EXPERT REVIEWS

FloTrac/Vigileo system monitoring in acute-care surgery: current and future trends

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As acute critical-care surgery evolves, it is imperative to introduce reliable devices that can intraoperatively assess a patient's cardiovascular functions. Owing to the fact that traditional methods are usually invasive, non- or less-invasive innovations have attracted the attention of clinicians in recent decades. The FloTrac system monitors cardiovascular performance by analyzing peripheral arterial waveforms and a preset database, and it decreases the invasiveness by using a pulmonary arterial catheter. The reliability of cardiac output measurements was confirmed in many critically ill subjects in cardiac surgeries and intensive care units. Moreover, the FloTrac system is easy to set up, and interpreting the information is simple. The FloTrac system also provides a useful preload predictor, that is, stroke volume variation (SVV), for fluid management, which has been proven to enhance surgical safety in the treatment of critically ill patients. Goal-directed therapy guided by SVV and other hemodynamic variables was advocated for peri-operative fluid optimization. Although the evolution of each updated algorithm of the FloTrac system has demonstrated improved accuracy and limited shortcomings, the latest third-generation algorithm is still not equal to the gold standard reference. The accuracy of the latest third-generation algorithm is controversial in septic conditions, and its use is still unacceptable in liver transplantation. Due to vasoactive challenges, especially in the administration of norepinephrine, a conclusion could not be reached. Clinicians should recognize the appropriate uses and limitations when using the algorithm during acute critical surgeries.

Keywords: cardiac output • FloTrac system • fluid responsiveness • less invasiveness • stroke volume variation • third generation

In the management of acute critical-care surgeries, we frequently encounter high-risk patients with comorbidities, such as impaired heart or lung function, or septic shock. Under stresses as surgical manipulations and anesthetic depression, these patients could experience instabilities of cardiopulmonary function or hypovolemia, especially after massive bleeding [1,2]. Inadequate circulation could result in poor tissue perfusion. If the appropriate correction, such as adequate blood or volume expander, inotrope or vasopressor interventions, cannot be prescribed at the right time and in the right magnitude, vital organs might be damaged. Treating this situation in a timely manner with a correct diagnosis and effective reactions is the best approach to protecting critically ill patients from morbidity or mortality.

It is challenging to maintain the hemodynamic fluctuations in critically ill patients within narrow safe ranges during surgeries. Depending solely on traditional parameters, such as heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), urine output or individual practice experience, is not sufficiently reliable for clinicians to make the right decisions. We need a reliable, precise and expedient method for tracing hemodynamic parameters and evaluating tissue perfusion. Such a method should be capable of assessing cardiac contractility, volume status and peripheral vascular resistance. Many devices have been invented to measure cardiac output (CO)/cardiac output index (CI), fluid responsiveness and systemic vascular resistance

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(SVR)/systemic vascular resistance index (SVRI). It is also important to consider the application of goal-directed therapy peri-operatively and the possibilities of post-operative care in intensive care units. Previous studies have demonstrated that a preemptive strategy using these devices coupled with therapy in peri-operative or post-operative patient management significantly reduces the risk of complications and mortality [3].

Calculation of CO values

Ideal CO measuring device

The ideal device for CO measurements is considered to be not only precise, reliable, easy and rapidly equipped, but also operator-independent, non- or less-invasive, continuous and highly efficient with regard to time, expertise, cost and complication. Use of an intermittent thermodilution method for CO measurement through a pulmonary arterial catheter (PAC) is commonly recognized as a bedside technique. In addition, medical doctors are only allowed to perform right heart catherization. Currently, no ideal CO measurement device exists. Among the available techniques, the best choice for use is dependent on the individual physician's experience. In recent decades, non-invasive or less-invasive devices have attracted attention for future development.

Commonly used non- or less-invasive commercial devices

Two popular techniques are used for non-invasive or less-invasive CO measurements: one technique uses ultrasound volumetric or Doppler flow analysis, for example, transesophageal echocardiography (TEE), transesophageal Doppler ultrasound (TED) and continuous wave Doppler ultrasound (USCOM, Sydney, Australia); the other technique measures arterial pressure-based CO by analyzing the arterial pressure waveform; such systems include uncalibrated system FloTrac (Edwards LifeSciences, Irvine, CA, USA), and calibrated systems PiCCO (Pulsion, Munich, Germany) and LiCCO (LiDCO, London, UK) devices.

The ultrasound/Doppler-based CO monitoring devices

Use of non-invasive ultrasound or Doppler devices for CO assessment has proven to be interchangeable with the PAC thermodilution method in operative applications [4,5]. The shortcomings of these methods are that expertise is necessary and that the techniques are operator-dependent. TEE and TED are less invasive than PAC. However, locating the correct probe position to get a good image can be difficult, especially during upper abdominal surgery. Additionally, with the exception of TED, the devices are time-consuming to use and do not produce continuous measurements. Noise occurs when electrosurgical units are used simultaneously, as when using a TEE device. Additionally, if the heart is focally ischemic and not symmetrically contracting, the values of CO measurements provided by TEE are questionable due to the fact that a measurement of LV volume is performed by manual tracing of an endocardial border [6].

