

REVIEW

Clinical review: What are the best hemodynamic targets for noncardiac surgical patients?

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Abstract

Perioperative hemodynamic optimization, or goal-directed therapy (GDT), has been shown to significantly decrease complications and risk of death in high-risk patients undergoing noncardiac surgery. An important aim of GDT is to prevent an imbalance between oxygen delivery and oxygen consumption in order to avoid the development of multiple organ dysfunction. The utilization of cardiac output monitoring in the perioperative period has been shown to improve outcomes if integrated into a GDT strategy. GDT guided by dynamic predictors of fluid responsiveness or functional hemodynamics with minimally invasive cardiac output monitoring is suitable for the majority of patients undergoing major surgery with expected significant volume shifts due to bleeding or other significant intravascular volume losses. For patients at higher risk of complications and death, such as those with advanced age and limited cardiorespiratory reserve, the addition of dobutamine or dopexamine to the treatment algorithm, to maximize oxygen delivery, is associated with better outcomes.

Introduction

Noncardiac surgery in high-risk patients is associated with a high incidence of postoperative complications and high mortality rates; multiple organ failure is the main cause of death in these patients [1]. Only about 10% of all anesthetic procedures are performed in high-risk surgical patients [2]; however, these patients account for more than 80% of perioperative deaths. Surgical complications are common and often preventable, yet have a huge impact on outcomes of surgical patients. The occurrence of one of a wide range of possible complications reduces median survival by 69% [3].

Total tissue perfusion relies on adequate arterial oxygen saturation, hemoglobin concentration, and cardiac output (CO), the main components of oxygen delivery (DO_2). Perioperative derangements in DO_2 have been closely correlated to the development of multiple organ failure and death [4]. Meta-analyses of randomized controlled trials have shown that goal-directed therapy (GDT) or perioperative optimization, defined as the use of the DO_2 , CO, or a surrogate to guide intravenous fluid and inotropic therapy, significantly reduces postoperative complications and risk of death [5-13].

Perioperative physiology of oxygen delivery and consumption

The metabolic rate drives regional blood flow such that individual tissues determine their own blood flow according to their metabolic needs. Hence, CO is determined by peripheral metabolic demand. Major surgical trauma increases oxygen requirements from an average of 110 ml/minute/ m^2 at rest to an average of 170 ml/minute/ m^2 in the postoperative period [14]. This increase in oxygen demand is normally met by increases in CO and tissue oxygen extraction. Patients with limited cardiorespiratory reserve who cannot increase CO sufficiently to meet the increased oxygen demand during and after major surgery will develop an imbalance in the DO_2 /oxygen consumption (VO_2) relationship, with an increased oxygen extraction ratio followed by decreases in mixed venous oxygen saturation (SvO_2) and central venous oxygen saturation ($ScvO_2$), oxygen debt and lactic acidosis. Lactic acidosis and prolonged lactate clearance are related to increased mortality in surgical ICU patients [1,15,16].

Tissue hypoxia is the central pathophysiological process in the development of organ dysfunction [1]. We ultimately wish to improve tissue perfusion, but most trials to date have targeted surrogates. Variables that are commonly used to monitor hemodynamic and oxygenation status, such as blood pressure, heart rate, urine output and arterial blood gases, can be normal in the presence of tissue hypoxia and cannot be used to rule out imbalances between oxygen supply and demand during surgical trauma [4]. SvO_2 is a sensitive indicator of the

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adequacy of whole-body tissue oxygenation but requires placement of a pulmonary artery catheter (PAC). $ScvO_2$ requires insertion of a central venous catheter and can be used as a surrogate for SvO_2 because changes and trends in both variables parallel each other [17]. Both measures have been shown to reflect oscillations in the oxygen extraction ratio and an imbalance in the DO_2/VO_2 relationship in various clinical scenarios.

What are the best hemodynamic targets?

Uncovering and correcting hypovolemia

Correcting hypovolemia is a crucial step. Fluid deficits may occur for various reasons in surgical patients in the absence of obvious fluid losses because of disturbances in capillary permeability and vasodilation. Occult hypoperfusion is associated with increased mortality after major surgery even in hemodynamically stable patients [18]. Hypovolemia may be present despite normalization of the heart rate, mean arterial pressure and urine output, resulting in inadequate blood flow for the increased metabolic requirements.

