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Chapter

Hemodynamic Perspectives in Anemia

Nakul Ravikumar, Geoffrey R. Sheinfeld and William T. McGee

Abstract

Oxygen delivery in normal physiologic states is determined by cardiac output, hemoglobin, oxygen saturation, and to a lesser extent, dissolved oxygen in the blood. Compensatory mechanisms such as an increase in stroke volume, heart rate, and re-distribution of blood flow helps in scenarios with increased oxygen demand. In cases of acute hemodynamic decompensation, this pre-existing physiologic relation between oxygen delivery and oxygen consumption is altered, resulting in tissue hypoxia and resultant anaerobic metabolism. A persistent state of sub-critical O_2 delivery correlates with increased mortality. Oxygen consumption itself is usually independent of delivery unless a critical threshold is unmet. We can use various parameters such as serum lactate, oxygen extraction, and central venous oxygen saturation to determine this pathology. A basic understanding of this physiology will help better tailor therapy to improve outcomes in critically ill patients.

Keywords: oxygen delivery (DO_2), oxygen consumption (VO_2), central venous oxygen saturation ($ScVO_2$), anemia, stroke volume variation (SVV), pulse pressure variation (PPV), passive leg raising (PLR), oxygen extraction (O_2ER)

1. Introduction

Anemia in critically ill patients is almost inevitable. The etiology of this can be varied, including overt blood loss, bone marrow suppression, functional iron deficiency, and decreased erythropoiesis [1]. Reports indicate that more than 95% of patients in an ICU are anemic by Day 8. Interventions such as scheduled daily phlebotomies lead to about 70-100 cc/day blood loss, while body turnover is about 15-20 cc/day. Little do we realize that this "anemia of chronic investigation" can lead up to 1/3 of transfusions when considering the current transfusion threshold practice of hemoglobin (Hb) less than 7 g/dL [2]. However, with numerous methods currently available to assess transfusions' physiological response, treating an arbitrary number is not the most refined approach. Parameters such as oxygen delivery (DO_2), oxygen consumption (VO_2), oxygen extraction ratio (O_2ER), and cardiac output are of paramount importance in the decision to transfuse RBCs.

This chapter aims to discuss the physiology of oxygen delivery, the pathophysiology of lung injury related to volume overload, and transfusion-related injury. Ultimately, we would like to demonstrate how employing a simple physiologic algorithm using parameters such as stroke volume, and stroke volume variability can lead to better care in this population.

2. Transfusion threshold in critically ill patients

The trigger to order blood products in the medical ICU is often a reflex action. In critically ill patients, the goal of transfusion in a volume replenished patient should aim to improve oxygen delivery and thereby accomplish the end goal of improving oxygen uptake in tissues. There is much evidence regarding liberal vs. restrictive transfusion limits in various subsets of patients. Vastly discussed strategy being restrictive transfusion (less than 7 g/dL) vs. liberal transfusion goals (9-10 g/dL). We can all agree that 7 g/dL is presently the customary number across many diseases. The TRICC trial randomized 838 critically ill patients to liberal (goal hemoglobin 10–12 g/dL) versus restrictive (goal hemoglobin 7–9 g/dL) transfusion strategies observed no benefit to liberal transfusion. However, the study almost achieved (p=0.11) statistical significance for finding increased mortality in patients randomized to liberal transfusion. This trial showed that there was no 30-day mortality difference between restrictive strategy vs. liberal strategy. Still, it showed harm in the subset of younger patients with lower APACHE scores and clinically significant cardiac disease [3]. Current data suggests that restrictive strategy in critically ill patients decreases the number of transfusion reactions, length of stay, and mortality [4]. Various studies focusing on patients with ARDS, trauma, and sepsis have shown that tissue oxygenation and extraction does not improve with transfusion alone. This disparity is attributable to poor flow characteristics, high O_2 affinity secondary to reduced 2,3 DPG concentration in transfused blood and increased viscosity affecting functional capillary diameter. While large multicenter trials recently have shown a higher threshold to transfuse is beneficial or at least non-injurious, it is prudent to focus on the physiological response a patient may have to blood transfusion.

