Undifferentiated Shock

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Case Presentation

A 39-year-old woman with a history of rheumatoid arthritis and localized breast cancer status post lumpectomy was admitted to the intensive care unit (ICU) for suspected septic shock from a biliary source. She had presented with right upper quadrant abdominal pain worsening over the last 3 days. She endorsed lightheadedness, shortness of breath, and vomiting, and denied cough or fever. On initial examination, her vitals included a heart rate of 110, respiratory rate 22, blood pressure 86/58, SpO_2 94 % on room air, temperature 37.5 °C. She was ill appearing, anxious but alert, visibly dyspneic, with clear heart and lung sounds. She had tenderness with voluntary guarding of her right upper quadrant. Her extremities were cool with delayed capillary refill and 1+ pretibial edema bilaterally. Her electrocardiogram showed sinus tachycardia with small T wave inversions in the anterior leads and no ST elevations. Her chest radiograph showed a small right pleural effusion but was otherwise clear. Pertinent labs included: WBC 13,000, hemoglobin 11.9, platelets 180,000, creatinine 1.9 mg/dL, AST 250, ALT 300, alkaline phosphatase 110, total bilirubin 1.8, lipase 120, troponin-I 1.1 (negative <0.10), and INR 1.5. Arterial blood gas revealed pH 7.32, PCO_2 28, PO_2 64, and lactate 4.2 mmol/L. Pregnancy testing was negative. Urinalysis was pending as her urine output was poor. She was treated empirically with broad-spectrum antibiotics and intravenous fluids. After 1500 mL of saline, the patient's heart rate was 120, respiratory rate 26, blood pressure 80/54, and SpO_2 now 90 % on 2 L nasal cannula. While awaiting diagnostic imaging, a foley catheter, central venous catheter, and arterial line were placed.

Question How should the clinician determine this patient's shock type and the appropriate resuscitation strategy?

Answer Assessment of volume responsiveness plus bedside echocardiography

This patient presents with clinical features of, and risk factors for, multiple shock types with many possible etiologies. The differential diagnosis includes septic shock due to biliary, gastrointestinal, or genitourinary causes, severe pancreatitis, hemorrhagic shock possibly from a ruptured ovarian or hepatic cyst, adrenal crisis, massive pulmonary embolism, right ventricular failure, cardiac tamponade, or left ventricular failure. The fact that she is more hypotensive after fluids might suggest cardiac failure, or may be due to progression of septic shock. The indications for IV fluid boluses,

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blood products, vasopressors, and inotropes differ widely among these possibilities, and both under-resuscitation and volume overload carry potential harm.

After placement of a left subclavian central line and radial arterial line, central venous pressure (CVP) averaged 10 mmHg, and a pulsus paradoxus was noted on the arterial pressure waveform. A 90-s bilateral passive leg raise resulted in a 12-point drop in systolic blood pressure. Based on this, intravenous fluids were discontinued. A bedside echocardiogram demonstrated a dilated inferior vena cava (IVC) with no respiratory variation, no pericardial effusion, massive dilation of the right ventricle (RV) with poor RV contractility, marked right-to-left interventricular septal bowing, and a small, hyperdynamic left ventricle (LV). A diagnosis of cardiogenic shock due to RV failure was made, and the patient was started on high-flow oxygen at 15 L/min with inhaled nitric oxide blended in at 20 parts per million. Norepinephrine and dobutamine infusions were initiated. After application of these therapies, her skin temperature and capillary refill improved, her blood pressure improved to 110/70, and urine output increased. A formal right upper quadrant ultrasound showed no gallstones, gallbladder wall thickening, or biliary dilation; her right upper quadrant pain was attributed to congestive hepatopathy. A CT of the chest showed no pulmonary embolism. She was scheduled for right heart catheterization for a suspected index presentation of pulmonary arterial hypertension.

Standard Approach to Undifferentiated Shock

Shock is defined as a state of inadequate oxygen delivery to tissues resulting in cellular dysoxia, which is often accompanied by, but may be completely independent of, decreased systemic arterial blood pressure [1]. The classic approach to determining shock type begins with utilizing history and cardiopulmonary and skin examinations to categorize the patient's condition into one of four shock types: hypovolemic, distributive, cardiogenic, or obstructive [1]. This can be quite challenging in patients with multiple comorbidities, difficult body habitus, or atypical physical exam findings (e.g. "cold" septic shock or "high output" cardiac failure).

In the past, static hemodynamic parameters such as central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), estimated stroke volume (SV), cardiac index (CI), and systemic vascular resistance (SVR) obtained invasively via central venous and pulmonary artery catheterization were used to attempt to differentiate cardiac failure, obstruction, hypovolemia, or inappropriate vasodilation. Various combinations of fluids, vasopressors, and inotropes would be then employed to target certain goals; for example, CVP of 8–12 mmHg, PAOP of 12–15 mmHg, and CI greater than 2.2. CVP-guided fluid management is still emphasized in a number of resuscitation protocols, including early goal directed therapy of septic shock and the post-cardiac arrest syndrome [2, 3], and utilization of the pulmonary artery catheter (PAC) remains a standard monitoring strategy for patients in cardiogenic shock or post cardiac surgery. As described in greater detail below, these parameters are notoriously unreliable in determining shock type and predicting response to intravenous fluid.

