

Prediction of Volume Responsiveness by Stroke Volume Variation vs. Central Venous Pressure in Children Undergoing Fontan Operation

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Abstract

Background: Fontan operation is a palliative medical procedure performed on children with single-ventricle defects. As postoperative success of the procedure largely depends on the preload volume, it is necessary to ensure the effective volume of systemic circulation by maintaining an appropriate pressure gradient between the systemic vein and the left atrium. However, there is a lack of effective indexes to evaluate volume responsiveness in Fontan patients. Stroke volume variation (SVV) is a dynamic hemodynamic parameter based on cardiopulmonary interaction in mechanical ventilation. This study is to validate the sensitivity and specificity of SVV vs. central venous pressure (CVP) in assessing volume responsiveness of Fontan patients.

Method: 64 children were included in this prospective study with single-ventricle who underwent modified Fontan operation between May 2018 and January 2020. Patients were given $10\text{ml}\cdot\text{kg}^{-1}$ albumin for volume challenge within 10 min after CPB. Before and after volume challenge, the invasive arterial pressure module was connected to Mostcare™ equipment to collect SBP, MBP, DBP, SVV, CI and SVRI dynamically in a time window of 30 s at a frequency of 1000 Hz. According to the range of CI change, patients with $\Delta\text{CI} \geq 15\%$ were classified into response (R) group and patients with $\Delta\text{CI} < 15\%$ into non-response (NR) group. Using SVV and CVP as indicators, the ROC of the patients was established, and the AUC, diagnostic threshold, sensitivity and specificity were calculated.

Results: The 64 pediatric patients included with a mean age of 4.85 ± 1.20 years, a mean height of 98.00 ± 16.74 cm and a mean weight of 15.65 ± 5.37 kg. The SVV value was $17.15 \pm 3.97\%$ and $13.45 \pm 2.45\%$ before and after fluid challenge treatment vs. 18.60 ± 1.83 mmHg and 20.20 ± 2.39 mmHg for CVP in responders. The AUC of SVV was 0.74 (95% confidence interval [CI] 0.54–0.94, $P < 0.05$) and the cutoff value was 16%, offering a sensitivity of 50% and a specificity of 91.7% vs. 0.70 (95% CI 0.50–0.92, $P > 0.05$), 19.5 mmHg, 58% and 76% for CVP.

Conclusion: SVV exhibited a good predictive value for volume responsiveness in pediatric Fontan patients. Appropriate volume therapy according to SVV could improve the cardiac function of such patients.

Trial registration: This research was registered in Chinese Clinical Trial Registry on Jan 26, 2018. Registration number is ChiCTR1800014654. Registry URL is <http://www.chictr.org.cn/showproj.aspx?proj=25019>. This observational prospective study was approved by the Local Ethics Committee of Shanghai Children's Medical Center affiliated to Shanghai Jiao Tong University (SCMCIRB-K2017035)

Background

Fontan operation is a palliative medical procedure normally performed on children with birth defects of the heart, in which, the systemic blood flow of the heart is attached directly to the pulmonary artery.⁽¹⁾ As there is a lack of the pumping function of the right atrium, the ideal systemic venous (pulmonary artery) pressure (SVP) should be maintained between 12–15 mmHg and left ventricular end-diastolic pressure

(LVEDP) between 7–10 mmHg after Fontan operation to maintain the transpulmonary gradient (TPG) at a rational level of 2–8 mmHg. In the process of anesthesia management, it is even more necessary to optimize intravascular hemodynamics, fluid volume, cardiac output and tissue perfusion. Unnecessary expansion of the preload volume may lead to adverse results and even increase mortality.⁽²⁾ In addition, some studies have pointed out that assessing the responsiveness of volume challenge can help distinguishing between postoperative cardiogenic and pulmonary circulatory failure, which is instructive for the subsequent treatment in Fontan patients.⁽³⁾ To the best of our knowledge, there has been less study reporting the assessment of volume responsiveness following Fontan operation. Although the reliability of stroke volume variation (SVV) in predicting fluid response in children with congenital heart disease such as ventricular septal defects has been well demonstrated,^(4–6) whether SVV can also be used in Fontan patients remains unclear. Compared with central venous pressure (CVP), the method and meaning of SVV calculation are different and therefore it is unclear whether SVV is suitable for patients with single ventricular circulation. In addition, there is little simple and effective golden standard method for prediction of volume responsiveness in pediatric patients.⁽⁷⁾ The aim of the present study is to determine whether SVV vs. CVP could accurately evaluate the volume responsiveness of children with Fontan circulation and provide evidence-based clues for clinically reasonable volume therapy in such patients.