3. Importance of measuring DO_2 and VO_2

Does it make a difference? Each gram of Hemoglobin can carry 1.34 cc of O_2, with each molecule 100% saturated as it enters systemic circulation.

DO_2 is derived from the following (Eq. (1)):

$$DO_2 = \text{Cardiac output} \times \text{Arterial oxygen content}\left(CaO_2\right) ml/\min/kg \quad (1)$$

$$CaO_2 = \left(1.34 \times Hb\right) \times SaO_2 + \left(0.003 \times PaO_2\right) ml/dl \quad (2)$$

$$\left(0.003 \times PaO_2 = \text{Dissolved oxygen in the blood}\right)$$

VO_2 is calculated by the difference between oxygen content in arterial blood and venous blood (Eq. (4)).

$$\text{Venous oxygen content}\left(CvO_2\right) = \left(1.34 \times Hb\right) \times SvO_2 + \left(0.003 \times PvO_2\right) ml/dl \quad (3)$$

Hence,

$$VO_2 = \text{Cardiac output} \times \left(1.34 \times Hb\right) \times \left(SaO_2 - SvO_2\right) \quad (4)$$

The fundamental goal of RBC transfusion is to improve oxygen content and to improve tissue oxygenation and delivery. While decreasing hemoglobin concentration can lead to critical oxygen content and delivery, this can be compensated by improving cardiac output and maintaining a euvolemic status.

VO_2 calculated with this equation is called the reverse Fick method. With an increase in oxygen demand, VO_2 increases from a baseline of 25%. Although there is no clear-cut point, oxygen extraction number between 33 and 40% is considered acceptable and not critical. If the oxygen extraction is high, emphasis should be on delivery components, i.e., Hb, O_2 saturation, and cardiac output. If oxygen extraction is standard, there is no physiologic reasoning to increase oxygen delivery by transfusion. Critical oxygen delivery at which anaerobic metabolism sets in and causes lactate production is not well defined.

The ratio of oxygen uptake to delivery is known as the oxygen extraction ratio. The standard O_2ER is around 25%. This number is essential and the body tries to compensate by increasing the cardiac output to maintain DO_2 when there is a drop in Hb [5]. It is imperative to understand critical oxygen delivery as we now have enough evidence pointing towards euvolemic management rather than increasing the hemoglobin concentration to help with oxygen delivery. We can argue that increasing the inhaled oxygen and keeping a patient on supra-normal FiO_2 can increase oxygen delivery, but as noted in the equation above, this intervention does not increase the dissolved oxygen component by much. Hence, cardiac output and hemoglobin concentration plays the primary role in oxygen delivery. Furthermore, we know from animal studies that there is a constant oxygen extraction ratio even under stress, so to secure adequate oxygen delivery or tissue perfusion, the body adjusts by ensuring enough blood flow and hence volume. DO_2 is approximately three times and 1.5 times VO_2 for the brain and heart muscle, respectively. Brain, heart, and skeletal muscle can maintain adequate blood flow in the setting of varying blood pressure within limits – the phenomenon known as 'autoregulation' [6].

Transfusion of blood products is a daily occurrence in many medical ICUs with a predefined goal to improve tissue perfusion. A decline in Hb is likely to cause a decrease in DO_2 if cardiac output remains unchanged since DO_2 = Cardiac output × CaO_2. When delivery is decreased, the body can compensate by increasing VO_2 to a certain extent. Since DO_2 incorporates Hb, cardiac output, and arterial oxygen saturation, measuring central venous O_2 ($ScvO_2$) can help determine oxygen extraction. The constant relationship between VO_2-DO_2 keeps the body functioning at an optimal level, and the 'critical level' at which this dependency is lost leads to tissue dysoxia. This critical level at which tissue dysoxia is usually present when central venous oxygen falls below 40–50% or DO_2:VO_2 is 2:1 (**Figure 1**).