Shock Types

The basic phenotypes of shock are only three: hypovolemic, distributive, and cardiogenic; cardiogenic shock includes obstructive causes of RV failure (Fig. 3.1). In the modern approach to undifferentiated shock, it is essential to first recognize that a large proportion of patients in shock are suffering multiple insults resulting in *mixed shock phenotypes*, and therefore a linear approach to diagnosis and management is inappropriate. For example, patients with cardiogenic shock, post-cardiac arrest syndrome, or massive hemorrhage may also suffer distributive shock due to systemic inflammation and vasoplegia [4]; over half of patients with septic shock will develop cardiac dysfunction during their course [5]; and patients with hypotension and severe congestive

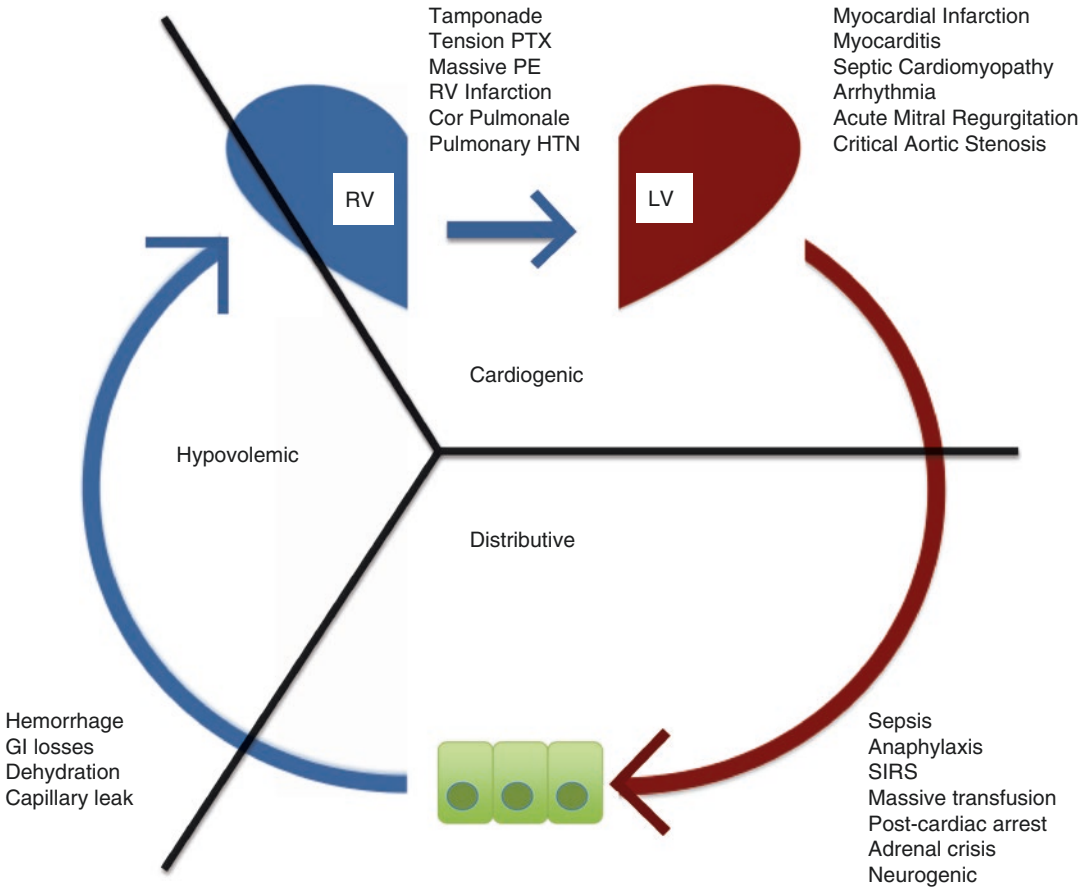

Fig. 3.1 Shock types and examples. *RV* right ventricle, *PTX* pneumothorax, *PE* pulmonary embolism, *HTN* hypertension, *LV* left ventricle, *SIRS* systemic inflammatory response syndrome, *GI* gastrointestinal

heart failure may in fact be initially volume responsive [6, 7], particularly if they are suffering concomitant gastrointestinal fluid losses, overdiuresis, or occult bleeding.

Hypovolemia is categorized as either hemorrhagic or non-hemorrhagic. Mechanistically, hypovolemic shock results from inadequate cardiac output due to diminished stroke volume, which itself is the result of decreased venous return. Venous return depends upon maintaining a gradient of blood flow from large capacitance veins in the body towards the right atrium, and this gradient depends in part on the difference between mean systemic pressure (P_{ms}) and right atrial pressure (Fig. 3.2) [8]. P_{ms} can be thought of as the intrinsic blood pressure within the venous system and depends on "stressed" intravascular volume—the volume of blood pressurized by the elasticity of the distended blood vessels in which it is contained. Normally when intravascular volume is lost, compensatory venoconstriction maintains an adequate stressed volume and thus adequate P_{ms}; however, when a patient becomes critically hypovolemic or is subject to inappropriate vasodilation, P_{ms} drops and venous return to the right atrium falls. The treatment is thus replacement of intravascular volume to restore P_{ms}. In the profoundly vasoplegic patient (e.g. advanced cirrhosis or anaphylaxis), venous return can be increased by using vasoconstrictors such as norepinephrine to increase venous tone and stressed volume [8, 9]; however, excessive vasoconstriction increases resistance to blood flow and may impede venous return.

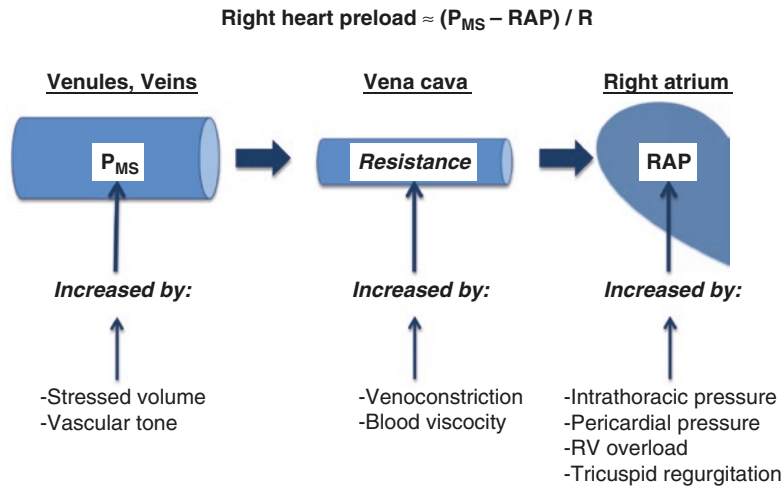

Fig. 3.2 Physiologic determinants of right heart preload. P_{MS} mean systemic pressure, *RAP* right atrial pressure, *R* resistance, *RV* right ventricle

