

Research Article

# Monitoring Variations in Stroke Volume Enables Precise Evaluation of Fluid Resuscitation in Patients with Septic Shock on Pressure Support Ventilation

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## Abstract

**Purpose:** To determine whether stroke volume variation (SVV) is a useful indicator of fluid resuscitation in patients with septic shock on pressure support ventilation.

**Subjects:** We assessed 37 patients with septic shock who were fitted with FloTrac sensors (Edwards Lifesciences Ltd., Tokyo, Japan), hospitalized between October 2011 and August 2013 and managed using pressure support ventilation.

**Methods:** This is a prospective, observational, pilot study. Lactate (Lac), IVC diameter, IVC variation ( $\Delta$ IVC), stroke volume index (SVI), and SVV (mean value at one hour) during initial fluid resuscitation were measured and the SVV value was continuously monitored. These parameters were measured again when the SVV curve decreased and flattened (stable SVV). Fluctuations in SVV during initial fluid resuscitation and stability were analyzed using fast Fourier transformation.

**Result:** The mean values of Lac, IVC diameters, and SVV during initial fluid therapy vs. stable SVV were 6.0 vs. 1.8 mmol/L, 11 vs. 19 mm, and 18.6 vs. 8.8%, respectively ( $p < 0.001$ ). Fluctuations in SVV curves calculated by fast Fourier transformation resulted in a Lorentzian spectrum. The amplitude of all curves peaked at a frequency of 0 and became significantly lower when SVV was stable than during fluid therapy (1.3% vs. 3.7%;  $p < 0.001$ ).

**Conclusion:** Continuous monitoring of SVV trends enables precise evaluation of fluid resuscitation in patients with septic shock on pressure support ventilation.

**Keywords:** Stroke volume variation; SVV; Stroke volume index; SVI; Septic shock; Fluid resuscitation; Lactate

## Introduction

Fluid resuscitation for severe sepsis can be based on either dynamic or static variables. Stroke volume variation (SVV) is considered a dynamic variable despite being ungraded for recommendation [1].

Continuous analysis of the arterial pulse contour from the arterial line of peripheral arteries, including the radial artery, has recently enabled measurements of cardiac stroke volume (SV) [2]. The SVV can be calculated using the formula:

$$\left[ \frac{(SV_{\max} - SV_{\min})}{SV_{\text{mean}}} \times 100 \right] \quad (1)$$

where  $SV_{\max}$  is the maximum variation in stroke volume during the respiratory cycle,  $SV_{\min}$  is the minimum variation in SV, and  $SV_{\text{mean}}$  is  $(SV_{\max} + SV_{\min})/2$ . The SVV has been described as a functional preload parameter that can indicate fluid responsiveness after a fluid challenge [2]. Patients on the steep or flat portions of the Frank-Starling curve will have high or low SVV, respectively. This implies that a greater SVV will result in a greater increase in SV and a decrease in SVV after a fluid challenge. Namely, the main advantage of using SVV to predict fluid responsiveness is that it dynamically predicts the status

of individual patients from Frank-Starling curves [3]. The sensitivity and specificity of SVV is higher and its ability to determine fluid responsiveness is better than that of traditional indicators of volume status, namely, heart rate, mean arterial pressure, central venous pressure, pulmonary artery diastolic pressure, and pulmonary capillary arterial pressure [4-6]. When a 15% increase in stroke volume index (SVI) or cardiac index is defined as fluid responsiveness with an SVV cutoff of  $11.6 \pm 1.9\%$ , the sensitivity and specificity are 0.82 (0.75-0.98) and 0.86 (0.77-0.92) respectively [6]. However, the effectiveness of SVV is limited to patients who are 100% mechanically ventilated (controlled ventilation) with tidal volumes of  $> 8$  mL/kg and fixed respiratory rates.

