Flow-directed vs. goal-directed strategy for management of hemodynamics

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Purpose of review
For the past 15 years, there has been a strong push to use goal-directed protocols for resuscitating critically ill patients and to manage perioperative patients. However, recent large clinical trials have failed to find evidence of improved outcome with this approach.

Recent findings
A striking feature in the recent three large prospective randomized trials of septic patients and the one in high-risk perioperative patients is that outcomes in the control groups have markedly improved. This implies improvement in care and clinical acumen. Perhaps the clinical approach should be more toward further helping clinicians with their clinical choices. A good example is cardiac output. The objective of most hemodynamic interventions is to increase cardiac output. It would thus make sense to assess what happened to cardiac output after the intervention to determine if the intervention actually increased cardiac output. If it did not, another therapy should be chosen. I call this a flow-directed responsive protocol.

Summary
A clinical approach that uses monitored values such as cardiac output as a feedback tool to evaluate the response to therapeutic interventions in individual patients may be better than protocols that set fixed targets for all study participants.

Keywords
cardiac output, oxygen delivery, perioperative management, resuscitation, volume management

INTRODUCTION
Choosing appropriate hemodynamic targets for managing septic and perioperative patients remains a challenge. Treatments are ‘technologies’ and it is thus worth considering the words of the late Postman [1], an expert on the study of technologies. Whenever evaluating a new technology the first consideration should be what is the problem to which this technology is a solution? Second, whose problem is it, and one might add what are the benefits? The next two questions are critical: what new problems might be created by solving the original problem, and which people and what institutions will be most seriously harmed by the new technology?

It is best to separate hemodynamic management into resuscitation vs. management of perioperative patients [2]. The primary goal in resuscitation is to restore matching of oxygen delivery to metabolic needs of tissues. In perioperative patients, the primary goal is to prevent a decline in oxygen delivery relative to tissue needs.

Much of the interest in goal-directed therapy (GDT) began with Shoemaker and coworkers in the 1980s. They found that use of supra-normal values of oxygen delivery reduced postoperative complications in high-risk surgical patients [3]. It was subsequently observed that patients with adult respiratory distress syndrome have increased oxygen demands and also could benefit from supra-normal values of oxygen delivery [4]. However, two large randomized studies in the 1990s on septic patients found that this strategy was either harmful or of no benefit [5,6], although a benefit was found in perioperative patients [7].

In 2001, Rivers et al. [8] published a landmark study on early GDT for patients with septic shock in the emergency department. Based on the very positive results in this study, the concept was
Oxygen delivery is the product of cardiac output (Q), hemoglobin concentration (Hb), a constant for the amount of oxygen per gram of hemoglobin (range 1.34–1.39 ml/gm Hb) and arterial oxygen saturation ($Sat_a$), which in turn is determined by the partial pressure of oxygen ($PO_2$). Q can be increased by a decrease in afterload or an increase in heart rate (HR), contractility, or volume (increased preload). The percentage changes in any of the three variables equally affect oxygen delivery. The variable with the greatest potential impact on oxygen delivery is Q. The $^*$ indicates the dominant factors affecting Q.

### PHYSIOLOGICAL BACKGROUND

A mismatch of oxygen delivery and tissue needs can occur because not enough oxygen is delivered or because the oxygen is not delivered to the places that need it. The latter can be because of mal-distribution of the delivered oxygen or because tissues are unable to utilize the oxygen. These states usually present with a low systemic vascular resistance and a normal or more often oxygen delivery. As cardiac output is the major determinant of oxygen delivery, and systemic vascular resistance is calculated, cardiac output can be used to separate these two processes. A low cardiac output indicates that it is the primary problem, assuming that there is no severe hypoxemia or anemia, and therapy should be aimed at increasing it. A normal or elevated cardiac output indicates a primary utilization problem and therapy should be directed primarily at improving the distribution of flow although increasing oxygen delivery can still be helpful because demands are usually higher than normal.

Oxygen delivery is the product of cardiac output, hemoglobin concentration, and the oxygen saturation of hemoglobin (Fig. 1). Thus only these three variables can be manipulated to correct inadequate oxygen delivery. The same percentage change in any of these equally alters oxygen delivery. For example, increasing oxygen saturation from 90 to 99%, hemoglobin from 90 to 99 g/l or cardiac index (CI) from 2.0 to 2.21/min/m² equally change oxygen delivery. Although changes in oxygen saturation and hemoglobin concentration of these magnitudes may be comforting to the bedside team, a change in CI of this magnitude is not impressive and is below the magnitude of change often used to indicate that CI truly increased [23]. It thus becomes apparent that the major variable that can be manipulated to improve oxygen delivery is cardiac output.

