ICU MANAGEMENT & PRACTICE

ICU Volume 14 - Issue 4 - Winter 2014/2015 - Cover Story

Perioperative Goal-Directed Therapy

Prof. Azriel Perel
******@***shani.net

Professor of Anesthesiology and Intensive Care - Sheba Medical Center, Tel Aviv, Israel

Some Remaining Questions

What is Perioperative Goal-Directed Therapy?

Perioperative mortality of patients undergoing high-risk surgery has been steadily declining over recent years. And yet this reduced mortality rate is still considered to be higher than anticipated (Pearse et al. 2012). Newer approaches aimed at improving perioperative outcome and reducing its associated costs have been recently proposed. These include fast-track surgery (Kehlet and Wilmore 2008), enhanced recovery after surgery (ERAS) (Knott et al. 2012) and the surgical home (Kain et al. 2014). However, the most significant and extensively studied strategy that has been suggested to decrease major perioperative complications and even death is that of goal-directed therapy (GDT). Perioperative GDT describes a variety of proactive therapeutic strategies that aim to achieve better patient outcome by improving the haemodynamic status in the perioperative period, especially in high-risk patients undergoing non-cardiac surgery (Boyd and Bennett 1999; Lees et al. 2009; Gurgel and do Nascimento 2011; Hamilton et al. 2011). Although the term 'GDT' has never been well defined, it is most often used to describe cardiac output (CO) maximisation by fluid loading ('flow-guided optimisation'), with or without additional therapies aimed at increasing global oxygen delivery (DO2) to pre-defined 'supra-normal' values. These and other physiological 'goals' have been used to guide GDT in a variety of clinical protocols and patient populations.

Although as early as 1999 the proponents of this approach claimed that “it may be considered unethical not to use perioperative GDT” (Boyd and Bennett 1999), and in spite of the large body of evidence that presumably supports its routine use, GDT has not been widely adopted (Cannesson et al. 2011; Miller et al. 2011; Cecconi and Rhodes 2014). This review attempts to examine some of the possible reasons for this considerable gap between 'evidence' and practice and to highlight some of the remaining questions surrounding the practice of perioperative GDT.

Questions Regarding the Pathophysiological Rationale of Perioperative GDT

The main physiological rationale for the claimed benefit of perioperative GDT is that major surgery generates a strong systemic inflammatory response and an overall substantial increase in oxygen demand. This response is normally met by increases in CO and in oxygen extraction. Patients that do not have the physiological reserve to increase CO to the required level that is necessary for adequate tissue perfusion may therefore be at higher risk of postoperative complications. Therapy aimed at increasing oxygen supply may therefore prevent or correct the oxygen deficit that may develop during an initial period of poor perfusion. GDT has been shown to improve sublingual and cutaneous microvascular flow, as well as blood flow to the gut mucosa, as evidenced by a higher gastric mucosal pH (pHi) and an increased oxygen tension in the perianastomotic colonic tissue. These mechanisms may well be responsible for the frequently reported decrease in postoperative complications in patients undergoing perioperative GDT, a decrease which has also been associated with their longer term survival (Rhodes et al. 2010).

However, the available pathophysiological data that may explain the benefits of GDT are still limited and incomplete (Kehlet and Bundgaard-Nielsen 2009), and the few studies that have shown improvement in microvascular blood flow due to GDT raise some further questions. For example, the finding that GDT is associated with increased gut mucosal pH could not be confirmed in a later study (Kehlet and Bundgaard-Nielsen 2009), and an observed GDTinduced increase in microvascular blood flow was not associated with differences in inflammatory markers or in overall complication rate (Jhanji et al. 2010).

The fact that the exact mechanisms by which GDT may provide benefit remain unclear may account for the existing confusion as to when exactly

it should be instituted. Studies demonstrating the benefit of GDT were done in the pre-, intra-, and, very often, in the postoperative period. Since we have widely adopted the concept of early GDT in haemodynamically unstable critically ill patients, it may seem logical to apply the same approach to the perioperative period in order to prevent tissue hypoxia as early as possible. It is therefore unclear why those who believe that GDT be practised only in the postoperative ICU, do so because of pathophysiological reasons or because of pragmatic ones.

More questions surround the pathophysiologic rationale of using GDT that is aimed at increasing cardiac index (CI) and oxygen delivery (DO2) to 'supra-normal' levels (> 4.5 L/min/m2 and > 600 ml/ min/m2, respectively) (Lees et al. 2009). This approach has first gained popularity in the care of critically ill patients more than 20 years ago following Shoemaker et al.'s early studies (Shoemaker et al. 1988). However, it has since been abandoned in the critically ill as further studies failed to prove its effectiveness in this patient population. Its adoption as the recommended GDT approach stands in contradistinction to the main alternative strategy of GDT, which recommends that optimisation of flow-related parameters be done in an individualised manner and within the limit of the individual patient's cardiac capacity (Kehlet and Bundgaard-Nielsen 2009). From a purely clinical point of view, it seems also questionable that such 'supra-normal' values can be achieved in all patients undergoing high-risk surgery, including the old and frail. For example, in a small study where such a GDT approach was used in patients undergoing elective total hip arthroplasty under regional anaesthesia, only 65% of patients reached a DO2 > 600 mL/minute/m2 in the GDT group (Cecconi et al. 2011). Even the proponents of this approach admit that the continued pursuit of haemodynamic goals in patients who do not respond, and especially those with significant heart disease, is harmful (MacDonald and Pearse 2011). Hence without a better pathophysiological reasoning it is hard to support this practice.

