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Central venous pressure as an adjunct to flow-guided volume optimisation after induction of general anaesthesia

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Abstract

Background: Although the central venous pressure (CVP) is often used as a guide to volume status in major surgery and intensive care, fluid therapy should be guided by the response of the stroke volume (SV) to a fluid bolus. The present study evaluates whether the central venous pressure (CVP) can serve as an adjunct to decisions of whether or not fluid should be infused.

Methods: Stroke volume (SV) and stroke volume variation (SVV) was monitored with FloTrac/Vigileo and the CVP were measured in 80 patients just before general anaesthesia was induced (baseline) and then, before each of three successive bolus infusions of 3 mL kg^{-1} of 6% hydroxyethyl starch 130/0.4. A patient showed fluid responsiveness and was denoted a "responder" if SV increased by ≥10% from the bolus infusion.

Results: The CVP was higher in non-responders (mean 7.2 mm Hg) than in responders (mean 5.8 mm Hg, $P < 0.0001$). In non-responders but not in responders, the absence or presence of a rise in CVP improved the prediction of whether the patient would show fluid responsiveness during the next fluid bolus. For example, if no rise in CVP occurred the chance was 48% of subsequent fluid responsiveness, while this chance was only 9% for those who had an increase in CVP ($P < 0.004$). There was only a fair concordance between fluid responsiveness as indicated by SV and SVV (Cohen´s kappa 0.28).

Conclusions: A low CVP suggests that the patient is lower on the Frank-Starling curve than indicated by SV as measured by FloTrac/Vigileo.

Key words: central venous pressure; fluid therapy; fluid responsiveness; general anesthesia; stroke volume; stroke volume variation

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The use of central venous pressure (CVP) to monitor fluid therapy has been questioned during the past decade [1]. CVP increases because of rapid accidental or deliberate volume loading [2] and is a widely used haemodynamic measure of cardiovascular filling [3]. However, the scientific view which has received support in outcome studies [4, 5], is that fluid responsiveness, rather than CVP, should be used to guide fluid therapy.

Fluid responsiveness is present if the stroke volume (SV) increases by 10% or more in response to a bolus infusion, which is usually tested by a colloid fluid. The bolus infusion is repeated until the incremental increase in SV no longer reaches 10%, at which point the patient is considered volume optimized. In some studies, a co-requirement has been that more fluid should be avoided if CVP has increased by > 3 mm Hg [5] although it is unknown whether CVP can be used to improve decisions based on SV. Fluid responsiveness can also be obtained by other means, such as stroke volume variation (SVV), which is an index of the beat-to-beat variation in SV over the respiratory cycle. Values exceeding 10–11% suggest fluid responsiveness [6–8].

The present study compares CVP with SV and SVV when patients are volume optimized with colloid fluid bolus infusions after the induction of general anaesthesia. The hypothesis was

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that CVP could serve as an adjunct to SV and SVV when making decisions about whether or not to provide more fluid.

METHODS

PATIENTS

Eighty patients with suspected or established gastric, colonic or rectal cancer were recruited to participate in this study, which was part of larger open-label clinical trial of colloid and crystalloid fluids that was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (Hangzhou, PR of China; No. 2011150, Official in charge: Zhangfei Shou) and registered at the Chinese Clinical Trial Registry (http://www.chictr.org/en; No. ChiCTR-TNRC-14004479).

The studied patients belonged to American Society of Anesthesiologists [ASA] class I or II and underwent laparoscopic or open gastrointestinal surgery under combined intravenous and inhalational general anaesthesia between July 2011 and March 2013. The exclusion criteria were liver or renal dysfunction (liver enzymes > 50% or serum creatinine > 50% of normal), coagulation disturbances, obstructive pulmonary disease, atrial fibrillation and mental disorders. Written informed consent was obtained from each subject.

ANAESTHESIA

The patients fasted overnight, and no premedication was given. At 8:00 am, anaesthesia was induced and tracheal intubation performed after injecting appropriate amounts of propofol, fentanyl and cisatracurium. The patients were mechanically ventilated by using a tidal volume of 8 mL kg^{-1}, 12 breaths min^{-1} and a positive end-expiratory pressure of 3 cm H_2O. The anaesthesia was guided with 1–2 vol% of sevoflurane and continuous infusions and remifentanil to reach a bispectral index (BIS) value of between 40 and 60.

