

## Review Article

# The History of Goal-Directed Therapy and Relevance to Cardiopulmonary Bypass

Laurie Dijoy, BS; John Scott Dean, BS; Carla Bistrick, MS CCP; Joseph J. Sistino, PhD, CCP

Medical University of South Carolina Division of Cardiovascular Perfusion, College of Health Professions, Charleston, South Carolina

---

**Abstract:** Goal-directed therapy is a patient care strategy that has been implemented to improve patient outcomes. The strategy includes aggressive patient management and monitoring during a period of critical care. Goal-directed therapy has been adapted to perfusion and has been designated goal-directed perfusion (GDP). Since this is a new concept in perfusion, the purpose of this study is to review goal-directed therapy research in other areas of critical care management and compare that process to improving patient outcomes following cardiopulmonary bypass. Various areas of goal-directed therapy literature were reviewed, including fluid adminis-

tration, neurologic injury, tissue perfusion, oxygenation, and inflammatory response. Data from these studies was compiled to document improvements in patient outcomes. Goal-directed therapy has been demonstrated to improve patient outcomes when performed within the optimal time frame resulting in decreased complications, reduction in hospital stay, and a decrease in morbidity. Based on the successes in other critical care areas, GDP during cardiopulmonary bypass would be expected to improve outcomes following cardiac surgery. **Keywords:** goal-directed perfusion, goal-directed therapy, cardiopulmonary bypass. *JECT. 2015;47:90–94*

---

Goal-directed therapy (GDT) is a patient care strategy that is designed to improve patient outcomes. This patient care strategy incorporates aggressive patient management and monitoring during periods of critical care. The periods of critical care may include peri-, intra-, or postoperative treatment (1). Early intensive treatment is beneficial when directed toward restoring maximal tissue perfusion through aggressive management of various parameters, which may include cardiac index, oxygen delivery, mean arterial pressure, and fluid therapy (2,3).

GDT has been adapted to the field of perfusion, and many of the physiologic parameters in previous GDT studies are similar to those monitored by perfusionists during cardiopulmonary bypass (4). This new application has been designated “goal-directed perfusion” (GDP) (5). The purpose of this

study is to review GDT research in other areas of critical care management to help understand the GDT process related to perfusion. A conceptual model for this research can be seen in Figure 1.

## HISTORY OF GDT

Dr. William C. Shoemaker was one of the first physicians who study the effects of GDT. In his initial publication in 1988, he reported a trend of decreased mortality following high-risk surgery when focusing on certain critical values. He used the term “supranormal values” to describe the elevated levels of cardiac index, oxygen delivery, and maximal oxygen consumption seen in the survivors (6). Following his observations, GDT was applied to other areas of medicine.

In the field of emergency medicine, improved treatment of septic shock with reduced complications was observed when GDT was applied (7). This was accomplished by augmenting the oxygen delivery index with a combination of intravenous fluids and inotropes (8). One of the earliest and most interesting studies using GDT was in the emergency room before admission to the intensive care unit (ICU) (9).

---

Received for publication December 2, 2014; accepted May 17, 2015.  
Address correspondence to: Joseph J. Sistino, PhD, CCP, Division of Cardiovascular Perfusion, College of Health Professions, Medical University of South Carolina, 151B Rutledge Avenue, MSC 962, Charleston, SC 29425.  
E-mail: sistinoj@musc.edu

The senior author has stated that the authors have reported no material, financial, or other relationship with any healthcare-related business or other entity whose products or services are discussed in this paper.

