Published in final edited form as:

Curr Opin Anaesthesiol. 2016 February ; 29(1): 80–84. doi:10.1097/ACO.0000000000000273.

Goal-directed therapy in the operating room: is there any benefit?

Jason B. O'Neal and Andrew D. Shaw

Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Abstract

Purpose of review—This article reviews the current evidence behind goal-directed therapy (GDT) in multiple medical settings.

Recent findings—Although some studies advocate for the use of GDT, others do not and more studies are necessary to evaluate the efficacy of GDT in medicine. Previously accepted guidelines for treating patients in septic shock which include GDT in their algorithms are not supported by the findings in recent randomized, controlled trials. No generally accepted guidelines for GDT are available for perioperative use, but there is evidence supporting GDT in high-risk surgery such as major abdominal surgery and cardiac surgery. Clinicians should be aware of the potential benefits of GDT in these settings and use these evidence-based findings to help guide clinical decisions in these patient populations.

Summary—The use of GDT may be beneficial depending on the clinical setting, but more evidence supporting its use is necessary before it can be considered standard of care.

Keywords

anesthesia; cardiac surgery; goal-directed therapy

INTRODUCTION

The use of goal-directed therapy (GDT) has been investigated in many different settings, including the emergency room, ICU, and operating room. The typical patient population in the emergency room and ICU include patients suffering from septic shock. In the surgical setting, higher risk procedures, such as gastrointestinal, vascular, and cardiac surgery patients are usually chosen for evaluating the potential benefits of GDT. Given the nature of these procedures, the patients are often already deemed to be at higher risk for a poor outcome regardless of the type of surgery. Therefore strategies, which may improve complications, morbidity, and mortality such as GDT are frequently explored by clinicians and researchers in an attempt to guide clinical care. This review will focus on the use of

Correspondence to Jason B. O'Neal, MD, Vanderbilt University Medical Center, Department of Anesthesiology, Nashville, TN, USA. Tel: +1 252 292 6792; jason.b.oneal@vanderbilt.edu.

Conflicts of interest

There are no conflicts of interest.

GDT in cardiac and high-risk surgery while also including evidence from other settings and surgical procedures.

TEXT OF REVIEW

Goal-directed therapy in septic shock

The implementation of GDT to clinical practice is not a new concept. It dates back many years, and remains a major focus in medicine especially in treating patients with septic shock. In 2001, Rivers *et al.* [1] published a study in the New England Journal of Medicine which showed an improvement in in-hospital mortality for patients randomized to a GDT group over the control group in patients presenting to the emergency room in septic shock (30.5 vs. 46.5%, $P = 0.009$). Although this study was conducted at an urban hospital and included only 263 patients, it led to the implementation of GDT in the widely known and accepted Surviving Sepsis Campaign [2–4]. Since its publication, many studies including the recent Australasian Resuscitation In Sepsis Evaluation (ARISE) and Protocolized Care for Early Septic Shock (ProCESS) trials, have failed to demonstrate benefits of GDT as neither showed an improved mortality with its use in patients diagnosed with septic shock.

The ARISE trial randomized 1600 patients presenting to the emergency room with septic shock into either an early GDT (EGDT) or usual-care group [5]. All-cause mortality at 90 days (primary outcome) was similar between groups, as was in-hospital mortality, survival time, length of hospital stay, and duration of organ support. Another similar study which included 31 emergency departments across the USA randomly assigned patients to one of three groups: 439 to protocol-based EGDT, 446 to protocol-based standard therapy (no central venous catheter placed), and 456 to usual care [6]. When comparing 60-day mortality between the three groups, no difference was shown [relative risk (RR) with protocol-based therapy vs. usual care, 1.04; 95% confidence interval (CI), 0.82 to 1.31; $P = 0.83$; RR with protocol-based EGDT vs. protocol-based standard therapy, 1.15; 95% CI, 0.88 to 1.51; $P = 0.31$]. Several studies on GDT in the perioperative setting also lack evidence supporting its use.

