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Original Article

Prediction of Fluid Responsiveness by Means of Stroke Volume Variation Measured by Pulse Wave Transit Time-Based Cardiac Output Monitoring

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ABSTRACT

Introduction: Evaluation of the stroke volume and stroke volume variation (SVV), which could predict fluid responsiveness, is important for perioperative cardiovascular management. In this study, we evaluated fluid responsiveness using a noninvasive pulse wave transit time (PWTT)-based cardiac output monitor, the estimated Continuous Cardiac Output (esCCO).

Methods: Forty-six adult patients who underwent open abdominal surgery were included. Fluid loading with a 300 mL colloidal solution in 15 min was performed during surgery under general anesthesia. Fluid responsiveness was defined as a 10% or more increase in stroke volume index (SVI) measured by the esCCO. Several parameters were measured before and after fluid loading, and an SVV cutoff value for fluid responsiveness was calculated using the receiver operating characteristic (ROC) curve analysis.

Results: Fluid responsiveness was observed in 27 of the 46 patients. SVV and cardiac index exhibited significant changes in the responsive group. In addition, the area under the ROC curve was 0.904 (range, 0.819-0.988) for a 10% or more increase in SVI after fluid loading. The cutoff SVV value was 6.4%.

Conclusion: In this study, we successfully used the noninvasive monitor esCCO to show fluid responsiveness during general anesthesia for open abdominal surgery, and the esCCO-derived SVV has an excellent diagnostic value, which is evidenced by the high AUC of ROC curve analysis.

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1. Introduction

With the increasing average age of patients undergoing surgery, more patients present with reduced tolerance for surgery involving various organs. Intraoperative cardiovascular management is particularly important for patients with risks of cardiovascular involvement. Therefore, hemodynamic assessments are required to ensure proper cardiovascular management.

Selecting the right monitoring equipment and parameters is important to evaluate cardiac function. Moreover, a comprehensive assessment of the cardiac preload, afterload, and cardiac contractility is required to assess the cardiac function, in particular, the use of a pulmonary artery

catheter or central venous catheter.[1]

However, large clinical studies conducted over the past 20 years have revealed doubts on the significance of using catheters and concluded that prognoses do not improve with their use.[2-4]

However, in those studies, treatment protocols or parameters were unclear, and the fluid infusion and catecholamine amounts used were only determined based on central venous pressure (CVP) and pulmonary artery wedge pressure (PAWP) values, and the cardiac function was not evaluated. In other words, the CVP and PAWP values reported in these large clinical studies were not representative of the cardiac preload values.[5, 6]

The classic Frank-Starling curve demonstrates a correlation between the preload and cardiac contractility, and the cardiovascular status can be evaluated by fluid responsiveness. However, the traditional fluid responsiveness assessment requires fluid loading and may not be appropriate in patients with cardiac failure or renal dysfunction. Therefore, calculation of the stroke volume variation (SVV), which is the result of the changes in the intrathoracic pressure during positive pressure ventilation, has gained attention, because the actual fluid loading is not necessary.[7-9]

The objective of this study was to evaluate the stroke volume index (SVI) and SVV, using a novel, noninvasive cardiac monitor called the estimated Continuous Cardiac Output (esCCO), and elucidate its diagnostic value to predict fluid responsiveness.

2. Methods

2-1 Patients

The study protocol was approved by the Institutional Review Board of Toho University Medical Center Omori Hospital (approval number: M180831730216262; UMIN register number: UMIN000029471). All patients provided informed consent.

The included subjects were 46 adults with an American Society of Anesthesiologists Physical Status score of 1-2 who were scheduled to undergo laparotomy at our institution from April to July 2019. The exclusion criteria were as follows: persistent arrhythmia and renal dysfunction (estimated glomerular filtration rate $<$ 60) in the preoperative examination.