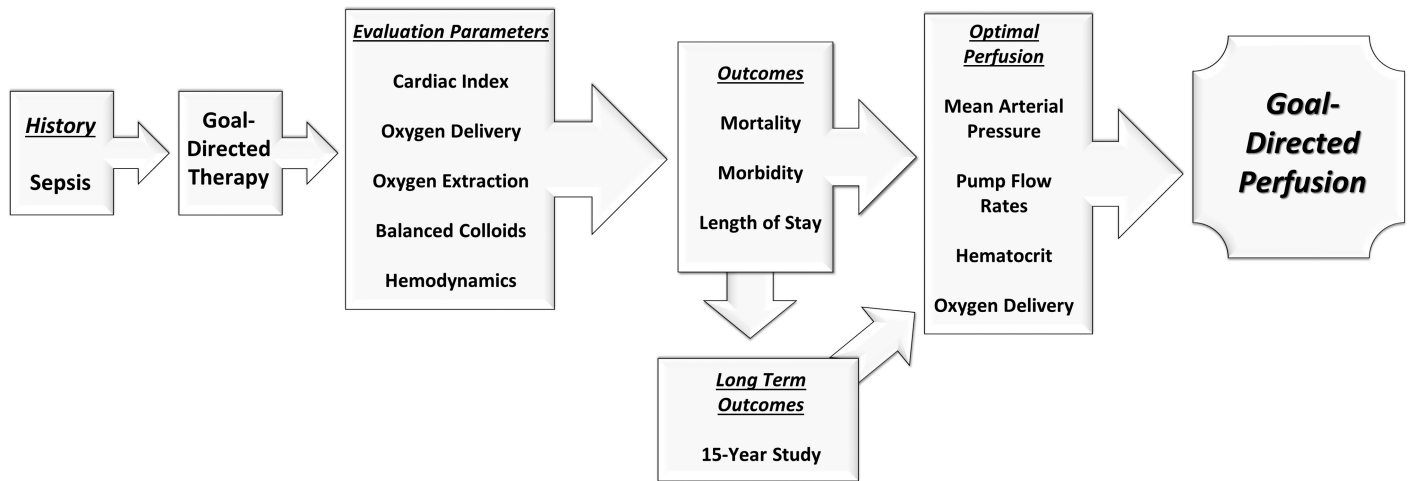


Figure 1. Conceptual model for reviewing goal-directed therapy (GDT).

This application of GDP focused on adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand to improve survival.

**LITERATURE SEARCH**

PubMed was used to search for publications on the subject of GDT and goal-directed perfusion (GDP). The initial search term was “goal-directed perfusion,” which yielded only three articles. The search was then expanded to “goal-directed therapy” combined with “cardiac surgery,” “intra-operative care,” and “high risk surgery.” A total of 1,221 articles were found and 13 were selected for this review on the basis of the inclusion parameters. The inclusion parameters were stroke volume, cardiac index, oxygen delivery, oxygen consumption, and fluid therapy. Three additional

references were identified in the selected papers. A flow chart for the selection of papers can be seen in Figure 2.

**GDT PARAMETERS**

**Balanced Colloid Solution**

GDT using hemodynamic algorithms for the administration of a balanced crystalloid solution vs. a 6% hydroxyethyl starch colloid solution was reported (10,11). This double-blinded study was randomized in 50 patients undergoing major pelvic surgery. Each patient received fluids to optimize stroke volume. Renal function was normal in both groups when fluid administration was targeted to optimize cardiac preload. There was no difference between the patient groups in either ICU or hospital length of stay. However, patients that received a balanced colloid solution had an increased stroke volume with less fluid administration and required less units of fresh frozen plasma compared with those that received the crystalloid solution.

**Oxygen Extraction Ratio**

GDT using the oxygen extraction ratio ( $O_2ER$ ) as a measure of tissue hypoxia leading to organ dysfunction was reported. All patients received treatment to maintain a mean arterial pressure >80 mmHg and urinary output >.5 mL/kg/h. The study group was treated to maintain an  $O_2ER < 27%$  (11). In this randomized study, the primary outcomes were the rate of postoperative organ failure and the length of hospital stay. The results revealed that overall mortality was the same in both groups. However, there were significantly less patients with single organ failure or multiple organ system failure in the study group. This resulted in a decrease in the length of hospital stay for the study group.

**Hemodynamic Algorithm**

This study looked at a combination of functional and volumetric parameters to improve outcomes in cardiac

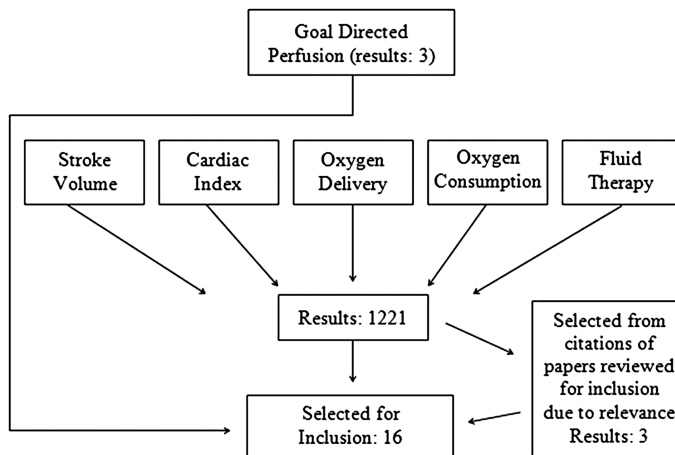


Figure 2. Flow chart for selection of research papers related to goal-directed therapy (GDT).

