Hemodynamic Monitoring and Resuscitation

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Introduction

Shock is a life-threatening condition that results from inadequate tissue blood flow to maintain homeostasis. Shock results from a reduction in cardiac output (CO) due to loss of circulating volume, a dysfunctional vascular network, or cardiac pump failure. Shock is traditionally classified as hypovolemic (absolute – due to blood or fluid loss, relative due to maldistribution of fluid within the body), cardiogenic (due to a loss of inotropy, atrioventricular synchrony, valvular insufficiency, or ventricular interdependence), vasoplegic (due to sepsis, anaphylaxis, or brain/spinal cord injury (neurogenic)), and obstructive (due to obstruction of the circulation – abdominal compartment syndrome, pericardial tamponade, tension pneumothorax, pulmonary embolism, or valvular stenosis). Critically ill patients frequently present with shock, often from multiple causes, for example, a patient septic shock complicated by abdominal compartment syndrome secondary to fluid overload. Hypotension is not necessary to diagnose shock [1]. This chapter will look at commonly encountered mechanisms of shock and methods employed to diagnose and manage them.

Injury Stress and Fluid Loss

Regardless of the mechanism of injury, patients presenting in shock will manifest clinical signs of the "stress response," a neurohormonal host reaction to injury driven by cortisol and catecholamines and characterized by dramatic changes in fluid and electrolyte distribution in the various spaces within the body. These changes are predictable and follow a characteristic pattern described by Cuthbertson and Tilstone [2] and Moore [3, 4]. An understanding of this process is central to understanding the dynamics of fluid and electrolyte flux in critical illness, and surgical critical care is helpful in guiding therapy.

The stress response has traditionally been described as a biphasic "Ebb and Flow" process. Initially, after an injury or surgical incision, there is a dramatic increase in circulating catecholamine levels. At rest approximately 30% of blood volume is active in the circulation, typically referred to as the "stressed" blood volume. The remainder, pooled in the extremities and splanchnic beds, is referred to as "unstressed" [5]. In situations where blood is lost, there is widespread vasoconstriction of the extremities and the splanchnic bed, and the unstressed volume is mobilized. Blood is principally redistributed into the heart and brain [6]. There is a reduction in blood flow to the intestines, kidney, and liver.

The EBB phase is associated with a reduction in body temperature and an increased peripheral to core temperature gradient. There is a fall in capillary hydrostatic pressure, promoting a rapid shift of protein-free fluid from the interstitium into the capillaries [7]. This is known as "transcapillary refill" [6]. The result is extravascular volume contraction and compensated hypovolemia associated with a dramatic increase in the release of vasopressin (antidiuretic hormone) and activation of the renin-angiotensin-aldosterone system that conserves salt and water. Of note, the mobilization of unstressed blood functions as a form of physiologic reserve, with the result that static measures of circulating volume such as mean arterial pressure, central venous, and pulmonary artery pressure, may fail to identify hypovolemia [5].

The stress response progresses to the hypermetabolic "flow" phase, within hours or following initiation of fluid resuscitation. This is characterized by a dramatic increase in cardiac output, manifest by tachycardia, driven by catecholamines, peripheral vasodilatation, localized or systemic

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capillary leak, and increased core temperature. This is associated elevated circulating cortisol and insulin resistance resulting in hyperglycemia and visceral and systemic protein catabolism. There is increased oxygen extraction in the extremities and elevated serum lactate as a result of increased glycolysis, secondary reduced oxygen delivery and/or increased beta-adrenoceptor activation, and reduced metabolism [8].

The magnitude of the stress response is proportional to the degree of tissue injury or extent of surgery. Significant intracellular fluid deficit may be incurred to maintain circulating volume. Sacral and extremity edema may be present, due to increased capillary permeability. Urinary output falls due to neurohormonal factors and reduced renal perfusion pressure. There is intravascular dehydration secondary to vasodilatation. During this period, patients are typically administered resuscitation fluids to maintain blood pressure, circulating volume, and tissue perfusion. Weight gain ensues and tissue edema worsens. Serum albumin falls in proportion to degree of injury and volume of fluid administered. Depending on the composition of the resuscitation fluids administered, patients typically develop varying levels of hypernatremia and hyperchloremia [9].

Eventually a state of equilibrium arrives, usually day 2 postoperatively or when source control has been achieved, when active extravascular fluid sequestration stops. Subsequently, the patient progresses to a "diuresis" phase, during which the patient mobilizes fluid and recovers. This is known as "deresuscitation." Serum albumin levels recover. Intracellular fluid volume returns to normal, associated with a significant inward shift of ions such as potassium, magnesium, and phosphate. Consequently, hypokalemia, hypomagnesemia, and hypophosphatemia occur at this time, and electrolyte supplementation is usually necessary. Time to recovery and deresuscitation may be influenced by the volume of fluid administered to the patient during critical illness and the quantity of solute (principally sodium and chloride) that must be excreted.

Each stage of the stress response requires a thoughtful approach to the positive and negative impact of fluid resuscitation. Under-resuscitation may result in tissue hypoperfusion and organ injury. Over resuscitation may lead to edema in highly perfused tissues such as the lungs and bowel, resulting in respiratory failure, wound dehiscence, and abdominal compartment syndrome [10, 11]. Failure to mobilize resuscitation fluids and electrolytes may result in prolonged dependence on mechanical ventilation, failure to mobilize, and ileus.

The critical care practitioner may encounter the shocked patient either in the ebb or flow phase, as a result of the patient triggering physiological limits of an early warning system in the hospital. The patient may be symptomatic with hypotension, tachycardia, tachypnea, altered level of consciousness, hypoxemia, or oliguria. In each scenario, the patient requires a full clinical examination, intravenous access, noninvasive blood pressure monitoring, and labs to include complete blood count, serum chemistry, troponin, and a venous lactate level. A patient who has been involved in an assault or motor vehicle collision or whom has undergone surgery within the previous 12 h is likely to be bleeding and in hypovolemic shock.

If there is no obvious injury, the practitioner must distinguish cardiogenic from septic from obstructive shock. Cardiogenic shock is primarily caused by acute myocardial ischemia – there is usually a history of chest pain, dyspnea or cardiac arrest, electrocardiographic changes, and a troponin rise. Following cardiac surgery, bleeding, tamponade, and right ventricular failure should be considered. If the patient has had recent pelvic or major orthopedic surgery, acute cardiogenic shock secondary to pulmonary embolism should be considered.

