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ESSENTIALS Cardiovascular dysfunction is common in critically ill patients and is the primary cause of death in a vast array of illnesses. The prompt identification and diagnosis of its probable cause, coupled to ap- propriate resuscitation and (when possible) specific treatments, are cornerstones of intensive care medicine. Cardiovascular monitoring and diagnosis—cardiovascular per- formance can be assessed clinically at the bedside and through haemodynamic monitoring, and with therapeutic or other proactive interventions. Rapid assessment of shocked patients by bedside echocardiography is becoming increasingly popular in those insti- tutions where equipment and expertise are available. Diagnostic approaches or therapies based on data derived from invasive haemodynamic monitoring assume that specific patterns of de- rangement reflect specific disease processes, which will respond to appropriate intervention. Interpretation of haemodynamic variables—the various adaptive cardiovascular controls and varying metabolic demands make rules about specific haemodynamic variables of limited clinical utility. It is simply not possible to say that, when looking after a critically ill patient, the central venous pressure, or any other single measurable variable, must be kept at x or y. Key points in this context are: (1) tachycardia is never a good thing; (2) hypotension is always patho- logical; (3) there is no such thing as a normal cardiac output; (4) cen- tral venous pressure is only elevated in disease; and (5) peripheral oedema is of cosmetic concern. Oxygen delivery—while there is no level of cardiac output which is ‘normal’, there are oxygen delivery thresholds below which normal metabolism can no longer occur. One cardinal sign of increased cir- culatory stress is an increased O2 extraction ratio, which manifests it- self as a decreasing mixed venous O2 saturation (Svo2): a value of less than 70% connotes circulatory stress, less than 60% identifies signifi- cant metabolic limitation, and less than 50%

frank tissue ischaemia. Pathophysiology of shock Circulatory shock can be defined as a decreased effectiveness of cir- culatory blood flow to meet the metabolic demands of the body. Four basic functional aetiologies are recognized. (1) Hypovolaemic shock (e.g. haemorrhage, dehydration)—effective circulating blood volume is inadequate to sustain a level of cardiac output necessary for normal function without supplemental sympa- thetic tone or postural changes to ensure adequate venous return. (2) Cardiogenic shock (e.g. myocardial infarction)—pump dysfunc- tion can be due to either left ventricular or right ventricular failure, or both. Left ventricular failure is usually manifest by an increased left ventricular end-diastolic pressure, left atrial pressure and (by exten- sion) pulmonary artery occlusion ('wedge') pressure, which must exist to sustain an adequate left ventricular stroke volume. (3) Obstructive shock—mechanical obstruction of blood flow (e.g. pulmonary embolism) or of ventricular filling (cardiac tamponade). In the acute setting, neither pulmonary vascular resistance nor mean pulmonary artery pressure need be grossly elevated for right ven- tricular failure to occur. In cardiac tamponade, the cardinal sign is diastolic equalization of all pressures, central venous pressure, pul- monary arterial diastolic pressure, and pulmonary artery occlusion ('wedge') pressure. (4) Distributive shock—loss of blood flow regulation occurs as the end stage of all forms of circulatory shock, but as the initial pre- senting process it is common in sepsis, neurogenic shock, and ad- renal insufficiency. The haemodynamic profile of resuscitated sepsis is one of increased cardiac index, normal pulmonary artery occlusion ('wedge') pressure, elevated Svo2, and a low to normal arterial pres- sure, consistent with loss of peripheral vasomotor tone. Circulatory support of the haemodynamically unstable
patient If the cause of hypotension is intravascular volume loss, either ab- solute or relative, then cerebral and coronary perfusion pressures must be maintained while fluid resuscitation is begun, otherwise car- diac pump failure may develop and limit the effectiveness of fluid resuscitation. Pharmacotherapies for cardiovascular insufficiency—these are directed at the pathophysiological processes that either induce or compound the problem. They can be loosely grouped into one of three types: (1) vasopressor therapy—agents that increase vascular smooth muscle tone include noradrenaline (norepinephrine), adrenaline (epineph- rine), dopamine, and phenylephrine; (2) inotropic support—agents that increase cardiac contractility include dobutamine, dopexamine, levosimendan and phosphodiesterase inhibitors; (3) vasodilator therapy—agents that decrease smooth muscle tone include sodium nitroprusside and glyceryl trinitrate (nitroglycerine). It is important to 17.6 Circulation and circulatory support
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 recognize that most inotropes and vasopressors in clinical use are sym- pathomimetics that have direct effects on the adrenoreceptor system, and there is a quantitatively unpredictable variation in adrenoreceptor density and function in many pathophysiological states, hence agents acting upon them need to be titrated to effect rather than being given at a defined infusion or dose rate. Resuscitation strategies—the only prospective clinical trials documenting benefit from particular interventions were applied early in the course of sepsis or in high-risk surgical patients. However, it makes physiological sense to prevent organ ischaemia by maintaining blood flow, hence the following strategies seem warranted. (1) Loss of vasomotor tone requires both fluid resuscitation to achieve the increased vascular volume needed to restore an effective pressure gradient for venous return, and increased α-adrenergic tone via sympathomimetic agents to restore arterial and venous vaso- motor tone. Targets for resuscitation are an Svo2 greater than 70% with a mean arterial pressure greater than 65 mm Hg. (2) Impaired contractility requires afterload reduction, as toler- ated, up to a decrease in mean arterial pressure