Monitoring of cardiac filling pressures, such as central venous pressure and pulmonary artery occlusion pressure, is unreliable for assessing cardiac preload in mechanically ventilated patients [19]. Assessment of filling pressures or end-diastolic volumes (preload) can better predict the individual response to fluid loading than can static indices (Frank–Starling curve) [19,20]. The concept of preload dependence/independence describes the effect of fluid infusion on CO. Fluid responders convert fluid loading into a significant increase in CO as long as they have both ventricles operating in the steep portion of the curve. A fluid challenge causing an increase in stroke volume (SV) >10% (steep portion of the curve) defines a patient as a fluid responder and suggests that subsequent fluid challenge is unlikely to result in overfilling. Increases <10% (flat portion of the curve) indicate that further fluid challenge is inappropriate and could decrease ventricular performance, resulting in pulmonary or tissue edema. Nonresponders may benefit with the administration of inotropes by shifting the Frank–Starling curve up-leftwards, thereby improving the response to fluid challenges. Under similar loading conditions, patients working on the flat portion of the curve may be moved to the steep portion of the new curve.

Dynamic predictors of fluid responsiveness are increasingly used. Many studies of GDT have used repeated boluses of artificial colloids to test fluid responsiveness [21–27]. Fluid challenge-induced responses on surrogates of CO, such as the corrected flow time or SV, have been used to guide fluid resuscitation. Bundgaard-Nielsen and colleagues [5], Abbas and Hill [6] and Walsh and colleagues [7] reviewed data from studies in which a GDT strategy was used to maximize flow-derived hemodynamic

variables, mostly measured using transesophageal Doppler. These authors reported reductions in postoperative nausea and vomiting, time to first bowel movement, complications and hospital length of stay. Another recent randomized controlled trial in which patients undergoing radical cystectomy were managed with cardiovascular optimization guided by transesophageal Doppler reported similar benefits [28]. In one meta-analysis, a reduction in complications >60% was reported [7].

Functional hemodynamic monitoring is used to evaluate volemia according to indices derived from cardiorespiratory interactions. Positive pressure ventilation is associated with different effects on the left and right sides of the heart. Cyclic changes in intrathoracic pressure can result in concurrent changes in SV and oscillations in arterial pulse pressure [29]. The magnitude of these oscillations is proportional to the degree of preload dependency of the patient. In patients operating on the flat portion of the Frank–Starling curve, pulse pressure variation (PPV) is low and volume loading does not result in a significant increase in SV. In patients operating on the steep portion of the preload–SV relationship, PPV is high and volume loading leads to a significant increase in SV. PPV >13% indicates that the patient is very probably on the steep part of the curve and will be a fluid responder [20].

In a study performed in 33 patients, minimization of PPV to values <10% during surgery by volume loading significantly decreased the median duration of hospital stay (7 days vs. 17 days, $P < 0.01$), postoperative complications, and the median duration of mechanical ventilation [30]. Another study used variability in the pulse oximeter plethysmogram, the pleth variability index [31]. The intraoperative intervention was directed to fluid loading with colloids to minimize the pleth variability index to <13%. Intraoperative crystalloids, the total volume infused, and lactate levels were significantly lower in the pleth variability index group. SV variation or systolic pressure variation as measured by the analysis of the arterial pressure waveform also enables prediction of volume responsiveness in ventilated patients. The greater the variation of these indices, the more CO can be expected to increase in response to volume loading. Fluid optimization guided by minimization of SV variation to <10% during major abdominal surgery was associated with better intraoperative hemodynamic stability, lower serum lactate and fewer postoperative complications [32]. Conversely, compared with conventional treatment, systolic pressure variation-guided intraoperative fluid management in patients undergoing elective major surgery was associated with slightly increased fluid administration, whereas organ perfusion and function were similar [33].

A number of indices based on ventilation-induced variability of the arterial pressure wave are useful during

Table 1. Goals of therapy, monitors and main outcomes

Variable	Monitor	Reported clinical effects [references]
Dynamic indices of fluid responsiveness		
Corrected flow time	TED	Decrease LOS or complications [22,24,28], increase LOS [61,62]
Stroke volume	TED, Vigileo FloTracsystem™, LiDCOrapid™	Decrease LOS or complications [23-28]
Pulse pressure variation	Multiparametric monitor, LiDCOrapid™	Decrease LOS and complications [30]
Plethysmography variability index	Plethysmography	None [31]
Stroke volume variation	Vigileo/FloTracsystem™, LiDCOrapid™	Decrease LOS and complications [32]
Systolic pressure variation	PiCCOplus™	None [33]
Flow indices		
Oxygen delivery	PAC, LiDCOplus™, Vigileo/FloTracsystem™	Decrease mortality [35-38], decrease complications [35-38,64,65,68], none [66]
Cardiac index	PAC	Decrease complications [39], none [40-43]
Indices of adequacy of perfusion		
Venous oxygen saturation	PAC	None [52]
Oxygen extraction ratio	Blood gas	Decrease complications [53]

