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Invited Review / Davetli Derleme

Perioperative Haemodynamic Optimisation

Perioperatif Hemodinamik Optimizasyon

Hollmann D. Aya, Maurizio Cecconi, Andrew Rhodes
St George's Healthcare NHS Trust and St George's University of London, UK

Abstract / Özet

During the latest years, a number of studies have confirmed the benefits of perioperative haemodynamic optimisation on surgical mortality and postoperative complication rate. This process requires the use of advanced haemodynamic monitoring with the purpose of guiding therapies to reach predefined goals. This review aim to present recent evidence on perioperative goal directed therapy (GDT), with an emphasis in some aspects that may merit further investigation. In order to maximise the benefits on outcomes, GDT must be implemented as early as possible; intravascular volume optimisation should be in accordance with the response of the preload-reserve, goals should be individualised and adequacy of the intervention must be also assessed; non-invasive or minimally invasive monitoring should be used and, finally, side effects of every therapy should be taken into account in order to avoid undesired complications. New drugs and technologies, particularly those exploring the venous side of the circulation, may improve in the future the effectiveness and facilitate the implementation of this group of therapeutic interventions.

Key Words: Goal-directed, post-operative care, haemodynamic, fluids

Son yıllarda, bir dizi çalışma, cerrahi mortalite ve postoperatif komplikasyonların oranı üzerine perioperatif hemodinamik optimizasyonun faydalarını doğrulamıştır. Bu işlem, önceden belirlenmiş hedeflere ulaşmak için tedavilere rehberlik amacıyla ileri düzeyde hemodinamik izlem kullanımını gerektirmektedir. Bu derleme perioperatif hedefe yönelik tedavi (HYT) hakkında ileri araştırmayı hak edebilen bazı yönleri vurgulayarak yeni kanıtlar sunmayı amaçlamaktadır. Sonuçlar üzerindeki yararlarını maksimize etmek için, HYT mümkün olduğunca erken uygulanmalıdır; intravasküler hacim optimizasyonu önyük rezerv cevabı ile uyum içinde olmalıdır, hedefler bireyselleştirilmeli ve müdahalenin yeterliliği ayrıca değerlendirilmelidir; non-invazif veya minimal invazif izleme kullanılmalıdır ve son olarak istenmeyen komplikasyonları önlemek için her bir tedavinin yan etkileri dikkate alınmalıdır. Yeni ilaçlar ve teknolojiler, özellikle dolaşımın venöz tarafını araştıranlar, gelecekte bu grup terapötik girişimlerin etkinliğini artırabilir ve uygulanmasını kolaylaştırabilir.

Anahtar Kelimeler: Hedefe yönelik, postoperatif bakım, hemodinamik, sıvılar

Introduction

The concept of peri-operative goal directed haemodynamic optimisation (EGDT) has seen increasing interest over the last two decades following the publication of several studies and meta-analysis (1-12) that have evidenced the benefits on patient's outcomes. EGDT can be defined as a sequence of pre-emptive therapeutic interventions on the cardiovascular system based on haemodynamic monitoring and pre-defined goals. The main objective of this individually adapted therapy is to provide an optimal oxygen supply to organs and tissues in critical situations, such as high-risk surgery. Oxygen delivery (DO_2) depends on oxygen transport capacity, which in turn is defined by the haemoglobin (Hb) concentration, its saturation with oxygen (SaO_2) and cardiac output (CO). Hence, therapy is based on optimisation of cardiovascular function, including the use of intravascular fluids, inotropes and vasopressors.

In a recent large prospective international epidemiological study (13), the mortality rate for patients undergoing inpatient non-cardiac surgery across 28 countries in Europe was 4%, which was higher than expected when compared with previous studies (14-16). This suggests that there is still a need to expand and implement measures to improve postoperative outcomes. The present review aims to provide a comprehensive examination of the development of early goal-directed therapy, discussing the current evidence and providing an outlook on future developments.