If VO_2 is low or normal (<33%), the rationale to increase oxygen delivery is disputable. On the other hand, if extraction is more than 40%, this is critical, and an attempt should be to increase delivery. Simple means of measuring oxygen extraction would be to obtain central venous Oxygen concentration. Central venous oxygen concentration can be obtained simply from an indwelling central catheter in internal Jugular or subclavian vein, and this should not be mistaken for a mixed venous oxygen concentration. Mixed venous oxygen concentration (MVO_2) from an indwelling pulmonary artery catheter measures the oxygen extraction from both upper and lower extremities. However, both central and mixed venous oxygen concentrations correlate well in assessing sufficient perfusion and are often used interchangeably.

There are multiple studies available that suggest the use of this physiological parameter than an arbitrary lab-based number as a trigger for blood products is a better approach. Kocsi *et al.* performed a study on anesthetized pigs, looking at the capability of $ScvO_2$ as a parameter to reflect changes in the VO_2-DO_2 relationship.

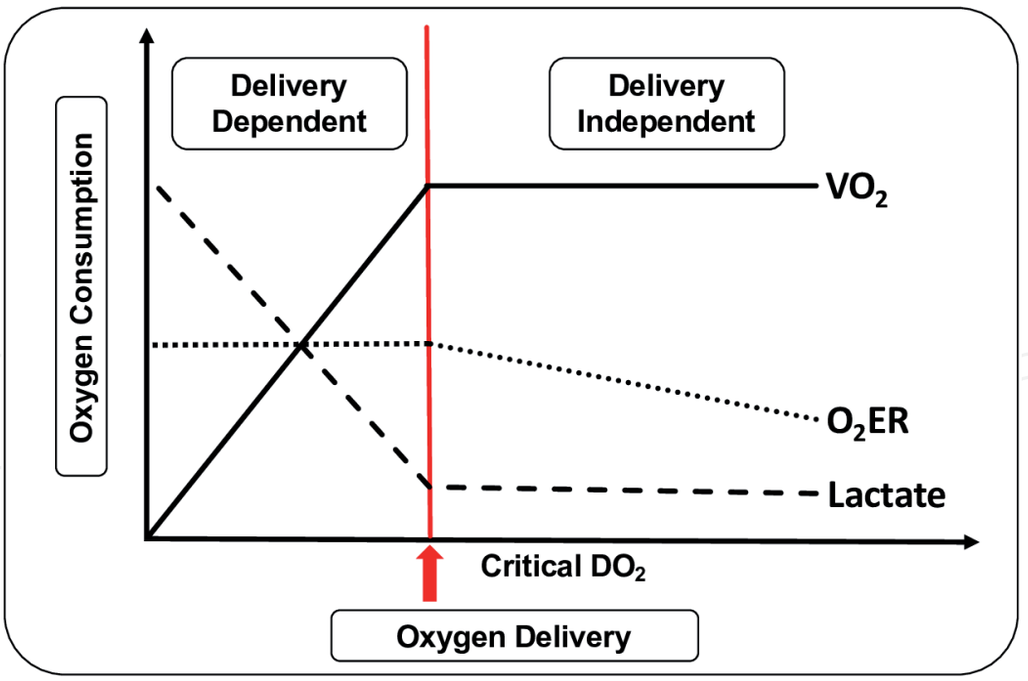


Figure 1.
Critical O_2 delivery. The body responds by extracting more oxygen in cases of decreased DO_2. However, once DO_2 drops below the critical threshold cellular metabolism becomes anaerobic with the subsequent production of lactate.