to approximately 70 mm Hg, targeting pulmonary artery occlusion (‘wedge’) pressure (if measured) less than 18 mm Hg and Svo2 greater than 70%. Inotropic support is often required. In sepsis, Svo2 is usually elevated following fluid resuscitation, hence reasonable resuscitation targets are a mean arterial pressure greater than 65 mm Hg and normalizing serum lac- tate concentration. (3) In right ventricular failure, maintaining a mean arterial pressure greater than pulmonary arterial pressure is essential to minimize right ventricular myocardial ischaemia. Introduction Cardiovascular dysfunction is common in critically ill patients and is the primary cause of death in a vast array of illnesses including sepsis, pulmonary embolism, and acute respiratory failure, as well as in those with cardiac disease. The prompt identification of car- diovascular dysfunction, the diagnosis of its probable cause, and ap- propriate specific treatments (when possible) coupled to appropriate resuscitation and restorative management are cornerstones of inten- sive care medicine. Cardiovascular performance can be assessed at the bedside and through haemodynamic monitoring and therapeutic or other pro- active interventions. Diagnostic approaches or therapies based on data derived from invasive haemodynamic monitoring assume that spe- cific patterns of derangement reflect specific disease processes, which will respond to appropriate intervention. Why such constellations of measured abnormalities occur is due to the underlying cardiovascular interactions that define normal and pathological states, hence it is es- sential that the practising clinician be well versed in the underlying principles of cardiovascular physiology and pathophysiology in order to appropriately diagnose and then treat the critically ill. Principles of cardiovascular homeostasis Physicians often consider disease states as involving only one organ, such as the heart, during acute coronary ischaemia or the circulation during haemorrhage. However, no organ system operates in the body without numerous and redundant feedback processes which both amplify and inhibit the specific response of the organ and the rest of the body to stress, disease, and treatment. These interactions form the basis of haemodynamic profile pattern recognition. Specific combinations of changing cardiovascular and metabolic variables better reflect specific disease processes than do individual values for specific variables. Furthermore, the change in these variables in re- sponse to time and treatment define the progression or resolution of disease, its severity, and subsequent responsiveness to therapy. Although specific combinations of haemodynamic variables often reflect certain disease states, there may be considerable overlap of haemodynamic data sets among markedly different pathological states, which may require different therapies. These vagaries reflect individual patient differences, complex cardiovascular interactions not considered in the original logic, and also inaccuracies in the measures themselves and incorrect assumptions as to what the pri- mary force is, and what is its response. This confusion can be minim- ized, however, by performing an experiment at the bedside to force the cardiovascular system into doing one thing or another. This is the essence of a ‘clinical trial’ of positive pressure breathing, passive leg raising, fluid therapy, diuresis, or increased inotropy. Thus, by examining the specific haemodynamic response of the individual to a specific therapy, the clinician at the bedside can gain essential in- sight into the process that is dysfunctional and also tailor therapy to the individual. Let us first consider normal cardiovascular physi- ology, then pathophysiology, and finally how to diagnose and treat. Ventricular pump function Frank–Starling relationship Our understanding of cardiac pump function has evolved greatly since the initial studies of Frank and Starling in the 1890s. Frank, a German physiologist, noted that when cardiac muscle strips were stretched they (unlike skeletal muscle strips) increased their force of contraction. Starling used these data to reason that since the left ventricular (LV) cavity approximated a sphere, increases in LV end- diastolic volume (EDV) should proportionally increase LV myocar- dial fibre stretch. Thus, he explained the observation that the

force of LV contraction was related to left ventricular end-diastolic volume (LVEDV). Based on this construct, increasing left ventricular end- diastolic volume when LV function is normal will increase LV stroke volume and—for a constant heart rate—cardiac output as well. However, if LV pump function is impaired, then for the same in- crease in left ventricular end-diastolic volume stroke volume will not increase as much, if at all. Most studies of ventricular func- tion revolve around LV function, assuming that the right ventricle follows suit. The Frank–Starling relationship is central to most diagnostic and therapeutic protocols used to assess cardiac function. In fact, clinically, the immediate treatment of acute cardiovascular insuffi- ciency and arterial hypotension is to increase intravascular volume. If arterial pressure increases, then the subject is said to be 'preload-responsive' and the presumptive diagnosis of hypovolaemia is made. However, this common therapeutic response of fluid resuscitation will only increase cardiac output in half the patients who are haemo- dynamically unstable, hence understanding better the determinants

17.6 Circulatory support in the critically ill 3883 of cardiovascular insufficiency and how to assess them are important goals in the training of critical care physicians. When modelling LV pump function, one assesses both stroke volume and pressure work, or stroke work, needed to cause that flow. LV stroke volume varies inversely with outflow pressure (ar- terial pressure) for a constant left ventricular end-diastolic volume and LV contractility, whereas stroke work will remain constant. Thus, LV stroke work, rather than stroke volume, is often used to as- sess LV functional status because it is relatively pressure (afterload) independent. If stroke work is less for the same left ventricular end- diastolic volume, then LV contractility is also said to be less under this condition (Fig. 17.6.1). The measure of LV function best used to assess cardiovascular status is highly dependent on the question being asked. If the ques- tion is the adequacy of LV output to meet the metabolic demands of the body, then stroke volume and cardiac output are the relevant measures. However, if the question is 'what is the functional status of the heart, and can it be counted on to sustain blood flow as ejection pressures rise?', which in essence is asking 'what is the level of myo-cardial contractile reserve, independent of the level of blood flow?', then the change in LV stroke work relative to the change in left ven- tricular end-diastolic volume is a better index. LV pressure–volume loop LV pump behaviour is best described using the LV pressure–volume relation, wherein a single cardiac cycle is described as a loop with LV volume on the x-axis and pressure on the y-axis (Fig. 17.6.2). In this construct no time units are used. Filling occurs during diastole when LV chamber pressure decreases to less than left atrial pressure. The slope of the passive LV distention is diastolic compliance. At end- diastole, defined by the electromechanical coupling of contraction, the pressure/volume ratio is at its minimum. This point is often used to assess diastolic compliance, but is influenced by external forces independent of the LV, such as the pericardium, lungs, and right ventricle. Left ventricular end-diastolic volume is synonymous with LV preload as applied to the Frank–Starling relationship. With mechanical contraction, the LV intracavitary pressure rises, forcing mitral valve closure and changing the shape of the LV from an elongated ellipsoid into more of a sphere. As contraction progresses, intracavitary pressure rises as the end-diastolic blood volume is trapped in the LV. Once intracavitary pressure exceeds aortic pressure, the aortic valve passively opens and ejection begins. In a subject with a normal heart, the point where ejection occurs represents the maximal LV wall stress, itself the product of radius of curvature and developed pressure. Thus, diastolic arterial pressure is a major determinant of LV wall stress, and this LV wall stress is the LV afterload. Any therapy which selectively decreases diastolic arterial pressure will then reduce LV afterload more than therapies which selectively decrease systolic arterial pressure. Similarly, if an inovasodilator, such as dopexamine, were given

that decreased left ventricular end-diastolic volume but increased LV stroke volume and ejection pressure, one may erroneously conclude that LV afterload increased, when in fact it decreased. Ejection occurs as LV volume decreases and both LV pressure and aortic pressure rise. Due to the filling characteristics of the aorta, aortic pressure increases most towards the end of ejection as the distensible volume of the aorta is finally reached. Thus, most of the increase in arterial pressure occurs when the LV volume is already small. As a result, the maximal LV wall stress usually occurs at the start of ejection and the LV unloads itself during ejection. That the left ventricle unloads itself during ejection has important clinical implications. First, systolic hypertension is better tolerated without much increase in myocardial oxygen demand (MVo2) than is dia- stolic hypertension. However, if left ventricular end-diastolic volume is increased such that LV volumes do not decrease much during ejection (as is the case in congestive heart failure), then systolic pres- sure will be a major contributor to both LV wall stress and MVO2. Accordingly, in dilated heart failure states, the LV performance is sensitive to changes in systolic arterial pressure, and end-systolic volume (ESV) then is a function of both afterload and contractility. As such, increases in afterload will increase ESV, whereas increases in contractility will decrease ESV. LV relaxation occurs once ejection has finished. Diastolic re- laxation or lusitropy is an energy-dependent process, causes LV intracavitary pressure to decrease faster than would be predicted by passive relaxation alone, and is impaired by myocardial ischaemia. Impaired active diastolic relaxation is the earliest manifestation of myocardial ischaemia and can be readily identified by echocardi-ography and as an S3 gallop on cardiac auscultation. Since coronary artery blood flow occurs primarily in diastole, when LV wall stress is low and perfusion pressure is high, any process which impairs dia- stolic relaxation will decrease coronary blood flow. LV ejection phase indices: Hypereffective Ejection fraction stroke volume stroke work LV dP/dt VCF Preload (end-diastolic volume) Hypoeffective Normal Fig. 17.6.1 Relationship between left ventricular (LV) end-diastolic volume (preload) and LV ejection phase indices, including ejection fraction, stroke volume, stroke work, rate of change of LV pressure
(dP/dt), and velocity of circumferential fibre shortening (VCF). Shown in the example are three curves of varying performance referred to as hypereffective, normal, and hypoeffective performance. Each ejection phase index is affected to a greater or lesser extent by changes in afterload and contractility. Ejection End-systole Aortic valve opening LV volume (ml) LV pressure (mm Hg) Isometric contraction Isometric relaxation Diastolic filling End-diastole Mitral valve opening Fig. 17.6.2 The LV pressure–volume relationship describing all aspects of the cardiac cycle.

