# COMPARISON OF DELTA DOWN, SUPERIOR VENA CAVA COLLAPSIBILITY INDEX AND AORTIC VELOCITY TIME INTEGRAL VARIABILITY AS PREDICTORS OF FLUID RESPONSIVENESS IN PATIENTS WITH SUBARACHNOID HAEMORRHAGE

*Thesis submitted for the partial fulfilment for the requirement Of*
*The degree of*
*DM Neuroanaesthesia*
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***The meaning of Karma is in the Intention. The intention behind action is what matters. Those who are motivated only by desire for the fruits of action are miserable, for they are constantly anxious about the about the results of what they do.***

***You have the right to work, but never to the fruit of work. You should never engage in action for the sake of reward, nor should you long for inaction.***

***Bhagwat Gita: chapter two; verse 47***

# DECLARATION

I hereby declare that the thesis titled " **Comparison of Delta Down, Superior Vena Cava Collapsibility Index and Aortic Velocity Time Integral variability as Predictors of Fluid Responsiveness in patients with Subarachnoid Haemorrhage**.", has been prepared by me under the capable supervision and guidance of Dr. Manikandan.S, Additional Professor, Department of Anaesthesiology, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

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# CERTIFICATE

This is to certify that the thesis titled " **Comparison of Delta Down, Superior Vena Cava Collapsibility Index and Aortic Velocity Time Integral variability as Predictors of Fluid Responsiveness in patients with Subarachnoid Haemorrhage**.", is a bonafide work of Dr Ajay Prasad Hrishi P, DM. Neuroanesthesia Resident, and has been done under my direct guidance and supervision at Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram. He had shown keen interest in the research and was very active in performing this clinical study during all its phases.

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This is to certify that the thesis titled " **Comparison of Delta Down, Superior Vena Cava Collapsibility Index and Aortic Velocity Time Integral variability as Predictors of Fluid Responsiveness in patients with Subarachnoid Haemorrhage** ", has been prepared by Dr Ajay Prasad Hrishi P, DM Neuroanesthesia Resident, under the guidance of Dr. Manikandan S, MD, PDCC, Additional Professor, Department of Anaesthesiology at Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram. He has shown keen interest in preparing this project.

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# CONTENTS

# ABBREVIATIONS

| | | |
|---|---|---|
| ABP | : | Arterial blood pressure |
| AHA | : | American Heart Association |
| AV | : | Aortic valve |
| BBB | : | Blood brain barrier |
| BSA | : | Body surface area |
| BMI | : | Body Mass Index |
| CBF | : | Cerebral blood flow |
| CBV | : | Cerebral blood volume |
| CI | : | Cardiac index |
| CO | : | Cardiac output |
| CI | : | Cardiac Index |
| CIV | : | Cardiac Index Variation |
| CPP | : | Cerebral perfusion pressure |
| CSA | : | Cross sectional area |
| CSF | : | Cerebro spinal fluid |
| CSW | : | Cerebral Salt Wasting Syndrome |
| CVP | : | Central Venous pressure |
| CWD | : | Continuous Doppler |
| DCI | : | Delayed Cerebral Ischemia |
| DD | : | Delta Down |
| DPP | : | Delta pulse pressure |
| DV | : | Delta Velocity (Aortic) |
| EF | : | Ejection fraction |
| ESA | : | End systolic area of left ventricle |

| | | |
|---|---|---|
| Et | : | End Tidal |
| FAC | : | Fractional area changes |
| FB | : | Fluid balance |
| FI | : | Fluid intake |
| FL | : | Fluid Loading |
| GEDV | : | Global End Diastolic Volume |
| HR | : | Heart rate |
| ICP | : | Intra cranial pressure |
| ITBV | : | Intra Thoracic Blood Volume |
| IVCD | : | Inferior Vena Cava Diameter |
| LAP | : | Left atrial pressure |
| LV | : | Left ventricle |
| LVOT | : | Left ventricular outflow tract |
| LVEDV | : | Left Ventricular End Diastolic Volume |
| MAP | : | Mean arterial pressure |
| MV | : | Mitral valve |
| PAC | : | Pulmonary artery catheter |
| PAP | : | Pulmonary artery pressure |
| PIP | : | Peak Inspiratory Pressure |
| PPV | : | Pulse Pressure Variation |
| PVI | : | Pleth Variability Index |
| PWD | : | Pulsed wave Doppler |
| RAP | : | Right atrial pressure |
| RCT | : | Randomised Control Trial |
| RR | : | Respiratory Rate |
| RV | : | Right ventricle |
| RVEDP | : | Right ventricular end diastolic pressure |
| RVEDV | : | Right ventricular end diastolic volume |

| | | |
|---|---|---|
| SAH | : | Subarachnoid Haemorrhage |
| SBP | : | Systolic blood pressure |
| SPV | : | Systolic Pressure Variation |
| SV | : | Stroke volume |
| SVC | : | Superior Vena Cava |
| SVCCI | : | Superior vena cava collapsibility index |
| SVR | : | Systemic vascular resistance |
| TEE | : | Transesophageal Echocardiography |
| TDI | : | Tissue Doppler imaging |
| TTE | : | Transthoracic Echocardiography |
| UO | : | Urine output |
| VTIAo | : | Aortic velocity time integral |
| VTIAoV | : | Aortic VTI variation |

# INTRODUCTION

# INTRODUCTION

Subarachnoid haemorrhage (SAH) caused due to intracranial aneurysm rupture, is a potentially devastating event with high mortality rate causing global neurological dysfunction associated with deleterious systemic consequences.[1, 2]

In a patient with SAH, due to the associated hypothalamic dysfunction and brainstem activation there is a "catecholamine storm", which is thought to be responsible for various neuro-cardiogenic injuries, such as a stunned myocardium and neurogenic pulmonary edema'.[3-6]. These insults on the myocardium manifest as both systolic and diastolic myocardial dysfunction seen clinically as a decrease in cardiac output resulting in hypotension and documented by echocardiographic as well as electrocardiographic evaluation.[1, 4]. Pulmonary edema, a delayed complication, is attributed to the above mentioned myocardial dysfunction, and occurs in 28.8% of patients after SAH.[6]

Hypovolemia is another common complication encountered in patients who present with SAH. This may be due to various factors such as the cerebral salt wasting syndrome, a common anticipated complication which usually manifests within first few days, leading to a depreciation of extracellular fluid volume through cerebrospinal mediated mechanisms.[7, 8] This hypovolemia is further compounded by the use of aggressive measures to reduce the raised intracranial pressure ,e.g.; osmotic therapy using drugs like mannitol which induce a phase of hypervolemia, followed by hypovolemia as in the case of uncompensated diuresis[9].

This leads to volume loss with resultant fall in blood pressure and loss of neuro- auto regulatory mechanism which increases the risk of the dreaded complication of cerebral vasospasm and Delayed cerebral ischemia (DCI). Prior studies have proven that a careful fluid management strategy in patients with SAH resulted in better outcome.[8, 10]

It has been proven that the mainstay of management of hypovolemic patients is nevertheless intravenous fluids. Calculation of dosage parameters of intravenous fluids is of paramount importance.

Inadequate volume replenishment leads to hypo perfusion of tissues and thereby worsens organ dysfunction which may be further compounded by uncorrected hypovolemia, resulting in the use of inappropriate infusions of vasopressor agents, thus worsening the viscous cycle of ischemia [1, 11].

However, fluid overloading also impedes oxygen delivery and compromise patient outcome. Overzealous fluid resuscitation results in increased complications in SAH patients, the most common being pulmonary edema and cardiac failure thereby resulting in poor outcome i.e. duration of hospitalisation in ICU setting and increased morbidity and mortality.[2, 6]

Recent studies have put forth the concept of timely and aggressive resuscitation of critically ill patients which may limit and/or revert tissue hypoxia and thereby improve the outcome.[1] The landmark study by Rivers et al concluded that early goal-directed therapy driven protocols, will prevent organ dysfunction and improve overall survival rate in patients with severe

sepsis and prevent subsequent septic shock.[12] Likewise protocols which optimize the preload and resultant cardiac output improvement in patients undergoing surgery have significantly reduced postoperative morbidity and duration of hospital stay.[13-15]

Similarly for patients with SAH, associated with hemodynamic instability, it is essential to have a protocol driven rapid evaluation of intravascular volume status as well as volume responsiveness to reduce the morbidity and mortality.[6, 15]

Various indices are described in the literature for assessment of fluid status in critically ill and perioperative patients. [14, 16] They are classified as static and dynamic indices. Static indices are simple to measure; however various studies have found them unreliable in the critically ill. Hence dynamic indices are usually the preferred guide to assess the responsiveness of fluid challenge and requirement.[17-19].

Monitoring of Central Venous Pressure (CVP) and Pulmonary artery pressure (PAOP) are found to be poor tools in differentiating subjects who respond to fluid loading and those who do not. [14, 16, 20] Static volumetric indicators namely global end-diastolic volume (GEDV), Intra Thoracic blood volume (ITBV) and left ventricular end-diastolic area (LVEDA) are not efficient predictors of volume responsiveness, since the response to fluid loading (FL) depends on Frank Starling law that explains the relation between LV preload and the slope of the left ventricular Frank Starling curve.[20, 21]

Various dynamic indices include Delta down(DD),Pulse pressure variation (PPV), Stroke volume variation(SVV),Systolic pressure variation

( SPV), Aortic velocity time integral variation( VTI Ao V),Superior vena cava( SVC) and Inferior vena cava (IVC) diameters and derived indices. Many of these variables have been evaluated in ICU as well as perioperative settings and found to be reliable indices.[18, 21]

Delta down (DD) is found to be an efficient indicator in predicting hypovolemia and responsiveness to fluid loading (FL) in pre op subjects undergoing intracranial surgery. DD of > 5 mm of Hg is taken as the critical value for starting fluid therapy (FL). [22, 23]

Aortic VTI variation is another important indicator in predicting the outcome to fluid resuscitation.[23] This index being easily recordable with a Trans Oesophageal Echocardiography (TEE), predicts with high sensitivity and specificity, the increase in cardiac output following fluid loading in subjects who are in shock.[24, 25] It is also proved that TEE is of paramount importance in recording two other variables namely- the superior vena cava diameter and SVC collapsibility index which helps to accurately distinguish responders from non-responders [24, 26]. VTI Ao variability and SVC collapsibility index appears to be one of the most effective and reliable predictors of fluid responsiveness but it does require TEE and thus is out of reach of most anaesthesiologists[26].

TEE is a far more specific and objective method of assessment when compared to impedance plethysmography especially in terms of measuring stroke volume, cardiac output and cardiac index. Moreover, TEE has got very little inherent risk, in comparison to invasive methods of measuring such indices like pulmonary artery catheter.[19, 25, 28] Further, as per ACC/AHA

guidelines, TEE ought to be routinely used in neurosurgical procedures where there are anticipated risks of major fluid shifts, and hemodynamic perturbations (Class II a indication).