surgery patients (12). A prospective trial was conducted in patients who underwent either a coronary artery bypass grafting (CABG) procedure, an aortic valve replacement (AVR) procedure, or combined AVR/CABG procedures. Fifty patients were randomized into two groups. In the control group, the mean arterial pressure (MAP) was maintained greater than 65 mmHg and central venous pressure (CVP) greater than 8 mmHg. The study group had hemodynamic therapy guided by stroke volume, end-diastolic volume index, mean arterial pressure, and cardiac index. Therapy started after induction of anesthesia and continued until ICU discharge. The study group had significantly lower intraoperative norepinephrine requirements, decreased postoperative complications, and a reduction in ICU length of stay.

### Review of GDT in Cardiac Surgery

A review paper for the use of GDT in cardiac surgery included five studies. Patient mortality and morbidity following cardiac surgery were studied related to the pH of gut mucosa, stroke volume index, cardiac index, systemic vascular resistance, and oxygen delivery (1). This review article concluded that even if GDT does not reduce postoperative mortality, it does reduce morbidity and therefore warrants inclusion in high-risk patients.

### Meta-Analysis GDT

A meta-analysis was done to determine the effects of perioperative GDT on mortality and morbidity in cardiac and vascular surgery (13). Their search consisted of key words including “cardiac index, oxygen delivery, oxygen consumption, stroke volume, fluid therapy, and fluid loading.” Eleven articles were included in the analysis ( $n = 1,179$  patients). Patients were randomized to either perioperative GDT or routine hemodynamic management. The results demonstrated that perioperative GDT did not reduce mortality following cardiac or vascular surgery and there were no significant reduction in complications in the vascular surgery patients. However, GDT significantly reduced the number of complications in cardiac surgery patients with an odds ratio of .35 (13).

A second meta-analysis was conducted to determine if GDT could reduce surgical mortality, morbidity, and length of hospital stay in cardiac surgical patients (14). Although there was no significant reduction in mortality, GDT significantly reduced postoperative complications and the length of hospital stay.

### Long-Term Outcome

One experimental study in cardiac surgery patients in whom GDT was used demonstrated a significant reduction in mortality (15). In a long-term follow-up (15 years) of these patients, survival was significantly greater in the study group (16). Of the GDT patients, 20.7% were still alive vs. 7.5% of the control group (16). Long-term survival was

associated with three independent factors; age, randomization to GDT, and the avoidance of significant postoperative cardiac complications. Although many papers do not demonstrate an improvement in short-term survival, GDT is associated with a reduction in complications, which significantly improves long-term survival.

## GOAL-DIRECTED PERFUSION

GDT has been practiced for nearly 30 years, but it still remains to be determined if there is a significant role for GDT in perfusion. The role of the perfusionist in providing cardiopulmonary support has been historically outlined in broad terms (17), but is continually being redefined as evidence-based patient care is updated (5).

GDP aims to use intensive monitoring during cardiopulmonary bypass (CPB) to reduce mortality and postoperative complications. Perfusionists have the opportunity to administer therapy to patients intraoperatively, which is one of the most critical times for GDT. There have been many advances in perfusion to improve the mortality and the morbidity of the patients undergoing cardiac surgery, and these should be included as part of GDP (5,15,18).

New guidelines and standards for perfusionists were published in 2013 by the American Society of ExtraCorporal Technology (4). These guidelines include standards for the perfusionist to minimize prime volume, evaluate and optimize gas exchange, and calculate oxygen delivery and consumption for each patient. Though these guidelines are in strong agreement and promote the philosophy of GDP, they do not give suggested values or parameters for perfusionists to take into consideration for patient care while on CPB.

