Defining Goals of Resuscitation in the Critically Ill Patient

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KEYWORDS

• Oxygen delivery • Oxygen consumption • Goal-directed fluid therapy
• Cardiac output optimization

KEY POINTS

- Understand the goals of resuscitation in the critically ill patient using target perfusion pressures, flows, and oxygen delivery/consumption targets for specific patient groups based on disease process.
- Understand the difference in management approaches for intraoperative and intensive care unit critically ill patients.
- Understand the major physiologic variables used for defining cardiopulmonary medicine.
- Understand the major physiologic endpoints for assessment of adequate fluid optimization.
- Be familiar with the concept of goal-directed fluid therapy and understand the importance of such a therapeutic protocol in the future of fluid management.

INTRODUCTION

As stated by Arthur Guyton in his *Textbook of Medical Physiology*:

> *The function of the circulation is to service the needs of the body tissues, to transport nutrients to the body tissues, to transport waste products away, to conduct hormones from one part of the body to another, and, in general, to maintain an*

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appropriate environment in all the tissue fluids of the body for optimal survival and function of the cells. To be achieved, this goal requires two physiological objectives:

Adequate perfusion pressure in order to force blood into the capillaries of all organs.

Adequate cardiac output to deliver oxygen and substrates, and to remove carbon dioxide and other metabolic products.[1,2]

In daily practice, we are often confronted by critically ill patients in different settings that require hemodynamic optimization to restore or maintain sufficient tissue perfusion. Hemodynamic optimization is specific to each "patient population" and the critically ill patient in the intensive care unit (ICU) is not the same as the surgical patient undergoing high-risk surgery. Optimal perfusion therefore depends on patient-specific disease processes. For example, in the ICU, clinicians have to deal with very unstable patients with their main objective being the restoration of adequate circulation through careful correction of the blood flow and resulting oxygen delivery (Do_2). On the other hand, the major concern of the anesthetist in the perioperative period is to (1) optimize the patient's volemic status by maximizing Do_2 through "well-defined" goals using flow-related hemodynamic parameters and (2) avoid any impairment in Do_2 or cardiac output (CO). Regardless of setting, critically ill patients often present with hypovolemia, and volume expansion is one of the most frequent clinical interventions performed in daily practice. It is commonly the first treatment for hemodynamic resuscitation because it can increase Do_2 to the tissues, through increasing left ventricular stroke volume (SV) and CO.

As with most critical interventions, an appropriate end point for such fluid therapy has been widely researched and is constantly adapting to new technologies and outcome investigations. This concept of targeting predefined goals of resuscitation in critically ill patient is not novel. Goal-directed therapy (GDT) has come to encompass the concept of using established targets of continuous blood flow and/or tissue oxygenation to guide therapy (intravenous fluid and/or inotropes). This strategy is becoming the standard of care in the ICU and in the operating rooms. However, despite studies suggesting that this approach is beneficial, GDT is still poorly adopted in clinical practice[3,4] and, in many cases, fluids are still administered without adequate goals and monitoring to guide volume therapy. This can lead to adverse clinical outcomes related to hypovolemia or hypervolemia (**Table 1**). Both risks can potentially lead to a decrease in Do_2 to the tissues and to an increase in postoperative morbidity (**Fig. 1**).[5] Therefore, the optimization of the patient's hemodynamics through targets of resuscitation is one of the most important goals to improving patient morbidity and mortality.

PHYSIOLOGY

In this article, the physiologic basis of Do_2, oxygen consumption (Vo_2), and their implications for the clinician are described. One of the most important questions for a clinician at the bedside of a critically ill patient must be: "Is oxygen delivery sufficient to meet the patient's cellular oxygen demand?" If the answer to this question is not confidently affirmative, a clinician risks exposing his patient to cellular ischemia, organ dysfunction, and death. Knowing the adequacy of the patient's oxygen transport balance is essential to the understanding of the pathophysiology and management of critically ill patients. Therefore, one should always keep in mind the determinants of Do_2 and consumption (**Fig. 2**).

Oxygen delivery (Do_2) is the total amount of oxygen delivered to body tissues by the heart per minute and is expressed using the following equation (HR, heart rate; Sao_2,

Table 1
Comparison between complications associated with hypervolemia and hypovolemia

Complications of Hypervolemia	Complications of Hypovolemia
Increases venous pressure resulting in loss of fluid from the intravascular to interstitial space, which can lead to pulmonary and peripheral edema impairing tissue oxygenation	Reduces effective blood circulatory volume resulting in diversion of blood flow from nonvital organs (skin, gut, kidneys) to vital organs (heart and brain)
Increases demand on cardiac function	Activates the sympathetic nervous and renin angiotensin system
Decreases tissue oxygenation with delayed wound healing	Increases inflammatory response
May cause coagulation disturbances through hemodilution	May also lead to vasopressor agent administration, which may increase hypoperfusion and ischemia[99]
Is associated with increased daily fluid balance and mortality.[100] Chappell et al also demonstrates a relationship between weight gain related to excessive fluid administration and mortality[101]	

arterial hemoglobin oxygen saturation; Hb, hemoglobin concentration; Pao_2, arterial oxygen partial pressure):

$$Do_2\,(mL/min) = Cardiac\ output\,(CO, L/min) \times Arterial\ oxygen\ content\,(Cao_2, mL\,O_2/dL)$$

$$Do_2\,(mL/min) = HR \times SV \times [(Sao_2 \times Hb \times 1.34) + (0.003 \times Pao_2)]$$

Increasing Do_2 is achieved through 2 different approaches: increasing CO and Cao_2. Generally, CO is more frequently manipulated by using fluids and/or inotrope agents. Conversely, Cao_2 is most commonly increased by augmenting Sao_2 and/or Hb concentration because the quantity of dissolved O_2 is low.