Physicians in intensive care units must always consider lung-protective strategies during mechanical ventilation for critically ill patients. These strategies include lower tidal volumes (6 mL/kg) for positive-pressure ventilation. Several studies have attempted to determine effective dynamic parameters that might predict fluid responsiveness in such patients, but the findings require further analysis [7,8]. Perner et al. and Machare-Delgado et al. reported that SVV is unlikely to serve as an indicator of fluid responsiveness in

patients under pressure support ventilation [9,10]. Whereas, Lanspa et al. recently reported on a prospective observational pilot study that SVV can predict hemodynamic response to fluid challenge in 14 septic shock patients with spontaneously breathing patients [11].

We considered that evaluating fluid responsiveness with SVV would be limited to one fluid challenge test in patients under pressure support ventilation. The present study aimed to determine whether SVV could serve as an indicator of fluid resuscitation in patients with septic shock under pressure support ventilation who undergo continuous fluid challenges as initial fluid resuscitation.

## Materials and Methods

### Patients

The Ethics Committee at our institution approved this prospective, observational, pilot study and written informed consent was waived because the study design is part of the current standard of care at our intensive care unit (ICU). The study was registered with the University Hospital Medical Information Network Clinical Trials Registry: UMIN-CTR ID UMIN00008339. All authors have any conflict of interest.

We defined septic shock as sepsis-induced hypotension persisting despite adequate fluid resuscitation (minimum of 30 mL/kg of crystalloids). Hypotension induced by sepsis was defined as systolic blood pressure (SBP) < 90 mmHg, mean arterial pressure < 70 mmHg, or a decrease in SBP > 40 mmHg or < 2 SD below normal for age in the absence of other causes of hypotension [12].

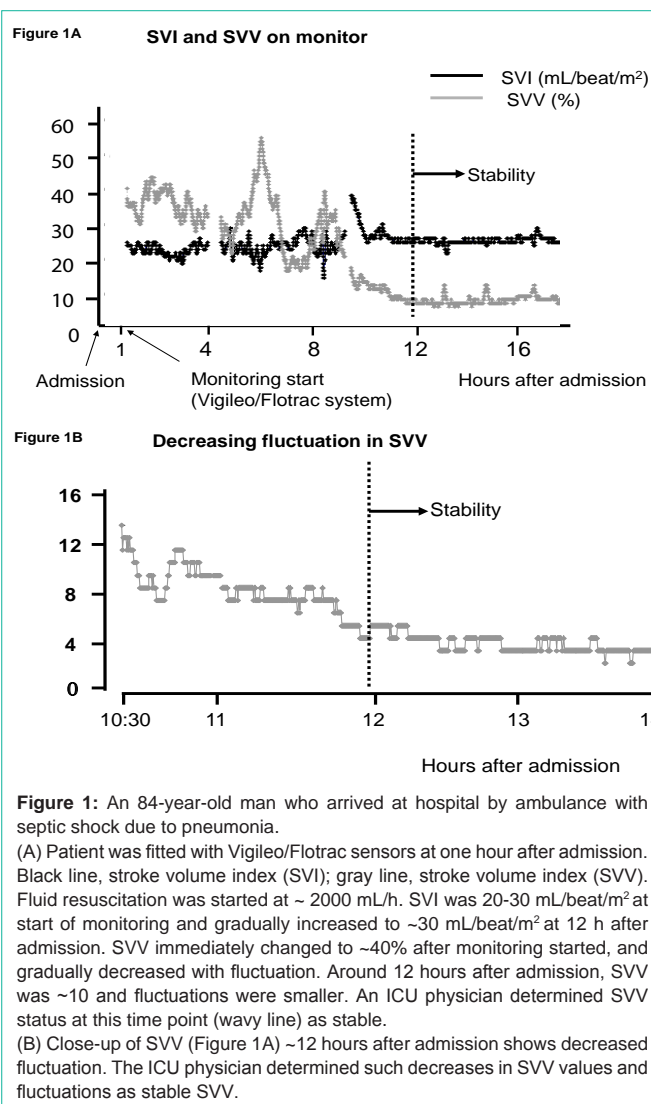
The enrollment criteria comprised patients with septic shock aged  $\geq 16$  years who were hospitalized between October 2011 and August 2013. In addition, patients must have met the definition of the International Sepsis Definitions Conference, been initially treated based on the Surviving Sepsis Campaign 2008 [12], had hemodynamics in the radial artery invasively monitored, and been fitted with Vigileo/FloTrac version 3.01 sensors (Edwards Lifesciences Ltd., Tokyo, Japan) during initial fluid therapy and managed under pressure support ventilation.