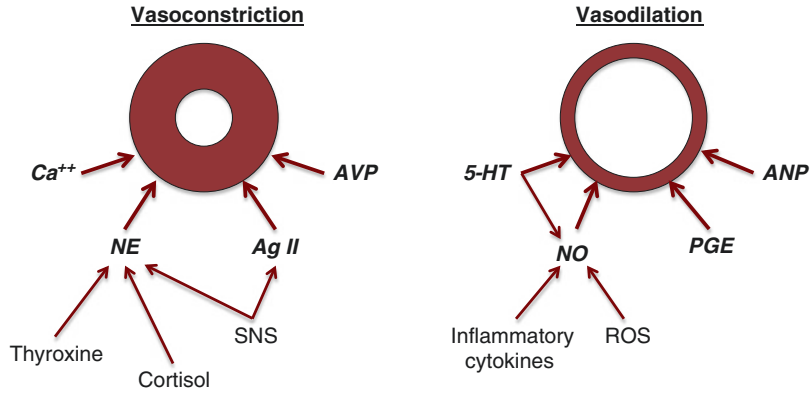

Fig. 3.3 Physiologic determinants of vascular tone. Ca^{++} calcium, *NE* norepinephrine, *Ag II* angiotensin, *AVP* arginine vasopressin, *SNS* sympathetic nervous system, *5-HT* serotonin, *NO* nitric oxide, *PGE* prostaglandin, *ANP* atrial natriuretic peptide, *ROS* reactive oxygen species

Distributive shock is due to vasoplegia, the failure to maintain vascular tone, and can occur via multiple mechanisms. Vascular smooth muscle tone is affected by a balance of several chemical mediators: catecholamines, vasopressin, angiotensin II, and free calcium cause vasoconstriction, while prostaglandins, histamine, atrial natriuretic peptide, and nitric oxide cause vasodilation (Fig. 3.3) [4, 10, 11]. Catecholamine induced vasoconstriction is influenced by the integrity of the sympathetic nervous system as well as by adrenal and thyroid function. Nitric oxide induced vasodilation is heightened by histamine, inflammatory cytokines, and possibly reactive oxygen species during ischemia-reperfusion. The interplay of these factors explains why such varied disease processes such as septic shock, anaphylactic shock, post-cardiopulmonary bypass, post-cardiac arrest syndrome, massive transfusion, adrenal failure, and high cervical spine injury may all result in distributive shock via different mechanisms. The mainstay of treatment is an adrenergic vasopressor agent such as norepinephrine or phenylephrine, and other intravenous agents such as ephedrine, vasopressin, angiotensin II, antihistamines, corticosteroids, thyroxine, and nitric oxide scavengers such as methylene blue may be indicated in certain clinical situations.

Cardiogenic shock is a broad category encompassing depressed cardiac output related to failure of either the right ventricle, left ventricle, or both. The causes of "obstructive shock" such as tension pneumothorax, cardiac tamponade, or massive pulmonary embolism, can be thought of as a subset of cardiogenic shock as they directly

impede the filling and/or output of the right heart. After a cautious trial of intravenous fluids, the mainstays of treatment are to support hemodynamics with a combination of vasopressors and inotropes while working to correct any potential mechanical lesion (e.g. pericardiocentesis for tamponade, tube thoracostomy for tension pneumothorax, thrombolysis for massive pulmonary embolism, percutaneous coronary intervention for ST-elevation myocardial infarction, emergent valve repair for severe regurgitation, etc.). Mechanical ventilation and mechanical circulatory devices such as implantable ventricular assist devices, intraaortic balloon counterpulsation, or extracorporeal life support may be needed until resolution or definitive therapy [6].

Evidence Contour

Rarely will one simple shock type exist in isolation, and one should approach shock as a potential combination of three simultaneous insults: hypovolemia, vasoplegia, and cardiac dysfunction. In all-comers with shock, these three parameters must be addressed systematically. The two most important maneuvers guiding the resuscitation of undifferentiated shock are (1) assessment of volume responsiveness and (2) bedside echocardiography.

Assessment of Volume Responsiveness

Accurate assessment of volume responsiveness is the most important first step in the resuscitation of a patient in shock, as it directly influences management in real time. Volume responsiveness is defined as a 10–15% increase in stroke volume (SV) or cardiac output (CO) after the administration of an intravenous fluid challenge, usually 250–500 mL of crystalloid, theoretically corresponding to the steep portion of the Starling curve (Fig. 3.4). There are many methods of assessment described, which are divided into static measurements of filling pressure or dynamic measurements of cardiopulmonary interaction.

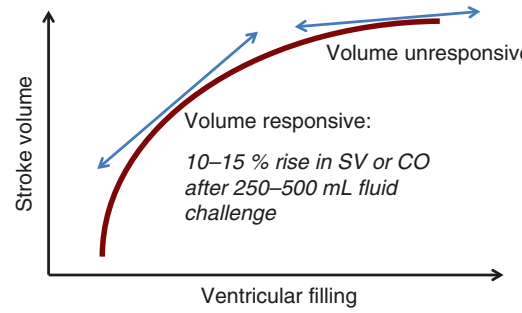

Fig. 3.4 Starling curve. *SV* stroke volume, *CO* cardiac output

When caring for patients in shock, the routine use of CVP or PAOP to guide fluid management is not recommended [1]. Despite their widespread use, static measurements such as CVP, PAOP, or estimated end-diastolic volumes do not accurately reflect volume responsiveness or intravascular volume status, even in combination, and even at extreme highs and lows [12–14]. Randomized trials and large systematic reviews have not demonstrated that targeting a specific CVP or routinely using a PAC are of benefit to critically ill patients [15–18]. Blindly administering intravenous fluids to increase CVP is not recommended, as there is a worrisome correlation between elevated CVP, positive fluid balance during resuscitation, and mortality, at least in septic shock [19].