Oxygen consumption (Vo_2) is the volume of oxygen consumed by the tissues per minute (Cao_2; Cvo_2, venous oxygen content).

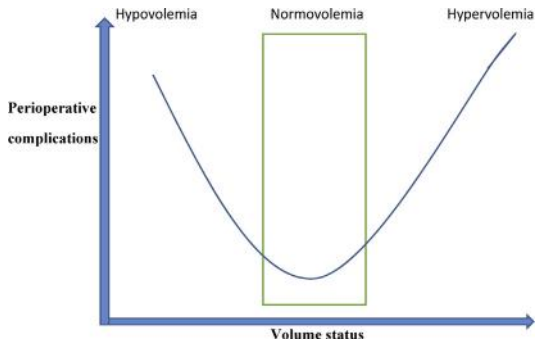

Fig. 1. The classic relationship between perioperative volume status and perioperative complications. The relationship describes a U shape with an increased risk of complication for both perioperative hypovolemia and perioperative hypervolemia, emphasizing the importance of perioperative fluid optimization.

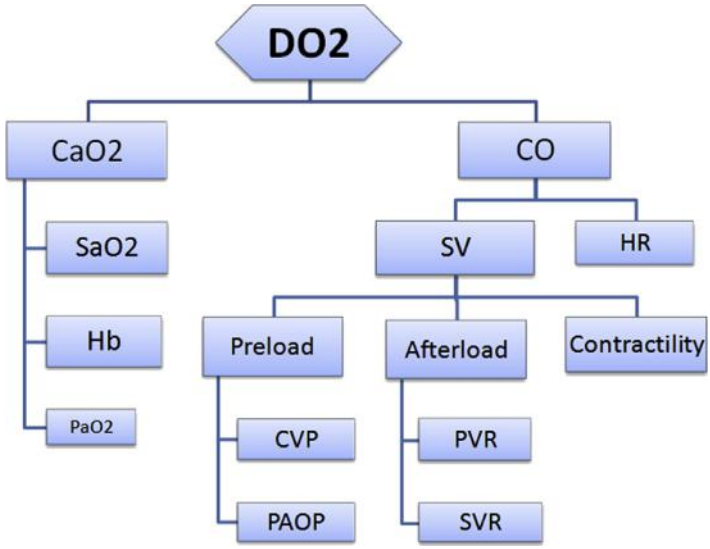

Fig. 2. Flowchart describing composition of the delivery of oxygen to tissues throughout the body. PVR, peripheric vascular resistance.

$$Vo_2\ (mL/min) = CO\ (L/min) \times [Cao_2 - Cvo_2\ (mL\ O_2/dL)]$$

Oxygen demand is the amount of oxygen required by the tissues to function aerobically.

Extraction oxygen ratio (EOR) in the tissues is defined as follows:

$$EOR = Vo_2/Do_2$$

$$EOR = [CO \times (Cao_2 - Cvo_2)]/[CO \times (Sao_2 \times Hb \times 1.34)]$$

Venous oxygen saturation (Svo_2) can then be calculated and reduced to the following formula:

$$Svo_2 = Sao_2 - (Vo_2/(CO \times Hb \times 1.34))$$

Any decrease in Svo_2 may therefore result from a decrease in Sao_2, a decrease in CO, a decrease in hemoglobin level, or an increase in Vo_2. Providing that Sao_2, Vo_2, and hemoglobin level are in normal ranges, Svo_2 can then be used as a surrogate for CO.

Also, if $Vo_2 = CO \times (Cao_2 - Cvo_2)$, $Do_2\ (mL/min) = CO \times [(Sao_2 \times Hb \times 1.34) + (0.003 \times Pao_2)]$, and $EOR = Vo_2/Do_2$, then after simplification: $EOR = (Sao_2 - Svo_2)/Sao_2$.

Consequently, when $Sao_2 = 100\%$, then $EOR = 1 - Svo_2$ and $Svo_2 = 1 - EOR$. Thus, Svo_2 can also be a good surrogate for EOR. Clinically, Svo_2 is one of the most used parameters to assess the balance between tissue O_2 supply and O_2 demand and therefore the hemodynamic status of the patient. Svo_2 and central venous O_2 saturation ($Scvo_2$) have commonly been used for both GDT protocols in severe sepsis and in the operative room (OR). When $Scvo_2$ is low, it reflects that something is wrong and should lead clinicians to understand the reasons for it and to propose an appropriate optimization strategy.

Normally, V_{O_2} is maintained constant, whereas D_{O_2} varies. If D_{O_2} declines following a decrease in CO or CaC_{O_2}, V_{O_2} is maintained by a compensatory increase in the oxygen extraction. If D_{O_2} continues to decrease, a threshold is reached wherein the OER is maximal and cannot increase further (critical D_{O_2}). Any further reduction in D_{O_2} will lead to tissue hypoxia, anaerobic metabolism, and lactate production (V_{O_2} becomes D_{O_2}-dependent).