Cardiac output is determined by heart rate and stroke volume and stroke volume is determined by preload, afterload, and contractility. Heart rate already is elevated in most patients. Blood pressure is usually low so that afterload reduction is not an option although this raises the question as to what should be the blood pressure (BP) target [24]. This means that the only two substantial clinical options are to increase preload with volume or contractility with an inotrope. Of importance, the therapeutic goal is not to increase cardiac ‘function’ but to increase cardiac ‘output’ [25]. It has become evident that too little or too much fluid worsens outcomes [26–30]. Thus algorithms for fluid management must try to ensure that enough volume is given but also when to switch to pharmacological therapy.

There are important limits to the use of volume. Only 25–30% of total blood volume, that is, 1300–1400 ml, stresses blood vessels and determines blood
flow [31]. Thus only a small proportion of an infusion greater than 10 ml/kg remains in the vasculature. Increasing blood volume also increases capillary hydrostatic pressure and capillary filtration. Finally, not a lot of volume is needed to test volume responsiveness. If the cardiac function plateau is at a central venous pressure (CVP) of 10 mmHg and cardiac output is 51/min, the cardiac output should go up by 0.5 l/min for each 1 mmHg increase in CVP and this is an underestimate of the potential increase because this calculation is not limited to the steep part of the cardiac function curve and the plateau of the function curve is often below 10 mmHg.

**GOAL-DIRECTED THERAPY IN SEVERE SEPSIS**

The archetypical example of GDT is the study by Rivers et al. [8] in which study participants with severe sepsis in the emergency department were randomized to early GDT protocol or standard care. Because of the marked improvement in survival the protocol was quickly adopted as the standard of care [9]. Study participants had to meet the broad systemic inflammatory response criteria [32] and have either a SBP less than 90 mmHg after a fluid bolus of 20–30 ml/kg or a lactate more than 4 mmol/l. Only about half were actually hypotensive as was the case in Protocol-based Care for Early Septic Shock (PROCESS) [12] and Protocolized Management in Sepsis (PROMISE) [13], whereas 70% of were hypotensive in Australasian Resuscitation in Sepsis Evaluation (ARISE) [14]. They first gave 500 ml of crystalloid every 30 min to achieve a CVP of 8–12 mmHg. Thus CVP acted as a goal in and of itself. The next goal was to keep mean arterial BP between 65 and 90 mmHg, which was achieved by giving norepinephrine if mean pressure was less than 65 and a vasodilator if more than 90 mmHg. The third key goal was to maintain central venous oxygen saturation at 70% or higher. If it was less than 70% and hematocrit less than 30 blood was transfused. If that did not work, the inotrope dobutamine was infused.

Three large trials PROCESS [12], PROMISE [13], and ARISE [14] re-evaluated this approach. There was not even a tendency for a benefit in GDT subject but overall mortality was more than 40% lower than the mortality in the treated group of the Rivers study (~20% vs. 35%). Although the protocols were the same and baseline characteristics similar, treatments were different in the later studies. Approximately, 13 l of fluid were given in the Rivers trial over 72 h but only 5–8 l in the other three. Approximately, 30% received vasopressors in the first 6 h in the Rivers trial, whereas 50–60% received vasopressors in the later studies and 20% received vasopressors in ARISE and PROCESS even before being enrolled. There also were large differences in the use of blood transfusions even though the initial hematocrits were similar.

What lessons can to be learned? First, use of CVP as a goal in and of itself can lead to excess use of fluid and this larger amount of fluid does not improve survival. As volume responsiveness was not considered it is likely that a large percentage of patients were on the flat part of the cardiac function curve. In this situation, raising CVP just increases vascular leak which could itself have led to more fluid administration. The decreased use of volume and greater use of vasopressors in the subsequent studies indicates a change in physicians’ approach and that even with a rigid protocol there is a subjective component. For example, what does the clinician do if the CVP reached 8 mmHg and was 7 mmHg 5 min later? Rigid adherence to the protocol would require another bolus. This would happen if the clinician’s bias was toward use of volume but would not if the clinician’s bias was for less volume.