Section 17 Critical care medicine 3884 Time-varying elastance The entire LV contractile process can be understood better from the perspective, not of a single pressure–volume loop, but of the pressure–volume domain of contraction. In this context, as time progresses from the start of contraction to end ejection, the left ventricle becomes progressively more stiff (e.g. more elastic), such that the pressure may increase and the volume may decrease inde- pendent of preload and afterload characteristics, but where on the pressure–volume domain this point lies is a function of the stiffness or elastance of the ventricle. Time-varying elastance (E(t)) describes the progressive stiffening through systole and then its relaxation in diastole in the pressure–volume domain. It can be calculated as a plot of the slopes of the isochronic (similar point in time) pressure– volume relations during ejection as end-diastolic volume is rapidly varied (Fig. 17.6.3) by either rapid volume loading or occlusion of venous drainage. The slopes of these sequential pressure–volume lines reflect the obligatory LV pressure–volume domain that must be followed during systole. The end-systolic elastance (Ees) is usually calculated from the re- gression line of the end-systolic

pressure–volume data pairs of re- petitive LV pressure–volume loops, as either preload or afterload are rapidly varied. Ees is also referred to as the LV end-systolic pressure–volume relationship (ESPVR). Maximal elastance (Emax) is the maximal LV pressure–volume ratio and usually occurs just after end-systole due to the inertial and impedance hydrodynamic characteristics of the arterial tree. Increased contractility results in both a more rapid rise of (E(t)) to Ees and a higher Ees value. Using this construct, it becomes clear that the Frank–Starling relationship is the unidimensional description of the mechanical quality of ven- tricular ejection as described by time-varying elastance. Applied cardiac physiology at the bedside The preload-dependent nature of LV performance is central to the understanding of applied cardiac physiology. In fact, documenting that left ventricular end-diastolic volume is above some minimal value, despite cardiac output and stroke work both being depressed, is essential for the diagnosis of cardiac pump dysfunction. Similarly, demonstrating that left ventricular end-diastolic volume is reduced in the setting of haemodynamic instability presumes the diagnosis of inadequate circulating blood volume as the most likely cause of the haemodynamic instability, even though other aetiologies, such as tamponade, cor pulmonale, and restrictive cardiomyopathies can coexist and require different treatments. However, knowing left ventricular end-diastolic volume does not predict if LV stroke volume will increase in response to volume loading. Since a fundamental aspect of haemodynamic monitoring is to predict which patients will be preload-responsive, meaning that their cardiac output will increase in response to a fluid challenge, this lack of concordance between right atrial pressure, pulmonary artery occlusion pressure (‘wedge’ pressure), and even ventricular volumes, and subsequent changes in cardiac output in response to volume challenge can be disquieting. Still, it is a reality. However, there are three techniques of proven utility in defining preload re-sponsiveness: the classic volume challenge, noting the magnitude of (1) the arterial pulse pressure, or (2) left ventricular stroke volume variation during fixed tidal volume positive pressure ventilation, and (3) noting the change in mean cardiac output in response to a passive leg raising manoeuvre. For either pulse pressure variation (PPV, the ratio of maximal minus minimal pulse pressure to mean pulse pressure over five or more breaths) or stroke volume variation (SVV, the ratio of maximal minus minimal stroke volume to mean stroke volume over five or more breaths) to reflect preload respon- siveness, the tidal volume must be fixed during unassisted positive pressure breathing and the sequential R-R intervals must be con- stant (i.e. no arrhythmias). In patients who are breathing spontan- eously, and those with arrhythmias, the mean increase in flow 20 s after a passive leg raising to 30° gives a similar predictive value. In all cases, having a PPV greater than 13% or a SVV or mean increase in flow of more than 10% accurately predicts preload responsiveness as validated by many independent studies. PPV can be measured from the arterial pressure waveform and SVV calculated using numerous devices that assess beat-to-beat stroke volume using the arterial pressure waveform. Arterial pressure and the vascular circuit Organ perfusion is dependent on organ perfusion pressure and local vasomotor tone. Local vasomotor tone varies inversely with local tissue metabolic demand. For most organs, except the kidneys and heart, independent changes in arterial pressure above some min- imal value are associated with increased vasomotor tone to main- tain organ perfusion constant, hence this is essentially independent of cardiac function and cardiac output. In this circumstance, car- diac output is only important to allow parallel circuits to maintain flow without inducing hypotension, and cardiac function is only important in sustaining cardiac output and a given output pressure without causing too high a back pressure in the venous circuits. Operationally, mean arterial pressure (MAP) is the input pres- sure to all organs other than the heart. Diastolic aortic pressure is the input pressure for coronary blood flow. Usually, mean ar- terial pressure is equal to the diastolic pressure plus one-

third the pressure pulse between diastole and systole. If, in a previously nonhypertensive subject, mean arterial pressure decreases below 65 mm Hg, then tissue perfusion will decrease independent of meta- bolic demand. Hypotension directly reduces organ blood flow and is synonymous with cardiovascular instability and is the essence of circulatory shock. However, the assumption is often false that be- cause mean arterial pressure is the major central determinant of LV volume LV pressure 20 ms 40 ms 60 ms 80 ms 100 ms 140 ms 200 ms ESPVR Vo Fig. 17.6.3 Multiple LV pressure–volume relations over time with isochronic pressure–volume domains (time-varying elastance) drawn for all ventricles ending at the end-systolic pressure–volume relationship (ESPVR). Isochronic lines at 20-ms intervals. Note that LV time-varying elastance increases progressively from end diastole to end systole.