LiDCOplus™, LiDCO system (LiDCO Ltd, London, UK); LiDCOrapid™, LiDCO system ((LiDCO); LOS, length of stay; PAC, pulmonary artery catheter; PiCCOplus™, PiCCO system (Pulsion Medical Systems AG, Munich, Germany); TED, transesophageal Doppler; Vigileo, Vigileo system (Edwards, Irvine, CA, USA).

GDT for patients deeply sedated, anesthetized, mechanically ventilated, and with normal cardiac function. Based on current knowledge we can target values of PPV, SV variation or pleth variability index <10 to 13% for these patients, although more studies on the optimal thresholds to predict fluid responsiveness during GDT are warranted as variations may occur even with different devices [34]. For the other patients, monitoring of CO or surrogates and use of dynamic predictors of fluid responsiveness would be more suitable (Table 1).

Targeting tissue perfusion in high-risk surgical patients

Many small single-center studies have demonstrated impressive reductions in morbidity and mortality associated with a treatment strategy aimed at preemptive optimization by increasing the DO₂ index to levels >600 ml/minute/m² [35-38]. These protocols had the following circumstances in common: they were carried out preemptively in high-risk patients, they started before and continued some hours after surgical trauma, and they used inotropes, blood, and vasodilators if necessary, in addition to fluids.

Systematic reviews and meta-analyses [8-13] have explored whether preemptive strategies of hemodynamic monitoring and manipulation in the perioperative period could improve outcomes for moderate-risk and high-risk surgical patients. These systematic reviews showed that interventions aimed at preemptive hemodynamic optimization did reduce mortality.

Hamilton and colleagues identified 29 randomized clinical trials comprising 4,805 moderate-risk or high-risk surgical patients [12]. The use of a preemptive

hemodynamic intervention significantly reduced mortality (pooled odds ratio (95% confidence interval) = 0.48 (0.33 to 0.78); *P* = 0.0002) and surgical complications (odds ratio (95% confidence interval) = 0.43 (0.34 to 0.53); *P* <0.0001). Complications were reduced in all studies, but subgroup analysis revealed that mortality was reduced solely in those studies using a PAC as opposed to minimally invasive methods of monitoring, in those using fluids and inotropes as opposed to fluids alone, in those using the cardiac index or DO₂ as the end point, and in those studies using a supranormal resuscitation target.

Gurgel and do Nascimento identified 32 studies involving 5,056 high-risk surgical patients in which well-defined protocols were used to maintain tissue perfusion with fluids and/or inotropes [13]. Trials that included perioperative interventions aimed at the hemodynamic optimization of higher-risk surgical patients (studies with mortality rates in the control group >20%) reported significantly reduced mortality rates (pooled odds ratio (95% confidence interval) = 0.32 (0.21 to 0.47); *P* ≤0.00001). Studies using a PAC for hemodynamic monitoring and the cardiac index, DO₂ or VO₂ as therapeutic goals achieved statistical significance for reductions in mortality. The results of this meta-analysis confirm the findings of an older review by Kern and Shoemaker indicating that patients with higher mortality rates are the most likely to benefit from preoperative or intraoperative GDT [9].

In other preoperative or intraoperative interventional studies, different goals – such as normal values of cardiac index or DO₂ – were used, mainly to guide fluid resuscitation [39-43]. These studies did not report better

outcomes with this strategy, except for a decrease in the rate of complications in one study [39]. This observation suggests that normal values may not be normal during surgical trauma. One study using DO_2 -oriented optimization therapy with fluids and dobutamine to achieve levels >600 ml/minute/ m^2 during the first 8 hours after operation showed a significant decrease in postoperative complications but no differences in mortality rates [44].