Unlike static filling pressures, dynamic measures of cardiopulmonary interaction are highly accurate in determining volume responsiveness [20–25]. In mechanically ventilated patients, such dynamic measurements include pulse pressure variation (PPV), stroke volume variation (SVV), and plethysmography variation index (PVI). Variations in pulse pressure (PP), stroke volume (SV) or plethysmography amplitude indicate that cardiac output is linked to changes in ventricular filling that occur with swings in intrathoracic pressure, which reflects volume responsiveness. Respiratory variation of IVC diameter (ΔD_{IVC}) using bedside ultrasound may also be used to predict volume responsiveness, again linking changes in venous return and cardiac output with changes in intrathoracic pressure.

SVV, PPV, and PVI specifically predict left ventricle (LV) volume responsiveness. During a positive pressure breath, venous return from the pulmonary vascular bed to the LV is briefly increased; if the LV is volume-responsive, then PP, SV, and plethysmography amplitude will transiently increase immediately after each ventilator-delivered breath. However, a positive pressure breath at the same time impedes the cardiac output of the RV—the source of LV preload. If the LV is volume responsive, PP and SV will dip after several cardiac cycles to reflect this decrease in preload to the LV, and then return to baseline during exhalation (Fig. 3.5). There are several minimally invasive methods available to assess SV, including pulse contour analysis from arterial pressure tracings (e.g. FloTrac [Edwards Lifesciences, Irvine, CA], PiCCO [Philips, Netherlands], LiDCO [LiDCO Group PLC, London, UK], etc.), esophageal Doppler monitoring (EDM) of aortic blood flow (e.g. CardioQ-ODM, Deltex Medical, West Sussex, UK), and left ventricular outflow tract velocity-time integral (LVOT VTi) obtained by transthoracic echocardiography (TTE).

An end-expiratory occlusion (EEO) maneuver can be used to determine volume responsiveness of both the right and left ventricle together. This is essentially an end-expiratory hold for 15 s in a passive, mechanically ventilated patient, during which time preload to the right heart and then left heart increases. If both the RV and LV are volume responsive in parallel, then PP, SV, and CI will increase during this maneuver. Table 3.1 compares these techniques.

There are important limitations to these dynamic measurements. Most of these measurements have only been validated in patients who are in a sinus rhythm, completely passive, and receiving

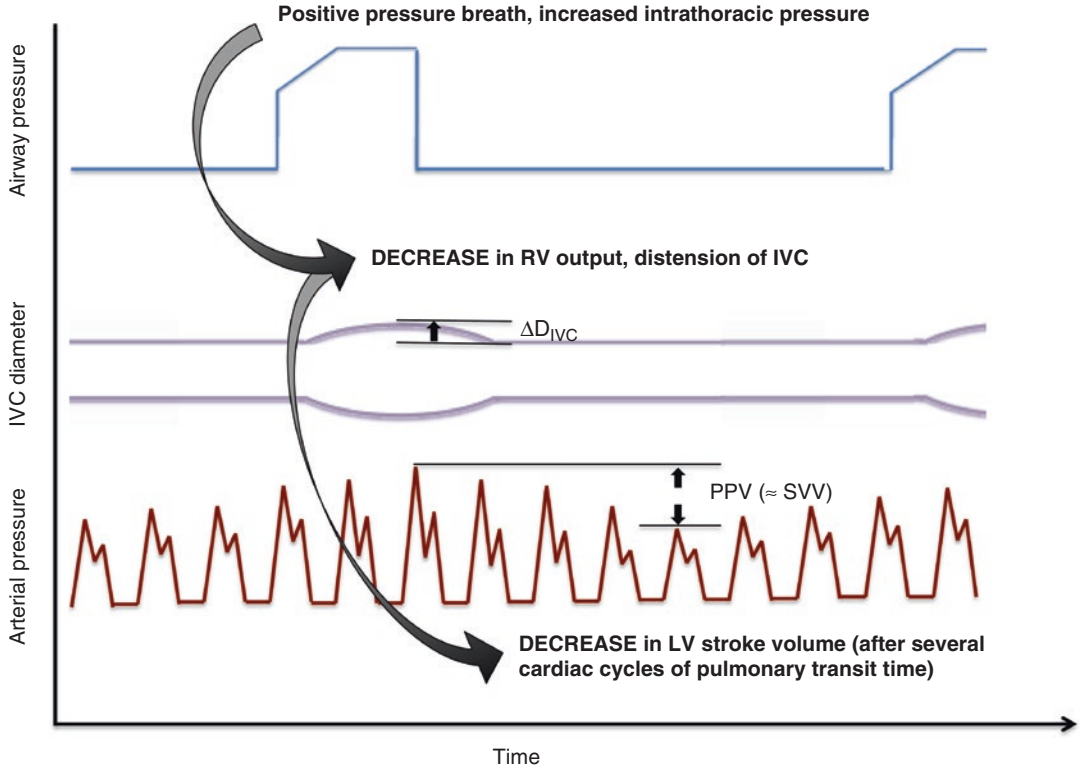

Fig. 3.5 Effects of positive pressure ventilation on IVC diameter and stroke volume variation. *RV* right ventricle, *IVC* inferior vena cava, ΔD_{IVC} change in diameter of IVC, *PPV* pulse pressure variation, *SVV* stroke volume variation, *LV* left ventricle

