YALE JOURNAL OF BIOLOGY AND MEDICINE 96 (2023), pp.107-123.

REVIEW

Current Commonly Used Dynamic Parameters and Monitoring Systems for Perioperative Goal-Directed Fluid Therapy: A Review

Chin Fung Kelvin Kan* and John D. Skaggs

Department of Anesthesiology, University of Utah School of Medicine, Salt Lake City, UT, USA

Goal-directed fluid therapy (GDFT) is usually recommended in patients undergoing major surgery and is essential in enhanced recovery after surgery (ERAS) protocols. This fluid regimen is usually guided by dynamic hemodynamic parameters and aims to optimize patients' cardiac output to maximize oxygen delivery to their vital organs. While many studies have shown that GDFT benefits patients perioperatively and can decrease postoperative complications, there is no consensus on which dynamic hemodynamic parameters to guide GDFT with. Furthermore, there are many commercialized hemodynamic monitoring systems to measure these dynamic hemodynamic parameters, and each has its pros and cons. This review will discuss and review the commonly used GDFT dynamic hemodynamic parameters and hemodynamic monitoring systems.

INTRODUCTION

Fluid resuscitation is critical during perioperative periods to ensure vital organs receive adequate oxygen perfusion. Especially since patients usually fast for 8 hours before surgery, which leads to dehydration [1]. Poor intraoperative fluid resuscitation can lead to poor patient outcomes [2].

Traditionally, intravenous (IV) fluid regimens are "liberal," meaning high fluid amounts are given intraoperatively. In abdominal surgery, that amount is up to 7 liters (L) of fluids. However, these regimens lead to a weight gain of 3 to 6 kilograms, which suggests fluid overloading [3]. Other problems associated with liberal

*To whom all correspondence should be addressed: Chin Fung Kelvin Kan, MD, MPhil, Department of Anesthesiology, University of Utah School of Medicine, Salt Lake City, UT; Email: Kelvin.Kan@hsc.utah.edu.

Abbreviations: OPTIMIZE, Optimization of Cardiovascular Management to Improve Surgical Outcome; ERAS, Enhanced recovery after surgery protocols; GDFT, goal-directed fluid therapy; PPV, pulse pressure variation; PP, pulse pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; SVV, stroke volume variation; CVP, central venous pressure; ΔVpeak, aortic blood flow peak velocity variation; PPV, pulse pressure variation; SVV, stroke volume variation; Pvi, pleth variability index; RCT, randomized clinical trials; LV, left ventricular; SV, stroke volume; RV, right ventricular; PAC, pulmonary artery catheter; PP, pulse pressure; PEEP, positive end-expiratory pressure; CO, cardiac output; ECHO, echocardiography; OPVI, Optimization Using the Pleth Variability Index; ED, esophageal doppler; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram; VTI, velocity time integral; IV, intravenous; RELIEF, Restrictive versus Liberal Fluid Therapy in Major Abdominal Surgery; AUC, area under the curve; CI, cardiac index; ΔIVCD, inferior vena cava diameter variations.

Keywords: Goal-directed fluid therapy, fluid resuscitation, pulse pressure variation, pleth variability index, stroke volume variation, aortic blood flow peak velocity variation, hemodynamic monitor, Flotrac, esophageal doppler, echocardiogram, LiDCO, ClearSight, PiCCO, enhanced recovery after surgery protocol

Author Contributions: CFK conceived the idea and wrote the manuscript, JDS provided substantial comments and edits to this manuscript.

Table 1. Commonly Used Dynamic Hemodynamic Parameters and Monitors

Static Hemodynamic Parameters	Dynamic Hemodynamic Parameters	Hemodynamic Monitors
Central Venous Pressure (CVP)	Pulse Pressure Variation (PPV)	Flotrac™
Mean arterial pressure (MAP)	Stroke Volume Variation (SVV)	LidCO™
Cardiac Output (CO)	Pleth Variability Index (PVi)	Masimo Radical 7 Pulse CO-Oximeter™
	Aortic blood flow peak velocity variation (ΔVpeak)	ClearSight™
		PiCCO™
		Esophageal Doppler
		Transthoracic and Transesophageal Echocardiogram

Table 2. Commonly Used Commercialized Hemodynamic Monitor Systems

Monitor	Company	Measured Parameters	Technique
Flotrac™	Edwards Lifesciences	CO, SV, SVV, and SVR	Arterial pulse contour analysis
LiDCO™rapid	Masimo	SV, SVR, SVV, oxygen delivery, and PPV	Arterial pulse power analysis
ClearSight™	Edwards Lifesciences	CO, SV, SVV, SVR, and MAP	Arterial pulse contour analysis
Radical 7 Pulse CO-Oximeter™	Masimo	PVi and Perfusion Index	Plethysmograph waveform analysis
PiCCO™	Pulsion Medical System	CO, CI, ejection fraction, global end-diastolic volume, global ejection fraction, intrathoracic blood volume, and extravascular lung water	Thermodilution
Esophageal Doppler	Deltex Medical	Aortic blood flow	Ultrasound
Echocardiogram	Multiple Vendors	VTI and cardiac blood flow	Ultrasound

regimens include pulmonary complications [4,5], prolonged wound healing [6], and bowel edema causing prolonged ileus [7]. Moreover, hypervolemia may lead to an increase in atrial natriuretic peptide release from the heart, which enhances the deterioration of endothelial glycocalyx, a vital part of the vascular permeability barrier. This leads to vascular barrier loss and an increase in interstitial edema [8]. On the other hand, in patients undergoing low- to moderate-risk surgeries, a liberal fluid approach may be beneficial. For example, Holte et al. showed that patients who underwent laparoscopic cholecystectomy, when given 40 ml/kg IV fluids instead of 15 mL/kg IV fluids, had significantly improved postoperative pulmonary function, with less nausea, dizziness, and fatigue [9].