Perioperative goal-directed therapy

In the Optimisation of Cardiovascular Management to Improve Surgical Outcome (OPTIMISE) study, investigators conducted a randomized controlled trial, which included 734 patients at 17 hospitals in the UK undergoing major gastrointestinal surgery [7]. Patients were divided into a cardiac output guided group with intravenous fluids (IVFs) and dopexamine administration or a usual care group. The study found that the GDT group did not reduce complications or 30-day mortality when compared with the usual care group (RR 0.84, 95% CI, 0.71–1.01, $P = 0.7$). Secondary outcomes also were not different between the two groups. A recent study, also on patients undergoing major abdominal surgery, shared similar findings to OPTIMISE. The perioperative goal-directed therapy in major abdominal surgery study was conducted across six tertiary medical centers on 142 patients and divided patients into a standard practice group or study group, which used blood pressure, cardiac index, and stroke volume to guide fluid administration and vasoactive [8]. The only significant finding was a reduction in reoperation in the GDT group (5.6 vs 15.7%; $P =$

0.049). No significant differences in complications, mortality, or length of stay were found. To date, OPTIMISE is the largest randomized, controlled trial on GDT in surgical patients and no statistically significant benefit for patients randomized to receive GDT was shown. Other studies and the recent perioperative goal-directed therapy in major abdominal surgery study have shown similar results. But some systematic studies and meta-analyses go against these results and have demonstrated several advantages to GDT in the operating room.

A meta-analysis of 14 randomized controlled trials on GDT and published in *Critical Care* showed a decrease in postoperative morbidity (odds ratio 0.51; CI 0.34 to 0.75; $P < 0.001$) with reductions in infection, cardiovascular, and abdominal complications in patients receiving GDT [9]. A decrease in length of stay was also shown (weighted mean difference -0.75 days; CI -1.37 to -0.12 ; $P = 0.02$). Another study published in *Critical Care* aimed to further evaluate GDT on patients subdivided into three groups – extremely high risk, high risk, and intermediate risk of mortality as defined by mortality rates of $>20\%$, 5 to 20% , and $< 5\%$ mortality rates respectively [10]. This clinical review included 27 trials and although mortality rate was only reduced in the extremely high-risk group (OR = 0.20, 95% CI 0.09 to 0.41; $P < 0.0001$), complication rates were reduced in all groups (OR = 0.45, 95% CI 0.34 to 0.60; $P < 0.00001$). Interestingly, the authors of OPTIMISE added data from their study to 37 other trials and completed a meta-analysis. The analysis suggested a lower complication rate in GDT patients (488/1548 [31.5%] vs. 614/1476 [41.6%]; RR 0.77 [95% CI, 0.71–0.83], $P < 0.001$), but did not demonstrate a reduction in hospital, 28-day, or 30-day mortality when comparing intervention groups to the control [7]. Thus, recent randomized controlled trials do not show evidence supporting GDT, yet there are meta-analyses which do.

Goal-directed therapy in cardiac surgery

Similar to GDT in septic shock, its use in cardiac surgery dates back many years. A study on 60 patients undergoing elective cardiac surgery conducted 20 years ago, aimed to decipher the role of intravascular volume expansion on gut mucosal perfusion [11]. The protocol group received boluses of 200 ml 6% hydroxyethyl starch every 15 min with a goal to maintain maximum stroke volume as measured with an esophageal Doppler. The primary endpoint of gastric mucosal perfusion showed a benefit of lowering the incidence of hypoperfusion in the protocol group (7 vs 56%, $P < 0.001$). Reductions in complications, hospital stay, and time in the ICU were also shown in the study. The positive results seen in the secondary outcomes of this study led the way for future trials in GDT, which concentrated on the reduction in complications, morbidity, and mortality when using GDT in cardiac surgery.

One of the larger randomized, controlled trials investigating GDT in cardiac surgery enrolled 403 patients with a goal of maximizing oxygen delivery and consumption in the protocol group [12]. The protocol group had a goal central venous oxygen saturation (SvO₂) $>70\%$ and lactate <2.0 mmol/l utilizing dobutamine infusions up to 15 mcg/kg/min. The study found both median hospital stay (6 vs. 7 days, $P < 0.05$) and morbidity was lower (1.1 vs 6.1%, $P < 0.01$) in the protocol group. Although most GDT regimens begin in the operating room, some groups have looked into initiating them early in the postoperative period.

McKendry *et al.* [13] evaluated a nurse led protocol on 174 patients undergoing cardiac surgery in which the study group used an esophageal Doppler to maintain stroke index >35 ml/m². Mortality between the GDT group and standard care group was not different, but a reduction in median and mean hospital stay was shown (7 vs. 9 days, $P=0.02$; 11.4 vs. 13.9 days, respectively). These studies were able to show significant differences when comparing GDT to standard care. Other trials in cardiac surgery have not.

