

AZRIEL PEREL

Department of Anaesthesiology and Intensive Care, Sheba Medical Center,
Sackler School of Medicine, Tel-Aviv University
Tel-Aviv, Israel

Saturday May 28, 2005

14:00-14:45

Room H

WHAT IS GOAL-DIRECTED THERAPY?

The term 'goal-directed therapy' in anaesthesia and intensive care is currently applied to describe therapeutic strategies that focus on the achievement of pre-defined values for physiological parameters with the aim of improving patient outcome. However, defining a therapeutic strategy aimed at obtaining specific physiological end-points is not a simple endeavor. This difficulty can be illustrated by the simple example of the goal-directed approach we normally employ to keep vital signs within a normal range during the management of anaesthesia. Even this very mundane aspect of our practice already presents us with the need to define the acceptable ranges of vital signs during anaesthesia. These ranges, as well as the upper limit for the systolic arterial pressure, have been found to vary according the type of patient and the anesthesiologist's personal approach.

A number of goal-directed approaches have been proposed in recent years for the haemodynamic management of high-risk surgical patients in order to decrease major complications and even death after various types of surgical procedures [1-4]. The rationale behind the claimed benefit of perioperative 'optimization' is that major surgery generates a strong systemic inflammatory response and an overall substantial increase in oxygen demand, which is normally met by increases in cardiac output (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. The gut has been specifically shown to be sensitive to hypoperfusion. Inadequate splanchnic perfusion may disrupt the enteric mucosal barrier, leading to translocation of endotoxin and microorganisms into the circulation, the initiation of the cytokine pathway, and to an increased risk of sepsis and multiple organ failure. Low gastric mucosal pH (pHi) and increased gastric luminal CO₂ tension have been shown to be highly predictive of postoperative complications. When oxygen demands are not met, anaerobic metabolic pathways are activated, leading to the generation of hydrogen ions and lactic acid. Goal-directed therapy may prevent or minimize the imbalance (the oxygen debt) between oxygen delivery (DO₂) and oxygen consumption (VO₂). However, increasing DO₂ may not necessarily increase in VO₂ even in the presence of an oxygen debt due to an inability of the tissues to extract or utilize oxygen as may happen during sepsis. The relationships between DO₂, VO₂ and oxygen extraction, and their relevance to the care of the critically ill, have been very recently reviewed [5].

Unlike approaches that adopt a specific clinical practice like increased preoperative fluid loading or, on the contrary, a restrictive fluid regimen, goal-directed approaches employ various monitoring techniques and interventions in order to achieve specific end-points for the cardiac index (CI), stroke volume (SV), oxygen delivery (DO₂), mixed venous (SvO₂) or central venous (ScvO₂) oxygen saturation, lactate concentration, or pHi. Since goal-directed approaches are generally more invasive, costly and time-consuming, the justification for their use has to be clearly confirmed. However, the many studies that examined this issue have produced contradictory results. A critical evaluation of the relevant literature should therefore include the following: (a) what was the effect of the selected approach on patient outcome; (b) patient population; (c) type of surgery; (d) targeted parameter(s); (e) specific selected end-points; (f) interventions used to attain the goal; (g) timing of intervention; (h) how often were the goals actually met during the study.

EARLIER STUDIES

The modern concept of goal-directed therapy started with the studies of Bland [6] and Shoemaker [7]. In critically ill surgical patients, Bland et al have found that in comparison to survivors, the non-survivors generally had (a) reduced myocardial performance as judged by lower CI in the presence of high filling pressures; (b) impaired oxygenation; (c) pulmonary vasoconstriction; (d) decreased DO_2 despite normal O_2 saturation and hemoglobin values [6]. In a later study, high-risk surgical patients were randomized to achieve standard clinical values as therapeutic goals using either a CVP or a pulmonary artery catheter (PAC). In a third protocol group supra-normal levels of CI ($> 4.5 \text{ L/min/m}^2$) and DO_2 ($> 600 \text{ ml/min/m}^2$) were achieved with fluid loading, packed red blood cells, inotropes and vasodilators [7]. Mortality was 33% and 23% in the PAC and CVP control groups, respectively, and only 4% in the protocol group, which also had a significant reduction of major complications and of ICU length of stay [7]. Following these studies, these values of CI and DO_2 are commonly referred to as supra-normal haemodynamic values. These studies have also established the criteria for the definition of the high-risk surgical patient (see appendix in ref. 15). Later studies have examined the benefit of goal-directed therapy in other surgical populations as well.