Table 3.1 Predictors of volume responsiveness during mechanical ventilation[a]

Measurement	Technique	Threshold for predicting volume responsiveness
PPV	Arterial waveform tracing	>13 %
SVV	Pulse contour analysis Esophageal Doppler monitor LVOT VTi using TTE	>10–13 %
PVI	Plethysmography	>10–15 %
ΔD_{IVC}	TTE	>12–18 %
ΔPP or ΔCI during EEO	Arterial waveform tracing PAC Pulse contour analysis Esophageal Doppler monitor	>5 % increase

PPV pulse pressure variation, *SVV* stroke volume variation, *LVOT* left ventricular outflow tract, *VTi* velocity-time integral, *TTE* transthoracic echocardiography, *PVI* plethysmography variation index, ΔD_{IVC} change in diameter of inferior vena cava, *ΔPP* change in pulse pressure, *ΔCI* change in cardiac output, *EEO* end-expiratory occlusion, *PAC* pulmonary artery catheter

[a]Requirements include: passive patient, tidal volume at least 8 mL/kg ideal body weight, sinus rhythm

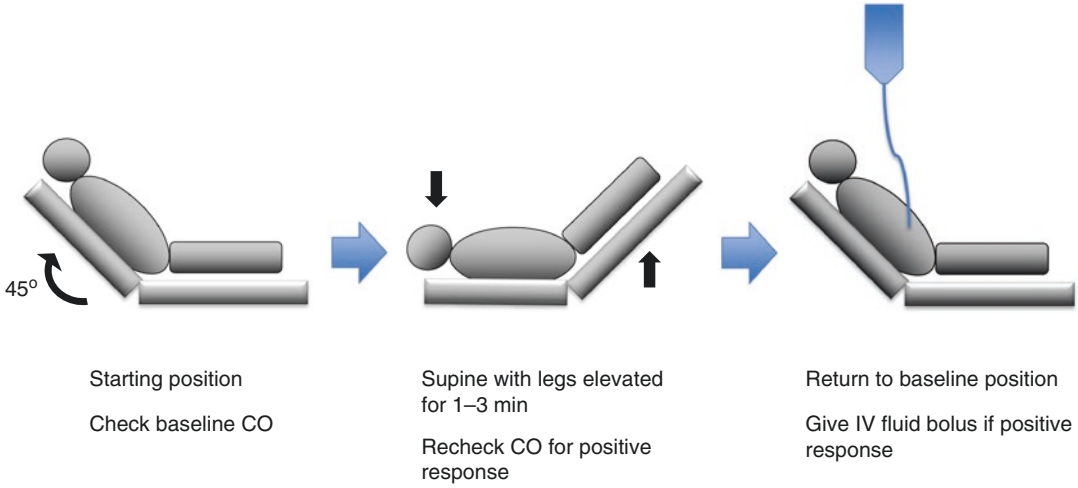

Fig. 3.6 Technique for positive passive leg raising. *CO* cardiac output

volume controlled breaths of at least 8 mL/kg tidal volume—conditions that apply to very few ICU patients in common practice. Furthermore, using indices of LV volume responsiveness in isolation may be misleading in patients with RV dysfunction (i.e. massive pulmonary embolism or pulmonary hypertension). These patients will have marked respiratory variation of SV and PP because the LV is relatively empty and preload dependent; however, the RV may be completely volume overloaded. If the RV itself is overloaded, giving intravenous fluid will not improve LV output and may cause hemodynamic deterioration (as seen in the case presentation). Combining SVV or PPV with an EEO maneuver or bedside echocardiography will help prevent this misinterpretation. Finally, decreased respiratory system compliance (e.g. severe ARDS, massive ascites, morbid obesity, etc.) may decrease the sensitivity of SVV or PPV; however, the accuracy of EEO appears unaffected by changes in compliance or positive end-expiratory pressure [26, 27].

Passive leg raising (PLR) may be the most accurate and widely applicable assessment of volume responsiveness (Fig. 3.6). For this test, a patient is laid supine and his/her legs are lifted up

Table 3.2 Thresholds for predicting volume responsiveness using passive leg raising (PLR)

Measurement	Technique	Threshold for predicting volume responsiveness
Pulse pressure	Arterial waveform tracing	Increase >12–15 %
Stroke volume	Pulse contour analysis Esophageal Doppler monitoring LVOT VTi using TTE PAC	Increase >12–15 %
Cardiac output, Cardiac index	Pulse contour analysis Esophageal Doppler monitoring LVOT VTi using TTE PAC	Increase >12–15 %
	Quantitative end tidal CO_2	Increase >5 %

LVOT left ventricular outflow tract, *VTi* velocity-time integral, *TTE* transthoracic echocardiography, *PAC* pulmonary artery catheter

to 45° and held up for 1–3 min; if SV, PP, CO or CI increase by 12–15 %, the patient is highly likely to be volume responsive (Table 3.2) [26, 28, 29]; continuous cardiac output monitoring is preferred for real-time assessments. As a surrogate for increased CO, a 5 % or more increase in $ECTO_2$ during PLR is also predictive of volume responsiveness, although this is not as sensitive [30]. The PLR retains its accuracy regardless of active respiratory efforts, tidal volume, level of sedation, or cardiac rhythm. Interpretation may be difficult in cases of massive ascites, abdominal compartment syndrome, or high pain response to the maneuver, and it should not be attempted in patients with elevated intracranial pressure.

