Original Article

Quest for the Holy Grail: Assessment of Echo-Derived Dynamic Parameters as Predictors of Fluid Responsiveness in Patients with Acute Aneurysmal Subarachnoid Hemorrhage

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Abstract

Background: Acute aneurysmal subarachnoid hemorrhage (aSAH) is a potentially devastating event often presenting with a plethora of hemodynamic fluctuations requiring meticulous fluid management. The aim of this study was to assess the utility of newer dynamic predictors of fluid responsiveness such as Delta down (DD), superior vena cava collapsibility index (SVCCI), and aortic velocity time integral variability (VTIAoV) in patients with SAH undergoing neurosurgery. **Materials and Methods:** Fifteen individuals with SAH undergoing surgery for intracranial aneurysmal clipping were enrolled in this prospective study. Postinduction, vitals, anesthetic parameters, and the study variables were recorded as the baseline. Following this, patients received a fluid bolus of 10 ml/kg of colloid over 20 min, and measurements were repeated postfluid loading. Continuous variables were expressed as mean ± standard deviation and compared using Student's *t*-test, with a $P < 0.05$ considered statistically significant. The predictive ability of variables for fluid responsiveness was determined using Pearson's coefficient analysis (r). **Results:** There were 12 volume responders and 3 nonresponders (NR). DD >5 mm Hg was efficient in differentiating the responders from NR ($P < 0.05$) with a sensitivity and specificity of 90% and 85%, respectively, with a good predictive ability to identify fluid responders and NR; $r = 0.716$. SVCCI of >38% was 100% sensitive and 95% specific in detecting the volume status and in differentiating the responders from NR ($P < 0.05$) and is an excellent predictor of fluid responsive status; $r = 0.906$. VTIAoV >20% too proved to be a good predictor of fluid responsiveness, with a sensitivity and specificity of 100% and 90%, respectively, with a predictive power; $r = 0.732$. **Conclusion:** Our study showed that 80% of patients presenting with aSAH for intracranial aneurysm clipping were fluid responders with normal hemodynamic parameters such as heart rate and blood pressure. Among the variables, SVCCI >38% appears to be an excellent predictor followed by VTIAoV >20% and DD >5 mmHg in assessing the fluid status in this population.

Keywords: *Fluid responsiveness, subarachnoid hemorrhage, transoesophageal echo*

Introduction

Acute subarachnoid hemorrhage (SAH) is a potentially devastating event resulting in global neurological dysfunction associated with deleterious systemic consequences and high mortality rates.[1,2] Patients with aneurysmal SAH (aSAH) have an associated hypothalamic dysfunction and brainstem activation resulting in a "catecholamine storm," which is thought to be responsible for various neurocardiogenic injuries, such as a stunned myocardium and neurogenic pulmonary edema.[3,4] Furthermore, there are insults on the cardiac conducting system and myocardium which manifest as arrhythmia and myocardial dysfunction presenting clinically as decreased cardiac output (CO) states causing unstable hemodynamics which are commonly documented during electrocardiographic as well as echocardiographic evaluation.[4-6]

Hypovolemia, a frequent complication encountered in these patients, is due to a multitude of causative factors, the most important being cerebral salt-wasting syndrome, which usually manifests within the first few days, leading to a depreciation of extracellular fluid.[7,8] Intravascular hypovolemia is further compounded by the aggressive use of osmotic diuretics used as a measure to reduce the raised intracranial pressure. This intravascular volume loss resulting in a fall in blood pressure (BP) along with loss of cerebral autoregulatory mechanisms in the setting of aSAH increases the risk of dreaded complications,

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i.e., cerebral vasospasm and delayed cerebral ischemia. It has been proven beyond doubt that the use of judicious fluid management strategies in these patients results in better outcomes.[8-11]

Till date, there have been no landmark studies regarding fluid responsiveness in patients with SAH to optimize perioperative fluid management efficiently. Hence, we proposed to study the efficacy of dynamic indices derived from hemodynamic monitors and transesophageal echocardiography (TEE) in assessing fluid responsiveness in patients with acute SAH undergoing surgery. We aim to evaluate the efficacy of dynamic predictor indices, namely Delta down (DD), the superior vena cava collapsibility index (SVCCI), and aortic velocity time integral variability (VTIAoV) in predicting fluid responsiveness in patients with SAH undergoing elective craniotomy for aneurysm clipping. We also intended to validate the threshold for these predictor variables in differentiating responders from nonresponders (NR) in the aSAH population. We want to validate the efficacy of these variables in good grade SAH (World federation of neurosurgical societies Grade I and II) population before evaluating their response in severe grade SAH as these patients will be in a state of homeostatic and hemodynamic instability.