A much smaller randomized controlled trial which included 27 patients undergoing coronary artery bypass grafting (CABG) set goals of central venous pressure (CVP) 6–8 mmHg, mean arterial pressure (MAP) 90–105 mmHg, normal arterial blood gas, hematocrit >30 , and urine output >1 ml/kg/h in the GDT group [14]. Both IVFs and inotropes/vasodilators were used to obtain these hemodynamic goals. Trends toward supporting GDT were shown in duration of ventilation (13.8 ± 3.2 vs. 20.7 ± 7.1 h), days of use of inotropic agents (1.6 ± 0.9 vs. 3.8 ± 1.6 d), ICU stay (2.6 ± 0.9 vs. 4.9 ± 1.8 d) and hospital stay (5.6 ± 1.2 vs. 8.9 ± 2.1 d), but these findings were not significant ($P > 0.05$ for every outcome). This was a small study and likely not powered adequately to show a difference if one existed. Another small randomized study took 40 patients undergoing off-pump CABG and divided them into advanced monitoring or conventional monitoring groups [15]. Each group received inotropes, vasopressors, and/or IVFs to maintain CVP, MAP and HR, but in addition to these parameters, the advanced monitoring group had specific targets for intrathoracic blood volume index, MAP, HR, central venous oxygen saturation SvO₂, and CI. The findings showed that the advanced monitoring group had a decreased time to ICU discharge and a reduction in hospital stay by 15 and 25%, respectively ($P < 0.04$). Both Pölönen *et al.* and McKendry *et al.* had sufficient power to show a difference, but many other studies have lacked adequate sample sizes, and therefore produced mixed results.

A systematic review with meta-analysis on GDT studies including both cardiac and vascular surgery patients used 11 articles (five cardiac and six vascular) with a total of 1179 patients [16]. When including both studies on cardiac and vascular patients, perioperative GDT did not reduce mortality (pooled OR 0.87; 95% CI 0.37–2.02). But although no effect on complications was observed in vascular patient studies (OR, 0.84; 95% CI 0.45–1.56; $P=0.58$), complications were reduced in the GDT groups for cardiac studies (OR 0.34; 95% CI 0.18–0.63; $P=0.0006$). Another meta-analysis that included only five studies which met their inclusion criteria analyzed data on 699 patients [17]. This study found GDT to reduce postoperative complication rate and also length of stay in the hospital (OR 0.33, 95% CI 0.15–0.73; $P=0.006$, mean difference -2.44 , 95% CI 4.03 to -0.84 ; $P=0.003$, respectively). The previous studies are slightly dated, but investigators continue to research the effects and different methods of GDT in cardiac surgery.

A recent prospective, controlled trial randomized 100 elective CABG patients to a study group which utilized an endotracheal cardiac output monitor to measure stroke volume variation (SVV) and CI to guide therapy or a control group which received standard care [18]. Only a reduction in time to extubation was significant (510 vs. 570 min, $P=0.05$) whereas other outcomes, such as length of stay, mortality, and complications were not statistically different between the groups. Some authors believe the use of pulmonary artery catheter (PAC) measurements to direct care after cardiac surgery is not as effective as once

thought and may be associated with several dangerous complications [19]. A study which aimed to compare GDT utilizing either a PAC or noninvasive cardiac output monitor (NICOM) enrolled and randomized 59 patients undergoing heart valve surgery to the two groups [20]. One group used a goal pulmonary capillary wedge pressure taken with a PAC, whereas the other group directed therapy on changes in stroke volume index after passive leg raise utilizing a NICOM. Length of stay was not different between the groups. The PAC group required more epinephrine and ventilator care (5 vs. 0 pts, $P=0.019$; 6 vs. 1 pts, $P=0.044$, respectively) than the NICOM group and also required more colloid (1652 vs. 11430 ml, $P=0.004$). As with the PAC, some clinicians question the accuracy and reliability of the NICOM.

CONCLUSION

The use of GDT in septic shock has been advocated for and accepted for many years. Recent trials such as ARISE, ProCESS, and also OPTIMISE have not shown significant benefit of GDT with regards to morbidity or mortality. Given the influence and recognition of the Surviving Sepsis Campaign, clinicians have become more aware of the necessity for fluids in this patient population, which was not present during the Rivers *et al.* trial. This may have impacted the 'control groups' in the more recent trials that have shown no true benefits to GDT. Interestingly, the use of GDT is more widely accepted in the septic population than high-risk surgical patients despite data suggesting no benefit when GDT is utilized in sepsis whereas some recent studies in high-risk surgery support GDT. A lack of uniformity with study design may be a factor. For years investigators have come up with many different algorithms and guidelines trying to improve patient outcomes with the use of GDT (see Table 1). The results are definitely mixed when sifting through the studies, but several meta-analyses have shown multiple benefits. The issues with completing a meta-analysis on GDT studies are the inconsistencies with both the hemodynamic variables which guide therapy and the interventions used to achieve the desired hemodynamic ranges. From CI to SVV to CVP, no study has shown one parameter to be better than the other for guiding therapy. And for interventions, crystalloid versus colloid, inotrope versus vasopressor; there is no consensus as to which fluid or medication to choose. The use of GDT forces physicians to stick to a defined algorithm (that potentially improves outcomes), and also helps to reduce variation in care. Patient outcome is always the top priority for any doctor, but until studies aim to define the optimal hemodynamic parameter(s) and intervention(s) for GDT, the use of GDT in the perioperative setting will not be accepted by the majority.