More recently, major surgeries and enhanced recovery after surgery protocols (ERAS) have been adopting more "restrictive" IV fluid regimens. In previous studies, intraoperative restrictive fluid regimens varied from 1.0 to 2.7L in abdominal surgeries [10]. While these regimens may avoid the side effects of the liberal method, it may cause hypotension leading to organ damage. For example, The Restrictive versus Liberal Fluid Therapy in Major Abdominal Surgery (RELIEF) trial, which randomized 3,000 patients to a liberal fluid regimen vs a restrictive fluid regimen, showed an increase in acute kidney injury (8.6% vs 5.0%). However, there is no difference in the rate of disability-free survival at one year. Other studies have shown that restrictive fluid regimens do have significant benefits in major surgeries. For example, multiple studies have shown that restrictive fluid regimens decrease postoperative ileus recovery in colon resections [11,12], and in the length of stay as well as 60-day surgical complications in patients who underwent hyperthermic intraperitoneal chemoperfusion [13].

While liberal and restrictive fluid regimens have pros and cons, the definition of "liberal" or "restrictive" is arbitrary and depends on individual institutions or clinicians. Therefore, Goal-Directed Fluid Therapy (GDFT) has been utilized in several surgeries to avoid hypotension and fluid overloading by giving the "just right" fluid amount. This review aims to evaluate the current evidence and literature on commonly used dynamic parameters and hemodynamic monitor systems, which have been used for multicenter GDFT randomized clinical trials (RCT), and verified perioperatively in other studies (Table 1 and Table 2).

WHAT IS PERIOPERATIVE GOAL-DIRECTED FLUID THERAPY?

Perioperative GDFT aims to maximize oxygen delivery to tissue by optimizing cardiac output (CO) through fluid resuscitation. *Optimal cardiac output* is defined as the top of the Frank-Starling preload-stroke volume curve [14]. At max capacity, which is at the top of the curve, the increase in end-diastolic pressure increases the stroke volume (SV) less when compared to the lower part of the curve. Thus, less "elastic." The ideal fluid status will be at max capacity where the increase in end-diastolic volume does not change the SV significantly (Figure 1).

CURRENT EVIDENCE FOR GOAL-DIRECTED FLUID THERAPY

Multiple large-scale RCTs have shown GDFT's benefits in the perioperative setting. Additionally, smaller studies demonstrated that GDFT has clinical benefits in non-cardiac, cardiac, and vascular surgery high acuity patients [15-18]. PubMed and clinicaltrials.gov searches with the terms "Goal-Directed Fluid Therapy" and "multicenter randomized clinical trials" are summarized in Table 3. On the other hand, pushing the patient to the top of the Frank-Starling curve will lead to increased natriuretic peptides secreted by the heart, which provokes vasodilation, capillary leakage, and diuresis [19].

The largest GDFT multicenter RCT to date, the Optimization of Cardiovascular Management to Improve Surgical Outcome (OPTIMIZE) trial, randomized 734 high-risk adult patients undergoing major gastrointestinal surgeries. The GDFT group which used LiDCO™rapid (LiDCO Ltd, Cambridge, UK) as a monitor to guide fluid resuscitation had lower 30-day moderate or major complications and mortality (36.6% vs 43.4%) when compared to control. Though there was no difference in morbidity on day 7; infection, critical care-free days, and all-cause mortality at 30 days; all-cause mortality at 180 days; length of hospital stay [20]. Serum biomarkers from participants in the OPTIMIZE trial also showed no evidence of GDFT induced cardiac damage, as there was no elevation of troponin I concentration and N-terminal pro-brain natriuretic peptide [21]. Furthermore, a sub-study of the OPTIMIZE trial showed GDFT reduced health care costs [22]. Another multicenter RCT on GDFT, the FEDORA trial, randomized 450 low- to moderate-risk patients undergoing major abdominal, urological, gynecological, or orthopedic surgery to GDFT-guided by esophageal doppler or control groups. The FEDORA trial showed that patients in the GDFT group had fewer moderate to severe complications, such as acute kidney injury, pulmonary edema, and respiratory distress syndrome (8.6% vs 16.6%), and a shorter length of stay. However, there was no change in mortality [23].

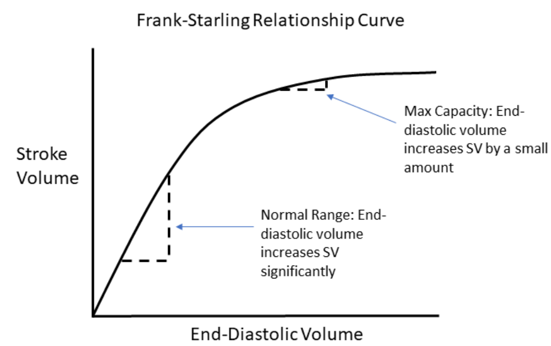

Figure 1. **Frank-Starling Curve**. At the curve plateau, the end-diastolic volume increase does not increase the stroke volume as much. In contrast, at the lower part of the curve, the same amount of increase in end-diastolic volume increase the stroke volume much greater.

Conversely, some studies have shown that GDFT lacks benefits. For instance, Gómez-Izquierdo et al. demonstrated that GDFT using esophageal doppler did not decrease the incidence of postoperative ileus in a RCT of 128 patients; even though it did increase CO and SV, and reduced perioperative IV fluids administration [24]. Moreover, Challand et al. showed no difference in discharge readiness and length of stay between patients who underwent major colorectal surgery in the GDFT group guided by esophageal doppler and the control group [25]. Besides abdominal surgeries, GDFT has been shown to lack effect in major vascular surgeries. Bisgaard et al. showed that in patients who underwent open elective abdominal aortic surgery, GDFT-guided by LiDCO™plus (LiDCO Ltd, Cambridge, UK) did not decrease postoperative complications or length of stay in the intensive care unit [26]. Additionally, very recently, Fischer et al. demonstrated in a RCT involving 447 intermediate-risk patients who underwent hip or knee arthroplasty that GDFT-guided by the Pleth Variability Index (PVi) had no effect in hospital stay, acute renal failure, and cardiac complications when compared to the control group [27].

While there are currently mixed GDFT trial results, more large-scale multicenter trials with a heterogeneous patient population may help resolve debates about its clinical benefits. Two notable differences in all these clinical trials are that they use different fluid responsiveness parameters and monitoring systems to guide fluid resuscitation.

