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REVIEW

One approach to circulation and blood flow in the critical care unit

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Abstract

Evaluating and managing circulatory failure is one of the most challenging tasks for medical practitioners involved in critical care medicine. Understanding the applicability of some of the basic but, at the same time, complex physiological processes occurring during a state of illness is sometimes neglected and/or presented to the practitioners as point-of-care protocols to follow. Furthermore, managing hemodynamic shock has shown us that the human body is designed to fight to sustain life and that the compensatory mechanisms within organ systems are extraordinary. In this review article, we have created a minimalistic guide to the clinical information relevant when assessing critically ill patients with failing circulation. Measures such as organ blood flow, circulating volume, and hemodynamic biomarkers of shock are described. In addition, we will describe historical scientific events that led to some of our current medical practices and its validation for clinical decision making, and we present clinical advice for patient care and medical training.

Key words: Shock; Volume status; Fluid; Vasopressors; Mean systemic pressure; Pulse pressure; Plethysmography variability index

Core tip: In this review, we depict the historical understanding of circulation and blood flow physiology. Also, by characterizing the different approaches to circulatory failure, we attempt to provide a simplified tool for education and one summarized clinical guideline for management in the critical care unit.

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INTRODUCTION

In the era of evidence-based medicine and quality measures, shock has become a synonym for critically ill patients. Shock has a significant effect on morbidity, mortality, and costs; septic shock has been associated with 40%-80% of all sepsis-related deaths in the hospital and has increased hospital costs to more than $3000 per day for these patients[1]. The management of patients with shock remains a challenge for clinicians and subspecialists involved in their care. Not only is circulatory failure common in the hospital and intensive care unit (ICU) setting (to the point that administrative efforts by the hospitals are now made to protocolize management), but it is also such a common problem that physicians sometimes focus more on symptomatic stepwise approaches than on understanding the disease process to determine the best treatment.

In this review we will discuss the pathophysiology of shock, the assessment of volume status, and approaches to management.

DEFINITIONS AND PATHOPHYSIOLOGY

Shock

For the medical practitioner in charge of the ICU, shock is the clinical manifestation of inadequate blood flow and circulatory failure[2]. Some define it as insufficient oxygen delivery; the problem with this definition is that there are overlapping diseases of the respiratory tract associated with hypoxemia, which cause inadequate tissue oxygenation but not necessarily a state of shock.

Hypotension

Blood pressure determines the blood flow distribution but does not define the state of shock or the adequacy of circulation. Manual blood pressure readings are an appropriate way to determine blood pressure, but an arterial line continues to be the best practice when more accurate readings are needed, even though arterial lines are invasive, painful, and difficult in patients with vascular disease and have a variety of complications.

To understand circulatory failure, it is paramount to recognize that blood pressure and flow are uncoupled physiological processes. From basic physiology, we know that in the range of acceptable blood pressures and normal circulation, all vital organs (including the brain and kidneys) have a wide array of blood flow patterns that are completely disengaged from blood pressure; thus, clinicians will be incapable of making any assumptions about organ flow and cardiac output based on blood pressure alone (Figures 1 and 2, Table 1)[3,4].

Regulation of blood flow

In basic science classes, we learn about the physiology of cardiovascular circulation based on the idea that organ blood flow is similar to electric voltage and currents; consequently, we have adapted Ohm's principle of conduction for a better understanding of the cardiovascular system: Voltage (V) = electric current (I) x resistance (R). Replacement with hemodynamic parameters results in mean arterial pressure (MAP) – right atrial pressure (PRA) = cardiac output (CO) x systemic vascular resistance (SVR): MAP – PRA = CO x SVR.

For explaining the theoretical bases of hemodynamics and flow, this equation is adequate. The clinical application of this equation fails since it neglects the fact that humans have baroreceptors and reflex responses to changes in pressure. Therefore, when CO decreases, there is an instantaneous vasoconstrictor response to maintain equilibrium within the system, thereby maintaining a normal blood pressure. Understanding this concept is imperative, since patients may become overtly hypertensive with low cardiac output or uncalibrated/dysfunctional baroreceptors[5,6].

The sicker the patients become, the more difficult it is for the cardiovascular system to increase the SVR to maintain balance; when the ability to increase the SVR is

Table 1 Types of shock and relationship with blood pressure and cardiac output

	Blood pressure	Cardiac output
Hypovolemic	?	↓
Cardiogenic	?	↓
Obstructive	?	↓
Distributive	↓ (Most of the time)	?

?: May be high, normal, or low.

exhausted, patients develop hypotension. Conversely, when patients present with a vasodilated state (*e.g.*, septic shock), they will attempt to increase the CO to preserve an adequate MAP, and as the blood pressure continues to drop, they may reach a point at which the ability to increase the CO is surpassed, following which they become overtly hypotensive. These ideas indicate that low blood pressure is a late and insensitive indicator of inadequate circulation[7]. Furthermore, this concept applies when you are describing cardiogenic shock[8], sepsis[9], cardiac tamponade[10], or traumatic shock[11]. For example, an ICU patient with class 3 hypovolemic shock (Table 2) exemplifies the fact that 40% of the blood volume needs to be lost before the blood pressure decreases.

Understanding this concept will afford a clinical advantage when assessing the patient as one will know that hypoperfusion may be the result of a low SVR, a low CO, or a high SVR in the setting of a critically depressed CO. As a result, planning medical care and prognosis based solely on blood pressure may not work. In 2013, Lehman *et al*[12] reported interesting data related to the clinical applications of these concepts and observed that only when the MAP dropped below 70 mmHg did the risk for acute kidney injury and/or mortality increase.

Adequacy of circulation and venous oxygenation

For more than 20 years, critical care medicine has been trying to assess the adequacy of circulation. There are overwhelming data and information on mixed venous oxygen saturation (SvO_2), lactic acid, and clinical signs and symptoms, such as mental status and urine output.

We should start with an understanding of adequate oxygen (O_2) delivery and consumption to assess SvO_2. A healthy individual deliver approximately 1,000 ml/min of oxygen to peripheral tissues, and the tissues extract nearly 25% of the oxygen [extraction ratio (ER)]. In low-oxygen delivery states, such as low CO, anemia, or hypoxia, there is an increase in the extraction of oxygen that continues until the low O_2 state is either corrected or surpasses the capacities of the tissues to extract O_2 (approximately 60%–70% ER). At this point, any further decline in O_2 delivery will cause an abrupt decline in O_2 consumption, with deterioration of the clinical condition (Figure 3, Table 3). As a result, assessing SvO_2 provides a quantitative method of assuring that patients do not encounter the critical points of O_2 consumption and extraction. With a better understanding of oxygen physiology in ICU patients, the concepts of venous oxygen saturation in central venous catheters ($ScvO_2$) *vs* mixed venous oxygen saturation in pulmonary artery catheters (SvO_2) were developed. The conclusion from regression analysis and determination coefficients (R^2) was that there is no significant difference between the two assessment tools with R = 0.945, SvO_2 = 1.16 ($ScvO_2$)$^{0.96}$[9,13]. In clinical practice, this translates to two different procedures with different risks, costs, and complications but with similar medical utility.

Early goal-directed therapy

Because of the similar findings and the lesser risk associated with the insertion of a central venous catheter compared to a pulmonary artery catheter, $ScvO_2$ became an important measurement in the original "early goal-directed therapy (EGDT) in the treatment of sepsis and septic shock"[9] (Figure 4). With the implementation of the EGDT across the board as a standard of care for sepsis and septic shock, it was found that the clinical validity for $ScvO_2$*vs* SvO_2 performed well for sepsis and septic shock (R = 0.88 – R = 0.89, $P < 0.001$)[14,15], but not as well for cardiac surgery patients (R = 0.72, $P < 0.001$ – $ScvO_2$ most reliable > 70%)[16]. Therefore, for patients with significant cardiac disease/cardiac surgery, $ScvO_2$ and SvO_2 are not interchangeable for medical decision making.