EVIDENCE SUPPORTING THE USE OF PERIOPERATIVE GOAL-DIRECTED THERAPY

Boyd and colleagues have used a deliberate strategy to increase DO_2 perioperatively, using a dopexamine hydrochloride infusion in high-risk surgical patients [8]. The dopexamine protocol group had significantly higher DO_2 pre- and postoperatively, and had a 75% reduction in mortality (5.7% vs. 22.2%), as well as a decrease in the number of complications. In patients undergoing elective high-risk surgery, Wilson and colleagues have administered either epinephrine or dopexamine by double-blind infusion to a target $\text{DO}_2 > 600 \text{ ml/min/m}^2$, following preoperative colloid administration to a target pulmonary artery occlusion pressure (PAOP) of 12 mmHg [9]. Compared with hospital mortality of 17% in the control group, the mortality of the protocol groups was only 3%, while morbidity and hospital length of stay were significantly reduced in the dopexamine group [9].

In a smaller study in high-risk patients undergoing major elective surgery, dobutamine was used as the primary inotrope in order to achieve normal ($520\text{--}600 \text{ mL/min/m}^2$) or supra-normal DO_2 [10]. Mortality was reduced from 50% in the control group to 15.7% in the protocol group. In another study of patients undergoing peripheral vascular surgery, fluid loading, vasoactive and inotropic agents were used to achieve more modest end-points, which included a CI greater than 2.8 L/min/m^2 and PAOP of 8–15 mmHg [11]. The patients in the PAC group had fewer adverse intra-operative events, less postoperative cardiac morbidity, less early graft thrombosis and lower mortality [11]. The PAC was also used for preoperative optimization in the ICU, according to the discretion of the attending physicians, prior to major elective surgery [12]. Patients who had normal initial preoperative haemodynamic parameters, or abnormal initial parameters that were normalized preoperatively, experienced significantly fewer perioperative cardiovascular complications than those with abnormal initial values that were not normalized preoperatively [12].

An esophageal Doppler was used in order to maximize SV in patients undergoing repair of proximal femoral fracture, major elective or cardiac surgery (for references of these studies by Sinclair, Gan and McKendry and their colleagues, the reader is referred to the recent review by Davies and Wilson [1]; see also Venn et al, *Br. J. Anaesth.* 2002;88:65-71). These studies have found a higher CO, less overall complications and significantly faster postoperative recovery in the protocol groups compared with the conventionally managed groups. Polonen and colleagues increased DO_2 to achieve $\text{SvO}_2 > 70\%$ and lactate concentration of 2 mmol/L or less, in cardiac surgery patients during the first 8 h in the ICU, and found median hospital stay and morbidity at the time of hospital discharge to be reduced in the protocol group [13]. Mythen and colleagues have optimized SV during cardiac surgery, and found improvement in gastric pHi, lower incidence of postoperative complications and a shorter ICU and hospital stay [14].

The accumulation of evidence showing that increasing DO_2 in high-risk surgical patients may reduce morbidity and save lives have led Boyd and Bennett to claim that it may be considered unethical not to use goal-directed perioperative therapy once patient identification and the methods to be used in treating them are refined [3].

EVIDENCE THAT GOAL-DIRECTED THERAPY MAY NOT BE BENEFICIAL

In a well-controlled multi-center study Takala and colleagues have studied 412 high-risk patients undergoing major abdominal surgery [15]. Patients were preoperatively stabilized to reach $CI \geq 2.5$ L/min/m², mean arterial pressure of 70 mmHg, PAOP ≥ 10 mmHg, Hb of 100 g/L, and SaO₂ of 94%. Once these end-points were reached, patients received placebo, low- or high-dose dopexamine infusion for 24 hrs after surgery. Dopexamine had no effect on organ dysfunction, duration of ICU or hospital stay, or 28 day mortality (13%, 7%, and 15%, for the placebo, low- or high-dose dopexamine groups, respectively). The authors concluded that dopexamine in doses that result in increased CO and DO_2 after preoperative stabilization with fluids does not improve outcome after major abdominal surgery compared with fluids alone [15].