The understanding and appreciation of this relationship (**Fig. 3**) during critical illness are capital and have led to the proposition that therapies designed to induce a "supra-physiologic" state could be beneficial for tissue perfusion. Specifically, this idea came from Shoemaker and colleagues,[6] who observed that survivors of critical illness had supranormal levels of D_{O_2} compared with nonsurvivors. Unfortunately, studies comparing supranormal to conventional resuscitation in critically ill patients have been deleterious: Hayes and colleagues[7] found that achieving supranormal values (cardiac index [CI] >4.5 L/min/m^2, D_{O_2} >600 mL/min/m^2, V_{O_2} >170 mL/min/m^2) increased mortality compared with normal goal levels. Gattinoni and colleagues[8] similarly targeted critically ill patients by using 3 optimization goals: normal CI (2.5–3.5 L/min/m^2), supranormal CI (>4.5), or normal Sv_{O_2} (>70%) and found no benefit in achieving supranormal values for cardiac index. A meta-analysis showed that interventions designed to achieve supraphysiologic goals of cardiac index, D_{O_2}, and V_{O_2} did not significantly reduce rates of mortality in all critically ill patients.[9] The current conclusion is that D_{O_2} must be optimized, not maximized. Using that mindset, different therapeutic targets (using the determinants of D_{O_2}) have been proposed to manage patients. How these different strategies have been implemented in clinical practice and in different departments (ICU and OR) through well-defined GDT algorithms and protocols are discussed in the next sections.

GOAL-DIRECTED FLUID THERAPY IN THE INTENSIVE CARE UNIT

As explained in previous sections, the maintenance of adequate D_{O_2} to meet the demands of various tissues is essential in critical care medicine. The different determinants of D_{O_2} can be especially impaired in this patient population and the importance of recognizing and treating them correctly should be stressed. Therefore, careful monitoring and adjustment of these variables are required to achieve the best clinical outcome.

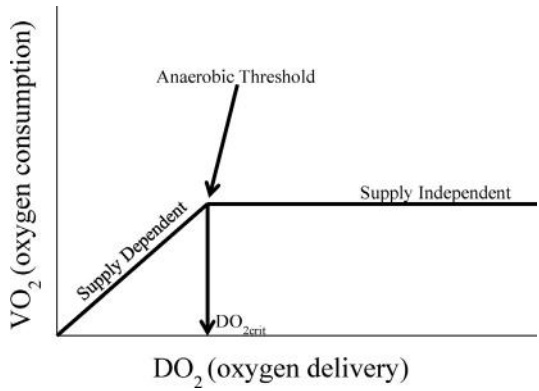

Fig. 3. Relationship between O_2 delivery and consumption: curve showing a defined "knee" where consumption of oxygen by the tissues becomes dependent on delivery.

The first goal in the hemodynamic management of the critically ill patient is to determine the adequacy of tissue/organ perfusion. The evaluation of end-organ delivery of oxygen should first be quickly assessed using broad and widely understood clinical markers (poor peripheral perfusion, altered mental status, and urine output). The details of the other variables are discussed later.

Blood Pressure

Initial hemodynamic management of critically ill patients should include the restoration of blood pressure (BP) with a goal of a mean arterial pressure greater than 65 mm Hg in a previously normotensive patient. This variable must be closely followed because hypotension can lead to impaired cerebral and coronary blood flow (particularly susceptible tissues). A recent trial showed that targeting a mean arterial pressure higher than 65 mm Hg (80–85 mm Hg) in patients with septic shock undergoing resuscitation did not result in significant differences in mortality at either 28 or 90 days.[10] Except for obstructive or cardiogenic shock, volume expansion remains the fundamental treatment to increase intravascular volume. Some clinicians administer an initial fluid bolus (fluid challenge) and assess the effect (increase SV) by measuring static parameters such as central venous pressure (CVP) and/or pulmonary artery occlusion pressure (PAOP). Unfortunately, they think that CVP reflects intravascular volume and that patients with a low CVP are fluid depleted and vice versa. It is well recognized that neither the PAOP nor the CVP can predict ventricular preload and fluid responsiveness.[11]

Volume expansion is important for the initial resuscitation of severe hypotension. Subsequent fluid administration should be given cautiously and only when there is evidence of fluid responsiveness to avoid fluid overload.[12] Indeed, several studies correlate excessive amounts of fluid (positive fluid balance) with increased mortality in acute respiratory distress syndrome or septic patients and failure of weaning from mechanical ventilation.[13–16] Moreover, only 50% of hemodynamically unstable patients are fluid responsive.[17,18]

In contrast to static preload measures, which only rely on hemodynamic values at a given point in time, there are newer dynamic parameters currently available using the change in SV during mechanical ventilation to assess fluid responsiveness. New noninvasive CO monitoring is available today to measure or estimate CO, pulse pressure variation, or SV variation. Resuscitation should, of course, target normalization of BP, HR, and urine output, but also tissue perfusion indices because occult tissue hypoperfusion may persist despite normalization of these vital signs.