The pulse wave analysis devices

Calibrated pressure waveform devices

Although CO assessments are less invasive, operator-independent and performed continuously by using arterial waveform analysis, the use of a device is innately limited for arrhythmia patients. The PiCCO system requires a central venous catheter for transpulmonary thermodilution CO measurements for calibration, and a large arterial route for arterial waveform analysis; therefore, the device is more invasive than the other two arterial pressure-based CO monitors. Physicians may be discouraged from using the PiCCO system when they consider its invasiveness, although it offers useful data on extravascular lung water content and global end-diastolic volume additively. When patients experience massive bleeding or receive high-dose vasoconstrictors (norepinephrine), dramatic fluctuation occurs in the vasomotor tone, and the original relationship between the peripheral arterial waveform and the cardiac stroke volume is changed. The ability to accurately re-calibrate is the key to achieving precise CO measures in such situations. The PiCCO and LiDCO devices require re-calibration in regular hourly intervals and in response to major hemodynamic instabilities. The recently launched LiDCOrapid algorithm requires no calibration; however, additional validation to support its reliability is required.

Uncalibrated pressure waveform device

The FloTrac system was introduced in 2005. It has the advantage of auto-calibration and thus has no need for manual calibration, and it theoretically meets the needs for rapidly assessing dynamic vasomotor tone in major or critical-care surgeries. The PiCCO and LiCCO systems need time-consuming re-calibrations to reduce errors in these conditions [7,8]. However, a recent comparison study demonstrated that the reliability of the FloTrac system was similar to that of the PiCCO and LiDCO systems, but the precision of the FloTrac system was lower [9]. In acute critical-care surgeries, the FloTrac system is only connected with an originally existing arterial catheter and there is no additional invasiveness. Recently, there has been increasing interest in research in this area, but in different populations, the accuracy of CO measurement using the FloTrac system is controversial [10].

The promising but not yet totally validated devices

Another arterial pressure-based CO monitor, MostCare (Vytech Health, Padova, Italy), also known as the Pressure Recording Analytical Method (PRAM), analyzes arterial pressure waveforms morphology to estimate SV, and hence CO. This method estimates the CO by calculating the area under the curve of arterial pressure waveform. It needs no calibration, and has automatic re-calibration. Only a peripheral artery catheter is needed. However, few validation studies are available to make a conclusive appraisal in acute-care surgeries.

Bioreactance (Cheetah Medical, Tel Aviv, Israel), an improved bioimpedance technique, is a non-invasive device used to continuously monitor CO. It analyzes the variation in

the frequency spectra that occurs when an oscillating AC current is applied to traverse the thoracic cavity. The pulsatile blood flow in the ascending aorta causes small changes in time delays or phase shifts between the applied current and the measured voltage. These phase shifts are highly correlated with stroke volume, and can thus be used to calculate CO. The conclusions of validated studies are controversial [11–13], and only a limited amount of literature is available, especially in surgical territory.

With the ccNexfin System (BMEYE, Amsterdam, The Netherlands), the finger arterial pressure measurement method can offer real-time, beat-to-beat values on blood pressure and CO. It also provides the values of SVV, PPV and SVR. The ccNexfin system uses an inflatable finger cuff equipped with a photoplethysmographic sensor. The software algorithm generates a brachial pressure curve, and the arterial waveform from the finger artery is applied to calculate CO. No external calibration is needed, but it is not suitable for use with small children.

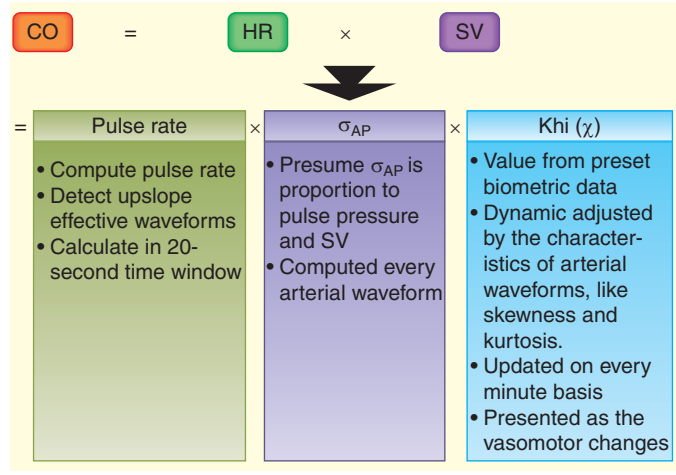

Figure 1. Modified formula of cardiac output analyses for the FloTrac algorithm.
CO: Cardiac output; HR: Heart rate; SV: Stroke volume; σ_{AP}: Standard deviation of arterial blood pressure.