Table 3. Multicenter Randomized Control Trials

	n	Types of Surgery	Parameter	Monitor	Results
Sá Malbouisson et al. [38]	84	Open major surgery	PPV	DX 2020™	Decrease in postoperative complications and hospital length of stay
Brandstrup et al. [123]	150	Elective colorectal surgery	SV	Esophageal Doppler	No significant differences in postoperative complications
Phan et al. [124]	100	Major colorectal surgery	SV index	Esophageal Doppler	No difference in length of stay and postoperative complications
Aaen et al. [125]	312	Emergency surgery for obstructive bowel disease or GI perforation	SV	Flotrac™ and EV 1000™	No difference in major complications and death within 90 days, increase in hospital length of stay
De Waal et al. [126]	482	High risk elective, abdominal surgery	CI and SVV	Flotrac™ and Vigileo™	No difference in the number of minor complications, hospital length of stay, PACU/ICU length of stay or grading of complications
Davies et al. ClearNOF trial [94]	240	Orthopedics Surgery	SV	ClearSight™	No reduction in complications; however, a potential reduction in length of stay
Stens et al. COGUIDE trial [92]	175	Moderate risk abdominal Surgery	PPV, MAP, and CI	Nexfin™ (ClearSight™)	No reduction in complication rates
Sandham et al. [127]	1994	Urgent or elective major abdominal, thoracic, vascular, or hip-fracture surgery	Oxygen-delivery index, CI, MAP, pulmonary-capillary wedge pressure, HR, Hct	PAC	No benefit in care directed by PAC
Pearse et al. OPTIMISE trial [20]	734	Major abdominal surgery	SV	LiDCOrapid™	No reduction in complications and 30-day mortality but updated meta-analysis was associated with a reduction in complication rates
Calvo-Vecino et al. FEDORA trial [23]	450	Major abdominal, urological, gynecological, or orthopedic surgery	SV, CI, and MAP	Esophageal Doppler	Reduced postoperative complications and hospital length of stay in low to moderate risk patients
Pestaña et al. POEMAS Study [128]	142	Open colorectal surgery, gastrectomy, or small bowel resection	MAP and CI	NICOM™	No decrease in the incidence of overall complications or length of stay
Voldby et al. GAS-ART trial [129]	310	Urgent gastrointestinal surgery due to gastrointestinal perforation or obstructive bowel disease	SV	Flotrac™ and EV 1000™	Ongoing currently

Salzwedel et al. [130]	160	Elective abdominal surgery including general, gynecological, and urological surgery	PPV, CI, and MAP	ProAQT™	Decrease in complications, no change in length of stay in hospital or PACU, no change in return of bowel function time
Weinberg et al. [131]	48	Elective major liver resection	SVV	Flotrac™ and EV 1000™	No change in length of hospital stay or fluid related complications
Parke et al. [132]	750	Cardiac surgery	SVV	Flotrac™ and EV 1000™	No differences in ICU stay time, development of organ dysfunction, quality of life or disability-free survival
Scheeren et al. [133]	64	High risk surgery	SVV and SV	Flotrac™	Decreases postoperative wound infections
Diaper et al. [134]	401	Major abdominal, urological, or vascular surgery via open laparotomy	Stroke volume index, MAP, and PPV	LiDCO™	No change in moderate-to-severe postoperative complications
Peng et al. FAB trial [135]	80	Spinal or sacral surgery	SVV	Flotrac™ and Vigileo 3.0™	Arterial and gastric intramucosal pH were higher, decrease time to flatus. No differences in the length of hospital stay, complications or mortality
Weinberg et al. [136]	52	Pancreaticoduodenectomy	SVV, MAP, and CI	Flotrac™ and EV 1000™	Decrease complication rates and length of hospital stay
Olivier Fischer et al. OPVI trial [27]	447	Hip or knee arthroplasty	PVi	Radical 7 Pulse CO-Oximeter™	No change in hospital length of stay, serious postoperative cardiac complications, acute postoperative renal failure, troponin Ic concentration and lactate level
Edwards et al. OPTIMISE II trial [116]	2502	Resection of colon, rectum or small bowel, pancreas and bowel, stomach (non-obesity surgery), resection of esophagus, obesity surgery and other surgery involving gut resection	SV and SVV	Flotrac™ and EV 1000™ or ClearSight™	Ongoing

DYNAMIC PARAMETERS FOR GOAL-DIRECTED FLUID THERAPY

The criterion standard of CO measurement remains using intermittent thermodilution with a pulmonary artery catheter (PAC). However, this measurement requires a PAC, making it impractical in many perioperative settings. As such, there are many CO surrogates and parameters developed to measure a patient's fluid status and SV as defined by "static" and "dynamic." These parameters are summarized in Table 1.

Although CVP is traditionally used as a static parameter to assess fluid responsiveness, multiple studies showed that it is unreliable [28]. In contrast, dynamic parameters were shown to estimate fluid responsiveness and status with reasonable accuracy [29-32].

DYNAMIC PARAMETERS AND THE FRANK-STARLING CURVE

These dynamic parameters depend on the Frank-Starling relationship. Under the relationship, the left ventricle (LV) SV changes due to intrathoracic pressure. This is because increased intrathoracic pressure compresses the right ventricle (RV), which decreases RV preload. If a patient's fluid status is at the Frank-Starling curve plateau, respiratory pressure will have little effect on the RV preload. Thus, the RV preload respiratory variations will be low, and there will be no effect on the LV SV [33]. Because the LV SV and arterial compliance correlate with the arterial pressure, thus arterial pressure parameters, such as pulse pressure (PP), correlate with the LV SV variations.

As shown in Figure 2a and b, the arterial wave area under the curve (AUC) is the LV SV, whereas the wave peak is the systolic blood pressure (SBP) and the wave trough is the diastolic blood pressure (DBP). PP equals SBP – DBP. Both LV SV and PP vary during the respiration cycle (Figure 2d). If a patient is at the Frank-Starling curve plateau, both the arterial pressure AUC and the PP will have minimal variations during the respiration cycle. Figure 2c shows the pulse oximetry plethysmography which also correlates with the arterial pressure waves and thus also oscillates during the respiratory cycle. In the section below we will discuss the four commonly used fluid responsiveness dynamic parameters for GDFT guidance: pulse pressure variation (PPV), pleth variability index (PVi), stroke volume variation (SVV), and aortic blood flow peak velocity variation (ΔVpeak).