A series of clinical trials concerning EGDT and clinical outcomes have been performed through the years. The ProCESS trial published in 2014 compared the EGDT *vs* an alternative protocol *vs* usual care. There was no difference in 60-d (P =

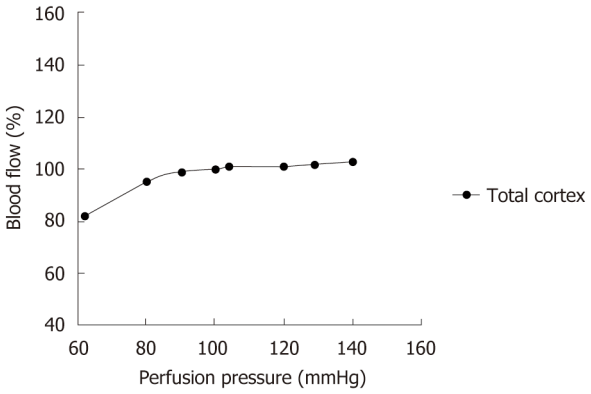

Figure 1 Renal autoregulation. Total renal blood flow over a range of perfusion pressure. Adapted from[61].

0.52) or 1-year mortality (P = 0.92)[17]. Similar findings were published in 2015 in a trial by Mouncey *et al*[18], in which 1200 patients were randomized to EGDT *vs* usual care, with no difference in mortality outcomes (P = 0.63).

Lactate

Lactic acid measurement has become an important method for the assessment of critically ill patients while avoiding the cumbersome process of obtaining central venous oxygen saturation. Some of the initial algorithms for the use of lactate measurements in the ICU involved combining the measurements with $ScvO_2$, to provide a stepwise approach for guiding the resuscitation of patients with circulatory failure: If lactate > 3.0 meq/L, then the $ScvO_2$ should be checked, and if it is not more than 3.0 meq/L, then there is no need to check the $ScvO_2$[19]. However, when serum lactic acid was compared to $ScvO_2$ as the goal for resuscitation of patients with sepsis and septic shock, there was no difference in outcome[20]. Considering these outcomes, there has been a shift in clinical practice from using central venous oxygen saturation to lactate in patients with sepsis and septic shock (*i.e.*, for patients without major cardiovascular disease).

Circulating volume/volume status

What is the volume status in the ICU patient? We do not know. A more definite answer is "nobody knows". However, to better understand, assess, and manage volume in critically ill patients, we need to first recognize what we do know about circulating volume and the fact that physical examination, regardless of many years of training and experience, is neither sensitive nor specific[21].

In the 1950s, Guyton *et al*[22]'s experiments with the Frank and Starling models of cardiac physiology gave rise to some interesting concepts regarding circulation and blood flow. One of his conclusions regarding venous return (VR) physiology is that when the PRA and the mean systemic filling pressure (PMS) are equal, there will be no return of blood to the heart: VR = (PMS – PRA)/resistance to the venous return (RVR).

Furthermore, Guyton *et al*[23]'s model established that PRA is not an indicator of circulating volume but a marker of pressure exerted by the venous system for the return of blood to the heart; thus, the lower the PRA, the higher the venous return[23] (Figure 5). With his description, we understood the importance of the PMS as the driving force for the return of blood volume back to the heart and one of the most useful parameters for assessing the actual circulating volume status[24].

Central venous pressure and capillary wedge pressure

With the understanding of the mechanistic aspect of circulatory physiology described with the Starling curve (Figure 6) and the notion of venous return by Guyton's model, it is possible to extrapolate the central venous pressure (CVP) as a product of the interaction between the venous system and cardiac function. Under those circumstances, the clinical inference from the CVP measured in patients is that, regardless of the number, it is lower than the mean systemic venous pressure (Figure 7).

Although the bedside utility of CVP alone for predicting volume responsiveness and medical decision making is not ideal, it is, however, a measurement available for the evaluation of critically ill patients with circulatory failure. The CVP alone in the ICU does not correlate with either the circulating volume status (R = 0.27)[25] or the clinical response to volume/fluid administration[26]. Similarly, the estimated left atrial pressure by pulmonary capillary wedge pressure (PCWP) via the more invasive

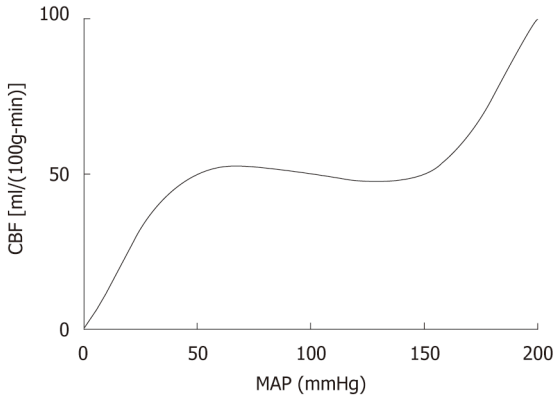

Figure 2 Cerebral autoregulation. Blood flow over a range of perfusion pressures. Reproduced from[4] with permission of the Society of Photo Optical Instrumentation Engineers (SPIE)

pulmonary artery catheterization (Swan-Ganz catheter) was once considered to be one of the most reliable methods to assess the ventricular preload and circulating volume. This method was one of the characteristic features of critical care medicine, but has been shown to underperform in the clinical setting in predicting responsiveness to intravascular volume administration[27].

Peripheral vs central venous pressure

As an available tool, the CVP continues to be widely used alone or in combination with other parameters to enable an educated guess about the venous system volume status. An alternative and less invasive method, which provides an equivalent physiological estimation of the volume status, is the peripheral venous pressure (PVP). The PVP is a tool that is inadequately and seldom used, is less invasive, requires the same transducer/equipment as the CVP, and has similar results. Any patent peripheral intravenous access (for flushing and drawing) may be used for measuring PVP. One does need to adjust the value of PVP by subtracting 2 mmHg. Thus, PVP = CVP + 2 or PVP – 2 = CVP[28]. The PVP not only is useful but also has been validated in many clinical scenarios in humans and animals (R = 0.97)[29,30]; its validity has been tested and proven in surgical patients (for surgical scenarios such as brain, abdominal, and cardiac surgery), in ICU patients, and in pediatric patients[28,31,32].

ASSESSMENT OF THE PATIENT WITH CIRCULATORY FAILURE

Once the basic concepts of blood flow and circulating volume are understood for a critically ill patient with circulatory failure, the next step is to determine if the patient responds to volume expansion. The most physiologically correct method to determine this is by measuring the mean systemic pressure (PMS). Currently, we do not have a validated clinical tool to measure the PMS in the hospital. However, there is research in the Netherlands with noninvasive devices to quantify the PMS and predict volume responsiveness, which may entirely change our methods of approaching and managing shock and volume administration[33].

Mean systemic pressure, systolic pressure variation, and pulse pressure variation

Since we do not currently have a way to measure PMS in our patients, what has been done through the years for assessing the circulating volume status and volume administration is to measure indices, such as the systolic pressure variation (SPV) and pulse pressure variation (PPV) in mechanically ventilated patients with circulatory failure[34] (Figure 8). The idea behind using these volumetric indicators (SPV and PPV) comes from the expected fluctuation of the Frank-Starling curve with mechanical ventilation and the minimal variability in the systolic and pulse pressures on the flat portion of the Starling curve. However, as volume depletion develops, the venous return decreases, and the system shifts towards the steep portion of the Starling curve, resulting in an increase in the variability in systolic pressure and pulse pressure. The implication is that the higher the PPV and SPV, the greater the expected response to volume administration, and this provides a guide for volume resuscitation[35].