Materials and Methods

A prospective pilot study was carried out on patients undergoing craniotomy for surgical clipping of intracranial aneurysms. The study was approved by the institutional ethics committee, and written informed consent was obtained from all participants. Fifteen patients aged between 18 and 60 years, undergoing surgery in the supine position were enrolled. The exclusion criteria included patients with posterior circulation aneurysms, WFNS Grade III or more, presence of cardiac and pulmonary pathologies, surgery other than in supine position and those having contraindications for TEE monitoring.

None of the patients received sedative premedication. In the operating room, after attaching the standard monitors, i.e; electrocardiogram (ECG), noninvasive blood pressure (NIBP)and pulse oximetry (SPO_2); anesthesia was induced with injection Propofol 1-2 mg/kg and Injection Fentanyl 2-3 µg/kg. After confirming ability to ventilate with bag and mask Injection vecuronium 0.1 mg/kg was administered to facilitate tracheal intubation. Mechanical ventilation was instituted in a volume-controlled mode (tidal volume 8 ml/kg); the respiratory rate was adjusted to obtain an end-tidal carbon-di-oxide ($EtCO_2$) of 32–38 mmHg without PEEP. Anesthesia was maintained with 1–2 volume% sevoflurane and a continuous infusion of fentanyl at 1–2 µg/kg/h. An arterial line through radial artery and central venous catheter through right internal jugular vein were inserted under ultrasound guidance. Monitoring consisted of heart rate (HR), IBP, central venous pressure (CVP), pulse oximeter (SpO_2), $EtCO_2$, end-tidal anesthetic gas, ventilator parameters, and arterial blood gas. A forced-air warming system (Bair Hugger Warming system, Augustine Medical, Eden Prairie, MN, USA) was applied to avoid hypothermia, and nasopharyngeal temperature was monitored. TEE probe (GE Vivid 7 with 9T 4.0–10.0 MHz multiplane TEE probe, GE Healthcare, Wauwatosa, WI 53226, USA) was inserted before positioning the patient for surgery. TEE measurements recorded as part of our protocol were the SVC diameter, aortic velocity time integral (VTI), left ventricular outflow tract (LVOT) diameter, and derived variables such as stroke volume, CO, and cardiac index (CI). Calculation of the predictor variables used in the study is described below.

Delta down

Maximal systolic pressure, minimal systolic pressure, and reference systolic pressure at the end of the expiratory pause were manually measured by freezing the waveform on the monitor (Philips Intellivue, MX700, Philips Medizin systems, Germany). Each parameter was measured thrice during 3 consecutive respiratory cycles by a single investigator, and the average was taken for statistical analysis. DD was measured as the difference between the systolic arterial pressure at the end of a 5 s respiratory pause, immediately before lung inflation, and its lowest peak value during the course of one mechanical breath. DD = apneic baseline – systolic BP (SBP) minimum. DD of more than 5 mmHg has been found to be effective in differentiating fluid responders from NR.[12]

Superior vena cava collapsibility index

The SVC was examined using the midesophageal bicaval view. After obtaining the midesophageal right ventricular (RV) inflow-outflow view, the multiplane angle was rotated forward to 90°–110° and the probe turned clockwise (or rightward) to obtain the bicaval view. The anatomical M-Mode was used to measure the required diameters [Figure 1]. The SVC diameters measured were the maximum diameter on expiration (SVCmax) and minimum diameter on inspiration (SVCmin).The measurements were done during the same respiratory cycle [Figure 1]. The average of two values was used for statistical purposes. Calculation of SVC collapsibility index was done using the formula: SVC collapsibility index = ([SVCmax – SVCmin]/[SVCmax]). A cutoff value of >38% for SVC collapsibility index was used to separate responders from NR.[13,14]

Aortic velocity time integral variability and cardiac index

The LVOT and the aortic valve opening are visualized after obtaining the deep transgastric long axis (TG-LAX) view. In this deep TG-LAX view, the aortic valve is located in the far field at the bottom of the display with the left ventricular (LV) outflow directed away from the

