

Hemodynamic Goal-Directed Therapy in High-Risk Surgical Patients

Elliott Bennett-Guerrero, MD

Most clinicians agree that during stress, such as acute critical illness or surgery, maintaining adequate perfusion and oxygen delivery reduces the risk of injury to vital organs. However, the best way to achieve these general goals remains controversial. A growing body of evidence suggests that



Related article page 2181

“goal-directed therapy” (GDT) to increase blood flow can reduce postoperative complications and cost.¹ Goal-directed therapy typically uses a monitoring tool to continuously assess cardiac performance, and through a set of protocolized instructions, fluid administration and vasoactive agents are titrated to optimize cardiac performance. A central tenet of many of these studies is that GDT should not be defined by the presence or absence of a monitoring device but rather by explicit goals of care, such as maintenance of sustained maximal stroke volume. In other words, a GDT protocol should clearly define how data from the monitor trigger specific changes in care.

Pearse and colleagues² report the results of OPTIMISE, a pragmatic multicenter trial conducted at 17 hospitals that randomized 734 high-risk patients undergoing gastrointestinal surgery to receive usual care or GDT intraoperatively and for 6 hours after surgery. Consistent with the core principles of GDT, the intervention tested in this study consisted of an infusion of dopexamine plus administration of 250-mL boluses of colloid to maintain maximal stroke volume during the study period. Stroke volume was determined by a cardiac output monitor, which required an arterial catheter for pulse pressure analysis. The incidence of the primary outcome—a composite of prespecified postoperative complications through 30 days after surgery—was lower in the GDT group (36.6% vs 43.4%). This reduction, while consistent with benefit observed in many previous trials (eFigures 2-5 in the article),² was not statistically significant ($P = .07$), even after adjusting for baseline risk factors.

This study has numerous strengths, including a large number of patients and participating sites. Self-assessment of blinding by outcome evaluators further enhances the quality of the study. In addition, several important prespecified secondary analyses were performed, including adjustment for protocol adherence and adjustment for a learning curve; ie, exclusion of the first 10 patients at each of the 17 sites. Both of these analyses yielded a more robust treatment effect, which might be expected for an intervention that requires experience and training.

The study is further strengthened because study team members were present during the intervention period in more than 80% of the cases (eTable 2 in the article), which probably improved adherence to the protocol. Of note, study team members were also

present during surgery in almost half of the usual care cases, which may have increased the presence of senior anesthesia or surgical staff and may have improved the care and outcomes of the control group. Greater attention to detail, such as avoidance of hypovolemia and hypotension, also may have played a role, as the clinicians were aware that they were being monitored. Thus, study team presence may account in part for the lower composite event rate in the control group (43.4%) compared with the higher value (68%) from preliminary data, which was used to calculate the sample size for the trial. Another factor that may have lowered the occurrence of the primary outcome rate in the control group was the protocol recommendation that patients in the usual care group receive dynamic central venous pressure-guided fluid administration. These data were not presented, but if used frequently, they may have minimized hypovolemia/tissue hypoperfusion and related complications in the control group.

Adherence to the protocol is important in this setting, where the presence of a monitor does not ensure that it is used correctly or actually triggers changes in care. The investigators report adherence in more than 90% of patients in each group (eTable 1 in the article). However, nonadherence focused largely on the administration of dopexamine. Nonadherence to the fluid algorithm was defined as “failure to monitor,” which does not provide information about whether monitoring resulted in sustained maximal stroke volume. No objective data are provided regarding cardiac output and stroke volume at different time points. Analysis of the colloid and crystalloid fluid volumes (Table 2 in the article) does not directly shed light on whether maximal stroke volume was achieved. The extent to which dopexamine and additional colloid boluses increased blood flow (ie, cardiac output) was not reported. Thus, the observed benefit from GDT may be less than was expected if the protocol for the intervention was not followed.

Initial studies in GDT focused on critically ill patients (often with sepsis), and augmentation of global oxygen delivery was often achieved with high doses of dobutamine guided by a pulmonary artery catheter. In many of these studies, however, investigators concluded that GDT provided no benefit and may even cause potential harm.³ Thus, many speculated that in these very sick patients, organs were already too injured to respond to care and that future studies should focus on prevention of organ injury. This led to the concept of early GDT for patients with sepsis⁴; however, a recent large multicenter trial (ProCESS) showed no benefit.⁵ In contrast, since 1988, more than 30 randomized trials have tested GDT in high-risk surgery patients and yielded encouraging results.²

An evolution in the choice of monitors used to optimize patient hemodynamics has led to a move away from pulmon-

ary artery catheters toward minimally invasive monitors of cardiac output. These include esophageal Doppler, bioreactance/bioimpedance, and pressure waveform analysis, which uses an arterial catheter or finger probe.⁶ Goal-directed therapy is easier to implement with these newer technologies because they require less training and, in most cases, are easily interpreted by a wide range of caregivers. However, their comparative effectiveness to guide fluid administration is unclear, so results from trials using one monitor cannot necessarily be generalized to other monitors.

Goal-directed therapy requires a monitor and an intervention, usually intravenous fluid with or without a vasoactive agent. Although colloid has generally been promoted over crystalloid as the intravenous fluid because colloid has more sustained volume expansion and possibly lower risk of edema,⁷ the optimal choice of fluid has been unclear. Clinical trials are only now beginning to address this question.⁸ The OPTIMISE trial did not standardize the type of colloid used and, other than reporting the volumes administered, did not analyze for possible effects of colloid type on the primary outcome.