Indeed, in patients with a high risk of perioperative death, PAC-guided hemodynamic optimization using dobutamine to obtain $\text{DO}_2 >600$ ml/minute/ m^2 was associated with better outcomes, whereas fluids alone increased the incidence of postoperative complications [45]. The use of two different treatment algorithms of GDT comparing fluids alone with fluids and dobutamine suggests that dobutamine was associated with better recovery of the left ventricular stroke work index during operative trauma and with higher tolerance to fluids. Nevertheless, dobutamine is also able to improve microcirculation [46]. Jhanji and colleagues reported microvascular alterations in patients undergoing major surgeries who developed postoperative complications [47,48]. By adding SV-guided fluid therapy and low-dose dobutamine to the algorithm of treatment, DO_2 increased along with significant improvements in sublingual and cutaneous microcirculatory blood flow [48].

In studies performed in high-risk patients submitted to major surgery, ScvO_2 levels of 65% [49] and 73% [50] at ICU admission were found to discriminate best between patients with and without complications. Other authors reported much higher levels of ScvO_2 ($>80\%$) intraoperatively and that only preoperative levels of $\text{ScvO}_2 <70\%$ were predictive of postoperative complications [51].

Use of SvO_2 or ScvO_2 as a target variable to improve outcomes in high-risk patients has been tested in a few studies. In vascular surgery patients, optimization of DO_2 to achieve SvO_2 levels $>65\%$ was not associated with better outcomes [52]. However, early management with fluid challenges, dobutamine and blood transfusion directed to maintain the oxygen extraction ratio estimated from ScvO_2 values at levels $<27\%$, both during major abdominal surgery and postoperatively, significantly reduced the number of organ failures and duration of hospital stay [53].

Despite the fact that the oxygen extraction ratio, SvO_2 or ScvO_2 could in theory be a good monitor of the systemic balance between global DO_2 and consumption and of the favorable effects on morbidity, pooling of studies using GDT guided by these variables did not demonstrate beneficial effects on mortality [12,13]. Perioperative oxygen consumption is determined by various factors, particularly the depth of anesthesia and body temperature. Perioperative disturbances in ScvO_2

therefore cannot be assumed to relate solely to DO_2 . Finally, replacing SvO_2 monitoring with ScvO_2 monitoring in order to avoid the use of a PAC is still controversial, at least in cardiac surgery patients, in severe sepsis during the first 24 hours after ICU admission and in other heterogeneous groups of critically ill patients [54-56].

In view of these conflicting results and the various thresholds reported, we would rather say that SvO_2 or ScvO_2 should not currently be used as a target in anesthetized high-risk patients. However, postoperatively in the recovery room or ICU, additional therapy titrated to achieve normal levels of ScvO_2 , serum lactate and venous-to-arterial carbon dioxide difference is necessary to restore adequate systemic oxygenation [57-59].

Does the most current evidence support these targets?

We acknowledge that the small size of the majority of the studies into GDT is a potential source of bias [60]. In addition, many of these studies were carried out several years ago. Indeed, in the last decade invasive hemodynamic monitoring with a PAC has been increasingly replaced by various minimally invasive technologies, and new practices such as enhanced recovery after surgery strategies, restrictive strategies of fluid maintenance, and fast-track surgeries have been adopted. Outcomes have improved as a result, making the benefits of GDT more difficult to demonstrate.

In patients undergoing laparoscopic colectomy, Senagore and colleagues reported a longer time to discharge in the two groups of patients undergoing transesophageal Doppler-guided GDT with an enhanced recovery after the surgery protocol compared with control patients [61]. In patients undergoing elective colorectal surgery, Brandstrup and colleagues found no differences when comparing maximization of SV guided by transesophageal Doppler with a restrictive strategy of fluid maintenance aiming at zero fluid balance [62]. Challand and colleagues reported detrimental effects of GDT on hospital length of stay in aerobically fit patients undergoing open or laparoscopic colorectal surgery [63].

Nevertheless, more small clinical trials continue to add to the literature in favor of GDT. Cecconi and colleagues found that GDT with fluids and dobutamine reduced postoperative cardiovascular complications in patients undergoing elective total hip replacement under regional anesthesia [64]. Bisgaard and colleagues showed that the intraoperative optimization of SV, using dobutamine if necessary, in patients undergoing lower-limb arterial surgery significantly decreased postoperative complications [65]. These two studies target $\text{DO}_2 >600$ ml/minute/ m^2 . Interestingly, using the same algorithm of treatment in another study performed in patients undergoing aortic surgery, Bisgaard and colleagues found no differences in outcomes [66].