Figure 3 shows the dynamic parameter equations, which are crucial to understand how to interpret each parameter accurately, and for providers to judge the appropriateness to use each parameter in different physiological states or surgeries. For example, PVi may not be accurate in low perfusion states due to its use of perfusion index.

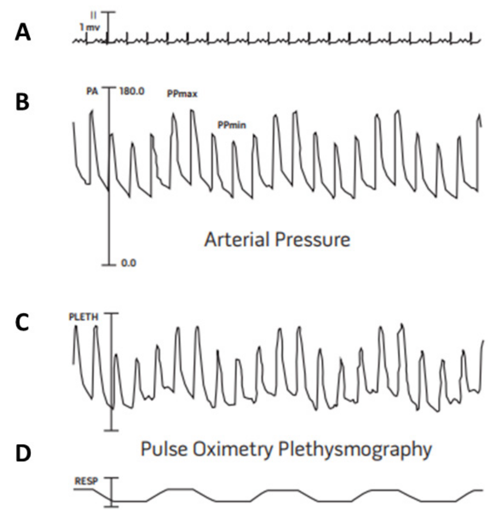

Figure 2. **PPV and SVV calculations**. **A-D**, EKG, arterial pressure, pulse oximetry plethysmography, respiratory pattern, respectively. **B** and **C**, both arterial pressure and pulse oximetry plethysmography oscillate during the respiratory cycles, which is shown in **D**, due to the change in intrathoracic pressure, preload, and LV SV during mechanical ventilation. In **B**, the area arterial pressure wave under the curve is the LV SV. SVV (%) can be calculated with the equation (SV max – SV min) / SV mean. The arterial pressure wave peak is the SBP, and the trough is the DBP, PP is the difference between SBP and DBP. PPV (%) is calculated from 100 × (PP max – PP min) / ([PP max + PP min]/2) [121,122].

PULSE PRESSURE VARIATION (PPV) IN GOAL-DIRECTED FLUID THERAPY

PPV is a fluid responsiveness dynamic parameter described by Coyle et al. in 1983 [34]. PPV is calculated by measuring PP alterations during the respiratory cycle (Figure 2b) [35]. In general, patients with a PPV <12% are unlikely to benefit from further fluid therapy, whereas those with >12% are more likely to benefit from fluid resuscitation [36]. Compared to CVP, which requires a central venous catheter, PPV requires a minimally invasive or noninvasive monitor, commonly an arterial catheter. It is important to note that PPV does not indicate a patient's fluid status or preload; rather, it is only an indicator of the patient's position on the Frank-Starling curve [37].

PPV has been used to guide GDFT. For example, Malbouisson et al. showed that PPV-guided GDFT reduced postoperative complications such as respiratory, renal, and hepatic dysfunctions, and hospital length of

	Equation
Cardiac Output (CO)	Heart Rate × Stroke Volume
Pulse Pressure (PP)	Systolic blood pressure – Diastolic blood pressure
Pulse pressure variation (PPV %)	100% × [(Pulse pressure max – Pulse pressure min) / ([Pulse pressure max + Pulse pressure min] / 2]
Perfusion Index (PI %)	(Arterial pulsation absorbance / Non-pulsatile blood absorbance) × 100%
Pleth Variability Index (PVi %)	[(Perfusion index max – Perfusion index min) / Perfusion index max] × 100%
Stroke Volume Variation (SVV %)	(Stroke volume max – Stroke volume min) / Stroke volume mean
Caval Index (%)	(Inferior vena cava expiratory diameter – Inferior vena cava inspiratory diameter) / (Inferior vena cava expiratory diameter) × 100%

Figure 3. **Dynamic Parameters and Physiology Equations**.

stay, in high-risk patients undergoing open surgeries [38]. However, there have been small RCTs with negative clinical results on PPV-guided GDFT. For instance, Suzuki et al. found that PPV-guided GDFT did not significantly affect renal, hemodynamic, and metabolic variables in patients after they underwent cardiac surgery [39].

Moreover, PPV faces some limitations. To ensure accurate PPV measurement, the patient must be mechanically ventilated, the chest must be closed (an open chest will affect the interaction between the pericardium and mechanical ventilation), be in sinus rhythm, and intra-abdominal pressure must be within the normal range [33]. Other parameters that may affect PPV readings include extreme bradycardia or high respiratory rate, low tidal-volume ventilation (must be between 6 to 8 ml/kg), high positive end-expiratory pressure (PEEP) (PEEP should be between 0 and 5 cm H_2O), low arterial compliance (high dose vasopressors, severe atherosclerosis), and RV or LV failure [32,33,40,41]. Also, if respiratory system compliance is ≤30 mL/cm H_2O, such as in patients with ARDS, PPV will become less accurate [41,42].

PLETH VARIABILITY INDEX (PVi) IN GOAL-DIRECTED FLUID THERAPY

PVi is calculated from plethysmographic waveform amplitudes and PP derived from pulse oximetry or other devices. It was commercialized in 2007 [43]. This dynamic parameter has been shown to predict fluid responsiveness as accurate as Stroke Volume Variation [44], esophageal doppler [45], and PPV [46]. PVi also depends on the increased intrathoracic pressure interaction with the RV preload and the LV SV upon mechanical ventilation, which causes variation in the plethysmographic waveform amplitudes and area under the curve (Figure 2c). PVi is calculated by measuring perfusion index (PI) alterations during the respiratory cycle, which is described as the percentage of light absorbed as a result of

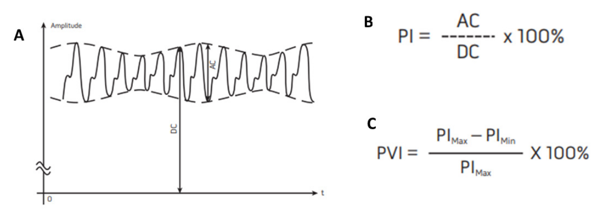

Figure 4. **PVi and PI calculations**. In **A**, DC is the total amount of light absorbed and AC is the light absorbed as a result of arterial pulsation, which oscillates during respiration. **B**, PI (%) is calculated with the equation (AC/DC) × 100%. **C**, PVi (%) is then calculated from the PI with the equation [(PI max – PI min) / PI max] × 100% [121].

arterial pulsation (AC) relative to total amount of light absorbed (DC). PVi is then calculated from the PI (Figure 4a-c) [48].

