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Haemodynamic coherence in perioperative setting.

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ABSTRACT

Over the last decade, there has been an increased interest in the use of Goal Directed Therapy (GDT) in patients undergoing high risk surgery and various haemodynamic monitoring tools have been developed to guide perioperative care. Both the complexity of the patient and the surgical procedure need to be considered when deciding whether GDT will be beneficial. Ensuring optimum tissue perfusion is paramount in the perioperative period and is reliant on the coherence between both the macrovascular and microvascular circulations. Although global haemodynamic parameters may be optimised with the use of GDT, microvascular impairment can still persist. This review will provide an overview of both haemodynamic optimisation and microvascular assessment in the perioperative period.
Introduction

It is well established that a surgical intervention leads to the rapid activation of the stress response in a living organism. This response results in an increase in adrenocorticotropic hormone (ACTH) along with an excess of cortisol release, insulin resistance and a rise in catecholamine levels [1]. This metabolic alteration induced by the surgical stress response is responsible for both proteolysis and muscle breakdown [2]. Immunomodulation also occurs as a consequence of the surgical insult with an increase in leukocyte infiltration, raised levels of circulating dendritic cells and reduced natural killer cell toxicity and T-cell responses [3]. In addition, the stress response is responsible for an increase in oxygen consumption. In the 1990’s, Shoemaker et al demonstrated that an oxygen debt starts to develop intraoperatively in high-risk surgical patients and that if these patients are unable to overcome this deficit during the first few hours postoperatively, an increase in morbidity and mortality was observed [4]. They also observed that the incidence of organ failure and mortality were reduced when the oxygen deficit was rapidly compensated by optimizing haemodynamic variables, using a protocol aimed to reach the same haemodynamic values recorded in patients who survived [4]. These data clearly demonstrated that some patients required haemodynamic support to overcome the surgical stress. Therefore, over the last two decades, several protocols have been developed to optimise haemodynamic parameters, with the aim of reducing tissue hypoperfusion and meeting the increased metabolic demands of the tissue as soon as possible. The effectiveness of this goal directed therapy (GDT) is strictly time related and a reduction in morbidity and mortality can be shown only when organ failure is not yet established [5]. Thus, haemodynamic optimisation should be started intraoperatively to prevent organ hypoperfusion and continued for at least 6-8 hours postoperatively to rapidly compensate the oxygen debt.

It is well known now that not all patients are able to overcome the oxygen debt and therefore these patients may benefit from haemodynamic modulation. The inability to repay the oxygen debt may be due to firstly; the characteristics of the surgical procedure which are related to the significant derangement of homeostatic milieu as a consequence of severe tissue damage and secondly; to whether the patient has a limited physiological reserve and is unable to sustain even minor stress [6]. Thus, the decision to perform
GDT should take into consideration both surgical and patient factors. The risk of mortality related to the surgical procedure should also be taken into account and patients undergoing a procedure with a probable mortality greater than 20% are considered as extremely high-risk patients [7,8]. Regarding patient status, patients with an individual risk of death greater than 5% are considered to be high-risk [7]. This risk can be assessed using several tests [8], scores [9–12] or physical status classifications e.g. the American Society of Anesthesiologists Physical Status (ASA PS) [13]. Evidence has shown that GDT is only able to improve survival in high-risk surgical patients and reduce complications in the intermediate-risk population.

However, the adequacy of perfusion in each peripheral tissue cannot be derived only from macro-haemodynamic assessment. Each organ and each tissue within the organ regulates local blood flow according to local conditions [14] and several clinical studies have shown that microvascular alterations are not always associated with classic macro-haemodynamic parameters [15–18]. Impaired microvascular perfusion is responsible for organ failure even though macro-haemodynamic and blood flow have been optimized by clinical interventions [18,19]. For this reason, the clinician should adequately optimise haemodynamic parameters with the microcirculation as the target in mind. All information obtained from a haemodynamic monitoring system should recognise any incoherence between macro- and micro-haemodynamics.

The Haemodynamic Puzzle

The main haemodynamic elements that clinicians must assess and optimise during perioperative period are preload, afterload and contractility. Their interaction determines blood flow and pressure.