Septic shock is usually associated with fever, leukocytosis, raised inflammatory markers (such as C-reactive protein or procalcitonin), and a source – that may or may not be obvious. Irrespective of cause, unless the patient is already symptomatic with fluid overload, such as pulmonary edema, rehydration with 30 ml/kg of crystalloid is warranted [12].

If the patient does not respond to fluid and immediate interventions, medical or surgical, to control the source of shock, arterial cannulation and hemodynamic monitoring are indicated. There is a strong argument for using focused cardiac ultrasound at this stage [13]. The goal of echocardiography is to determine whether or not the heart is under- or overfilled, whether it is dilated on either the right or left side, and whether or not there is outflow obstruction. It is important to note that uncontrolled fluid bolus therapy has no role in modern critical care [14], in particular in states where hypotension results from vasoplegia and fluid redistribution [15]. In addition, modern hemodynamic monitors perform poorly in the presence of vasopressors which may camouflage significant volume depletion by mobilizing unstressed blood volume [16]. Importantly, clinicians should also be aware of misdiagnosis or the development of secondary causes of shock, in particular abdominal compartment syndrome [17]. We strongly recommend routine monitoring of intra-abdominal pressure in any patient requiring mechanical ventilation, treated with fluid boluses and vasopressors in ICU [18].

Measuring Hypovolemia

If a patient is bleeding profusely, or is severely hypotensive, then the decision to volume resuscitate is clear. In cases of more subtle volume loss, clinical examination may not uncover hypovolemia, and decision support by way of

Table 7.1 Predictive value of techniques used to predict fluid responsiveness [24]

Most accurate				Least accurate	
Pulse pressure variation (PPV)	Systolic pressure variation (SPV)	Stroke volume variation (SVV)	LV end-diastolic area (LVEDA)	Global end-diastolic volume (LVEDV)	Central venous pressure (CVP)
Derived from:	*Derived from:*	*Derived from:*	*Derived from:*	*Derived from:*	*Derived from:*
Arterial line waveform	Arterial line waveform	Arterial line pulse contour analysis	Echocardiography	Transpulmonary thermodilution (PiCCO)	Central venous pressure
AUC 0.94	AUC 0.86	AUC 0.84	AUC 0.64	AUC 0.56	AUC 0.55

LV left ventricle, *PiCCO* pulse contour continuous cardiac output, *AUC* area under the receiver operating curve

hemodynamic monitors would appear helpful. The simplest monitor is an arterial line, transduced to give invasive arterial pressures and a waveform. Beyond this there are lots of invasive and noninvasive hemodynamic monitoring devices on the market, many offering elaborate and impressive colorful displays and large amounts of information. For the clinician choosing such a device, several questions must be answered: (1) Is my patient hypovolemic? (2) How much fluid should I give initially? (3) When do I know enough is enough? (4) How do I measure ongoing volume loss? (5) Can I monitor fluid removal? Unfortunately no existing monitor provides answers to all of these questions.

Traditional teaching on cardiovascular physiology is based on interpretation of the Frank-Starling curve (FSC). This describes the phenomenon by which increasing diastolic blood volume in the left ventricle (LVEDV), leading in greater stretch on myofibrils, results in increased stroke volume. By increasing preload one may increase cardiac output. This assumes that preload dependence is an indication for fluid resuscitation, and such therapy will benefit the patient. As there is no easy method of measuring preload, surrogate static methods were developed and became popular – the central venous pressure (CVP) to measure right-sided filling pressures and the pulmonary artery occlusion pressure (PAOP) to measure left-sided filling pressures. To accept that these pressures represent "preload," several assumptions must be made: (1) that there is a relationship between CVP/PAOP and right and left ventricular volume, (2) that there is little impact of transmural and transpulmonary pressure on CVP/PAOP, (3) that each patient has an optimal CVP/PAOP that represents a "full" ventricle, and (4) that fluid loading to that CVP/PAOP will optimize cardiac output. In reality, despite decades of belief in CVP/PAOP as "preload," none of these assumptions are true.

Modern approaches to resuscitation require dynamic prediction of "fluid/volume responsiveness." This is an umbrella term that refers to an improvement in cardiac output, stroke volume, and blood pressure following a fluid bolus. Volume responsiveness is considered evidence of efficacy of hemodynamic monitors. These include esophageal Doppler measurement of stroke volume, stroke volume/pulse pressure variability monitors (SVV/PPV), pulse contour analysis, etc. None of these monitors are ideal (Table 7.1). For example, SVV/PPV monitors are accurate only when ideal conditions are present: mechanical ventilation, sinus rhythm, large tidal volumes, and the absence of vasopressors.

In this section we will explore the strengths and weaknesses of the various monitoring devices in current use in the operating room and ICU.

Invasive Blood Pressure Monitoring

Peripheral arterial cannulation is the gold standard for blood pressure monitoring in critically ill patients. The arterial line apparatus generates a characteristic waveform. The mean arterial pressure (MAP) is calculated by integrating the area under the waveform and the systolic and diastolic pressures calculated using an algorithm. This "invasive" blood pressure (IBP) measurement is accurate, continuous, reproducible, and immediate. IBP facilitates early diagnosis and treatment of hypotension. It is considered to be the particularly reliable in hypotensive and vasoconstricted patients [19, 20]. The waveform can also be analyzed by a variety of modern devices to determine stroke volume (SV), cardiac output (CO), and stroke volume variability (SVV).

The major problems associated with invasive blood pressure monitoring are damping and resonance; these can affect the accuracy of the blood pressure waveform and pressure measurement. Damping, caused by kinking or occlusion (e.g., with air bubbles), decreases the rate of signal change, leading to low pulse pressure with low systolic and high diastolic pressure reading. If the waveform is damped, the mean pressure is accurate, but the systolic and diastolic are not. In general, in critical care, MAP is considered the target perfusion pressure of choice, since autoregulated organs such as the bowel, kidney, and brain are MAP dependent (myocardial perfusion is dependent on diastolic blood pressure). The major problem with MAP is that, being a function of cardiac output and peripheral resistance, it is maintained in states of compensated shock and may not fall until up to 40 % of circulating volume is lost. As blood pressure is a function of peripheral resistance, which increases during shock, and stroke volume, which may fall, blood pressure readings may be misleading and falsely reassuring. Also, there is no clear intervention for treating a low MAP – should one give fluid

or should one administer vasopressors, or both? Although textbooks and guidelines suggest a MAP target of 65 mmHg in critical illness [12], there are no clear data to support this contention [21]. Nor is there any clear method of determining the pressure level that the individual patient's organs autoregulate. In practical terms many ICU nurses target at the MAP at which urine flows. Walsh and colleagues have demonstrated that an intraoperative MAP of <55 mmHg is associated with an increased risk of renal and myocardial ischemic insults [22].