## OPTIMAL PERFUSION

Clinical evidence can be used to guide CPB parameters to achieve “optimal” perfusion (19). Optimal perfusion requires intensive and focused monitoring to maintain the desired parameters within a very narrow therapeutic range for each individual patient. This goal-directed patient management should be associated with optimal oxygen delivery ( $DO_2$ ) and tissue perfusion with reduced inflammatory response, preservation of the coagulation cascade, maintenance of colloid oncotic pressure, and fluid balance. This results in “the best long-term patient outcome in terms of survival and function of all major organ systems” resulting in low morbidity and reduced postoperative recovery periods (19).

### Optimal Mean Arterial Pressure

A randomized study of patients assigned to either high (>70 mmHg) or low (50–60 mmHg) mean arterial pressures

on CPB was conducted for patients undergoing CABG. The study concluded that there were improved short- and long-term outcomes in the higher pressure group. Mortality rates in this group were approximately 50% less than the lower pressure group and the incident of stroke was three times lower. Cardiac and neurological complications were two and one-half lower as well (20).

### Optimal Arterial Blood Flow

Arterial blood flow rates to deliver optimal tissue perfusion were evaluated. The most commonly used flow rates during CPB ranged from 2.2 to 2.5 L/min/m<sup>2</sup> (21). High and low flow rates were examined in various clinical experiments with inconclusive results on the optimal flow for all patients. It was suggested that lower pump flows may compromise visceral organs because of the lower blood flow to these areas.

### Optimal Hematocrit

The optimal hematocrit during CPB appears to be above 23–24% in both adult and pediatric patients (21,22). The studies reviewed showed that hematocrits below this level trended toward increased morbidity and mortality, with significant association of postoperative complications including in-hospital mortality ( $p < .001$ ), intra- or postoperative placement of an intra-aortic balloon pump ( $p < .001$ ) and return to CPB after initial separation ( $p < .001$ ). It was found that in the adult patients whose hematocrit was less than 19%, there was an approximate 100% increase in morbidity (21). However, increasing the hematocrit with the transfusion of packed red blood cells is associated with its own risks, including mortality, renal failure, prolonged ventilatory support, serious infection, cardiac complications, and neurological events (23).

### Optimal Oxygen Delivery

It is difficult to evaluate both optimal flow rate and hematocrit independently because they both influence oxygen delivery. Therefore DO<sub>2</sub> must be considered as one of the most significant determinants of “optimal” perfusion during CPB. Targeting DO<sub>2</sub> levels above a critical threshold (>262 mL/min/m<sup>2</sup>) is more important in preserving organ function than targeting individual hematocrit or pump flow values (5). Even though critical values for DO<sub>2</sub> have been determined, it was also noted that normally accepted whole body DO<sub>2</sub> values may not ensure that all organs are being optimally perfused. Studies have shown a reduction in renal complications associated with the use of increased oxygen delivery above this critical threshold (24). This provides strong evidence of the importance of this parameter in optimizing tissue perfusion and is consistent with earlier publications describing oxygen plateauing (25).

## DISCUSSION

Although some of the information provided in the review of optimal perfusion parameters may seem contradictory, we must also consider differences in patients. GDP aims to deliver specialized care to each patient on the basis of their unique history and distinct needs. Individualized patient care is critical to reducing postoperative complications and mortality. GDP can target individual patient requirements by making focused, micro-level adjustments based on the needs of a specific patient. It takes into account real-time values of the patient and can use computer-based notification when critical values are trending outside their accepted ranges. Increased use of electronic medical records will allow perfusionists to improve patient management in a more proactive manner, rather than identifying outlying parameters when reviewing the perfusion record following the procedure. GDT applied to perfusion provides a new opportunity to improve patient care during the critical period of cardiac surgery.

## CONCLUSION

GDT has provided a strong basis for the development of GDP. Many studies have attempted to determine optimal patient management parameters; however, newer evidence has shown that intensive monitoring of key parameters during critical periods of patient treatment have a profound impact on improving long-term survival.