The role of preload pressure parameters has been evaluated over the last few years and the current approach is based on assessment of fluid responsiveness. In the operating theatre, dynamic parameters such as stroke volume variation (SVV) and pulse pressure variation (PPV) could be more reliable and useful than in intensive care unit, where the preconditions for their accuracy are not always available (such as during spontaneous/assisted ventilation) [20]. Alternatively, a fluid challenge remains the simplest way to assess the ventricle preload-dependence status [20,21].
Afterload is an important determinant of cardiac output under given conditions of contractility and preload. In clinical practice, the most common way to evaluate afterload is by calculating the systemic vascular resistance (SVR). However, we must consider that the arterial SVR value only represents opposition or resistance to a constant flow, which is found fundamentally at arteriolar level, where the compensating mechanisms that control vasomotor tone keep the perfusion pressure within a physiological range. Therefore, this parameter is not able to provide a complete description of global arterial impedance, due to the fluctuating nature of blood flow and arterial pressure [22]. Arterial elastance (Ea) has been proposed as a more accurate parameter of estimating arterial tone. It is defined as the ratio of change in pressure to change in volume rather than resistance, and takes into account the pulsating characteristic of flow. Dynamic arterial elastance (Eadyn) can be simply calculated by the ratio between PPV and SVV. Assessment of Eadyn has been recently proposed to predict the arterial pressure response after volume loading in preload-dependent patients [23–25]. Optimisation of afterload is important to maintain blood pressure within autoregulation range values [14].

Echocardiography offers clinicians alternative parameters to assess the contractility function of the heart. The ejection fraction is the parameter most commonly used for evaluating contractility, even if it is dependent on the afterload. However, echocardiography offers other parameters less dependent upon loading condition, such as dP/dt. The limits of echocardiography are the expertise needed to perform it and the limited role of the transthoracic approach in theatre, where the only possible technique is the transoesophageal one. Nowadays, several monitoring systems based on pulse contour analysis are able to calculate dP/dt max assessing the steep part of arterial curve. Moreover, transpulmonary thermodilution allows the cardiac function index (CFI) and the global ejection fraction (GEF) to be measured. These parameters could serve as an easy bedside detection of alteration in contractility that may require an extensive evaluation by echocardiography and could be used to monitor the efficacy of inotropic therapy [26].

Finally, peripheral perfusion should be carefully assessed to verify the adequacy of haemodynamic values. Mixed/central venous oxygen saturation, arterial lactate level and the difference between central venous
and arterial PCO\textsubscript{2} (Pcv-aCO\textsubscript{2}) can be measured to trigger further interventions [27,28]. Alteration of perfusion parameters without an impairment in global haemodynamics may reflect a local hypoperfusion, altered microvascular flow with shunting or inability of oxygen utilisation by cell. The last condition is characteristic of sepsis, where mitochondrial dysfunctions are associated to microvascular shunting.

Like a puzzle, the myriad of information generated from several haemodynamic monitoring tools must be integrated and correctly interpreted to provide an accurate overview on cardiovascular status.

**The right monitoring system for the right patient**

Nowadays, clinicians can choose between several haemodynamic monitoring systems, ranging from less invasive to more complex and invasive tools [29]. Clinicians should select the most appropriate device according to the complexity of the single patient. Taking into consideration the surgical procedure and the morbidity of the patient, use of an invasive haemodynamic system and application of a GDT protocol should only be considered in high risk patients. Nevertheless, several GDT protocols are based on dynamic parameters of fluid responsiveness that can be easily assessed using mini-invasive systems based on pulse contour analysis.

To help the anaesthesiologist interpret the information from the haemodynamic monitor, a closed-loop technology has been recently proposed. An automated closed-loop system has been developed to control fluid administration in the context of a GDT protocol for SV maximisation. This new approach of perioperative haemodynamic optimisation has been evaluated only in few studies and other trials are needed to verify its utility on outcome compared with current practice [30–33].