The exclusion criteria comprised patients who declined intensive care, those with end stage malignant disease, arrhythmia, or abnormal blood flow due to congenital heart disease, or with a focus of infection that was surgically treated during initial fluid therapy.

### Methods and measurements

Patient care was directed by the ICU team and did not involve the present findings.

Fluid and catecholamine administration was based on the Surviving Sepsis Campaign 2008. In addition to routine tests at our institution, we measured the diameter of the retrohepatic inferior vena cava (IVC diameter) and its respiratory variations ( $\Delta$ IVC), as well as blood lactate values (Lac). The  $\Delta$ IVC was calculated as (maximum IVC diameter - minimum IVC diameter) / maximum IVC diameter  $\times 100$  (%). The IVC was examined in subcostal sagittal sections. A 5-Mhz probe was attached to the echo unit of a Sonosite m-turbo ultrasound diagnostic system (Fujifilm Sonosite Inc., Tokyo, Japan). The origin of the major hepatic vein was initially detected and parameters were measured at the IVC diameter immediately proximal to the junction of the hepatic veins. The IVC was observed during



**Figure 1:** An 84-year-old man who arrived at hospital by ambulance with septic shock due to pneumonia.

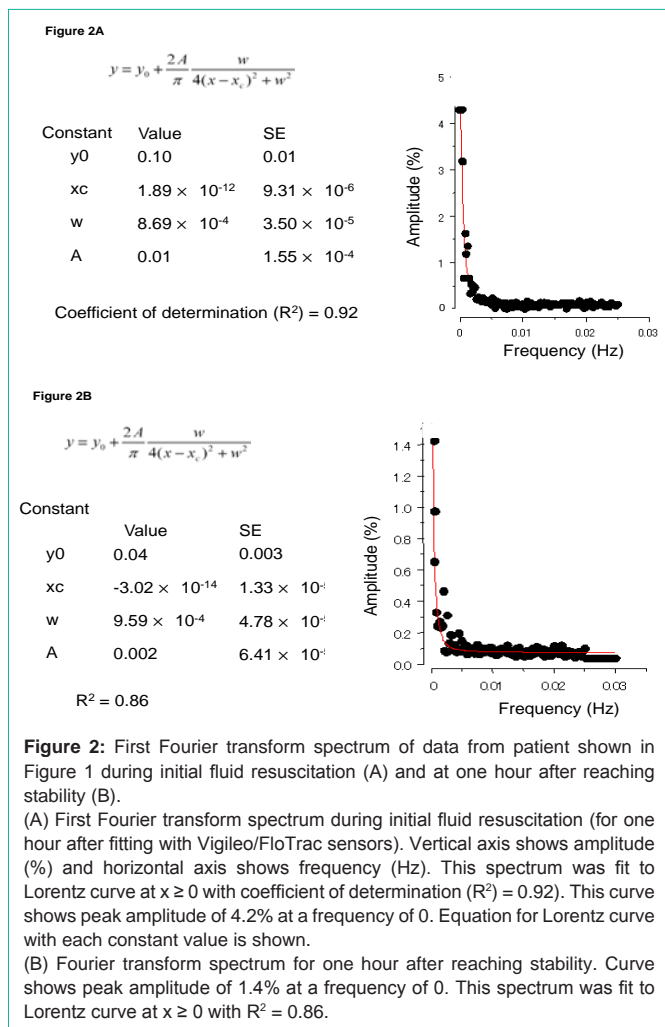
(A) Patient was fitted with Vigileo/FloTrac sensors at one hour after admission. Black line, stroke volume index (SVI); gray line, stroke volume index (SVV). Fluid resuscitation was started at  $\sim 2000$  mL/h. SVI was 20-30 mL/beat/m<sup>2</sup> at start of monitoring and gradually increased to  $\sim 30$  mL/beat/m<sup>2</sup> at 12 h after admission. SVV immediately changed to  $\sim 40\%$  after monitoring started, and gradually decreased with fluctuation. Around 12 hours after admission, SVV was  $\sim 10$  and fluctuations were smaller. An ICU physician determined SVV status at this time point (wavy line) as stable.