BP is not a good indicator of low CO, low Do_2, or hypovolemia: shocked patients may appear adequately resuscitated based on BP even with significant hypoperfusion! That is why other markers of tissue well-being should also be assessed, such as Svo_2, $Scvo_2$, ΔPco_2, and lactate. They may be also very useful goals of resuscitation when vasopressors are required for persistent hypotension once adequate intravascular volume expansion has been achieved and to evaluate the efficacy of treatment.

Venous Oxygen Saturation

This variable gives an estimation of O_2 saturation of blood returning to the right heart. It is correlated with tissue O_2 extraction and the balance between O_2 delivery and demand. However, it needs a pulmonary artery catheter (PAC), which is very invasive. In this context, $ScvO_2$ may represent an interesting alternative because it can be easily measured by obtaining a blood sample from the central venous catheter. Reinhart and colleagues[19] have shown a good correlation between Svo_2 and $Scvo_2$. Despite this, there is still debate regarding the equivalence between them,[20–23] especially when

comparing lower values.[24] However, the surviving Sepsis Campaign recognized the clinical utility of $Scvo_2$ by recommending a Svo_2 of 65% and $Scvo_2$ of 70% in the resuscitation of severe sepsis and septic shock patients.

Arterial Lactate Elevation

This variable is directly proportional to oxygen debt and is commonly taken as an indicator of impaired tissue perfusion because of inadequate O_2 delivery resulting in anaerobic metabolism. It has been shown that during circulatory shock, repeated lactate determinations represent a more reliable prognostic index than an initial value taken alone. Changes in lactate concentration can provide an early and objective evaluation of the patient's response to an intervention.[25] Furthermore, elevation or nonnormalization of serum lactate concentration is predictive of adverse outcome in the critically ill patient in shock.[26] Altered levels of serum lactate must also be examined alongside the larger clinical picture because multiple nonhypoxic causes can also result in lactic acidosis, including renal or metabolic disturbances.

Difference Between Venous-Arterial Carbon Dioxide Partial Pressure

The difference between venous-arterial carbon dioxide partial pressure (ΔPCo_2) has also been used to guide the treatment of shock. In the absence of a shunt, Co_2 from the venous blood must be higher than from the arterial blood. The ΔPCo_2 may be a marker of the global hemodynamic status. For example, ΔPCo_2 has been shown to be an indirect marker of the adequacy of systemic flow, which allows for more directed resuscitation.[27] The Fick equation applied to Co_2 indicates that combing $\Delta PCo_2 = CvCo_2 - CaCo_2$ with $VCo_2 = CO \times (CvCo_2 - CaCo_2)$ leads to $\Delta PCo_2 = VCo_2 \times k/CO$ (k is constant) and further indicates that ΔPCo_2 is proportionally related to Co_2 production and inversely proportional to CO.[28] Therefore, with all other variables constant, if CO is low, ΔPCo_2 is high (>6 mm Hg).[29] Vallee and colleagues[30] found that patients with a ΔPCo_2 higher than 6 mm Hg had worse prognosis when compared with those with lower than 6 mm Hg, despite a $Scvo_2$ greater than 70% in both groups. **Fig. 4** gives example of the algorithm used in the critically ill patient to guide therapy based on $Scvo_2$ and ΔPCo_2.

Using the above physiologic variables, a "goal-oriented" protocol of resuscitation seems encouraging. In fact, Rivers and colleagues[31] published a study 13 years ago showing that an early aggressive goal-directed resuscitation protocol (EGDT) administered in the emergency setting reduced mortality from septic shock by 16%. In the ICU and in the emergency department, the Rivers protocol (**Fig. 5**) for the management of the septic patient has been widely accepted. This protocol relies on the early optimization (within 6 hours following the diagnosis of sepsis) of mean arterial pressure, CVP, and $Scvo_2$. The 3 interventions used in this protocol are volume expansion to keep CVP between 8 and 12 mm Hg, vasopressors to maintain mean arterial pressure between 65 and 90 mm Hg, and transfusion and/or inotropes to keep $Scvo_2$ more than 70%.

Over the last decade, multiple investigations have validated the end points used in EGDT.[32] In addition, more than 50 studies and 3 meta-analyses have repeatedly shown the same or better outcome benefits than the original study (18%) in patients of similar illness severity.[33–41] This robust mortality reduction has also been accompanied by a modulation of systemic inflammation,[42] decreases in the progression of organ failure,[43] and decreased health care resource consumption (20% decrease in hospital costs).[44–47] However, a newly published multicenter randomized trial found no significant advantage in morbidity or mortality when comparing a protocol-based resuscitation to standard care in septic shock patients.[48] It puts into question the