The FloTrac system

CO measurement

The FloTrac system comprises a FloTrac sensor and a Vigileo monitor. This system is different from other arterial pressure-based devices, in which CO measurements are derived from the area under the curve calculation. The proprietary FloTrac algorithm modifies the equation CO = heart rate (HR) × stroke volume (SV) to CO = pulse rate (PR) × SV. PR was detected from the upslope effective waveforms, which is different from the HR. SV is proportional to the pulse pressure (PP), and PP is proportional to the standard deviation of the arterial blood pressure (σ_{AP}). Subsequently, the equation is converted to CO = PR × σ_{AP} × Khi (χ) (Figure 1). χ is a conversion factor that is characterized as vascular tone, and it incorporates the effects of both peripheral vascular resistance and compliance. After inputting the patient's age, sex, body weight and height, the data are auto-calibrated in 1-min intervals and updated by a preset biometric database and the integration of arterial waveform characteristics (skewness and kurtosis). The system compensates for real-time vascular compliance and impedance. PR is computed every 20 s, and σ_{AP} is determined on a beat-by-beat basis. The FloTrac system analyzes data at a frequency of 100 Hz; thus, 2000 data points are computed every 20 s to produce hemodynamic parameters, such as CO/CI, SV/SVI and SVV. χ is re-adjusted and updated every 1 min, in contrast to the PiCCO and LiDCO devices whose periodic re-calibrations are manually performed in long intervals; it therefore seems appropriate to adopt the FloTrac system in operations that may encounter dramatic alterations of vasomotor tone.

Transpulmonary thermodilution (TPTD) is required as an initial calibration for the PiCCO system. Patients must have a central venous catheter inserted for injecting ice-cold indicator and a large thermistor-tipped artery catheter for detecting the temperature change; catheter insertions are usually femoral or brachial accesses. The algorithm analyzes the area under the curve of the systolic portion of arterial waveform (until dicrotic notch) by a Fourier transformation to estimate continuous CO. LiDCO devices are periodically calibrated by the transpulmonary lithium dilution (TPLD) method which uses lithium chloride as the indicator for analyzing CO. The LiDCO system estimates SV from the pulse power analysis by converting arterial waveforms using a pressure-volume transformation, but is not based on the area under the curve nor the characteristics of waveform. As a result, the LiDCO system is less influenced by the damping effect than the FloTrac or PiCCO devices.

Predictor for intravascular volume

The FloTrac system provides another useful physiologic parameter: SVV. SVV is a reliable indicator for fluid optimization information in patients who are positive-pressure ventilation-controlled [14,15]. SVV correctly predicts intravascular volume in patients under controlled ventilation with a tidal volume of >8 ml/kg, positive end-expiratory pressure (PEEP) of <5 cm H_2O and no spontaneous respiration [16]. However, the study by Renner *et al.* revealed that SVV derived from the PiCCO system was still a sensitive predictor of fluid responsiveness even in higher PEEP levels in pediatric animal model, and the limitation of PEEP <5 cm H_2O is still controversial [17]. Intermittent positive-pressure ventilation leads to cyclic variations in loading conditions of both ventricles. When mechanically insufflating, it decreases preload and increases afterload of right ventricle (RV). The decreased venous return which is related to an inspiratory increase in pleural pressure causes a decrease in RV's preload. The increase in RV afterload is related to an increase in transpulmonary pressure during inspiratory period. Both preload decrease and afterload increase of RV lead to decrease SV of RV, which is minimal in the end of the inspiratory phase. The inspiratory decrease of RV ejection leads to a decrease of LV filling after a short lag due to blood pulmonary transit time. Next, the decrease in LV preload may lead to a

decrease in LV SV, which is the minimal value (SV_{min}) in expiratory period. The cyclic changes in SV of both ventricles are greater when ventricles are operating at the steep ascending part of the Frank-Starling curve rather than at the flat plateau. The ascending part of the Frank-Starling curve represents a large preload reserve, and the plateau part of the curve indicates a small preload reserve. Hence, the extent of LV SVV caused by mechanical ventilation can be used as a parameter to indicate biventricular preload dependence [14]. SVV is calculated as $SVV\ \% = (SV_{max} - SV_{min}) \times 100/SV_{mean}$. Cyclic fluctuations in SV generate synchronous variations in pulse pressure (PP) with related amplitude. PPV that is not provided by FloTrac system is similarly expressed as $PPV\ \% = (PP_{max} - PP_{min}) \times 100/PP_{mean}$. SVV and PPV are augmented and related to the deficiency of intravascular volume. They indicate the severity of hypovolemia. Heart–lung interaction may fail when patients undergo open-chest surgeries [16].

If patients are not ventilation-controlled (e.g., if they are breathing spontaneously or with assisted ventilations), the automatically measured SVV can be misleading. Other nonstandardized ventilator settings, such as tidal volume, airway pressure or respiratory rate, also significantly affect SVV estimates. Open chest conditions may fluctuate the respiration variations in SV and also in reasonable cutoff values. In right heart failure patients, SVV can be falsely increased by respiratory increase in RV afterload.