FLUID PROGRAM

No fluid was induced during the induction of general anaesthesia. Beginning at 10 min after the tracheal intubation, three bolus infusions of 6% hydroxyethyl starch 130/0.4 (Voluven®; Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany) were given in a volume of 3 mL kg^{-1} over 7 min via an infusion pump (IEC 601–1; Abbott Laboratories, Chicago, IL, USA). The haemodynamic response was recorded 5 min after the end of each bolus infusion. The patients retained a flat recumbent body position, and surgery did not begin until all three optimizations had been completed.

MEASUREMENTS

When the patient entered the operating theatre, catheterization of the left radial artery and right interval jugular vein was performed under local anaesthesia, with sedation by midazolam. The arterial line was connected to a FloTrac™ sensor from which data was sent for analysis to a Vigileo monitor (Software version 3.6; Edwards Lifesciences, Irvine, CA, USA). The arterial waveform pulse contour was used to calculate stroke volume (SV) and stroke volume variation (SVV). The measurements also included central venous pressure (CVP), pulse oximetry, electrocardiography and heart rate. The CVP was calibrated before the anaesthesia was induced. Zero level was the 4th rib in the anterior axillary line.

Data on central haemodynamics were collected and saved digitally (Datex-Ohmeda, Hoevelaken, the Netherlands) before and after the induction of anaesthesia, immediately before the first bolus infusion, and then 5 min after the completion of each bolus infusion.

TERMINOLOGY

In flow-guided optimization with fluid loading, the target is to reach the top of the Frank-Starling curve. Therefore, the patient was considered a responder when a bolus infusion raised SV by ≥ 10% and a non-responder when the increase was < 10% [7]. Because flow-guided optimization implies a titration process, a bolus was indicated if it was given after an infusion in which the patient was fluid responsive.

STATISTICAL ANALYSIS

The data are presented as mean (SD) and differences between groups evaluated by a one-way analysis of variance (ANOVA). Incidence data were tested by contingency table analysis. Receiver operator characteristic (ROC) curves were created with IBM SPSS Statistics Version 22 to calculate the optimal sensitivity and specificity of CVP and SVV to predict fluid responsiveness as obtained from SV. The strength of the indication was expressed as the area under the curve (AUC). Significance was defined as $P< 0.05$.

Details on the responses of selected haemodynamic parameters to the induction of anaesthesia and the bolus infusions, for which the study was powered, have been presented elsewhere [9]. A *post hoc* power analysis was performed based the actual SD (= 1.0) for all 240 CVP measurements and the distribution of responders and non-responders during the 3 bolus infusions (45% and 55%) showed that a mean difference in CVP change of 0.5 mm Hg between the two groups could be demonstrated at a significance level of $P < 0.05$ with a power of 95%.

RESULTS

The patients were aged 56 (13) years and had a body weight of 60 (8) kg. Thirty patients (35%) were female. The three bolus infusions increased SV (mean) by 15%, 10% and

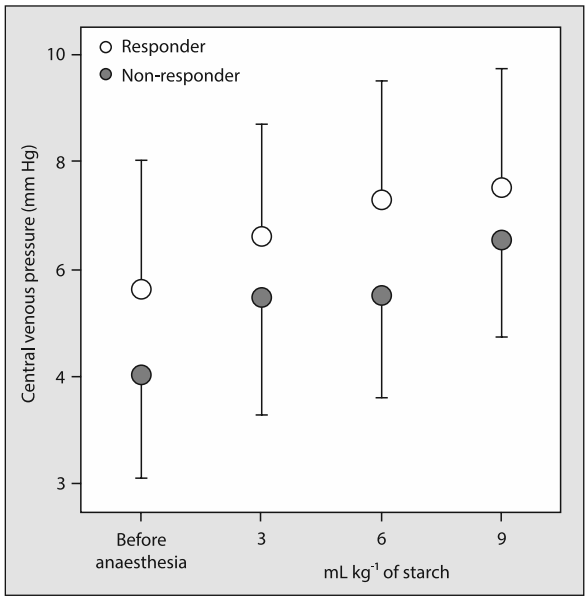

Figure 1. Central venous pressure before anaesthesia is induced and immediately before three sequential bolus infusions of hydroxyethyl starch 130/0.4 depending on whether the patient was fluid responsive or not

