# SPECIAL ARTICLE

# Perioperative Goal-Directed Therapy

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MORBIDITY AFTER MODERATE-TO-MAJOR surgery remains a current issue, with perioperative organ dysfunction being responsible for a significant portion of these unfortunate events. The topic of perioperative goal-directed therapy (GDT), defined as the deliberate optimization of hemodynamics and oxygen delivery using intravenous fluid and/or vasoactive infusions, has been increasing in popularity over the last 20 years because of its proven benefit in reducing perioperative risk. This benefit likely is because of a reduction in tissue dysoxia and avoidance of organ dysfunction. Over time, perioperative GDT has been demonstrated to have both morbidity and mortality benefits for high-risk patients undergoing high-risk surgery, and there is ongoing work to define the optimal patients and situations for perioperative GDT. The authors review the history and supporting evidence behind perioperative GDT. In addition, the authors will discuss the evidence behind 2 key concepts within their current knowledge of perioperative GDT: Monitors and fluids. Finally, the authors hope to outline the status of their current knowledge regarding perioperative GDT, as well as remaining unanswered questions. The authors completed this review by searching prominent biomedical databases with the terms "perioperative" and/or "goal-directed" and "therapy", as well as "fluids", "GDT", and "hemodynamic optimization." In addition, the authors manually have searched the references of past reviews and original investigations for related papers.

## DEFINING PERIOPERATIVE GDT

The primary role of anesthesiologists is to mitigate risk and improve outcomes throughout the perioperative period. While shepherding patients through the pre-, intra-, and postoperative periods, there are seemingly endless hazards to avoid and details to be checked to provide optimal care. However, despite the unique details of each and every surgical procedure, the final common pathway in many perioperative organ insults is tissue dysoxia or an imbalance between oxygen supply and demand.[1] As such, an important way in which the authors are able to reduce perioperative risk and improve outcomes is through ensuring optimal end-organ perfusion during surgery.

Adverse outcomes have been associated with both under- and over-resuscitation.[2] Inadequate intraoperative resuscitation can lead to inadequate end-organ perfusion,[3] which may worsen perioperative outcomes.[2] Conversely, excessive intraoperative fluid volumes or over-resuscitation can result in increased intra- as well as extravascular volumes, which may precipitate peripheral and/or pulmonary edema. Certain surgical types, such as gastrointestinal and thoracic surgery, necessitate diligent attention to preventing perioperative fluid overload, as this may impair gastrointestinal[2] and pulmonary[4] function. To try to address this need for optimal tissue oxygen delivery, the concept of goal-directed therapy was introduced, whereby hemodynamic parameters and/or oxygen delivery are monitored closely (typically using flow-based monitors) and optimized with fluids and/or inotropes.[5]

## A BRIEF HISTORY OF PERIOPERATIVE GDT

Given the remarkably high mortality and morbidity in elderly hip fracture patients in the early days, Schultz et al[6] demonstrated an impressive reduction in mortality (2.9% *v* 29%) by instrumenting patients with a pulmonary artery catheter (PAC) and performing nonspecific preoperative optimization. The concept of goal-directed hemodynamic optimization began in earnest, however, with the work of Shoemaker et al,[7] who in 1988 showed that placement of a PAC and attainment of supraphysiologic hemodynamic parameters (ie, CI $\geq$ 4.5 L/min/m$^2$, $DO_2 \geq$ 600 mL/min) were associated with a greater chance of survival in high-risk surgical patients. In addition, Shoemaker et al[8] conducted a prospective cohort study of 300 surgical patients with septic shock and discovered that survivors had a higher cardiac index as well as higher oxygen consumption and delivery. Drawing on this work, other investigators tested early GDT protocols and found decreased mortality in patients who received preoperative PAC and hemodynamic optimization.[9] From these discoveries came the concept of superoptimization or using vasopressors and inotropes to target supranormal indices of cardiac performance and oxygen delivery. Superoptimization has been associated with mixed outcomes. Using inotropes to increase oxygen delivery (DO2) during surgery decreased perioperative morbidity and mortality in high-risk surgical patients[9] as well as patients undergoing major elective surgical procedures.[10] In addition,

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patients undergoing cardiothoracic surgery,[11] as well as major general surgery,[12] whose oxygen delivery was superoptimized upon arrival in the intensive care unit (ICU) had decreased hospital length-of-stay (LOS). However, studies utilizing superoptimization in septic[13] as well a mixed group of critically ill ICU patients[14] have not demonstrated an effect on mortality. However, these studies have been critiqued for starting resuscitation >12 hours after arrival to the ICU, after patients perhaps had irreversible tissue dysoxia and organ damage.