In this background, we proposed the present study to compare these three variables and to find out its reliability as predictors of fluid responsiveness in mechanically ventilated patients with extra axial bleed, particularly SAH. These patients have a complex homeostasis due to coexistence of cardiac dysfunction, neuroendocrine disturbance, hypovolemia and diuretic therapy.[1, 3, 5, 27]

This study aims at describing the various changes in hemodynamics and of the different predictor indices namely- Delta down, the SVC collapsibility index and Aortic VTI variability in response to fluid loading using Transesophageal echocardiography (TEE), which is accurate when compared to any other non-invasive or lesser invasive methods, having an extremely lesser inherent risk to the patient.

Till date , there has been no major research, where the effect of fluid loading on hemodynamics and fluid responsiveness in perioperative neurosurgical patients have been studied with TEE derived measurements. In fact a systemic search in PUBMED/MEDLINE could not find any substantiative articles on "SAH" and "DD","SVC collapsibility index" and Aortic VTI variability."

The results of this study might throw more light on hemodynamic responses to fluid loading in SAH patients undergoing craniotomy.

# AIMS AND OBJECTIVES

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1. To assess the feasibility of Delta down , SVC collapsibility index and Aortic VTI variation as predictors of fluid responsiveness of patients with aneurysmal subarachnoid haemorrhage and in those with supratentorial tumours presenting for neurosurgery.

2. To determine the predictive abilities of these three variables in identifying and differentiating fluid responders from non responders.

3. To evaluate how these variables behave in a spectrum of neurosurgical patients and to observe whether they are affected by the presence of neuroendocrine and sympathetic surge present in SAH by comparing with the tumour population in whom this phenomena is absent.

# REVIEW OF LITERATURE

# REVIEW OF LITERATURE

The global estimated incidence of Aneurysmal SAH is 9/ 100,000 persons/year .[28]. The World Health Organization study named Multinational Monitoring Trends and Determinants in Cardiovascular Disease (WHO MONICA stroke study), was a large cross sectional observational study done on the population of Europe and China, observed a 30 day mortality rate of above 42%[29].It also commented on the morbidity inflicted by SAH with high risk of permanent disability among survivors, and a very high dependency rate of approximately over 50%[29]

Subjects with Aneurysmal SAH usually present with electrolyte and intravascular volume abnormalities in the immediate post rupture period. Hyponatremia is observed more often compared to hypernatremia.[30, 31]

Most often hyponatremia is attributed to cerebral salt wasting syndrome (CSW) or Syndrome of inappropriate secretion of antidiuretic hormone (SIADH); sometimes both these conditions can coexist. Hyponatremia in SAH can be multifactorial i.e. Raised levels of rennin / angiotensin- II, atrial natriuretic peptide and in some cases increased arginine vasopressin with or without hypoaldosteroinism.[31] Increased sympathetic tone is also identified as one of the etiologies.[31] Patients presenting with CSW show a triad of hypovolemia, hyponatremia and increased urine sodium concentration (> 50mmol/L) .Individuals presenting with SIADH are usually normovolemic but sometimes present with mild hypervolemia along with hypernatremia.

Etiology is most likely iatrogenic attributed as secondary to hypertonic saline or mannitol infusion.[32]

In rare occasions hypernatremia happens due to DI (diabetes insipidus) as a result of hypothalamic ischemia associated with SAH. Multiple reasons which can cause hypothalamic ischemia are: decreased cerebral perfusion pressure (CPP), increased ICP with resultant reduction of CPP, vasospasm of anterior cerebral artery (ACA) and/ or ACom artery. Partial hypopituitarism also presents in such patients possibly due to secondary vasospasm and decreased CPP.[33]

Subjects following subarachnoid bleed are very likely to exhibit a wide spectrum of electrocardiographic (ECG) variations including ST and T changes (which is suggestive of the associated myocardial ischemia),as well as prolongation of QT interval and presence of U waves.[34] Additionally they may present with ventricular, supraventricular arrhythmias with elevated troponin levels, and cardiac dysfunction not attributed to coronary vasospasm. [34].The exact rationale behind this presentation still remains unknown. The most commonly agreed upon cause is the sympathetic surge along with associated parasympathetic dysfunction thereby causing inflammation of cardio- myocytes. It is proven that elevated troponins levels are associated with a high risk for cardiovascular complications and Delayed cerebral ischemia (Vasospasm-induced) and poor neurological outcome.[3]

Neurogenic pulmonary edema (NPE) is another common complication which presents in patients with SAH. This is caused due to massive sympathetic discharge resulting from neurological injury and presents with

decreased segmental as well as global cardiac systolic function especially of the left ventricle. NPE reflects the severity of the SAH and is one of the indicators of poor outcome.[4, 35]

Delayed Cerebral Ischemia (DCI) is a very serious complication seen in SAH patients.[36] DCI is associated with poor neurological outcome and it can occur with or without vasospasm. The term DCI is now preferred over vasospasm as cerebral ischemia can happen following subarachnoid haemorrhage without angiographically positive vasospasm.[37]

There are multiple etiologies for Delayed cerebral ischemia. The commonly agreed upon mechanisms are: destruction of blood-brain integrity as a result of early brain injury with associated cerebral edema resulting in loss of cerebral autoregulation.[37, 38] Other popular theories are cortical spreading depression as well as microthrombosis of cerebral vasculature.

Cortical spreading depression happens as a result of depolarization waves that propagate across the cerebral gray matter at a speed of 2 to 5 mm/min thereby causing depression of spontaneous and evoked EEG potentials. The spread of such clusters of slow waves results in severe vasoconstriction, as well as disruption of cerebral ion homeostasis, resulting ultimately as recurrent tissue ischemia. [39, 40]Microthrombosis is attributed to coagulation cascade activation following initial haemorrhage.

Delayed Cerebral Ischemia is managed aggressively by maintenance of adequate intravascular fluid status, nimodipine along with induced hypertension. The effectiveness of Triple H therapy (Hypervolemia, induced Hypertension and Hemodilution) is not fully

validated and needs to be studied in RCTs.[41] Hypertension is now considered as the only useful component of HHH therapy as it improves cerebral blood flow resulting in increased brain tissue oxygen levels and thereby reversing the neurological symptoms. [42].There is insufficient data as of now to confirm the effectiveness of hypervolemic therapy. Hypervolemia results in decreased brain tissue oxygenation, intra/extravascular fluid overload causing deleterious cardiac and pulmonary events.[10]

The current recommendation is to avoid hypovolemia which occurs frequently in SAH subjects and to maintain isovolemia. So to conclude on the management of DCI is oral nimodipine, maintenance of euvolemia, and induced hypertension.

Now there is increasing evidence on the management of SAH. This may help in further enhancing the practice of the anaesthesiologist and thus improve the short as well as long-term survival of SAH patients.

During the perioperative period, it is mandatory to optimise blood volume in patients with subarachnoid haemorrhage .This is required for ensuring adequate tissue perfusion and thereby preventing perioperative neurological complications such as delayed cerebral ischemia (DCI)[10, 42].The study conducted by Rothberg et al in 1980 threw light on the fact that SAH subjects with increased blood loss had an added risk of developing DCI.[43].This conclusion was further proved by Rooij and Rinkel in 2007 who brought out conclusive figures of the incidence of developing DCI as 30% to 40%, with a highest incidence occurring 4 to 10 days after onset of

subarachnoid haemorrhage. Hence, the occurrence of DCI was without a doubt established as a major contributor to poor outcome [28, 44].

Further correlative studies were performed by Mori et al to evaluate SAH patients with cerebral vasospasm who required fluid and volume expansion therapy and also to determine various clinical indices which were required to guide therapy.[9]

Kasuya et al paved the way for advanced fluid management for SAH patients based on principal clinical variables like heart rate, arterial systolic and central venous blood pressures, pulmonary capillary wedge pressure, fluid balance and serum sodium concentration.[45] But these parameters were found to have a poor relation with actual measured blood volume. These results were consistent with the observations in subsequent studies of Lennihan et al in 2000 and Stephan et al in 2001.[7]

Hofer et al assessed another important facet of fluid management-whether volume resuscitation altered by daily evaluation of blood volume parameters had a better outcome than conventional fluid balance guided fluid therapy. They did daily assessment of blood volume (BV) with Pulse Dye Densitometry (PDD) and concluded that guiding fluid management on daily BV-measurements resulted in less hypovolemia after SAH.[46]

Volume status of patients with SAH can be assessed using various static or dynamic indices.[16, 21, 27]. Many static parameters were suggested to predict how patients' would respond to fluid therapy. [47-50]

Critical care specialists make use of different measures like the central venous pressure (CVP), right atrial pressure (RAP) and pulmonary artery occlusion pressure (PAOP) to make decisions regarding optimal fluid therapy in patients. Other static measures such as Right ventricular end diastolic volume (RVEDV) and LV end-diastolic area (LVEDA), which reflect the preload to the left ventricle have also been extensively researched in search of the ideal parameter which can predict the responsiveness of patients' to fluid resuscitation.[51]

With the thought that the CVP is a constant reflection of the intravascular volume status of patients, this was used as a routine measurement to guide physicians in managing complex fluid resuscitations. It is assumed that subjects with a low intravascular volume would present with a low CVP and those with fluid overload would have a subsequently raised CVP.[52-55]

Much research has been done in this context and they have proved that the above mentioned assumption was false and that there actually exits no relationship between the CVP (or change in CVP) and fluid responsiveness in different clinical scenarios [52-55]. It has been demonstrated by some studies where in even patients with a CVP as high as 15 mm Hg have shown an increase in the cardiac output in response to fluid infusion.[56]

The other static index which was hoped to reflect the volume status of a patient is the Right Atrial Pressure (RAP). In 1981, Calvin et al studied as to what would happen to patients who were administered a fast infusion of fluids based on the RAP of these critically ill patients. Their study concluded with the

observation that the baseline RAP was not clinically nor significantly different between the two groups, namely the responders and the non-responders.[57]

In contrast to the above mentioned study, Wagner and Leatherman in 1998 emphasized through their informative research that, in the group of patients that they had studied, they found that the baseline RAP was significantly lower in the responders when compared and contrasted with those patients who were non- responders. They also stressed on the fact that there was definitely a co-relation between the baseline RAP and the corresponding increase in stroke volume after a fluid infusion was administered. The limitation of this study was the fact that there was a great deal of concurrence in the RAP values between the recruited patients and thus it was a challenge to find a single baseline RAP value to differentiate between patients who would respond to a fluid therapy and those who would not respond to a similar therapy.[58]

With the advancement in technology, many invasive methods to determine the fluid status of a patient were postulated. One of these being the pulmonary artery occlusion pressure (PAOP), which was suggested to be a reliable index to predict the volume status in patients who were critically ill. Tousignant and Diebel, after extensive research on PAOP, came to the final conclusion that the PAOP had a lower baseline value in patients who were responders in comparison with those who were not responsive. Furthermore, studies conducted by Wagner and Leatherman brought to the notice of all that, in patients who had an increase in the LV stroke volume after fluid therapy had a co-relation with the baseline PAOP in a linear manner. Inspite of this linear relationship, no single PAOP cut off value has been determined to gauge the

hemodynamic response to volume expansion prior to giving fluid infusion to the patient.[58]

Since there was no consensus on the cut-off value which was found to be the baseline to initiate fluid administration, it was concluded that though the RAP and the PAOP showed values that were significant statistically, and they could not be used to discriminated between patients who were responders or non-responders. Many other studies came to prove a fact that the baseline values of RAP and PAOP were comparable between the responder and the non-responder groups of patients. Studies also came to the conclusion that there was absolutely no co-relation when cardiac filling pressures were compared before volume expansion and also the hemodynamic response to volume expansion.[26, 51, 58, 59].