Several studies have shown that SVV and PPV are more reliable than traditional parameters (HR, MBP, CVP value and urine output) to predict volume status in clinical practice, to improve patient outcome and to reduce hospitalization days and morbidity when intraoperative goal-directed therapy was guided by SVV optimization [18–21]. Recent studies suggest that SVV and PPV show comparable performance in prediction of fluid response [22,23]. Theoretically, assessment of SVV, rather than PPV, is considered to be a more accurate tool for analyzing the variations of cardiac SV. However, SVV derived from the FloTrac system is computed from peripheral arterial waves, and not directly from assessing heart contractions. Therefore, the SVV assessed by mathematical modeling by different pulse wave analysis devices seems to be less reliable than the directly measured PPV. A central venous catheter is usually present in the patients who are critical ill or undergoing major surgeries. If needed, CVP values can be monitored from the distal port of the central venous catheterization. SVR and SVRI are also able to be calculated or automatically displayed after connecting with the input port in Vigileo monitor.

According to the literature, the referenced cutoff point of SVV is commonly suggested to be set in a gray zone (9–13%) [14,18]. The cutoff of 10% is used by Benes *et al.*, and 12.4% is concluded by Marik *et al.* In addition, Cannesson *et al.* suggest that the cutoff value is 14% [24]. Fluid responsiveness is determined when SVV is above this value, and the use of a volume expander is encouraged. SVV monitoring offers no relevant safety limit. If the hypervolemia is suspected, other measures have to be used.

Severe premature cardiac contractions limit the accuracy of SVV and its utilities. A new algorithm (SVVxtra, Edwards Lifesciences) has been developed to solve these limitations and has proved its refinements in animal model [24]. More researches are needed to validate its accuracy under severe arrhythmia in humans.

Considerations of FloTrac utility

Simplicity

The FloTrac system can be connected to a general arterial catheter with its input port and it can export hemodynamic information via two output ports: one port is connected to an ordinary monitor for displaying arterial pressures, and the other port is connected to a Vigileo monitor for analyzing CO, SV and SVV. Peripheral arteries are recommended, but in specific situations central arteries are more reliable. Vasdev *et al.* and De Backer *et al.* found that CO measurements derived from the femoral arteries are more accurate than those obtained from the radial arteries during cardiac surgery and sepsis management; use of radial access is still acceptable in these patients [25,26]. CO values measured in radial arterial locations may be more influenced in severe peripheral constriction during shock states or hypothermic episodes, and the aortic and radial arterial pressures may be also decoupled.

Femoral arterial catheterization is frequently available in emergency rooms, and connecting it with the existing central artery route is preferred. If femoral arterial catheterization is not already prepared, however, to insert an additional central artery catheterization may be difficult in emergencies or with severely impaired patients; therefore, the FloTrac system may be a more welcome choice than other techniques in which central artery catheterization is needed. The FloTrac system is preferred on account of its simplicity, easy set-up, and the fact that it requires less expertise to use.

Compared with the intermittent thermodilution method using a PAC, the FloTrac system performs nearly in real time, that is, in a 20-s window. It closely follows rapid hemodynamic changes.

Optionally obtainable hemodynamic variables

The FloTrac system basically provides measurements for CO/CI, SV/SVI and SVV. It calculates cardiac afterload, SVR or SVRI, if central venous pressure is available and input. Additionally, the system can obtain continuous central venous oxygen saturation by using a PreSep oximetry central venous catheter (PreSep, Edwards Lifesciences).

Usage in pediatric patients

The FloTrac device has not been approved for use in children thus far, and as of now only a limited amount of literature is available to evaluate its pediatric use. Teng *et al.* found that this device demonstrated poor agreement with the PAC for assessing CO in pediatric cardiac patients [27]. By contrast, the PiCCO system is a good standard for use in children [6,28], and it can evaluate the severity of right-to-left cardiac shunts. The

LiDCO device is not allowed for use in children whose body weights are less than 40 kg [6]. Because considerable blood sampling is required for transpulmonary lithium dilution, the LiDCO device may not be suitable for use in small children.

Fluid optimization

The optimization of intravascular volume can be achieved by using SVV or PPV as a predictor [14,15]. Marik *et al.* meta-analyzed 685 patients from 29 studies [14]; the predictive ability of SVV and PVV for changes in stroke volume index or cardiac index after fluid challenge in ventilation-controlled patients was calculated, and the pooled correlation coefficients were 0.72 and 0.78. The areas under the curves were presented as 0.84 and 0.94. This finding was compatible with the review by Zhang *et al.*, who meta-analyzed 568 patients from 23 studies and found that the pooled correlation coefficient between the baseline SVV and fluid responsiveness was 0.718 [15]. Predicting fluid responsiveness by SVV, the diagnostic odds ratio, sensitivity and specificity were 1.84, 0.81 and 0.80, respectively. Benes *et al.* maintained the SVV below 10% using colloid boluses of 3 ml/kg in patients undergoing elective intra-abdominal surgery. They found that fluid optimization guided by SVV during operation led to better hemodynamic stability and lower incidence of post-operative organ complications [18]. Scheeren *et al.* have shown that a SVV-based fluid optimization strategy reduces post-operative wound infections, and might decrease post-operative organ dysfunction in high-risk surgical patients [19]. Ramsingh DS *et al.* concluded that SVV optimization was associated with faster gastrointestinal recovery and higher recovery scores in patients receiving major abdominal surgery [20].