The correlation between PPV/SPV and respiratory changes has been widely

Table 2 Hypovolemic shock categories

	I	II	III	IV
Blood loss (mL)	Up to 750	750-1500	1500-2000	> 2000
% of blood loss	Up to 15	15-30	30-40	> 40
Blood pressure	Normal	Normal	Decreased	Decreased
Mentation	Preserved	Anxious	Confused	Lethargic

Summary as described by the American College of Surgeons in The Advanced Trauma Life Support training program.

validated as a means to predict volume responsiveness in different scenarios, with sensitivities and specificities of 94% and 96%, respectively. For septic shock, the correlation (R = 0.85) is higher than the PCWP and PRA (R = 0.5 for both RAP and PCWP)[35]. It also performs well after cardiac surgery compared with the CVP and PCWP (PPV/SPV: R = 0.8, CVP/PCWP: R = 0.5)[36,37]. The two most important clinical scenarios in which PPV/SPV are known to fail are right ventricular failure (*e.g.*, right ventricular infarction, cardiomyopathy, and pulmonary hypertension) and obstructive shock (*e.g.*, tension pneumothorax, abdominal compartment syndrome, and cardiac tamponade)[35,38].

However, what if the patient is not mechanically ventilated, is spontaneously breathing, does not have a regular heart rate or on adequate tidal volume—can PPV and SPV still be used? The answer is yes, they can. The requirement for specific ventilatory parameters has been challenged, and both PPV and SPV tests work well in patients breathing spontaneously, with an AUC (area under the curve) of more than 0.8 for both. However, it is important to be cautious when using PPV/SPV with spontaneously breathing patients due to the varying reliability and results with changes in breathing patterns[39,40]. Similarly, the need for arterial catheter insertion to measure the changes in PPV/SPV has been questioned, and plethysmographic waveform changes by pulse oximetry make it possible to calculate the plethysmography variability index (PVI). Subsequently, validated with comparable results as the more invasive PPV/SPV, the PVI can detect circulatory volume changes as low as 4%. Measurements with blood pressure require > 30% reduction in circulatory volume for hypotension to be present. A PVI of more than 17% will correlate with volume responsiveness. Furthermore, the PPV will change in parallel to the PVI (R = 0.85, $P < 0.001$), making it an excellent tool for evaluating patients with circulatory failure[41,42].

Cardiac output

Interestingly, in the acute care setting when the patient has developed circulatory failure, knowing and calculating the current blood flow is not as essential as understanding and assessing the consequences of appropriate blood flow, such as mental status, urine output, lactic acid level, and even central venous oxygen saturation. Moreover, pulse pressure (PP) is one of the more reliable correlates of low cardiac output (Table 4) since the aorta functions as a left ventricular counterpulsation balloon pump, stretching during systole and contracting during diastole while maintaining the mean arterial pressure with changes in flow, but the PP will vary with the amount of volume per stroke. This translates to a scenario in which the more that the stroke volume decreases, the more that the PP will decrease, giving enough information for medical decision making in the ICU. However, if the need is to know and quantify the cardiac output, then there are numerous devices available in hospitals to do so.

In summary, before adding more accessories to measure cardiac output, we recommend going back to your previous answers when assessing the patient. If your biological markers (*e.g.*, urine output, mental status) and your surrogates of blood flow (*e.g.*, lactate, central venous saturation) are within normal limits, then the cardiac output should not be the major concern. On the other hand, if the available bedside tools fail to support your clinical assessment about the cardiac output, we recommend more physiological substitutes for blood flow and stroke volume, such as the PP to make inferences and medical decisions.

VOLUME MANAGEMENT IN A NUTSHELL

The "silver lining" of restoring adequate circulation is the balance between

Table 3 Conditions that affect the venous oxygen saturation measurement

Condition	SvO_2 change
Anemia (Hemoglobin < 8)	↓
Low cardiac output	↓
Agitation	↓
Sepsis	↑
States of hypoxia	↓
Anesthesia (↓ O_2 utilization)	↑

Normal SvO_2: 60%-80%.

reestablishing tissue perfusion with the appropriate/physiological distribution of blood flow by improving circulatory volume and avoiding iatrogenic volume excess. In the event of hypovolemic failure (regardless of the state of shock), the treatment is to replace the volume. Needless to say, hemorrhagic shock necessitates blood transfusion.

The classic example of the most common type of shock seen in the ICU is a septic shock patient who has not felt well before admission, not eating or drinking, and who developed a low volume state from lack of water (dehydration) and solutes (nutrition). This is in addition to the associated loss of fluid from increased capillary permeability, which is part of the septic process, and this loss of extra volume from the intravascular space into the interstitium leads to a state of relative hypovolemia superimposed on actual hypovolemia. Additionally, septic shock also induces maladaptive venous vasodilation, which decreases the circulatory blood flow return to the heart even after adequate fluid replacement[43]. It may also cause cardiac dysfunction and vasomotor paralysis to the point that patients need inotropes and sometimes corticosteroids[2].

Protocols for optimal preload optimization and volume administration have been used in the clinical setting to improve outcomes (as previously discussed in the section: "Definitions and Pathophysiology"), but no benefit in survival or prevention of developing new organ failure has been achieved using protocolized fluid therapies. If anything, when comparing the fluid administration for patients receiving a lower total amount of fluid per usual care against the protocols, there may, in fact, be an association with renal dysfunction and the need for dialysis (P = 0.04) with the protocolized fluid therapies[17,44].

Type of fluid

The type and composition of fluid given do seem to matter. Recently published, the Isotonic Solutions and Major Adverse Renal Events Trial concluded that the use of balanced crystalloid solutions is overall better than the use of saline solutions, with less adverse kidney events (P = 0.04) and lower 30-d mortality (P = 0.02)[45]. Normal saline (0.9% NaCl) is the most commonly administered solution in our hospital and around the world[46]. Some of the problems associated with chloride-rich solutions include the development of hyperchloremic acidosis with an increase in morbidity and mortality outcomes[47-50]. On the other hand, the Saline vs Plasma-Lyte for ICU fluid Therapy trial did not show any difference in outcomes between the two solutions studied (P = 0.85), although it is important to mention that these patients received, on average, a total of less than 2 liters of either solution throughout the whole study. Additionally, this amount of fluid may not be enough compared with the fluid quantities used for resuscitation and maintenance for ICU patients with circulatory failure[51]. One clinical scenario in which normal saline should be the principal solution to use is in patients with intravascular volume depletion, metabolic alkalosis, and hypochloremic hyponatremia (*e.g.*, over diuresis).

Hydroxyethyl starch is known to be nephrotoxic and is not used currently in the United States for fluid resuscitation (it was never used that much before either)[52]. Other colloids, such as albumin and gelatins, remain valuable tools when used appropriately (Table 5). However, no significant clinical benefit from using colloids instead of crystalloids for volume resuscitation has been demonstrated[53,54].

Vasopressors and corticosteroids

Several different classes of vasopressors, including inotropic agents, are widely available and used in the treatment of shock for primarily inducing vasoconstriction, increasing mean arterial pressures, and optimizing blood flow and tissue perfusion.

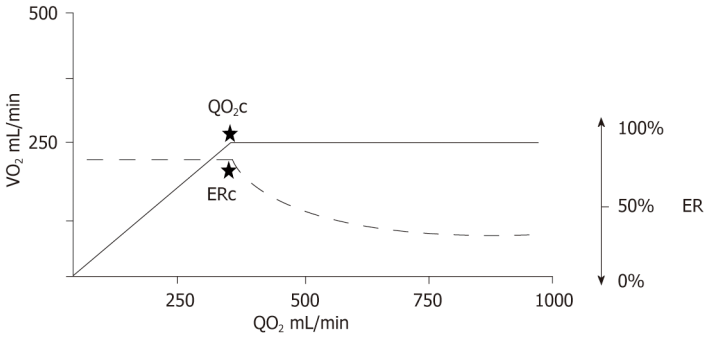

Figure 3 Relationship between oxygen delivery and venous oxygenation/oxygen consumption. VO_2: Oxygen consumption; QO_2: Oxygen flow delivery; ER: Extraction ratio; ERc: Critical point of extraction; QO_2c: Critical point of delivery.