(B) Close-up of SVV (Figure 1A)  $\sim 12$  hours after admission shows decreased fluctuation. The ICU physician determined such decreases in SVV values and fluctuations as stable SVV.

one or more respiratory cycles in M mode and then the maximum and minimum anterior-posterior diameters during one respiratory cycle were measured. After fitting each patient with Vigileo/FloTrac sensors (FloTrac), cardiac output (CO), cardiac index, stroke volume, SVI and SVV were continuously monitored and stored as digital data every 20 seconds. The IVC diameter,  $\Delta$ IVC, and LAC were measured at least every four hours during initial fluid resuscitation.

SVV was defined as stable when < 15% and the curve flattened without a decrease (Figure 1A and B). The flattened curve was visually assessed on the monitor by the attending physician. The diameters of the IVC,  $\Delta$ IVC, and Lac, in addition to routine tests, were measured once again.

The SVI and SVV values obtained during initial fluid resuscitation and at stability are expressed as means ( $\pm$  SD) for 60 min after starting measurements and until 60 min after SVV stability was initially defined, respectively. The power spectrum (indicated in decibels; dB) in the first Fourier transform was calculated with a 20-second interval for data acquisition (sampling cycle) to measure the degree of fluctuation. The amplitude of the power spectrum was transformed into a linear indication so that the units of amplitude were indicated



**Figure 2:** First Fourier transform spectrum of data from patient shown in Figure 1 during initial fluid resuscitation (A) and at one hour after reaching stability (B).

(A) First Fourier transform spectrum during initial fluid resuscitation (for one hour after fitting with Vigileo/FloTrac sensors). Vertical axis shows amplitude (%) and horizontal axis shows frequency (Hz). This spectrum was fit to Lorentz curve at  $x \geq 0$  with coefficient of determination (R<sup>2</sup>) = 0.92. This curve shows peak amplitude of 4.2% at a frequency of 0. Equation for Lorentz curve with each constant value is shown.

(B) Fourier transform spectrum for one hour after reaching stability. Curve shows peak amplitude of 1.4% at a frequency of 0. This spectrum was fit to Lorentz curve at  $x \geq 0$  with R<sup>2</sup> = 0.86.

as ratios (%) like the SVV units (linear spectrum = 10 power spectrum (dB)/20) (Figure 2A and B).

### Statistical and numerical analyses

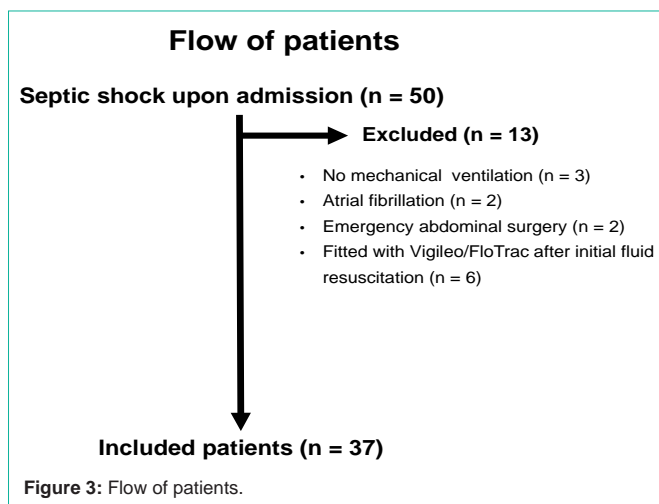
The background factors of all patients, IVC diameter,  $\Delta$ IVC, and Lac are expressed as means with 95% confidence intervals (CI). For comparisons between paired groups, normality was first analyzed using the Shapiro-Wilk's test. A t-test was applied when the distribution was normal and the Wilcoxon signed-ranks test when the distribution was not normal. P < 0.05 was considered to indicate significance. Categorical data were compared using the chi-square test or Fisher's exact test. All data were statistically analyzed using JMP 7 (SAS Institute Inc., Cary, NC, USA) software.