In addition to SVV, CO and SV provided by FloTrac system are also helpful to operate the fluid optimization. When used with the PreSep oximetry catheters, the Vigileo monitor measures and displays continuous central venous oxygen saturation. Clinicians may assesse fluid responsiveness via fluid challenge and observance of the corresponding change in SV or CO.

Clinical limitations for applying a FloTrac monitor

Limitations for FloTrac usage include peripheral arterial occlusion disease, aortic valve anomaly, ventricular assistance device and intra-aortic balloon pump support. Under these conditions, interpretations may be distorted and results are not valid.

Upgrades of FloTrac algorithms

Statistical methods for new device validation

The Bland–Altman statistical method is a well-recognized tool for assessing the reproducibility and validation of newly invented devices for CO measurements [29]. This method quantifies the agreement between both methods by calculating bias and limits of agreement. Bias was de?ned as the mean difference between the paired CO measurements from the two devices. The limits of agreement were de?ned as the range of the 95% confidence interval mathematically described as the mean bias ±1.96 standard deviations (SD). Critchley and Critchley proposed the calculation of the percent error to examine the interchangeability of the new method [30]. The percentage error is represented as 1.96 SD of the bias divided by the mean of CO. They described a precision of approximately 20% when using a PAC as a referenced thermodilution technique, and the percentage error was calculated as 30% by the Bland–Altman analysis. If the percentage error is less than 30% with the referenced method, equally the limits of agreement are less than 30% of the mean CO; the tested device is to be considered clinically acceptable.

However, validation studies for CO monitors analyzed solely on calculated percentage error as the major statistical criterion have recently been challenged [31]. The precision of the reference technique may be less or more than is commonly expected. The rigid application of the ±30% cutoff for the percentage error hides important information as two separate levels of precision contribute to it, which only in combination add up to the value of ±30%. Specifically, when another referenced technique is compared, the precision of the two devices should be reported separately. Inappropriate conclusions could be made if a percentage error of <30% is quoted as an interchangeable criterion with a different referenced method. The total percentage error could include the combined errors from both techniques and thus be inaccurate.

Even an imprecise but trending accurate device might be helpful for treatment, but CO trending ability is not assessed by the Bland–Altman statistical method. Besides assessing precision by the Bland–Altman method, it is suggested to apply concordance analysis, polar plot analysis and 4-quadrant plot with exclusion zones for tracking serial changes in CO, namely trending ability [32]. Generally, good CO trending is determined if a concordance rate is more than 92% when applying a 15% exclusion zone.

Table 1. Comparisons of FloTrac algorithms across its three generations.

Comparison	First generation	Secondary generation	Third generation
Year	2005–2006	2006–2008	2008–2012
Software versions	1.01–1.03	1.07–2.0	3.0–3.05
Vasomotor tone adjustment	10-min average	Improved 1-min average	Enhancement on waveform analysis in hyperdynamic patients
Database	Most are cardiac patients	More high-risk surgical patients included	Hyperdynamic patients included

Table 2. Validation studies of the third-generation FloTrac algorithm.

Study (year)	Software	Patient population	Referanced device	Investigated parameter	Patients (n)	Setting
Slagt *et al.* (2013)	3.02	Septic shock	PAC (ITD)	CO	19	Dobutamine or norepinephrine use
Marqué *et al.* (2013)	3.02	Septic shock	PAC (continuous thermodilution)	CI	18	Fluid challenges
Suehiro *et al.* (2013)	3.02	Cardiac surgery	PAC (ITD)	CO	40	Phenylephrine use (grouped by SVRI): Low (<1200 dyn/cm^{-5}/m^2) Normal (1200–2500 dyn/cm^{-5}) High (>2500 dyn/cm^{-7})
Mutoh *et al.* (2012)	3.02	SAH	PiCCO (TPTD)	CI	20	Dobutamine use
Broch *et al.* (2012)	3rd generation	Cardiac surgery	PiCCO (TPTD)	CI	50 50	CPB
Mahjoub *et al.* (2012)	3.02 3.02	Septic shock	Doppler echocardiography	CO	20	Norepinephrine use
Tsai *et al.* (2012)	3.02	Liver transplantation	PAC (ITD)	CO	20	
Su *et al.* (2012)	3.02	Liver transplantation	PAC (ITD)	CO	28	
Vasdev *et al.* (2012)	3.02	Cardiac surgery	PAC (ITD)	CO	40	
Monnet *et al.* (2012)	3rd generation	Critically ill patients	PiCCO (TPTD)	CI	60	Norepinephrine use
Meng *et al.* (2011)	3.02	Elective surgery	esophageal Doppler	CO, trending ability	33	Vasopressor use
Biancofiore *et al.* (2011)	3.02/1.10	Liver transplantation	PAC (ITD)	CI, trending ability	21	Cirrhotic patients
Metzelder *et al.* (2011)	3.02/1.14	Cerebral vasospasm after SAH	PiCCO (TPTD)	CO	n = 14 for v.3.02 n = 10 for v.1.14	High-dose norepinephrine use
De Backer *et al.* (2011)	3rd generation	Sepsis	PAC (ITD)	CO	58	Four ICUs

[†]Not given for the LOA.
AUC: Area under curve; CBP: Cardiopulmonary bypass; CI: Cardiac output index; CO: Cardiac output; ICU: Intensive care unit; ITD: Intermittent thermodilution; SD: Standard deviation; SVRI: Systemic vascular resistance index; TPTD: Transpulmonary thermodilution; $^{\Delta}$CO: Changes of cardiac output.