Address for Correspondence/Yazışma Adresi: Dr. Andrew Rhodes, Department of Intensive Care Medicine St George's Healthcare NHS Trust, London SW17 0QT UK Phone: +44 208 725 1307 E-mail: andrewrhodes@nhs.net

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Early means …early!

High-risk surgical patients represents only 10-15% of surgical procedures but they account for more than 80% of deaths (17) and the highest mortality rates (39%) are seen in the population of patients admitted to the ICU following initial postoperative care on a standard ward (17). These data emphasise the importance of anticipation in postoperative care. Pearse et al. (13) reported in a large prospective international epidemiological study that only 8% of patients undergoing non-cardiac surgery were admitted to critical care at some point during their hospital stay whereas 73% of patients who died were never admitted to critical care at any stage after surgery. Only 5% of patients underwent a planned admission to critical care and unplanned admissions were associated with higher mortality rates than were planned admissions. These data may suggest an underestimation of risks and a failure in planned allocation of resources for patients that could have benefited from them. The high-risk surgical population is particularly vulnerable for developing organ dysfunction due to their poor cardio-pulmonary reserve, so that they are at an increased risk of failure to provide enough oxygen to the tissues during periods of high metabolic demand such as surgery. If the impaired oxygenation balance is not corrected early enough, mitochondrial damage takes place and the insult becomes permanent (18), which is also known as *cytopathic tissue hypoxia* (19). Once cytopathic hypoxia is established, correction of oxygen delivery is futile.

Clinical studies on optimisation of oxygen delivery confirm the benefit of anticipation. In 1999 Boyd et al. (20) conducted a review of clinical trials that have deliberately increased tissue oxygen delivery by increasing cardiac output. They conclude that a treatment policy by which oxygen delivery is deliberately increased improves patient outcome if it is initiated early, prior to the onset of organ failure. Kern et al. (1) also corroborated this concept in a meta-analysis that showed a decrease in mortality when high-risk patients with acute critical illness were treated early to achieve optimal goals prior to the development of organ failure and when therapy produced differences in oxygen delivery between the control and protocol groups. More recently, a meta-analysis of 26 RCT on patients undergoing major surgery demonstrated that GDT initiated in the perioperative period confirmed the reduced risk of post-operative infections (6). Likewise, early initiation of haemodynamic optimization reduces the risk of postoperative acute renal injury and gastrointestinal complications following major surgery (3, 4).

When or where to stop?

Although EGDT attempts to avoid under-treatment and prevent the deleterious effect of tissue hypoxia, overtreatment can also be harmful. Positive fluid balance is associated with an increased risk of complications after vascular surgery (21), thoracic surgery and other interventions (22). Likewise, the use of catecholamines such as epinephrine, norepinephrine and dobutamine has been associated with well-recognised complications, such as digital ischaemia and tachyarrhythmias. Additionally, other not so obvious detrimental effects (23) such as stimulation of bacterial growth (24), immunosuppression (25), insulin resistance and increase of oxidation of fatty acids which might play a relevant role in myocardial ischaemia (26) have also been associated with the use of catecholamines. So it seems reasonable to think that manipulating haemodynamics in some patients with pharmacologic agents (fluids and inotropes) to reach predefined goals may expose them to unnecessary risks. In the study reported by Lobo et al. (27) 58% of the protocol group patients did not achieve the predefined goals despite the high doses of dobutamine (19±12 mcg $kg^{-1}min^{-1}$ vs. 10±5 mcg kg^{-1} min^{-1} in achievers) and more fluid (median value 6.5 vs. 4 L). Interestingly, in a recent meta-analysis (11) EGDT with fluids and inotropes in high-risk surgical patients was not associated with an increased risk of cardiac complications, and actually the benefit was most pronounced in patients receiving fluids and inotropes with the use of minimally invasive cardiac output monitors.