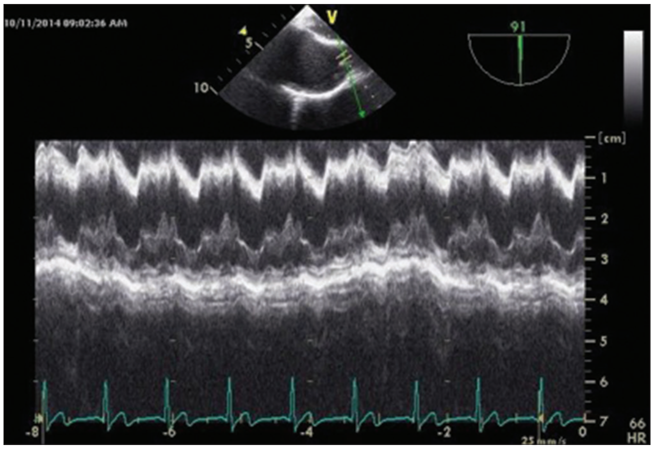

Figure 1: Transesophageal echocardiography image of the midesophageal bicaval view in anatomical M-mode showing the trace of superior vena cava diameter over a respiratory cycle

transducer [Figure 2]. Aortic velocity is obtained using a pulsed wave Doppler/continuous wave Doppler. Three recordings were made in close succession, and images of the loops are recorded. Aortic VTI is calculated from the recorded velocity loops, and the average of three recordings was taken as the final value. VTIAoV is obtained using the following formula: VTIAo variation = ([VTImax–VTImin]/[VTIavg]). Variability of VTIAo of >20% is considered as the cutoff to differentiate fluid responders from NR.[14,15] CO was obtained in this view by multiplying the cross-sectional area of LVOT with the VTI and HR. CI was calculated by dividing the CO with the body surface area.

Study protocol

Baseline variables were recorded after a 5-min interval of hemodynamic stability (SBP and HR stabilized to ± 5%) after the initiation of surgery. Volume expansion was achieved by administering 10 ml/kg of colloid solution (TetraHES, hydroxyethyl starch 130/0.4, Claris Otsuka, India) over 20 min. All study variables were again measured after fluid loading. The anesthetic concentration and ventilator parameters were kept unchanged during the period of data acquisition. Individuals were grouped into responders (R), those who showed an increase in the CI of 15% or more following fluid loading and as NR, those who did not show an increase in CI of >15%.

Statistical analysis

All statistical analyses were obtained using SPSS software version 17.0 (SPSS Inc., Chicago, IL., USA). Power analysis was not done as these variables have never been used before this during the intraoperative period, especially in the neurosurgical population with aSAH and its complex hemodynamics. The observations obtained from the study were expressed in mean ± standard deviation. Comparison of categorical variables was done using Chi-square test. Comparison of normally distributed continuous variables was evaluated with Student's *t*-test, and $P < 0.05$ was considered as statistically significant. The correlation

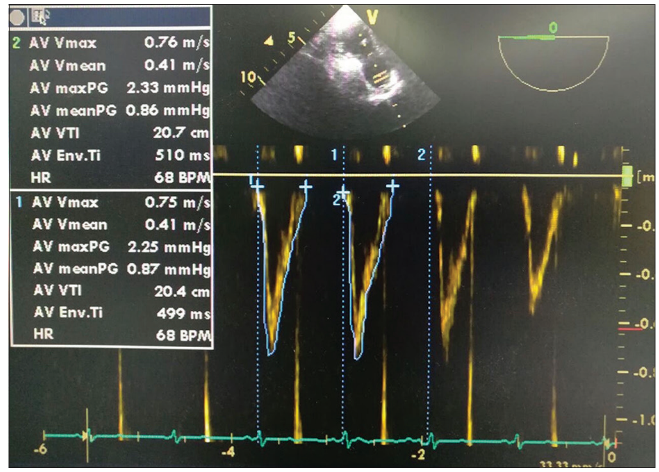

Figure 2: Transesophageal echocardiography image showing the deep transgastric long axis view with the Doppler cursor positioned at the aortic root. Velocity time integral of three consecutive Doppler waves recorded and averaged to get the desired values

between the predictor variables i.e; DD, SVCCI, and VTIAoV with Cardiac Index variability (CIV) which is considered the gold standard for identifying fluid responders and non responders was tested using Pearson's correlation coefficient. Pearson's coefficient (*r*) of more than 0.8 was considered as a strong correlation and 0.5–0.8 was considered as a good correlation. Pearson's coefficient (*r*) was preferred over receiver operating characteristic analysis as the study population was small.