2-2 Methods

2-2-1 Anesthesia management

For the monitoring during anesthesia, an electrocardiograph (ECG), a pulse oximeter, a noninvasive blood pressure, a capnograph, a thermometer, and a neuromuscular monitor were attached to all patients. When necessary, the arterial pressure was directly measured.

The arterial pulse pressure obtained in the first blood pressure measurement after entering the operating room was used as the blood pressure control value. Anesthesia was induced using propofol (1-2 mg/kg), remifentanil (0.05-0.2 µg/kg/min), and rocuronium (0.6-1.0 mg/kg). Mechanical ventilation was initiated after tracheal intubation.

Anesthesia was maintained using desflurane (4%-6%), remifentanil (0.05-0.2 µg/kg/min), and rocuronium (0.1-0.2 mg/kg). Patients receiving epidural anesthesia were additionally administered 1% lidocaine or 0.375% levobupivacaine during surgery.

2-2-2 Fluid and cardiovascular management

Fluid loading was performed while the systolic arterial pressure decreased to 10% or more after induction of anesthesia, and hemodynamic status was determined as stable for more than 5 min. However, when the mean arterial pressure fell to 50 mmHg or below, vasopressors were prioritized to maintain adequate blood flow to the organs. Fluid loading was performed once the mean arterial pressure was maintained at 50 mmHg or higher for at least 10 min.

For fluid loading, 300 mL of a 6% Voluven colloid solution was administered in 15 min *via* an infusion pump.

2-2-3 Ventilator settings

The ventilator settings for all patients were a tidal volume of 8-10 mL/kg (ideal weight) at 12 breaths/minute and a positive end-expiratory pressure of 5 cmH₂O. End tidal CO_2 was set at 40 ± 5 mmHg.

2-2-4 Data sampling

After inducing anesthesia, the pulse wave transit time (PWTT) was calculated based on ECG and pulse oximeter values using an HDM-3000 bedside monitor (Nihon Kohden, Tokyo, Japan). The esCCO was calibrated from the indirect blood pressure measurements.

SVI, SVV, and cardiac index (CI) were measured using the esCCO for about 5 min immediately before and after fluid loading.

2-2-5 Data recording and analysis

All hemodynamic data were recorded by the minute.

Based on the SVI values before and after fluid loading, patients who exhibited an increase of 10% or more were considered "responders," and those with an increase of less than 10% were considered "non-responders." For both

Table 1　Patients baseline characteristics

	overall (n = 46)	responder (n = 27)	non-responder (n = 19)
age (years)	60.1 ± 14.1	62.5 ± 14.4	54.8 ± 10.8
height (cm)	157.7 ± 6.7	156.4 ± 6.9	158.8 ± 5.7
weight (kg)	59.2 ± 13.4	58.7 ± 15.2	59.9 ± 10.8
BMI (kg/m²)	23.8 ± 5.4	24.0 ± 6.3	23.7 ± 4.2
Operation time (min)	267.5 ± 115.3	257.8 ± 104.6	268.9 ± 125.2
Anesthesia time (min)	332.6 ± 122.6	326.4 ± 113.4	329.5 ± 131.5
Infusion amount (mL)	2298.1 ± 878.0	2356.8 ± 912.7	2118.2 ± 804.0
Type of suegry			
Stomach cancer	8		
Pancreatic cancer	5		
Liver cancer	2		
Colon cancer	2		
Gallbladder cancer	1		
Spleen tumors	1		
Gynecologic cancer	24		
Benign gynecological tumors	3		
ASA-PS (1/2)	21/25		

Data are mean ± SD　　　　　no statistical difference
ASA-PS: American Society of Anesthesiologists Physical Status score

groups, the mean and standard deviation were calculated for patient characteristics (age, height, weight, BMI, operation time, anesthesia time, and infusion amount) and hemodynamic parameters (mean arterial pressure or mean blood pressure [mBP], heart rate, SVI, SVV, and CI).