3.5%, respectively. The corresponding changes in CVP were + 0.6, + 0.7 and + 0.9 mm Hg, respectively. The number of patients that showed increased SV ≥ 10% in each of the three successive fluid boluses represented 67%, 47% and 23% of the cohort.

STATIC CVP IN RESPONDERS AND NON-RESPONDERS

The CVP before the induction of anaesthesia was lower in patients who showed fluid responsiveness during the first bolus infusion (4.2 vs. 5.6 mm Hg; $P < 0.01$). Moreover, the CVP was usually lower before any bolus infusion in which the patient showed fluid responsiveness (Fig. 1). For all boluses, the mean CVP was 5.8 mm Hg before the infusions in the responders and 7.2 mm Hg before the infusions in the non-responders ($P < 0.001$; Table 1).

The ROC curves showing the ability of CVP to indicate fluid responsiveness confirmed that the point of highest sensitivity and specificity increased as the number of infusions increased (Fig. 2).

Table 1. Central venous pressure (CVP) and stroke volume variation (SVV) depending on whether the patient proved to be a responder or not during the subsequent fluid bolus infusion. Data are the mean (SD)

	Bolus No	Responder	Non-responder	Statistics
CVP before anaesthesia (mm Hg)	1	4.2 (1.9)	5.6 (2.4)	$P < 0.01$
CVP when a bolus starts (mm Hg)	1	5.5 (2.2)	6.6 (2.1)	$P < 0.04$
	2	5.5 (1.9)	7.3 (2.2)	$P < 0.001$
	3	6.5 (1.8)	7.5 (2.2)	$P = 0.10$
	1–3	5.6 (2.0)	7.2 (2.2)	$P < 0.0001$
Stroke volume variation (SVV)	1	17.3 (5.9)	13.0 (4.2)	$P < 0.001$
when a bolus starts (%)	2	13.4 (4.4)	10.9 (3.5)	$P < 0.005$
	3	12.1 (3.0)	8.9 (2.9)	$P < 0.0001$
	1–3	15.1 (5.5)	10.4 (3.8)	$P < 0.0001$

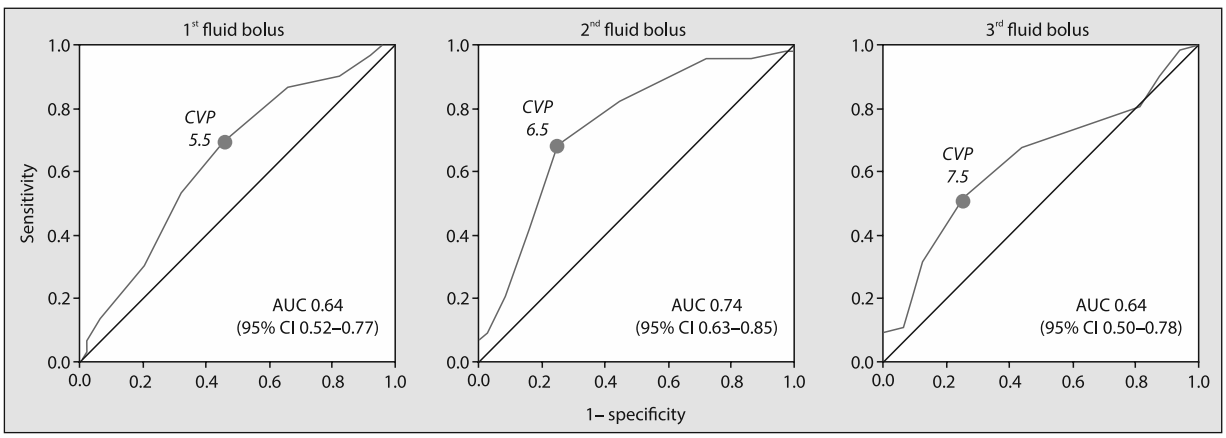

Figure 2. Receiver-operator (ROC) curves showing the ability of the central venous pressure (CVP) to indicate fluid responsiveness as given by an increase of ≥ 10% in stroke volume according to Flo-Trac/Vigileo

