogenous micro- and macrovascular blood flow [39, 40] and abnormal oxygen utilization [41], typified by the syndrome of septic shock (or latter stages of cardiogenic shock), such that critical tissue hypoxia may occur in the presence of a high SvO_2. This relationship between ERO_2 and VO_2/DO_2 is exemplified during cardiopulmonary arrest, when venous blood is fully desaturated due to maximum oxygen extraction (central venous oxygen saturation may be < 20%), while successful chest compression leads to an immediate increase of venous oxygen saturation > 40% [42], and return of spontaneous circulation was observed in most patients who achieve a central venous saturation > 72% during resuscitation [43]. However, a normal or high (> 80%) central venous oxygen saturation in the presence of a very low oxygen delivery after resuscitation probably reflects failure of tissue oxygen utilization and is associated with poor outcome [44]. A drop in SvO_2 has been shown to be a good and early marker of circulatory deterioration in acute myocardial infarction [45].

Central Venous Oxygen Saturation as a Surrogate for SvO_2

Central venous oxygen saturation ($ScvO_2$) can be easily measured from the ubiquitous central venous line (unlike SvO_2 which necessitates the insertion of a PAC) and has been advocated as a simple method to assess changes in the adequacy of global oxygen supply. However, there are major physiological differences between $ScvO_2$ and SvO_2.

Venous oxygen saturations differ among several organ systems due to the differing oxygen requirements or extraction. As a result, venous oxygen saturation is dependent on the site of measurement and the oxygen demand of the corresponding organ system. Under normal resting circumstances, the oxygen saturation in the inferior vena cava is higher than in the superior vena cava, as the kidneys and abdominal organs extract less oxygen compared to the brain [46]. The $ScvO_2$ from the right internal jugular vein (cerebral venous drainage) is thus lower than the mixed SvO_2. Deoxygenated myocardial venous blood that drains directly into the right atrium via the coronary sinus and the Thebesian veins also exacerbates the difference between jugular venous and pulmonary arterial blood oxygen saturation. Hence, the venous oxygen saturation in the inferior vena cava > pulmonary artery (mixed venous) > superior vena cava under normal conditions [47, 48].

Central venous blood sampling from catheters inserted via the internal jugular or subclavian vein primarily reflects the venous blood of the upper body and as it is upstream of the heart, does not reflect changes in myocardial oxygen consumption. The position of the tip of the central venous catheter may also be variably positioned in the superior vena caval/atrial junction or in the right atrium [49]. In the latter, some admixture of blood from the inferior vena cava and right atrium may be possible, which (under normal circumstances) may result in slightly higher venous oxygen saturation compared to blood from the superior vena cava. Venous blood from the femoral venous catheter is upstream of any vital organs, reflecting predominantly oxygenation of the lower limb and therefore of limited clinical utility.