In a single-center RCT, Cesur et al. showed that in 70 ASA I and II patients, PVi-guided GDFT decreased the amount of fluids administered and the return of bowel function time [47]. Additionally, Patrice et al. demonstrated that PVi-guided GDFT decreases lactate level and fluid administration during major abdominal surgery [48]. Likewise, a study by Yu et al. found Pvi-guided GDFT decreases blood lactate level in the first hour of surgery and reduces fluid administration. However, the study found no changes in lactate level beyond the first hour, possibly due to its small sample size of 30 patients [49].

Currently, most GDFT studies using PVi are in abdominal surgeries. While there are great promises for this parameter, more studies must be done on other types of surgery to verify its use. Moreover, there is no definitive PVi cutoff in predicting fluid responsiveness, but most RCTs decided that it is around 13% to 14% [48,50]. Additionally, because PI is measured by pulse oximetry, nail coloring, skin coloring, and altered physiological states (such as methemoglobin) may change infrared light absorption leading to inaccurate calculations. Finally, because PVi is based on the same principle as PPV, both suffer the same limitations.

STROKE VOLUME VARIATION (SVV) IN GOAL-DIRECTED FLUID THERAPY

SVV is calculated from the difference between the maximum and minimum SV over the respiratory cycle and is caused by changes in RV preload due to alterations in intrathoracic pressure (Figure 2b). Patients with a SVV of <10% are unlikely to be fluid responsive, whereas those with SVV >15% are likely to benefit from fluid resuscitation [51].

SVV-guided GDFT has been shown in multiple single-center RCTs that it is an effective way to decrease postoperative complications in bowel, orthopedics, and neurosurgery [52-56]. For instance, Gottin et al. compared three methods of resuscitation in patients undergoing pancreatic surgery: liberal, restrictive, and SVV-guided GDFT. This study demonstrated that SVV-guided GDFT and restrictive fluid resuscitation decreased major surgical complications such as postoperative fistula, abdominal collection, and hemorrhage compared to liberal fluid resuscitation [57]. However, while most studies showed that SVV-guided GDFT improved postoperative outcomes, some studies showed the contrary. For example, Iwasaki et al. showed that SVV-guided GDFT hepato-biliary-pancreatic surgery patients had greater amount of fluids administered, and lower PaO_2/FiO_2 ratio on postoperative day one [58].

Interestingly, Wang et al. showed that in elective retroperitoneal tumor resections, patients who were resuscitated at SVV 9% has increased serum syndecan-1, interleukin-6, and tumor necrosis factor-α, as well as higher incidence of fever and blood transfusion when compared to patients resuscitated at SVV 14%. This suggests that increased fluid administration may enhance perioperative glycocalyx shedding leading to significant inflammatory responses [59].

Because SSV is based on the same principle as PPV, it also faces the same restriction as discussed above [41].

AORTIC BLOOD FLOW PEAK VELOCITY VARIATION (ΔVpeak) IN GOAL-DIRECTED FLUID THERAPY

Because LV SV changes during different phases of mechanical ventilation, the aortic blood flow peak velocity will also vary. If the patient is at the plateau of the Frank-Starling relationship and thus fluid nonresponsive, such variations will be minimal. If the patient is fluid responsive, it will be vice versa. Marc et al. first described this parameter in 2001, where he reported that ΔVpeak of 12% has a sensitivity of 100% and a specificity of 89% to distinguish fluid responders from non-responders in adults [60].

ΔVpeak can be used to determine a patient's fluid responsiveness in situations when PPV, SVV, or PVi cannot be measured accurately. This is especially true in pediatric and neonatal patients since they are ventilated by small tidal volumes, have higher arterial vascular compliance, and have higher chest wall and lung compliance. Therefore, in these patients, changes in intrathoracic pressure during mechanical ventilation may not cause the same circulatory changes as with adults. For example, Gan et al. demonstrated in a systemic review that ΔVpeak is the only dynamic or static variable that can predict fluid responsiveness in pediatric patients. PPV, SVV, and PVi did not predict fluid responsiveness in children [61].

Currently, there are no optimal cutoff points for ΔVpeak to assess fluid responsiveness. Furthermore, vasoactive drug effects on this parameter in the pediatric population are largely unknown [62]. However, this newer dynamic parameter holds many promises in pediatric resuscitation. A multicenter RCT is currently investigating ΔVpeak-guided GDFT on postoperative outcomes in pediatric patients undergoing elective or urgent major noncardiac surgery [63]. It will be interesting to see what this RCT shows and how ΔVpeak can further enhance pediatric surgery fluid optimization and postoperative outcomes.

GOAL-DIRECTED FLUID THERAPY MONITORING SYSTEMS

Currently, there are many methods to monitor fluid responsiveness dynamic parameters in the perioperative setting [51]. Traditionally, the Swan–Ganz catheter has been used to measure CO, a fluid responsiveness static parameter, despite multiple studies showing Swan–Ganz catheters do not improve clinical outcomes [64]. Moreover, it is invasive and can lead to numerous complications such as thrombosis, pulmonary artery rupture, infection, and arrhythmia on insertion [51]. Therefore, other minimal or noninvasive hemodynamic monitoring systems have been developed [65,66]. In the section below, we will focus on common and popular monitoring systems which have been verified and used preoperatively for GDFT. A summary of the monitoring systems is shown in Table 2.