Questions Regarding the Evidence Supporting Perioperative GDT

Many studies have examined the potential benefit of a variety of perioperative GDT approaches. These studies have been included in a number of meta-analyses, which have concluded that perioperative goal-directed care reduces postoperative complications, days of hospital stay and subsequent mortality, especially in highrisk surgical patients (Boyd and Bennett 1999; Lees et al. 2009; Gurgel and do Nascimento 2011; Rhodes et al. 2010 Hamilton et al. 2011; Cecconi et al. 2013). The accumulating volume of evidence in favour of GDT has affected clinical practice in many places, the most prominent example being the endorsement of the use of oesophageal Doppler (ODM) for GDT in high-risk surgical patients by the United Kingdom National Institute of Health and Care Excellence (2011). This large body of evidence cannot be simply ignored, and therefore puts pressure on clinicians to either adopt GDT strategies or find a good explanation for why they do not. One such explanation may be the remaining doubt that many clinicians still have about the robustness of the GDT concept and the quality of the evidence supporting it.

It is well recognised that there are some distinct problems that are associated with the design and conduct of GDT trials (MacDonald and Pearse 2011; Cecconi and Rhodes 2014). These problems may have affected the results of many such trials, and may have contributed to the possibly erroneous conclusions of the many meta-analyses that GDT is indeed beneficial. Many of the GDT studies have included only a very small number of patients, and thus may have been affected by bias due to the lack of blinding. The treatment protocol of the control group may have also affected the results, as substandard care and learning contamination bias of this group may, respectively, either over- or under-estimate the true difference between the groups. Other factors that may have affected the quality of GDT 'evidence' are a possible publication bias, and the inclusion of early studies that showed a very significant GDT impact (that could not be repeated) in these meta-analyses. In addition, generalising the results of these 'positive' studies is not straightforward, as they have been done in very heterogeneous patient populations, undergoing different surgical procedures and carrying different levels of risk.

Evidence that Goal-Directed Therapy May Not Be Beneficial

There are a growing number of recent well-conducted randomised clinical trials, which have found that perioperative GDT does not provide clinical benefit. In patients undergoing laparoscopic segmental colectomy, GDT with a colloid/balanced salt solution was found to offer no advantage over standard therapy (Senagore et al. 2009). Another randomised study in major gynaecological surgery found no difference in the length of postoperative hospital stay and postoperative morbidity survey scores between the ODM-guided GDT and the control groups (McKenny et al. 2013). Another double-blinded controlled trial, including 179 patients undergoing major open or laparoscopic colorectal surgery, found that intraoperative strokevolume (SV) optimisation conferred no additional benefit over standard fluid therapy. Moreover, in an aerobically fit subgroup of patients, intraoperative ODM-guided GDT was associated with delayed readiness for discharge and longer hospital stay (Challand et al. 2012). Another multi-centre trial found that GDT to near-maximal SV guided by ODM added no extra value to the fluid therapy using zero balance and normal body weight in patients undergoing elective colorectal surgery (Brandstrup et al. 2012). A randomised clinical trial of GDT within an enhanced recovery protocol (including fluid restriction) for elective colectomy did not reduce number of complications or hospital length of stay (Srinivasa et al. 2013b). A more recent randomised multi-centre trial in 142 patients scheduled for open major gastrointestinal surgery found that a perioperative haemodynamic protocol guided by a noninvasive CO monitor was not associated with a decrease in the incidence of overall complications or length of stay (Pestana et al. 2014). Last, but not least, the OPTIMISE multicentre trial of 734 high-risk patients undergoing major gastrointestinal surgery that used a CO–guided haemodynamic therapy algorithm, did not show any reduction in a composite outcome of complications and 30-day mortality compared with usual care (Pearse et al. 2014).

Although the OPTIMISE trial has failed to show the benefit of GDT, it also included an updated meta-analysis, indicating that GDT is associated with a reduction in complication rates. This meta-analysis, however, includes many studies done more than 10 years ago, and many in which a variety of GDT protocols and monitoring modalities have been used. As such, this metaanalysis cannot be used in support of the routine practice of straightforward CO maximisation. Furthermore, two other recent meta-analyses and systematic reviews have found no difference between GDT and control groups (Grocott et al. 2013; Srinivasa et al. 2013a). A third one concluded that GDT may lead to better outcome compared with liberal fluid therapy without haemodynamic goals; however, whether it is superior to a restrictive fluid strategy remains uncertain (Corcoran et al. 2012). In summary, there is currently no evidence-based consensus on questions such as which goals should be targeted for various surgical procedures and which patient groups most benefit from a GDT strategy. Moreover, the accumulating negative evidence regarding GDT has created new and significant criticism of this approach (Minto and Struthers 2012; Morris 2013; Wilson 2013).