Several tools aim to assess microvascular function at different levels. Near-infrared spectroscopy (NIRS) is an indirect method to evaluate tissue perfusion and can measure tissue oxygen saturations (StO\textsubscript{2}). The NIRS signal, applied to thenar muscle, is limited to vessels that have a diameter less than 1 mm (arterioles, capillaries, and venules), but, as 75% of the blood in a skeletal muscle is venous, NIRS StO\textsubscript{2} measurements mostly represent local venous haemoglobin O\textsubscript{2} saturation and the local balance between DO\textsubscript{2} delivery and VO\textsubscript{2} [34]. Vaso-occlusive test can be performed to assess microvascular reactivity. In this test, arterial
occlusion is caused by transient inflation of a cuff placed around the arm. After StO₂ reaches approximately 40%, the ascending slope of the StO₂ value observed just after the release of the cuff reflects the quality of flow recovery. Abdelmalak et al. performed an observational study to evaluate the relationship between perioperative StO₂ and surgical outcomes in patients undergoing major non-cardiac surgery. StO₂ was measured at the thenar eminence during surgery and for two postoperative hours. The minimum StO₂ was inversely associated with 30 day mortality and serious in-hospital complications ($p = 0.02$) [35]. Moreover, Govinda et al showed that the evaluation of StO₂ during the postoperative period after colorectal surgery was able to predict the development of postoperative surgical site infection (SSI). StO₂ at the upper arm was lower in patients who developed SSI than in those who did not develop SSI (52% ±22% vs. 66% ±21%; $p = 0.033$). A cut-off of 66% had a sensitivity of 71% and specificity of 60% for predicting SSI [36].

Direct visualisation of the microvascular bed at sublingual level can be easily performed using special cameras but a fast and operator independent analysis cannot yet be performed [37]. Orthogonal polarization spectral (OPS) and sidestream darkfield (SDF) are two video-microscopic imaging techniques that can be used at the bedside to visualise the microcirculation. However, analysis of microvascular parameters is offline, time consuming and operator dependent [38,39]. This represents the main limitation of using microvascular imaging in clinical practice as a “point-of-care” tool. Only microcirculatory flow index (MFI) has been evaluated in real-time [40]. Recently a third generation handheld microscope based on incident dark field (IDF) imaging has been introduced. This technique is able to provide higher quality images than SDF imaging, visualizing approximately 20-30% more capillaries than SDF device [41–43]. This camera is provided with an automatic analysis software that could allow us to obtain results quickly. However, the ability of this new software to obtain microvascular parameters need to be improved and validated [37]. Anyway, future technological developments are promising.

No microvascular monitor systems have been used in clinical practice to guide haemodynamic optimisation during the perioperative period in a specific GDT protocol.