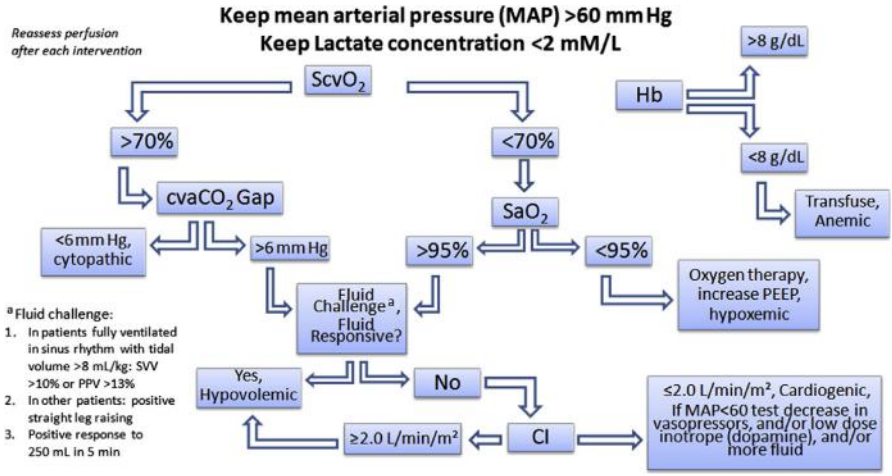

Fig. 4. The $Scvo_2$-$cvaCo_2$ gap-guided protocol. $cvCo_2$gap, central venous-to-arterial PCo_2 difference; PEEP, positive end-expiratory pressure. (*Data from* Vallet B, Pinsky MR, Cecconi M. Resuscitation of patients with septic shock: please "mind the gap"! Intensive Care Med 2013;39(9):1653–5.)

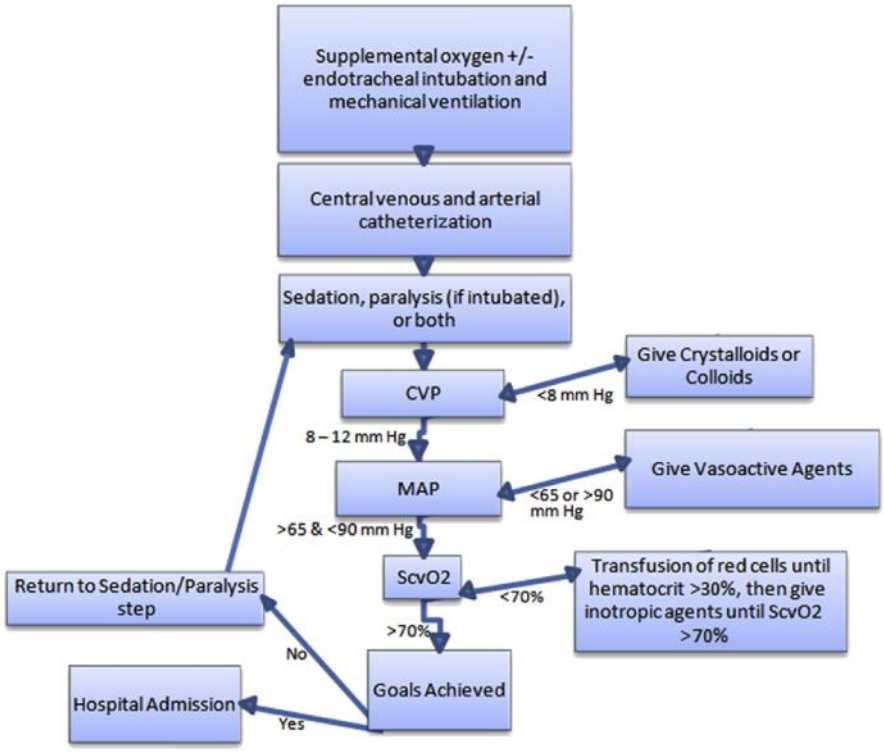

Fig. 5. GDT protocol developed by Emmanuel Rivers for sepsis. MAP, mean arterial pressure. (*Data from* Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345(19):1368–77.)

"EGDT approach" in critically ill patients and will surely stimulate more research and exploration into the issue.

Even with a validated resuscitation algorithm, a physiologic approach should still be used to maintain a BP that will sustain vital organ perfusion and optimize blood flow. If possible, this approach should be individualized using noninvasive monitoring to address individual variations. Once again, no monitoring device can replace the close observation of clinical variables and "no monitoring device can improve outcome unless coupled to a treatment which itself improves outcome."[49]

INTRAOPERATIVE GOAL-DIRECTED THERAPY FOR HIGH-RISK SURGICAL PATIENTS

It is estimated that about 240 million anesthesia procedures are performed each year around the world.[50] Among them, 24 million (~10%) are conducted in "high-risk" patients. Although it can be considered a small percentage of the whole population, one must remember that this sample accounts for more than 80% of the overall mortality related to surgery.[51] Moderate-risk surgery is much more common and represents approximately 40% of the whole population (96 million patients a year). Thankfully, most of these patients present with uncomplicated postoperative course. However, it is estimated that approximately 30% of them (~29 million patients a year) present with a "minor" postoperative complication, most commonly a gut injury inducing delayed enteral feeding, abdominal distension, nausea, vomiting, or wound complications, such as wound dehiscence or pus from the operation wound.[52] Even if these complications are said to be "minor," they still induce increased postoperative medication, increased length of stay (LOS) in the hospital, and an increase in the cost of the medico-surgical management. In most of these patients, postoperative complications are related to tissue hypoperfusion and inadequate perioperative resuscitation.[52,53]

Upgrading surgical patients from moderate risk to high risk depends on surgical and patient-related factors. High-risk surgical patients are those with an individual mortality risk greater than 5% or undergoing a surgery carrying a mortality of 5%. These patients commonly have a limited cardiopulmonary reserve and an inability to meet the increased oxygen demand imposed by the perioperative surgical stress during major surgery, which is associated with a significant mortality risk.