Methods

Patients

This study was approved by the Medical Ethics Committee of Shanghai Children's Medical Center in Shanghai, China (SCMCIRB-K2017035) and certified by China clinical research registration (Registration No. ChiCTR1800014654). All parents or guardians of the patients voluntarily signed written informed consent before operation.

Included in this prospective single-center non-randomized study were 64 children with single-ventricle American Society of Anesthesiologists (ASA) physical status II-III who underwent modified Fontan operation under cardiopulmonary bypass (CPB) at Shanghai Children's Medical Center between May 2018 and January 2020. Written informed consent was obtained from the parents or guardians of all pediatric patients included. The inclusion criteria were children aged 3–8 years with ASA II or III who were scheduled for stage II modified Fontan operation with fenestration using cardiopulmonary bypass (CPB). The exclusion criteria were patients with arrhythmia before surgery whose mean pulmonary artery pressure was ≥ 18 mmHg, oxygen saturation was lower than 80%, age was older than 9 years, aortic occlusion time was > 60 min, and the positive inotropic agents score was > 10 points.⁽⁸⁾ Volume challenge was observed in patients with sufficient hemostasis after CPB.

Anesthesia management

All patients were pre-medicated with oral midazolam $0.5\text{mg}\cdot\text{kg}^{-1}$ 30 min before operation, and then induced with intravenous (IV) midazolam $0.1\text{mg}\cdot\text{kg}^{-1}$, etomidate $0.3\text{mg}\cdot\text{kg}^{-1}$, sufentanil $2\mu\text{g}\cdot\text{kg}^{-1}$ and rocuronium $0.6\text{mg}\cdot\text{kg}^{-1}$. Intubation was performed using a cuffed endotracheal tube. Mechanical ventilation was implemented by maintaining the pressure and keep the tidal volume at $10\text{ml}\cdot\text{kg}^{-1}$, fraction of inspired oxygen at 50%, the inspiratory to expiratory ratio at 1:2, and the respiratory rate at 14–20 times per min to maintain P_{ETCO_2} at 30–35 mmHg. Anesthesia was maintained by using propofol $4\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$, sufentanil $2.5\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ and rocuronium $0.6\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$. A 5.0 Fr double-lumen catheter was set up in the right internal jugular vein for monitoring CVP and positive inotropic drug administration. A 20 Ga catheter was retained in the left femoral vein for fluid infusion. A 22 Ga catheter was instrumented in the left radial artery to allow for routine arterial pressure monitoring and advanced hemodynamic monitoring by Pressure Recording Analytical Method (PRAM) using Mostcare™ device.

Before cardiac resuscitation, Dopamine $5\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ was administered, and the dose of positive inotropic agents was adjusted by the end of CPB using the maximal slope of systolic upstroke (dp/dt_{max}) monitored by PRAM and systolic arterial pressure. The dose of Dopamine was reduced at least to $1\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in case dp/dt_{max} was > 1.2 mmHg/ms and systolic arterial pressure was > 100 mmHg. Additionally, Epinephrine was administered at $0.01\text{--}0.03\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in case dp/dt_{max} was < 0.8 mmHg/ms and systolic arterial pressure was < 60 mmHg. Positive inotropic agents remained unchanged during the study period. After CPB and removal of the aortic cannulation, all patients received volume challenge with 5% albumin $10\text{ml}\cdot\text{kg}^{-1}$ within 10 min.