Nevertheless, we need to be aware of these possible harmful effects and move towards the concept of *adequacy* of the treatment provided. The intervention planned in a protocol of GDT needs to be in accordance not only with predefined goals but also with the patient's metabolic needs at any particular time. Possibly, a gradual reduction of goals might minimise the risk of complications associated with some cardiovascular manipulations. Unfortunately, there is no evidence about the weaning of GDT in post-operative patients. In the future several areas need to be explored. We need alternatives to the traditional catecholamines and agents such as vasopressin or levosimendan merit further investigation. In addition, we need to take into account the venous side of the circulation as a source of information to assess the adequacy and efficiency of the treatment provided.

Goals…

One of the largest clinical trials examining the impact of goal-directed therapy optimisation was performed in 19 Canadian hospitals between 1990 and 1999 with 1994 patients in total (28). Patients in the intervention group were monitored with a pulmonary artery catheter (PAC) and the following goals were used to guide the therapy: pulmonary artery occlusion pressure (PAOP) ≥18 mmHg, mean arterial pressure (MAP) ≥70 mmHg, heart rate <120 bpm, cardiac output 3.5-4.5 L/m, haematocrit ≥27%, DO_2I 550-600 mL min^{-1} m^{2-1}. The control group was treated with "standard" care and not equipped with a PAC. Interestingly, no difference in terms of morbidity, length of stay and one-year mortality was observed between the two groups. Importantly, about one third of patients in the intervention group did not achieve the predefined goals. Whilst these results were initially disappoint-

ing, this study introduced the important discussion about the right goals.

Some hemodynamic variables are commonly measured and displayed at the bedside, and their values are often used in clinical practice. However, the utility of each variable as a goal for a specific treatment may be questionable. The main objective of perioperative optimization is to provide adequate oxygenation to vital organs and tissues and prevent hypoperfusion and hypoxia. Assuming an adequate concentration of haemoglobin and sufficient oxygenation, cardiac output is the main determinant of oxygen delivery (DO_2). Thus, EGDT is at first based on optimization of stroke volume, which in turn depends on preload, contractility and afterload. These three concepts have been the main goals of haemodynamic optimisation.

For preload

The objective of this first goal is to avoid or correct hypovolaemia, which in some cases may be the main cause of hypoperfusion. A decreased end-diastolic ventricular volume correlates with a decreased SV and CO. However, static indicators of preload, regardless of how accurate they are measured, do not provide information about the preload reserve, and should not be used as goals for fluid resuscitation (29-31).

The pragmatic concept of *stroke volume maximization* was first proposed by Mythen et al. (32), and has been incorporated into many protocols of GDT. The best heart performance under a given contractile state is achieved by using consecutive fluid challenges until the initial flat portion of Frank-Starling curve is reached. A positive response is defined by an increase in stroke volume (usually 10 or 15%). The main advantage of this approach is that can be used in many different situations including spontaneous ventilation or cardiac arrhythmias. In addition, the issue of accuracy of measurements is of lesser importance since relative changes are considered, allowing the use of non-calibrated monitors. Importantly, a fluid challenge is not volume resuscitation; it is merely a test to identify those who are preload responsive. Volume responders can then be given additional fluid resuscitation with minimal risk for fluid overload (33).

However, there are some limitations with regards to the fluid challenge in this context. First, there is little agreement regarding what volume and infusion rate defines an adequate fluid challenge. Second, a fluid challenge, particularly when large volumes are used, may worsen or precipitate pulmonary oedema in patients with poor ventricular function.

The effect of a fluid challenge can be better understood when taking into consideration the venous side of the circulation. About 70% of the blood is stored in the veins, as their compliance is greater than other parts of the cardiovascular system. Under steady conditions, the blood flowing into the heart is equal to the blood ejected from the heart, so that the venous return (VR) is equal to cardiac output. Guyton (34) proposed that VR is proportional to the pressure gradient of venous return (dVR) and inversely related to the resistance to venous return (RVR). The gradient of pressure for VR is defined by the difference of pressure between the right atrial pressure (RAP) and the mean systemic filling pressure (Pmsf).