A series of additional studies, done mainly in patients undergoing vascular surgery, have also shown no benefit, and even potential harm, when the goal-directed approach is applied. In separate studies, Valentine, Ziegler and Bender and their colleagues (for references see review by Davies and Wilson [1]), have inserted a PAC prior to vascular surgery in order to 'optimize' PAOP, CI and/or SvO₂. In none of the studies did this preoperative optimization improve patient outcome, although overall mortality was low (<10%). A less well-known study by Sandison and colleagues, examined the outcome of 145 patients undergoing emergency and urgent infra-renal abdominal aortic aneurysm surgery at two hospitals under the care of a single vascular surgeon [16]. PAC was placed in 18% of patients at hospital 1 compared with 96% at hospital 2. However, the hospital that used less PAC's and less intervention (in the form of colloid and inotropes) showed a reduced mortality (9% vs. 28%, $p=0.0068$). Even though patients at hospital 2 received more crystalloids, more colloids (median 4775 vs. 1500 ml) and more inotropes, their incidence of acute renal failure was significantly higher. ICU and hospital length of stay for survivors was longer at hospital 2 as well [16].

Goal-directed therapy guided by a PAC was also examined by Sandham and colleagues in a large randomized trial of 3803 eligible high-risk patients (age ≥ 60 yrs, ASA class 3-4), who were scheduled for urgent or elective major surgery followed by a stay in an ICU, and of which 1994 underwent randomization [17]. End-points in order of priority were DO_2 of 550-600 ml/min/m², CI 3.5-4.5 L/min/m², mean arterial pressure of 70 mmHg, and PAOP of 18 mmHg. In-hospital mortality was similar in the 2 groups (7.7 vs. 7.8%), as well as survival rates at 6 and 12 months, and there was a higher rate of pulmonary embolism in the PAC group. The authors concluded that there is no benefit to therapy directed by PAC over standard care in elderly, high-risk surgical patients [17]. This study was criticized on the grounds that the patients were not very high-risk, and that the goals for the CI and DO_2 were reached in only about 20% of the PAC group preoperatively. In addition, the high incidence of congestive heart failure during the postoperative period in the PAC group, despite frequent use of inotropic support, may have been due to the selection of an 18 mmHg as a target PAOP value. Polanczyk and colleagues have also found a 3-fold increase in incidence of major postoperative cardiac events, increased risk of postoperative congestive heart failure and of major non-cardiac events, in 221 patients (≥ 50 yrs) who were managed with a PAC during elective major non-cardiac surgery, compared with 3838 similar patients that did not have PAC [18]. This has led Dalen to claim that the presence of the PAC may be associated with a more aggressive style of treatment [19].

GOAL-DIRECTED THERAPY IN CRITICALLY ILL PATIENTS

Studies of goal-directed therapy in critically ill patients have also shown conflicting results [20-22]. A thorough literature review is beyond the scope of this chapter, though some studies are worth mentioning in this context. In severely traumatized patients Bishop and colleagues have shown that resuscitation to supra-normal values of CI, DO_2 and VO_2 decreased mortality and organ failure [23]. However, in a similar traumatized patient population, Balogh and colleagues found that 'supra-normal' resuscitation was associated with more fluids, decreased intestinal perfusion, increased incidence of intra-abdominal hypertension and abdominal compartment syndrome, multiple organ failure, and death [24]. The fact that fluid overload may cause intra-abdominal hypertension may explain the increased incidence of renal failure seen occasionally in patients who were subjected to aggressive fluid resuscitation [16].

In a multi-center study Gattinoni and colleagues randomly assigned 762 patients, including patients at high risk after surgery, to one of three treatments designed to achieve a normal CI (2.5-3.5 L/min/m²), a supra-normal CI (> 4.5 L/min/m²) or a normal SvO₂ (>70%) [25]. Only 94.3% of the 'normal CI', 44.9% of the supra-normal CI, and 66.7% of the SvO₂ groups reached their haemodynamic targets. Overall, ICU mortality (about 50%), mortality in patients in whom haemodynamic targets were reached, the number of dysfunctional organs and the length of the stay in the ICU were similar in all three groups. The authors concluded that haemodynamic therapy aimed at achieving supra-normal values for the CI or normal values for the SvO₂ does not reduce morbidity or mortality among critically ill patients. However, in this study, like in many similar ones, many patients who did not have an actual oxygen debt may have suffered potentially negative clinical consequences due to unnecessary fluid loading, blood transfusion, and administration of inotropic medications.