Acknowledgments

None.

Financial support and sponsorship

Research reported in this publication was supported by the National Institutes of Health under award number 5T32 GM108554. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■ ■ of outstanding interest

1. 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; 345:1368–1377. [PubMed: 11794169]
2. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med*. 2004; 32:858–873. [PubMed: 15090974]
3. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med*. 2008; 34:17–60. [PubMed: 18058085]
4. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013; 41:580–637. [PubMed: 23353941]
- 5■. ARISE Investigators; ANZICS Clinical Trials Group. Peake SL, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med*. 2014; 371:1496–1506. The ARISE trial randomized 1600 patients presenting to the emergency room with septic shock into either an early GDT (EGDT) or usual-care group and found all-cause mortality at 90 days (primary outcome) was similar between groups, as was in-hospital mortality, survival time, length of hospital stay, and duration of organ support. [PubMed: 25272316]
- 6■. Investigators ProCESS. Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014; 370:1683–1693. The ProCESS study included 31 emergency departments across the United States and randomly assigned patients to one of three groups: 439 to protocol-based EGDT, 446 to protocol-based standard therapy (no central venous catheter placed), and 456 to usual care. When comparing 60-day mortality between the three groups, no difference was shown. [PubMed: 24635773]
- 7■ ■. Pearse RM, Harrison DA, MacDonald N, et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. *JAMA*. 2014; 311:2181–2190. In the OPTIMISE study, investigators conducted a randomized controlled trial which included 734 patients undergoing major gastrointestinal surgery into a cardiac output guided group with IVFs and dopexamine administration or a usual care group. The study found that the GDT group did not reduce complications or 30 day mortality when compared with the usual care group. To date, OPTIMISE is the largest randomized, controlled trial on GDT in surgical patients and no statistically significant benefit for patients randomized to receive GDT was shown. [PubMed: 24842135]
- 8■. Pestaña D, Espinosa E, Eden A, et al. Perioperative goal-directed hemodynamic optimization using noninvasive cardiac output monitoring in major abdominal surgery: a prospective, randomized, multicenter, pragmatic trial: POEMAS Study (Perioperative goal-directed therapy in Major Abdominal Surgery). *Anesth Analg*. 2014; 119:579–587. The POEMAS study was a randomized controlled trial over 6 tertiary medical centers on 142 patients undergoing abdominal surgery. The GDT group utilized blood pressure, cardiac index, and stroke volume to guide fluid administration and vasoactive drugs. The only significant finding was a reduction in reoperation in the GDT group (5.6% vs 15.7%; $P = 0.049$). No significant differences in complications, mortality, or length of stay were shown. [PubMed: 25010820]
- 9■. Benes J, Giglio M, Brienza N, Michard F. The effects of goal-directed fluid therapy based on dynamic parameters on postsurgical outcome: a meta-analysis of randomized controlled trials. *Crit Care*. 2014; 18:584. A meta-analysis of 14 randomized controlled trials on GDT which found a decrease in postoperative morbidity with reductions in infection, cardiovascular, and abdominal complications in patients receiving GDT. A decrease in length of stay was also shown. [PubMed: 25348900]