PRAM and hemodynamic recording

The standard arterial pressure transducer was routinely connected to the monitor using an anesthesia workstation (Datex-Ohmeda Aisys CS², GE Healthcare, USA), which was also directly connected to the Mostcare™ to allow for transmission of the original signal and sampling at 1000 Hz.⁽⁹⁾ SVV was calculated simultaneously as the variation of beat-to-beat pulse pressure from the mean value during the most recent 30 s data and was displayed continuously using the following equation:

$$SVV (\%) = \frac{(SV_{\text{max}} - SV_{\text{min}})}{(SV_{\text{max}} + SV_{\text{min}}) / 2}$$

Detailed 2-min measurements at 30 s intervals of each parameter were recorded by Mostcare™ and then downloaded to Excel sheets for offline analysis. Subsequently, the four consecutive measurements were averaged and adopted before or after volume challenge.

Study protocol

This study was designed to evaluate the accuracy of SVV in predicting fluid responsiveness in pediatric patients undergoing Fontan operation. They received fluid challenge with 5% albumin at $10\text{ml}\cdot\text{kg}^{-1}$ for 10 minutes. Patients were defined as “responders” if the cardiac index increased more than 15% after a fluid

infusion (group R), or “non-responders” if the cardiac index increase less than 15% (groups NR).⁽¹⁰⁾ The medications remained unchanged during the study period. SVV was recorded by PRAM along with systolic and diastolic blood pressure, heart rate, stroke volume index, cardiac index, and CVP before and after fluid challenge.

Statistical analysis

Data are described as the mean \pm standard deviation (SD). The clinical continuous and categorical data between R and NR groups were compared by *Student-t* test and *Fisher* exact probability test respectively. Differences in hemodynamic parameters before and after volume challenge between group R and NR were examined by *Student-t* test. Hemodynamic parameters before and after volume challenge within group R or group NR were constructed by *paired t* test. ROC curves were established to assess the capacity of SVV and CVP for predicting fluid responsiveness. The optimal cutoff was confirmed when the sum of sensitivity and specificity was maximal. Statistical data were computed using SPSS 20.0 (IBM Corp, Armonk, NY, USA). ROC curves were mapped using Sigmaplot 12.0 (Systat Software Inc, San Jose, CA, USA).

Results

No significant adverse event occurred in any of the 64 Fontan patients successfully included in this study during the study protocol. Among them, 30 were responders and the remaining 34 were non-responders. The clinical data of all included patients are shown in Table 1. There was no significant difference in gender, age, height or weight between the two groups ($p > 0.05$).

Table 1
Clinical data of 64 Fontan patients in responders and non-responders

Group	Gender M/F (n)	Age (y)	Height (cm)	Weight (kg)
R	30 (18/12)	4.97 \pm 1.14	98.76 \pm 16.54	15.84 \pm 5.69
NR	34 (19/15)	4.87 \pm 1.27	97.73 \pm 17.43	15.64 \pm 5.98
Total	64(37/27)	4.85 \pm 1.20	98.00 \pm 16.74	15.65 \pm 5.37
Data is shown as (\pm SD). There was no significant difference between the two groups.				

The hemodynamic parameters before and after volume challenge in group R and NR are shown in Table 2. There were significant differences in hemodynamic parameters (SBP, DBP, MBP, SVV, CI and CVP) before and after volume challenge in group R, in which CI was $2.27 \pm 1.04 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ and $2.76 \pm 1.09 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ before and after volume challenge vs. $2.00 \pm 1.17 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ and $2.18 \pm 1.02 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ in group NR, respectively. After volume challenge, CVP was $20.20 \pm 2.39 \text{ mmHg}$ in Group R vs. $19.64 \pm 3.83 \text{ mmHg}$ in group NR, showing no significant difference ($p > 0.05$). SVV in group R was significantly lower than that in group NR (13.45 ± 2.45 vs. 14.91 ± 2.21 , $P < 0.05$) after volume challenge.