Flotrac™ for Goal-Directed Fluid Therapy

Flotrac™ (Edwards Lifesciences, Irvine, CA, USA) was first introduced in 2005 to be used with the EV1000 monitor or Vigileo monitor [67]. It uses a blood flow sensor that is attached to an arterial catheter. Hemodynamic parameters such as CO, SV, SVV, and systemic vascular resistance (SVR) are calculated every 20 seconds with a proprietary algorithm using pulse contour analysis. SV is derived from the equation: K × Pulsatility (standard deviation of the arterial pressure wave over 20 seconds), where K is a constant. K is derived from the sex, age, height and weight according to methods described by Langewouters et al. [68] and the skewness and kurtosis of the individual arterial waveform. K is recalculated automatically every minute based on the patient's specific vascular compliance. Then, the CO is calculated by multiplying SV with pulse rate [69].

Flotrac™ does not need to be calibrated for use [67]. However, because the hemodynamic parameter calculations are heavily dependent on the constant, K, the software needs to recognize changes in vasodilation or vasoplegia to calculate an accurate CO.

Some studies have found that Flotrac™ is comparable to other hemodynamic monitoring systems. For example, Mclean et al. found that Flotrac/Vigileo™ is comparable to transthoracic doppler echocardiography when measuring CO [70]. Also, Cannesson et al. showed that in patients undergoing coronary artery bypass grafting, the CO estimated by Flotrac™ is comparable with PAC thermodilution [71]. However, many studies questioned its accuracy, even when it was updated to its newest software version: the fourth generation. While Flotrac™ is reasonably accurate in stable patients, in patients with low SVR, Flotrac™ does not provide accurate CO measurement when compared to invasive CO monitoring [67]. For instance, Murata et al. showed that in end-stage liver failure patients, fourth-generation Flotrac™ and PAC readings had poor agreement with each other during liver transplantation [72]. Moreover, Lin et al. found that fourth-generation Flotrac™ had a 61.82% and 51.80% error in estimating the CO before and after cardiopulmonary bypass, respectively. Therefore, found it unsuitable to be used during or after cardiopulmonary bypass [73].

Nonetheless, Flotrac™ remains popular and has been used in multiple RCTs to guide GDFT with good clinical outcomes [53,74]. For example, Yu et al. demonstrated that in major gynecologic oncology surgery patients, Flotrac™-guided GDFT decreased postoperative complications risk significantly (OR = 0.572), especially in surgical site infection risk (OR = 0.127). Furthermore, GDFT patients received significantly less fluid infusion than the control group [74].

While Flotrac™ is easy and convenient to use, many questions remain of its use in high-risk patients, especially in patients suffering from vasoplegia. In the future, newer software updates from the manufacturer may resolve such issues and allow it to better estimate hemodynamic parameters.

LidCO™ for Goal-Directed Fluid Therapy

LiDCO™plus (Masimo, Irvine, CA, US) must be calibrated by lithium dilution before being used. This calibration method boluses 0.5 to 1.0 ml of lithium chloride (0.15 mmol ml^{-1}) through a central or peripheral venous line. Then, blood is aspirated through an arterial catheter at a constant rate of 4 ml min^{-1} with a disposable electrode selective for lithium. The change in electrode voltage is converted to plasma lithium concentration, and a lithium concentration vs time curve is plotted to calculate plasma flow. Blood flow is calculated with plasma flow divided by 1 – packed cell volume [51].

After calibration, it uses a propriety PulseCO™ algorithm, a pulse power algorithm, to calculate the CO. The algorithm uses the conservation of mass, rather than pulse contour, and assumes the net power change in a heartbeat between the input of a mass (SV) of blood minus the blood mass lost to the periphery during the beat has a linear relationship with net flow [75]. By doing so, LiDCO™ can also calculate the SV, SVR, SVV, oxygen delivery, and PPV.

LiDCO™plus has been validated and compared against other hemodynamic monitoring systems. For example, Mora et al. showed that LiDCO™plus is comparable to PAC thermodilution in patients with impaired LV SV after cardiac surgery [76]. The newer models of LiDCO™, such as the LiDCO™rapid and LiDCO™ LXi, are noninvasive and require no calibration. Instead, they use a two-finger cuff applied to the patient's hand to measure the parameters. These newer models still use the same algorithm and have shown benefits in multiple RCTs [77,78]. More importantly, the OPTIMIZE trial used LiDCO™rapid-guided GDFT, which showed postoperative clinical benefits.

However, like Flotrac™, some studies have questioned LiDCO™rapid's accuracy. For example, Asmaoto et al. examined Flotrac™ and LiDCO™rapid across a broad range of cardiac indexes (CI). Both monitors tended to underestimate CIs when the PAC measured CIs were relatively high [79]. LiDCO™rapid is a convenient and noninvasive option to guide fluid therapy, though there are unanswered questions about its utility in different physiological states. More studies on different types of surgery may help address some of these issues.

Masimo Radical 7 Pulse CO-Oximeter™ for Goal-Directed Fluid Therapy

Masimo Radical 7 Monitor (Masimo, Irvine, CA, US) can measure the PVi using a Masimo pulse oximeter, which can be attached to the ear, digits, or forehead [80]. This monitor does not need to be calibrated and is noninvasive. It is also the only commercially available monitor to measure PVi.

Multiple studies used Masimo pulse oximetry for GDFT to achieve improved postoperative outcomes. For instance, Saugel et al. showed that PVi-guided GDFT reduced ileus significantly and decreased fluid administrated in colorectal surgical patients [81]. Also, Collange et al. found that a PVi >9% before renal artery unclamping is an individual risk for delayed graft function in renal transplant patients [82]. However, the Optimization using the Pleth Variability Index (OPVI) trial, in which 447 ASA I and ASA II patients were randomized, showed that forehead measured Pvi-guided GDFT did not shorten hospital stay, or reduce postoperative complications such as AKI. This study, however, attributed these results to patients being of lower acuity [27].

Compared to other dynamic parameters, PVi is equivalent. For example, Coeckelenbergh et al. showed that in low- to intermediate-risk abdominal surgeries, patients who underwent PVi-guided GDFT or PPV-guided GDFT had no significant differences in hospital length of stay, postoperative outcomes, and amount of fluids administered [83]. In another study, Pişkin et al. showed that PVi and inferior vena cava distensibility index could predict fluid responsiveness comparably in intensive care patients [84].