10. Cecconi M, Corredor C, Arulkumaran N, et al. Clinical review: goal-directed therapy-what is the evidence in surgical patients? The effect on different risk groups. *Crit Care*. 2013; 17:209. [PubMed: 23672779]
11. Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. *Arch Surg*. 1995; 130:423–429. [PubMed: 7535996]
12. Pölönen P, Ruokonen E, Hippeläinen M, et al. A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. *Anesth Analg*. 2000; 90:1052–1059. [PubMed: 10781452]
13. McKendry M, McGloin H, Saberi D, et al. Randomised controlled trial assessing the impact of a nurse delivered, flow monitored protocol for optimisation of circulatory status after cardiac surgery. *BMJ*. 2004; 329:258. [PubMed: 15242867]
14. Kapoor PM, Kakani M, Chowdhury U, et al. Early goal-directed therapy in moderate to high-risk cardiac surgery patients. *Ann Card Anaesth*. 2008; 11:27–34. [PubMed: 18182756]
15. Smetkin AA, Kirov MY, Kuzkov VV, et al. Single transpulmonary thermodilution and continuous monitoring of central venous oxygen saturation during off-pump coronary surgery. *Acta Anaesthesiol Scand*. 2009; 53:505–514. [PubMed: 19183113]
16. Giglio M, Dalfino L, Puntillo F, et al. Haemodynamic goal-directed therapy in cardiac and vascular surgery. A systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg*. 2012; 15:878–887. [PubMed: 22833509]
17. Aya HD, Cecconi M, Hamilton M, Rhodes A. Goal-directed therapy in cardiac surgery: a systematic review and meta-analysis. *Br J Anaesth*. 2013; 110:510–517. [PubMed: 23447502]
18. Fellahi JL, Brossier D, Dechanet F, et al. Early goal-directed therapy based on endotracheal bioimpedance cardiography: a prospective, randomized controlled study in coronary surgery. *J Clin Monit Comput*. 2015; 29:351–358. A prospective, controlled trial randomized 100 elective CABG patients to a study group which utilized an endotracheal cardiac output monitor to measure SVV and CI to guide therapy or a standard care control group. Outcomes including length of stay, mortality, and complications were not statistically different between the groups. Only time to extubation, shorter in the GDT group, was statistically significant. [PubMed: 25380955]
19. Schwann NM, Hillel Z, Hoeft A, et al. Lack of effectiveness of the pulmonary artery catheter in cardiac surgery. *Anesth Analg*. 2011; 113:994–1002. [PubMed: 21918165]
20. Lee S, Lee SH, Chang BC, Shim JK. Efficacy of goal-directed therapy using bioreactance cardiac output monitoring after valvular heart surgery. *Yonsei Med J*. 2015; 56:913–920. [PubMed: 26069111]

KEY POINTS

- The use of GDT may be beneficial depending on the clinical setting.
- More evidence supporting the use of GDT is necessary before it can be considered standard of care.
- The verdict on GDT has yet to be defined.

Table 1

List of prospective randomized controlled trials on goal-directed therapy in different patient populations with choice of hemodynamic parameter, type of fluid, and medication used to guide therapy

Study	Population	Hemodynamic parameter(s)	Fluid(s)	Medication(s)
Rivers (2001) [1]	Sepsis	CVP, MAP, ScvO ₂ , Hct	Crystalloid, packed red blood cells	Vasopressor and/or dobutamine
ARISE 2014 [5■]	Sepsis	CVP, MAP, ScvO ₂ , Hct	Crystalloid, packed red blood cells	Vasopressor and/or dobutamine
ProCESS 2014 [6■]	Sepsis	CVP, MAP, ScvO ₂ , Hct	Crystalloid, packed red blood cells	Vasopressor and/or dobutamine
Pearse (2014) [7■]	Major GI surgery	CO, SV	Colloid	Dopexamine
Pestana (2014) [8■]	Major GI surgery	CI, SV, MAP	Colloid	Dobutamine and/or norepinephrine
Mythen (1995) [11]	Cardiac surgery	SV	HES	–
POIOnen (2000) [12]	Cardiac surgery	SvO ₂ , lactate	Crystalloid, colloid, blood products	Dobutamine
McKendry (2004) [13]	Cardiac surgery	SVI	Colloid, blood products	Epinephrine
Kapoor (2005) [14]	Cardiac surgery	CI, SVI, SVV, SVRI, ScvO ₂ , ODI	Colloid, packed red blood cells	Inotrope or vasodilator
Smetkin (2009) [15]	Cardiac surgery	ITBVI, CVP, HR, MAP, ScvO ₂ , CI	Colloid, blood products	Phenylephrine, ephedrine, dobutamine, nitroglycerin, verapamil, furosemide
Fellahi (2014) [18■]	Cardiac surgery	SVV, CI	HES	Dobutamine

CI, cardiac index; CO, cardiac output; CVP, central venous pressure; GI, gastrointestinal; Hct, hematocrit; HES, hydroxyl ethyl starch; HR, heart rate; ITBVI, intrathoracic blood volume index; MAP, mean arterial pressure; ODI, oxygen delivery index; ScvO₂, central venous oxygenation; SV, stroke volume; SVI, stroke volume index; SVRI, systemic vascular resistance index; SVV, stroke volume variation.