In addition to these patient-specific risk factors, perioperative risk factors include multiple interventions that can negatively influence the balance between oxygen demand and consumption. Nociceptive surgical stimulations, volume variations due to acute blood losses or transfusions, and administration of anesthetic agent can significantly influence this V_{O_2}-D_{O_2} relationship. Some studies evaluated the V_{O_2}-D_{O_2} relationship in major surgery[54–56] and showed a decreased capacity for tissue O_2 extraction, which may have led to tissue hypoxia.[57] These observations demonstrate the importance of adequately evaluating the D_{O_2}-V_{O_2} relationship in conjunction with the patient's metabolic demand, which is once again strongly affected by surgical conditions.

Initially, significant perioperative cardiopulmonary optimization information came from observational data published by Shoemaker and colleagues[58] 30 years ago. They recognized that, during the perioperative period, the patient developed an "oxygen debt" (imbalance between global D_{O_2} and V_{O_2}). If their cardiopulmonary reserve was limited, they were less likely to meet the increased oxygen demand incurred during major surgery.[59] They used predefined hemodynamic measures (D_{O_2} index) to guide therapy and observed that patients who survived major surgery had higher D_{O_2} values than nonsurvivors. Using these data, an early GDT aimed at supra-optimizing postoperative D_{O_2} resulted in lowered complications, LOS, mechanical ventilation, and overall cost. The patients who experienced postoperative

complications tended to be those that could also not increase their CO to meet the increased demand of surgery. However, this approach is not beneficial to every high-risk surgical patient because their level of oxygen demand, degree of cardiac function alteration, and capacities of oxygen extraction may significantly vary. Thus, the major concern of the anesthetist in the perioperative period is to optimize the patient's *individual* volemic status by aiming to achieve well-defined goals (based on flow-related parameters such as SV) to maximize end-organ Do_2.

Several studies have demonstrated that CO optimization during high-risk surgery has the ability to improve postoperative patient outcome while also decreasing the cost of surgery.[60–63] However, recent survey studies suggest that goal-directed fluid management is poorly adopted in clinical practice.[3] Most anesthetists use the combination of formulas and fixed-volume calculations with vital sign optimization (BP, HR, CVP, urine output) to guide their perioperative fluid therapy. Le Manach and colleagues[64] showed that changes in BP cannot be used to track changes in SV induced by volume expansion. Consequently, optimization of Do_2 to the tissues during surgery cannot be conducted by monitoring arterial pressure alone. Because arterial pressure and CO both depend on systemic vascular resistance, a normal or even supranormal arterial pressure does not guarantee an adequate CO.

Ideally, one would like to monitor the volume change instead of the pressure change. However, although flow measuring technology is steadily improving, it is still not as technologically straightforward as pressure measurements. Outside of such CO monitoring devices, new parameters (called functional hemodynamic parameters) have been developed and used much more commonly. These parameters can be obtained from arterial pressure waveforms (pulse pressure variation or SV variation) and rely on cardiopulmonary interactions in patients undergoing general anesthesia on mechanical ventilation.[65,66]

As is known, hypovolemia induces hypotension, oliguria, and tachycardia. That is a fact. However, one has to be very careful: these signs are not related to all levels of hypovolemia. They are related to severe hypovolemia![67,68] Moreover, they are not specific and can be present even in the absence of hypovolemia. They are therefore neither sensitive nor specific and should not be used independently for assessing a patient's fluid status. In addition, CVP and pulmonary capillary wedge pressure (PCWP) have been used for years for monitoring a patient's volume status. Unfortunately, almost all the studies focusing on the ability of CVP and PCWP to predict fluid responsiveness have failed to demonstrate any accuracy of these parameters for predicting the effects of volume expansion on CO.[69]

In fact, the main question the anesthesiologist has to answer before performing volume expansion is, "will my patient increase cardiac output in response?" or, more correctly, "is my patient preload dependent?". Preload dependence is defined as the ability of the heart to increase SV in response to an increase in preload. To understand this concept, the Frank-Starling relationship has to be revisited. This relationship links preload to SV and presents 2 distinct parts: a steep portion and a plateau. If the patient is on the steep portion of the Frank-Starling relationship, then an increase in preload (induced by volume expansion) is going to induce an important increase in SV. Alternatively, if the patient is on the plateau of this relationship, then increasing preload will have no effect on SV. Moreover, the Frank-Starling relationship does not only depend on preload and SV but also depends on cardiac function. When cardiac function is impaired, the Frank-Starling relationship is flattened and for the same level of preload the effects of volume expansion on SV are going to be less significant. This concept further explains why preload parameters such as CVP or PCWP are not accurate predictors of fluid responsiveness.

Instead of monitoring a given parameter, functional hemodynamic monitoring assesses the effects of a stressor on commonly recorded variables.[49] For the assessment of preload dependence, the stress is a "fluid challenge" and the parameter is SV. In mechanically ventilated patients under general anesthesia, the effects of positive pressure ventilation on preload and SV are used to detect fluid responsiveness. If mechanical ventilation induces important respiratory variations in stroke volume (SVV) or in arterial pulse pressure (PPV), it is more likely that the patient is preload-dependent.[5] These dynamic parameters (SVV, PPV) have consistently been shown to be superior to static parameters (CVP, PCWP) for the prediction of fluid responsiveness. Our best clinical evidence currently demonstrates that CVP and PCWP, as well as oliguria, hypotension, and tachycardia, should not be used for predicting the effects of volume expansion on CO.[17,69]