Table 2

Hemodynamic parameters recorded before and after volume challenge in responders and non-responders undergoing Fontan operation

Parameter	Group	Before volume challenge	After volume challenge
HR (beats·min ⁻¹)	R	117 ± 16.89	121.61 ± 15.93
	NR	124.5 ± 13.64	122.73 ± 12.12
SBP (mmHg)	R	96.7 ± 12.32	102.4 ± 10.00 ^a
	NR	95.71 ± 11.11 ^b	94.85 ± 13.83
DBP (mmHg)	R	48.4 ± 7.91	59.3 ± 7.25 ^a
	NR	58.07 ± 7.80 ^b	58 ± 10.67
MBP (mmHg)	R	62.4 ± 8.23	75.3 ± 6.85 ^a
	NR	72.07 ± 7.51 ^b	70 ± 8.05
SVV (%)	R	17.15 ± 3.97	13.45 ± 2.45 ^a
	NR	15.75 ± 2.67 ^b	14.91 ± 2.21 ^b
SVI (ml·m ⁻²)	R	31.49 ± 5.88	37.51 ± 4.84
	NR	33.70 ± 6.20	32.62 ± 5.41
CI (L·min ⁻¹ ·m ⁻²)	R	2.27 ± 1.04	2.76 ± 1.09 ^a
	NR	2.00 ± 1.17	2.18 ± 1.02
CVP (mmHg)	R	18.60 ± 1.83	20.20 ± 2.39 ^a
	NR	18.57 ± 2.34	19.64 ± 3.83
Data is shown as (± SD)			
HR heart rate; SBP systolic blood pressure; DBP diastolic blood pressure; MBP mean blood pressure; SVV stroke volume variation; SVI stroke volume index; CI cardiac index; CVP central venous pressure; R responders; NR non-responders.			
^a P < 0.05 compared with that before volume challenge;			
^b P < 0.05 compared with responders.			

There were significant differences in SBP, DBP, MBP, CI and CVP before and after volume challenge in Group R (all p < 0.05), while no significant difference was observed in these parameters in group NR (p > 0.05). SBP, DBP and MBP values were significantly different between group R and NR before volume challenge (p < 0.05). The value of SVV in group NR was significantly different from that in group R both

before and after volume challenge ($p < 0.05$). In addition, SVV in group R was decreased significantly after volume challenge ($p < 0.05$).

The AUC of SVV was 0.74 (95% CI 0.54–0.94, $P < 0.05$) and the cutoff value was 16%, offering a sensitivity of 50% and a specificity of 91.7% (Fig. 1). The AUC of CVP was 0.70 (95% CI 0.50–0.92, $P > 0.05$) and the cutoff value was 19.5 mmHg, offering a sensitivity of 58% and a specificity of 76% (Fig. 2).

SBP, DBP, MDP, SVV, CI and CVP values were significantly different before and after volume challenge in group R. SBP, DBP, MBP and SVV values were significantly different between responders and non-responders before volume challenge. SVV was significantly different between responders and non-responders after volume challenge.

Discussion

PRAM is a method for monitoring continuous cardiac output based on changes in arterial pressure, which is based on radial expansion caused by changes in volume of a given blood vessel. Many studies have demonstrated a good correlation of PRAM with other classical methods such as cardiac catheterization and Doppler ultrasound.^(11, 12) SVV is a dynamic hemodynamic parameter that reflects changes in stroke volume.^(13–15) SVV in patients with mechanical ventilation is less than 10–15%. According to cardiopulmonary interaction under mechanical ventilation and Frank-Starling principle, a change in stroke volume caused by mechanical ventilation is more significant when the blood volume is insufficient, showing a negative correlation between SVV and the blood volume.^(16, 17) Theoretically, SVV can therefore be used to estimate the intravascular volume state and predict the responsiveness of the circulatory system to the infusion treatment.

SVV has been used in predicting volume response in children receiving cardiac surgery. Some studies have shown that its accuracy is higher than CVP.^(18, 19) To the best of our knowledge, this is the first study that demonstrated the good predictability of SVV for assessing fluid responsiveness after volume challenge in pediatric Fontan patients, proving that SVV is a simple, fast, direct and noninvasive method with good reproducibility. SVV can be measured with high-quality values in any individual patients. In this study, we implemented aggressive volume therapy by infusing $10\text{ml}\cdot\text{kg}^{-1}$ 5% albumin instead of crystalloid solution within 10 minutes.^(20, 21) The result of our experiment demonstrated that the hemodynamic parameters including the mean arterial pressure and cardiac index were significantly improved in the Fontan patients after volume challenge, as represented by a stable hemodynamic state, a balanced internal environment, an increase in urine volume, and the absence of significant adverse events. $\text{SVV} < 16\%$ indicated an insufficient blood volume of the patient and continuous volume expansion treatment had little effect in further improving the cardiac function in such a condition. Therefore, we believe that an appropriate volume and fluid type are primarily important for improving the circulation capacity and cardiac function of Fontan patients after operation. This may be related to the increase in TPG and pulmonary forward blood flow, though it needs to be verified in future research.