The Pmsf is the mean pressure in the cardiovascular system when there is no blood flow, and depends on the stressed volume (Vs) and the mean compliance of the vascular wall. The Vs is the part of the intravascular volume that stretches the vascular wall and generates pressure, and the rest of the volume (unstressed volume) is the volume that fills the cardiovascular space without generating any pressure. This volume represents a big reservoir of blood that can be recruited to increase VR in accordance with the tissues metabolic demands. This is actually the main regulatory system of cardiac output: the amount of blood required for each tissue is accurately controlled by a combination of local signals (such as tissue pressure of O_2 and CO_2) and the sympathetic activity. Then, in the case of increased metabolic demand in any territory, the local signals generate vasodilatation, increasing the blood in-flow into the organ and, thus, increasing venous return.

Then, when we are optimising "preload" by giving fluids, we are actually attempting to increase the stressed volume, the Pmsf, the dVR and thus also the VR. This is one of the reasons why RAP should not be considered as a parameter of intravascular filling: RAP is the result of venous return and cardiac performance. Thus, if after a fluid challenge the RAP increases by as much as the Pmsf, the dVR will not increase and the VR does not change. This has been recently showed in a study observing the changes of Pmsf-analogue in 101 fluid challenges in post-operative patients (31).

An effective fluid challenge should be small enough to avoid complications related to fluid overload, but big enough to increase Vs and Pmsf. Otherwise, the system is not challenged. Vs represents about 30% of the total intravascular volume (35), but in practice is very difficult to measure as well as Pmsf. But the important message from the Guytonian approach to the circulation is that the maximal VR can be achieved by increasing the venous return gradient (dVR) which means keeping the RAP as low as possible and the Pmsf as high as possible. In other words, increasing the efficiency of the heart.

The same physiological principles apply to dynamic variables such as pulse pressure variation (PPV) or stroke volume variation (SVV), obtained from heart-lung interactions during positive pressure ventilation(36). An increase in intra-thoracic pressure generates an isovolaemic increase in RAP, which decreases dVR and decreases VR. Some of these variables have been used in GDT protocols (37, 38). A systolic pressure or a pulse pressure variation of 13% or more in septic patients breathing with a tidal volume of 8 mL kg^{-1} is highly sensitive and specific for preload responsiveness (39). Unfortunately, these variables only work reliably during fully

controlled mechanical ventilation in patients with a regular heart rhythm. Furthermore, as various devices calculate stoke volume differently, the threshold values for each parameter in predicting preload responsiveness may be different between devices, and may exhibit different degrees of robustness under varying clinical conditions (40).

Importantly, being preload responsive is not equivalent to requiring more fluids. Normal individuals are preload responsive but do not require resuscitation. Critically ill patients may be fluid responsive but not necessarily hypovolaemics. However, at the current state-of the art, specific markers of hypovolaemia are not available, making the pragmatic approach of stroke volume maximization using small fluid challenges a sensible way to avoid hypovolaemia and fluid overload.

For cardiac ouput

Since blood flow changes to match the metabolic demands from peripheral tissues, which in turn varies considerably between individuals and moments, there is no specific value of cardiac output or oxygen delivery that can be considered as "normal". This explains the difficulty for defining a specific goal for CO or DO_2 for every patient. Instead of normal or supranormal, the real question is if the blood flow is *adequate* to meet the metabolic demands of the body at a particular time. To do that, we need to look again at the venous side.

$ScvO_2$ has been used as a marker of the balance between global oxygen supply and demand (41), and low $ScvO_2$ perioperatively has been associated the with an increased risk of complications in high-risk surgical patients (42). The oxygen extraction ratio (O_2ER) has been also proposed by Donati et al. (43) as a goal with a cut-off value of 27%, which is consistent with values previously proposed (42, 44). Two more studies reported the use of central venous oxygen saturation ($ScvO_2$) (37, 45) as a goal with a cut-off value of 70%, both of them in cardiac surgery. Oxygen extraction indices are useful targets that allow us to assess the balance between oxygen demand and delivery and may fit better individual patient needs. Actually, the use of these variables as goals for EGDT has been associated with a reduced postoperative complication rate (8). However, there are a number of limitations that need to be mentioned:

1. The invasiveness of these parameters may limit its application to patients with a PAC or a central venous catheter (CVC). Usually, to measure $ScvO_2$ a blood sample is required, and this also limits the decision-making process to few points in time in the context of a GDT protocol.