The use of vasoactive agents in GDT is controversial, especially the choice of agent and the need for it. Dopexamine is a reasonable choice; however, clinicians in countries that do not have this drug (eg, the United States) will be unsure as to what drug (and dose) is the best substitute. Some clinicians will wonder why dopexamine was infused in all intervention patients in the OPTIMISE trial and not titrated to explicit targets of cardiac performance. A simple response may be that this was a pragmatic trial, and it was easier to give the drug to all patients. Furthermore, since dopexamine is an inotrope and selective vasodilator, there may be no simple explicit goal to titrate against. Some staunch supporters of GDT will argue that fluid alone should be used to begin hemodynamic optimization and that an inotropic agent should be added only if necessary. Indeed, some data suggest that adding dopexamine may not provide incremental benefit for patients who are already

receiving GDT.⁹ Future studies are needed to determine which tools (monitor, fluid, drugs) and targets are best for balancing safety, effectiveness, cost, and practical considerations.

There was little evidence to suggest that the intervention was harmful to patients. As an inotrope and vasodilator, dopexamine can potentially cause myocardial ischemia, arrhythmias, and hypotension. However, cardiovascular adverse events occurred in only a small percentage of patients in the intervention group (1.4%), and these events did not appear to translate into increased cardiovascular mortality. This favorable safety profile was perhaps due in part to exclusion of patients at higher risk of cardiac events; eg, recent acute myocardial ischemia or aortic stenosis. The volumes of fluid administered to intervention patients were modest (median of 1250 mL more colloid) and not associated with pulmonary edema (Table 3 in the article).

As recommended by many in the field of evidence-based medicine, the authors conducted an additional analysis, the inclusion of the OPTIMISE results in an updated systematic review.² These results further strengthen the overall conclusion that GDT of some type is probably beneficial for high-risk patients and has few documented adverse effects. Compared with the previous review,¹⁰ this updated analysis added 7 additional trials and reported statistically significant reductions in complications, infections, and hospital stay for patients who received GDT. These findings are consistent with reports by the Centers for Medicare & Medicaid Services¹¹ and the National Institute for Health and Care Excellence,¹² which recommend the use of hemodynamic therapy algorithms. The extent to which GDT will be translated into routine practice is difficult to predict and will depend on many factors. Goal-directed therapy is best achieved in environments that emphasize a multidisciplinary team approach to patient care, including anesthesiologists, surgeons, intensivists, and nurses. This approach is exemplified in the “perioperative surgical home,” which is gaining momentum as a model to improve outcome and reduce costs.¹³

ARTICLE INFORMATION

Author Affiliation: Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina.

Corresponding Author: Elliott Bennett-Guerrero, MD, Duke Clinical Research Institute, Duke University Medical Center, 2301 Erwin Rd (HAFS 5675), Durham, NC 27710 (benne011@mc.duke.edu).

Published Online: May 19, 2014.
doi:10.1001/jama.2014.5306.

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

REFERENCES

- Ebm C, Cecconi M, Sutton L, Rhodes A. A cost-effectiveness analysis of postoperative goal-directed therapy for high-risk surgical patients. *Crit Care Med*. 2014;42(5):1194-1203.
- Pearse RM, Harrison DA, MacDonald N, et al; OPTIMISE Study Group. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review [published online May 19, 2014]. *JAMA*. doi: 10.1001/jama.2014.5305.
- Hayes MA, Timmins AC, Yau EH, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med*. 1994;330(24):1717-1722.
- Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368-1377.
- ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014;370(18):1683-1693.
- Chamos C, Vele L, Hamilton M, Cecconi M. Less invasive methods of advanced hemodynamic monitoring. *Periop Med (Lond)*. 2013;2(1):19.
- Vercueil A, Grocott MP, Mythen MG. Physiology, pharmacology, and rationale for colloid administration for the maintenance of effective hemodynamic stability in critically ill patients. *Transfus Med Rev*. 2005;19(2):93-109.
- Yates DR, Davies SJ, Milner HE, Wilson RJ. Crystalloid or colloid for goal-directed fluid therapy in colorectal surgery. *Br J Anaesth*. 2014;112(2):281-289.
- Davies SJ, Yates D, Wilson RJ. Dopexamine has no additional benefit in high-risk patients receiving goal-directed fluid therapy undergoing major abdominal surgery. *Anesth Analg*. 2011;112(1):130-138.
- Grocott MP, Dushianthan A, Hamilton MA, Mythen MG, Harrison D, Rowan K. Perioperative increase in global blood flow to explicit defined goals and outcomes following surgery. *Cochrane Database Syst Rev*. 2012;11:CD004082.
- Agency for Healthcare Research and Quality. *Esophageal Doppler Ultrasound-Based Cardiac Output Monitoring for Real-Time Therapeutic Management of Hospitalized Patients*. 2007. <http://www.cms.gov/determinationprocess/downloads/id45TA.pdf>. Accessed May 7, 2014.
- National Institute for Health and Clinical Excellence. *CardioQ-ODM Oesophageal Doppler Monitor*. 2011. <http://www.nice.org.uk/nicemedia/live/13312/52624/52624.pdf>. Accessed May 7, 2014.
- Vetter TR, Boudreaux AM, Jones KA, et al. The perioperative surgical home. *Anesth Analg*. 2014;118(5):1131-1136.