The lung and blood vessel wall compliance in children is better than that in adults. However, the lung of children with a Fontan procedure is pathologically different from that of people with a biventricular structure.⁽²²⁾ The higher positive airway pressure caused by mechanical ventilation will significantly reduce pulmonary blood flow and LVED volume. As Fontan patients have no normal right atrial and right ventricular structures in whom pulmonary vascular resistance (PVR) is relatively high, SVV produced by cardiopulmonary interaction may be significantly different between Fontan and normal children.

Currently, CVP is commonly used as a static hemodynamic parameter in clinical practice. However, some studies have demonstrated that CVP could not be used as a single reference in patients with volume therapy.⁽²³⁾ As the linear relationship between cardiac pressure and volume is weakened in Fontan patients, the pressure parameter such as CVP cannot really reflect the volume state. In addition, the superior vena cava of Fontan patients is connected to the pulmonary artery, and therefore CVP is significantly affected by pulmonary artery pressure. As a result, the value of CVP to predict the volume reactivity of Fontan patients could be influenced by many factors and the result is unreliable.

There is few studies reporting the application of SVV in children with single-ventricle Fontan circulation. In this study, we found that the cutoff of SVV was 16%, the sensitivity was 50%, and the specificity was 91.7%, suggesting that SVV is more specific than CVP in reflecting the volume state of children undergoing Fontan operation after CPB. Statistically, children with less SVV variation are more likely to be in a non-response state. Yoshitake et al⁽²⁴⁾ used noninvasive hemodynamic monitoring to evaluate the cardiac output after Fontan operation by measuring the parameters of cardiac function in the patients with single left ventricular (SLV) and single right ventricular (SRV). Their results showed that the mean SVV (SLV : SRV) was 13.9% : 15.5%, which is similar to our study. However, the sensitivity and specificity of SVV in our study suggest that SVV may have a high false-positive rate as a predictor of capacity reactivity in Fontan patients. This may be due to the more significant reduction of pulmonary blood flow in patients with single ventricle caused by positive pressure mechanical ventilation. In addition, the inhibition of myocardial contractility and the use of positive inotropic agents in early postoperative patients may affect the results. We believe that SVV derived from the expansion of the PPV index is a relatively safe volume reactivity parameter for patients who are not suitable to use volume dilation treatment, and therefore more suitable for patients whose current volume state is on the reaction section (steep section) of Frank-Starling curve rather than the smooth section. As each inspiratory and expiratory during mechanical ventilation can cause change in stroke volume, SVV can be used to indicate volume responsiveness and the current volume state of the patient.

This study has some limitations. First, the response of Fontan patients to volume infusion is affected by many factors. But as we only observed the effect of volume challenge alone, the influence of mechanical ventilation on the research results could not be excluded. In addition, we only observed the result of volume response immediately after volume challenge treatment without tracking changes in dynamic parameters in the cardiac intensive care unit. Finally, we did not use PiCCO as the control parameter for cost consideration.

Conclusion

In summary, SVV has a good value for predicting changes in volume responsiveness in pediatric Fontan patients, although it may be affected by respiration and special physiological and anatomical structures. Appropriate volume challenge therapy can significantly improve the hemodynamic of patients and increase the cardiac output, devoid of significant impact on the internal environment. We believe that SVV can be used as a monitoring indicator in carrying out appropriate volume challenge treatment in pediatric Fontan patients, knowing that it can positively improve the cardiac function of the patients.