Further research among patients who were classified as responders and non-responders by other important researchers such as Diebel et al revealed that, Right Ventricular End Diastolic Volume (RVEDV) definitely had a lower value in patients who were considered as responders when compared with the non-responder group.[51].The upper limit to the cut-off value was 138ml/m2 and the lower limit was 90ml/m2 with regard to the RVEDV. But when patients fell in the intermediate values between 90ml/m2 and 138ml/m2, this index proved to be in-efficient and so was not a good predictor in discriminating responders from non-responders. This was further emphasized by Wagner and Latherman who demonstrated that there was a good response to administration of volume in patients with a RVEDV index >138 mL/m2, and a definite paucity of response in patients with RVEDV < 90 mL/m2[58].

One of the other commonly used static indices of volume status is the left ventricular end diastolic area (LVEDA), and this has been studied by many researchers in great detail. Tousignant et al on their research on medical-surgical ICU patients, found that the LVEDA cannot be used to ascertain the fluid responsiveness in that subgroup of patients.[59]

Feissel et al conducted a study on patients who were in septic shock and came to the conclusion, that when they compared mean values of LVEDA index in responders and non-responders at the baseline, there was no significant difference between the two groups. They also found that there was no connection between the LVEDA at baseline measurement and the cardiac index variation in response to administration of a fluid infusion.[24]

Hence in an attempt to overcome the pitfalls and fallacies associated with volume replacement based on the static parameters mentioned in detail thus far, various attempts have been made to determine the ideal dynamic parameter which would fulfil all the criteria to detect a responder to fluid resuscitation.

Over the last decade, innumerable dynamic tests have been described which assess the response of patients to volume loading have been extensively evaluated. These tests monitor the change in stroke volume in response to a change in the venous return which reflects the preload to the left ventricle. [47, 48, 60-63]This allows the care giving intensivists to find out exactly where on the Frank-Starling curve the patients' position is, and so helps in determining if that patient will respond to fluids or not.

Morgan et al in 1968 and by Landstorm et al in 1972 studied in detail intermittent positive pressure ventilation (IPPV) and its various effects on the hemodynamics.[64] They suggested that since IPPV resulted in a decrease in venous return and thus in the pressure gradient, it may also cause a decrease in the filling of the right ventricle, thus finally resulting in a decrease in the output of the right ventricle. They also mentioned that can occur only if the right ventricle is responsive to changes in the preload.

Due to the reduction in the RV output as reasoned in the paragraph above, there is a subsequent fall in the preload which reaches the left ventricle, thus resulting in a decrease in the output of the LV if the LV is responsive to such changes. This response by the heart, secondary to the respiratory dynamics has been suggested to be used as a dynamic index which can be used to predict the response of a particular patient to fluid loading. [65-68]. Thus it was postulated that the changes in the heart which were attributed to the respiratory system which is subject to mechanical ventilation maybe used as a dynamic index of fluid responsiveness[69-72]

The various dynamic indices which reflect a patient's responsiveness to fluid therapy are based on the above mentioned mechanism and are attributed to the effect of mechanical ventilation on the respiratory system and its further consequence on the cardiovascular system. The popular dynamic indices in vogue are the Pleth Variability Index (PVI), respiratory variations in aortic blood flow peak velocity (DV peak), Pulse Pressure Variation (PPV), Systolic Pressure Variation (SPV), difference between SPref and SPmin (Ddown), difference between SPmax and SPref (Dup), respiratory changes seen in

inferior vena cava diameter (IVCD) and superior vena cava diameters.[26, 65, 73-79]

During the respiratory cycle, there are changes observed in the pulse oximeter waveform in its amplitude, this can also be used as a dynamic index to monitor a patients' response to fluid loading and this is defined as the Pleth Variability Index (PVI).

This arena of dynamic indicator was extensively evaluated by Cannesson et al in 2008. Their study was done on patients in the operating theatre. [73] They assessed the effect of mechanical ventilation and its hemodynamic effects on the cardiovascular system as reflected in the amplitude changes seen in the pulse oximeter tracings. From their research they came to the understanding that PVI can definitely be used as an index which predicts the fluid responsiveness in a patient on mechanical ventilation. Forget et al and Sandaroni did research based on the above mentioned principal. They practised a goal directed fluid therapy completely based on the PVI which was completely derived from the pulse oximeter tracings. This was finally used to interpret and administer fluid therapy. They also found that fluid regimens based on this concept improved the hemodynamics and also reduced the lactate levels.[74, 80, 81]

Zimmermann M et al subsequently in the same year conducted further studies and added more authoritative evidence that PVI was well in par with stroke volume in ascertaining the response to fluid therapy in patients who were being mechanically ventilated and undergoing major surgery.[82]

All these studies concluded that PVI is an accurate non-invasive dynamic index which can be lavishly used to find out the volume status of a patient. And this parameter was volume based and not based on pressure. Therefore, based on these studies it was concluded that, usage of PVI in order to determine if a patient will be responsive to fluid loading has been extrapolated to the paediatric population as well. Though this has a sound theoretical background much more research is required to totally comply by this assumption.

The widespread use of PVI is limited by the fact that there is a lack of availability of monitors to assess the PVI and the algorithms to derive these values are cumbersome and complicated.

The next dynamic index of fluid responsiveness that has been widely researched and found to be clinically relevant is the Pulse Pressure Variation (PPV)[67, 77, 83-85]. Beassurier et al, demonstrated through their extensive research that because the arterial pulse pressure (PP), which is the systolic minus diastolic pressure, is considered to be directly proportional to left ventricular stroke volume, the corresponding changes in the PPV which are caused due to respiration are thought to reflect in changes of the left ventricular output as well.[65]

From their vast research work on mechanically ventilated patients, Jardin and Robotham postulated that the cyclic changes reflected in the PP with each respiratory cycle, can be used to and does definitely predict the response of patients to fluid infusions.[86]

Furthermore, Denault and Robotham undertook a study to assess the spectrum of changes in systolic pressure with respect to the respiratory cycle, and to analyse volume responsiveness.[87] Their study threw light on the fact there were two factors which influenced the systolic pressure variation (SPV) that was induced by mechanical ventilation. The first factor was the changes which occurred in the aortic transmural pressure which was attributed to the corresponding changes in the LV output and the second factor being changes in the pleural pressure which resulted in changes in the extramural pressure, thus attributing to the SPV.

Michard et al in their extensive research came to the conclusion that SPV was indeed not a good or dependable indicator of the stroke volume of the left ventricle. Hence they emphasised a point in saying that the SPV when compared to the PPV was not a very accurate method of predicting which patient might benefit from fluid loading. [23, 88]

In 1989,Pizov et al in their study conducted on critically ill patients emphasized that in these patients with acute heart failure, there definitely was a co-relation between the arterial waveform and external chest compressions which were synchronized. They concluded that SPV could be an indispensable tool in diagnosing as well as managing hypovolemia and that it indicates the presence of heart failure.[88] The presence of SPV in euvolemic patients may cause suspicion of myocardial dysfunction. Positive pressure ventilation leads to a decrease in the afterload which in turn causes a reduction in the wall stress. This further results in a better and more efficient LV output which is shown by these patients' as an increment in the delta-up component.

Rooke et al, conducted a study on humans and they looked at the SPV in patients subjected to a gradual controlled haemorrhage with simultaneous replacement of the intra vascular volume. They evaluated the SPV in these patients as two groups; one group was being mechanically ventilated while the other group had spontaneous respiration. A resultant cut off for SPV was decided to assess the volume status. They came to the conclusion that hypovolemia was absent if the SPV value was < 5 mm of Hg and the delta-down was less than 2 mm of Hg.[89]

Perel and Coriat conducted a study where they aimed to find the difference between the increase in systolic blood pressure which is seen during inspiration and delta down which is an index that actually conveys a change in the LV output or LV stroke volume (SV). Many studies further conducted by Perel and Coriat were aimed to show that the volume status of the patient actually affects the delta down (DD). They were keen to prove that the DD values would have an inverse relation to the intra vascular volume status of the patient. [18, 23, 65, 78]. This was further brought to light in studies done by Tavernier et al on septic patients who were in shock. They demonstrated that in this particular group of patients, DD definitely could be relied upon to gauge their response to fluid therapy.[90, 91]

Michard F and Teboul JL, in 2002 conducted a meta-analysis where in they analysed different parameters that could be used to predict how critically ill patients in the ICU will respond to fluid administration.[85, 92] Multiple parameters were assessed based on the effect of administering volume to these patients. The effect on SV and the cardiac output was compared. After which

these patients were further classified into two groups based on whether they responded to the fluid infusions or not. They were categorized as responder group and as the non-responder group and various patient characteristics were compared. After they analysed their results they came to the conclusion that in the responder group, the DD and the Delta V peak values at the baseline were higher than in the non-responder group. The cut off value that was chosen for the DD was 5 mm of Hg. This value gave a good prediction of how this subset of patients would respond to fluid administration with good positive and negative predictive values.

Deflandre et al further researched on the useful pre-op markers and showed that DD and DPP had good correlation between DD and DPP, when they were used as predictors of intravascular volume in patients undergoing neurosurgery under general anaesthesia and controlled mechanical ventilation.[22, 85] According to this study, a threshold DD value of > 5 mm of Hg could be used to differentiate responders from non responders in neurosurgical patients. This was consistent with prior studies reported in the literature.[93-97] .They also observed that Fluid Loading (FL) in patients suspected to be hypovolemic resulted in a sustained decrease of DPP and DD below their respective cut-off values.