Haemodynamic Targets
Originally, Shoemaker et al. based their optimisation protocol on targeting supranormal value for cardiac index, oxygen delivery (DO₂) and VO₂. These goals were derived empirically from the mean values observed in patients who survived. The majority of perioperative optimisation protocols continue to use a DO₂ > 600 ml/min/m² as the principal goal to reach, whilst other are based on SV maximisation. Nowadays, these parameters can be easily monitored using several mini-invasive monitoring systems which are responsible for a wide range of GDT application. DO₂ is regionally regulated according to tissue metabolism and an inadequate global DO₂ may be associated with impaired local tissue perfusion. Although a supranormal DO₂ value will most likely result in a lower probability of tissue hypoperfusion, it should not be the only parameter to examine when we try to optimise tissue perfusion. An inadequate tissue DO₂ is responsible for an increase in oxygen extraction rate (O₂ER), a decrease in SvO₂ or its surrogate ScvO₂ and finally an increase in lactate level. Pearse et al. [44] monitored ScvO₂ for 8 hours postoperatively and demonstrated that a cut-off value of 64.4% was able to discriminate patients at higher risk of developing complications. Other studies have confirmed these results even if with different cut-off values [45,46]. Based on the concept that O₂ER reflects the balance between DO₂ and VO₂, Donati et al. [47] performed a multicentre randomised controlled trial to evaluate the effectiveness of a GDT protocol based on O₂ER estimation (O₂ERE) calculated as (SaO₂ - ScvO₂)/SaO₂. The patients in the protocol group were optimised to maintain an O₂ERE < 27% using fluids, dobutamine and/or packed red blood cells (RBCs). These patients developed a significantly lower incidence of organ failure postoperatively compared to the control group (9 vs. 27; p < 0.001). Despite this evidence, doubts currently still exist about the ability of ScvO₂ to guide haemodynamic optimisation during the perioperative period. Firstly, the ScvO₂ is dependent on several conditions including hypoxia, shivering, anaesthesia, haemorrhage and myocardial ischaemia. Secondly, it is reflected by the relationship between global DO₂ and VO₂ and might not be able to unmask regional hypoperfusion [48]. To overcome this problem, Pcv-aCO₂ has been proposed as a better predictor of tissue hypoperfusion [49]. Futier et al. showed that between patients with an intraoperative ScvO₂ ≥ 71%, Pcv-aCO₂ was higher in those that developed postoperative complications (7.7 ± 2 vs. 5 ± 2 mmHg, p < 0.001) [39]. The cut-off to discriminate these two conditions was 5 mmHg. Moreover, Ospina-Tascon [50] recently demonstrated that a higher value of Pcv-aCO₂ was associated with a lower percentage of small perfused vessels (PPV), lower
functional capillary density and a higher heterogeneity of microvascular blood flow in patients with septic shock. Pcv-aCO$_2$ significantly correlated to PPV ($p<0.001$) and changes in Pcv-aCO$_2$ between baseline value and 6 hours after resuscitation were significantly related to changes in PPV ($R^2 =0.42$, $p <0.001$). Interestingly, absolute values and changes in Pcv-aCO$_2$ were not related to global haemodynamic variables.

Stens et al. [51] have recently evaluated the effect of two haemodynamic optimisation protocols on sublingual microcirculation during abdominal surgery. Thirty-one patients were randomised to pulse pressure variation (PPV) and cardiac index (CI) or mean arterial pressure (MAP) guided protocol and microvascular parameters were recorded at one, two and three hours after anaesthesia induction. Despite the administration of more fluids in PPV/CI group resulted in lower PPV values and higher CI values, no differences were noted between the two groups in microvascular parameters.

**Haemodynamic optimisation therapy**

The major determinants of DO$_2$ are cardiac output (CO), haemoglobin level (Hb) and arterial oxygen saturation (SaO$_2$). From the haemodynamic aspect, DO$_2$ optimisation can be achieved by modulating CO and then increasing Hb with RBCs transfusions if needed. An inadequate CO may be optimised using fluids as first line therapy and then inotropes. In mechanically ventilated patients, the heart-lung interaction is useful to determine in which part of the Frank-Starling curve the heart is sitting upon and whether CO is able to rise after fluid administration. Several parameters based on mini-invasive monitor systems are available to assess fluid responsiveness [20]. As fluid overload and hypovolemia are both detrimental and associated with adverse outcomes [52], optimisation of functional haemodynamic parameters should allow individualised fluid titration [53]. Several meta-analysis have recently demonstrated that using dynamic parameters to guide fluid therapy was associated with less complications and shorter length of stay in the intensive care unit (ICU) and/or hospital [54,55]. Benes et al showed that the overall morbidity was reduced when dynamic parameters were used to guide fluid therapy (odd ratio [OR] 0.51; 95% confidence interval [CI] 0.34 to 0.75; $p <0.001$) [45]. In particular, a significant reduction in infectious (OR 0.45; 95% CI 0.27 to 0.74; $p =0.002$), cardiovascular (OR 0.55; 95% CI 0.36 to 0.82; $p =0.004$) and abdominal complications (OR 0.56; 95% CI 0.37 to 0.86; $p =0.008$) was observed, in association with a significant reduction in ICU length
of stay (weighted mean difference [WMD] −0.75 days; 95% CI −1.37 to −0.12; \( p =0.02 \)). Dynamic parameters have several limitations [20] and monitoring the effect of a fluid challenge on SV is an alternative approach. GDT protocols based on SV maximisation (that consist of administering a fluid challenge until the SV increases by no more than 10%) were able to reduce complications rates [56]. No difference seems to exist between colloids and crystalloids. A double-blind randomised controlled trial was not able to show any difference in terms of morbidity when the two different kinds of fluid were used in a perioperative GDT protocol [57].