As the statistical methods, unpaired t-test was used to compare the data between groups, and paired t-test was used to compare the data within the group when normality was demonstrated with the Shapiro-Wilk test. Statistical analyses were performed using the SPSS Statistics ver. 20.0 (IBM SPSS, Chicago, USA). P-values less than 5% were considered statistically significant. The receiver operating characteristic (ROC) curve analysis was performed to calculate the area under the ROC curve (AUC) and cutoff values for SVV using Youden's index to predict the responders and non-responders (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3-1 Patient characteristics

The subjects included in this study underwent laparotomy from April to July 2019. Table 1 shows the patient characteristics. There were 13 men and 33 women, with the mean age of 60.1 ± 14.1 years (Table 1).

3-2 Changes in hemodynamic variables after fluid loading

Fluid loading was performed with a 300 mL colloidal so-

lution in 15 min. Comparing the parameters measured using esCCO before and after fluid loading showed that mBP increased from 66.4 ± 11.7 mmHg to 71.5 ± 15.2 mmHg ($P < 0.05$). The heart rate exhibited almost no change from 67.8 ± 12.5 to 67.9 ± 12.6 beats/min ($P = 0.97$). SVI increased from 34.2 ± 8.1 to 37.9 ± 8.1 mL/m² ($P < 0.05$). SVV decreased from 7.56% ± 4.15% to 5.47% ± 1.75% ($P < 0.05$). CI increased from 2.31 ± 0.68 to 2.58 ± 0.73 L/min/m² ($P < 0.05$) (Table 2).

3-3 Comparison of parameters between responders and non-responders

Table 2 shows the comparison of various parameters before and after fluid loading among the responders (n = 27) and non-responders (n = 19). Among the responders, mBP, SVI, SVV, and CI changed significantly after fluid loading, but the heart rate did not. In contrast, among the non-responders, only the SVV decrease was significant.

We also compared the change in parameters before and after fluid loading between the responders and non-responders. Before fluid loading, significant differences were observed between the responders and non-responders in mBP, SVI, SVV, and CI, but not in the heart rate. After fluid loading, only SVI was significantly different between the responders and non-responders (Table 2).

3-4 Evaluation of SVV fluid responsiveness

Fluid responsiveness was observed in 27 of the 46 patients (59%). SVV decreased from 7.5% before fluid loading

Table 2　Hemodynamic data before and after fluid challenge (overall, responder, non-responder)

	overall (n = 46)		responder (n = 27)		non-responder (n = 19)	
	control	fluid challenge	control	fluid challenge	control	fluid challenge
mBP (mmHg)	66.4 ± 11.7	71.5 ± 15.2 *	63.2 ± 11.3	71.2 ± 17.2 *	71.1 ± 11.0#	72.0 ± 12.1
HR (bpm)	67.8 ± 12.5	67.9 ± 12.6	67.5 ± 12.9	67.6 ± 12.8	68.3 ± 12.4	68.2 ± 12.6
SVI (ml/m²)	34.2 ± 8.1	37.9 ± 8.1 *	29.7 ± 7.2	35.7 ± 9.1 *	40.4 ± 4.2#	41.1 ± 5.2#
SVV (%)	7.56 ± 4.15	5.47 ± 1.75 *	9.15 ± 4.78	5.81 ± 2.03 *	5.32 ± 1.08#	4.99 ± 1.13 *
CI (L/min/m²)	2.31 ± 0.68	2.58 ± 0.73 *	2.05 ± 0.67	2.49 ± 0.77 *	2.65 ± 0.55#	2.70 ± 11.1