Abbreviations

SVV

Stroke volume variation; CVP:Central venous pressure; ROC:Receiver operating characteristic; AUC:Area under curve; CI:Cardiac index; HR:Heart rate; SBP:systolic blood pressure; DBP:diastolic blood pressure; MDP:Mean blood pressure; SVI:Stroke volume index; CPB:cardiopulmonary bypass; TPG:Transpulmonary gradient

Declarations

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Authors' contributions

This study was accomplished by four co-authors. The contributions of each author are as follows: YAS was involved in designing the study, collecting most of the data and wrote the original manuscript; HYH participated in the designing the study protocol and assisted YAS in collection of clinical data and Statistical analysis; JB and JJZ gave some instructions in designing the study scheme and performed general anesthesia management; HBG gave a lot of guidance to the design and writing of the manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

This observational prospective study was approved by the Local Ethics Committee of Shanghai Children's Medical Center affiliated to Shanghai Jiao Tong University (SCMCIRB-K2017035) and all parents or guardians of the patients voluntarily signed written informed consent before operation.

Consent for publication: Not applicable

Availability of data and material: We have included the questionnaire used in this study as supplementary information. The datasets used and analysed during the current study are available from the corresponding author upon request.

Competing interests: All authors declare no competing interests.

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Figures

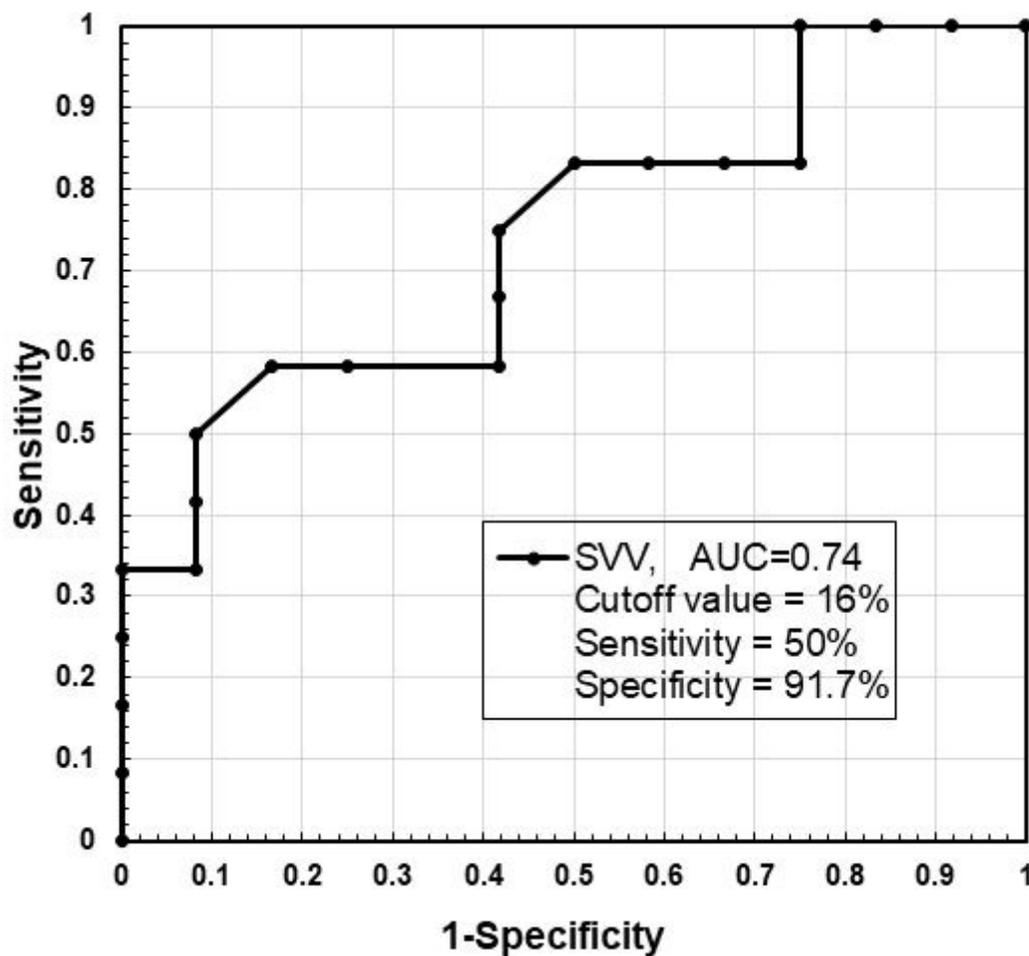


Figure 1

Receiver operating curves of SVV to predict fluid responsiveness in Fontan patients; AUC was 0.74 (95% CI 0.54-0.94, $p < 0.05$) and the cutoff value was 16%, offering a sensitivity of 50% and a specificity of 91.7%.