However, PVi may be inaccurate in specific patient populations. Konur et al. found that in liver transplant patients, PVi cannot distinguish fluid responders from non-responders. PVi value was similar at baseline between responders and non-responders in the dissection and anhepatic phase. Only SVV measured by the PiCCO™ monitoring system was reliable [85]. Likewise, Le Guen et al. showed that PVi does not respond to fluid challenges and had poor agreement with esophageal doppler measurements in renal transplant patients [86].

Because PVi measurements require adequate perfusion, a change in blood flow may affect its reading. Currently, Masimo Radical 7 Pulse CO-Oximeter™ cannot determine if a decrease in blood flow is due to a depressed cardiovascular system or impaired blood flow to the tissue. Additionally, any physiological or pathological influences on the peripheral vascular flow, such as in patients with severe Raynaud's phenomenon or with peripheral vascular disease, may affect PVi readings [87]. Thus, PVi should be used and interpreted cautiously.

ClearSight™ for Goal-Directed Fluid Therapy

ClearSight™ (Edwards Lifesciences, Irvine, CA, USA) is a noninvasive monitor which uses a finger cuff to estimate CO, SV, SVV, SVR, and mean arterial pressure (MAP). It was introduced in 2007 as Nexfin™. The finger cuff inflates and deflates to keep the diameter of finger arteries constant throughout the cardiac cycle. From the finger pressure waveform, it calculates the brachial pressure waveform using an algorithm. Then, it uses the pulse contour method to estimate CO [88].

Conflicting studies have shown that ClearSight™ may or may not be comparable to other invasive or minimally invasive hemodynamic monitoring systems. For example, Wang et al. showed that ClearSight™ is comparable to PAC thermodilution in estimating CO in cardiac surgery patients [89]. However, while Tanioku et al. found that ClearSight™ was interchangeable with arterial catheters in measuring MAP, it had significant biases when measuring SBP and DBP in cardiovascular surgeries [90]. Moreover, Kanazawa et al. demonstrated that ClearSight™ was inaccurate in estimating CI in patients with reduced cardiac ejection fraction (<55%) when compared to PAC thermodilution. However, it is accurate in measuring MAP [91].

Some studies also found that ClearSight™-guided GDFT has no postoperative benefits. Stens et al. showed that using ClearSight™ calculated CI, PPV and MAP for GDFT guidance had no impact on postoperative complications [92]. Furthermore, Fischer et al. found that in low-risk colorectal patients, using ClearSight™-guided GDFT does not affect hospital length of stay, postoperative mortality, and the total number of complications [93]. Similarly, Davies et al. found that ClearSight™-guided GDFT offers no postoperative complication benefits in high-risk patients undergoing hip fracture repair [94]. Given these questionable study results, this monitoring system needs to be studied more in multicenter RCTs to verify its benefit in GDFT.

PiCCO™ for Goal-Directed Fluid Therapy

PiCCO™ (Pulsion Medical System, Munich, Germany) uses the transpulmonary thermodilution technique for CO estimations. To calibrate the monitor, it requires a bolus of cold saline in a central venous catheter, then a thermo-sensor tip arterial catheter senses the decrease in blood temperature. The difference between this system and PAC transpulmonary thermodilution is that the cold solution is bolused into a central vein, not in the right atria. Therefore, the temperature change detection is at a peripheral artery rather than the pulmonary artery. Uniquely, this monitoring system can also measure global end-diastolic volume [95], global ejection fraction, intrathoracic blood volume, and extravascular lung water [96].

Goedje et al. found that PiCCO™ had a comparable and robust correlation with PAC thermodilution with a mean bias of 0.07-liter min^{-1} (2 SD 1.4-liter min^{-1}) in post-cardiac surgery patients. These patients had various CO (ranging from 3.0 to 11.8 liter min^{-1}) and SVR (ranging from 252 to 2434 dyn s cm^{-5}) [97]. Moreover, it has been shown to improve postoperative outcome when used to guide GDFT. For instance, Jing et al. demonstrated that PiCCO™-guided GDFT decreased volume infusion, hospital stay length, and time needed for ambulation [98]. However, in emergency surgeries, PiCCO™-guided GDFT increased major complications (95% vs 40% in the control group) and did not decrease in-hospital mortality [99].

While PiCCO™ offers a less invasive approach than PAC, it still requires a central venous catheter and arterial catheter, which may be impractical in many surgeries and can only be used in high-risk patients. Therefore, this method continues to have many limitations.

Esophageal Doppler for Goal-Directed Fluid Therapy

Esophageal Doppler (ED) is an ultrasound-based technique introduced in the 1970s, which allows aortic blood flow measurements in the descending thoracic aorta to calculate CO and SV [100]. It is the only minimally invasive CO monitor evaluated and endorsed by the United States Agency for Healthcare Research and Quality and the United Kingdom Centre for evidence-based purchasing [101].

The ED is a 6-mm probe positioned at the distal esophagus to measure blood flow velocity in the descending thoracic aorta. The blood flow velocity waveform also can be used to measure flow time, which is the time from the start of the waveform upstroke to return to baseline. When corrected for HR, flow time is found to be a sensitive measure of LV filling, thus an accurate RV preload measurement [102].

ED is comparable to PAC thermodilution in measuring intensive care patients' CO [103]. Studies also showed that ED produced similar clinical results as Flotrac™-guided GDFT [104] and NICOM-guided GDFT [105]. Furthermore, a systemic review by ECRI Evidence-based Practice Center, an independent federally certified patient safety organization by the US Department of Health and Human Services, has found that there is high quality evidence that ED reduces postoperative complications and hospital length of stay [106]. Due to its accuracy and longevity, ED had become the noninvasive fluid status monitor of choice. Both the RELIEF and FEDORA trials used ED-guided GDFT.

Despite much evidence supporting ED's use in GDFT, some limitations exist. First, it requires some skills; thus, the user must be trained. Secondly, it cannot be used in esophageal surgeries, patients with esophageal anatomical anomalies, or with recent esophagus surgeries. Thirdly, liver cirrhosis patients may have esophageal varices and ED can induce bleeding. Finally, the doppler signal can be poor due to aorta or user issues.