First Fourier transformation was achieved using FFT-PLOT Rev. 1.0.006, which runs on Microsoft Excel (software creator: Y. Akiyama, akiyamay@zd5.so-net.ne.jp). Values obtained from the linear spectrum indication were fit to curves using OriginPro 9.1J (OriginLab Corporation, Northampton, MA, USA). The curve with the lowest Akaike's information criteria (AIC) was selected.

## Results

### Patient's backgrounds

Thirteen of the 50 patients with septic shock who were hospitalized



during the study period were excluded (Figure 3) and 37 were included in the present study (Table 1). Males (n = 28) significantly outnumbered females (p = 0.002). Ten patients died, of which four were within the first seven days. Infections were most frequently of pulmonary origin. The mean initial fluid volume was 6.1 L, which required a mean of nine hours for resuscitation. Norepinephrine was most frequently administered (23 patients, 62%) at a mean maximal dose of 0.15  $\mu$ g/kg/min. Sedation for 25 (68%) patients was managed at Richmond agitation-sedation values of -3 to -4 and fentanyl was the most frequently administered anesthetic (29 of 37 patients, 78.4%) at a mean dose of 25.3  $\mu$ g/h.

Mean tidal volume was 7.2 mL/kg and mean peak pressure was 14.7 cm H<sub>2</sub>O. All patients were mechanically ventilated in pressure support mode. The mean pressure support and mean positive end-expiratory pressure were both 7 cm H<sub>2</sub>O.

### Evaluation of SVV stability

Mean arterial pressure, systemic vascular resistance (SVR, index), and SVI significantly increased when ICU physicians judged SVV as being stable compared with those during fluid resuscitation. In addition, heart rate and SVV significantly decreased (Table 2).

Fluctuations in SVV derived from all patients during fluid resuscitation and while stable in Fourier transformation formed Lorentz curves with a peak amplitude at a frequency of 0 (Figure 4A and B). The peak amplitude became significantly lower during stable SVV than during fluid resuscitation (Table 2).

### Evaluation of static parameters

Table 2 shows that the IVC diameter was significantly increased during stable SVV compared with that during fluid resuscitation;  $\Delta$ IVC and lactate values were significantly decreased and the mean IVC diameter, mean  $\Delta$ IVC, and lactate values were 19 mm, 10%, and 1.8 mmol/L, respectively, at the time of stability.

## Discussion

We believe that the effects of initial fluid resuscitation can be evaluated by observing SVV trends even in patients under pressure support ventilation. All static parameters measured at the time of SVV stability indicated that the hypodynamic state was improved. These findings support the notion that flattened SVV values without a

**Table 1:** Background of patients.

Patient characteristics	
Sex (male/female)	28/9 (76%/24%)
Age (y)	72 ± 16
Mortality within 7 hospital days (n)	4 (11%)
Mortality within 28 hospital days (n)	10 (27%)
APACHE II score	22 ± 6
Source of sepsis	
Pulmonary	20 (54%)
Abdominal	3 (8%)
Urinary tract	11 (30%)
Soft tissue	3 (8%)
Initial resuscitation	
Volume of initial fluid resuscitation (mL)	6100 ± 2600
Time for initial fluid resuscitation (h)	9 ± 3
Urinary volume (mL)	659 ± 594
Water balance (initial fluid resuscitation volume – urinary volume; mL)	5441 ± 2495
Norepinephrine* (n = 23)	0.15 ± 0.11
Epinephrine* (n = 4)	0.29 ± 0.17
Dopamine* (n = 12)	5.6 ± 2.3
Sedation	
Richmond agitation-sedation scale (n)	
0, -1, -2, -3, -4, -5	0, 4, 6, 12, 13, 2
Fentanyl, dose (µg/h; n = 29)	25.3 ± 10.5
Propofol, dose (mg/h; n = 9)	58.9 ± 34.4
Midazolam, dose (mg/h; n = 19)	3.0 ± 1.6
Ventilator setting	
Frequency of spontaneous respiration (beats/min)	17.7 ± 5.4
PF ratio	234.0 ± 189.7
PSV (cm H <sub>2</sub> O; n = 37)	7 ± 3
PEEP (cm H <sub>2</sub> O; n = 37)	7 ± 2
Tidal volume (mL/kg body weight)	7.2 ± 1.2
Peak pressure (cm H <sub>2</sub> O)	14.7 ± 4.1