 organ perfusion pressure, then organ perfusion must be adequate if mean arterial pressure exceeds some minimal value. Intraorgan vascular resistance and venous outflow pressure are the two other determinants of organ blood flow. Furthermore, in severe stress situations, such as shock states, normal homeostatic mechanisms functioning through carotid body baroreceptors vary arterial vas- cular tone to maintain mean arterial pressure relatively constant despite varying cardiac output, this vasoconstriction being done to maintain cerebral and coronary blood flow at the expense of the remainder of the body. In subjects with normal renal function, im- mediate oliguria is the manifestation of this adaptive response, re- flecting marked reduction in renal blood flow and solute clearance by the kidneys despite persisting normal arterial blood pressure, hence normotension does not ensure haemodynamic sufficiency. Indirect measures of sympathetic tone, such as heart rate, respira- tory rate, and peripheral capillary filling and peripheral cyanosis, are better estimates of cardiovascular status than is mean arterial pressure. Despite the lack of sensitivity of mean arterial pressure to reflect haemodynamic sufficiency, measures of it are essential in the as- sessment and management of haemodynamically unstable subjects for several reasons. Measures that increase mean arterial pressure will also increase organ perfusion pressure. Hypotension causes coronary hypoperfusion, impairing cardiac function and cardiac output. Vasoconstrictor therapies will increase vasomotor tone in nonvital peripheral organs, but will maintain flow to the cerebral and coronary beds. It is also important to remember that the normal mechanism allowing autoregulation of blood flow distribution is local changes in organ inflow resistance, such that organs with in- creased metabolic demand vasodilate to increase their blood flow. If there is hypotension, then local vasodilation will not result in in- creased blood flow because the pressure gradient for that flow will also be reduced. Thus, hypotension impairs autoregulation of blood flow distribution. Vasopressor therapy can reverse systemic hypo- tension, but at a price: the only way that it can increase MAP is by reducing blood flow through vasoconstriction. Importantly, cere- bral and coronary vascular circuits have minimal α-adrenergic re- ceptors so their beds will not constrict. Regrettably, in hypovolaemic states vasopressor support may improve transiently both global blood flow and MAP, but at the expense of worsening local non- vital blood flow and hastening tissue ischaemia. Initial resuscitative efforts should therefore always include an initial volume expansion component and fluid challenge or other diagnostic approaches that identify preload-responsive shock states, before relying on vasopres- sors alone to support the unstable patient. Cardiac output, oxygen delivery, and oxygen consumption To support cellular metabolism, the circulation must deliver ad- equate amounts of oxygen (Do2) and blood flow (cardiac output) to support oxidative phosphorylation. Do2 is the product of cardiac output and arterial O2 content. Within this construct, cardiac output and Do2 are often used interchangeably, primarily because

the greatest gain in Do2 comes from varying cardiac output, not arterial O2 content. However, like all simplification constructs, this one is also limited. Nonmetabolic blood flow, such as renal and splanchnic and skin blood flow, are essential to normal homeostasis. All of these processes need to be maintained under normal conditions and cannot be excluded for long in stress states without inducing marked end-organ dysfunction. Haemodynamic homeostasis Since the primary goal of the cardiorespiratory system is to continu- ously maintain adequate Do2 to meet the metabolic demands of the tissues, how can one assess its adequacy? As described here, neither LV preload nor MAP are sensitive or specific measures of adequacy of cardiovascular function. Although the best measure of circulatory sufficiency is the maintenance of normal bodily functions, this ana- lysis is often difficult to assess accurately at the bedside during states of stress. Furthermore, since metabolic demand can vary widely, there is no value of cardiac output or Do2 that ensures circulatory sufficiency. Under normal conditions, Do2 and metabolic demand vary in parallel. However, as metabolic demands start to exceed Do2 limits, either because of increased metabolic demand (e.g. seizures, fever, fighting the ventilator) or decreased delivery (e.g. circula- tory shock and respiratory failure), the ability of the cardiovascular system to sustain O2 consumption is stressed. One cardinal sign of increased circulatory stress is an increased O2 extraction ratio, which manifests itself as a decreasing mixed venous O2 saturation (Svo2). However, even this concept is useful only in limited conditions. Muscular activity effectively extracts O2 from the blood because of the set-up of the microcirculatory flow patterns and the large concentration of mitochondria in these tis- sues. Thus, normal vigorous muscular activity can be associated with a marked decrease in Svo2 despite a normal circulatory system. Muscular activities, such as moving in bed or being turned, ‘fighting the ventilator’, and breathing spontaneously increase O2 consump- tion. In the patient with an intact and functioning cardiopulmonary apparatus, this will translate into an increase in both Do2 and O2 consumption and a decrease in Svo2. However, in a sedated and ven- tilated patient, Svo2 is a very sensitive marker of circulatory stress. There is no level of cardiac output which is ‘normal’, but there are Do2 thresholds below which normal metabolism can no longer occur. Using Svo2 as a sensitive but nonspecific marker of circula- tory stress, values less than 70% connote circulatory stress, less than 60% identify significant metabolic limitation, and values less than 50% frank tissue ischaemia. The various adaptive cardiovascular controls and varying meta- bolic demands make rules about specific haemodynamic vari- ables of limited clinical utility. It is simply not possible to say that, when looking after a critically ill patient, the central venous pres- sure, or any other single measurable variable, must be kept at x or y. Table 17.6.1 lists some haemodynamic monitoring key points rele- vant to critically ill patients. Pathophysiology of shock The heart, vascular integrity, vasomotor tone, and autonomic con- trol all interact to sustain circulatory sufficiency. Circulatory shock reflects a failure of this system and results in an inadequate perfu- sion of the tissues to meet their metabolic demand, which can lead to cellular dysfunction and death. Numerous disease processes can result in circulatory shock, displaying surprisingly similar gross

 phenotypic expressions despite being caused by divergent processes whose treatments are equally different. Weil and Shubin defined circulatory shock in 1968 as a decreased effectiveness of circulatory blood flow to meet the metabolic de- mands of the body. Four basic functional aetiologies of circulatory shock can be defined: (1) hypovolaemic, due to inadequate venous return (haemorrhage, dehydration); (2) cardiogenic, due to inad- equate ventricular pump function (myocardial infarction); (3) ob- structive, due to vascular obliteration (pulmonary embolism or tamponade); and (4) distributive, due to loss of vasoregulatory con- trol