Echocardiogram (ECHO) for Goal-Directed Fluid Therapy

Transesophageal (TEE) or Transthoracic Echocardiogram (TTE) are frequently used to guide fluid therapy in high-risk cardiothoracic and liver transplant surgeries. They are ultrasound imaging techniques that can visualize the heart or the aorta directly [107]. This direct visualization allows multiple hemodynamic parameters to be calculated or measured in real-time. For example, the LV outflow tract velocity time integral (VTI) is a measurement by ECHO of how far blood travels during the flow period. It is a LV systolic function surrogate, which can be used to calculate the SV and then the CO, by multiplying with HR [108]. Moreover, TEE can estimate the preload using the LV end-diastolic area [109]. These visualized changes in preload can detect even minor volume deficits. TEE and TTE can also detect inferior vena cava diameter variations (ΔIVCD) during tidal respiration in mechanically ventilated patients, which correlates with SVV [110]. ΔIVCD can also be used to calculate the caval index (Figure 3); a caval index <50% is strongly associated with a CVP of <8 mmHg [111].

While TEE and TTE are well-established monitors for fluid resuscitation intraoperatively and has shown benefits in intensive care patients, it lacks studies on postoperative outcomes in low- and moderate-risk surgeries. Furthermore, TEE has limitations. It cannot be used in patients with previous esophageal surgeries and cannot be used in esophageal surgeries. Probe insertion can lead to bleeding in cirrhotic patients with esophageal varices. Also, both TTE and TEE probes must be positioned by a trained professional to interpret the images. Finally, the TEE probe cannot be used in awake patients.

Currently, TEE-guided GDFT is being investigated in a multicenter RCT for pediatric surgery postoperative outcomes [112]. It will be interesting to see how it will impact pediatric resuscitation.

CONCLUSION

In the last 20 years, there has been much advance in noninvasive detection of fluid status perioperatively, as an alternative to using PAC thermodilution. Each monitoring system uses different physiological principles and offers various pros and cons. Furthermore, these systems use different algorithms and methods to calculate dynamic parameters. Because of these different calculations, different monitors can display different values for the same dynamic parameter. As such, a clinician should consider the type of surgery being done, and the current evidence for GDFT-guided by that monitoring system and dynamic parameter. Moreover, a clinician should understand and be familiar with how dynamic parameters are calculated, and how they are derived from the monitoring systems.

Dynamic parameters are all based on the physiological principles of mechanical ventilation, intra-thoracic pressure, and LV SV changes. Thus, they have the same limitations. To ensure accurate measurement, the patient must be: 1) Mechanically ventilated, 2) Chest must be closed, 3) In sinus rhythm, and 4) Intra-abdominal pressure must be in the normal range. In addition, low arterial compliance and respiratory system compliance ≤30 mL/cm H_2O can decrease the accuracy of parameters [42,43]. However, these factors may be compensated by the monitoring systems' algorithm.

The selection of dynamic parameters for GDFT guidance is also affected by the surgery itself. For example, PVi has been shown to be unreliable in predicting fluid responsiveness in cardiac surgery patients when compared to PPV and SVV [113]. Even if the dynamic parameter is selected carefully, it has been demonstrated that few patients fit all the criteria for accurate dynamic parameter measurements in both perioperative and intensive care settings [40,114]. For example, Maguire et al. found that only 39% of surgical patients met the criteria for accurate noninvasive plethysmographic waveform variations monitoring [40]. Therefore, suggests that many providers may not be aware of all the requirements and surgical nuances for using dynamic parameters, leading to false readings and wrong interpretations.

Currently the American Society of Anesthesiologists nor other international medical societies endorse the use of any hemodynamic monitoring systems or dynamic parameters to guide GDFT. Furthermore, there are no GDFT clinical guidelines due to ongoing debates of its uses and benefits. However, there is strong evidence that esophageal doppler, as endorsed by the United States Agency for Healthcare Research and Quality and the United Kingdom Centre for evidence-based purchasing, can improve postoperative outcomes [101].

OUTLOOK

While GDFT has been more prevalent than in previous decades, there continues to be slow adaptation of this fluid regimen, even though multiple studies have reported that GDFT offers postoperative benefits and is cost-effective. In a survey of anesthesiologists, only 35% reported they "always" use GDFT in the United States. Worse yet, only 15% and 10% of the anesthesiologist in the United Kingdom and Australia/New Zealand reported they "always" use GDFT respectively. The most common reason was the lack of monitoring tools availability, followed by a lack of experience with instruments [115].

With more RCTs, hopefully, there will be a change in attitude towards using GDFT and purchasing hemodynamic monitoring systems. It will be exciting to follow the current global multicenter RCT, the OPTIMISE II trial, which launched in January 2017. With over 30 participating centers in multiple countries, it has enrolled 2,502 patients undergoing major elective gastrointestinal surgery. This study will be the largest GDFT trial to date and will be using ClearSight™ or Flotract™ as hemodynamic monitors, with SVV as the dynamic parameter. Primary outcomes will be 180 day mortality, 30-day AKI rate, and acute cardiac event within 24 hours and 30 days [116].

As technology advances, perioperative hemodynamic monitors have also become more non-invasive. One exciting technology is the wireless and wearable doppler which may be comparable to TEE. For example, Kenny et al. showed that a wearable wireless carotid doppler at the common carotid artery is equivalent to TEE during coronary bypass surgeries; it can accurately detect the common carotid artery VTI, and significant changes in SV and aortic VTI after a straight leg raise test [117,118]. Wang et al. also described a wearable and flexible ultrasound doppler device similar to an electrocardiogram lead which can monitoring real time blood flow velocities in human arteries [119]. These new technologies and devices can circumvent the minimally invasive or invasive hemodynamic monitor systems' limitations.

Another exciting progress is the increasing use of artificial intelligence, machine learning and big data to solve hemodynamic problems. Hatib et al. described the hypotension prediction index, which is developed by machine learning from the arterial waveform of 13,000 past hypotensive events and 12,000 non-hypotensive events. HPI can predict hypotension 15 minutes before the actual event occurs [120]. In the future, a new hemodynamic algorithm may go beyond PPV or SVV to allow patient fluid resuscitation before hypotension happens.

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