The three main categories that divide vasopressors are catecholamines (*e.g.*, epinephrine, norepinephrine, dopamine), non-adrenergic drugs (*e.g.*, vasopressin, angiotensin II), and other adrenergic agonists (*e.g.*, phenylephrine, midodrine, dobutamine).

Despite the fact that there is no difference in survival between norepinephrine and dopamine as the first-line agent for the treatment of shock (P = 0.07), there are significantly more adverse events related to arrhythmias (atrial fibrillation, ventricular tachycardia, ventricular fibrillation) with dopamine, and for this reason, its use has declined significantly over the years[55]. Although phenylephrine has not been tested against norepinephrine and continues to be widely available, there have been observational data reported after the 2011 shortage of norepinephrine in the United States which showed increased in-hospital mortality when phenylephrine is used as first line agent[56].

Vasopressin performs as well as norepinephrine and is a useful medication for second-line therapy if needed[57]. The new vasopressor being used more frequently in the ICU is angiotensin II. The Angiotensin II for the Treatment of Vasodilatory Shock (ATHOS-3) trial demonstrated that it works well for vasodilatory/high output shock, has a great safety profile, and has minimal side effects. It is an excellent second-line therapy currently and will be so the near future, with appropriate concerns about price and availability[58]. Corticosteroid use in septic shock has been debated throughout the years and is recommended for refractory shock per Surviving Sepsis guidelines. These drugs do not have any other proven benefit in this clinical setting[59,60].

In summary, we recommend avoiding dopamine as a first line drug due to the severity of side effects and possibility of harm. We continue to use norepinephrine as the first line agent, but vasopressin is also an option for either first or second drug choice. If available, angiotensin II will work well as second line vasopressor; it is possible that phenylephrine may lead to worse outcomes if used as first line therapy.

CONCLUSION

Accuracy in diagnosis with selection of the right tool for assessment and not simply symptomatic treatment must be a strategic element in the care provided to patients with circulatory failure. Understanding physiological concepts is vital. More importantly, learning and practicing medicine based only on protocols and flowcharts will always exclude an important portion of the science. The careful understanding and management of circulation must be part of daily clinical practice. Changing dogmas in medicine generates apprehension as the illusion of knowledge and expertise becomes vulnerable, but we as health care providers should continue evolving for the benefit of our patients.

Intravenous fluid solutions are more similar to drugs than is acknowledged and therefore need to be used with care and precision. The composition of the fluid does matter, but only if the patient is alive. When administering intravascular fluids, targets such as the restoration of intravascular volume should have more impact on medical decisions than urine output or blood pressure. Extravasation of water and solutes can occur, and for this reason, we need to be mindful that not every patient in a hospital bed needs a fluid bolus.

Table 4 Correlates of low cardiac output

	Low CO	High CO
Blood pressure	↓	↓
Heart rate	↑	↑
Systemic vascular resistance	↑	↓
CO	↓	↑
Pulse pressure	↓	↑

CO: Cardiac output.

Table 5 Crystalloid *vs* colloid solutions

Crystalloid	Colloid
Lower price	Expensive
Believed to be safer	Some toxic (hydroxyethyl starch)
Higher amount needed for resuscitation	Less required
Slower action	Faster action
Moves out the intravascular space faster	Remains in circulation longer

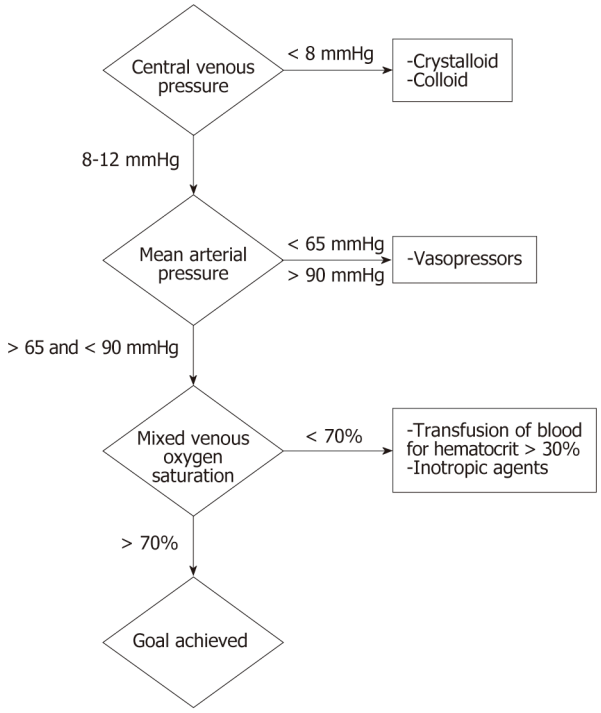

Figure 4 Protocol for early goal-directed therapy. Adapted from[9].

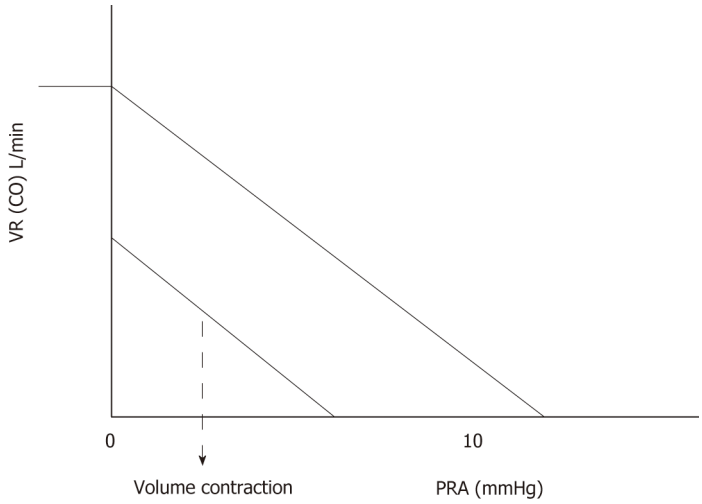

Figure 5 Guyton's model of venous return and cardiac output in relation to the right atrial pressure. Adapted from[62].

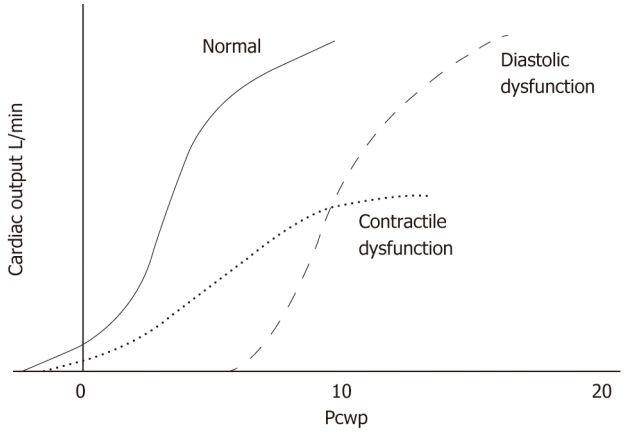

Figure 6 Frank-Starling curves representing normal contractility, diastolic dysfunction, and contractile dysfunction. Pcwp: Pulmonary capillary wedge pressure. Adapted from[63].