As $ScvO_2$ may reflect imbalances in delivery and consumption, this study aimed to investigate the value of $ScvO_2$ as an indicator of oxygen balance in isovolemic anemia. This study showed that $ScvO_2$ reflects changes of VO_2/DO_2 in isovolemic anemia better than Hb alone [7]. Adamczyk *et al.* studied the value of $ScvO_2$ as a trigger for transfusion in post-surgical stable patients and followed French guidelines for blood transfusion (2003). They noticed that the $ScvO_2$ increased significantly (from 57.8 to 68.5%) in the group with initial $ScvO_2$ less than 70%, whereas it was unchanged in patients with initial $ScvO_2$ greater or equal 70% (from 76.8 to 76.5%) following blood transfusion [8].

4. Newer modalities in assessing volume status

Hemodynamic monitoring has essentially become the cornerstone in guiding resuscitation for ICU patients. This serves as guide and marker for impending crisis and help determine the therapy that is best fitting. The parameters defined herein are to assist in the bedside assessment and only acts as a supplement to clinical judgment i.e., it should be considered in the context of pathophysiology, and the time point in the disease process [9]. An accurate assessment of volume status and its management remains a challenging issue with clinicians. Stroke volume is the amount of blood ejected (ml) from the left ventricle with each cardiac cycle and is the ultimate response we are trying to improve during resuscitation. Clinicians predict probable response to a fluid challenge by considering various static and dynamic parameters. The age-old tradition of using 'fluid challenge' and assessing clinical response has now been contested and multiple studies have shown increased morbidity in surgical and nonsurgical patients when not guided by a parameter. Using parameters such as cardiac index or mixed venous oxygen saturation alone do not help in guiding optimal therapy either. Gattinoni et al. showed that achieving higher levels of oxygen delivery through supranormal cardiac index or normal values of mixed venous oxygen saturation do not change mortality [10].

The static parameters previously used to assess fluid status have proven to be unreliable. Static measurements such as central venous pressure (CVP) or pulmonary artery occlusion pressure (PAOP) have low sensitivity and specificity when used to assess fluid responsiveness. Osman et al. showed that baseline CVP was similar in responders and non-responders by subjecting 96 septic mechanically ventilated patients to fluid boluses. Hence CVP measurements have a low predictive value. Also, many clinicians assume that increases in CVP with a fluid bolus indicate positive fluid responsiveness. The poor reproducibility is explained by the Frank-Starling curve, which varies among patients depending on cardiac function. These parameters are also affected by the change in respiratory system compliance and other cardiac factors. An example of this is the study done by Rivers et al. In the early goal-directed therapy arm of the trial wherein fluids administered targeted a goal CVP measurement [11]. The physiological goal of the fluid administration is to increase preload accompanied by an increased stroke volume and hence cardiac output. A notable increase in CVP with minimal change in the cardiac output or a slight change in CVP but with a notable change in cardiac output can be misleading and used alone can be confusing for clinicians. Targeting CVP, although tempting, should be combined with the after-effects, which include measurement of cardiac output in real-time.

Dynamic measurements are gaining popularity in the current era, and various modalities are available, including passive leg raise testing (PLR), stroke volume variation (SVV), and pulse pressure variation (PPV). PLR although can be used in spontaneously breathing patients, SVV and PPV come with some restrictions and best served in patients on positive pressure ventilation. A systematic review demonstrated that dynamic parameters can be reliably used in predicting fluid responsiveness. Pulse pressure variation during the Valsalva maneuver (ΔPPV) of 52% (AUC ± SD: 0.98 ± 0.03) and passive leg raising-induced change in stroke volume (ΔSV-PLR) greater than 13% (AUC ± SD: 0.96 ± 0.03) showed the highest accuracy to predict fluid responsiveness in spontaneously breathing patients [12]. Technological advances have allowed us to obtain arterial waveform analysis non-invasively or invasively in the modern-day ICU. By studying the arterial waveform, we can obtain stroke volume variation (SVV) and pulse pressure variation (PPV). A systemic review by Marik et al. demonstrated that fluid responsiveness using area under the curve (AUC) demonstrated the superiority of arterial waveform technology as compared to central venous catheters and transpulmonary dilution. Arterial waveform analysis is instrumental in the intensive care unit (ICU) and key in resuscitation for our ICU patients who already have an arterial line placed.