Overemphasis on central venous saturation may also have been an issue. When patients start to stabilize central venous saturation can fall because of a rise in oxygen consumption because of increased wakefulness and or even repayment of oxygen debt. These do not require the physician to drive the system higher. Finally, although central venous saturation can be related to flow, it is not flow. During exercise, cardiac output increases with a large fall in mixed venous oxygen saturation.

**GOAL-DIRECTED APPROACH WITH FLOW MEASUREMENT IN SURGICAL PATIENTS**

The recent publication by Pearse et al. [20] is a good example of GDT in perioperative study participants. These investigators have had a long interest in this subject [7,10]. In this study, they used a larger population and a composite end point but failed to find a benefit for GDT. As in the sepsis trials, mortality and morbidity of the control group markedly decreased over the past 20 years and the study was very underpowered. The control mortality was 22% in 1993 [7], 15% in 2005 [10], and 3% in 2014 [20]. This again indicates an important change in clinical practice. Of note the devices that were used to measure cardiac output were progressively less accurate, in the first a pulmonary artery catheter, in the second lithium dilution, and in the most recent study the pulse contour method. This suggests that it may be more important to follow trends than having an accurate value of cardiac output.
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It is useful to review the steps in the protocol. The two primary interventions in the GDT group were a continuous infusion of the inotropic drug doxapamine, and keeping stroke volume on the flat part of the cardiac function curve which was established at the start of the case by giving boluses of colloids until there was no further increase in stroke volume. However, the heart normally functions on the ascending part of the cardiac function curve, which allows rapid fine adjustments through the Starling mechanism. When the heart is on the flat part of the Starling curve only an increase in heart rate or contractility or a decrease in afterload can increase cardiac output and they require neurohumeral mechanisms. Furthermore, oxygen delivery is dependent upon cardiac output and not just stroke volume. An increase in heart rate with an increase in wakefulness or other factors [33] can decrease stroke volume without a decrease or even an increase in cardiac output. The use of a percentage change in stroke volume also is a potential problem. Patients with low stroke volumes require smaller absolute changes in stroke volume to be called fluid responsive but are also more likely to have depressed cardiac function and be better treated with an inotrope. These same criticisms apply to studies that have used Doppler technology [2,11,16,34–39] and respiratory changes in stroke volume, pulse pressure, or the amplitude of the pulse oximetry wave [40–43]. The use with Doppler probes of a corrected flow time more than 350 ms to indicate maximal left ventricular filling has its own problems. A low corrected flow time can occur because of right heart limitation, in which case more volume will not help. Right heart dysfunction is not common in general surgical patients but is frequent after cardiac surgery and in septic patients.

A fundamental question to ask is do most patients actually need the therapy? If vital signs are stable and there are no signs of decreased tissue perfusion most patients will likely do well without an intervention as indicated by the control group. However, it must be noted that in most of these studies there were no obvious signs of harm from the protocols [44] although harm has been seen [16]. There also was a trend in a number of these studies for a reduced rate of infections [45]. This benefit could have been because tissue perfusion was higher in the protocol group but could equally be because of undertreatment of control patients. If the latter is the explanation a better solution would be to identify undertreated patients rather overtreat all patients.

Maximization of cardiac filling is a common feature of GDT. However, the circulatory system is designed to naturally respond to increased needs. Most therapies likely increase oxygen delivery by no more than 50% but oxygen delivery can increase more than five-fold at peak aerobic exercise without an intravenous bolus of fluid! Reflex adjustments may be blunted in the anesthetized patient but reserves still are very large.

One of the biggest problems with GDT is the validity, reliability, and accuracy of the chosen end points as guides to therapy [2]. It also seems to be the case from the studies over the last 20 years that less is better [46]. Perhaps rather than having protocols that target unsubstantiated end points, protocols should be designed to identify deterioration from normal and monitor the effectiveness of the treatments used to try to restore normalcy. Perioperative patients start from a relatively normal state and it is possible to assess decreases in function from their normal baseline state. Volume losses can be followed or at least predicted depending upon what happens during the operation. During active resuscitation, protocols should aim to correct an inadequate state rather than target a specific value. The monitoring device should be used to determine if the therapy actually corrected the identified abnormality. For example, if hypotension is the problem, did the therapy correct the hypotension? If the problem is lactic acidosis, did the therapy correct the acidosis? If treatment was aimed at increasing cardiac output, did cardiac output or at least a surrogate improve?