Dynamic parameters of fluid responsiveness based on cardiopulmonary interactions have several limitations that need to be clearly stated before they can be adequately used in the clinical setting. First, these parameters have to be used in mechanically ventilated patients under general anesthesia. Up to now, studies conducted in spontaneously breathing patients failed to demonstrate that PPV can predict fluid responsiveness.[70] Moreover, tidal volume has an impact on the predictive value of PPV and a tidal volume of 8 mL/kg of body weight is required.[71] In addition, patients have to be in sinus rhythm; chest must be closed (open chest as well as open pericardium strongly modify the cardiopulmonary interactions), and intra-abdominal pressure has to be within normal ranges.[72] Unfortunately, only 39% of the patients undergoing surgical procedures in the OR met the criteria for the monitoring of fluid responsiveness using noninvasively measured PPV.[73] Also, despite a strong predictive value, PPV may be in the inconclusive "gray zone" (between 9% and 13%) in approximately 25% of patients during general anesthesia.[74]

The use of flow-related parameters to guide intraoperative goal-directed fluid therapy has appeal because these parameters provide a numeric representation of the patient's volume status, which can be difficult to ascertain using standard monitors, urine output, or even CVP.[69,75,76] **Fig. 6** demonstrates an example of a GDT algorithm using SVV and PPV in the OR. Gan and colleagues[60] in 2002 reported earlier return to bowel function, lower incidence of postoperative nausea and vomiting, and decrease in length of postoperative hospital stay with the use of the esophageal Doppler to maximize SV. Intraoperative GDT has also been reported to improve outcome following surgery in high-risk patients by decreasing both morbidity and hospital LOS.[77–80] Previously published studies have shown decreased complications and hospital LOS in high-risk patients undergoing major abdominal surgery with SVV-guided GDT therapy.[63,81] In addition, similar results have been shown in non-high-risk surgical patients undergoing elective total hip arthroplasty[82] and major abdominal surgery.[83] **Table 2** lists the major studies demonstrating that goal-directed therapy is associated with decreased postoperative complications associated with GDT when compared with more conventional fluid management.

In addition, Svo_2 can provide information about Vo_2 and can be used to calculate CO through a pulmonary catheter. A study of cardiac surgery patients found that GDT aimed at normalizing Svo_2 (>70%) and lactate (<2 mmol/L) in the first 8 hours after surgery demonstrated decreased LOS and perioperative organ dysfunction.[84] Unfortunately, Svo_2 has the disadvantage of requiring a PAC, which comes with its own inherent risks.[85] $Scvo_2$, taken from a catheter in the internal jugular or subclavian vein, has also been shown to parallel Svo_2.[19,86] Donati and colleagues[87] demonstrated improved outcome in patients treated with GDT using fluids and dobutamine titrated to optimize oxygen extraction (ERo_2) at less than 27% ($Scvo_2$ >73%). Reductions in $Scvo_2$ in the perioperative setting are independently associated with a higher risk of

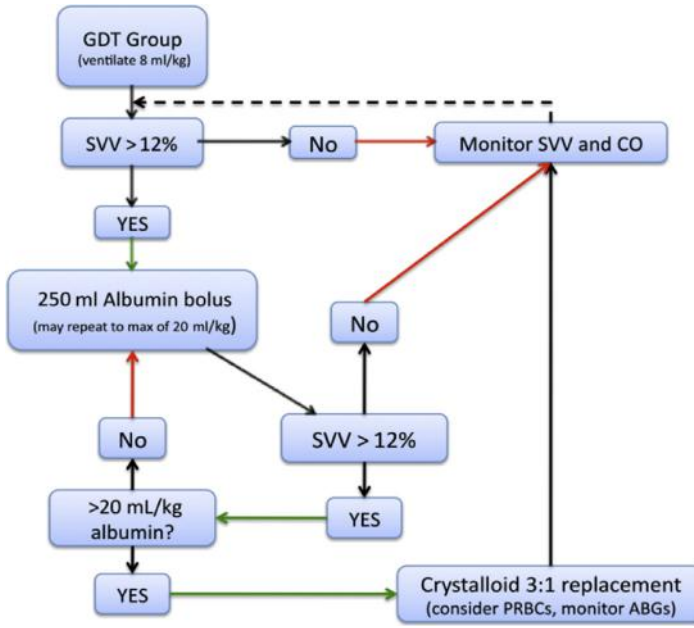

Fig. 6. GDT protocol based on PPV/SVV alone. ABG, arterial blood gas; PRBC, packed red blood cells. (*Adapted from* Ramsingh DS, Sanghvi C, Gamboa J, et al. Outcome impact of goal directed fluid therapy during high risk abdominal surgery in low to moderate risk patients: a randomized controlled trial. J Clin Monit Comput 2013;27(3):51; with permission.)

postoperative complications.[88] The central venous to arterial carbon dioxide difference $P(v-a)Co_2$ has been proposed by some authors for assessment of tissue perfusion.[30,89] Values of $P(v-a)Co_2$ larger than 6 mm Hg were found to be associated with poor outcome and organ dysfunctions.[27,30] Other markers, such as as lactate serum,[90,91] base deficit, and tissue hypercarbia, require further investigation as GDT end points before conclusions can be drawn in high-risk surgery.