Dynamic parameters should be used preferentially over static parameters to predict fluid responsiveness in ICU patients. An analysis of 12 studies showed that static parameters such as right atrial pressure, pulmonary artery occlusion pressure, right ventricular end-diastolic volume were not significantly lower in responders vs. non-responders to fluid bolus [13].

4.1 Passive leg raise (PLR) testing

A relatively easy bedside test that essentially transfers 300 mL of venous blood to the right heart acts as a fluid bolus. It has significant advantages as it does not require any special equipment, easily performed at bedside and rapidly reversible with no risk of fluid overload. An important point is to directly measure cardiac output before and after the PLR test to assess if there was a notable change to cardiac output. The technique used to measure the cardiac output needs to assess short-term and transient changes to the cardiac output because the effects of PLR usually go away after one minute. This procedure can be performed by sitting the

patient at 45 degrees head up in a semi-recumbent position. We lower the patient's upper body to horizontal and passively raise legs to 45 degrees. This position is sustained for about 30–60 seconds. An assessment of stroke volume (using cardiac output monitor) or pulse pressure change is conducted simultaneously.

A PLR increase of aortic blood flow higher or equal to 10% predicted fluid responsiveness with a sensitivity of 97% and a specificity of 94%. A PLR increase of pulse pressure higher or equal to 12% predicted volume responsiveness with significantly lower sensitivity (60%) and specificity (85%) [14]. A meta-analysis of 21 studies, including more than 900 patients in which cardiac output was measured by echocardiography, pulse contour analysis, bioreactance, esophageal Doppler, transpulmonary thermodilution, or pulmonary artery catheter, showed PLR-induced changes in cardiac output to have a pooled sensitivity of 0.85 and a pooled specificity of 0.91. The area under the curve was 0.95. The best threshold was a PLR-induced increase in cardiac output of greater than 10± 2%. For the PLR induced changes in pulse pressure, the pooled sensitivity was 0.56 (0.49–0.53), the pooled specificity was 0.83 (0.77–0.88), and the pooled area under the ROC curve was 0.77 [15]. Physiologically informed volume resuscitation with the use of the PLR-induced stroke volume change to guide management of shock is safe and demonstrated lower net fluid balance and reductions in the risk of renal and respiratory failure. In this modified intent-to-treat analysis that included 83 intervention and 41 usual care eligible patients, fluid balance at 72 hours or ICU discharge was significantly lower (−1.37 L favoring the intervention arm; 0.65 ± 2.85 L intervention arm vs. 2.02 ± 3.44 L usual care arm; P = 0.021). Fewer patients required renal replacement therapy (5.1% vs. 17.5%; P = 0.04) or mechanical ventilation (17.7% vs. 34.1%; P = 0.04) in the intervention arm compared with usual care [16].

4.2 Stroke volume variation (SVV) and pulse pressure variation (PPV)

The rationale for using SVV and PPV is that a varying left ventricular stroke volume as a response to cyclic positive pressure indicates that both ventricles are pre-load dependent as described here. SVV is derived from pulse contour analysis and the variation of the amplitude of the pulse oximeter waveform, and PPV is derived from analysis of the arterial waveform.

SVV is defined as a change in volume during the respiratory cycle and calculated as (SV max-SV min)/SV mean. This change represents dynamic variation occurring as a result of changing pleural pressure during a breath. During a positive pressure breath, intermittent increase in the intrathoracic pressure as ventilator cycles causes increased right ventricular afterload and decreased right ventricular preload. Clinically, this manifests as a decrease in left ventricular output and stroke volume after several cardiac cycles. This pressure manages to increase left ventricular preload and reduces left ventricular afterload, resulting in an acute increase in the left ventricular stroke volume harmonizing with the inspiratory phase of positive pressure ventilation. The variability in stroke volume occurring here has been well correlated with fluid responsiveness (**Figure 2**) [17, 18].