(sepsis). Tissue hypoperfusion is common in all forms of shock, with the possible exception of hyperdynamic septic shock. This results in tissue hypoxia and associated hyperlactataemia and metabolic acidosis. However, hyperlactacidaemia, per se, is not a marker of ongoing tissue hypoperfusion because lactate clearance is often de- layed or impaired in shock states, and processes such as exercise (seizure activity) can induce hyperlactacidaemia without cardio-vascular insufficiency. Sustained circulatory shock results in cellular damage, not from anaerobic metabolism, but from an inability to sustain intermediary metabolism and enzyme production necessary to drive normal mitochondrial performance. Metabolic failure due to sustained tissue hypoxia may explain why preoptimization and early goal-directed therapy can improve outcome, whereas aggres- sive resuscitation after injury is not effective at reducing mortality from a variety of insults. As stated here, measures of cardiac output, mean arterial pres- sure, and their changes in response to both shock and its treatment poorly reflect both regional and microcirculatory blood flow. Since most forms of haemodynamic monitoring measure global param- eters like arterial pressure, heart rate, other vascular pressures, and cardiac output, it is clear that assessment of severity of shock and its initial response to therapy is often limited if monitoring is limited to these variables alone. Potentially, measuring Svo2 or the differ- ence between tissue Pco2 and arterial Pco2, referred to as the Pco2 gap, would allow one to assess effective tissue blood flow since de-creases in capillary blood flow initially causes CO2 from aerobic metabolism to accumulate. Gastric tonometry describing Pco2 gaps identifies gastric ischaemia and may be useful in guiding resuscita- tion in critically ill patients: sublingual Pco2 gaps are much easier to measure and offer a readily simple bedside monitoring approach. However, gastric tonometry is confounded by CO2 production from nonoxidative phosphorylation, and sublingual Pco2 is not yet valid- ated as a routine measure. Thus, at the present time, characteristic groupings of abnormalities of global measures of circulatory func- tion are often used to determine which of the four shock categories is the most likely cause of organ dysfunction; this is referred to as haemodynamic profile analysis. More recently the availability in many countries of relatively simple and portable cardiac ultrasound machines, combined with formalized training programmes, has resulted in widespread use of rapid bedside echocardiography in the initial and ongoing as- sessment of shocked patients. Echocardiography can be used to decide when fluid resuscitation should be stopped, for example, if there is evidence of right ventricular overload (e.g. paradoxical septal shift, increased tricuspid regurgitation). Echocardiographic imaging can quantify both right and left ventricular contractility, the presence of mechanical causes of cardiac pump failure (e.g. pericardial effusion and tamponade, acute and severe valvular dis- ease, acute right ventricular dilatation and failure due to massive pulmonary emboli). Hypovolaemic shock Hypovolaemia is the cardiovascular state in which the effective cir- culating blood volume is inadequate to sustain a level of cardiac output necessary for normal function without supplemental sym- pathetic tone or postural changes to ensure adequate venous return. It is a relative process and can occur through absolute blood loss as with haemorrhage, or fluid and electrolyte loss, as with massive diuresis, diarrhoea, vomiting, or evaporation from large burn sur- faces. The normal reflex response to hypovolaemia is increased sym- pathetic tone, vasoconstriction, and tachycardia. Cardiac output is often sustained by these mechanisms such that heart rate is in- creased and stroke volume decreased, whereas blood flow distribu- tion is diverted away from the skin, resting muscles, and gut. Lactic acidosis develops and has been considered as a marker of tissue an- aerobic metabolism, although increased lactate production due to β-adrenergic stimulation may be the dominant or only mechanism. Thus, hypovolaemia initiates as tachycardia, reduced arterial pulse pressure, and (often) hypertension with a near normal resting car- diac output, followed by signs of organ hypoperfusion (oliguria,

confusion) as cardiac output decreases. Systemic hypotension is the final presentation of hypovolaemic shock and—if the clinician waits for this before acting—ischaemic tissue injury is almost always present. Table 17.6.1 The critically ill patient: haemodynamic monitoring key points Key point Explanation Tachycardia is never a good thing Tachycardia defines stress or an adaptation to stress. It may be necessary to sustain adequate blood flow, as in heart failure, but it still reflects heart failure. Hypotension is always pathological Hypotension impairs blood flow distribution and thus any patient with a MAP <65 mm Hg is impaired. They may have hepatic cirrhosis with adequate tissue blood flow at rest, but they have a markedly limited ability to adapt to increased metabolic demand. There is no such thing as a normal cardiac output Since blood flow is regulated to meet the metabolic demand of the body, and that metabolic demand can vary widely and rapidly, there is no value of total cardiac output that guarantees adequate tissue perfusion. Blood flow is either adequate or inadequate, no matter what the absolute value is. Central venous pressure is only elevated in disease Under most conditions, the central venous pressure is very close to zero as the heart pumps all venous return immediately back to the body. The CVP will rise if either right or left sided heart failure develops, or fluid overload (e.g. renal failure or iatrogenic). The presence of an elevated CVP before medical intervention connotes disease of some sort. Peripheral oedema is of cosmetic concern Tissue perfusion is independent of interstitial fluid accumulation. Since the primary concern is maintenance of organ perfusion, which requires an adequate venous return and MAP, restricting fluid resuscitation in an unstable patient because of peripheral oedema is illogical and should be avoided. CVP, central venous pressure; MAP, mean arterial pressure.

17.6 Circulatory support in the critically ill 3887 Cardiogenic shock Cardiac pump dysfunction can be due to either LV or right ven- tricular (RV) failure, or both. LV failure, as just described, is usually manifest by an increased LV end-diastolic pressure, left atrial pressure, and (by extension) pulmonary artery occlusion (‘wedge’) pressure, which must exist to sustain an adequate LV stroke volume. Tachycardia is universal in the patient who is not β-blocked. The most common cause of isolated LV failure in a critically ill patient is acute myocardial infarction. Usually, LV stroke work is re- duced and heart rate increased. In chronic heart failure both car- diac output and systemic vasomotor tone may be normal, whereas in acute LV failure states both may be reduced. These combined haemodynamic interactions lead Forrester and colleagues to use a pulmonary artery occlusion (‘wedge’) pressure of 18 mm Hg and a cardiac index of 2.2 as the cut-off to define heart failure states fol- lowing acute myocardial infarction. However, neither cardiac output nor systemic vascular resistance is a sensitive marker of LV failure until cardiogenic shock develops. Since pulmonary artery occlusion (‘wedge’) pressure is the back pressure to pulmonary blood flow, increases associated with LV failure may lead to pulmonary oedema and hypoxaemia, and secondary pulmonary hypertension may sub- sequently impair RV ejection, inducing biventricular failure, peripheral venous hypertension, and peripheral oedema formation, the so-called ‘backward failure’. The normal adaptive response of the host to impaired LV con- tractile function is to increase sympathetic tone, induce tachycardia, activate the renin-angiotensin system, retain sodium by the kid- neys, and thus increase the circulating blood volume. Fluid reten- tion takes time, whereas acute impairments of LV contractility can occur over seconds in response to myocardial ischaemia. Thus, the haemodynamic profile of acute and chronic LV failure can be dif- ferent. Acute LV failure is manifest by increased sympathetic tone (tachycardia, hypertension), impaired LV function (increased filling pressure and reduced stroke volume), with minimal RV ef- fects (normal central venous pressure), and increased O_2 extrac- tion manifest by a low Svo_2. Cardiac output need not