Results

We recruited 15 individuals undergoing neurosurgery for aneurysmal clipping and the study cohort comprised of 8 males and 7 females. None of the patients required vasoactive drug therapy during the surgery, including the times of data acquisition. There were 12 volume responders (80%) and 3 NR (20%). The clinical characteristics of responders and NR were similar, and no difference was observed between these two groups in terms of anesthetic requirements and ventilator parameters such as $EtCO_2$ [Table 1]. There were no significant differences in hemodynamic variables such as HR, SBP, or MAP between responders and NR before fluid loading [Table 2]. After fluid loading also, there was insignificant change in HR, SBP, and MAP in both responders and NR [Table 2].

Our results showed that DD with a cutoff of 5 mmHg was effective in differentiating the responders from NR with a sensitivity and specificity of 90% and 85%, respectively. Fluid loading in patients suspected to be hypovolemic and who were later diagnosed as responders showed a baseline DD below the threshold value of 5 mmHg ($P < 0.05$) [Table 2]. There was a significant correlation (*r*) between DD and CIV; $r = 0.716$, which was considered as the gold standard in predicting the volume status of the patients [Table 3].

SVCCI with a threshold value of >38% had a sensitivity of 100% and a specificity of 95% in detecting the volume status of patients. The mean value of SVCCI was significantly elevated above the 38% cutoff ($P < 0.05$) in the responder group, whereas in the nonresponder population, it was below the threshold value. Responders had a significant decrease in SVCCI postfluid loading which demonstrated the positive response of these individuals to fluid therapy [Table 2]. It also had an excellent correlation with the outcome predictor CIV; $r = 0.906$ [Table 3].

A VTIAoV >20% had sensitivity and specificity of 100% and 90%, respectively, in differentiating the responders from NR. Responders had a baseline VTIAoV >20% ($P < 0.05$). In the fluid responder group the post fluid loading VTIAoV was <20%, which showed that the patient's volume status has been replenished and that they were grossly fluid deficient prior to fluid loading as the baseline VTIAoV was >20%. In the nonresponder group, there was no much difference in the VTIAoV pre- and postfluid loading as the patient's volume status was adequate before fluid bolus. VTIAoV had good correlation to the CI variation; Pearson's coefficient; $r = 0.732$ [Table 3].

Discussion

We designed this study with the aim to identify predictors of fluid responsiveness and to validate the threshold values in differentiating fluid responders from NR in patients with SAH undergoing neurosurgery. Our study showed that 80% of patients with SAH were fluid responders despite having a normal baseline HR and BP implying that there was an underlying fluid deficit. Our results show that indices such as DD at a cutoff value of 5 mmHg, SVCCI of >38%, and VTIAo Variation >20% were sensitive and specific for predicting the fluid responsiveness in SAH patients during surgery.

Evaluation of data offered by recent studies suggests that inspite of minor limitations, changes in arterial pressure track blood flow changes accurately, following a fluid challenge.[12,16-19] Thus, we opted to use an arterial pressure-based variable, DD for determining fluid responsiveness. Prior studies done in perioperative and ICU populations using DD showed that a cutoff of 5 mmHg can be used for differentiating fluid responders from NR and can also be used to diagnose hypovolemia and initiate fluid loading.[12] DD had shown excellent correlation with delta pulse pressure (DPP) which is a widely used dynamic index derived from the arterial trace, gained widespread acceptance due to its noninvasiveness and its good predictive power. The calculation of DD compared to DPP is easier since it does not require specialized software or the cumbersome algorithms as for pulse pressure variation (PPV) and DPP.[12] The advantage of DD is that it can be easily calculated from arterial waveform trace. The reason for using Delta down is that Delta up which is a component DPP/PPV influences the accuracy of these variables as Delta up reflects the sequestrated amount of blood in the lungs which is driven out during mechanical inspiration and does not effectively contribute to the circulating blood volume.[12,16] This uniqueness of DD kindled our interest to further evaluate this variable in the neurosurgical population.