Data are shown as numbers (n) of patients (%) or as means ± SD (n = 37). Volume of initial fluid resuscitation: total fluid volume from initial fluid resuscitation to stability of SVV curve. \*Max dose during initial resuscitation (µg/kg/min). Time for initial fluid resuscitation: Elapsed time from initial fluid resuscitation to stability of SVV curve. Max dose, maximum dose applied during initial resuscitation; PEEP, positive end-expiratory pressure; PF ratio, PaO<sub>2</sub>/FIO<sub>2</sub>; PSV, pressure support ventilation.

decrease, or smaller fluctuations in SVV values on a monitor indicate an improved hypodynamic state.

The FloTrac system algorithm is based on the principle that the arterial pressure waveform depends not only on stroke volume but also on arterial compliance, vascular tone, and reflection waves. Cardiac output (CO) is computed from the following equation:

$$CO = \text{pulse rate} \times \text{sd}(AP) \times K \tag{2}$$

The sd(AP) is the standard deviation of arterial pressure. K is an autocalibration factor derived from a proprietary multivariate equation that compensates for differences in vascular tone (compliance and resistance), patient to patient differences estimated from biometric data, dynamic changes estimated by data and waveform analysis.

The question arises as to whether the pulse contour method included in FloTrac can accurately measure CO. Biaiset et al. [13]

**Table 2:** Comparison of parameters during fluid resuscitation and parameter stabilization.

	During fluid resuscitation	Stability	p
Dynamic parameters			
Heart rate (beats/minute)	116 (110 - 122)	95 (88 - 102)	0.04
Mean arterial pressure (mmHg)	58 (56 - 60)	81 (77 - 85)	<0.001
CO (L/minute)	4.5 (4.2 – 5.6)	5.1 (4.3 – 5.9)	0.17
CI (L/minute/m <sup>2</sup> )	2.9 (2.6 - 3.2)	3.1 (2.7 - 3.4)	0.38
SV (mL/beat)	43.9 (39.3 – 48.5)	55.2 (46.7 – 63.7)	0.003
SVI (mL/beat/m <sup>2</sup> )	29.3 (26.3 – 32.3)	36.8 (31.2 – 42.5)	0.003
SVV (%)	18.6 (16.2 – 21.0)	8.8 (7.8 – 9.9)	<0.001
PA of SVV fluctuations (%)	3.7 (2.6– 4.8)	1.3 (1.0 – 1.72)	<0.001
SVR (dyn-sec/cm <sup>5</sup> )	1152 (1031 - 1274)	1447 (1289 - 1605)	<0.001
SVRI (dyn-sec/cm <sup>5</sup> /m <sup>2</sup> )	1705 (1827 - 2229)	2274 (2089 - 2458)	<0.001
Static parameters			
IVC diameter (mm)	11 (9-13)	19 (18-20)	<0.001
ΔIVC (%)	60 (50-70)	10 (10-15)	<0.001
Lactate (mmol/L)	6.0 (4.5-7.4)	1.8 (1.4-2.1)	<0.001

Data are shown as mean (95% confidence interval). CI, cardiac index; CO, cardiac output; IVC, inferior vena cava; ΔIVC, (maximum IVC diameter - minimum IVC diameter)/maximum IVC diameter × 100 (%); PA, peak amplitude; SVI, stroke volume index; SVR, systemic vascular resistance; SVRI, systemic vascular resistance index; SVV, stroke volume variation. Values for dynamic parameters are expressed as means (95% confidence interval) for 60 min.

reported that the relationship between the first generation FloTrac accuracy and SVR is logarithmic, and that the lower the SVR, the greater the bias between FloTrac and reference thermodilution CO values. Several studies have similarly shown that the FloTrac system might underestimate CO in hyperdynamic and vasoplegic states [14,15].