Measurement number	Percentage error (%)	Bias ± 1.96 SD (or 1 OA)	Correlation	Trend tracking ($^{\Delta}$CO)	Ref.
314	53	1.7 ± 4.75		r = 0.67	[46]
1201	64	-0.1 ± 2.1	r^2 = 0.22	AUC of ROC curves for detecting the same direction were 0.72	[47]
155	Before/after phenylephrine use	Before/after phenylephrine use		Concordance rate:	[48]
44	46.3/41.5	1.85 ± 2.54/ 1.16 ± 2.34		67.5%	
63	26.4/37.6	0.52 ± 1.15/ -0.45 ± 1.58		28.8%	
48	61.4/75.7	-1.34 ± 1.49/ -2.2 ± 1.65		7.7%	
95	14.9	-0.33 ± 0.51	r^2 = 0.77	NA	[35]
pre-CPB: 245	31	0.01 ± 0.73	r^2 = 0.72	r^2 = 0.52	[40]
post-CBP: 223	25	0.007 ± 0.686	r^2 = 0.62	r^2 = 0.67	
107 (CO)	81	-1.7 ± 4.5	r = 0.16		[41]
90 (^{D}CO)		0.1 ± 2.65		r = 0.41	
200	54.93	0.22 ± 3.345	r = 0.63		[39]
3234	75	-0.8 ± 4.8			[42]
342	20	-0.28†			[25]
120	54	0.26 ± 1.88		Volume expansion: r^2 = 0.26 (n = 20) Norepinephrine adjust: r^2 = 0.11(n = 40)	[43]
176	66	0.14 ± 4.17		Concordance rate: 23% after phenylephrine treatment 69% after ephedrine treatment 96% after whole-body tilting	[44]
210	52	0.4 ± 2.3	r = 0.67	Concordance rate: 72% (exclusion zones of 05 l/min^{-1}/m^{-2}) 74% (exclusion zones of 1.0 l/min^{-1}/m^{-2})	[38]
158	27.9 % (third generation) 29.6 % (second generation)	0.9 ± 2.5		r = 0.037 (CO decrease >10%) r = 0.346 (CO increase >10%)	[45]
401	30%	0 ± 22		AUC of ROC curves for detecting the same direction were 0.79	[26]

LOA: Limits of agreement; NA: Not available; PAC: Pulmonary arterial catheter; ROC: Receiver operating characteristic curve; SAH: Subarachnoid hemorrhage;

The drawbacks of last generation of FloTrac algorithms

The second-generation FloTrac algorithm were developed by recruiting more high-risk surgical patients to broaden the database and refine the Khi factor to a 1-min average compared with the first-generation algorithm (Table 1). Many studies validated the second-generation algorithm in patients who underwent cardiac arterial bypass graft surgeries or received postoperative care in intensive care units [10,33]. However, Mutoh *et al.* revealed that the second-generation algorithm (version 1.14) is not reliable for peri-operative monitoring in patients suffering from subarachnoid hemorrhages [34]. They reanalyzed the same population with a third-generation algorithm later, and found the newer algorithm improved its accuracy [35].

Otherwise, unreliability of the second-generation algorithm was demonstrated in patients with sepsis and liver transplants [36,37]. The inaccuracy was observed especially in low-SVR-status (SVR <800 dyn·s/cm^5) patients who were characterized as hyperdynamic and vasoplegic. Other authors reported that the second-generation algorithm failed to estimate real CO values in patients who were treated with high-dose norepinephrine [36]. These studies encouraged the development of the upgraded third-generation algorithm.

To improve the weaknesses of CO measurements in hyperdynamic and transplant fields, the third-generation FloTrac system included more hyperdynamic and transplant patients (those with sepsis or kidney transplantation) into the database. The third-generation algorithm demonstrated improvements and accuracy in septic patients [26]. Although the low SVR still affected its accuracy, the algorithm demonstrated considerable improvement in meeting the criteria for acceptance on SVR <800 dyn·s/cm^5. In liver transplantation, Biancofiore *et al.* found that the third-generation algorithm was refined compared with the second-generation algorithm, but it was still unreliable [38]. This finding was compatible with our study, and we discourage its clinical use in this population [39]. The latest version may still require more refinement in hyperdynamic cases, especially in liver transplant patients.

Validation studies for the third-generation algorithm of the FloTrac system

Literature searches

We performed literature searches to review the publications related to the latest third-generation algorithm of the FloTrac/Vigileo system through March 2013. We searched MEDLINE and PUBMED databases by using the keywords 'FloTrac,' 'arterial waveform analysis,' and 'third generation'. Animal studies, case reports and review articles were not included. We found 14 studies (Table 2) [25,26,35,38–48].