2. The use of $ScvO_2$ as a surrogate of SvO_2 may have important clinical implications, particularly in patients undergoing surgery in the lower part of the body. The increased metabolic demand may be missed by sampling blood only from the upper part.

3. $ScvO_2$ can only provide a global estimation of the total oxygen demand. That means that still regional perfusion abnormalities may not be adequately corrected.

For blood pressure

The arterial blood pressure is commonly used at the bedside to detect shock states or direct the use of fluids or inotropes. There is some evidence of lack of benefit in increasing mean arterial pressure (MAP) with noradrenaline without clinical improvement of CO in terms of organ perfusion, which is the ultimate determinant of survival. Deruddre et al. (46) showed that increasing MAP from 65 to 75 mmHg with noradrenaline was associated with significant increases in cardiac output and urinary output and a significant decrease in the renal vascular resistance assessed with Doppler ultrasonography. However, some other studies reported that increasing MAP with noradrenaline above 65 mmHg (to 75, 85 and 90), on balance was not associated with improved organ perfusion, in spite of the increased cardiac output (47-49). However, in those studies the increase of CO was not clinically significant (>10%) after the first step (from 65 to 75 mmHg) of the MAP escalation. Further increments in MAP did not increase the CO significantly in those studies.

The mean systemic filling pressure (Pmsf) proposed by Guyton (50) represents an important parameter to study the effects of vasopressors on the circulation. Guyton observed a significant increase in Pmsf after massive stimulation of the sympathetic nervous system. He pointed out that it"…*is not the blood volume alone that is important in determining the degree of filling of the circulation but, instead, it is the mean systemic pressure that is important, and this is determined by the ratio of blood volume to the momentary capacity of the circulatory system*" (51). Then one can deduce that a modification of the vascular wall tone (especially the venous tone) can affect Pmsf and CO.

Several studies in animal models have reported an increase in Pmsf and VR using a vasoconstrictor (52-56). In these studies, the venoconstriction generated by noradrenaline recruits part of the unstressed volume into the stressed volume, due to small changes in venous compliance (57-59). This mechanism allows a transfer of blood volume from the splanchnic beds to the heart increasing right ventricular filling (60-62). Interestingly, in the study of Sennoun et al. (63) the use of noradrenaline was associated with better tissue oxygenation when compared with the use of fluid for resuscitation alone in a rat-model of septic shock.

Hamazaoui et al. (64) performed a clinical cohort study in 105 septic-shock, fluid resuscitated patients receiving early administration of noradrenaline. Noradrenaline infusion increased preload, measured by the global end-diastolic volume index (GEDVI), and cardiac index (CI). Maas et al. (65) studied the effects of noradrenaline infusions on cardiac output in sixteen postoperative cardiac surgical patients using an increase of 20 mmHg in MAP as a target. Cardiac output de-

creased in 10 and increased in 6 patients, while in all patients Pmsf increased. This is explained by the fact that noradrenaline increases the resistance to venous return (RVR) reducing CO and VR, so that the final effect of noradrenaline is the balance between the increase in RVR and increase in preload. Furthermore, the authors concluded that the response of cardiac output to noradrenaline could be predicted by baseline stroke volume variation (SVV), which is actually a dynamic parameter of preload. These effects of noradrenaline on Pmsf and CO suggest that an infusion of noradrenaline may be titrated according to the response on CO and not only to a randomly selected target of arterial blood pressure. Further studies are required to elucidate if the titration of noradrenaline according to CO in the context of EGDT have any benefit on outcomes.