Bedside Echocardiography

After assessment of volume responsiveness and initiating intravenous fluids as indicated, bedside echocardiography (BE) is the first test of choice to investigate undifferentiated shock [1]. Bedside echocardiography has been demonstrated to assist greatly in the determination of shock etiology in multiple clinical arenas. In the emergency setting, BE (along with multi-organ focused ultrasonography) can accurately differentiate between hypovolemic, cardiogenic, and obstructive causes of shock in patients with undifferentiated hypotension, and allow the examiner to correctly prioritize the most likely diagnoses in a timely fashion with high specificity and accuracy [31–34]. A simple, standardized approach to bedside ultrasound in undifferentiated hypotension has been shown to reduce diagnostic uncertainty, alter medical management, and influence the diagnostic or therapeutic plan in about one quarter of emergency cases [35].

In the ICU setting, BE within the first 24 h has been shown to significantly alter management in patients with hypotension, leading to less fluid administration and earlier use of inotropic support in many patients, reducing absolute mortality by 10 % in a small series [36]. In the perioperative, postoperative, and general ICU settings, echocardiography has been shown to accurately differentiate hypovolemia, volume overload, cardiac tamponade, and hemodynamically significant right or left ventricular dysfunction that otherwise may have otherwise gone undiagnosed [37–40].

There are several protocols for the use of point-of-care ultrasound in the hypotensive patient, and the key similarities among them are the systematic evaluation of cardiac function, pericardial effusion, IVC diameter and variability, pneumothorax, and sources of potential hemorrhage [41, 42]. When examining a hypotensive patient with ultrasound, the echocardiographic portion is the most important. The examiner should start with a subxiphoid view of the heart, determining any obvious decrease in global contractility as well as the presence of any significant pericardial effusion. A large pericardial effusion in the presence of hypotension is highly concerning for tamponade (Fig. 3.7). From the same location, the IVC should be located and assessed for respiratory variation, with a varying diameter or collapse suggestive of volume responsiveness (Fig. 3.8). Parasternal and apical

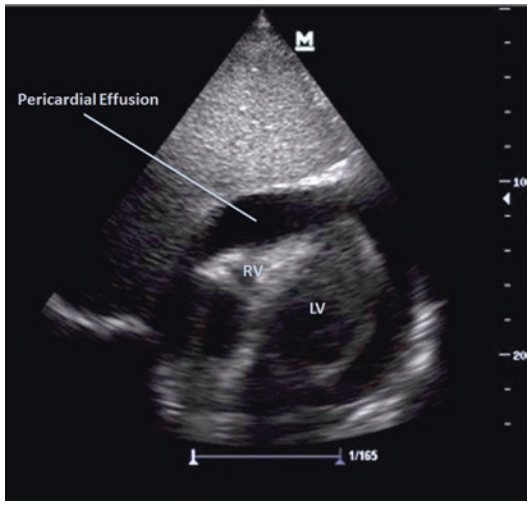

Fig. 3.7 Cardiac tamponade causing right ventricular collapse (transthoracic echocardiogram, subxiphoid view). *RV* right ventricle, *LV* left ventricle

views should be used to estimate global RV and LV systolic function (Fig. 3.9), RV size compared to LV size, and of utmost importance, the relationship of the interventricular septum (Fig. 3.10). Dilation of the RV (i.e. RV diameter approaching or exceeding LV diameter) and bowing of the septum from right to left suggests RV strain, which should prompt a search for pulmonary embolism or other causes of RV failure, as well as dissuade the clinician from using large fluid boluses or positive pressure ventilation if it can be helped [7]. After the cardiac portion, the examiner should look for bilateral lung sliding to rule out pneumothorax, free intraperitoneal fluid suggestive of hemorrhage, and abdominal aorta dilation >3 cm concerning for aneurysm. Echocardiographic patterns of shock type are summarized in Table 3.3.