Finally, high-risk surgical patients have been shown to benefit from CO optimization using semi-invasive technologies. Unfortunately, a recent survey with the American Society of Anesthesiology and the European Society of Anesthesiology showed a considerable gap between accumulating evidence about the benefits of perioperative hemodynamic optimization and the available technologies that may facilitate its clinical implementation and clinical practices in both Europe and the United States.[3] In the future, GDT using more sophisticated and less invasive monitoring will help clinicians optimize their patients' hemodynamic status during surgery. In Irvine (California), a novel-closed loop fluid administration system and hemodynamic management system based on SV monitoring and optimization (Learning Intravenous Resuscitator) has recently been described.[92,93] The aim of this system is to ease implementation of protocols in clinical settings and to apply goal-directed fluid therapy protocols automatically. After conducting simulation,[92,93] engineering,[94] and animal studies,[95] it is now starting to be used in the OR.[96] The system is designed to titrate fluid administration until SV reaches the plateau of the Frank-Starling relationship and then maintain that plateau throughout patient care. To achieve this goal, the closed loop system monitors SV, tracks volume expansion–induced changes in SV, and uses pulse pressure variation or SV variation to refine fluid responsiveness predictions.[64,74] Future studies will help to evaluate the real benefits of this system.

Table 2
Comparison of perioperative goal-directed therapy research studies during major surgeries

Author	Surgical Type	Patient	Timing	Guiding Goals	Results
Benes et al,[102] 2010	Major abdominal	120	Intraoperative	SVV	↓ Complications and hospital LOS
Goepfert et al,[103] 2013	Cardiac	100	Postoperative	SVV	↓ Complications and ICU LOS
Mayer et al,[63] 2010	Major abdominal	60	Intraoperative	SVV	↓ Complications and hospital LOS No difference in ICU LOS
Ramsingh et al,[104] 2013	Major abdominal	38	Intraoperative	SVV	Faster return of GI function and ↓ hospital LOS
Scheeren et al,[105] 2013	Major abdominal	64	Intraoperative	SVV	↓ Infections in surgical sites
Zheng et al,[106] 2013	Major abdominal	60	Intraoperative	SVV	Faster return of GI function and ↓ hospital LOS and ICU LOS
Lopes et al,[107] 2007	Major abdominal	33	Intraoperative	PPV	↓ Complications and hospital LOS and ICU LOS, ↓ time of mechanical ventilation
Salzwedel et al,[108] 2013	Major abdominal	160	Intraoperative	PPV	↓ Complications, no difference in ICU LOS
Zhang et al,[109] 2012	Major abdominal	60	Intraoperative	PPV	Faster return of GI function and ↓ hospital LOS
Mythen & Webb,[110] 1995	Cardiac surgery	60	Intraoperative	ED/CVP	↑ Gut mucosal perfusion ↓ Complications, hospital LOS, and ICU LOS
Wackeling et al,[62] 2005	Major abdominal	128	Intraoperative	ED/CVP	↑ Gut function recovery ↓ GI complications and hospital LOS
Conway et al,[111] 2002	Major abdominal	55	Intraoperative	ED	↓* Complications, ↓ ICU LOS admissions, ↑* hospital LOS
McKendry et al,[112] 2004	Cardiac	174	Postoperative	ED	↓ Hospital LOS, ↓* ICU LOS, ↓* major complications and death
Buettner et al,[113] 2008	Major abdominal and gynecologic	80	Intraoperative	PICCO	No difference in ICU LOS, hospital LOS, morbi-mortality
Pearse et al,[61] 2005	Major general surgery	122	Postoperative	LidCO + Do_2	↓ Complications and hospital LOS
Donati et al,[87] 2007	Major abdominal	135	Intraoperative	ERo_2 < 27%	↓ Postoperative organ failure and hospital LOS No difference in mortality
Polonen et al,[84] 2000	Cardiac surgery	393	Postoperative	Svo_2 > 70%	↓ Morbidity

Abbreviations: ↓, decrease with $P<.05$; ↑, increase with $P<.05$; ↓*, decrease with $P>.05$; ↑*, increase with $P>.05$; ED, esophageal Doppler; PICCO, pulse induced contour cardiac output.

SUMMARY

When evaluating the critically ill patient in need of fluid management, GDT has mounted strong clinical evidence to support its extensive use. Despite these favorable results, widespread implementation of GDT has not yet been accomplished. Recently, significant progress has been made; most notably, recommendations have been published in the United Kingdom (Enhanced Recovery Partnership), France (French Society of Anesthesiology), and Europe (Enhanced Recovery After Surgery Society).[97,98] Some of the most significant progress has been made in the United Kingdom, where the National Health Service has created financial incentives to ensure hospitals implement hemodynamic optimization in at least 80% of eligible patients. Further creation and implementation of institutional GDT standards are necessary to minimize variability.

As seen by the multiple paths of research discussed above, there is still no universal consensus on an optimal end point for GDT in critically ill patients. As in other areas of medicine, when this occurs, providers must move toward a more "individualized approach" to ensure proper patient care. Hemodynamic optimization in the ICU and OR needs more than BP, HR, CVP, and urine output monitoring. It is essential to monitor dynamic parameters of fluid responsiveness (SV, PPV, and SVV) and CO as minimally invasively as possible. All of these small improvements and standardizations will provide a better hemodynamic assessment of patient status and ultimately improve outcome.

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