Directed means…monitorization

In the meta-analysis reported by Hamilton et al. (8), only the studies (n=11) that used flow-related goals, such as CO or DO_2, proved a significant reduction in mortality (OR 0.38, 95% CI 0.21-0.68) in comparison with other goals such as FTc, SV, Oxygen extraction ratio, pulse pressure variation, SvO_2, and lactate. This highlights the importance of flow monitoring at bedside.

Classic monitors

William Swan and Jeremy Ganz introduced the pulmonary artery catheter (PAC) in the 1970s (66) and changed the evaluation of the haemodynamic assessment at bedside. However, it was not until 1988 that Shoemaker and colleagues (67) first pointed out benefits of using supranormal values as therapeutic goals using the PAC in high-risk surgery patients, although a predefined protocol for guiding the therapy was not defined. Later, Berlauk et al. (68) published one of the first controlled studies proposing an EGDT algorithm based on PAC values demonstrating a reduction of postoperative complications. Several studies have been published since then. A recent meta-analysis (8) of 29 randomised clinical trials (RCT) evaluating the efficacy of EGDT in high-risk surgical patients attest to a reduction in mortality (OR 0.35, 95% CI 0.19-0.65, p=0.001) in studies using the PAC.

However, as long as the PAC was used, several types of complications were reported (69, 70) and in some cases the data obtained was poorly understood and misinterpreted (71). Some studies using PAC to guide haemodynamic optimisation yield conflicted evidence (72, 73). In addition, insertion of a PAC could be cumbersome and time-consuming. Despite its widespread use and advances in PAC technology, controversy surrounding the efficacy and safety of the PAC has been raging for many years (74). Hence, the development of less invasive haemodynamic monitoring devices was necessary.

Modern monitors

The ideal haemodynamic monitoring system should provide accurate measurements of relevant variables with a rapid response-time. It should also be easy to use and understand, operator-independent, cost-effective and should cause no harm (75). Although such a monitor does not exist, minimally invasive cardiac output monitoring offers a potentially safer alternative to the PAC. The ability of these devices to accurately track haemodynamic changes has been reported and reviewed in other studies (76). In this review we are going to focus on those devices used in the context of EGDT.

Oesophageal Doppler

Oesophageal Doppler was the next technology proposed for guidance of EGDT. Estimation of CO by oesophageal Doppler is achieved by multiplying the cross-sectional area of the aorta by the blood flow velocity measured in the descending aorta. This device can provide values for CO, stroke volume, and estimated flow volume-corrected time (FTc). Sinclair et al. (77) reported the use of Doppler-derived variables for EGDT in patients undergoing hip surgery and showed faster recovery of patients in the intervention group. Similar benefits have been also reported in patients undergoing abdominal surgery (78). Abbas et al. (79) showed in a meta-analysis that the use of this device was associated with fewer complication and ICU admission in patients undergoing major abdominal surgery, and this has been confirmed in a subsequent meta-analysis in high-risk surgical patients (8). This evidence has brought the National Institute for Health and Clinical Excellence (UK) to recommend routine use of this device in high-risk surgical patients (80).

In spite of the fact that oesophageal Doppler is a minimally invasive technique, the lack of stability of the signal during surgical manipulations or movement and the poor tolerance in awake patients hindered its use as a continuous monitor.

Arterial wave-form analysis

These devices obtain stroke volume values using different mathematic algorithms to analyse the arterial waveform obtained with an arterial catheter. The main common advantage of this technology is the ability to provide continuous information, allowing the assessment of an intervention in real time without catheterisation of the right heart.

PiCCOplus™ system (Pulsion Medical Systems AG, Munich, Germany) use a pulse contour analysis that requires frequent transpulmonary thermodilution calibration with a normal saline through a central venous catheter. This technique generates new variables that reflect cardiac preload, such as the global end-diastolic volume index (GEDVI) and pulmonary oedema, such as the extra vascular lung water index (EVLWI). This technique needs a central venous line and a specific thermistor-tipped arterial catheter, usually in the femoral artery. Goepfert et al. (81) used these variables in a GDT protocol in cardiac surgery and demonstrated a reduction in use of catecholamines, duration of mechanical ventilation and ICU length of stay. Apart from the determination of cardiac output, this generation of devices in-

troduce the pulse contour analysis (82, 83) that enables the continuous cardiac output monitoring and the evaluation of heart-lung interaction. Then the so-called dynamic indexes of preload have been pointed out as good predictors of fluid responsiveness: an increased variation in stroke volume (84) or pulse pressure over a period of time indicates fluid responsiveness (39).