Table 2. Changes in central venous pressure (CVP) used to predict whether fluid responsiveness was found during a subsequent fluid bolus of 3 mL kg^{-1} of hydroxyethyl starch

		RESPONDER 1st BOLUS			Statistics
		Yes No			
Responder 2nd bolus	Yes (A)	No (B)	Yes (C)	No (D)	
N	26	24	10	20	
ΔCVP induction (no bolus)	0.7 (1.3)	1.8 (1.2)	1.2 (1.4)	0.8 (1.6)	A vs B; $P < 0.01$
ΔCVP during 1st bolus	0.7 (0.4)	0.8 (1.0)	0.0 (1.5)	0.8 (0.8)	C vs D; $P < 0.03$
ΔCVP induction + 1st bolus	1.4 (1.3)	2.5 (1.3)	1.2 (2.2)	1.6 (1.4)	A vs B; $P < 0.003$
		RESPONDER 2nd BOLUS			
		Yes No			
Responder 3rd bolus	Yes (A)	No (B)	Yes (C)	No (D)	C vs D: $P < 0.001$
N	8	27	8	35	
ΔCVP during 2nd bolus	0.9 (0.6)	0.8 (0.6)	0.0 (0.5)	0.8 (1.3)	
ΔCVP induction + 1st + 2nd	2.5 (1.5)	2.0 (1.8)	1.6 (1.1)	3.0 (1.5)	C vs D: $P < 0.02$

Data are the mean (SD). For statistics, the one-way ANOVA was selectively applied to the A–B and C–D pairs

Table 3. Frequency of correct predictions of fluid responsiveness during a subsequent fluid bolus based on the change in stroke volume SV during the current fluid bolus (≥ 10% or not), with and without considering whether or not there was a rise in CVP

Current bolus	Prediction SV + CVP		Prediction only by SV	Next bolus
	CVP rise	*No CVP rise*		
Responder	43%	37%	40%	Responder
	57%	63%	60%	Non-responder
Non-responder	9%	48%	25%	Responder
	91%	52%	75%	Non-responder

CVP CHANGES PREDICT LATER FLUID RESPONSIVENESS

The ability of CVP to predict later SV responses was studied based on the change in CVP (ΔCVP). The results are shown in Table 2.

The key finding was that later fluid responsiveness was more likely if ΔCVP was small. Firstly, fluid responsiveness during the second bolus infusion was more likely when there had been only a small total increase in CVP between the induction of anaesthesia and the first bolus infusion [1.3 (1.9) mm Hg vs. 2.1 (1.4) mm Hg; $P < 0.03$]. The predictive value was particularly high if the patient had been a responder during the first infusion [mean ΔCVP +1.4 vs. +2.5 mm Hg, $P < 0.003$; Table 2].

Secondly, during the first or second bolus infusion with no increase in CVP, the non-responders had a 48% chance of becoming a responder during the subsequent bolus infusion. This chance was only 9% in those who showed a rise in CVP ($P < 0.004$, Table 2). The odds ratio for later becoming a fluid responder was only 0.11 (95% confidence interval, 0.03–0.38) if CVP increased, as compared to when CVP did not increase.

Conversely, assessment of CVP in non-responders improved the accuracy of a prediction of later fluid responsiveness from 75% (SV alone) to 91% (SV + rise in CVP).

CVP had no predictive value in responders (Table 3).

THE INTERMEDIATE SV RANGE

Patients who had a change in SV between 0% and 10% during the first fluid bolus infusion were more likely to become responders during the second infusion if their CVP at the end of the first infusion was on the low side [mean 5.8 (1.7) vs. 7.8 (1.6) mm Hg, $P < 0.01$].