Substantial evidence suggests that static indices such as CVP, pulmonary occlusion pressure, and variables obtained from echocardiographic evaluation such as right atrial pressure, RV end-diastolic volume, and LV end-diastolic area cannot accurately gauge changes in ventricular preload and are not good predictors of fluid responsiveness.[20,21] It has also been seen that these variables depend on the left ventricle compliance which is altered in SAH patients due to multiple reasons such as the neuroendocrine stress response,

Table 1: Patient demographics and intraoperative variables of the study population

Variables	Mean±SD	
	Responders (*n*=12)	Nonresponders (*n*=3)
Age (years)	44.5±5.9	40.3±5.5
Weight (kg)	63.62±7.87	69.28±7.95
Height (cm)	169.22±8.76	171.22±10.72
BMI (kg/m^2)	22.84±1.48	23.96±1.81
$EtCO_2$ (mm Hg)	38.1±2.1	36.5±3.4
EtSevo (%)	1.72±0.19	1.69±0.15
Temperature (°C)	36.6±0.3	36.3±0.2
PIP (cmH_2O)	16.14±2.26	17.12±2.74

BMI: Body mass index, $EtCO_2$: End-tidal carbon dioxide, EtSevo: End-tidal sevoflurane, PIP: Peak inspiratory airway pressure, SD: Standard deviation

Table 2: Comparison of hemodynamic and predictor variables between the responder and nonresponder population

Variables	Mean±SD			
	Responders (*n*=12)		Nonresponders (*n*=3)	
	Before FL	After FL	Before FL	After FL
HR (beats/min)	89.65±6.72	86.33±8.13	87.00±9.99	84.23±9.15
SBP (mm Hg)	134.51±7.38	129.25±9.64	139.02±9.23	135.00±7.65
DD (mm Hg)	9.50±3.15*	3.42±1.89	4.33±1.53	3.00±1.94
SVCCI (%)	66.71±16.64*	28.5±6.08*	36.18±5.32*	28.25±4.43
VTIAoV (%)	24.93±3.74*	6.05±3.18*	13.37±3.31*	6.26±2.33

*$P<0.05$. HR: Heart rate, SBP: Systolic blood pressure, DD: Delta down, SVCCI: Superior vena cava collapsibility index, VTIAoV: Aortic velocity time integral variation, FL: Fluid loading, SD: Standard deviation

Table 3: Correlation coefficient of the variables with the outcome predictor (percentage change in cardiac index)

Variables	Pearson's correlation coefficient (*r*)
HR	0.290
SBP	0.216
DD	0.716^{+}
SVCCI	0.906^{+}
VTIAoV	0.784^{+}

$^{+}r>0.70$. HR: Heart rate, SBP: Systolic blood pressure, DD: Delta down, SVCCI: Superior vena cava collapsibility index, VTIAoV: Aortic velocity time integral variation

high sympathetic surge, and associated cardiomyopathies, for example, Takotsubo cardiomyopathy.[1,4] In our study, we used TEE to obtain dynamic variables such as SVC diameters, aortic VTI, LVOT/aortic orifice diameter, and based on these variables, we calculated the SVCCI and VTIAoV. There are no previous studies done to assess the reliability of SVCCI and VTIAoV in predicting volume responsiveness in the perioperative period, especially in the neurosurgical population We considered aortic VTI variation as a surrogate measure of changes in preload and contractile function of the left ventricle. TEE also helped in simultaneous quantification of changes in loading conditions, CO, and diastolic function in our subset of patients with SAH who show a dynamic variability in their cardiac compliance. CO measured by TEE has been shown to correlate well with measurements of CO obtained using thermodilution techniques with pulmonary artery catheter which is currently considered as the gold standard for measurement of the same.[22-24]

Analysis of our observations showed that there were no differences in basic hemodynamic parameters such as the HR and SBP, between the responders and the NR. It was noted that SAH patients despite being grossly fluid deficient had a higher baseline HR and SBP which can be attributed to the underlying sympathetic surge secondary to the neuroendocrine response, resulting in higher levels of circulating catecholamines. Even after fluid loading, these indices did not change significantly, implying their poor correlation with the volume status. Thus, it is clear from our findings that these variables are unreliable in assessing and managing the volume status of patients with SAH.