LiDCO™*plus* and LiDCO™*rapid* systems (LiDCO Ltd, Cambridge, UK) use pulse power analysis techniques to trace continuous changes in CO. LiDCO™*plus* is calibrated with transpulmonary lithium chloride dilution(85, 86) but does not require a central venous catheter. LiDCO™*rapid* uses normograms to adjust patient's characteristics to the cardiac output obtained from the pulse power analysis and does not require any dilution technique. The LiDCO™*plus* monitor was used in a RCT in high-risk surgical patients where the EGDT group had less morbidity and a reduced length of hospital stay (87).

The Vigileo monitor (Flotrac/Vigileo, Edwards Lifesciences, Irvine, CA, USA) uses a specific arterial pressure transducer to characterize the pulse waveform. The data is analysed together with patient demographic characteristics to transform the arterial blood pressure data into stroke volume and provide an estimated CO. This monitor was used in a protocol of intraoperative GDT in high-risk patients undergoing abdominal surgery (88). The GDT group had less complications (20% vs. 50%, p=0.003) and a reduced length of stay compared with the control group. Also, in orthopaedic surgery the use of this monitor in a intraoperative GDT protocol reduced the number of patients with postoperative complications in comparison with the control group (75% vs. 100%, p=0.047) (89).

Therapies….

Perioperative GDT has changed the approach towards fluid administration and the use of inotropes and vasoconstrictors. We now know that these interventions during the perioperative period may change long-term outcomes (90).

Fluids

For a long time, the administration of intravenous fluids was based on empirical values. Large volumes of crystalloids were administered to replace the presumed volume deficit caused by preoperative fasting, blood and urine loss, perspiration and a so called "third space loss"(91). This hypothetical space, which was supposed to be traumatised tissue and the gastrointestinal tract, was the rationale for aggressive replacement of this hypothetical fluid loss. At that point, infusion of large volumes of crystalloids intra-operatively became standard clinical practice (92) and patients undergoing major surgery presented with an extremely positive fluid balance. In a systematic review of studies measuring extracellular volume changes, it was concluded that the original data and methodology supporting the so-called "third space" were fundamentally erroneous (93). Today this concept has been practically abandoned (92, 94), and EGDT has been associated with better postoperative outcomes in comparison with a liberal strategy (9).

Inotropes

When goals for DO2I or tissue perfusion indicators are not achieved by maximisation of preload, the use of inotropes is common in several protocols of EGDT. In a meta-analysis (8), the use of inotropes in combination with fluids reduced the mortality (OR 0.47, 95% CI 0.29-0.76), and was superior to those studies with only with fluids. Similarly, Pearse et al. (95) showed that the pre-emptive use of inotropes in the postoperative management was not associated with an increase of myocardial injury, and as mentioned above, another recent meta-analysis (11) showed that the therapy with fluids and inotropes in high-risk surgical patients was not associated with an increased risk of cardiac complications.

The ideal inotrope should improve contractility of both ventricles without increasing heart rate or increasing oxygen consumption. In addition, it should have beneficial effects on diastolic function, maintaining an adequate diastolic coronary perfusion. Pharmacokinetically, it should a rapid onset of action and a short half-life. Unfortunately, such an agent does not exist.

Inotropes, such as dobutamine or dopexamine, induce an increase in the cellular concentration of calcium and myocardial oxygen consumption (96), and the two main undesired effects are arrhythmias and myocardial ischaemia. Furthermore, in the general community, up to 25% to 30% of the individuals older than 45 years have asymptomatic diastolic dysfunction (97, 98) and 60% of the surgical patients older than 65 years and with normal left ventricular ejection fraction have isolated abnormal left ventricular filling pressures (99). Left ventricle diastolic dysfunction (LVDD) is predictive of all-cause mortality after controlling for age, gender, and ejection fraction even when congestive heart failure was not present (98). Inotropes are not particularly helpful in this population.