Similarly, at the end of the second infusion, the CVP was lower in patients who would later become fluid responders [mean 6.0 (1.8) vs. 8.3 (1.9) mm Hg, $P < 0.01$]. In these patients, the ΔCVP response during the second bolus was also absent [0.0 (0.6) mm Hg], which was not the case in those who were non-responders during the third bolus [0.9 (0.8) mm Hg, $P< 0.02$].

STROKE VOLUME VARIATION (SVV)

Before each bolus, the SVV was 15.8% (SD 5.8), 12.0% (4.1) and 9.7% (3.2), respectively. Although the SVV was

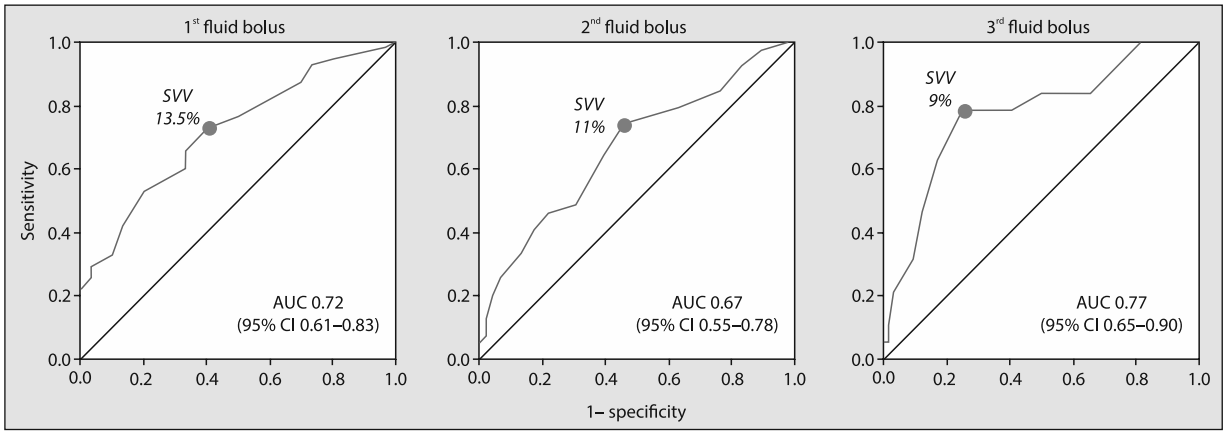

Figure 3. Receiver-operator (ROC) curves showing the ability of the stroke volume variation (SVV) to indicate fluid responsiveness as given by an increase of ≥ 10% in stroke volume, both according to Flo-Trac/Vigileo

higher before fluid boluses in which SV was increased by ≥ 10%, the difference was dependent on the amount of infused starch (Table 1, lower). The ROC curves showed that SVV had no better ability than CVP did to indicate fluid responsiveness (Fig. 3).

The concordance between the SVV and SV methods was 0.28 ($P < 0.002$; Cohen's kappa analysis). This calculation was based on the assumption that the indication of fluid responsiveness was given by a pre-infusion SVV of > 10%.

The ROC curves showed that CVP could not indicate fluid responsiveness as given by SVV during any of the three bolus infusions (AUC was 0.62, 0.52 and 0.60, respectively).

DISCUSSION

Fluid responsiveness after the induction of anaesthesia was more likely if the CVP was on the low side, although the absolute level was dependent on the amount of infused hydroxyethyl starch (Table 1). This observation was expected, as responders are positioned on the steep portion of the Frank-Starling curve [10].

The results also showed that the change in CVP during one bolus infusion could be used to predict the outcome of the subsequent bolus. A small CVP change during one infusion indicated that fluid responsiveness would be present during the subsequent one.

The presence or absence of a rise in CVP could help one to predict fluid responsiveness in non-responders but not in responders (Table 3). A patient with no rise in CVP during a bolus infusion in a non-responder had actually a good chance of becoming a responder during the next infusion. In contrast, the chance of becoming a responder again during the next bolus was negligible for a non-responder with an increase in CVP.