Data are mean ± SD　　* p＜0.05, compared with control

　　　　　　　　　　　# p＜0.05, compared with responder

mBP = mean arterial blood pressure, HR = heart rate, SVI = stroke volume index, SVV = stroke volume variation, CI = cardiac index

control = before fluid challenge, fluid challenge = after fluid challenge
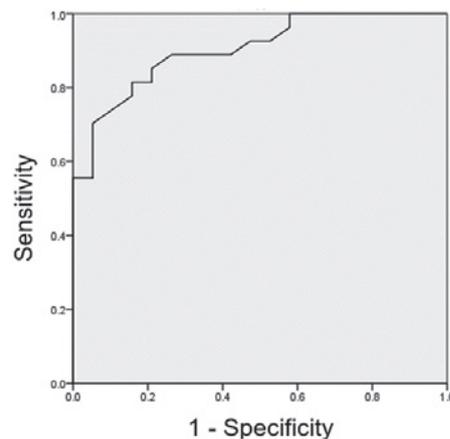
AUC (SVV)	Cutoff value	Sensitivity	Specificity
0.904 (0.819−0.988)	6.40%	0.815	0.842

AUC : Area under ROC curve　SVV : stroke volume variation

Fig. 1　Receiver operating characteristic curve for the ability of stroke volume variation to discriminate between responder and non-responder.

to 5.4% after fluid loading. In addition, AUC was 0.904 (0.819-0.988) for a 10% or more increase in SVI after fluid loading. SVV had a cutoff value of 6.4%, sensitivity of 81%, and specificity of 84% (Fig. 1).

4. Discussion

4-1 Role of esCCO

The esCCO is a noninvasive cardiac output monitoring, which uses ECG and pulse waves from a pulse oximeter. The accuracy of the esCCO has been compared with that of other cardiac output monitoring modalities. Studies have shown a good correlation and trackability with the cardiac output calculated using thermodilution, although other studies have found problems in the correlation and

trackability with the cardiac output calculated using the ECG and intraoperative cardiovascular data.[10, 11]

Previously, manipulations of the heart and major vessels during cardiovascular and other surgeries directly affected the pulse wave propagation time required for esCCO. This reduces the accuracy, which explains the findings of these studies.[12–14] In other words, monitoring equipment and its parameters should be selected taking into consideration both the patient condition and surgical manipulations involved.

The present study used data from the surgeries that did not include manipulations of the cardiovascular system. Thus, the subject population was similar to those used in previous studies that found strong correlations between

the esCCO and thermodilution. The purpose of the present study was to progress from comparisons of accuracy to examining whether this device can be used for cardiovascular management. Using the esCCO during surgery under mechanical ventilation, we investigated SVI as a representative of cardiac contractility, reflecting the increase in preload after fluid loading. We demonstrated that responsiveness could be predicted using variations in positive pressure ventilation.

4-2 Findings of this study

As shown in Table 2, the present study found that fluid loading with a 300 mL colloidal solution in 15 min increased SVI from 34.2 ± 8.04 mL/m^2 before loading to 37.9 ± 8.25 mL/m^2 after loading, which is a significant difference. SVV is a leading parameter used to predict the responsiveness for SVI, and we found that a 10% increase in SVI after fluid loading could be predicted using an SVV cutoff value of 6.4%. As shown in Table 2, patients with low SVI tended to exhibit fluid responsiveness and increase in both CI and SVI. In contrast, patients with high SVI did not exhibit fluid responsiveness or increase in SVI or CI. This indicates that responsiveness is a rational phenomenon and that esCCO could be used to evaluate the physiological responses during cardiovascular management.

In particular, the responder group exhibited significant changes after fluid loading in SVV, SVI, and CI, whereas the non-responder group only exhibited a significant decrease in SVV. On the Frank-Starling curve, we predict that the responder group would be located in the ascending portion, which indicates a high rate of cardiac output increase, whereas the non-responder group would be in the horizontal portion, where an increase in the cardiac output is not expected. These results suggest that the noninvasive esCCO monitor is suited for monitoring of the preload and cardiac contractility and can track rapid changes in the cardiac output.

4-3 Future prospects

These results suggest that the esCCO, which is noninvasive and does not require special probes or sensors, could be a useful monitor for predicting fluid responsiveness in vast majority of patients in perioperative period.