In summary, in early critical illness, MAP is a simple metric that can assist in early decision-making for moderate fluid resuscitation and initiation of vasopressor therapy. However, MAP does not distinguish the mechanism of shock nor whether cardiac output or peripheral resistance should primarily be supported.

Central Venous Pressure

Central venous pressure (CVP) has been used for decades to assess volume status and to assess volume responsiveness. Unfortunately, it is useful for neither. The belief that CVP could be used to infer ventricular filling is based on incorrect interpretations of the Starling hypothesis. Although, in some cases, a very low (less than 5 mmHg) or a very high (greater than 20 mmHg) CVP may be helpful in guiding decisions about volume status, in most patients, a single CVP value is rarely helpful [23] nor indeed is the CVP trend. The accuracy of CVP measurement at predicting volume responsiveness is scarcely better than "flipping a coin (area under the curve 0.55 (confidence interval 0.48–0.62))" [24].

The central venous or RA pressure is the pressure within the RA relative to atmospheric pressure. However, right ventricular preload, which is best defined as right ventricular end-diastolic volume (RVEDV), is equally dependent on the intrathoracic pressure and right ventricular compliance, neither of which can be determined reliably at the bedside. A variety of interventions and pathologies may impact the extracardiac pressure – PEEP/auto-PEEP, prone positioning, intra-abdominal hypertension, ARDS, pneumothorax, etc.

Even if CVP correlated with RVEDV, the latter correlates poorly with LVEDV because of discordance in ventricular afterload and contractility. Indeed, lung disease, and the PEEP used to treat it, increases pulmonary vascular resistance and may produce right ventricular failure. Furthermore, since the pericardium limits ventricular dilatation, ventricular interdependence further increases the disparity in LVEDV and RVEDV when differential contractility or loading conditions are present. This occurs because ventricular dilatation displaces the septum laterally and compresses the adjacent ventricle.

CVP has been listed as an endpoint of resuscitation in many international guidelines, such as "Surviving Sepsis [12]." However, there are accruing data that resuscitating patients to high right atrial pressure levels worsens outcomes [25]. It is unclear whether this negative impact occurs due to fluid overload or loss of peripheral to central venous blood flow. Irrespective, we recommend against using a specific CVP level as a resuscitation goal in critically ill patients.

Pulmonary Artery Occlusion Pressure

The pulmonary artery catheter has been in use since 1974, although its use has been declining over the past two decades. Insertion of a PAC involves passing a long balloon-tipped catheter through the right heart into the main pulmonary artery and lodging it in a distal vessel – this process is known as "wedging." A column of blood then exists between the catheter tip and the left atrium that can be transduced as left atrial pressure. The PAC directly measures pulmonary artery pressures, thermodilution cardiac output, core temperature, true mixed venous oxygen saturation, and pulmonary capillary wedge/occlusion pressure (PAOP). Interpretation of these data may be problematic and may lead to poor decision-making [26].

Many clinicians believe that PAOP reliably reflects preload and is useful for the construction of Starling curves. This is unlikely [27]. The pressure-volume relationship of the left ventricle changes dynamically, depending on clinical circumstances, and vascular pressures are altered by changes in ventricular and atrial compliance, ventricular systolic and diastolic function, valvular function, heart rate and rhythm, afterload, intrathoracic pressures, and abdominal pressures. They also change with therapeutic interventions [23, 27, 28].

PAOP pressures should not be used to guide volume resuscitation. The PAC does provide an accurate thermodilution. The so-called "continuous" cardiac output (CCO) monitors use a random sequence of temperature changes generated by a heating coil located in the right ventricle, with a thermistor within the pulmonary artery. The data is averaged over time to produce an accurate series of measurements. Hence there may be a delay of several minutes before the device indicates major hemodynamic changes. Consequently, CCO-PAC are unhelpful for assessing volume responsiveness, as some time may elapse before measured changes in stroke volume may become evident. In addition, significant time may be required to insert a PAC, calibrate it and wait for data, severely limiting its use in acute resuscitation scenarios.

When is the PAC useful? The principal use of PA catheters is currently in states of cardiogenic shock, in particular secondary to right ventricular dysfunction; the majority of utilization follows myocardial infarction or cardiac surgery.

The PAC may also be used to diagnose and treat pulmonary hypertension. This may occur, for example, in patients with severe acute hypoxic respiratory failure, and inhaled nitric oxide or prostacyclin may be administered and titrated using indices derived from the PAC.

Dynamic Measures of Fluid Responsiveness

The ability to predict volume responsiveness will ensure that patients are adequately resuscitated by not volume overloading. Excessive fluid administration has been shown to worsen outcomes in sepsis and ARDS and increase perioperative morbidity [10, 11]. To date, static measures of preload, such as CVP and PCWP, have proven ineffective for plotting FSC in critically ill patients. Dynamic estimates of fluid responsiveness have been developed that look for changes in cardiac output based on heart-lung interactions or following passive leg raising.

Esophageal Doppler

Esophageal Doppler monitoring (EDM) has been widely used in perioperative medicine to titrate fluid therapy, particularly in the United Kingdom. The thoracic aorta is located in close proximity to the esophagus. The device uses Doppler ultrasound to measure aortic blood flow – the flow velocity time – from which stroke volume and cardiac output are derived. The EDM, while small in diameter and pliable, cannot be inserted into nonsedated non-intubated patients or patients with known esophageal disease. The observer needs to be at the bedside, continuously adjusting the probe for optimal signal. Compared with many other noninvasive hemodynamic monitors, there is a substantial body of data to support the use of EDM in the operating room [29]. Insertion is rapid, and data can be derived that are clinically useful within seconds. However, there is a steep learning curve and significant interobserver variability and the need for frequent repositioning that renders the EDM of limited utility in the emergency room and ICU.