Can GDT Increase the Risk of Fluid Overload?

The majority of studies describing perioperative flow-directed GDT, with or without the achievement of 'supra normal' CI and DO2, have been associated with the intervention group receiving significantly more fluids (Cecconi et al. 2011; Challand et al. 2012). This is easily understandable as the 'classic' GDT protocol starts with a "fluid challenge" (usually colloids), with the recommendation that it be repeated until the CO (or SV) does not increase by more than 10%. Another part of this protocol recommends that fluids be given also when the SV drops by more than 10%. The assumption behind this latter recommendation is that any decrease in SV is due to a reduction in cardiac preload. This is not necessarily true, as many other factors (e.g. surgical stress, contractility) may account for a decrease in SV. This has been nicely demonstrated by Hood and Wilson (2011), who found that reductions in SV of >10%, as measured by ODM, have a sensitivity of only 37% in identifying fluid responsiveness, and therefore may be related to other factors aside from preload. The proclaimed aim of continuously keeping the patients on the flat portion of the left-ventricular function curve by fluid administration, carries an obvious risk of iatrogenic fluid overload, since a considerable (and variable) part of the administered fluids does eventually leave the intravascular space (Jacob et al. 2007), necessitating repeated fluid loading. Such fluid overload may damage the endothelial glycocalyx and lead to the development of interstitial oedema in various organs and a considerable postoperative weight gain. Excessive fluid administration has also been shown to have deleterious effects on anastomotic healing and postoperative complications in digestive surgery, possibly because of a marked bowel wall oedema (Marjanovic et al. 2009).

A 1999 *National Confidential Enquiry into Perioperative Death* in the UK highlighted over-hydration as a contributory cause in the genesis of postoperative problems leading to death (Callum et al. 1999), and recommended careful fluid management (the implication being restriction) in vulnerable patients and those most at risk, such as the elderly. The British consensus guidelines on intravenous fluid therapy for adult surgical patients (GIFTASUP) (Powell-Tuck et al. 2011) were also put together due to "concern that arose from a high incidence of postoperative sodium and water overload, and evidence to suggest that a more accurate fluid therapy would improve outcome". And yet the uncritical adoption of these guidelines may lead to fluid overload, as they recommend that GDT be applied in the pre-, intra- and postoperative periods. In order to prevent the possible complications of overzealous perioperative fluid administration, restrictive fluid management strategies have been explored. Such strategies have also been shown to reduce postoperative morbidity and to shorten hospital stay (Brandstrup et al. 2003; Nisanevich et al. 2005; Walsh et al. 2008). However, the concepts of 'liberal', 'standard' and 'restrictive' fluid management are not well-defined, and their lack of standardisation makes any pooling of data nearly impossible (Jacob et al. 2007). Nevertheless, the GDT approach should not be interpreted to recommend a forgiving attitude towards 'liberal' fluid administration without appropriate monitoring (Ghosh et al. 2011). Such an approach is demonstrated by the FOCCUS study, where fluid loading with 25 ml/kg of Ringer's solution was given in the 6 hours before major abdominal surgery (Cuthbertson et al. 2011).

Clinical Implications

The pathophysiological rationale and the evidence which support the adoption of GDT strategies in the care of patients undergoing major high-risk surgery cannot be disregarded. And yet, the emerging evidence that GDT may not be beneficial cannot be disregarded as well, leading some of the most enthusiastic proponents of this approach to ask whether it is "Time to move on?" (Cecconi and Rhodes 2014). GDT is safe when practised correctly, but there are still significant impending questions regarding how to best do it. Beyond the ones that have been raised in this review, these questions include the selection of the right patients, the right timing, the type of fluids that have to be used, the ability of new CO monitors to accurately track the response to fluid loading, the selection of specific protocol end-points, and more. When appropriate, the use of dynamic parameters, like the systolic (SPV) and pulse (PPV) pressure variations, stroke volume variation (SVV) and the plethysmographic variation index (PVI), may add important information regarding fluid responsiveness and prevent unnecessary fluid loading (Perel et al. 2013; Benes et al. 2014). The use of more advanced monitoring technologies may further improve perioperative haemodynamic management. Individual decisions about perioperative fluid management should be regarded as a 'therapeutic conflict', namely, recognising that each of the decisions (e.g., 'liberal', 'restrictive') may potentially cause harm, and taking into account the risk-benefit ratio of the individual patient. Last, but not least, the limitations of a single intervention (fluid management) to determine outcome have to be recognised, since many other factors, like type of anaesthesia, ICU availability, early mobilisation and adequate analgesia, may be of equal, and at times, greater importance.

Published on : Mon, 17 Nov 2014