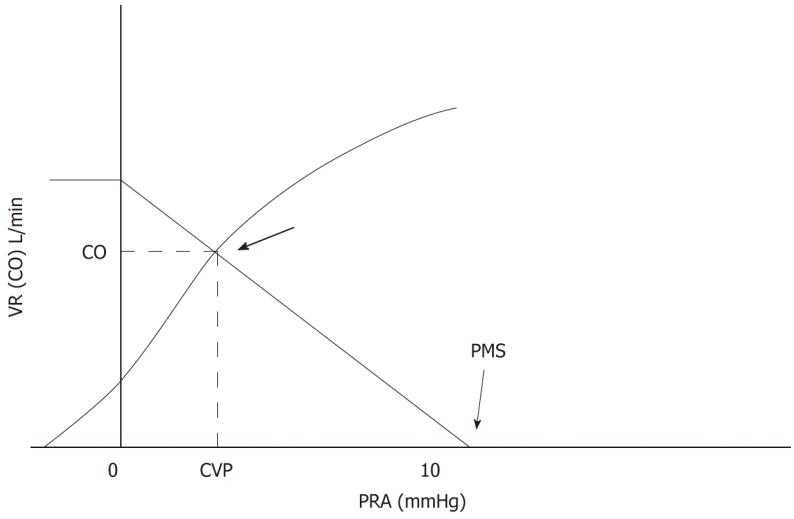

Figure 7 Modified cardiac function curve representing the central venous pressure measured in the clinical setting by superimposing Guyton's model of venous return and Frank-Starling contractility curve. CO: Cardiac output; CVP: Central venous pressure; PRA: Right atrial pressure; VR: Venous return; PMS: Mean systemic filling pressure. Adapted from[62].

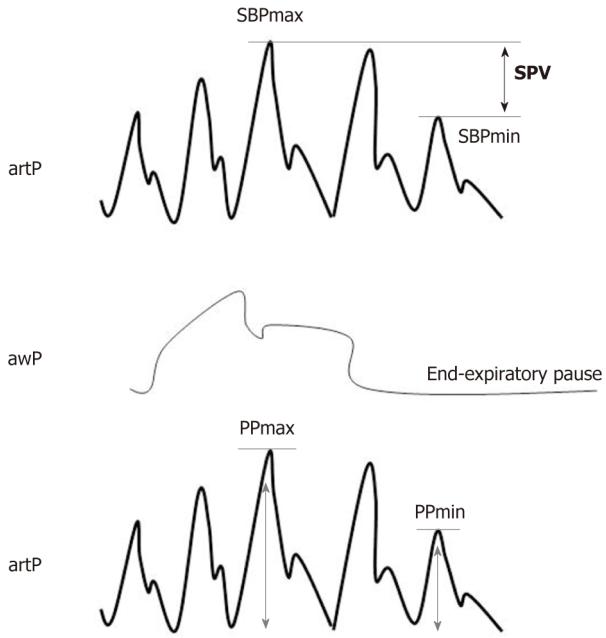

Figure 8 Description of the systolic pressure variation and pulse pressure variation during mechanical ventilation. SPV: Systolic pressure variation; PPV: Pulse pressure variation; artP: Arterial pressure; awP: Airway pressure; SBP: Systolic pressure. PP = 100 x (PPmax – PPmin) / [(PPmax + PPmin)/2].

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MINIREVIEWS

Independent lung ventilation: Implementation strategies and review of literature

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Abstract

Independent lung ventilation, though infrequently used in the critical care setting, has been reported as a rescue strategy for patients in respiratory failure resulting from severe unilateral lung pathology. This involves isolating and ventilating the right and left lung differently, using separate ventilators. Here, we describe our experience with independent lung ventilation in a patient with unilateral diffuse alveolar hemorrhage, who presented with severe hypoxemic respiratory failure despite maximal ventilatory support. Conventional ventilation in this scenario leads to preferential distribution of tidal volume to the non-diseased lung causing over distension and inadvertent volume trauma. Since each lung has a different compliance and respiratory mechanics, instituting separate ventilation strategies to each lung could potentially minimize lung injury. Based on review of literature, we provide a detailed description of indications and procedures for establishing independent lung ventilation, and also provide an algorithm for management and weaning a patient from independent lung ventilation.

Key words: Unilateral lung injury; Unilateral pneumonia; Double lumen tube; Differential lung ventilation; Acute lung injury; Ventilator induced lung injury

Core tip: Severe unilateral lung disease presents a unique scenario where the diseased lung has very poor compliance, while the non-diseased lung remains normally compliant. In these patients, conventional positive pressure ventilation causes preferential distribution of tidal volume to the non-diseased lung causing its

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overdistension and inadvertent volutrauma. Placement of a double lumen endotracheal tube and providing independent lung ventilation, with a ventilator for each lung, can potentially minimize lung injury. This will allow institution of lung protective ventilation strategies to each lung, individualized based on their respective compliances.

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INTRODUCTION

Independent lung ventilation (ILV), though infrequently used in the critical care setting, has been reported by various authors as a rescue strategy for patients with unilateral lung pathology. These are mostly confined to case reports or small case series, but span a variety of patient populations, including medical[1-3], surgical[4-6], pediatric[7-10], and trauma[3,11]. ILV involves anatomical as well as physiological separation of each lung into separate units, and the success of implementation depends on the experience of the critical care team with ILV. Outside of a critical care setting anatomical separation of the lung is routinely performed in thoracic surgical operating rooms to either facilitate lung surgeries or to improve surgical exposure during other intrathoracic procedures. The complexity and lack of experience of many providers with ILV makes it an underutilized ventilation strategy in the intensive care unit (ICU). Here, we describe the use of ILV for management of respiratory failure in a patient with unilateral diffuse alveolar hemorrhage. We then critically review available literature on the use of ILV and provide a detailed description of indications and procedures for establishing ILV and provide an algorithm for management and weaning a patient from ILV.

CASE

Recently, we cared for a 63-year-old man who presented to our surgical ICU with hypoxemic respiratory failure. His medical history was notable for hepatitis C, atrial fibrillation, myelodysplasia treated with allogenic stem cell transplantation complicated by graft *vs* host disease and persistent thrombocytopenia. His chest X-ray showing complete white out of the right lung. Though aspiration, and unilateral pneumonia were important differentials, unilateral diffuse alveolar hemorrhage was the most likely etiology in the setting of his severe thrombocytopenia. Severe hypoxemia persisted (P/F about 60) despite tracheal intubation and mechanical ventilation. X-ray continued to show complete white out of right lung, and suggested over inflation of the left lung. With continued worsening of hypoxemia, we decided to place a double lumen tube, and independent lung ventilation was initiated as a rescue measure. Independent lung ventilation lead to improvement in oxygenation, and allowed titration of ventilation parameters independently for each lung based on their best compliance. Once his unilateral lung pathology improved substantially, he was transitioned back to a single lumen endotracheal tube and conventional ventilation was resumed. He was eventually weaned and extubated after 10 d of mechanical ventilation.

DISCUSSION

Independent lung ventilation requires anatomical and physiological separation of the lungs. Anatomical separation involves physical isolation of one lung from the other, while physiological separation refers to ventilating the two lungs independently as separate units. The focus of this article is on physiological separation of lungs, specifically, indications as well as ventilation and weaning strategies in patients receiving ILV. Techniques for anatomical separation is well described elsewhere[12-14].

The indications for ILV in a critical care setting may be broadly classified into two types based on the need for anatomical separation alone *vs* need for physiological separation of the lungs (Table 1). Anatomical separation is typically sought for

conditions which require lung isolation to prevent cross contamination of the healthy lung by harmful material contained within the diseased lung. Physiological separation of lung is instituted for refractory respiratory failure resulting from unilateral lung disease, causing marked differences in pulmonary mechanics between right and left lung. For instance, in the presence of a poorly compliant diseased lung, such as in our case, conventional positive pressure ventilation would result in preferential over distension of the non-diseased lung potentially causing volutrauma to the non-diseased lung[15]. In addition, over distention of the non-diseased lung could result in diversion of pulmonary blood flow to the diseased lung thereby worsening shunt and hypoxemia[16]. Institution of an independent ventilation strategy for each lung may prevent volume trauma to the non-diseased lung, reduce shunting and allow for alveolar recruitment in the diseased lung.