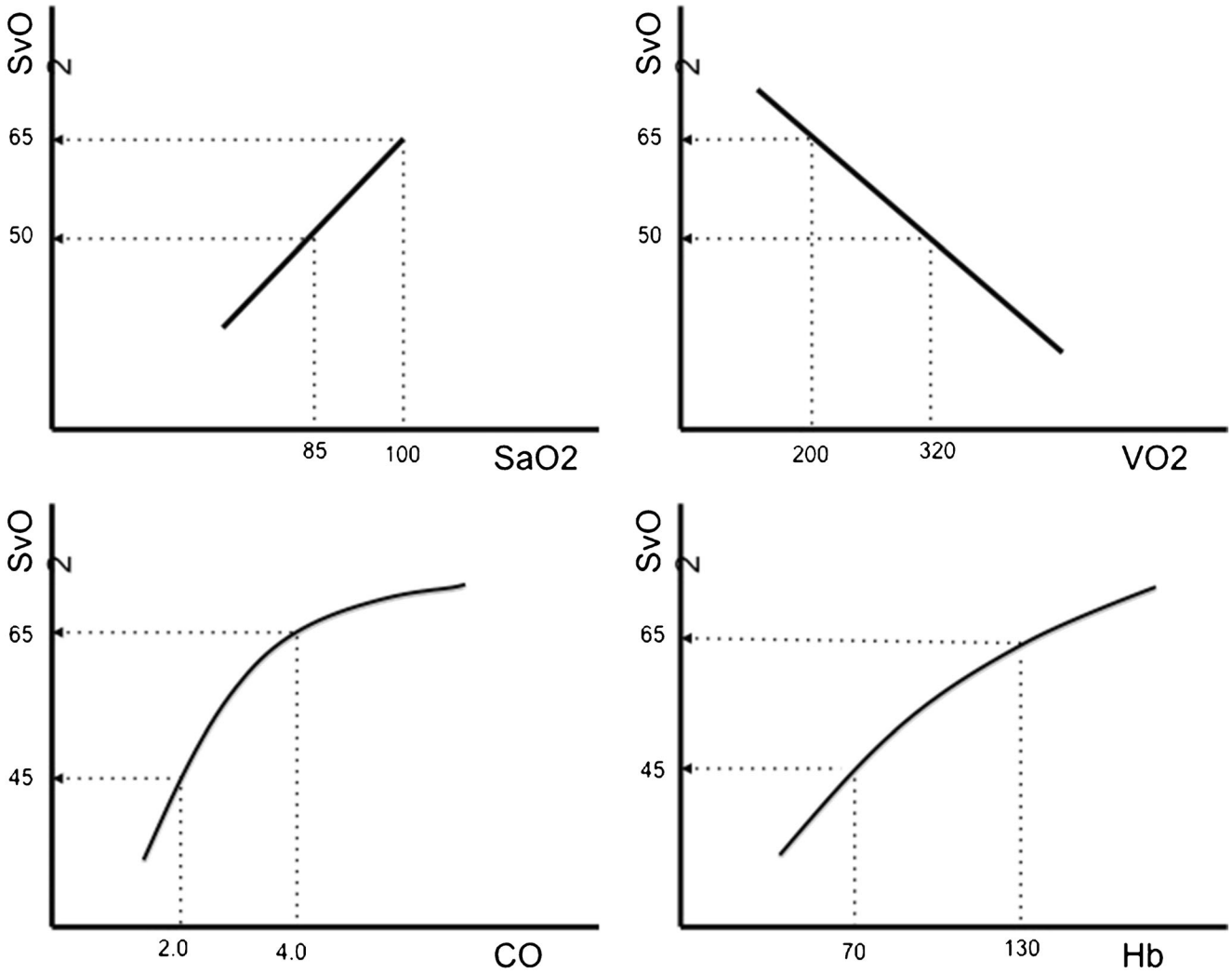

Fig. 5 Oxygen extraction and drop in SVO_2 are related to arterial oxygenation, oxygen consumption, cardiac output and haemoglobin. The drop in SvO_2 with cardiac output is non-linear, steepening in low output states. As a result, small drops in output will result in larger drops in SvO_2 in low output states

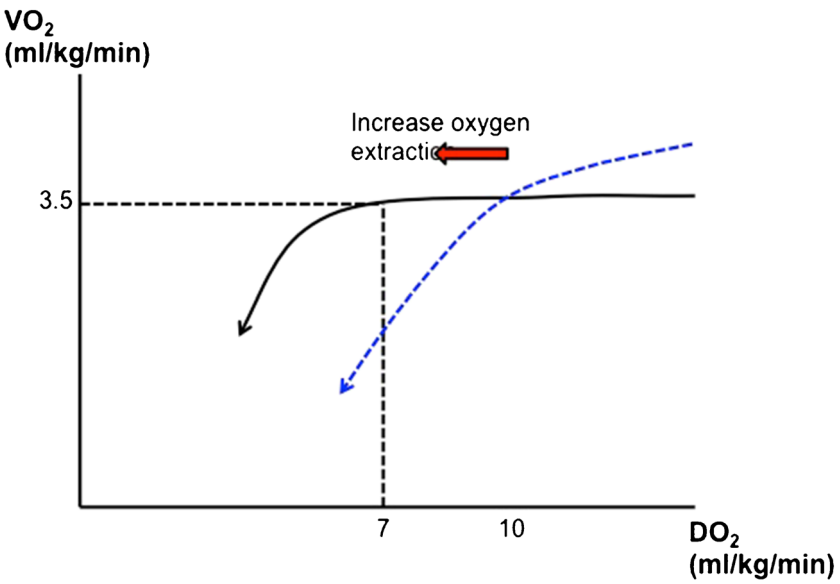

Fig. 6 Oxygen consumption is independent of DO_2 under normal conditions (solid line) but drops below a critical point and become supply-dependent. Supply dependence occurs at a higher DO_2 level (i.e. lower ERO_2) in the presence of macro- and micro-circulatory abnormalities, or failure of cellular oxygen utilization (dashed line)

However, under conditions of circulatory insufficiency, the redistribution of blood flow and differing oxygen demands of the various organ systems can exaggerate and even reverse the physiological differences between $ScvO_2$ and SvO_2. Increase in cerebral blood flow during anaesthesia (reduce cerebral oxygen extraction ratio) and/or reduced cerebral metabolism (elevated intracranial pressures and barbiturate use) may increase $ScvO_2$ and even exceed SvO_2 [50].

Indeed, the reversal of the physiologic difference between $ScvO_2$ and SvO_2 is well recognized in shock, as reduction in mesenteric blood flow increases oxygen extraction from the splanchnic circulation (thereby reducing inferior vena cava blood oxygen saturation) [51]. The superior vena cava oxygen saturation may exceed that of the inferior vena cava if changes in the splanchnic circulation are unaccompanied by a reduction in cerebral blood flow. This reversal of superior-inferior vena cava blood oxygen saturation difference is common in different shocked states [52–54]. Hence, despite good correlations ($r = 0.78–0.95$) [55–59] and general concordance between $ScvO_2$ and SvO_2 in a study of patients with acute lung injury ($ScvO_2$ of more than 70% is generally associated with a SvO_2 of over 60%) [60], absolute SvO_2 cannot be reliably extrapolated from $ScvO_2$, particularly in the critically ill patients. Correlation between SvO_2 and $ScvO_2$ was also shown to be insufficient in patients with heart failure [61]. Despite these limitations, low $ScvO_2$ may be useful in identifying high-risk patients with myocardial infarction [62], and some have shown that patients with $ScvO_2 < 60\%$ may be used to identify cardiogenic shock in patients with heart failure [63].