These findings warrant further comment. First, the use of individualized goals instead of a preset arbitrary value >600 ml/minute/ m^2 is more rational and would avoid potential adverse events related to GDT. However, no marker of adequacy is yet available to be used intraoperatively. The critical DO_2 is the point below which dependence between DO_2 and VO_2 is observed, and this point varies for different organs; regional hypoperfusion may therefore occur despite a normal global oxygen extraction rate. Achievement of the 600 ml/minute/ m^2 value is possibly not what determines better outcomes. Rather, keeping DO_2 above baseline while trying to reach this number and, as a consequence, preventing oxygen debt may be more important. By targeting a supranormal value, the likelihood of having more patients without tissue hypoxia and for longer periods probably increases. Supranormal values of DO_2 should perhaps be defined in relation to normal preoperative values and predicted increases in VO_2 for different types of surgery and not set at 600 ml/minute/ m^2 for all, but this suggestion requires further tests in future studies.

Second, despite what many believe to be conflicting bodies of evidence, volume optimization can in fact be complementary to a restrictive fluid approach, particularly with regard to crystalloids [67]. Lobo and colleagues evaluated two regimens of intraoperative fluid maintenance during optimization of DO_2 with fluids and dobutamine, and found that a restrictive regimen of crystalloid maintenance at 4 ml/kg/minute during surgery was associated with better outcomes than was a conventional regimen of 12 ml/kg/minute [68]. The total volume used as the maintenance fluid during and after surgery, particularly in prolonged surgeries, might be carefully considered.

Finally, although multicenter prospective randomized controlled trials are lacking, the evidence for the benefits is considered strong. Despite these promising results, this GDT approach has not been widely adopted. Unfortunately, clinical experience, blood pressure, central venous pressure and urine output are still the most widely used indicators of volume expansion and adequacy of resuscitation during surgery [69]. Implementing evidence-based practice such as perioperative hemodynamic optimization in high-risk patients undergoing noncardiac surgery remains a challenge.

Which targets for which patients?

We can separate the candidates for GDT into two groups of patients. The precise correction of hypovolemia will be enough to achieve the goals of therapy in the large majority of surgical patients. For high-risk patients, uncovering and correcting hypovolemia is crucial before other therapies likely to increase DO_2 – for example, blood transfusions, vasopressors or inotropes – are used.

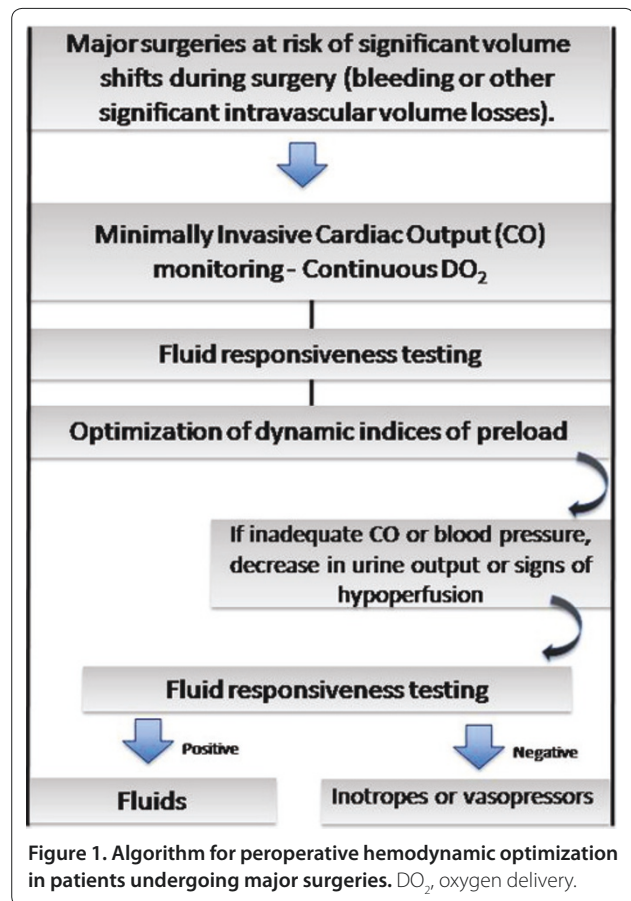
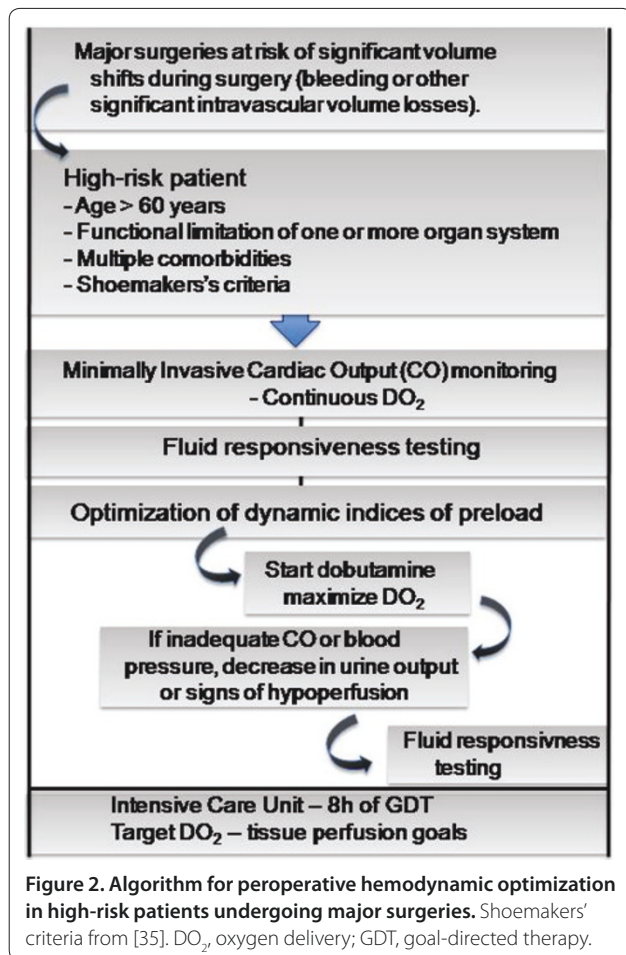