SVV has been widely studied in the operating room as it provides ideal conditions. A study by Willars et al., including high risk vascular surgeries compared SVV, PPV, CVP and Delta CVP [19]. The area under the receiver operator curve (AUROC) was 0.75 for SVV, 0.67 for PPV. The best cutoff value for SVV was 13.5%. At this level positive likelihood ratio was 2.7 and negative likelihood ratio of 0.34. They concluded that SVV was the only adequate predictor of fluid responsiveness in this cohort. SVV by itself has some limitations and needs to be used on a case by case basis.

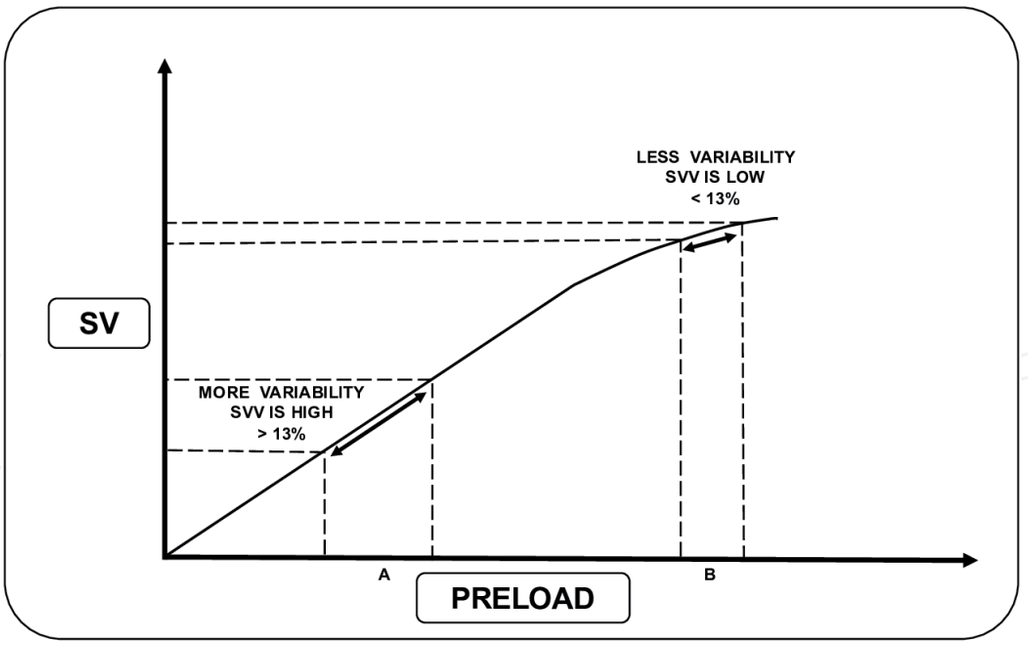


Figure 2.
SVV and Frank-Starling curve. SVV is a dynamic variable that predicts volume responsiveness and individualizes the Starling relationship. A: Volume responsive SVV > 13% B: Non-volume responsive SVV < 13%.

5. Physiologic algorithm guiding resuscitation

With various parameters now available, we suggest use of a simple physiologic algorithm to help clinicians guide therapy better for these patients. A 'volume responsive patient' can be defined using SVV, PPV, and Stroke volume index (SVI). Although there is not a true number that differentiates a true responder to non-responder, a change of 13% is thought to be appropriate. The reason being SVV is not a binary but more typically linear. Studies have defined the range to be around 10–15%. An algorithm has been proposed in detail going over the pathways that define a comprehensive approach in these patients.

In brief, dynamic changes are best observed with a significant rapid volume challenge. Colloid including blood or larger or lesser amounts of crystalloid may be used depending on the clinical scenario. In patients with SVV less than 13% you can further calculate stroke volume index (SI) as an aid to decide on the most appropriate intervention based on underlying pathophysiology. Because of the influence of heart rate on cardiac output, the preference is to use stroke index data as the measure of cardiac performance (**Figure 3**) [20].