be reduced and may in fact be elevated, owing to the release of catecholamines as part of the acute stress response; vascular resistance is increased. By contrast, in chronic heart failure, although sympathetic tone is elevated, the heart rate is rarely over 105/min, and filling pressures are elevated in both ventricles consistent with combined LV failure and fluid retention. Again, cardiac output is not reduced except in severe heart failure states, but a cardinal finding is the inability of the heart to increase output in response to a volume load or metabolic stress (exercise). Furthermore, owing to the increased sympathetic tone, splanchnic and renal blood flows are reduced and can lead to splanchnic or renal ischaemia. Obstructive shock Obstruction in this context means mechanical obstruction of blood flow or ventricular filling. The most common cause of obstructive shock is pulmonary embolism leading to acute RV failure, but iso- lated RV dysfunction can occur in the setting of an acute inferior wall myocardial infarction, also as a consequence of pulmonary vascular disease (chronic obstructive pulmonary disease, primary pulmonary hypertension). Acute RV distension and failure due to massive pulmonary embolism has a characteristic appearance, and bedside echocardiography aids in rapid diagnosis and decision-making about treatment (Fig. 17.6.4 and 17.6.5). When RV dys- function predominates and is induced by pulmonary parenchymal disease, it is referred to as cor pulmonale, which is associated with signs of backward failure, elevated RV volume and pressures, sys- temic venous hypertension, low cardiac output, as well as reduced renal and hepatic blood flow. LV diastolic compliance decreases as the right ventricle dilates due to ventricular interdependence, either from intraventricular septal shift or absolute limitation of biventricular volume due to pericardial restraint. Thus, pulmonary Fig. 17.6.4 Transthoracic echocardiogram of acute pulmonary embolism. A four chamber view reveals a dilated right heart. The echo- free space in front of the heart represents a pericardial fat pad. PF, pericardial fat; RA, right atrium; RV, right ventricle. From Galiuto et al. (ed) (2011). The EAE Textbook of Echocardiography. © European Society of Cardiology, by permission of Oxford University Press. Fig. 17.6.5 Transthoracic echocardiogram of acute pulmonary embolism. Cross-section of the right pulmonary artery from the suprasternal view reveals masses in the lumen, consistent with thrombi (arrow). Ao, aorta; RPA, right pulmonary artery. From Galiuto et al. (ed) (2011). The EAE Textbook of Echocardiography. © European Society of Cardiology, by permission of Oxford University Press.

Section 17 Critical care medicine 3888 artery occlusion (‘wedge’) pressure is often elevated for a specific LV stroke work, giving the erroneous appearance of impaired LV con- tractility, but if left ventricular end-diastolic volume were measured, it is possible that no change in LV function would be seen if this were plotted against LV stroke work. Neither pulmonary vascular resistance nor mean pulmonary ar- tery pressure need be grossly elevated for RV failure to be present. Indeed, and importantly, if pulmonary arterial pressures are greater than 30–35 mm Hg, then pulmonary hypertension is probably chronic in nature because acute elevations of pulmonary arterial pressures above this level are not consistent with life. Elevations in central venous pressure of more than 12 mm Hg also reflect fluid retention, suggesting further that there is a state of compensated RV failure. Cardiac tamponade can occur from either (1) ventricular dilation limiting biventricular filling due to pericardial volume limitation, (2) acute pericardial effusion due to either fluid (inflammation) or blood (haemorrhage), which needs not be great in quantity, and (3) hyperinflation, which can act like pericardial tamponade to limit biventricular filling. The first two aetiologies are rarely seen, whereas the third commonly occurs. The cardinal sign of tamponade is dia- stolic equalization of all pressures, central venous pressure, pul- monary arterial diastolic pressure, and pulmonary artery occlusion (‘wedge’) pressure. Since RV compliance is

greater than LV compli- ance, early on in tamponade there may be selective reduction in RV filling. The presence of a pericardial effusion is often obvious on bed- side echocardiography (Fig. 17.6.6). Distributive shock Loss of blood flow regulation occurs as the end stage of all forms of circulatory shock, but as the initial presenting process it is common in sepsis, neurogenic shock, and adrenal insufficiency. Sepsis is a sys- temic process characterized by activation of the inflammatory medi- ators and generalized endothelial injury, but it is not clear that tissue ischaemia is an early aspect of this process. At its onset, sepsis is as- sociated with increased sympathetic activity (tachycardia, diaphor- esis) and increased capillary leak with loss of intravascular volume. Before fluid resuscitation this combination of processes resembles simple hypovolaemia, with decreased cardiac output, normal to in- creased peripheral vasomotor tone, and very low Svo2, reflecting systemic hypoperfusion. LV function is often depressed, but only in parallel with depression of other organs, and this effect of sepsis is usually masked by the associated hypotension that maintains low LV afterload. However, most patients with such a clinical presentation receive fluid resuscitation, after which the clinical picture of resusci- tated sepsis is a hyperdynamic state rather than hypovolaemia; this has been referred to as ‘warm shock’ in contrast to all other forms of shock. The haemodynamic profile of sepsis is one of increased car- diac index, normal pulmonary artery occlusion (‘wedge’) pressure, elevated Svo2, and a low to normal arterial pressure, consistent with loss of peripheral vasomotor tone. Acute spinal injury, spinal anaesthesia, general anaesthesia, and central nervous system catastrophe all induce a loss of sympa- thetic tone. The resulting hypotension is often not associated with compensatory tachycardia, hence systemic hypotension can be profound and precipitate cerebral vascular insufficiency and myo- cardial ischaemia. Since neurogenic shock reduces sympathetic tone, biventricular filling pressures, arterial pressure, and cardiac output all decrease. Treatment consists of reversing the primary pro- cess and supporting the circulation with infusion of an α-adrenergic agonist, such as phenylephrine or noradrenaline. Acute adrenal insufficiency can present with hyperpyrexia and circulatory collapse. This is more common than might be guessed, based on the epidemiology of adrenal cortical disease, because many patients are receiving chronic corticocosteroid therapy for the management of systemic and localized inflammatory states, such as asthma or rheumatoid arthritis, and in such cases the added stress of trauma, surgery, or infection can precipitate sec- ondary adrenal insufficiency, as can the abrupt discontinuation of long-term steroid treatment. Presentation is with nausea and vomiting, diarrhoea, confusion, hypotension, and tachycardia. Cardiovascular collapse is similar to that seen in neurogenic shock, except that the vasculature is not as responsive to sym- pathomimetic support. Accordingly, failure to respond to vaso- active pharmacological support in a patient who is hypotensive should suggest the diagnosis of adrenal insufficiency, when giving stress doses of corticosteroids usually reverses the unresponsive nature of the shock process. Circulatory support of the haemodynamically unstable patient If the cause of hypotension is intravascular volume loss, either ab- solute, as would occur with haemorrhage or massive diarrhoea, or relative, as would occur with loss of vasomotor tone or increased capillary endothelial permeability, then cerebral and coronary per- fusion pressures must be maintained while fluid resuscitation is begun, otherwise cardiac pump failure may develop and limit the effectiveness of fluid resuscitation. Infusions of vasoactive agents will increase both cardiac output and mean arterial pressure at the expense of the remaining vascular beds, hence fluid resuscitation to achieve an adequate intravascular blood volume is essential for Fig. 17.6.6 Transthoracic echocardiogram of cardiac tamponade. A parasternal short-axis view demonstrates a large amount of pericardial fluid and diastolic right ventricular collapse, indicating tamponade physiology. Ao, aorta; PE, pericardial effusion; RV, right ventricle. From Galiuto et al. (ed) (2011).