Then came one of the dynamic indices of fluid status which can be measured with ease- the Aortic Velocity Time Integral VTI(Ao) recorded using a Trans-Thoracic Echocardiography(TTE). Slama et al studied whether the magnitude of variations in respiration will be reflected in the aortic velocity time integral (VTI (Ao), in patients in whom there was a protocol based blood withdrawal and replacement. They also studied whether this variable is a good

indicator of intra vascular volume depletion and whether it could be used as a reliable indicator of responsiveness to fluid therapy.[92] Respiratory changes of VTI (Ao) proved invariably to be a sensitive index of blood volume status. This dynamic variable predicted volume responsiveness more reliably than static markers of cardiac preload.[98-101]

Dynamic indices were evaluated in the paediatric population as well. Among the various studies, Durand et al demonstrated fluid responsiveness in ventilated children by measuring respiratory variations in aortic blood flow. They found that respiratory variations in aortic blood flow peak velocity (D V peak) > 20% proved to be an excellent indicator of fluid responsiveness.[102, 103].

Similar studies were done by Choi et al, who studied respiratory variations in aortic blood flow velocity as a predictor of volume responsiveness in paediatric subjects after surgical repair of ventricular septal defect.[102]. They demonstrated that a DV peak > 12 % could be used to ascertain fluid responders from non responders. In many different clinical situations, DV peak has been found to be a good predictor of fluid responsiveness with cut-off values from 10% to 20%.

Feissel et al further studied the respiratory changes exhibited in the aortic blood flow velocity as an indicator of fluid responsiveness in patients in shock who were mechanically ventilated. They came to the conclusion that V peak was significantly higher in responder patients compared to patients who were non-responders. They also demonstrated that a V peak threshold of 12%

accurately differentiated responders and non-responders, with a good positive and negative predictive value. Moreover, an excellent, positive correlation was noted between the V peak before volume expansion and the volume expansion-induced changes in cardiac output.[24]

The utility of DVpeak was further studied in detail by Byon et al as one of the predictors of fluid responsiveness in paediatric surgical patients and they came to the conclusion that DV peak >11 identified responders with acceptable sensitivity and specificity.[54]

Vieillard-Baron et al in 2004, studied Superior vena caval collapsibility as an indicator of intra vascular volume status of patients in shock who are on mechanical ventilation. [79]They concluded that the threshold superior vena caval collapsibility of 38 %, was an excellent tool in the discrimination of responders and non responders. They also concluded that the superior vena cava measurement should be routinely and systematically performed using echocardiography in patients who are in shock because it is an accurate index of fluid responsiveness.

This was further emphasized by a study done in 2006 by Charron et al. They evaluated the echo derived variables of fluid responsiveness and found that superior vena cava (SVC) diameter changes occurring during mechanical ventilation can be a good measure of fluid responsiveness.[26, 66, 79]. The superior vena cava diameter is recorded from Trans Esophageal Echo (LAX) longitudinal view at about 90 to 100◦. Cut-off values 38% for SVC (collapsibility index) were found to be accurate in separating responders and non-responders.

The effects of mechanical ventilation on the SVC are twofold. Firstly, since the SVC is an organ within the thoracic cavity it is subject to respiratory variations. Secondly, it is also affected by the various effects of mechanical ventilation as well. Hence, they concluded that though the SVC collapsibility appears to be a very reliable indicator of fluid responsiveness, it does require TEE and thus is out of reach of most clinicians.[104-107]

Carbonell et al researched as to whether respiratory variations in the superior cava vein diameter (dSCV) as measured by trans-esophageal echocardiography (TEE) predicted hypotensive episodes during Recruitment Manoeuvres (RM) in mechanically ventilated surgical patients. They found a strong correlation between the collapsibility of the superior vena cava and the decrease in mean arterial pressure when the RM ($r=0,84$. $p>0,05$) was being performed and came to the conclusion that measuring the collapsibility of the superior vena cava by TEE was useful in predicting hypotensive episodes associated with lung recruitment manoeuvres in mechanically ventilated surgical patients[108].

Reviewing these prior literature we realised that most of these dynamic parameters were not studied in neurosurgical scenarios .Thus we choose to assess the predictive nature of the Delta Down , SVC collapsibility index and Aortic VTI variation as predictors of fluid responsiveness in patients with SAH and Supratentorial Tumour population .Rationale behind selection of these variables was that they seemed to be promising predictors in non neurosurgical settings for assessing the volume status of the patients.

# MATERIALS AND METHODS

# MATERIALS AND METHODS

## Methodology

We designed a prospective, pilot study in neurosurgical patients undergoing craniotomy for surgical management of intracranial aneurysms e.g.: clipping/wrapping or for surgical excision of supra-tentorial tumours. The primary objective was to carry out an assessment of hemodynamic changes and specific predictors of volume responsiveness before and after fluid loading (FL), in both these sub groups of neurosurgical patients.

This study was approved by the Institutional Ethics Committee (IEC) and written informed consent(IC) was obtained from all the participants of the study.

The total numbers of patients (n) recruited were thirty. Two groups of patients were included. There were 15 patients in each sub-group and they were classified as group I and group II.

- Group I (SAH Group) consisted of patients who had aneurysmal Subarachnoid Haemorrhage (SAH) and were coming for surgical clipping of the aneurysm.
- Group II (Tumour Group) were patients coming for resection of Supratentorial tumours.

The following are the inclusion and exclusion criteria.

**Inclusion criteria:**

- Patients with aneurysmal SAH undergoing aneurysm surgery
- Patients with Supra-tentorial tumours undergoing craniotomy
- Age 19-60 years
- Patients who have undergone preoperative transthoracic echocardiographic evaluation
- Patients who are in Sinus Rhythm
- Patients undergoing surgery in supine position

**Exclusion criteria**

- Patient refusal.
- Age below 18 years and more than 60 years.
- Presence of Heart block or the presence of cardiac rhythms other than sinus rhythm
- Systemic hypertension stage III and above
- Cardiac pathologies such as valvular heart disease, intra-cardiac shunts, peripheral vascular disease or lung pathologies like asthma, COPD and tuberculosis
- Pregnant or Nursing woman
- Presence of oesophageal pathologies like oesophageal mass,stricture,tracheo-esophageal fistula, oesophageal varices
- History of active/recent upper GI bleed.
- History of previous oesophageal/upper GI surgery
- Cervical arthritis/Atlantoaxial joint disease with restricted mobility

- Abnormal coagulation profile
- Intraoperative positioning of patient other than supine or modified supine.

**Overview of Study Protocol**

- The patient was shifted to the operation theatre suite and standard monitors were connected. Baseline recordings of HR, NIBP and $SpO_2$ were noted.
- Under Lignocaine (2%) skin infiltration I.V access and arterial access with 20 G arterial cannula was obtained.
- Base line IV infusion of 4 ml/kg of crystalloid (Normal Saline /Ringer Lactate) was initiated.
- General Anaesthesia was induced in all patients using a standard protocol. (As described clearly in the text below in the methodology section).
- The Trans-esophageal echocardiography (TEE) probe was inserted before the patient was positioned for neurosurgery.
- After confirming the absence of active bleeding and after achieving a 5 min interval of hemodynamic stability (systolic arterial pressure and HR stabilized to +/- 5%) after skull pinning and positioning the baseline variables were measured.
- Hemodynamic variables like the Heart rate (HR), Blood oxygen saturation (Spo2) and the Systolic Blood Pressure (SBP) were monitored continuously.

- Anaesthesia monitoring included measurements of Peak Airway pressure (PAP), End tidal Co2 (EtCo2) and End Tidal Anaesthetic agent- Sevoflurane (ET Sevo).
- Systolic blood pressure baseline(SBP apneic), SBP max and SBP min were obtained from the arterial trace monitoring.
- Baseline SVC diameter, VTI Ao, Stroke Volume(SV),Cardiac output(CO) and Cardiac Index(CI) were measured using TEE.
- All patients received a fluid loading of 15ml/kg of crystalloid (NS/RL) over a period of 30 minutes.
- All the hemodynamic and predictor parameters were again reassessed immediately post fluid loading.
- Once the post loading values have been obtained , percentage increase in cardiac index (post fluid loading) is calculated and subjects demonstrating CI variation (CIV) > /= 15% was termed as "Responders"(R) and with < 15% were defined as "Non Responders"(NR)
- Regardless of the baseline ventilation setting, during data collection all the patients were mechanically ventilated using volume-controlled ventilation (Aestiva /5, Datex Ohmeda) with a square wave (constant inspiratory flow), an inspiratory/expiratory (I:E) ratio of 1:2, with respiratory rate (RR) of 8 breaths /min, a tidal volume of 8 ml/kg and keeping the positive end-expiratory pressure (PEEP) of 0 cmH2O.
- If necessary, the ventilator protocol was changed to achieve a PaCO2 of 35- 40 mm hg after data acquisition.
- No changes in anaesthetic doses were made during measurements.

**Detailed Discussion of Study Protocol**

The patients were shifted to the operation theatre suite and standard monitors were connected. Baseline recordings of HR, NIBP and $SpO_2$ were noted. Before induction of anaesthesia under local anaesthesia infiltration Lignocaine (2%) skin infiltration I.V access with 16 G /18 G venous cannula and arterial access with 20 G arterial cannula was obtained and the pressure transducer was positioned at the mid-axillary line. Following this a base line IV infusion of 4 ml/kg of crystalloid (Normal Saline /Ringer Lactate) was initiated.

General Anaesthesia for both the groups was induced using a standard protocol. The patients were pre-oxygenation with oxygen at 6 l/min for three to five minutes after which they were premeditated with Fentanyl 2-3mcg/kg and induced with Propofol 1-2mg/kg. Intubation was further facilitated with an intermediate acting muscle relaxant vecuronium, dosed at 0.1mg/kg. Post induction maintenance was achieved with an air: oxygen mixture of the ratio 1:1 and sevoflurane at a MAC of 0.5-1.0. Mechanical ventilation was instituted in volume-controlled mode (Aestiva /5, Datex Ohmeda) with a square wave (constant inspiratory flow) adjusted to obtain a PaCO2 of 35- 40 mm Hg during surgery. PEEP was not applied.

The Trans-esophageal echocardiography (TEE) probe was inserted after insertion of bite block and adequate lubrication with lubricant jelly. The probe was inserted before the patient was positioned for neurosurgery and skull pinning. A blanket and a warming system using forced air (Bair Hugger Warming system, Augustine Medical, USA) were applied in order to avoid

hypothermia. Body temperature was measured using temperature probe placed in the nasopharynx. Post optimization of ventilatory settings and final positioning the Peak Inspiratory Pressure (PIP) was recorded.

After confirming the absence of active bleeding and achieving a 5 min interval of hemodynamic stability ( systolic arterial pressure and HR stabilized to +/- 5% of the pre-induction values) post skull pinning and positioning the baseline variables were measured Baseline variables included routine hemodynamic variable waveforms such as the heart rate(HR), oxygen saturation(SpO2) and arterial pressures. These variables were recorded using a bedside monitor (Philips Intellivue, MX700, Philips Medizin systems, Germany) . End tidal Co2 (EtCo2) and End-tidal sevoflurane (Et Sevo) concentration was also measured/calculated and recorded.