The foundation of evaluating the preload during general anesthesia involves determining whether fluid responsiveness is present or absent. However, we propose an SVV of 6.4% as an alternative parameter for predicting fluid responsiveness in conditions similar to the present study. In the future, performing cardiovascular management using the esCCO as a part of the goal-directed therapy (GDT), with SVV as the indicator, could be clinically efficient.[15–17] Volkov et al. performed GDT with a protocol that included fluid loading in patients who exhibited increased stroke volume using the esCCO.[18] Their results showed that the GDT group was managed with less infusion volume compared with the group with no infusion restrictions. Therefore, based on the results of the present study, the impact of GDT should be examined using esCCO on perioperative outcomes, such as reduced total transfusion volumes during major surgeries, shorter hospital stays, or improved mortality rates.

4-4 Fluid loading methods

The fluid loading method used in the present study involved the administration of 300 mL of a colloidal solution in 15 min, with a cutoff value of 10% for the SVI increase rate, based on the infusion challenge classifications, which are the gold standard for predicting fluid responsiveness, as reported by Carsetti et al. and Marik et al.[9, 19] Regarding the infusion method, the use of Voluven is not appropriate for patients with renal failure, and on hemodialysis, another clinical study with crystalloid solution will be needed to elucidate the cutoff value of fluid responsiveness in such setting. Furthermore, studies are needed to determine if SVV measured with the esCCO could serve as an indicator of fluid responsiveness with prediction methods that do not require fluid loading, such as passive leg raising.[20, 21]

4-5 Limitations

There were several limitations to this study. First, patients with arrhythmia were excluded. esCCO, which is a completely noninvasive method and is the most important aspect of this study, cannot be used in patients with arrhythmia. This should be taken into account when using this method clinically.

Second, SVV is only effective during management with positive pressure ventilation and cannot be used in perioperative management with spontaneous breathing. Also, SVV can be affected by the level of tidal volume, level of PEEP, and body position as well as the monitoring method itself. Further study should be added to elucidate the difference of SVV and cutoff value among the different monitoring methods.

Third, fluid loading was performed both before and during surgery, suggesting that the stress from the surgery could have had an impact. Moreover, although we tried to eliminate the factors affecting cardiovascular dynamics,

such as catecholamine administration during maintenance, vasopressor administration immediately before fluid loading, and local anesthesia during epidural anesthesia, we probably did not eliminate all the influences.

Fourth, there were possible issues during the measurements. In some cases, measurements could not be performed for some time because the ECG and pulse oximeter were impacted by manipulations in the surgical field, such as electrocauterization. Furthermore, it took about 5 min for SVV to stabilize after fluid loading.

Fifth, the results of the present study described fluid responsiveness with a threshold SVV of 6.4% in adults, but the applicability of this method also needs to be examined in children. Pediatric patients have higher heart rates than adults; thus, the 64 beats required to measure the PWTT are completed faster in children than in adults, and the number of breaths in artificial respiration needs to be set higher in children than in adults. Therefore, the measurement principles may have a greater impact on the SVV results in children compared with the adults.

Finally, this study only examined laparotomy cases performed mainly in the supine or lithotomy positions. The effects of changing the position during surgery on hemodynamics also need to be examined. Currently, the esCCO is calibrated, and measurements can begin after attachment of the ECG and pulse oximeter and measurement of the blood pressure. In the future, there is room for further improvement of the systems and algorithms to enable regular calibrations to address factors that have a large impact on respiratory and circulatory dynamics, such as the ventilation conditions used in artificial respiration, postural changes, pneumoperitoneum, use of catecholamine, and administration of epidural anesthetics.

5. Conclusion

In this study, we demonstrated that the noninvasive esCCO monitor could be used to represent fluid responsiveness during general anesthesia for laparotomy. Especially, esCCO-derived SVV has an excellent diagnostic value to predict fluid responsiveness. In the future, GDT using esCCO without invasive monitors could contribute to perioperative management in a wide variety of perioperative cases.

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