Regarding \( \text{DO}_2 \), when the target is not achieved after SV maximisation with fluids and CO remains inadequate, many protocols propose the use of inotropic agents. \( \text{DO}_2 \) optimisation using fluids and inotropes can be thought as a stressful stimulus for the CVS system. However, it has been demonstrated that high-risk patients undergoing major non-cardiac surgery had a significant reduction in the total number of perioperative CVS complications when treated with GDT compared with control (OR 0.54; 95% CI 0.38 to 0.76; \( p =0.0005 \)), particularly when a supranormal \( \text{DO}_2 \) goal was targeted (OR 0.50; 95% CI 0.31 to 0.79; \( p =0.002 \)) [58]. The incidence of myocardial injuries was the same between patients treated with fluids and inotropes compared with control, with a median peak troponin I concentration of 10.0 (interquartile range [IQR]: 5.3-21.5) vs. 7.8 (IQR: 5.0-21.8) ng/l respectively (\( p =0.85 \)) [59]. Jhanji et al. also demonstrated that fluids and inotropes were able to improve microcirculatory parameters, showing an effective increase in tissue oxygenation [51]. The administration of fluids and dopexamine was associated with an increase in microvascular flow index and perfused vessel density in sublingual microcirculation and an increase in cutaneous tissue oxygen partial pressure [51]. However, the relationship between haemodynamics and microcirculation seems to be rather complex: some studies reported certain discrepancy between the changes in haemodynamics and microcirculation [60,61] while others reported a correlation between the changes in CO and MAP with the microcirculatory flow index (MFI) or the proportion of perfused vessel (PPV) [62,63]. Even if some of these results come from studies on septic shock where the microvascular shunt is the main characteristic of haemodynamic decoupling, a discrepancy between macro-haemodynamic and microcirculation was also be found in different conditions. Aya et al.
have recently shown that changes on haemodynamics and microcirculatory indices after fluid challenge were not related in post-cardiac surgery patients admitted in intensive care unit. There were no significant changes in microcirculatory parameters, either in responders or non-responders and no significant correlation between changes on PVD and changes in CO ($p = 0.59$) or mean systemic filling pressure ($p = 0.41$) [64].

Finally, RBCs transfusion may have a role in microvascular optimisation. Several experimental studies have shown that in extreme haemodilution conditions, microvascular perfusion can be improved by increasing blood viscosity using RBC transfusions [65–67]. High plasma viscosity may restore shear stress in the microcirculation favouring the production of vasodilators. Increased plasma viscosity has also been associated with vasodilatation and increased microvascular flow [65]. These experimental thoughts about the ability of blood transfusions to recruit the microcirculation have been confirmed by Yuruk et al. [68] in patients undergoing cardiac surgery. Blood transfusion resulted in increased microcirculatory density from 10.5 ±1.2 to 12.9 ±1.2 mm/mm$^2$ ($p < 0.01$).

**Conclusion**

In conclusion, global haemodynamic optimisation is the first step to guarantee organ perfusion. However, peripheral perfusion may be impaired despite adequate haemodynamics. Further research is required to demonstrate which microvascular monitoring tool is able to detect these alterations and improve patients’ outcomes.

**Practical Points**

- Goal directed therapy should be considered in selected patients intraoperatively and continued during the six hours postoperatively.
- Goal directed therapy is able to reduce mortality in high-risk patients and morbidity in moderate-risk patients.
- Optimisation of global haemodynamics is not necessarily related to optimisation of microvascular perfusion.
Research Agenda

- Further randomised controlled trials are required to confirm the role of GDT in current practice.
- Further studies are needed to verify whether a closed-loop system to guide intraoperative haemodynamic optimisation could improve patient’s outcome.
- Research is needed to evaluate whether goal-directed interventions based on microcirculation assessment during the perioperative period can improve patient’s outcomes.
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