Pulse Pressure/Stroke Volume Variability (PPV/SVV)

During inspiration, when the patient is being mechanically ventilated, blood pressure increases. It falls during the subsequent expiration. Positive intrathoracic pressure has multiple effects on both the right and left side of the heart. There is increased right ventricular afterload, due to increased pulmonary arterial resistance, reduced right atrial filling, and impaired venous return, and right ventricular dimensions are reduced. Simultaneously, there is increased pulmonary venous return, resulting in increased left atrial and ventricular filling, with increased LV compliance due to reduced transmural pressure, reduced LV afterload, and reduced ventricular interdependence [30]. Thus LV stroke volume (SV) and associated pulse pressure increases during inspiration, but falls during the subsequent expiration (Fig. 7.1). In the hypovolemic patient, LV is functioning on the steep portion of the FSC. Consequently, small changes in preload, associated with respiration, induce large changes in SV [30]. If the patient is euvolemic, on the flat part of the FSC, the respiratory cycle has minimal impact on SV [31].

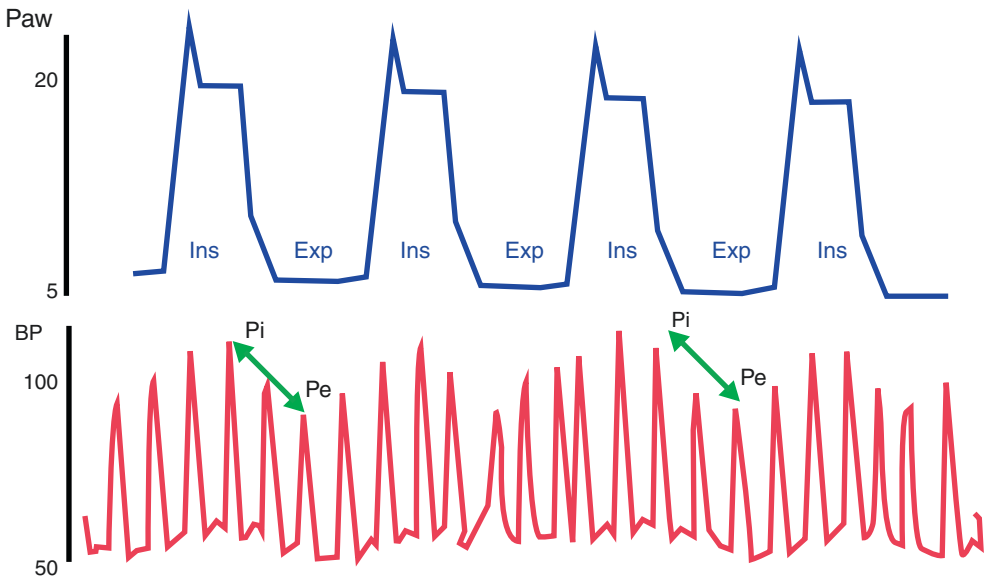

Fig. 7.1 Systolic and pulse pressure variability. *Upper panel*, airway pressure in cmH_2O (*ins* inspiratory phase, *exp* expiratory phase). *Lower panel*, blood pressure in mmHg (*Pi* systolic blood pressure in inspiration, *Pe* systolic blood pressure in expiration). Pulse pressure is systolic-diastolic blood pressure

Early studies of heart-lung interactions during the respiratory cycle used systolic pressure variability (SPV) (Fig. 7.1). However, this was replaced, subsequently, by pulse pressure variability (PPV). PPV predicts fluid responsiveness better than SPV [32] – as pleural pressure has equal effects on systolic and diastolic pressure, and PPV is more reflective of variations in stroke volume. In general, the patient must be mechanically ventilated and have a functioning arterial catheter in situ [33]. The respiratory cycle can be monitored using airway pressure or capnography (Fig. 7.1). A 13 % fall in pulse pressure appears to be a sensitive indicator of fluid responsiveness [32]. The greater the degree of PPV, the more accurate the measurement and the more fluid responsive the patient. PPV can be measured easily using modern ICU monitors (such as the Philips IntelliVue Monitor System), but accuracy depends on several factors: suitable for adults only, respiratory rates of >8 breaths per minute, tidal volumes >8 ml/kg, and no spontaneous ventilation.

The arterial pulse pressure is proportional to the SV (Fig. 7.2). Thus preload responsiveness may also be measured by stroke volume variability during the respiratory cycle. A variety of tools can be used to evaluate stroke volume variability (SVV) (Fig. 7.3).

FloTrac (sensor)-Vigileo (monitor Edwards Lifesciences, Irvine, Ca – F/V) is a hemodynamic monitoring system introduced in 2006 and currently in its fourth generation of software. A single sensor is attached to an arterial line at any site. The F/V device rapidly analyzes the arterial pressure waveform and uses demographic data and an evolving algorithm to calculate cardiac output. Arterial pulsatility is directly proportional to stroke volume. As changes in vascular tone and compliance occur dynamically, the device corrects for this by analyzing skewness and kurtosis of the arterial waveform. These correction variables are updated every 60 s, and the arterial waveform is analyzed and averaged over 20 s, thus eliminating artifacts, jitter, and extrasystoles. F/V does not require external calibration nor the presence of a central line or specialized catheter. Cardiac output is calculated utilizing the arterial waveform and the heart rate. These data may then be used to calculate SVV and hence fluid responsiveness. To date, under ideal conditions these data appear accurate [34].

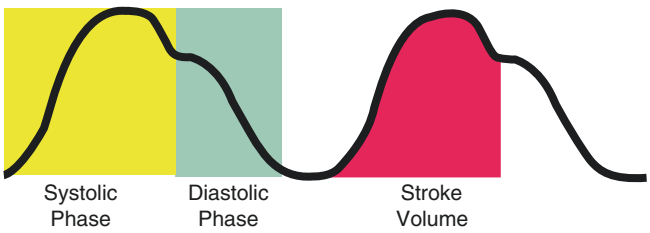

Fig. 7.2 Pulse waveform divided into the systolic and diastolic components. The stroke volume is the area under the curve of the systolic component

Mayer and colleagues meta-analyzed studies on F/V in 2009 [35]. Earlier studies demonstrated poor correlation between F/V and thermodilution methods; with newer software, the correlation has improved [36]. It should be borne in mind, however, that thermodilution methods, although considered the gold standard, are not ideal devices to compare with F/V: measurement intervals and averaging times are substantially longer with all thermodilution methods. Hence it is possible that F/V is more sensitive to dynamic changes in cardiovascular activity. F/V data is likely misleading in patients with aortic valve disease, those with intra-aortic balloon pumps in situ, those rewarming from induced hypothermia, and patients with intracardiac shunts.