Simultaneously Echo derived variables like SVC diameters, Aortic VTI, LVOT diameters and derived variables like SV, CO and CI were obtained using the echo machine (GE Vivid 7 with 9T 4.0-10.0 MHz multiplane TEE probe, GE Healthcare, Wauwatosa, WI 53226, USA).

All patients received a fluid loading of 15ml/kg of crystalloid (NS/RL) over a period of 30 minutes. Once again all the hemodynamic and predictor parameters were again reassessed immediately post fluid loading.

Regardless of the baseline ventilation setting, during data collection all the patients were mechanically ventilated using volume-controlled ventilation (Aestiva /5, Datex Ohmeda) with a square wave (constant inspiratory flow), an inspiratory/expiratory (I:E) ratio of 1:2, with respiratory rate (RR) of 8 breaths

/min, a tidal volume of 8 ml/kg and keeping the positive end-expiratory pressure (PEEP) of 0 cmH2O. If necessary, the ventilator protocol was changed to achieve a PaCO2 of 35- 40 mm hg after data acquisition. No changes in anaesthetic doses were made during measurements.

The entire study protocol was completed before the craniotomy was done by the neurosurgeons and initiation of any osmotherapy (3% Saline or Mannitol) if required.

**Measurements of Variables**

**Pressure measurements**

Maximal systolic pressure (SPmax), minimal systolic pressure (SP min) and reference systolic pressure at the end of the expiratory pause (SPref) were manually measured. Each parameter was measured thrice during the consecutive 3 respiratory cycles by a single investigator and averages were used for statistical analysis.

Delta Down (DD) is obtained as the difference between the systolic arterial pressure at the end of a 5 second respiratory pause, immediately prior to lung inflation, and its minimal value during the course of one mechanical breath. [Figure 1 & 2]

**∆Down = Apnoeic baseline – Systolic BP minimum**

This has been clearly demonstrated in the figures given below.

**Figure 1: Schematic representation of Delta Down**

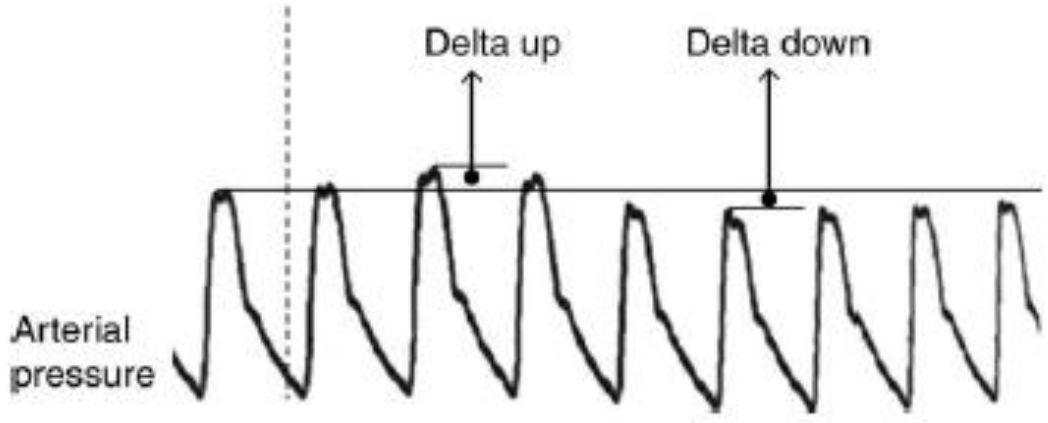
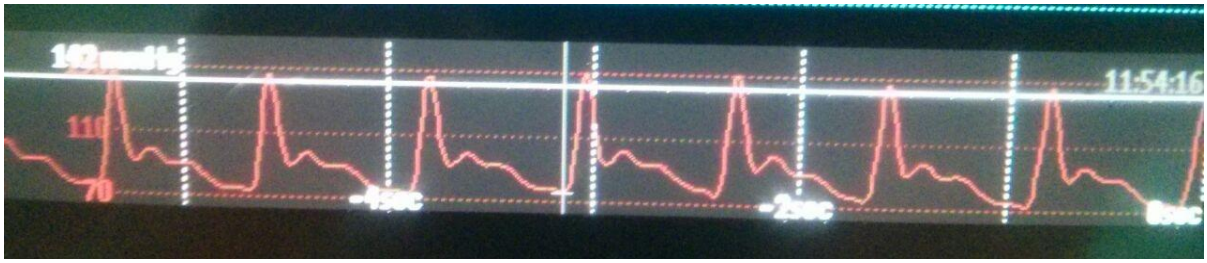



**Figure 2: Calculation of Delta down using marker trace from Arterial trace (Freeze mode)**



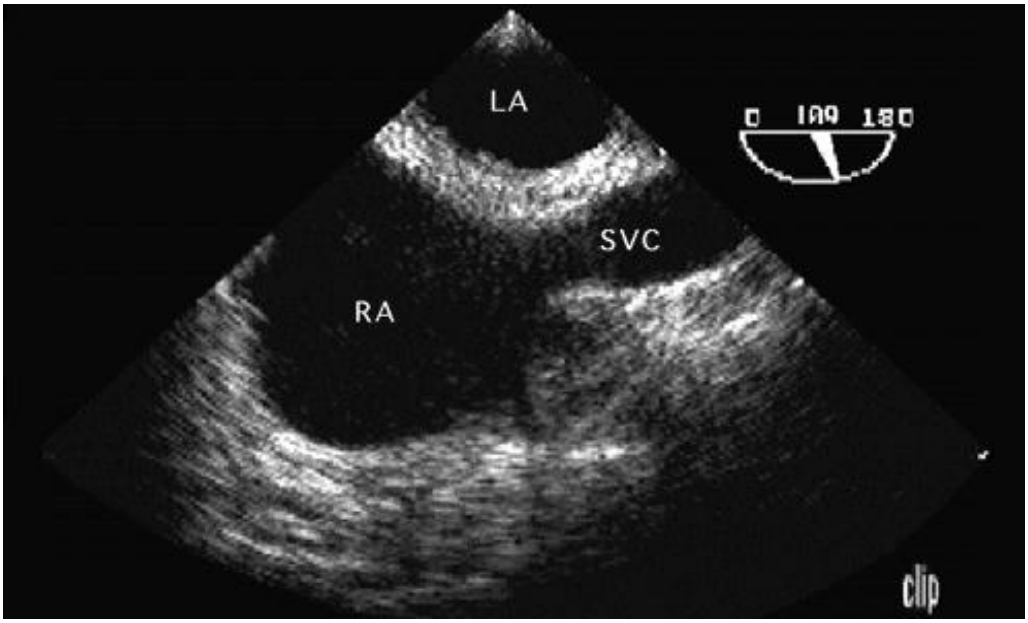
**Echocardiographic (TEE) based evaluation and measurements:**

Measurements/calculations obtained and recorded using trans-esophageal echo are described below:

**1) Superior vena cava collapsibility index(SVCCI)**

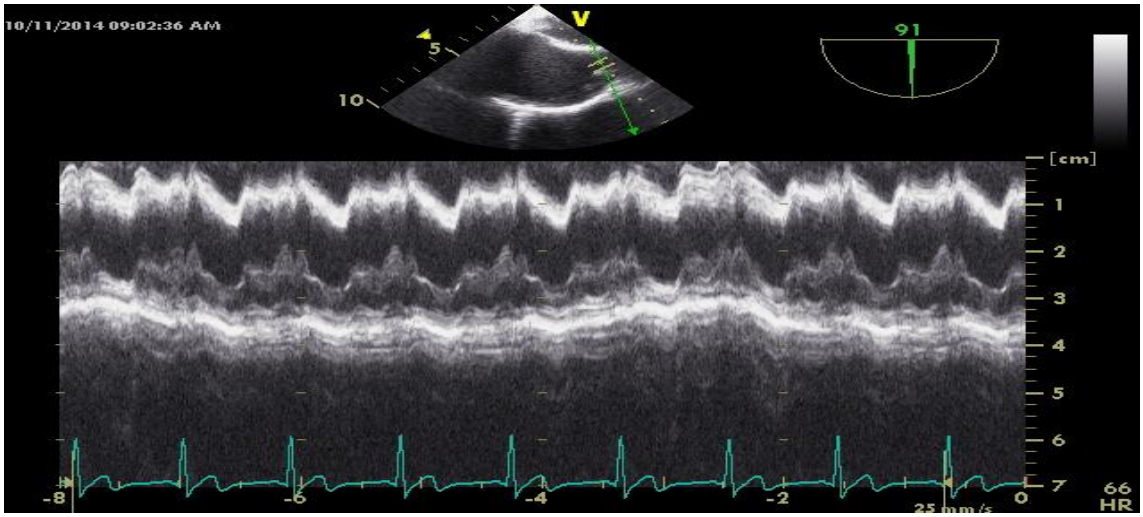
The Superior Vena Cava (SVC) was examined with a trans-esophageal probe using the mid esophageal bicaval view. The bicaval view was obtained from the Mid-esophageal RV inflow-outflow view, then the multiplane angle is rotated forward to 90 degrees - 110 degrees and the probe is turned clockwise or rightward. Structures visualized in bicaval view include the left atrium, right atrium, right atrial appendage, inter atrial septum, the Inferior Vena Cava (IVC) and the SVC as seen clearly in the figure below[Figure 3].

**Figure 3: Mid-oesophageal Bicaval View obtained with TEE**



Anatomical M-Mode was used to measure the required diameters [Figure 4]. The SVC diameters measured were the maximum diameter on expiration (SVCmax) and minimum diameter on inspiration (SVC min).The measurements were done during the same respiratory cycle. Average of two values was used for statistical purposes.

**Figure 4: Midoesophageal Bicaval View in Anatominal M mode showing the trace of SVC diameter**




Calculation of SVC collapsibility index is done by using the formula:

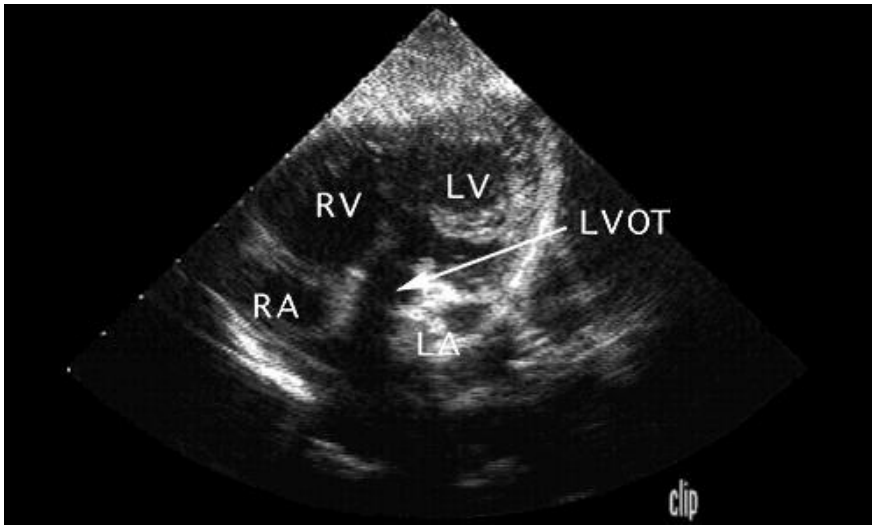
**SVC collapsibility index = [(SVCmax – SVCmin)/(SVCmax)]**

A cut-off value of >38 % for SVC collapsibility index was used to separate responders and non-responders.