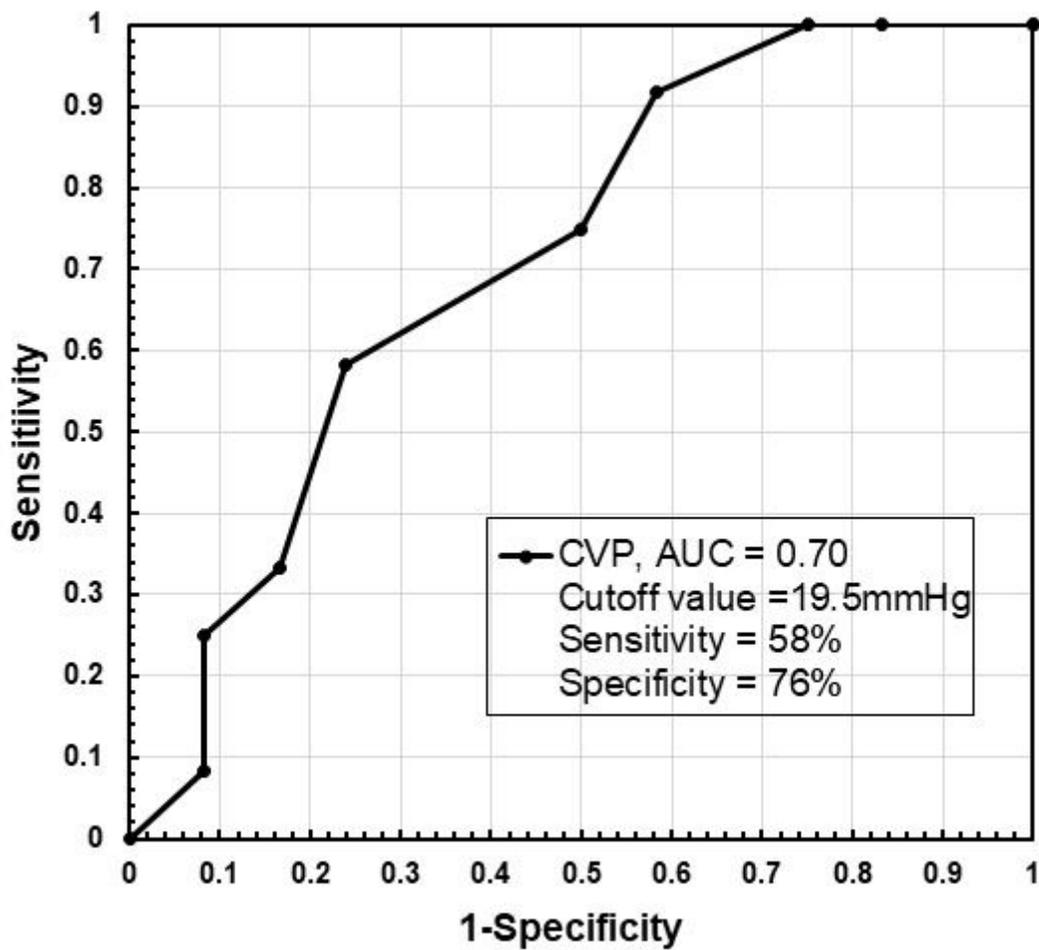


Figure 2

Receiver operating curves of CVP to predict fluid responsiveness in Fontan patients. AUC was 0.70 (95% CI 0.50–0.92, $P > 0.05$) and the cutoff value was 19.5mmHg, offering a sensitivity of 58% and a specificity of 76%.