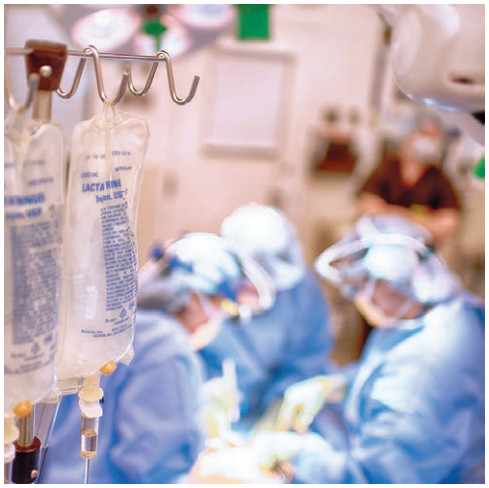
Goal-directed Therapy

Why Benefit Remains Uncertain

Kamal Maheshwari, M.D., M.P.H., Daniel I. Sessler, M.D.

The aim of goal-directed therapy or guided fluid management or individualized fluid management is to maximize oxygen delivery to sensitive tissues by optimizing cardiac output. The underlying basis for all guided fluid management is that optimal vascular volume improves cardiac output, with "optimal" being defined as sufficient volume to bring patients toward the top of the Frank Starling preload-stroke volume curve. In this issue of Anesthesiology, Fischer *et al.*[1] report randomizing 447 intermediate-risk orthopedic surgical patients to routine fluid management or fluid administration guided by the plethysmographic variability index in five French hospitals (the Optimization using the Pleth Variability Index [OPVI] Trial). In patients assigned to guided management, boluses of the colloid Gelofusion 6% were given to keep the plethysmographic variability index less than 13%. Patients received significantly larger amounts of cumulative fluid in the guided management group, 1,088 ± 606 ml *versus* 677 ± 608 ml in the control group. The primary outcome, postoperative hospital length of stay, was similar (6 ± 3 days) in both groups, as were the secondary outcomes including postoperative complications. The authors concluded that plethysmographic variability index–guided fluid management does not shorten the duration of hospitalization or reduce complications.[1]



"...recent robust trials [of goal-directed fluid therapy] with large sample sizes have shown little or no benefit."

Initial reports in critically ill patients showed substantial benefit from goal-directed therapy.[2] Maximizing oxygen delivery to tissue in the setting of high metabolic rate or previous hypoxia (oxygen debt) made sense. But in surgical patients, benefit has been inconsistent. Initial small trials showed substantial benefit, and guidance was therefore incorporated into many enhanced recovery pathways—and even into the British National Institute for Health and Care Excellence guidelines. The difficulty is that recent robust trials with large sample sizes have shown little or no benefit. For example, the Optimization of Perioperative Cardiovascular Management to Improve Surgical Outcome (OPTIMIZE) trial (n = 734) showed that in high-risk surgical patients, cardiac output–guided hemodynamic therapy algorithm did not significantly reduce a composite of serious complications and 30-day mortality compared with usual care.[3] The investigators powered the trial to detect a 25% relative risk reduction in a composite of serious complications from 50 to 38% in the intervention group. However, the actual incidence of complications was only 43% in the usual care patient *versus* 36% in the intervention group (just a 7% absolute risk reduction, number needed to treat =14). Because the incidence of the complications in the usual care group and the difference of complications between groups were both lower than anticipated, the trial was underpowered and the results were not statistically significant. In contrast, the FEDORA investigators reported a statistically significant factor-of-two reduction in complications corresponding to a similar absolute risk reduction of 8% (n = 450).[4] The opposing conclusions from the OPTIMIZE and FEDORA trials highlight the effect of baseline complications rates and absolute risk reduction on the statistical power of trials.

When evaluating goal-directed therapy reports, including those of Fischer *et al.*, we need to consider baseline patient and surgical risk, how fluid responsiveness was assessed and managed, and what outcomes were assessed. Baseline risk

Image: J. P. Rathmell.