When the SV response to one bolus was in the "intermediate range", that is, a rise between 0% and 10%, the clinician could assess the CVP at the end of the infusion and the change in CVP to ascertain the position of the patient on the Frank-Starling curve.

The central venous pressure has long been a key measure used to assess fluid volume status. CVP is still widely used in intensive care, although its value is being questioned. A recent consensus article described the clinical value of CVP in vague terms only [11]. CVP apparently represents the volume status only when the heart is stopped, whereas in CVP the intact circulation is modified by many factors, including intrathoracic and intra-abdominal pressures, transmural pressure and vessel distensibility [3]. The dependency on intrathoracic pressure probably explains why CVP rose after the induction of anaesthesia in the present study, despite the fact that general anaesthesia causes vasodilatation (Table 1).

Cardiac output is governed by venous return. However, the driving force of venous return is not CVP but the difference between the mean circulatory filling pressure and CVP. The mean circulatory filling pressure is difficult to measure in patients with intact circulation although complex empirical algorithms are used to estimate this parameter from CVP, mean arterial pressure and cardiac output [12].

Our results did not show that CVP is a useless circulatory parameter. Instead, they indicated that CVP could refine decisions regarding fluid therapy. A high CVP, or a rise in CVP, supports that the patient was high on the Frank-Starling curve and would be unlikely to be a responder to a subsequent bolus. One downside with this approach was that what could be considered a low or high CVP was dependent on the amount of starch that was infused (Fig. 1). In contrast, indications given by ΔCVP seemed to be independent of

the infused fluid volume. Here, CVP offered more refined evaluations of the fluid status in non-responders.

Many approaches have been used to determine fluid responsiveness. FloTrac/Vigileo records the pulse wave from a radial artery catheter and calculates SV by assuming that it is proportionate to the area under the systolic portion of the pressure wave. Although other systems on the market, such as LiDCO and PiCCO, need to be calibrated for each patient, FloTrac/Vigileo is auto-calibrated by a proprietary algorithm.

When a pulse contour monitoring system is used, fluid responsiveness can also be calculated as SVV, which is taken as the difference between the highest and lowest SV values, relative to the mean stroke volume throughout the respiratory cycle. As expected, the SVV indicating fluid responsiveness became lower as the amount of starch was increased, which was opposite to the pattern observed for CVP. The correlation between SV and SVV as indicators of fluid responsiveness was poor (Fig. 3). Our results do *not* support the idea that CVP could aid decisions about fluid therapy when SVV is used as the index of fluid responsiveness.

A recent consensus article holds that SVV can be used to indicate fluid responsiveness [11] although the ability has been quite variable in available original studies. Triepte *et al.* 10] administered three bolus infusions with hydroxethyl starch in 24 postoperative patients. They reported that the AUC for the ROC curve was 0.72, which should be compared to our overall average AUC at about 0.60 (Fig. 3). Davies *et al.* [13], relying on oesophagus-Doppler as the "correct answer", found the AUC to be only 0.57. Higher values have also been reported. Preistman [6] compared fluid responsiveness, obtained by echocardiography with SVV generated by PiCCO, and reported an AUC at about 0.80. However, similar to the results of this study, previous research did not find a statistically significant agreement between SVV and the control method. Our results showed that it is difficult to justify the use of SVV in clinical practice in light of the great variability and frequently poor concordance with the reference method found in previous studies.

The present study has the following limitations, namely: the SV was measured by the FloTrac/Vigileo system, which has a higher coefficient of variation than calibrated arterial waveform pulse contour modes. SV may then be obtained in conscious patients, whereas SVV requires that patients be mechanically ventilated. Another limitation is that the subjects were studied in groups of 25–30 instead of being randomized individually. Although the original case series also contained a group of patients that were given Ringer's lactate for fluid optimization, they were not included in this study as we found that 3 ml/kg of crystalloid could not adequately challenge fluid responsiveness [9].

In conclusion, a low CVP suggests that the patient is further down on the Frank-Starling curve than might be indicated by dynamic measures of fluid responsiveness. The use of CVP could offer more refined evaluations of the fluid status in non-responders, but not in responders. Furthermore, SVV showed poor ability to indicate fluid responsiveness.

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