**2) Aortic Velocity Time Integral (VTIAo) Variability**

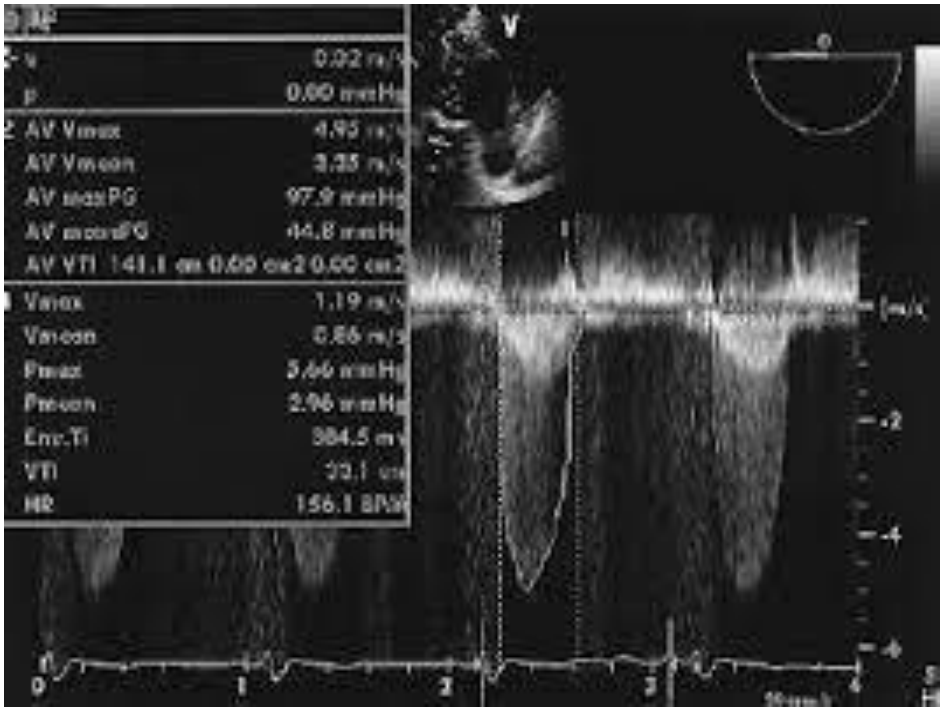
The Left Ventricular Outflow Tract (LVOT) and the aortic valve opening is visualised after obtaining the deep trans-gastric view [Figure 5]. This view is obtained by advancing the probe deep into the stomach and positioning the probe in proximity to the Left Ventricular (LV) apex. Ante-flexion of the probe is done until the imaging plane is directed superiorly towards the base of the cardia, thereby resulting in the visualisation of the deep trans-gastric long axis (deep 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 LV outflow directed away from the transducer as shown in the figure below. Detailed interrogation and evaluation of valvular anatomy is difficult in this section because the LVOT and AV are far away from the transducer, but quantification of flow velocities (using Doppler technique) through these structures is possible.

**Figure 5: Deep trangastric long axis view showing the structures**



Aortic Velocity is obtained using a pulsed wave Doppler (PWD)/continuous wave Doppler (CWD) measured by positioning the PWD sample volume in the centre of the LVOT just proximal to the Aortic Valve [Figure 6]. Flow velocities through the AV are measured by directing the CWD beam through the LVOT and across the valve cusps placed at the LVOT. Aortic VTI is calculated from the recorded velocity loops. Three different recordings were made in close succession and images of the loops were recorded as shown in the figure below [Figure 6].

**Figure 6: Deep transgastric long axis with Doppler analysis showing VTI Ao trace**




**VTIAo variability is obtained by using the following formula:**

**VTIAo variation= [(VTImax–VTImin)/(VTI avg)]**

Variability of VTIAo>20% is considered as the cut off to differentiate fluid responders from nonresponders.

**3) Stroke Volume (SV), Cardiac Output (CO), Cardiac Index (CI)**

Diameter of LVOT was measured from the mid-esophageal long axis view. The Stroke Volume (SV) measurements were made from the saved loops when all the recordings were completed. Further the Cardiac Output (CO) was calculated using the software provided in the echo machine (GE Vivid 7 with 9T 4.0-10.0 MHz multiplane TEE probe, GE Healthcare, Wauwatosa, WI 53226, USA). After this the cardiac index was automatically calculated by the echo machine.

## STATISTICS

All statistical analyses were obtained using SPSS software version 17.0 (Chicago,SPSS inc.) .Power analysis has no significance as study was initiated as a prospective pilot study as no prior studies of this kind had been done in the past to determine the power analysis. Observations obtained from the study were expressed in Mean+/- SD. Comparison of categorical variables were done using chi-square test. Comparison of normally distributed continuous variables were evaluated with students t-test. "p" value less than 0.05 was considered as statistically significant and a “p” value less than 0.01 as highly significant.

The correlation between the hemodynamic variables as well as the predictor variables like DD, SVCCI and VTIAo V with the outcome predictor variable CIV (Cardiac index variation) was tested using Pearson’s correlation coefficient. Pearson’s correlation coefficient is the measure of the strength of a linear relationship between two sets of data (paired data). In a sample it is denoted by r. Positive values reveal positive linear correlation and Negative values demonstrate negative linear correlation. 0 denotes no linear correlation and closer the value is towards 1 or –1, the stronger and more significant the correlation will be. Thus the predictive abilities of our predictor variables for fluid responsiveness were assessed using Pearson’s coefficient analysis. Pearsons coefficient of more than 0.8 is considered as strong correlation and 0.5 to 0.8 is considered as good correlation.

# RESULTS AND OBSERVATIONS

# RESULTS AND OBSERVATIONS

We recruited thirty patients for this prospective pilot study. The two groups we chose were, Group I (SAH Group) which consisted of patients with aneurysmal Subarachnoid Haemorrhage (SAH) who were planned for surgical clipping of the aneurysm and Group II (Tumour Group) included patients coming for surgical resection of supra-tentorial tumours.

There were 15 patients in each group. Each group was further classified as Responders (R) and Non responders (NR) based on the outcome variable, Cardiac Index Variation. Subjects who demonstrated >15% increase in cardiac index, post fluid loading (FL) were termed as "Responders" and those who had < 15% change post fluid loading were defined as "Non Responders"(NR).

The predictor variables we studied were Delta Down (DD), SVC collapsibility index (SVCCI) and Aortic VTI variability (VTIAo V) . We analysed the above mentioned variables in each group by comparing them in responders and non responders of each group (Intra group Analysis) and discussed the relevant findings. We then did a comparative analysis of how the Responders and Non responders of each group behaved (Inter group Analysis , SAH vs Tumour) and discussed the results obtained.

## Intragroup Analysis

### 1. Sub Arachnoid Haemorrhage (SAH) group

**Table 1: Sex Distribution of SAH group**

| Sex | Responder | | Non responder | | **Total** | |
|---|---|---|---|---|---|---|
| | **N** | **%** | **N** | **%** | **N** | **%** |
| Male | 5 | 41.7 | 1 | 33.3 | 6 | 40.0 |
| Female | 7 | 58.3 | 2 | 66.7 | 9 | 60.0 |
| Total | 12 | 100.0 | 3 | 100.0 | 15 | 100.0 |

$\chi^2 = 0.069$ *df =1* *p=0.792*

**Figure 7: Gender distribution in SAH group**

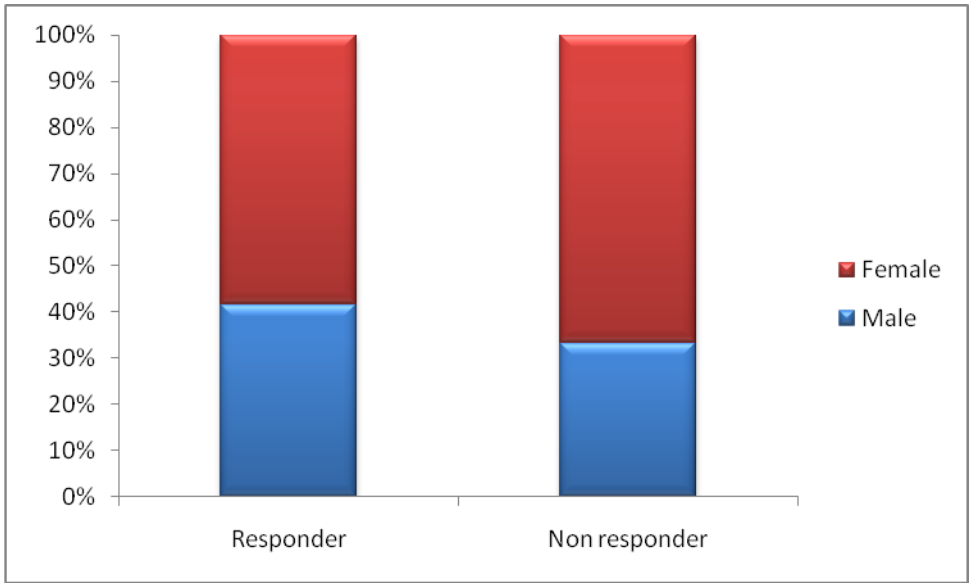


**Table 2: Demographic variables of SAH population**

| **SAH** | Responder (N=12) | | Non responder (N=3) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| Age | 46.50 | 7.70 | 39.67 | 8.02 | 1.365 | .195 |
| height | 162.25 | 8.04 | 175.00 | 5.57 | -2.563 | .024 |
| weight | 63.42 | 8.53 | 73.67 | 14.84 | -1.625 | .128 |
| BMI | 24.04 | 2.30 | 23.90 | 3.25 | .090 | .930 |
| BSA | 1.68 | 0.14 | 1.89 | 0.22 | -2.085 | .057 |

**Table 3: Intraoperative Anaesthetic Variables**

| **SAH** | Responder (N=12) | | Non responder (N=3) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| EtCo2 | 36.75 | 1.86 | 36.00 | 4.00 | .500 | .626 |
| EtSevo | 1.65 | 0.08 | 1.65 | 0.07 | .049 | .961 |
| Temp | 36.20 | 0.36 | 35.67 | 0.50 | 2.157 | .050 |
| PIP | 16.08 | 1.73 | 18.00 | 1.00 | -1.812 | .093 |

In the aneurysmal SAH group presenting for surgical clipping, we observed that 12 of the 15 subjects demonstrated an increase of > 15% in the cardiac index post fluid loading and thus were labelled as Responders in the aneurysmal SAH (Ra) group. 3 subjects failed to respond positively to the fluid therapy and were labelled as Non responders in the aneurysmal SAH group (NRa).