FLOW-DIRECTED RESPONSIVE APPROACH

We applied the concept of a flow-directed responsive approach in a study in which we compared use of hydroxyethyl starches with crystalloid solutions for the hemodynamic management of patients following cardiac surgery (Fig. 2) [47,48]. Cardiac output was measured with a pulmonary artery catheter but the same approach likely could be used with any device that measures cardiac output. Rather than have ‘goals’, fluid was given based on four ‘triggers’ which indicated clinical states that were below acceptable values and might benefit by giving volume to increase cardiac output. One trigger was a CI less than 2.2 l/min/m² which was used to indicate the lowest acceptable value rather than a higher than normal target as used in GDT. The others were SBP or mean arterial BP below a target chosen by the treating team, a CVP less than 3 mmHg (based on a level 5 cm below the sternal angle), and a urine output less than 20 ml/h. Most boluses were given either for a low CI or BP below the target (86%) [47]. Central venous oxygen saturation was not a trigger. Before volume was given,
major hemorrhage was excluded as well as a hyperdynamic state based on a CI more than 4 l/min/m^2 and likely right ventricular volume limitation based on CVP more than 12 mmHg [49]. If no exclusions were present a 250 ml fluid bolus was given.

The next step is the essence of a ‘responsive’ protocol. Following the bolus CI and CVP were reviewed. If CI rose by at least 0.3 l/min/m^2 (10% of a normal value) and the trigger was corrected, nothing else was done except taper inotropes or vasopressor agents if present. If CI increased but the trigger value was not corrected, another bolus was given and with the same algorithm. If CI did not increase, the CVP was checked. If CVP increased by less than 2 mmHg and CI increased by less than 0.3 l/min/m^2 further volume boluses are not given and the abnormality is treated pharmacologically. See text for further details. Reproduced from [48].

CONCLUSION

Over the last 30 years, there have been dramatic improvements in survival of high-risk surgical patients and patients with septic shock but it cannot be attributed to the initially promising GDT protocols because the biggest improvement occurred in the control groups. Perhaps that is the message. Through the previous studies physicians have gotten better at identifying patients’ needs and have learned to respond more quickly. Thus rather than trying to tell physicians what are the appropriate values, perhaps the better approach is to use monitoring tools to indicate downward drifts from baseline values, and even more importantly, as indicators that the chosen therapeutic approach is being an end point except at a very low value, which was necessary to maintain consistency in this experimental study. In practice, however, this value would not necessarily have to be treated vital signs were fine. In this type of protocol, it is the trends and relationship of values to the patient’s clinical status that count rather than a specific value. CVP was a trigger but only a very low value and was included to ensure adequate volume reserves in unstressed and interstitial volume. Even arterial pressure was not a fixed end point but rather a flexible target chosen based on the individual patient’s condition.

FIGURE 2. An example of a flow-directed responsive protocol for guiding fluid management. CI is cardiac index. CVP is central venous pressure. The protocol starts by identifying a ‘trigger’ that could be corrected by giving volume. Likely, maximal cardiac filling or a primary distributive process is next ruled out. After the volume is given the response of CI is checked. If CI did not increase by at least 0.3 l/min/m^2 CVP is checked to see if the volume bolus was adequate. The key box is in the lower left. If CVP rose by at least 2 mmHg and CI increased by less than 0.3 l/min/m^2 further volume boluses are not given.
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doing what it is hypothesized to do. As cardiac output is central to most hemodynamic therapies, measurement of a cardiac response should be a central part of hemodynamic management. An important feedback needs to be the overall clinical impression of the patient’s status which includes basics such as level of wakefulness and mental responsiveness, skin perfusion, urine output in patients with functioning kidneys, and metabolic indicators such as arterial lactate. There is no replacing a physician at the bedside.

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Conflicts of interest

There are no conflicts of interest.

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

13. One of the three recent large randomized trials that repeated the Rivers approach [8] to early GDT for septic patients in the emergency department. There was no improvement in morbidity or mortality with use of the Rivers protocol compared with another protocol group and a control group.
15. One of the three recent large randomized trials that repeated the Rivers approach [8] to early GDT for septic patients in the emergency department. There was no improvement in morbidity or mortality with use of the protocol.
17. One of the three recent large randomized trials that repeated the Rivers approach [8] to early GDT for septic patients in the emergency department. There was no improvement in morbidity or mortality with use of the protocol.
23. This is a preplanned meta-analysis of early GDT in septic patients, which includes the three recent trials. Because it was preplanned the data collection was the same in the three studies.
31. Magder S, De Varennes B. Clinical death and the measurement of stressed indicators such as arterial lactate. There is no replac-