The most commonly reported indications for ILV include differential lung injury due to unilateral pneumonia[1,3,7,17], large air leak from bronchopleural fistula[6,18], pulmonary hemorrhage[6,19], and pulmonary contusion[3,11,20]. ILV has been reported to be useful in patients who develop primary graft dysfunction following single lung transplantation, resulting in a poorly compliant graft lung and a native lung with markedly different lung mechanics[5,21]. However, the data on single lung transplantation is from one center, and additional factors such as role of early extracorporeal membrane oxygenation (ECMO), and effect of double lumen tube (DLT) on bronchial anastomotic healing needs to be considered.

When to perform lung isolation?

The severity of unilateral lung disease where one should consider ILV is unclear. Most reports have instituted ILV as a rescue strategy after conventional ventilation failed to maintain adequate oxygenation or ventilation. It can be argued that early institution of ILV may be more beneficial in reducing ventilator induced lung injury superimposed on the existing lung injury especially in the non-diseased injured lung. This is especially important with accumulating evidence favoring use of low tidal volumes during positive pressure ventilation of normal healthy lungs[22]. It is conceivable that by reducing lung injury and decreasing shunt, the use of ILV might decrease the need for utilizing more invasive strategies like ECMO, associated with a higher risk of complications. Moreover, ECMO is contraindicated in presence of thrombocytopenia (as in our patient), disseminated intravascular coagulation, or recent tPA use. In addition, ECMO requires a dedicated team and advanced institutional capabilities, which might not be available in resource poor locations. Thus, ILV is likely underutilized and there maybe potential benefit from earlier institution of ILV than typically reported.

Considerations for lung isolation in the intensive care unit

A DLT is most commonly used for lung isolation during thoracic surgery. Similarly, DLT is the most commonly reported method for instituting ILV. DLTs are endotracheal tubes with two lumens and two cuffs (tracheal and bronchial), the tracheal lumen terminating in trachea and the bronchial lumen in either the right or left main stem bronchus (Figure 1). Some others have described using two endotracheal tubes, one for each lung, placed via a tracheostomy[2]. Since the smallest available DLT (26F, outer diameter- 8.7 mm) is recommended for patients between 8 and 10 years of age[23], endotracheal intubation with two single lumen tubes is the only way to achieve ILV in younger pediatric patients[9].

Interruption of ventilation, though momentary, during placement of DLT has potential for significant hypoxemia, especially in a critically ill patient with limited reserve. This risk is especially significant in patients with high levels of ventilator support, or in patients with a difficult airway. Thus, these need to be performed by individuals experienced with airway management, with difficult airway equipment and bronchoscope at the bedside.

Though anatomical separation is confirmed with bronchoscopy, adequate functional separation needs to be established as well. In the past, investigators have assessed functional lung separation by either water bubble or balloon inflation techniques. However, these require temporary interruption of ventilation and might not be a feasible strategy for an ICU patient with limited reserve. Functional separation can be assessed with most modern ventilators by measuring the inspired and expired tidal volumes from each lung. Loss or gain of tidal volume would suggest a leak. However, interpretation may be more difficult in the presence of a bronchopleural fistula.

Management of patients on ILV, outside of ventilation strategies, should be guided by the patient's needs and not influenced by institution of ILV. Though paralysis was thought to be necessary for institution of ILV, use of ILV without paralysis is reported[4]. However, DLT is more stimulating to the airway than a single lumen tube

Table 1 Indications for independent lung ventilation[32]

Massive hemoptysis[6,19]
Pneumonia[1-3,17]
Aspiration
Single lung transplantation with graft dysfunction[5,21]
Bronchopleural fistula[3,6,18]
Lung contusion[3,31]
Copious infected secretions in one lung (*e.g.*, lung abscess)
Unilateral pulmonary edema[4]

and might require more sedation for patient tolerance and comfort.

Complications and limitations

Lung isolation is maintained in the operating room under the constant surveillance of an anesthesia provider experienced in airway and lung isolation. ILV may be safely performed in the ICU with nurses and respiratory therapists properly trained in the care of patients receiving ILV. They should be able to identify and notify a clinician when endotracheal tube dislodgement is suspected. Tube malposition may inadvertently occur during patient movement or during routine change of patient's position[24]. Malposition should be suspected with sudden change in tidal volumes, or an increase in airway pressure. When dislodgement is suspected bronchoscopic assessment should be performed quickly to re-establish appropriate tube position.

DLTs have low volume high pressure cuffs. If not monitored, bronchial cuff pressure may be as high a 50 mmHg with as little as 2 cc of air[25]. The effects of prolonged use of a bronchial cuff on bronchial mucosal blood flow is unknown, since most data is from intraoperative literature where lung isolation only lasts for a few hours. In addition, a critically ill patient might already have a compromised mucosal blood flow, increasing the risk of mucosal ischemia. Ideally, cuff pressure should be maintained at 25 to 30 cm H_2O by an automated continuous pressure cuff controller preventing tracheal mucosa injury and air leak at peak inspiratory pressure. Complications reported to be associated with DLT use include bronchial ischemia and stenosis, bronchial rupture resulting in pneumothorax, pneumo-mediastinum and subcutaneous emphysema[7]. Though the typical duration of ILV reported in literature ranges from 2 to 4 d, some have used it for over two weeks without complications[3,7].

How to achieve physiological separation of lungs?

Physiological separation of lungs requires ability to independently alter ventilator parameters for each lung. This is best achieved using two separate ventilators one for each lung. Historically, a single ventilator had been used to ventilate two lungs, however in most cases each lung requires a different PEEP level. This was accomplished by connecting one ventilator to both limbs of the DLT through a Y-connector. This strategy allows for independent titration of PEEP between the two lungs, by adding a PEEP valve between the Y-connector and the limb of DLT ventilating the lung requiring additional PEEP. This approach is suboptimal as the presence of a PEEP valve in the circuit may impede accurate measurement of airway pressure by the ventilator, and generation of high levels of auto-PEEP might not be detected by the ventilator. In addition, other parameters such as tidal volume, respiratory rate and inspired oxygen concentration cannot be independently altered with this approach. Using a separate ventilator for each lung allows for independent adjustment of ventilator parameters, an essential feature for optimization of patients with ILV.

Synchronous vs asynchronous ventilation

Synchronous *vs* asynchronous ventilation results from the presence or absence of coordination between ventilated breaths provided to each lung. A single ventilator strategy evidently delivers synchronous ventilation. While using two ventilators, the most common strategy for ILV, synchronous ventilation can be accomplished by electronically linking the two ventilators using an external cable. Initiation of ventilation by one ventilator would transmit a signal through the external cable triggering the second ventilator resulting in near simultaneous delivery of a breath by that ventilator. It was thought that asynchronous ILV might result in cardiovascular compromise, from decreased (systemic and pulmonary) venous return as inflation of each lung at different times would result in elevated intrathoracic pressure for a longer duration of time. Subsequently, it has been shown that asynchronous

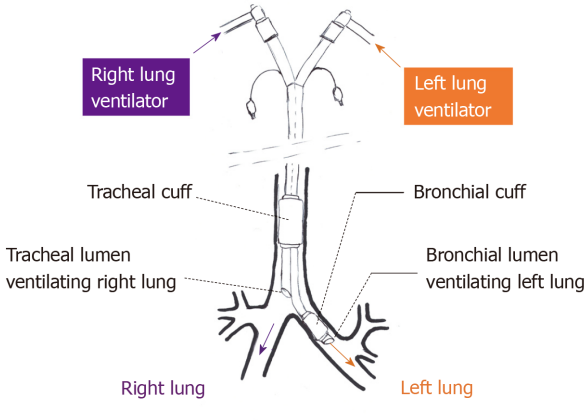

Figure 1 Institution of independent lung ventilation using a left sided- double lumen tube.

ventilation strategies can be instituted without these concerns and is equally well tolerated by patients[17]. Asynchronous ventilation strategy with two ventilators is much less complicated, offer greater flexibility allowing for individual titration of ventilation parameters, and thus is the preferred strategy for ILV.