There was no male or female preponderance between the two groups [Table 1].There was statistically no significant difference ($p > 0.05$) between the Ra and NRa group in terms of demographic characteristics such as age, weight, height, Body Mass Index(BMI) and Body Surface Area(BSA)[Table 2].

We observed that there was no statistical difference between the groups in terms of anaesthetic requirement as assessed by the Et Sevo ($p > 0.05$).Intraoperative ventilatory parameters as observed in terms of Peak Inspiratory Pressure(PIP) and Et $CO_2$ (End tidal $CO_2$) did not show any difference between the groups ($p>0.05$). The intraoperative body temperature between the Ra and NRa groups were also comparable [Table 3].

**Table 4: Intraoperative Hemodynamic Variables**

| **SAH** | Responder (N=12) | | Non responder (N=3) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| Heart rate | 88.08 | 10.31 | 87.00 | 11.14 | .161 | .875 |
| SBP | 137.42 | 11.56 | 139.00 | 8.54 | -.220 | .829 |
| HR-PL | 86.33 | 10.61 | 84.33 | 11.68 | .287 | .778 |
| SBP -PL | 129.25 | 6.68 | 135.00 | 5.00 | -1.382 | .190 |

**Figure 8: Comparison of Heart Rate in SAH group**

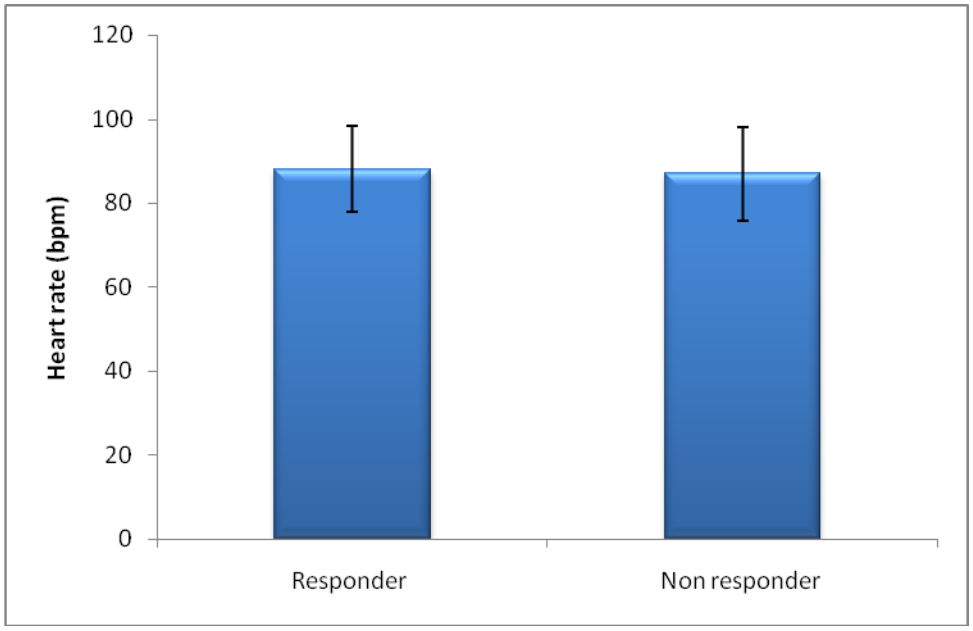
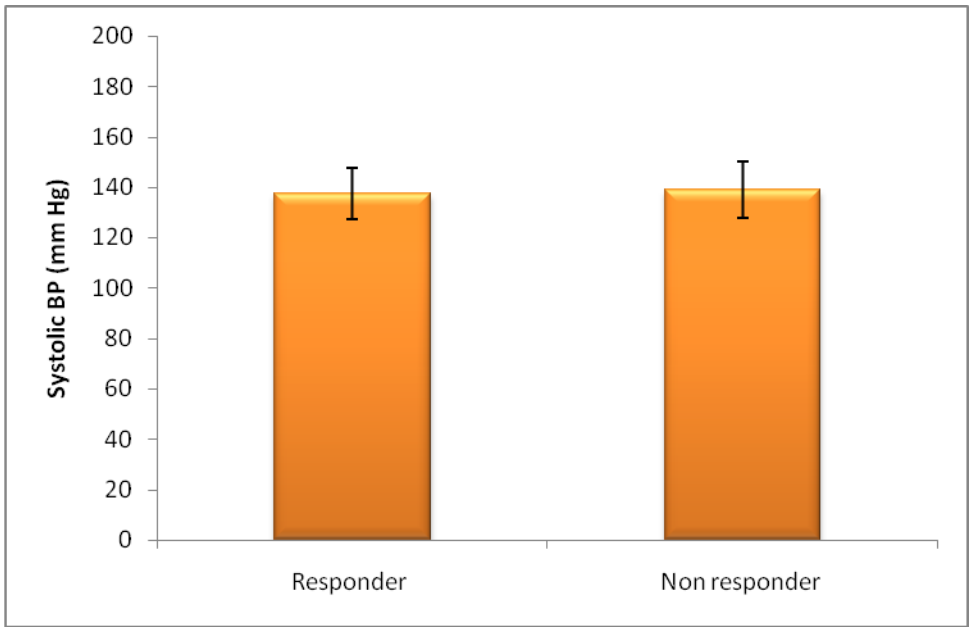



**Figure 9: Comparison of Systolic Blood Pressure in SAH group**



The Baseline Heart Rate(HR) and Systolic Blood Pressure (SBP) values between the two groups were comparable and did not show any significant difference between the groups (p>0.05). After fluid loading the HR reduced from the baseline values for both the groups but this was not statistically significant. SBP initially increased from baseline values post FL but this too was not statistically significant, and thereafter it remained almost similar to baseline [Table 4].

Both these parameters showed poor correlation (r=0.118) with the outcome predictor i.e. Cardiac Index Variability (CIV) thereby revealing that they are poor predictors of volume responsiveness and cannot differentiate the responders from the non responders effectively.

**Table 5: Analysis of Delta Down in SAH group**

| **SAH** | Responder (N=12) | | Non responder (N=3) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| DD | 9.50 | 3.15 | 4.33 | 1.53 | 2.707 | .018* |
| DD-PL | 3.42 | 1.88 | 3.00 | 2.00 | .340 | .739 |

* p< 0.05

**p< 0.01

**Figure 10: Comparison of Delta Down in SAH group (Baseline vs Post loading)**

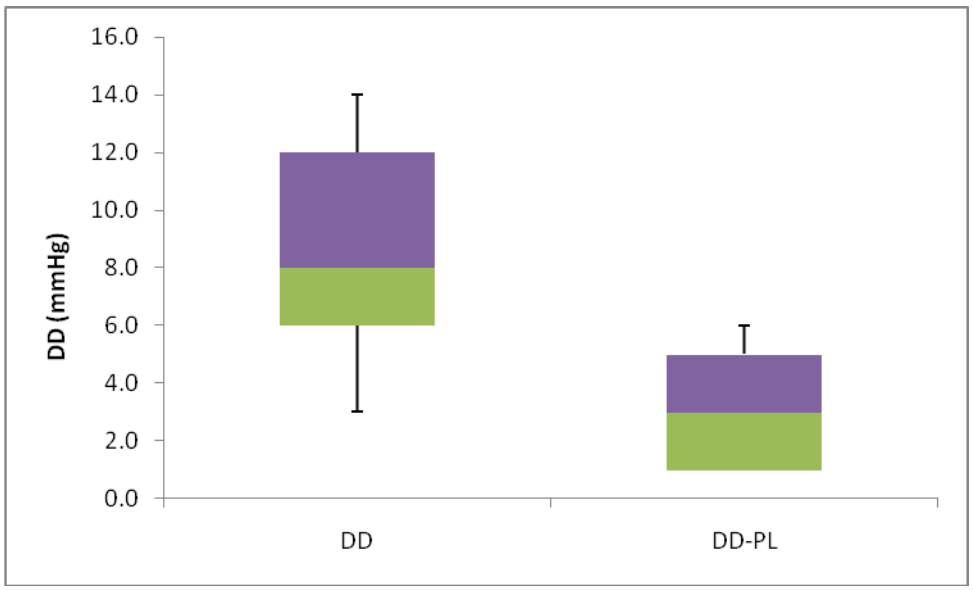


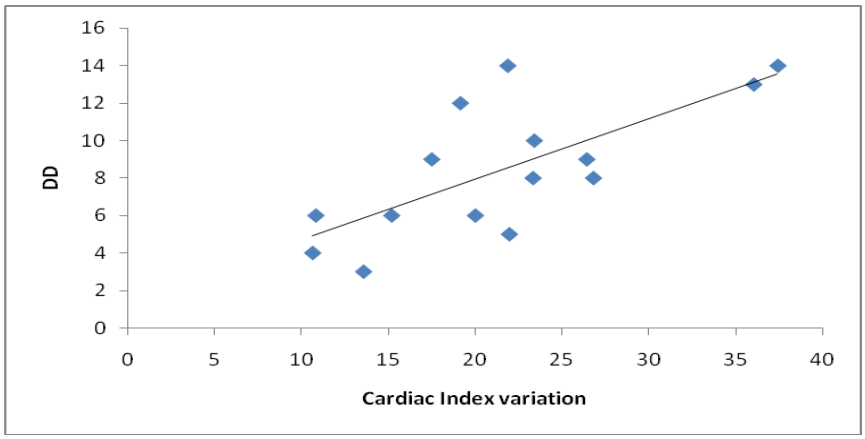

**Table 6 Correlation of DD and Cardiac Index Variation**

| SAH Group | | Cardiac Index Variation (%) | DD | SVC CI | VTI Variability |
|---|---|---|---|---|---|
| D | Pearson Correlation | .716** | 1 | .700** | .731** |
| D | Sig. (2-tailed) | .003 | | .004 | .002 |
| D | N | 15 | 15 | 15 | 15 |

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

**Figure 11: Correlation of Delta Down and Cardiac Index Variation (Outcome Variable)**




Our results showed that DD with a cut-off of 5mm Hg was very efficient in predicting responders from non responders with very good sensitivity[ 100%]but moderate specificity[66.66%].There was significant difference ($p< 0.05$) in between the Ra and NRa groups in the baseline values of DD prior to fluid loading [Table 5]

DD with a threshold of 5 mm Hg proved to be an excellent predictor of fluid status of subjects in this group demonstrating good sensitivity and specificity in differentiating the responders from non responders. Fluid loading in patients suspected of hypovolemia and diagnosed as responders resulted in a significant decrease of DD below the threshold value of 5 mm Hg post fluid loading [Figure 10]. In the Non responder group also DD reduced below the baseline value post FL but this was not found to be significant.

