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

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. 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. 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.

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. 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.
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.\textsuperscript{[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 transeosophageal 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\textsubscript{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\textsubscript{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\textsubscript{2}), EtCO\textsubscript{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.\textsuperscript{[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 (SVC\textsubscript{max}) and minimum diameter on inspiration (SVC\textsubscript{min}). 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 = \((SVC\textsubscript{max} – SVC\textsubscript{min})/SVC\textsubscript{max})\). A cutoff value of >38% for SVC collapsibility index was used to separate responders from NR.\textsuperscript{[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...
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 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 post fluid loading which demonstrated the positive response of these individuals to fluid therapy [Table 2]. It also had an excellent correlation with the outcome predictor CI; $r = 0.906$ [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 post fluid 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 VTIAoV 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. 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. 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. 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. 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. 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.

| Variables | 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/m²) | 22.84±1.48 | 23.96±1.81 |
| EtCO₂ (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 (cmH₂O) | 16.14±2.26 | 17.12±2.74 |

BMI: Body mass index, EtCO₂: End-tidal carbon dioxide, EtSevo: End-tidal sevoflurane, PIP: Peak inspiratory airway pressure, SD: Standard deviation

| Variables | Before FL | After FL |
|-----------|-----------|----------|
| HR (beats/min) | 89.65±6.72 | 86.33±8.13 |
| SBP (mm Hg) | 134.51±7.38 | 129.25±9.64 |
| DD (mm Hg) | 9.50±3.15* | 3.42±1.89 |
| SVCCI (%) | 66.71±16.64* | 28.5±6.08* |
| VTIAoV (%) | 24.93±3.74* | 6.05±3.18* |

| Variables | Before FL | After FL |
|-----------|-----------|----------|
| HR (beats/min) | 87.00±9.99 | 84.23±9.15 |
| SBP (mm Hg) | 139.02±9.23 | 135.00±7.65 |
| DD (mm Hg) | 4.33±1.53 | 3.00±1.94 |
| SVCCI (%) | 36.18±5.32* | 28.25±4.43 |
| VTIAoV (%) | 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
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 perioperati...
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.

**References**

1. Lerch C, Yonekawa Y, Muroi C, Bjejlac M, Keller E. Specialized neurocritical care, severity grade, and outcome of patients with aneurysmal subarachnoid hemorrhage. Neurocrit Care 2006;5:85-92.
2. Goto Y, Yamagata S. Deteriorating factors on the outcome in patients with fair grade of subarachnoid hemorrhage (WFNS grade I and II). No Shinkei Geka 2006;34:577-82.
3. Espiner EA, Leikis R, Ferch RD, MacFarlane MR, Bonkowski JA, Frampton CM, et al. The neuro-cardio-endocrine response to acute subarachnoid haemorrhage. Clin Endocrinol (Oxf) 2002;56:629-35.
4. Manea MM, Comsa M, Minca A, Dragos D, Popa C. Brain-heart axis – Review article. J Med Life 2015;8:266-71.
5. Salem R, Vallée F, Déprest F, Callebert J, Maurice JP, Marty P, et al. Subarachnoid hemorrhage induces an early and reversible cardiac injury associated with catecholamine release: One-week follow-up study. Crit Care 2014;18:558.
6. McLaughlin N, Bojanowski MW, Girard F, Denault A. Pulmonary edema and cardiac dysfunction following subarachnoid hemorrhage. Can J Neurol Sci 2005;32:178-85.
7. Lennihan L, Mayer SA, Fink ME, Beckford A, Paik MC, Zhang H, et al. Effect of hypertensive fluid therapy on cerebral blood flow after subarachnoid hemorrhage: A randomized controlled trial. Stroke 2000;31:383-91.
8. Sen J, Belli A, Albon H, Morgan L, Petzold A, Kitchen N, et al. Triple-H therapy in the management of aneurysmal subarachnoid haemorrhage. Lancet Neurol 2003;2:614-21.
9. Bundgaard-Nielsen M, Secher NH, Kehlet H. ‘Liberal’ vs. ‘restrictive’ perioperative fluid therapy – A critical assessment of the evidence. Acta Anaesthesiol Scand 2009;53:843-51.
10. Rowland MJ, Hadjipavlou G, Kelly M, Westbrook J, Pattinson KT. Delayed cerebral ischaemia after subarachnoid haemorrhage: Looking beyond vasospasm. Br J Anaesth 2012;109:315-29.
11. Keyrouz SG, Diringer MN. Clinical review: Prevention and therapy of vasospasm in subarachnoid hemorrhage. Crit Care 2007;11:220.
12. Deflandre E, Bonhomme V, Hans P. Delta down compared with delta pulse pressure as an indicator of volaemia during intracranial surgery. Br J Anaesth 2008;100:245-50.
13. Vieillard-Baron A, Augarde R, Prin S, Page B, Beauchet A, Jardin F, et al. Influence of superior vena cava zone condition on cyclic changes in right ventricular outflow during respiratory support. Anesthesiology 2001;95:1083-8.
14. Byon HJ, Lim CW, Lee JH, Park VH, Kim HS, Kim CS, et al. Prediction of fluid responsiveness in mechanically ventilated children undergoing neurosurgery. Br J Anaesth 2013;110:586-91.
15. Feissel M, Michard F, Mangin I, Ruyer O, Faller JP, Teboul JL, et al. Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. Chest 2001;119:867-73.
16. Michard F. Changes in arterial pressure during mechanical ventilation. Anesthesiology 2005;103:419-28.
17. Charron C, Fessenmeyer C, Cosson C, Mazoit JX, Hebert JL, Benhamou D, et al. The influence of tidal volume on the dynamic variables of fluid responsiveness in critically ill patients. Anesth Analg 2006;102:1511-7.
18. Kim SH, Kim MJ, Lee JH, Cho SH, Chae WS, Cannesson M, et al. Current practice in hemodynamic monitoring and management in high-risk surgery patients: A National Survey of Korean Anesthesiologists. Korean J Anesthesiol 2013;65:19-32.
19. Huang CC, Fu JY, Hu HC, Kao KC, Chen NH, Hsieh MJ, et al. Prediction of fluid responsiveness in acute respiratory distress syndrome patients ventilated with low tidal volume and high positive end-expiratory pressure. Crit Care Med 2008;36:2810-6.
20. Sabatier C, Monge I, Maynar J, Ochagavia A. Assessment of cardiovascular preloading and response to volume expansion. Med Intensiva 2012;36:45-55.
21. Wagner JG, Leatherman JW. Right ventricular end-diastolic volume as a predictor of the hemodynamic response to a fluid challenge. Chest 1998;113:1048-54.
22. Pouelaert J, Truauerch J, De Buyzere M, Everaert J, Colardyn FA. Evaluation of transesophageal echocardiography as a diagnostic and therapeutic aid in a critical care setting. Chest 1995;107:774-9.
23. Belloni L, Pisano A, Natale A, Piccirillo MR, Piazza L, Ismeno G, et al. Assessment of fluid-responsiveness parameters for off-pump coronary artery bypass surgery: A comparison among LiDCO, transesophageal echocardiography, and pulmonary artery catheter. J Cardiothorac Vasc Anesth 2008;22:243-8.
24. Coudray A, Romand JA, Treggiari M, Bendjelid K. Fluid responsiveness in spontaneously breathing patients: A review of indexes used in intensive care. Crit Care Med 2005;33:2757-62.