How to determine the optimal ventilator strategy?

The selection of ventilator strategy for ILV is guided by the underlying pathology of each lung based and on principles of lung protective ventilation. Institution of ILV in patients with different lung compliances can ensure delivery of an appropriate tidal volume to each lung. Most of the literature on ventilation strategies during single lung ventilation comes from thoracic anesthesia literature, but may be extrapolated to ILV. Below we describe some principles for determining optimal ventilator parameters during ILV (Figure 2).

Positive end expiratory pressure: As in conventional ventilation, positive end expiratory pressure (PEEP) in ILV should be determined based on a PEEP titration trial ('best PEEP' trial) to identify the optimal PEEP providing highest lung compliance and adequate oxygenation. Since compliance of the diseased and non-diseased lung are markedly different, the best PEEP for each lung should be determined separately and instituted independently. Certain factors unique to ILV, must be considered while performing a best PEEP trial for each lung. Due to the impairment in gas exchange associated with severe unilateral lung disease, the diseased lung largely functions as a shunt, contributing to hypoxemia. A high PEEP applied to the normal lung may further worsen shunting through the diseased lung, and thereby worsen oxygenation.

The best strategy would be to initially perform a best PEEP trial of the diseased lung. The PEEP trial in the diseased lung should be primarily driven by compliance, since the diseased lung has minimal contribution to gas exchange. The PEEP resulting in the lowest driving pressure or the highest compliance might be chosen as the optimal PEEP in the diseased lung. Subsequently, a best PEEP trial for the non-diseased lung may follow. Determination of best PEEP of the non-diseased lung should also consider chronic underlying pathology such as asthma, emphysema or pulmonary fibrosis. Since increasing PEEP on the non-diseased lung may worsen shunting and hypoxemia, titration of optimal PEEP in the non-diseased should be based on oxygenation and compliance, rather than compliance alone.

Tidal volume, driving pressure and minute ventilation: In patients with lung injury or adult respiratory distress syndrome (ARDS) receiving conventional ventilation, protective lung ventilation involves limiting tidal volume to 4 to 8 cc/kg of predicted body weight (kg PBW), plateau pressures < 28 cmH_20 and driving pressure < 15 cmH_2O. Maintaining a tidal volume lower than 5 cc/ kg PBW and a plateau pressure lower than 28 cmH_2O during one lung ventilation has consistently been associated with decreased lung injury in patients undergoing lung surgeries[26]. These estimates are based on ventilation for a few hours during surgery, as opposed to ILV in ICU which may last days. Also, there is strong evidence on the benefits of low tidal volume ventilation, even when used intraoperatively for a few hours, in patients with normal lungs[22]. Thus a low tidal volume strategy (3 to 5 cc/kg PBW) should be adhered to separately for each lung, including the non-diseased lung, during ILV. The

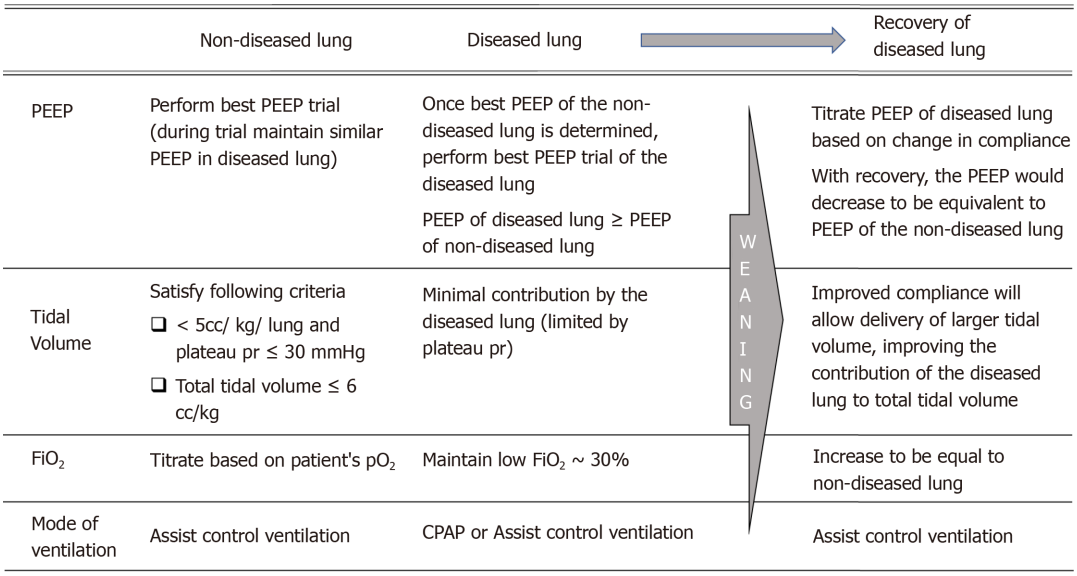

Figure 2 Guide to initial ventilator setting and weaning strategy during independent lung ventilation. PEEP: Positive end expiratory pressure; kg PBW: Kilogram predicted body weight; FiO_2: Fractional inspired oxygen concentration; PaO_2: Partial pressure of arterial oxygen.

tidal volume delivered to the diseased lung may be further limited by need to keep plateau pressure less than 28 cmH_2O and driving pressure < 15 cmH_2O. Since lower driving pressures is known to independently determine survival in ARDS, ability to keep driving pressure below 15 cmH_2O in the diseased lung should primarily drive the delivered tidal volume[27]. This might be best achieved by using a pressure control ventilation strategy in the diseased lung. Overall, it should be ensured that the additive tidal volume delivered to both lungs should not exceed 6-8 cc/kg PBW and that the plateau pressure and driving pressure for each lung is below 28 and 15 cmH_2O, respectively.

During ILV, each lung may have different minute ventilations, tidal volumes and respiratory rates. In the initial period, more benefit would be obtained by titrating the minute ventilation of the non-diseased lung to pCO_2, since it contributes most to ventilation. The ventilation strategy to be instituted for the diseased lung when it is not contributing to ventilation is unclear. There exists some evidence for providing lung rest (very low frequency positive pressure ventilation) and thus decreasing volutrauma, while instituting extracorporeal CO_2 removal in patients with hypercarbic respiratory failure[28,29]. Extrapolating that data to ILV, one may advocate for just providing continuous positive airway pressure to the diseased lung, especially in the presence of a severely diseased lung where the plateau and driving pressure are high. This may especially be considered when the diseased lung is not contributing much to oxygenation or CO_2 clearance. With improvement in compliance of the diseased lung and radiological improvement, ventilation can be resumed in a stepwise manner. One should favor permissive hypercapnia than to choose ventilator settings that contributes to lung injury.

Fractional concentration of inspired oxygen: Inspired oxygen concentration (FiO_2) of the non-diseased lung should be determined based on the systemic oxygenation. The FiO_2 of the non-diseased lung should be titrated to maintain the partial pressure of arterial oxygen between 55 and 80 mmHg and SpO_2 between 88% and 95%. Various considerations exist while choosing FiO_2 for the diseased lung. A lower FiO_2 in the diseased lung may result in poorer oxygenation of the blood circulating through the diseased lung, thereby worsening the impact of shunt. On the other hand, a higher FiO_2 may result in an increased risk for hyperoxic injury to the diseased lung. Also, the higher FiO_2 in the diseased lung might mitigate the hypoxic pulmonary vasoconstriction, thereby worsen shunt through the diseased lung. FiO_2 for the diseased lung should be titrated based on these competing factors. Thus, when the disease severity results in minimal contribution to oxygenation by the diseased lung, an FiO_2 between 40% and 60% might be favorable. This could be further titrated based on its impact on systemic oxygenation. Once the disease severity improves and the diseased lung contributes to oxygenation, the FiO_2 in that lung may be titrated similarly and equally with that of the non-diseased lung, to optimize systemic oxygenation.