Not long after the work of Shoemaker et al, Mythen et al[15] demonstrated a significant relationship between gut mucosal hypoperfusion during high-risk surgery and postoperative complications, including mortality. Interestingly, it was noted that patients who did not experience gut mucosal hypoperfusion had an increase in cardiac index during surgery, whereas patients who did experience hypoperfusion did not have an intraoperative increase in CI. Mythen et al followed this with the initial intraoperative goal-directed fluid therapy study, in which patients undergoing cardiac surgery receiving intravenous colloid boluses with the goal of optimizing stroke volume and central venous pressure (CVP) were found to have a lower incidence of gastrointestinal (GI) mucosal hypoperfusion, major complications, as well as shorter hospital and ICU LOS.[3] Following this work, Sinclair et al[16] utilized esophageal Doppler-guided GDT in 40 patients undergoing repair of femoral neck fractures and found that patients receiving colloid boluses to optimize stroke volume (SV) and corrected flow time had shorter hospital stays than control patients. With a growing literature base, the study and practice of GDT began to increase.

## ESTABLISHED BENEFITS OF GDT

Perioperative GDT repeatedly has been associated with improved outcomes following moderate-to-major surgery, including shorter hospital LOS, fewer ICU admissions, fewer GI complications, and decreased rates of acute kidney injury.[2,3,16–21] Excitingly, there are emerging data that suggest a long-term survival benefit (up to 15 years postoperatively) in ICU patients who underwent perioperative GDT associated with high-risk surgery.[22] In addition, there are 2 recent meta-analyses that show mortality and morbidity benefits in patients undergoing perioperative GDT.[23,24] However, a recent large multicenter prospective trial of hemodynamic optimization versus usual care in high-risk patients undergoing major gastrointestinal surgery showed no difference in postoperative morbidity or mortality, although an up-to-date meta-analysis including these data still shows a reduction in morbidity with perioperative GDT.[25] A brief overview of the supporting evidence for perioperative GDT will be reviewed here.

By optimizing oxygen delivery, GDT may improve perfusion of microvascular beds in the splanchnic circulation, thus improving postoperative bowel function. Two recent meta-analyses have shown reductions in postoperative nausea and vomiting (PONV) and ileus,[26] as well as a faster return of normal GI function,[18] in patients receiving perioperative GDT. Of note, these reviews and others[27] have found significantly fewer postoperative complications and shorter hospital LOS in GDT patients. A 2009 meta-analysis showed a reduction in both minor (eg, PONV) and major (eg, anastomotic leak) GI complications in patients receiving GDT.[19] These differences may result from improved visceral perfusion as well as an avoidance of interstitial edema, as there are animal data that increased volumes of crystalloid are associated with weaker intestinal anastomoses.[28,29]

Though GDT optimizes intravascular volume and oxygen delivery, concerns have been raised[30] that volume expansion during GDT could result in overload and/or cardiac decompensation. Furthermore, routine exposure to vasoactive infusions to optimize oxygen delivery is not without risk. As such, Arulkumaran et al[31] performed a meta-analysis of 22 trials that did not reveal any increase in cardiovascular risk in patients treated with GDT. In fact, they demonstrated a reduction in the risk of cardiovascular complications in patients receiving GDT that was most notable in studies using fluids and inotropes, supranormal oxygen delivery goals, and minimally invasive cardiac output monitors (ie, not a PAC).[32]

Ultimately, it would be ideal if the reduction in morbidity associated with GDT led to a reduction in perioperative mortality. In fact, 3 recent reviews demonstrated that GDT reduced perioperative mortality, potentially by reducing the number of postoperative complications. In a meta-analysis of 32 trials of perioperative GDT focusing on maintaining tissue perfusion (ie, optimizing cardiac index and/or DO2 or oxygen consumption), Gurgel and do Nascimento[23] found that although GDT reduced the incidence of organ dysfunction in all patients, it reduced mortality only in cohorts in which the baseline perioperative mortality exceeded 20%. In addition, a meta-analysis of 29 trials of perioperative GDT with various goals and monitoring techniques by Hamilton et al[24] found reductions in morbidity and mortality in GDT patients, but did note that subgroup analyses showed a mortality benefit predominantly in older trials, trials using a PAC, trials utilizing vasoactive infusions, and those targeting supranormal values. Similarly, Poeze et al[33] found decreased odds of mortality in perioperative GDT patients while noting in subgroup analyses that this benefit was found only in patients in whom supranormal values were targeted. Together, these data may suggest that perioperative GDT reduces a vast array of complications, and may reduce mortality in high-risk patient groups who receive aggressive GDT.

## IMPORTANT CONSIDERATIONS IN PERIOPERATIVE GDT

### Monitors/Goals

Unfortunately, there is no one best endpoint for perioperative GDT. The ideal endpoint would be representative of end-organ perfusion, readily available in the perioperative period, continuous, and reproducible. Traditional pressure-based parameters such as blood pressure (BP), heart rate (HR), CVP, and pulmonary artery occlusion pressure (PAOP or wedge pressure) are appealing as they are readily available. Unfortunately, these measures all fall short as accurate endpoints for perioperative GDT. Both HR and BP have been demonstrated to be insensitive indicators of volume status,[26] and it has been proposed that an intraoperative goal of normotension is inferior to GDT.[34] The utility of CVP and PAOP as measures of preload have been questioned in both