Thus, absolute SvO_2 values may not be reliably extrapolated from $ScvO_2$. However, $ScvO_2$ may nonetheless be useful in predicting the changes in SvO_2. Dueck et al. [64] compared the oxyhaemoglobin saturation in blood from the superior vena cava, right atrium and pulmonary artery during varying haemodynamic conditions and suggested that the correlation between changes of oxygen saturation at these sampling sites may be clinically acceptable. Early animal studies by Reinhart et al. showed that changes in $ScvO_2$ closely paralleled changes in SvO_2 in a range of cardiorespiratory conditions such as hypoxia and haemorrhagic shock [65]. Subsequently, the same authors showed that changes in either $ScvO_2$ or SvO_2 of > 5% were rapidly accompanied by similar changes in the same direction in almost 90% of cases (about 10% changed in the opposite direction) [66] in a study of patients in post-operative intensive care unit. These findings suggest that serial monitoring of $ScvO_2$ trend may be useful in tracking potential changes in SvO_2.

In summary, mixed venous oxygen saturation:

1. Should be sampled from the pulmonary artery where venous blood is mixed (but not applicable in the presence of left-to-right intra-cardiac shunting)
2. Can be used to estimate cardiac output if oxygen consumption is known (or estimated)
3. Is related to cardiac output, haemoglobin, arterial oxygen saturation and oxygen consumption, but the relationship with cardiac output is non-linear
4. If reduced, is useful as an indicator of inadequate oxygen delivery, but normal levels may not indicate normal oxygen delivery or utilization
5. If normal or elevated in the presence of tissue hypoperfusion would suggest regional malperfusion, microcirculatory dysfunction or cellular dysoxia

And central venous oxygen saturation:

1. Varies with sampling site, reflecting local oxygen extraction
2. Jugular or subclavian $ScvO_2$ normally lower than SvO_2
3. Generally do not adequately predict the absolute SvO_2, but changes in $ScvO_2$ may parallel changes in SvO_2 in majority of cases
4. Low $ScvO_2$ levels may identify patients with circulatory insufficiency

Discussion

Haemodynamic monitoring is central to the management of patients with cardiogenic shock. Recent physiological studies have shed light on the pathophysiology that underpins these haemodynamic parameters. The physiologic basis of these measurements also explains the apparent paradoxes: Vasoconstriction can simultaneously improve BP and worsen cardiogenic shock due to venoconstriction (reduced venous return) and/or impaired contractile reserve (failure to increase or maintain stroke volume in response to increased volume or afterload); mixed venous oxygen saturation may rise as shock evolves due to microcirculatory and/or cellular abnormalities; and CVP may drop despite poor cardiac function if there is concomitant reduction in stressed volume or increased resistance in venous return. The adverse effects of isolated α-agonists can also be predicted.

Limitations

A number of limitations are noteworthy. Firstly, the haemodynamic parameters discussed in this review have not been evaluated in randomized trials to guide therapeutic interventions in cardiogenic shock. Secondly, the pathophysiology of these haemodynamic parameters has been well studied in septic shock; similar data in cardiogenic shock are limited. Thirdly, a number of parameters have not been included in this review. For example, the veno-arterial carbon dioxide gradient may be

a useful surrogate of blood flow in circulatory shock [67]. The ratio of veno-arterial carbon dioxide gradient to arterio-venous oxygen content difference may detect anaerobic metabolism [68] and has been shown to offer additional pathophysiologic and prognostic information in addition to lactate levels in critically ill patients [69]. The ratio of veno-arterial carbon dioxide gradient to arterio-venous oxygen content difference also appears to be related anaerobic metabolism in cardiogenic shock [70].

Future Directions

Despite the ubiquity of arterial blood pressure and central venous monitoring, these haemodynamic measurements have not been evaluated in cardiogenic shock. For example, the role of arterial blood lactate in sepsis has been evaluated in large clinical trials [71, 72]. Similar studies should be conducted in cardiogenic shock to guide therapeutic interventions, including mechanical circulatory support.

Conclusion

Clinicians use a range of measurements to diagnose and guide interventions in cardiogenic shock. Indications for mechanical circulatory support may be defined: (i) increasing vasopressor for persistent hypotension (MAP < 65 mmHg) that is not accompanied by improvement in cardiac output and organ perfusion (e.g. SvO_2 and lactate); (ii) failure of inotropes to increase cardiac output in the presence of persistent hypotension (MAP < 65 mmHg), left ventricular dysfunction and pulmonary oedema; and (iii) CVP rises with inotrope and vasopressors without improvement in cardiac output or organ perfusion.

Compliance with Ethical Standards

Conflict of Interest Hoong Sern Lim declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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