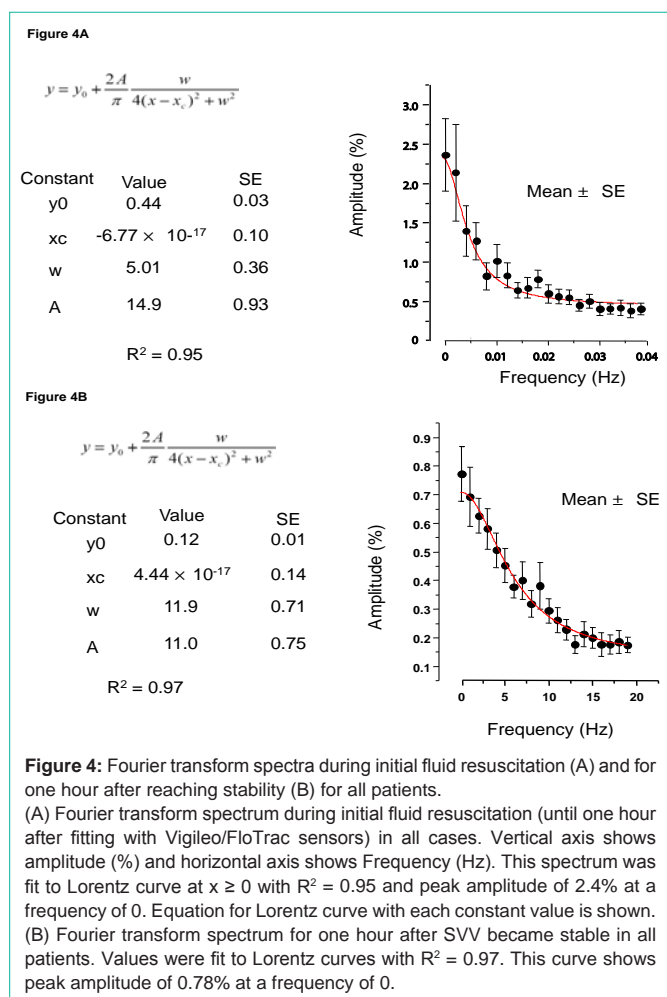
Third-generation FloTrac software was recently developed from an even larger human database comprising a greater proportion of hyperdynamic and vasoplegic patients. Backer et al. [16] compared the CO value derived from the third-generation FloTrac with that determined by bolus pulmonary thermodilution in 48 patients with septic shock given catecholamine. They reported that the mean bias and limits of agreement (LOA) were 0 and 30% (2.2 L/min) between the former and the latter CO values, respectively. They concluded that the overall performance of third-generation FloTrac is comparable to that of bolus pulmonary thermodilution, a technique that is often used for patients with sepsis. Slaght et al. [17] also reported that third generation FloTrac-derived CO considerably underestimated pulmonary or femoral artery CO derived using thermodilution in 19 patients with septic shock who had low SVR (< 700 (dyn sec)/cm<sup>5</sup>) and were administered catecholamine, but when the SVR of such patients is ≥ 700 (dyn sec)/cm<sup>5</sup>, the tracking ability of the FloTrac is fair for clinically relevant changes in CO.

The sd(AP) of third generation FloTrac is calculated by analyzing the arterial pressure waveform over 20 seconds 100 times per second. K is updated and applied to the FloTrac system algorithm on a rolling 60-second average. Therefore, K is considered constant compared with sd(AP).

As SV = CO/ (pulse rate), equation (2) changes the following;

$$SV = CO / \text{pulse rate} = \text{sd}(AP) \times K \tag{3}$$





Substituting equation (3) into equation (1), results in:

$$SVV = \frac{sd(AP)_{max} \times K - sd(AP)_{min} \times K}{sd(AP)_{mean} \times K},$$

and  $K$  is eliminated to finally obtain equation (4):

$$SVV = \frac{sd(AP)_{max} - sd(AP)_{min}}{sd(AP)_{mean}} \quad (4),$$

which indicates that the SVV calculation is not affected by  $K$  (a proprietary multivariate equation). Therefore, we believe that SVV could evaluate hemodynamics in patients with septic shock who are in hyperdynamic and vasoplegic states. We believe that FloTrac-derived CO values in our study are relevant because only four patients had low SVR values (533, 589, 604, and 648 (dyn sec)/cm<sup>5</sup>).