Data to date have suggested that F/V is quite accurate at measuring changes in cardiac output associated with volume expansion (preload sensitivity) [37] but not with changes associated the vasopressor use [38–40]. It is unclear whether derived data are of any value in the non-intubated or spontaneously breathing patient [41]. It is likely that the accuracy also depends on the patient having a regular cardiac rhythm and minimal variability in tidal volume [42].

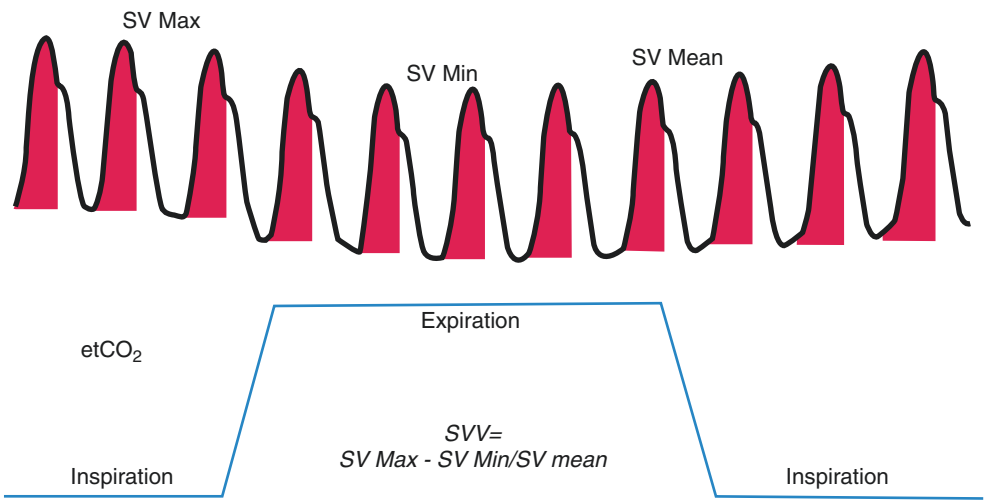

Fig. 7.3 Stroke volume variability (SVV). *SV* stroke volume, *etCO*$_2$ end-tidal carbon dioxide (in mmHg or kPa)

A simplified device that uses the pulse oximeter waveform and the pleth variability index (PVI) has been proposed and promoted. This has the obvious advantage of being truly noninvasive. To date, however, data have failed to demonstrate correlation of PVI with other monitors of fluid responsiveness, although the accuracy of these devices is likely to improve given the obvious commercial potential [43, 44].

Pulse Contour Cardiac Output

Systolic ejection results in the propulsion of a stoke volume into the arterial tree. The aorta and distal arteries distend, and the waveform is characteristic. It reflects the stroke volume and elastic properties of the arterial wall. The shape of the pulse waveform and the area under the curve are proportional to the cardiac output (Fig. 7.2). However, arterial compliance is not constant or consistent – there is tremendous inter- and intrapatient variability. As compliance is the mathematical relationship between pressure and volume, external calibration of the pressure signal with an alternative cardiac output technique is required. Pulse contour devices – Pulse CO LiDCO+ (lithium dilution cardiac output, LiDCO Ltd., Cambridge, UK) and PiCCO (pulse contour continuous cardiac output, PULSION, Germany) – combine pulse contour analysis to calculate stroke volume and indicator dilution or thermodilution cardiac output measurement to calibrate the system.

In addition to calculating cardiac output, devices that analyze pulse waveforms also analyze and display pulse pressure variability that can be used for dynamic preload assessment and fluid responsiveness (in mechanically ventilated patients).

LiDCO

Lithium is (in low doses) a nontoxic substance that is not metabolized. When injected, its concentration is easily measured using an ion-selective electrode. Lithium dilution cardiac output is calculated from the area under the concentration-time curve when injected from a central line and measured peripherally. Injection through the antecubital vein appears to be as accurate as a central line. Pulse CO LiDCO (LiDCOplus) combines pulse contour analysis with lithium dilution calibration.

The major disadvantage of LiDCOplus (LiDCO+) is the injection of lithium and the requirement for calibration of cardiac output at least every 8 h. In addition, in patients that are hyponatremic or have recently received neuromuscular blocking agents, the calibration data may be inaccurate. Data is unreliable with aortic valve disease or with intra-aortic balloon counterpulsation. The major advantage of LiDCO+ is that no specialized central or arterial line is needed, and little specialized training is required. There are few data supporting LiDCO as a decision-making tool [45].

PiCCO

PiCCOplus (PULSION Medical, Munich, Germany) calculates cardiac output continuously from pulse contour analysis of the aortic waveform via an arterial cannula. This must be placed in a large artery – femoral, brachial, or axillary. The system also requires a central venous catheter, usually in the internal jugular or subclavian vein. The central line is required in order to perform transpulmonary thermodilution cardiac output (TTCO) measurement – there is a thermistor in the arterial catheter. TTCO is used to calibrate the system. The principle advantage of PiCCO over a PAC is that there is no requirement to cannulate the right heart. However, two separate lines are required, and in the majority of cases, this involves a second arterial cannulation.

The PiCCO device measures the area under the aortic waveform – the systolic area is identified as that part of the waveform proximal to the dicrotic notch, and this is proportional to the stroke volume (Fig. 7.2). Although beat-to-beat volumes are measured, these are averaged over 30 s, to avoid inaccuracy associated with anomalous waveforms, extrasystoles, and interference. The continued accuracy of PiCCO depends on the frequency of calibration using thermodilution, which should be done at a minimum of eight hourly intervals [46]. By analyzing the changes in stroke volume during the respiratory cycle, stroke volume variability can be estimated (Table 7.1, Fig. 7.3).

In the PiCCO, the temperature differential detected using the arterial thermistor is composed of a series of exponential decay curves as the cold injectate passes through the various compartments of the circulatory system. As the injectate is administered centrally and the temperature difference is measured in a proximal artery, the majority of the temperature change occurs in the intathoracic compartment. Consequently, one can measure intrathoracic blood volume and extravascular lung water, which is helpful in titrating fluid therapy and fluid removal. Finally, in addition to stroke volume variability, the device also purports to measure global end-diastolic volume, hence permitting the construction of Starling curves and volume titration (Table 7.1).