Levosimendan could be a potential agent to be used in the context of perioperative EGDT. Levosimendan is a pyrisazinone-dinitrile derivative that increases troponin C affinity for Ca^{2+}. This mechanism increases the inotropic effect without impairing ventricular relaxation. It also increases heart rate and may increase the incidence of atrial fibrillation although it has not been associated with ventricular arrhythmias and prolongation of the QT interval.

Unfortunately hardly any evidence has been published about the use of Levosimendan in the context of non-cardiac EGDT. Katsaragakis et al. (100) showed that preoperative levosimendan treatment may be safe and efficient for the perioperative optimization of heart failure in patients undergoing non-cardiac surgery. In a clinical trial reported by Lahtinen et al.

(101) with 200 patients, levosimendan infusion reduced the incidence of heart failure in cardiac surgery patients but was associated with arterial hypotension and increased requirement of vasopressor agents postoperatively and no effect was demonstrated on mortality or morbidity. Finally, in a recent metaanalysis reported by Harrison et al. (102) including 14 randomised clinical trials, Levosimendan was associated with reduced mortality and other adverse outcomes in patients undergoing cardiac surgery, and these benefits were greatest in patients with reduced ejection fraction (EF).

Vasopressors

Noradrenaline is a neuro-trasmissor released by the postganglionic adrenergic nerves, and a hormone released by the adrenal medulla. Exogenous norepinephrine is commonly used intravenously to increase blood pressure in shock states. Noradrenaline activates α-receptors on the endothelial surface of peripheral arterioles. This leads to an activation of phospholipase C that results in splitting phosphatidyl-inositol into inositol-triphosphate-3 and 1,2-diacylglycerol. Inositol-triphosphate-3 stimulates the release of calcium ions from the sarcoplasmic reticulum into the cytosol. In addition to this, the activation of α-receptors results in the opening of receptor-operated non-selective cation channels that allows extracellular calcium ions to get into the vascular smooth muscle cell. Then, calmodulin can bind to four calcium ions to activate the myosin light chain kinase, which leads to phosphorylation of myosin heads that cause cross-bridge formation with actin and finally contraction of the vascular smooth muscle.

In a study (103) with 25 patients in septic shock, all of them preload-dependants as suggested by a positive passive leg rising test at the baseline, noradrenaline increased cardiac preload (assessed by central venous pressure (CVP), left-ventricular end-diastolic area and GEDV) and cardiac index and reduced the degree of preload dependency, as suggested by the results of passive leg rising test after noradrenaline infusion. Similar results have been reported by previous studies showing that pulse pressure variation (PPV), a good marker of preload dependency, decreased with noradrenaline administration (62, 63). Recently, some studies have reported the effect of noradrenaline on Pmsf in humans, using the method of inspiratory hold manoeuvres described by Maas et al. (104) in mechanical ventilated patients. Decreasing the dose of noradrenaline in septic shock patients induces a decrease of VR by reducing Pmsf and, to a lesser extent, the RVR (105). This may suggest that vasoconstrictors may play a crucial role in the context of preload optimisation.

Conclusion

Although the concept of preoperative haemodynamic optimisation has consistently been shown to improve outcomes after surgery, this intervention still needs to be implemented in order to reduce mortality and complications rates. Some key messages can be summarised from the published literature: GDT must be implemented as early as possible; fluid optimisation should be in accordance with the response of the preload-reserve, goals should be individualised and adequacy of the intervention must be also assessed; non-invasive or minimally invasive monitoring has reduced the risk of complications associated with invasive technologies; and finally, every therapy has side effects that should not be forgotten. New drugs and technologies may improve in the future the effectiveness and facilitate the implementation of this group of therapeutic interventions.

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