The most acclaimed study of the benefit of goal-directed therapy in critically ill patients was done by Rivers and colleagues [26]. Patients, who arrived at the emergency department with severe sepsis or septic shock, were randomly assigned to receive either six hours of early goal-directed therapy or standard therapy before admission to the ICU. The protocol included (a) fluid boluses to achieve a CVP of 8-12 mmHg; (b) vaso-pressors or vasodilators to keep mean arterial pressure more than 65 mmHg and less than 90 mmHg; (c) if the ScvO₂ was less than 70%, red cells were transfused to achieve a haematocrit of at least 30%, followed by incremental dobutamine administration to a target ScvO₂ ≥70%. In-hospital mortality was 30.5% in the early goal-directed therapy group, as compared with 46.5% in the standard therapy group (p= 0.009). During the interval from 7 to 72 hours, early goal-directed therapy was associated with significantly lower mean APACHE II scores, lower lactate concentration, and a higher pH. Even though it is too early, and to my mind unjustified, to extrapolate the results of the Rivers study from patients in early sepsis to other populations of critically ill patients, this study has reinforced the notion that goal-directed therapy has an important role in the care of the critically ill. The therapeutic goals applied by Rivers and colleagues have been adopted by the Surviving Sepsis Campaign [27], and serve as a basis for the recently updated practice parameters for haemodynamic support of sepsis in adult patients [28].

CLINICAL IMPLICATIONS

The expansion of circulating blood volume in order to increase tissue perfusion may be crucial for the individual high-risk surgical patient, especially when applied preoperatively. However, a deliberate attempt to increase oxygen delivery has never won widespread approval and cannot be recommended as a standard of care. In fact, it is still unclear whether the association of supra-normal values with improved survival is not due simply to the fact that survivors are more likely to develop a high CO, while sicker patients, who are naturally at a greater risk, are simply unable to generate these high CO values [5]. Aggressive therapy that is intended to achieve supra-normal values may be harmful in some cases, a fact that may explain the reported increased mortality associated with the use of the PAC in some studies. The conflicting evidence in the literature can be explained by the different patient populations studied, and by the different, and at times flawed, methodologies that have been applied in the various studies. In particular, important co-interventions may have affected outcome in some of these studies.

In the meantime, it seems that the ongoing debate on the benefit of perioperative optimization has affected our fluid management in general, as attested by recent studies that advocate a very liberal fluid administration even in low risk procedures such as laparoscopic cholecystectomy and ambulatory procedures. The over hydration of surgical patients is not without risk, as has been pointed out in a recent study by Brandstrup and colleagues [29]. In a randomized observer-blinded multi-center trial in patients undergoing elective colo-rectal surgery, a restricted intravenous fluid regimen, aimed at unchanged body weight, was found to significantly reduce cardiopulmonary and tissue-healing complications, anastomotic leakage, sepsis, bleeding, pulmonary edema, ventricular arrhythmia, bradycardia, and stroke. No patients died in the restricted group compared with 4 deaths in the standard group [29]. This is a thought-provoking article that should make us re-examine whether we have indeed started to underestimate the effects of fluid overload even in patients undergoing medium-risk surgery (see also editorial by Kudsk KA, *Ann Surg* 2003;238:649, and comments to the Brandstrup paper in *Ann Surg* 2004;240:384-8).

Another important point in applying the goal-directed approach is the type of the monitoring utilised, the selected parameters and the targeted end-points. The limitations of our commonly used monitoring tools have to be well realized. The reliance on the measurement of filling pressures as indicators of cardiac preload is still a mainstay in recently published guidelines [27,28], though these parameters have been repeatedly shown to reflect preload poorly. Hence, resuscitating a patient to obtain a certain value of CVP or PAOP may lead, in some cases, to incomplete fluid replacement or, conversely, to detrimental fluid overload. Similarly, a low SvO₂ or ScvO₂ value, though indicative of a low CO in most cases, does not offer information as to the source of the problem, namely, is it due to decreased preload or decreased cardiac function. On the other hand, the gradual abandonment of the PAC as the standard tool for the measurement of CO has led, in many cases, to the unjustified lack of monitoring, even when seemingly indicated. The lack of unequivocal evidence as to the benefit of specific target end-points of resuscitation should not preclude the use of advanced, less-invasive monitoring tools for the identification of an inappropriately low cardiac preload, contractility and output, in the high-risk surgical patient. Goal-directed therapy will certainly become an integral part of anesthetic management once we are able to better identify patients at risk, to better and more easily monitor haemodynamic status and tissue perfusion, and to better understand the complex relationship between what we monitor and what we do to patient outcome.

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