To date, this particular device appears to correlate very well with other thermodilution techniques [47–50] and is widely used in ICU to monitor both resuscitation and "deresuscitation."

End-Expiratory Occlusion (EEO)

During inspiration, the intrathoracic pressure rises, impeding venous return, resulting in reduced end-diastolic volume. Conversely, if the respiratory cycle is halted during

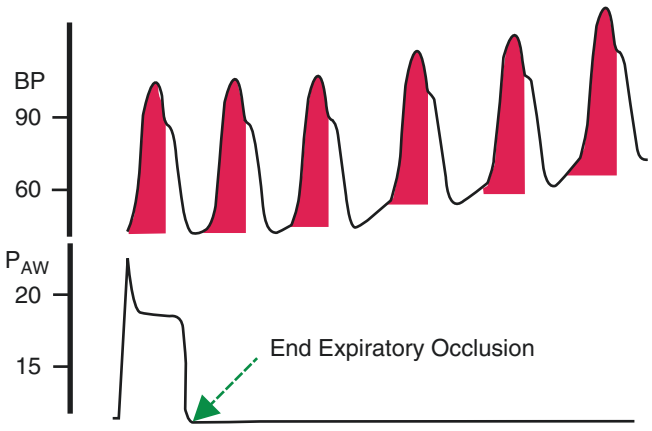

Fig. 7.4 End-expiratory occlusion test: blood pressure rises following a 15 s expiratory occlusion test in fluid responsive patients. *BP* blood pressure in mmHg, *PAW* airway pressure in cmH_2O

expiration, for example, for 15 s or so, then there is an increase in cardiac preload. A 5 % increase in cardiac output or pulse pressure during occlusion predicts fluid responsiveness (Fig. 7.4). A number of investigators have demonstrated the efficacy of this approach as an alternative to a fluid bolus [51–53]. In the majority of studies, transpulmonary thermodilution using PiCCO has been used to measure cardiac output.

The use of EEO appears to be more efficacious than SVV alone in the setting of low lung compliance and ARDS [53]. It also appears to be suitable for patients breathing spontaneously and those with arrhythmias, such as atrial fibrillation as EEO exerts its effects over several cardiac cycles. The magnitude of PEEP does not appear to influence the outcome of the test [53]. EEO has the benefit of simplicity compared with, for example, pulse contour analysis. Although EEO can be performed in patients who are not paralyzed or deeply sedated, recurrent inspiratory efforts may interrupt the occlusion and invalidate the test.

Passive Leg Raising

If a patient is lying supine, raising the legs from horizontal to vertical induces a significant translocation of blood volume from the extremities to the central circulation. Functionally, there is mobilization of unstressed blood volume and an increase in right ventricular preload. This increases cardiac output, which then falls when the legs are returned to the horizontal position. Essentially, the patient receives a fluid bolus without receiving exogenous fluid as a result of relocation of venous blood pooled in capacitance vessels. An increase in cardiac output during this maneuver predicts fluid responsiveness [54]. It does so irrespective of whether the patient is breathing spontaneously or mechanically ventilated or whether the patient is in atrial fibrillation [55], due to the fact that the test exerts its effects over several cardiac and respiratory cycles [56]. Various measures of cardiac output have been used, importantly only those with relatively rapid response are effective: esophageal Doppler, pulse contour analysis, bioimpedence, and end-tidal carbon dioxide ($etCO_2$) [56]. A 5 % increase in $etCO_2$ predicted a 15 % increase in cardiac index in volume responders [57]. Unfortunately, arterial pulse pressure changes in PLR do not predict volume responsiveness [57]. Passive leg raising appears to be more efficacious than SVV alone in the setting of low lung compliance and ARDS [51].

There is a strong argument for performing passive leg raising (PLR) in the semirecumbent rather than the supine position: unstressed blood is mobilized from the legs and the splanchnic circulation, so the volume delivered to the heart is greater and the sensitivity of the test higher [51].

Table 7.2 Targets for FoCUS (cardiac ultrasound) examination

Volume status
LV size and systolic function
Pericardial effusion/tamponade
Gross valvular abnormalities
Gross signs of chronic heart disease
Large intracardiac masses
RV systolic function

Echocardiography

The Current Role of Echocardiography in Critical Care

Echocardiography dramatically increases the intensivist's capability to diagnose a variety of causes of hemodynamic instability. There is a tremendous spectrum of competence in performance and interpretation of echocardiographic images. However, even rudimentary knowledge of bedside echocardiography may provide a life-saving diagnosis in, for example, cardiogenic shock, severe hypovolemia, and massive pericardial effusion/tamponade [58]. This has led to the development of "focused cardiac ultrasound (FoCUS)," a simplified approach that aims to ascertain only the essential information needed in critical scenarios and time-sensitive decision-making (Table 7.2) [59]. A FoCUS examination is brief and addresses a few clinical questions, mainly in a "yes or no" manner: the patient is hypotensive, is this due to hypovolemia – yes or no? Is it due to left ventricular dysfunction – yes or no? Is it due to pericardial effusion – yes or no?

Transthoracic echocardiography (TTE) should be the first modality in most cases of hemodynamic instability, because of its safety, reliability, and rapidity [60]. Image quality can be an issue, due to poor or limited acoustic windows, but new

technology, harmonic imaging and new echo contrast products, have significantly improved TTE signal acquisition [61].

Transesophageal echocardiography (TEE) is indicated, when the TTE study is inadequate, to evaluate of aortic dissection, to diagnose endocarditis of prosthetic valves, or to rule out intracardiac thrombus presence before semi-elective cardioversion. In early shock, TEE is limited by its invasiveness – it is preferable that diagnosis and management of shock precedes intubation, which can often be avoided. However, smaller TEE probes have been developed and in time will be as minimally invasive as a nasogastric tube.

Ventricular Function

Left ventricular (LV) dysfunction in critically ill patients is common and may be caused by ischemia, sepsis, or hyperadrenergic states (such as traumatic brain injury or subarachnoid hemorrhage). When the LV becomes dysfunctional, end-diastolic volume increases to maintain stroke volume, and ejection fraction (EF) falls. In addition echocardiography may also unveil regional wall motion abnormalities, usually associated with myocardial ischemia.