Figure 1. Algorithm for perioperative hemodynamic optimization in patients undergoing major surgeries. DO_2 , oxygen delivery.

The first group comprises the majority of patients undergoing major surgery, who are at risk of significant volume shifts during surgery because of bleeding or other significant intravascular volume losses. For these patients, the use of dynamic indices to ensure normovolemia and preemptive hemodynamic optimization with minimally invasive CO monitoring or surrogates guided by SV or CO responses to fluid challenge is suitable (Figure 1). Inotropes or vasopressors should be used in this group only in the presence of inadequate CO or blood pressure, a decrease in urine output or signs of hypoperfusion, after fluid responsiveness testing is negative.

The second group of candidate patients includes those with a higher risk of morbidity and mortality. In spite of the multifactorial origin of postoperative complications, compromised physiologic reserves and multiple comorbidities in combination with extensive surgery seem to be a hallmark of high complication and mortality rates [44]. In general, these patients are older, undergoing extensive ablative surgery with limited cardiopulmonary reserve, and/or with other organ dysfunctions/comorbidities (Figure 2) [38,45,65]. Shoemaker and colleagues' criteria for identifying a high-risk of perioperative complications



will also identify patients to be managed in this group [35]. For these patients we can monitor DO_2 continuously, with minimally invasive hemodynamic monitoring or a PAC, initially testing fluid responsiveness and maximizing SV and then preemptively augmenting DO_2 with dobutamine or dopexamine if necessary to achieve the best possible value.

Conclusion

A considerable number of randomized and controlled studies in high-risk surgical patients have reported improved outcomes with GDT. As the population ages and more complex surgery is performed, the number of patients requiring major surgery and at a high risk of complications is going to increase. In the intraoperative period, targeting dynamic predictors of fluid responsiveness or functional hemodynamics with minimally invasive CO monitoring is suitable for the majority of patients undergoing major surgery. For patients at a higher risk of complications and death, the maximization of DO_2 is associated with better outcomes. In the ICU, additional therapy titrated to increase $ScvO_2$ or the

venous-to-arterial carbon dioxide difference and to decrease serum lactate concentrations may be necessary to restore adequate systemic oxygenation.

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Abbreviations

CO, cardiac output; DO_2 , oxygen delivery; GDT, goal-directed therapy; PAC, pulmonary artery catheter; PPV, pulse pressure variation; $ScvO_2$, central venous oxygen saturation; SV, stroke volume; SvO_2 , mixed venous oxygen saturation; VO_2 , oxygen consumption.

Competing interests

The authors declare that they have no competing interests.

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