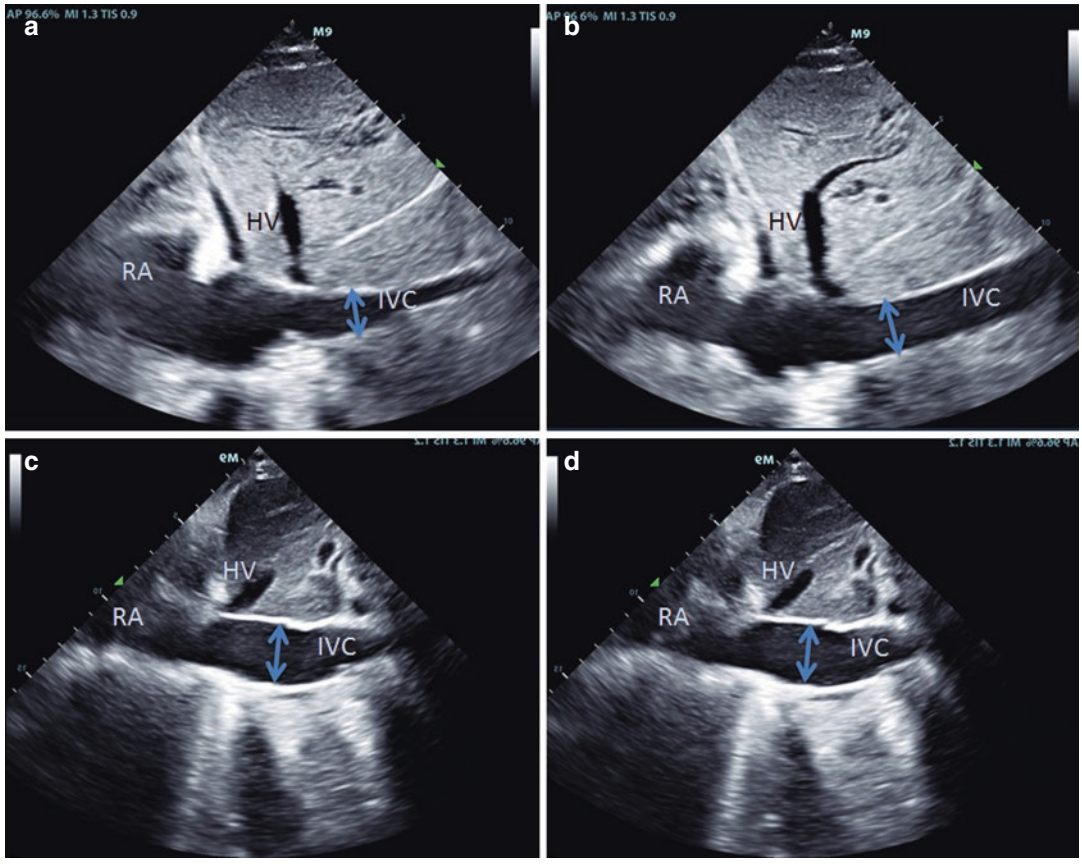

Fig. 3.8 IVC variation during respiration (transthoracic echocardiogram, subxiphoid view). **a** vs. **b**: roughly 50% IVC variation, suggests volume responsiveness. **c** vs. **d**: virtually no respiratory variation, suggests no response to fluid bolus. *IVC* inferior vena cava, *RA* right atrium, *HV* hepatic vein

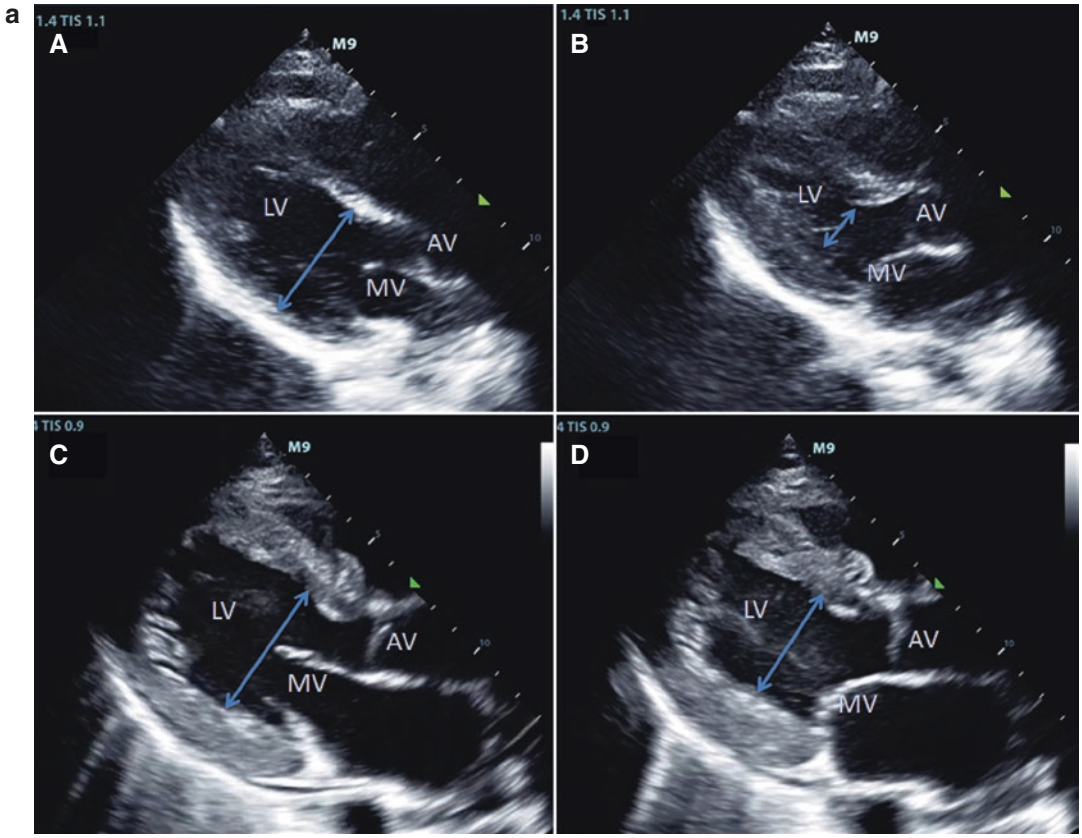

Fig. 3.9 (**a**) Global assessment of left ventricular contractility (transthoracic echocardiogram, parasternal long axis). *A* vs. *B*: roughly 50 % decrease in LV cavity, suggests normal contractility. *C* vs. *D*: roughly 25 % decrease in LV cavity, suggests moderately depressed contractility. *LV* left ventricle, *MV* mitral valve, *AV* aortic valve, *A and C* diastole, *B and D* systole. (**b**) Global assessment of left ventricular contractility (transthoracic echocardiogram, parasternal short axis). *A* vs *B*: roughly 40 % decrease in LV cavity, suggests mildly reduced contractility. *C* vs *D*: almost no decrease in LV cavity, suggests severely reduced contractility. *LV* left ventricle, *A and C* diastole, *B and D* systole