Mode of ventilation: Various modes of ventilation have been reported with ILV, based on the underlying pathology and the comfort of the critical care team instituting ILV. These include assist control volume or pressure ventilation, pressure support ventilation, or high frequency oscillatory ventilation. Assist control is the most commonly utilized mode for ILV reported in literature. In a severely diseased low compliant lung which is not contributing significantly to oxygenation or ventilation, continuous positive airway pressure may be utilized initially. Though various studies have shown no mortality benefit with using high frequency oscillatory ventilation in severe ARDS[30], its role when preferentially applied to the diseased lung in ILV is uncertain. As the diseased lung begins to recover, an assist control pressure ventilation targeting driving pressures < 15 cmH_2O might be a useful strategy.

When and how to wean?

Evaluation of the readiness to wean the ventilator requirements should happen regularly and independently for each individual lung. However, ventilator parameters of the diseased lung can only be weaned when its pathological process begins to resolve. An important goal of weaning ventilator support in ILV is continual assessment of lung mechanics of each lung independently, to evaluate feasibility of transitioning to conventional ventilation using a single lumen endotracheal tube and one ventilator.

Though weaning happens separately for each lung during ILV, changing support on one lung may affect the other. The following considerations and principles should be borne in mind while weaning from ILV (Figure 2).

FiO_2: When the diseased lung is not contributing to gas exchange, the FiO_2 of the non-diseased lung may be weaned based on systemic oxygenation. However, as the diseased lung starts recovering and contributes to gas exchange, its FiO_2 may be titrated similarly (and made equal) to that of the non-diseased lung.

PEEP: Weaning PEEP may occur separately for each lung based on the 'best PEEP' calculated for each lung, and principles previously discussed. The goal of PEEP titration is to maintain maximum compliance in each lung and thereby minimizing driving pressures. As the diseased lung recovers, its compliance improves resulting in a reduced level of PEEP, bringing it closer to that of the non-diseased lung.

Tidal volume: If delivery of adequate tidal volume was initially limited in the diseased lung to maintain a lung protective driving pressure (< 15 cmH_2O), improvement in disease process will allow delivery of adequate tidal volume (3- 5 cc/ kg PBW/ lung).

Mode of ventilation: If separate modes of ventilation were used for each lung during ILV, recovery of the diseased lung should allow use of same mode. Assist control ventilation is the preferred mode of ventilation for both lungs, before transitioning to conventional ventilation.

Various measures have been described in the literature to determine the readiness to transition back from ILV to conventional single ventilator ventilation (Table 2). These are primarily based on assessment of improvement in the underlying unilateral lung pathology. The goal is to ensure that restoration of standard single ventilator ventilation would not result in markedly unequal distribution of tidal volumes resulting in volutrauma, or exacerbation of leak in bronchopleual fistula. With resolution of the unilateral lung pathology, lung mechanics, which were initially markedly different between the lungs, will progressively converge. Perhaps the most important parameter to follow would be individual lung compliances. Similar compliance between the two lungs would ensure that tidal volume delivered during conventional ventilation would be comparably distributed to each lung. Some authors have successfully discontinued ILV when the tidal volume and compliance differed between the lungs by less than 100 mL and 20%, respectively[11,31]. Use of capnography for each lung has shown that the diseased lung often has a much lower end tidal carbon dioxide concentration, likely from its minimal contribution to ventilation. Equivalence of end tidal carbon dioxide concentration between the two lungs during ILV could point towards comparable contribution to ventilation by each lung[31]. Other indicators would be radiological improvement and decrease in air leak from the chest tube in patients with unilateral bronchopleural fistula.

Before institution of single ventilator ventilation, its feasibility should be measured by temporarily ventilating each lung with the exact same settings. It is best achieved by ventilating both lungs using assist control pressure ventilation. This allows one to use the same settings (FiO2, PEEP, driving pressure, and minute ventilation) when transitioning to conventional single ventilator ventilation. Maintaining oxygenation should not be the sole criteria for determining feasibility. Presence of markedly different compliances may result in adequate oxygenation, but could result in volutrauma to the healthy lung. Thus, comparable compliance and tidal volume (Table 2) in each lung on the same ventilator settings establishes feasibility for

Table 2 Criteria favoring transitioning from double lumen tube to single lumen tube[11,31]

Near complete or complete resolution of the disease process- clinically or radiologically
Difference in tidal volume between the two lungs < 100 cc
Difference in compliance between the two lungs < 20%
Difference in end tidal carbon dioxide concentration between the two lungs < 20%

switching to single ventilator ventilation. Figure 3 compares tidal volumes and compliance for each lung in our patient, before conventional ventilation was instituted. Continuation of ILV also needs to be weighed against the risks associated with the duration of ILV. The deeper sedation necessary with ILV prevents patient participation in physical therapy, and minimizes patient effort in ventilation causing respiratory muscle atrophy. Longer duration of ILV may also increase the risk of airway mucosal injury from DLT. Moreover, with resolution of underlying pathology, mucus plugging and secretion clearance could become important considerations. Suctioning or bronchoscopic clearance of secretions are difficult through a DLT due to its narrow lumen, but may be more easily accomplished through a single lumen tube. Once single ventilator ventilation is tolerated, the DLT can be exchanged to a single lumen tube and conventional ventilation instituted.

CONCLUSION

Unilateral lung injury presents a markedly different scenario from the heterogeneous lung injury seen with ARDS. ILV is likely the most optimal way to provide lung protective ventilation in patients with severe unilateral lung pathology, thereby avoiding ECMO, which is more invasive and unavailable in resource poor locations. Safe utilization of ILV requires education and a collaborative effort by critical care nurses, respiratory therapists and physicians. With the stepwise clinical flow-chart proposed here, we hope to encourage more utilization of ILV. However, optimal strategies for ventilating the diseased lung and weaning from ILV needs further characterization.

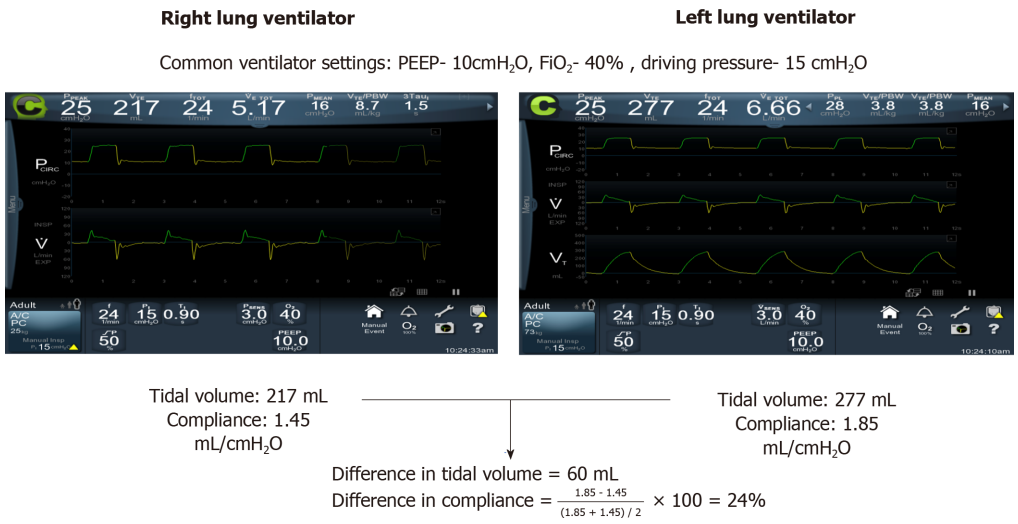

Figure 3 Test to determine readiness for transitioning from independent lung ventilation using double lumen tube to conventional single ventilator ventilation using a single lumen endotracheal tube. The tidal volumes and compliances of right and left lung are compared on identical ventilator settings. PEEP: Positive end expiratory pressure; FiO_2: Fractional inspired oxygen concentration.

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