Our study showed that DD with a threshold of 5 mmHg proved to be a reliable predictor in assessing the volume status of individuals in both the groups, with a sensitivity and specificity of 95% and 85%, respectively, and it definitely helped in differentiating the responders from the NR in the aSAH population. It also showed a good correlation (Pearson's coefficient, $r = 0.716$) with CIV, thereby accurately predicting the fluid responsiveness. There appears to be no effect of neuroendocrine response seen in acute SAH on the behavior of this variable or on the threshold of 5 mmHg, as we found a similar pattern of variation of DD in the study done by Deflandre *et al.*, who had arrived at the conclusion that DD >5 mmHg could be used to differentiate responders from NR.[12] They observed that DD recorded after fluid therapy and optimization of fluid status was below 5 mmHg (threshold value) which was observed in our study as well proving 5 mmHg threshold can be applied in our study population also.

Evaluation of SVC Collapsibility Index proved that this is an excellent predictor of the fluid status in acute SAH patients with high sensitivity of 100% and a specificity of 95%. The mean values of the responder group were significantly above the cutoff threshold of 38% ($P < 0.05$), and postfluid loading, these values reduced to <38%, thereby demonstrating its efficacy. The variations of SVCCI had an excellent correlation with CIV (Pearson's coefficient, $r = 0.906$), even in the nonresponder population. Our analysis also showed that this variable was not affected by the neuroendocrine effects as often seen in our study population. It concurred with the findings of Vieillard-Baron *et al.*, who studied SVCCI as an indicator of volume status in patients with sepsis and concluded that SVCCI >38% had a sensitivity of 90% and a specificity of 100%.[13] Our findings are further supported by Charron *et al.*, who proved the echocardiographic measurements of fluid responsiveness and found that the SVC diameter changes during mechanical ventilation are an accurate measure of fluid responsiveness.[17]

We observed that VTIAoV of >20% demonstrated a high sensitivity of 100% and a specificity of 90% in discriminating the responders from the NR. The mean value of the responder group was significantly above the cutoff threshold of 20% ($P < 0.05$), and postfluid loading, this reduced to below the threshold, thereby demonstrating its ability as a predictor of fluid status. It further exhibited a high level of correlation with CIV; Pearson's coefficient ($r = 0.784$), thereby proving the fact that this is indeed a very accurate predictor of fluid responsiveness. Our analysis revealed that VTIAoV behaved in a comparable manner in aSAH population, as similar to prior studies, thereby showing that it is not affected by the neuroendocrine effects. This proves its credibility as an excellent predictor in this subset of patients as our observations were comparable with the results obtained by Feissel *et al.*, in patients with septic shock who were being mechanically ventilated.[15] They had concluded that peak velocity (Vpeak) variation >12% allowed good differentiation between responders and NR, having a positive predictive value of 91% and a negative predictive value of 100%. Similarly, Byon *et al.* proved that Vpeak variation >11% identified responders with good sensitivity and acceptable specificity in pediatric patients undergoing neurosurgery.[14] Although the above-mentioned studies assessed the peak velocities and its variation, VTI is a variable derived from the aortic velocity and is thus comparable and more robust than Vpeak variation.

The result of this study throws light on some of the very important aspects of fluid therapy in patients with SAH presenting for surgical management. This will aid in planning a careful fluid management strategy that will improve the outcome in patients with SAH by preventing the incidence of vasospasm, pulmonary edema, and associated perioperative complications.

Limitations

We included only aneurysmal aSAH patients with WFNS Grade 1 and 2, as higher grades usually are not immediately operated upon since they require preoperative stabilization of their hemodynamic and cardiac and endocrine status. The TEE-based predictor variables can only be measured in patients undergoing surgery in the supine position. We also have not included all the indices of fluid responsiveness available currently in literature. Furthermore, our study focused on patients with acute SAH only and these results may not be applicable to other neurosurgical conditions or to other patients with associated cardiac ailments. As this was a pilot study to assess the feasibility of use of these dynamic indices, we had a small study population, so future studies with larger patient population involving severe grade SAH are warranted to address these scenarios.

Conclusion

Our study showed that 80% of patients presenting with aSAH for intracranial aneurysm clipping were fluid responders despite static indices of hemodynamics such as HR and BP being within the normal range. Among the variables studied, SVCCI >38% is an excellent predictor of fluid responsiveness followed by VTIAoV >20% and DD >5 mmHg in patients with SAH. In this era of TEE, this study will boost the confidence of physicians to use the readily available arterial waveform-derived indices such as DD when echocardiography is not a feasible option.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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