17.6 Circulatory support in the critically ill 3889 sustaining isolated vasopressor therapy in the setting of systemic hypotension. Many pathological states and acute stress conditions are associated with either adrenergic exhaustion or blunted respon- siveness to otherwise adequate circulating levels of catecholamines (e.g. diabetes, adrenal insufficiency, hypothermia, hypoglycaemia, and hypothyroidism). Furthermore, acute sepsis and systemic in- flammation are associated with reduced adrenergic responsiveness. Thus, even if the host makes an otherwise adequate sympathetic re- sponse, the vasomotor and inotropic response may be inadequate, requiring transient use of potent sympathomimetic agents to sustain cardiovascular homeostasis. Pharmacotherapy for cardiovascular insufficiency is directed at the pathophysiological processes that either induce or com- pound it. These therapies can be loosely grouped into one of three processes: (1) those that increase vascular smooth muscle tone (vasopressor therapy); (2) those that increase cardiac contractility (inotropic support); and (3) those that decrease smooth muscle tone (vasodilator therapy). Infusion of vasopressor agents are indicated to sustain a MAP greater than 60 mm Hg to prevent coronary or cerebral ischaemia, while other resuscitative measures, like volume resuscitation, and specific treatment of the underlying condition are ongoing. This level of MAP is clearly arbitrary since some patients maintain adequate coronary and cerebral blood flow at lower MAP levels, whereas others—notably those with either pre-existent sys- temic hypertension or atherosclerotic cerebrovascular disease—may not tolerate MAP decreasing more than 30 mm Hg from their base- line values. Once an adequate MAP has been achieved and intra- vascular volume losses corrected, care shifts towards maintaining adequate blood flow to metabolically active tissues to sustain organ performance. Several recent studies have underscored the principles described here. Three large prospective randomized trials comparing early goal-directed therapy (EGDT based on targeting ScvO2) to usual care reported that standard care based on maintaining good fluid resuscitation and bedside assessment was as good as targeted EGDT, and mortality rates were lower than predicted from historical con- trols. Similarly, a large prospective study showed that in previously nonhypertensive patients, targeting a mean arterial pressure of 65–75 mm Hg was as good if not better than targeting a mean ar- terial pressure 80–85 mm Hg. Finally, a large retrospective study of Australia and New Zealand ICU care from 2000 to 2012 demon- strated a clear progressive decline in mortality in all patient groups over this period with equal trends across all age groups and treat- ment settings. These progressive improvements in clinical outcomes have occurred without the use of new and proven treatment modal- ities. Thus, attention to detail, preventing complications, and with- drawing unneeded therapies and instrumentation reflect the new standard for patient care. Adrenergic receptor physiology and the role of vasopressin Most inotropes and vasopressors in clinical use are sympatho- mimetics that have direct effects on the adrenoreceptor system. Adrenoreceptors are complex membrane glycoproteins whose intracellular signal transduction is commonly, although not ex- clusively, mediated through G proteins and adenylate cyclase in an amplification-type system. Adrenoreceptors are classic- ally subtyped into six functional classes: myocardial β1 and smooth muscular β2, postsynaptic α1 and dopamine1 (DA1), and presynaptic α2 and DA2. Despite several recent reports indicating that there are more classes of adrenoreceptors, conceptually the six subtypes serve clinicians well, with most functional issues relating only to α and β adrenergic receptor modulation. Importantly, there is a quantitatively unpredictable variation in adrenoreceptor density and function in many pathophysiological states, hence agents acting upon

them need to be titrated to effect rather than being given at a defined infusion or dose rate. Vasopressor agents Phenylephrine The only noncatecholamine sympathomimetic used, phenylephrine differs chemically from other sympathomimetics by the absence of a hydroxyl group on position 4 of the benzene ring. This deletion reduces its potency relative to other sympathomimetics. It acts as a moderately potent α1-agonist and is used in those patients in whom hypotension is due to decreased arterial elastance (it only activates β-adrenoreceptors at high doses). A modest direct coronary vasoconstrictor effect appears to be offset by autoregulatory mechanisms in the absence of flow-limiting coronary disease. It is not metabolized by catecholamine O-methyltransferase (COMT), which metabolizes catecholamines, and therefore its absolute half-life is considerably longer than catecholamine sympathomimetics. Noradrenaline (norepinephrine) Noradrenaline has significant activity at α and β1-adrenoreceptors, resulting in a positive vasoconstrictor and inotropic effect. Its β1 activity makes it the α1-agonist of choice in patients with hypotension and known LV dysfunction. Its positive vasopressor effect may enhance renal perfusion and indices of renal function in haemodynamically stable patients, and this effect may also be seen at higher doses when noradrenaline is used as a vasopressor in those with sepsis. Both observations are likely related to elevation of MAP, the input pressure for organ perfusion. Adrenaline (epinephrine) Adrenaline is a very potent catecholamine sympathomimetic that has markedly increased β2-adrenoreceptor activity compared with its molecular substrate, noradrenaline. Adrenaline has potent chronotropic, inotropic, β2-vasodilatory, and α1-vasoconstrictor properties. Its net vasopressor effect is the end result of the balance between adrenaline-mediated β2 and α1 adrenoreceptor stimulation. At low doses this balance may result in no net pressor effect, with a fall in the diastolic blood pressure. Additionally adrenaline, unlike noradrenaline, has marked metabolic effects mediated through β2-adrenoreceptor stimulation that includes inducing a transitory, but apparently harmless, hyperlactataemia. Clearance rates are variable and mediated by both the COMT and monoamine oxidase systems. Vasopressin Vasopressin exerts its vasomotor effects by stimulating V1 receptors to cause an increase in intracellular calcium, and by potentiating the effects of β adrenergic receptor stimulation. In normal conditions the vasomotor effect is weak, but in shocked states—especially in septic shock, when vasopressin desensitization commonly occurs—vasopressin may act as a powerful vasopressor. In many

 pressor-dependent patients with septic shock, adding low-dose arginine vasopressin (0.01–0.02 μg/kg/min) may markedly improve the patient's vascular responsiveness. Indeed, several authors in this field recommend that when vasopressors are withdrawn in patients treated with norepinephrine and vasopressin, that the norepinephrine be decreased first as the vasopressin is acting more like a stress hormone than an actual vasopressor. This is an important concept, because if vasopressin is given in higher doses it may cause profound vasoconstriction on its own, and indeed it is used for this purpose as a treatment to cause splanchnic ischaemia in oesophageal variceal bleeding. Whether the addition of vasopressin to norepinephrine, or use of vasopressin instead of norepinephrine, results in improved outcomes in patients with septic shock has been investigated in blinded randomized trials. These have shown no significant difference in organ dysfunction, mortality, or adverse events, suggesting that while vasopressin is as safe as norepinephrine, it has not yet been proven to be superior. Further investigation of arginine vasopressin and vasopressin analogues is ongoing. Dopamine Dopamine is the most controversial of the clinically utilized catecholamine sympathomimetics. This stems largely from claims for selective, dose-dependent, splanchnic, and renovascular vasodilatory