Accuracy in CO measurement

In these 14 studies on the third-generation algorithm, we conclude that CO measurements are reliable in cardiac surgery and critical care as demonstrated on the second-generation algorithm without focusing on hyperdynamic status [25,35,40]. In the hyperdynamic status, the upgraded version shows increased accuracy and improves the previous disadvantage observed for low SVR status in the second-generation algorithm in the studies by De Backer *et al.* and Biancofiore *et al.* [26,38]. De Backer *et al.* tested the validation in septic patients, and revealed that the third-generation software is accurate and less influenced by SVR than the second-generation one. However, this finding was not supported by Slagt *et al.*, Marqué *et al.* and Mahjoub *et al.* [41,46,47] Unlike the study by De Backer *et al.* that observed septic patients in relatively steady conditions, these other groups tested the accuracy of the FloTrac device in patients with sepsis by abruptly adjusting vascular resistance and cardiac preload with norepinephrine administration or fluid challenges. The defined time points for evaluation almost coincided with the critical points of dynamic alterations of vasomotor tones. The third-generation algorithm fails to re-calibrate precisely in situations of rapidly changing vasomotor tones and loss of accuracy [41]. This finding is compatible with the studies of Suehiro *et al.*, Monnet *et al.* and Meng *et al.* on the FloTrac system's inaccuracy in the presence of vasoconstrictor effects in non-septic populations [43,44,48]. In our opinion, a 1-min interval of auto-calibration for vascular compliance updated by the Khi factor analysis is insufficient for effective analysis under difficult challenges, and it represents only the last 1-min average, not the absolute value in the comparison point. The researchers measured CO with a short time delay after each dosage administration; thus, the vasomotor state is still not steady but is dynamically varying. Otherwise, several reasons may also explain this finding. First, Mahjoub *et al.* used a different referenced technique. Second, 67% of the patients of the study by De Backer *et al.* demonstrated a steady background when infused with norepinephrine, in contrast to the rapid adjustments and measurements focused on critical turning points in the study by Mahjoub *et al.* The third-generation algorithm showed partially improved accuracy in the steady status of septic patients, but it showed disappointing results in its calculation of fast and dynamic fluctuations of vasomotor tones. In the study by Metzelder *et al.* on patients with ruptured cerebral aneurysms, the percentage error was calculated within the recognized criteria and was commonly considered as acceptable [45]. However, an intermittent transpulmonary thermodilution method was used as a reference, rather than the gold standard method suggested by Critchley and Critchley [30]. Thus, a high precision of <3% was achieved in the referenced technique in contrast to a precision of >20% for the CO measurements obtained using the FloTrac system. The third-generation algorithm failed to show agreement with the referenced technique in their study [45].

In research on other hyperdynamic conditions, such as liver transplantation, the modified third-generation algorithm is still inaccurate in CO assessments [38,39,42], possibly because of cirrhotic myopathy, surgical manipulations or rapid vasomotor tone changes induced by inotropes, vasopressors, hypothermia and massive active bleeding. Extreme vasodilatation in hyperdynamic conditions and rapid changes in the vasomotor tone

induced by high-dose vasopressors are both recognized as major factors in causing inaccuracies, and these factors were proved in other subjects. The application of the FloTrac system in liver transplantation remains difficult.

Ability of trend tracking for CO measurements

In addition to achieving accurate CO measurements, an ideal CO measurement device should trace the acute changes concordantly. The influences of time and multiple analyses over time should be considered [49]. The tracking ability to detect significant directional changes is valuable for clinicians to evaluate the progression of diseases and monitor the effects of a prescription or goal-directed therapy. Several studies have shown that the third-generation algorithm did not possess CO tracking ability [38,41,45,48]. Biancofiore *et al.* found the trending ability of new third-generation software was improved compared with second-generation software (version 1.10) but was still not acceptable in liver transplantation [38]. Exceptionally, Broch *et al.* found that the third-generation algorithm had a good ability to track CI trends in cardiac surgery and, in particular, that CI changes in the FloTrac system were significantly correlated with changes in the reference technique during before (r^2 = 052) or after (r^2 = 0.67) cardiopulmonary bypass [40].

In septic populations, De Backer *et al.* evaluated the tracking ability in septic patients and found that 88% were infused with vasoactive agents and presented a positive correlation. The area under the curve of the receiver operating characteristic curves for detecting changes in the same direction was 0.79 (0.78 for second-generation software), whereas the CO changes were greater than 15%. Trend tracking performances in CO were considered as moderate capacity [26]. The tracking ability of the third-generation algorithm is shown as moderate-good ($r = 0.67$; $p < 0.001$) in the study by Slagt *et al.* [46], and represented a moderate capacity to track trends in CO by fluid challenging in Marqué *et al.* [47]. However, the results were disputed in the study by Mahjoub *et al.* [41]. The authors concluded that the newer algorithm was inaccurate in tracking changes in CO under norepinephrine effects in patients with septic shock. These results conflicted with the finding by Slagt *et al.* in the same study settings.