Using this algorithm in ICU patients is quite challenging as it does not consider the rate of oxygen extraction and if volume is likely to alter it. Through advanced hemodynamic monitoring using a combination of SVV and Oxygen delivery we can further understand a patient's requirements better and an approach can be determined to patient's care. Most clinical studies were done in patients on positive pressure therapy with normal chest wall compliance, larger tidal volumes and with passive breaths. It should be considered that spontaneous breathing and arrhythmias will lead to misinterpretations of the respiratory variations in the pulse pressure/stroke volume. However, PLR has a higher sensitivity in these two scenarios and still holds value in assessment [14, 15].

The clinician must evaluate for SVV, SI and O_2 extraction on a case by case basis. Coupling these parameters assists in determination of adequate Oxygen delivery.

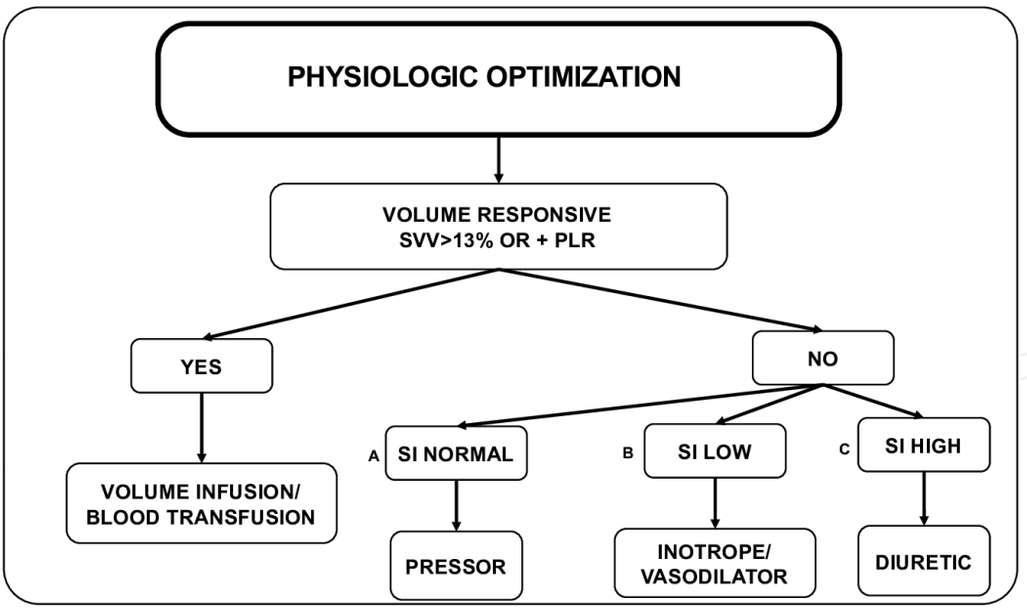


Figure 3.
Physiologic optimization. If SVV < 13% or passive leg raise test is negative, pathway A, B, C further utilizes stroke index (SI) to delineate therapy.

6. Conclusion

Physiological concepts, such as oxygen delivery and oxygen extraction, when combined with dynamic indices of fluid responsiveness, provide clinicians a more accurate assessment in predicting which cohort of patients accept additional blood or volume without resulting in lung injury. After the TRICC trial, it is a widespread practice to give blood if the Hemoglobin is less than 7 g/dL. However, if physiological parameters mentioned above are not examined, we may give blood or volume to people who do not need it and cannot accept it. By employing a simple physiologic algorithm, we can determine a specific population that will accept volume and prevents unwanted consequences of transfusion-associated lung injury and circulatory overload. This scenario prevents patients from harm and decreases various adverse outcomes, including acute lung injury, increased total body volume, higher morbidity, and mortality.

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