We measured IVC diameter and lactate as static parameters. Machare-Delgado et al. reported that echocardiographic assessments of  $\Delta IVC$  might prove useful for predicting fluid responsiveness [10]. At a  $\Delta IVC$  cutoff  $\geq 12\%$ , the sensitivity and specificity of predicting fluid responsiveness to a fluid challenge were 100% and 53%, respectively. Barbier et al. and Feissel et al. similarly reported that the sensitivity and specificity of predicting an increase in cardiac index  $\geq 15\%$  were both  $> 90\%$  [18,19]. The ability of normalized lactate values or lactate clearance to reflect fluid responsiveness has also been validated in many studies [20,21].

SVV is a naturally occurring phenomenon in which the arterial

pulse pressure falls during inspiration and rises during expiration due to changes in intra-thoracic pressure secondary to negative pressure ventilation (spontaneous breathing). Variations  $> 10$  mmHg are referred to as pulsus paradoxus. Reverse pulsus paradoxus in patients under controlled mechanical ventilation is an increase in arterial pressure during inspiration and a fall during expiration caused by changes in intra-thoracic pressure secondary to positive pressure ventilation [22]. Variations in both phenomena become larger and smaller during hypovolemic and normovolemic states, respectively.

Pressure support ventilation allows patients to determine the inflation volume. It is not used to provide full ventilator support, but to augment spontaneous breathing. Negative pressure generated with each spontaneous breath opens a valve that delivers inspired gas at a predefined pressure. During pressure support ventilation, the paradoxical and reversed paradoxical pulses might reach an irregular mixed state. Tissues fall into acidosis during septic shock before fluid is sufficiently recovered. Respiratory compensation proceeds to improve the acidosis, resulting in rapid and deep respiration. Consequently, the internal pressure of the thoracic cavity upon inspiration largely inclines to the negative. Under such conditions, factors involved in the paradoxical pulse might increase compared with sedation and improved tissue acidosis. Accordingly, factors involved in paradoxical and reverse paradoxical pulses might decrease and increase, respectively, as such status improves. Previous studies have shown that SVV cannot indicate fluid responsiveness in patients under pressure support ventilation [6,9]. We believe that this is due to the conflicting effects of the paradoxical and reversed paradoxical pulses that reduce the sensitivity and specificity of SVV. Fluctuations in SVV analyzed using first Fourier transformation assumed the shape of Lorentz curves with a peak amplitude at a frequency of 0, indicating that such SVV fluctuations consist of random signals. Mixtures of SVI change with the paradoxical pulse and SVI changes with the reverse paradoxical pulse might also produce such results.

We applied first Fourier transformation to analyze SVV fluctuations. This process digitized the decrease in fluctuations and allowed comparative statistical analyses because subjective judgment by an attending physician might affect a diagnosis concluded from a decrease displayed on a monitor. The results of static parameters shown herein supported the notion that ICU physicians can judge stability sufficiently from monitor displays.

### Study Limitations

The sample size of this study was small as this was performed on the pilot study. The multicenter clinical study will need to resolve this problem. And also, the weaknesses of the study are no real comparison between the different derived parameters for sensitivity or specificity. We think that the SVV should be compared with other authoritative hemodynamic index, e.g., a % fractional shortening, an ejection fraction, and a stroke volume measured by cardiac ultrasonography.

We will perform the further study with the multicenter clinical study and the authoritative hemodynamic index.

### Conclusion

A flattened SVI with a stopped increase, a flattened SVV with a stopped decrease, or a decrease in SVV fluctuations indicates that

initial fluid resuscitation is sufficient to improve hemodynamics in patients with septic shock under pressure support ventilation.

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