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is by far the most important determinant of perioperative complications. The OPVI trial included relatively healthy patients who had routine orthopedic surgery. For example, more than 80% of all patients were designated American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status I or II. Higher-risk patients are more likely to experience complications and possibly benefit more from goal-directed therapy. It therefore remains possible that using plethysmographic variability to guide fluid management will yet prove beneficial in higher-risk patients.

There are now many invasive and noninvasive systems that estimate stroke volume or cardiac output, all of which can be used to guide fluid management. However, the capabilities of each system need to be specifically evaluated; it does not follow that because one system works that others will as well. The fluid management protocol presumably also matters. For example, clinical experience suggests that many protocols are challenging to follow. Perhaps consequently, the goal of less than 13% plethysmographic variability index was actually achieved only a third of the time in the OPVI trial. Limited compliance with the protocol makes it difficult to determine whether comparable results in each group resulted from poor compliance, a failure of the index, or because guided fluid management had limited benefit for the enrolled patients. Automation of fluid management protocols using semi-closed or closed-loop fluid administration platforms may help improve compliance, but whether they will improve patient outcomes is presently unknown.[5]

The theory of goal-directed management is that it guides clinicians to provide the right amount of fluid at the right time. Interestingly, many guided fluid trials—including ones favoring guided fluid management—ended up giving similar amounts of fluid in each group, with benefit attributed to administration timing. For example, the FEDORA[4] trial used esophageal Doppler to guide fluid management and showed reduced postoperative complications and hospital length of stay in low-to-moderate-risk patients who had intermediate-risk surgery. However, the amount of fluid given to the patients in the guided and routine management groups was similar. The fluid volume difference in the OPVI trial was only about 500 ml, which *per se* seems unlikely to have much influence on the duration of hospitalization or risk of complications. In fact, despite a difference of more than 2,000 ml between restrictive and liberal fluid groups, the overall complication incidence was similar in each group although there was more renal injury in patients assigned to restrictive management.[6]

Another factor to consider is that all guided fluid systems are based on reaching the flat portion of the Starling curve, which presumably optimizes cardiovascular performance. But it is likely that vascular volume optimal for the heart is insufficient or excessive for other organs. For example, lower volumes might reduce incisional edema and thereby decrease infectious complications, especially after colon surgery. Conversely, higher vascular volume (and blood pressure) might improve outcomes in patients with some types of intracranial lesions.

And finally, most guided fluid trials—including OPVI—include duration of hospitalization as an outcome, often making it the primary outcome. Hospital length of stay is a reasonable outcome and theoretically reflects a sum of nonroutine events that delay discharge. But duration of hospitalization is also substantially influenced by clinical routine and irrelevant factors including disposition issues. A composite of serious complications is therefore probably a better outcome than length of stay because it identifies true morbidity and the relative contribution of individual complications. However, the OPVI trial was not powered to detect clinically meaningful differences in serious complications.

In conclusion, similar postoperative length of stay with and without plethysmographic variability–guided fluid management in the OPVI trial is a statistically robust result. However, equivocal results might be consequent to enrollment of low-risk patients having routine procedures. Furthermore, protocol compliance was poor, which makes it impossible to attribute comparable outcomes to plethysmographic variability or how the method was implemented. Available evidence suggests that if guided fluid management is beneficial, the treatment effect is relatively small even in high-risk patients—but nonetheless of a potentially clinically meaningful magnitude. Fischer *et al.* add important information to our understanding of goal-directed fluid management, but much additional work is needed, including trials in sicker patients using various guidance methods and various fluid administration algorithms, and trials assessing clinically meaningful outcomes.

Competing Interests

Drs. Maheshwari and Sessler are consultants for Edwards Lifesciences (Irvine, California).

Correspondence

Address correspondence to Dr. Maheshwari: maheshk@ccf.org

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