## REFERENCES

1. Ferguson BD, Manecke GR Jr. Goal-directed therapy in cardiac surgery: Are we there yet? *J Cardiothorac Vasc Anesth.* 2013;27:1075–8.
2. De Backer D, Aldecoa C, Njimi H, Vincent JL. Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis. *Crit Care Med.* 2012;40:725–30.
3. Ekbal NJ, Dyson A, Black C, Singer M. Monitoring tissue perfusion, oxygenation, and metabolism in critically ill patients. *Chest.* 2013;143:1799–808.
4. Baker RA, Bronson SL, Dickinson TA, et al. Report from AmSECT's International Consortium for Evidence-Based Perfusion: American Society of Extracorporeal Technology Standards and Guidelines for Perfusion Practice: 2013. *J Extra Corpor Technol.* 2013;45:156–66.
5. de Somer F, Mulholland JW, Bryan MR, Aloisio T, Van Nooten GJ, Ranucci M. O<sub>2</sub> delivery and CO<sub>2</sub> production during cardiopulmonary bypass as determinants of acute kidney injury: Time for a goal-directed perfusion management? *Crit Care.* 2011;15:R192.
6. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest.* 1988;94:1176–86.
7. Otero RM, Nguyen HB, Huang DT, et al. Early goal-directed therapy in severe sepsis and septic shock revisited: Concepts, controversies, and contemporary findings. *Chest.* 2006;130:1579–95.
8. 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.
9. 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;345:1368–77.

10. Feldheiser A, Pavlova V, Bonomo T, et al. Balanced crystalloid compared with balanced colloid solution using a goal-directed haemodynamic algorithm. *Br J Anaesth*. 2013;110:231–40.
11. Donati A, Loggi S, Preiser JC, et al. Goal-directed intraoperative therapy reduces morbidity and length of hospital stay in high-risk surgical patients. *Chest*. 2007;132:1817–24.
12. Goepfert MS, Richter HP, Zu Eulenburg C, et al. Individually optimized hemodynamic therapy reduces complications and length of stay in the intensive care unit: A prospective, randomized controlled trial. *Anesthesiology*. 2013;119:824–36.
13. Giglio M, Dalfino L, Puntillo F, Rubino G, Marucci M, Brienza N. Haemodynamic goal-directed therapy in cardiac and vascular surgery. A systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg*. 2012;15:878–87.
14. Aya HD, Cecconi M, Hamilton M, Rhodes A. Goal-directed therapy in cardiac surgery: A systematic review and meta-analysis. *Br J Anaesth*. 2013;110:510–7.
15. Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA*. 1993;270:2699–707.
16. Rhodes A, Cecconi M, Hamilton M, et al. Goal-directed therapy in high-risk surgical patients: A 15-year follow-up study. *Intensive Care Med*. 2010;36:1327–32.
17. Perfusion TCSoc. Role of the Perfusionist 1988. Available at: <https://www.cscp.ca/english/documents/RoleofthePerfusionist.pdf>. Accessed December 12, 2013.
18. Jameel S, Colah S, Klein AA. Recent advances in cardiopulmonary bypass techniques. *Contin Educ Anaesth Crit Care Pain*. 2009;10:20–3.
19. Murphy GS, Hessel EA 2nd, Groom RC. Optimal perfusion during cardiopulmonary bypass: An evidence-based approach. *Anesth Analg*. 2009;108:1394–417.
20. Gold JP, Charlson ME, Williams-Russo P, et al. Improvement of outcomes after coronary artery bypass. A randomized trial comparing intraoperative high versus low mean arterial pressure. *J Thorac Cardiovasc Surg*. 1995;110:1302–11, discussion 11–4.
21. DeFoe GR, Ross CS, Olmstead EM, et al. Lowest hematocrit on bypass and adverse outcomes associated with coronary artery bypass grafting. Northern New England Cardiovascular Disease Study Group. *Ann Thorac Surg*. 2001;71:769–76.
22. Wypij D, Jonas RA, Bellinger DC, et al. The effect of hematocrit during hypothermic cardiopulmonary bypass in infant heart surgery: Results from the combined Boston hematocrit trials. *J Thorac Cardiovasc Surg*. 2008;135:355–60.
23. Koch CG, Li L, Duncan AI, et al. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. *Crit Care Med*. 2006;34:1608–16.
24. Ranucci M, Romitti F, Isgro G, et al. Oxygen delivery during cardiopulmonary bypass and acute renal failure after coronary operations. *Ann Thorac Surg*. 2005;80:2213–20.
25. Mandl JP, Motley JR. Oxygen consumption plateauing: A better method of achieving optimum perfusion. 1979. *J Extra Corpor Technol*. 2008;40:281–9.