Monnet *et al.* and Meng *et al.* evaluated the tracking ability in critical or surgical patients who were vasoactively supported. They found that the latest generation demonstrated poor reliability in tracking the changes of CO or CI in patients who received vasopressor treatments, but an exception occurred in conditions when only the preload was altered (500 ml of saline for volume expansion or whole-body tilting) [43,44]. Suehiro *et al.* studied the track trends in CO induced by phenylephrine use with the third-generation algorithm in patients who underwent cardiac surgery, and they revealed similar conclusion. The concordance rates they found were: 67.5, 28.8 and 7.7% in the low, normal and high SVRI conditions, respectively [48]. In neurosurgical patients receiving high-dose norepinephrine support, the reliability of track changes in CO was not clinically acceptable in the study by Metzelder *et al.* [45] The third-generation algorithm seemingly fails to track trends in CO/CI under the high-dose vasopressor administration. Clinicians administering treatments adjusted according to the track trends in CO/CI should be aware of this limitation in present clinical practice.

Expert commentary

Although the arterial pressure-based CO monitors have proven to be practical in several clinical settings, they are not currently considered to be flawless. Further enhanced analyses on arterial waveforms or population demographics may permit next FloTrac algorithm to obtain more acceptance within the recognized criteria. We look forward to future launches of refined FloTrac evolutions that can more precisely re-calibrate σ_{AP} and Khi factor to represent the change of vascular tones or augment the database by recruiting more subgroups, for example, hyperdynamic, vasocompressor-treated or vasoplegic patients. How to correctly compute the Khi factor plays a critical role in determining its accuracy. Subgrouping the database by disease categories or severity may also be an alternative.

In our opinion, the latest version of the FloTrac system may still need refinement, especially in hyperdynamic and vasoconstrictor-treated patients.

Five-year view

Developments of non- or less-invasive CO measurement devices have been in the spotlight in recent decades, and they will continue to be in the forefront in the next decade. Designing user-friendly, easy-to-use and innovative devices to enable nurse-driven management in critical care patients is the other focus.

Presently, the latest algorithm of FloTrac system is controversial for analyzing CO and tracking trends whiling the vasomotor tones are vigorous challenging. The ability to more rapidly auto-calibrates in pace with vasomotor tones is a desired feature in the next-generation algorithm. Goal-directed fluid therapy guided by SVV has proven to be reliable and safe to achieve fluid responsiveness in critical surgical situations. Compared with traditional intravascular volume predicators, SVV is more reliable and easier to interpret, especially in urgent settings. The usefulness of SVV and goal-directed therapy in operating rooms will play an important role in the future.

Financial & competing interests disclosure

Y-F Tsai, F-C Liu and H-P Yu are employees of the Anesthesiology Department, Chang Gung Memorial Hospital, Taoyuan, Taiwan. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Key issues

- Peri-operative and post-operative complications and mortality can be significantly reduced by adopting cardiac output (CO) measuring devices for guiding fluid management. Although many promising devices for arterial pressure-based CO measurements have been approved for clinical practice, they are not yet equal to the gold standard method, which is intermittent thermodilution through a pulmonary arterial catheter (PAC). The development of more precise and reliable devices for use in acute critical surgery is a key focus of innovations. Reducing invasiveness and offering valuable parameters should increase safety during operations and decrease the occurrence of morbidity and mortality.
- The main purpose of the third-generation algorithm is to refine the inaccuracy of the second-generation device for CO measurements in hyperdynamic or vasoplegic patients, especially in patients with sepsis and liver transplantation. However, the third-generation device has failed validation in liver transplant surgery and some septic researches. Until now, the majority of published studies on this latest version have focused on its weakness, that is, application in highly selected populations or those with vigorously altering vascular tone; most studies have demonstrated its unreliability in these conditions. These findings may lead to some biases and may not be representative as a whole. This limited amount of research renders it difficult to decide whether the newer FloTrac algorithm can be precisely used in major surgeries.
- We believe that the third-generation algorithm preserves the inherited accuracy of the second-generation algorithm in already proven settings, such as in patients who underwent cardiac surgeries or who received post-operative care in intensive care units. We need additional confirmation to demonstrate whether the upgrades for hyperdynamic conditions may have reduced its original reliability.
- Stroke volume variation is supported by several studies to be a simple and dependable indicator that enables clinicians to make decisions on a patient's volume status. According to the recommended cutoff value, treatment of patients through a goal-directed fluid optimization protocol is advocated to reduce morbidity. The easy use of the device simplifies the treatment of critically ill patients; however, there are some limitations.
- There are no ideal CO measuring devices. Which device is the most suitable depends on the individual patient's conditions. We must evaluate indications, limitations, invasiveness, difficulties and details regarding the set-up and benefit/cost ratio.
- The standard method (intermittent thermodilution technique) commonly referenced is biased as 3–30%, and the rigid application of the ±30% cutoff for the percentage error is questionable without reporting the precisions of both methods separately.

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