Right ventricle (RV) dysfunction is also very common in critically ill patients. Pulmonary embolism (PE) and acute respiratory distress syndrome (ARDS) are the most frequent causes in medical surgical ICU [62], although RV failure not uncommonly complicates cardiac surgery. Pulmonary hypertension may be uncovered by pulmonary arterial catheterization, but echocardiography is required to diagnose the underlying cause.

The RV is generally small compared with the LV. In the four-chamber view, the ratio between RV and LV end-diastolic area is measured. A diastolic ventricular ratio >0.6 suggests moderate, and ratio >1.0 severe, dilatation [63]. An acute rise in right ventricular (RV) afterload, for example, consequent of profound hypoxic pulmonary vasoconstriction, can cause acute cor pulmonale. The RV dilates, the LV is small and underfilled, and the interventricular septum bows inward into the LV (ventricular interdependence) particularly during diastole [64].

Assessments of Cardiac Output (CO)

Thermodilution of CO measurement is not always accurate in critically ill patients. Very low or very high CO, severe TR, rapid temperature changes, or intracardiac shunt can result in incorrect data. In these conditions, echocardiography can relatively reliably measure SV and thus CO [65]. The most common technique is Doppler-derived instantaneous blood flow measurement through a conduit (LV outflow tract, pulmonic or mitral valve). Stroke volume is equal to product of cross-sectional area (CSA) of the conduit, determined by 2D echo, and integration of instantaneous blood flow, velocity time integral (VTI), through the conduit. CSA = diameter of conduit (D) squared × (pi/4). SV = CSA × VTI. SV multiplied by heart rate (HR) gives CO. CO = CSA × VTI × HR.

Volume Status

Echocardiography is an effective method of estimating volume status and fluid responsiveness. An empty LV, manifest by systolic obliteration, strongly suggests inadequate preload. A dilated LV, defined by an increase in diameter, may reveal a chronically failing heart, which may respond to a volume challenge [66].

In addition to visualizing the heart, significant information can be gleaned from observation of the great vessels. The collapsibility index of the superior vena cava (SVC) and respiratory variation in inferior vena cava diameter (the distensibility index – dIVC) have been validated [67–69]. dIVC is calculated using measurements of maximal IVC diameter during inspiration (Dmax) and minimal diameter during expiration (Dmin) [67].

$$\text{dIVC} = \text{Dmax} - \text{Dmin} / \text{Dmin}.$$

In ICU, this approach is limited due to the high prevalence of IVC dilation in mechanically ventilated patients [70].

Goal-Directed Resuscitation

Shoemaker, in the late 1980s, demonstrated that by driving up cardiac output with fluids and inotropes, perioperative outcomes could be improved [71]. A number of studies in the 1990s and 2000s utilized dynamic flow monitoring devices intraoperatively to hemodynamically optimize the patient. Early studies, using esophageal Doppler, suggested improved outcomes. Later studies were more disappointing [72]. The largest optimization study to date, by Pearse and colleagues, of 734 high-risk patients, undergoing gastrointestinal surgery aged 50 and older, in 17 hospitals in the United Kingdom, failed to demonstrate improved perioperative outcomes [73]. The authors subsequently performed a meta-analysis that included data from previous perioperative GDT trials (38 in total). In this analysis GDT was associated with fewer overall complications (intervention, 488/1,548 [31.5%] vs control, 614/1,476 [41.6%]; RR, 0.77 [95% CI, 0.71–0.83]) [74]. Another meta-analysis of 22 trials that reported cardiovascular outcomes suggested that GDR was associated with reduced total cardiovascular (CVS) complications [OR = 0.54, (0.38–0.76), $P = 0.0005$] and arrhythmias [OR = 0.54, (0.35–0.85), $P = 0.007$] [75]. There was no increase in the risk of pulmonary edema or myocardial ischemia.

In critical care research involving GDT, a surrogate of oxygen consumption, the mixed venous oxygen saturation (SVO_2,) has been used to estimate tissue blood flow by looking at oxygen extraction. Low SVO_2 is indicative of excessive extraction per unit volume, apparently suggestive of hypovolemia.

Critical care studies of GDR in the 1980s that used SvO_2 as the endpoint of fluid and inotrope therapy had disappointing outcomes [76, 77]. These studies were carried out in established rather than impending critical illness. Rivers et al. speculated early GDR may improve outcomes in patients presenting to the emergency room with early signs of sepsis. They randomized 263 patients to "standard" therapy versus aggressive goal-directed therapy that included the use of an oximetric ($ScVO_2$) central venous pressure line [78]. This measured SVO_2 in the superior vena cava distribution. Therapy was directed at CVP (8–12 mmHg), $ScVO_2$ (>70 %), and MAP (>65 mmHg) goals. The patients in the study group received significantly more fluid than the control group in the first 6 h, more red cell transfusions overall and equivalent volume of intravenous fluid over the first 72 h. There was a 16 % decrease in a 28-day mortality (number needed to treat, 6). The implication of this study was that early aggressive volume resuscitation restores tissue blood flow, prevents multiorgan failure, and saves live. Once goals are met, further resuscitation is not helpful and may be harmful.

There were many questions about this trial, not least that it was single operator and single centered. The mortality rate in the control group was apparently high; a number of patients appeared to be missing from analysis, and timing of antibiotics therapy was unclear (all refuted by Dr. Rivers).

Three follow-up studies were performed – ProCESS, ARISE, and ProMISe [79–81]. All three trials looked at volume resuscitation in early sepsis, comparing the Rivers' protocol to "usual care" – which appeared to be aggressive volume resuscitation without the inotropes, central line, and $ScVO_2$ monitor. Obviously, "usual care" had been influenced by a decade of "Surviving Sepsis" – derived mainly from the Rivers' approach. Nonetheless, there was no survival benefit associated with using dobutamine, CVP, and $ScVO_2$ goals. The cost of care was greater in the GDT groups, principally due to increased numbers of central venous cannulations, inotrope use, and ICU admissions [82]. Higher CVP levels have been shown to increase the risk of adverse outcomes [25], and hypervolemia is strongly associated with abdominal compartment syndrome [83].

Taking these data together, it appears that perioperative patients, undergoing major nonvascular surgery, may benefit from IGDVR. Dynamic monitoring of stroke volume is more effective than traditional monitors such as CVP, $ScVO_2$, mean arterial pressure, and urinary output. Patients appear to do better if resuscitated on the day of injury or surgery.