properties. Its dopaminergic properties do not reduce the incidence of renal failure in patients with shock when compared to noradren- aline. Dopamine stimulates the release of noradrenaline from sym- pathetic nerve terminals in a dose-dependent manner, with this indirect noradrenaline effect accounting for up to half of dopamine's clinically observed physiological activity. Cardiomyocyte noradren- aline stores are finite, accounting for tachyphylaxis to the positive inotropic effects of dopamine observed after approximately 24 h in patients with acute myocardial infarction. Recent clinical trials have compared the effect of dopamine versus noradrenaline as first line agents for the treatment of shock. Dopamine use resulted in no survival benefit overall, an increased incidence of cardiac arrhyth- mias, and it may increase mortality in patients with cardiogenic shock. As a result of these findings, dopamine is now much less com- monly used than in the past. Synthetic angiotensin II Recently synthetic human angiotensin II has been licensed for use in humans after it was shown to increase blood pressure in a trial in adult patients with vasodilated shock who were being treated with high-dose noradrenaline or equivalent vasopressors. The trial was not designed to assess important patient centred outcomes but reported no significant difference in adverse events or mortality. Whether adding angiotensin II as an alternative or supplementary vasopressor improves outcomes for critically ill patients requires further study. Inotropic agents Dobutamine Dobutamine is a synthetic analogue of dopamine. It is adminis- tered by continuous intravenous infusion as a positive inotrope, with the improvement in cardiac output noted to potentially in- crease renal blood flow, creatinine clearance, and urine output. As a β1-agonist it will increase myocardial oxygen consumption, although autoregulatory increases in coronary blood flow usually fully compensate in the absence of flow-limiting coronary artery disease. A noted problem with dobutamine is the development of tachyphylaxis with prolonged (as little as 72 h) infusions, suggested to be due to the down-regulation of β1-adrenoreceptors. Dopexamine Dopexamine is a synthetic dopamine analogue with significant β2- adrenoreceptor agonist activity. Its splanchnic blood flow effects and positive inotropic activity have led to enthusiasm for potential utility outside its primary indication, acute heart failure syndromes with hypertension and oliguria. Randomized controlled clinical inves- tigations have demonstrated improvement in morbidity and mor- tality outcomes when dopexamine was used as the pharmaceutical of choice in achieving goal-oriented oxygen delivery values in peri- operative critically ill patients. Phosphodiesterase inhibitors These agents are variably used in the management of circula- tory shock, with the two most commonly employed agents in this class being amrinone and milrinone. Both are bipyridines, and the class of drugs is otherwise known as 'inodilators', with reference to the two predominant dose-dependent modes of action iden- tified. Conventional wisdom is that these agents are much more potent vasodilators than inotropes, with the difference in potency approaching 10–100-fold. Milrinone has a shorter half-life and is a more potent (10–15-fold) inotropic agent than amrinone, but from all other aspects they are similar agents. Both are eliminated by conjugation, with amrinone's biological half-life known to be extended in the presence of congestive heart failure. Their mech- anism of action is not precisely known, but at least part of their ac- tivity is related to inhibition of phosphodiesterase type 3, found in high concentrations in cardiomyocytes and smooth muscle cells, and they may activate a sodium-dependent calcium channel. The end result is an increase in intracellular cAMP and calcium, with the physiological effect being an improvement in diastolic myocar- dial function, and for this reason these agents are felt to be posi- tive lusiotropes. Clinically, they are used as positive inotropes, given by continuous intravenous infusion following a loading dose, with their catecholamine-independent mechanism of action making them theoretically attractive as inotropic support of choice in pa- tients with potential β1-adrenoreceptor down-regulation. Levosimendan

Levosimendan is a calcium sensitizing agent that has positive ino- tropic effects and additionally causes vasodilatation by acting on vascular ATP-dependent potassium channels. Because its action is distal to calcium flux, there is no increased cardiac muscle oxygen demand. This feature is attractive in managing cardiac failure states in which coronary blood flow is either limited or cannot increase further. Levosimendan has been compared to dobutamine in pa- tients with severe low output heart failure, and in this patient group it provides no clear mortality benefit. Some trials have shown ad- vantage over dobutamine in other critically ill patients, but a limi- tation is that levosimendan's action requires its uptake into the cell and thus it has a slower onset of action and longer wash-out time compared with catecholamines and other agents, making it

 less titratable, and limiting its use in acute care situations. In pa- tients with sepsis, a recent well-conducted trial found that adding levosimendan to standard care decreased neither severity of organ dysfunction or risk of death, reduced the likelihood of suc- cessful weaning from mechanical ventilation, and increased risk of supraventricular arrhythmias. Vasodilators Afterload reducing vasodilators act via vascular smooth muscle re- laxation. Vascular dilatation is mediated by both nitric oxide (NO) and non-NO-based mechanisms, nitric oxide being a powerful, lo- cally acting vascular smooth muscle relaxant. Among commonly used vasodilators in haemodynamically unstable patients, both sodium nitroprusside and glyceryl trinitrate (nitroglycerine) func- tion as nitric oxide donors. Numerous other nonnitric oxide donor vasodilating agents are available, with hydralazine, clonidine, and inhibitors of the renin-angiotensin system being the most com- monly employed nonnitric oxide-based vasodilators in patients with cardiovascular instability. A simple approach to the pharmacotherapy of circulatory shock Loss of vasomotor tone requires both fluid resuscitation to achieve the increased vascular volume needed to restore effective venous re- turn, and increased α-adrenergic tone, usually via sympathomimetic agents, to restore arterial and venous vasomotor tone. Accepted targets for resuscitation are an Svo2 greater than 70% with a mean arterial pressure greater than 65 mm Hg. Impaired contractility re- quires afterload reduction, as tolerated, up to a decrease in mean ar- terial pressure to approximately 70 mm Hg, targeting an Svo2 greater than 70%. Since pulmonary arterial catheterization is now used less often, bedside echocardiographic evaluations are often substituted for it. Fluid resuscitation should be stopped if there is echocardio- graphic evidence of right ventricular overload (e.g. paradoxical septal shift, increased tricuspid regurgitation). Echocardiography can quantify both right and left ventricular contractility, the pres- ence of mechanical causes of cardiac pump failure (e.g. pericardial effusion and tamponade, severe valve disease, acute right or left ven- tricular failure). In sepsis, Svo2 is usually elevated following fluid resuscitation, hence resuscitation usually focus on restoration of end-organ function (e.g. urine output, improved sensorium) with individualization of resuscitation to achieve adequate end-organ perfusion pressure and the absence of evidence of hypoperfusion. Regrettably, the only prospective clinical trials documenting benefit from such resuscitation strategies were applied early in the course of sepsis or in high-risk surgical patients. However, it makes physio- logical sense to prevent organ ischaemia by maintaining adequate blood flow, hence strategies such as those described here are war- ranted while awaiting confirmation through the conduct of ran- domized trials. FURTHER READING Angus DC, et al. (2015). A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. Intensive Care Med, 41, 1549–60. Annane D, et al. (2007). Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. Lancet, 370, 676–84. Bellomo R, et al. (2000). Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care

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