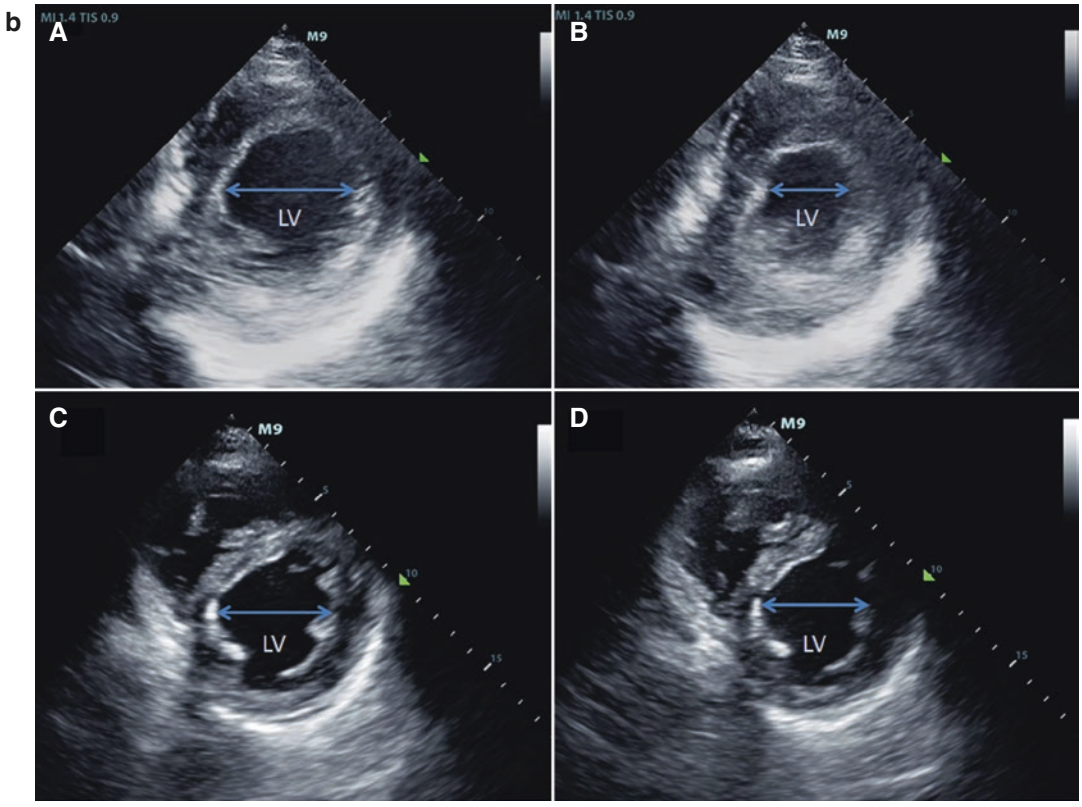

Fig. 3.9 (continued)

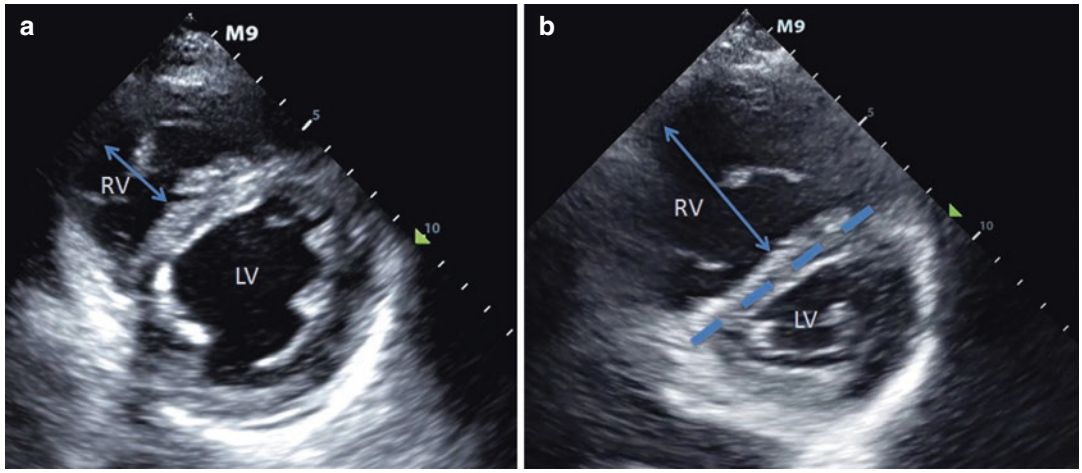

Fig. 3.10 RV-LV size relationship and position of intraventricular septum (transthoracic echocardiogram, parasternal short axis). (**a**) Normal relative RV and LV size, septum forms a contiguous circle with the LV. (**b**) Dilation of the RV with septal flattening ("D-sign") and compression of the LV, indicates RV strain/overload. *RV* right ventricle, *LV* left ventricle, *dashed line* flattened septum

Table 3.3 Echocardiographic patterns of shock types

Shock type	Suggestive echocardiographic findings
Hypovolemia	IVC collapsing on active inspiration Widely variable IVC diameter with respiration Hyperdynamic RV and LV
Distributive	IVC collapsing on active inspiration Widely variable IVC diameter with respiration Hyperdynamic RV and LV
Cardiogenic—Obstructive	*Pneumothorax*—absent lung sliding, identification of lung point *Tamponade*—pericardial effusion + distended, non-varying IVC ± RV collapse during diastole *Pulmonary Embolism*—distended, non-varying IVC, RV dilation, septal bowing, decreased RV contractility
Cardiogenic—RV	Distended, non-varying IVC RV dilation Septal bowing Decreased RV contractility
Cardiogenic—LV	Decreased LV contractility Dilated LV and/or LA ± distended, non-varying IVC

IVC inferior vena cava, *RV* right ventricle, *LV* left ventricle

Summary

Medically complex patients in shock should be assumed to have multiple shock types occurring simultaneously, and it may be difficult to differentiate these clinically. The use of static filling pressures such as CVP and PAOP are not helpful in determining which shock type(s) is/are present or in determining whether intravenous fluids will improve cardiac output. Targeting a specific CVP as a marker of adequate volume resuscitation is inappropriate, as positive fluid balance and elevated CVP have been associated with increased mortality, particularly in septic shock. The most important steps in the approach to undifferentiated shock are (1) determination of volume responsiveness, and (2) bedside echocardiography. There are multiple methods of determining volume responsiveness, with passive leg raising being the most accurate and widely applicable. After determining the appropriateness of a fluid challenge, bedside echocardiography should be used to look for IVC size and variation, pericardial effusion, RV size, and interventricular septal bowing, with added lung views for pneumothorax and abdominal views for free fluid and aorta caliber, to further differentiate shock type and guide the use of fluids, pressors, inotropes, or other specific therapies.

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