Lactate and Lactate Clearance

Raised serum lactate (lactic acidosis) is the only widely accepted biomarker of shocked states [1]. Lactic acidosis occurs when the production of lactate in the body is greater than the liver's capacity to metabolize it: there is a problem of overproduction or inadequate clearance.

Lactic acid is produced physiologically as a degradation product of glucose metabolism. Its formation from pyruvate is catalyzed by lactate dehydrogenase. Under normal conditions the ratio of lactate to pyruvate ratio is less than 1:20. In anaerobic conditions, for example, following vigorous exercise, lactate levels increase dramatically. In addition, lactate can be produced under aerobic conditions. Activation of beta-adrenergic receptors in skeletal muscle by stress (increased circulating catecholamines) or exogenous infusion (epinephrine/norepinephrine infusions) increases the lactate concentration resulting in aerobic glycolysis. Lactate is converted to glucose in the liver (the Cori cycle) and subsequently to CO_2 and H_2O. Hence the lactate in Ringer's lactate solution is functionally bicarbonate.

Serum lactate and arterial pH should be measured early in any critically ill patient. A lactate concentration >2 mmol/L is clinically significant, and a level of 5 mmol/L in the presence of metabolic acidosis is severe [84]. Isolated hyperlactatemia in the absence of acidosis is of unclear clinical significance [85].

There are two types of lactic acidosis: type A (global inadequate oxygen delivery) is seen in hypovolemic/hemorrhagic shock, while type B occurs despite normal global oxygen delivery and tissue perfusion (usually both coexist in critical illness). Lactic acidosis may also develop in situations where there is significant regional hypoperfusion. Examples include bowel ischemia, where lactate is produced in large quantity due to glycolysis despite global oxygen delivery that is normal. Type B lactic acidosis is associated with hyperadrenergic states where circulating catecholamines (endogenous or exogenous) are in excess. Examples include simple exercise and the hyperinflammatory state of trauma or sepsis. Type B lactic acidosis may also be seen in cyanide poisoning (associated with sodium nitroprusside), with biguanides (metformin), and in hypercatebolic diseases such as lymphoma, leukemia, AIDS, or diabetic ketoacidosis.

Lactic acidosis is a sensitive marker of disease severity [86], and failure to clear the acidosis is a strong predictor of adverse outcomes [87–89]. The presence of a low mixed venous oxygen saturation (SvO_2) with a high lactate is indicative of type A (hypoxia associated) acidosis. Following resuscitation, SvO_2 recovers rapidly and lactate slowly, due to saturated metabolic pathways.

The presence of normal systemic indices of perfusion does not exclude significant regional hypoperfusion or mitochondrial failure [90, 91]. Clinicians frequently misinterpret high serum lactate levels indicative of global tissue hypoperfusion and as a result may continue to administer intravenous fluid [91, 92]. Where possible, following initial resuscitation, fluid responsiveness should be determined by SVV or PPV. Dynamic measurements of lactate over time are better predictors of outcome than static measures [93]. Lactate clearance has been proposed as an endpoint of resuscitation in sepsis [94, 95], as lactate concentration would be expected

to fall with adequate resuscitation [95]. Rapid clearance of lactate has been associated with improved outcomes [96, 97]. A failure of lactate clearance in response resuscitation suggests that global perfusion is not the underlying problem and should prompt a search for a more sinister etiology.

Blood Transfusion

Current Status of Transfusion Therapy

Over the past decade, the approach to resuscitation of patients who are bleeding has changed dramatically. No longer are patients receiving large amount of crystalloid (or colloid) prior to blood transfusion. The emphasis is now placed on damage control surgery with earlier blood component therapy [98]. This approach results from the realization that coagulopathy is the major cause of mortality in the bleeding trauma patient [99], and reversing coagulopathy, in particular with fibrinogen, has resulted in dramatically improved outcomes [100]. Plasma and platelets are administered earlier in increased volume. There has been a corresponding decrease in the use of crystalloids, resulting in less hemodilution, tissue edema, and hypoxemia [101]. The multitrauma-center PROMMTT trial included approximately 1,000 patients involved in major trauma, transfused at least one unit of RCC in the first 6 h [102]. Using a multivariable time-dependent Cox model, it was demonstrated that earlier administration of higher ratios of red cells to plasma to platelets (e.g., 1:1:1) was associated with a significant reduction in mortality [102]. To find the optimal ratio, the PROPPR study was conducted by the same authors – comparing plama/platelets/RCC 1:1:1 (intervention) to 1:1:2 (control) [103]. Six hundred and eighty patients were randomized: 338 to intervention, 342 to control. There was no difference in 30-day mortality, but there were fewer deaths from exsanguination in the intervention group. For bleeding patients, who were not involved in trauma, it is unclear at what ratio blood components should be administered, and accumulated data to date are unhelpful.

It is unclear how these data will translate in the perioperative period, given that in low-risk patients, blood transfusion is associated with a significant increase in perioperative morbidity and mortality [104]. For the majority of patients with moderate blood loss and anemia, transfusion is likely unnecessary and potentially harmful [105].

Key Points

1. Shock is a major indication for referral to critical care services: it may be hypovolemic, cardiogenic, vasoplegic, or obstructive. Hemodynamic monitoring is used to diagnose and treat the cause of shock.
2. Invasive blood pressure monitoring is a standard intervention for monitoring shock. Measured pressures alone are often misleading and unhelpful. The pressure waveform is increasingly been used to titrate fluid therapy.
3. Central venous pressure and pulmonary artery occlusion pressure do not predict fluid responsiveness and therefore should not be used as endpoints of resuscitation.
4. Pulse pressure variability, stroke volume variability, and pulse contour analysis predict fluid responsiveness in a variety of shock settings.
5. Focused cardiac ultrasound is emerging as an essential component in the training of intensive care clinicians and for diagnosing and treating shocked patients.
6. Lactate is the only universally accepted biomarker of sepsis and other shocked states. Elevated lactate reflects increased production and reduced metabolism. A high lactate is an indication for intravenous rehydration, but it is not an "endpoint" of resuscitation.
7. Goal-directed resuscitation is not currently validated in critical care, though it does seem to have a role in the operating room.
8. The bleeding patient should be treated with blood products and minimum crystalloid resuscitation. Blood transfusion has little or no role in the management of the nonhemorrhaging anemia of chronic critical illness.

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