There was significant correlation between DD and the outcome variable, CI variability, which is considered as the gold standard in predicting the volume status of patients, thereby differentiating the responders from the non responders [Figure 11]

**Table 7: Analysis of SVC diameters and SVC Collapsibility index in SAH group**

| **SAH** | Responder (N=12) | | Non responder (N=3) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| SVC(Max) | 10.50 | 1.57 | 10.33 | 2.31 | .152 | .882 |
| SVC(min) | 3.67 | 2.10 | 6.67 | 2.08 | -2.213 | .045 |
| SVC CI | 66.71 | 15.29 | 36.18 | 7.27 | 3.296 | .006 |

* p< 0.05 , **p< 0.01

**Figure 12: Comparison of SVC collapsibility index in SAH group (Baseline vs Post loading)**

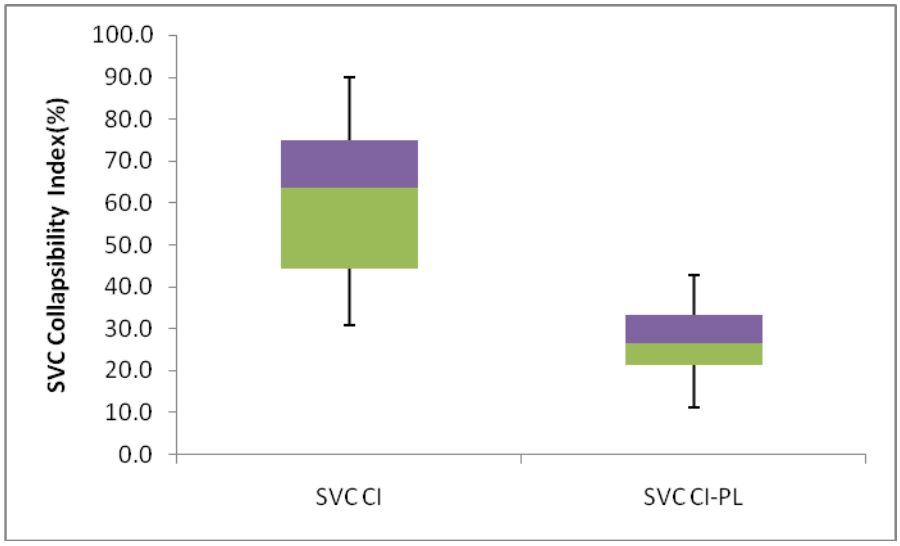
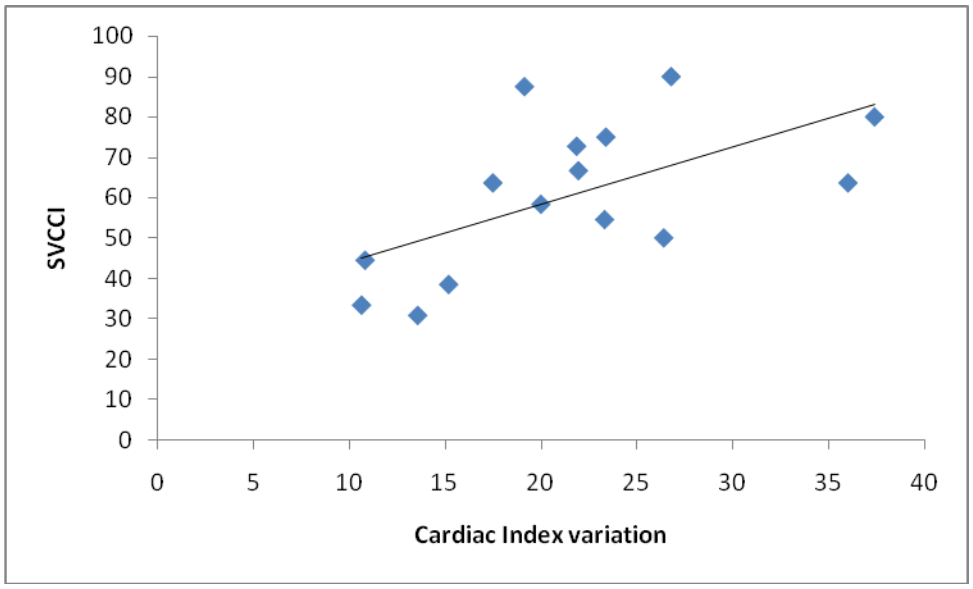


**Table 8: Correlation of SVCCI & CIV**

| SAH Group | | Cardiac Index Variation (%) | DD | SVC CI | VTI Variability |
|---|---|---|---|---|---|
| SVC CI | Pearson Correlation | .602* | .700** | 1 | .700** |
| | Sig. (2-tailed) | .018 | .004 | | .004 |
| | N | 15 | 15 | 15 | 15 |

*. Correlation is significant at the 0.05 level (2-tailed). **. Correlation is significant at the 0.01 level (2-tailed).

**Figure 13: Correlation of SVC Collapsibility Index and Cardiac Index Variation (Outcome Variable)**



Superior Vena Cava Collapsibility Index (SVCCI) with a cut off value of 38% was extremely efficient in differentiating the responders from the non responders in the SAH group. The mean value in the Ra group being significantly elevated compared to NRa ($p<0.01$) above the threshold value of 38 % whereas the mean value in the non responder population was found to be below the threshold value [Table 7].

In the responder subgroup there was a significant decrease in the post fluid loading value from the baseline which demonstrated that the patients responded to the fluid therapy positively [Figure 12]. The post FL mean value being significantly below the threshold cut off value helps in conveying the inference that the subjects have been adequately resuscitated with the fluid therapy. This significant difference exhibited by this variable pre and post fluid loading demonstrates the high sensitivity [100%] and specificity [90%] of this index in detecting the volume status of the subjects, as well as in differentiating the responders from non responders.

SVCCI also showed excellent correlation with the outcome predictor CIV, thereby predicting the change in the CI of the subjects which in turn helps in distinguishing the two subgroups [Figure 13, Table 8].

**Table 9: Analysis of VTI & VTI derived Variables in SAH**

| SAH | Responder (N=12) | | Non responder (N=3) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| VTI max | 20.87 | 0.94 | 23.67 | 0.50 | -4.875 | .000** |
| VTI min | 16.25 | 0.92 | 20.73 | 1.52 | -6.723 | .000** |
| VTI Avg | 18.56 | 0.91 | 22.20 | 1.00 | -6.113 | .000** |
| VTI Variability | 24.93 | 2.43 | 13.37 | 5.37 | 5.827 | .000** |
| VTI max-PL | 24.24 | 1.12 | 25.37 | 0.64 | -1.650 | .123 |
| VTI min-PL | 22.32 | 1.24 | 24.23 | 1.31 | -2.377 | .033* |
| VTI Avg-PL | 23.48 | 0.98 | 24.80 | 0.96 | -2.095 | .056 |
| VTIAoV-PL | 8.21 | 3.71 | 4.64 | 3.16 | 1.521 | .152 |

* p< 0.05,**p< 0.01

**Figure 14: Comparison of Aortic VTI variation in SAH group (Baseline vs Post loading)**

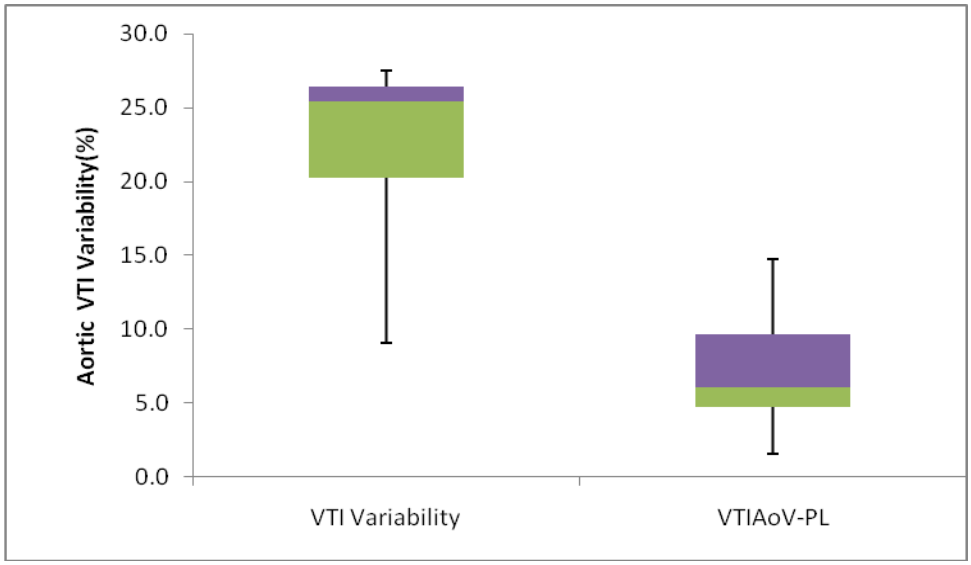
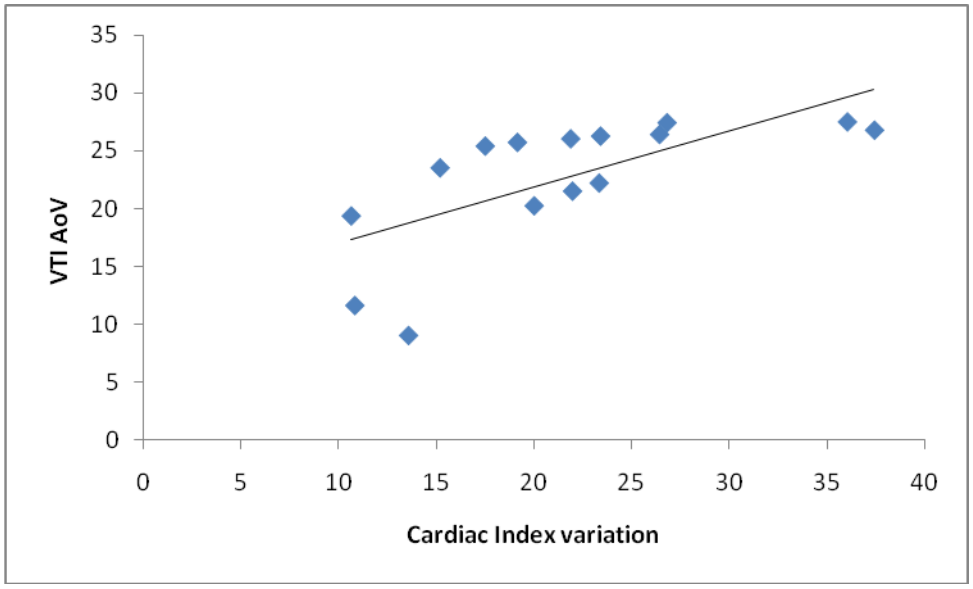


**Table 10: Correlation of VTIAoV & CVI**

| SAH Group | | Cardiac Index Variation (%) | DD | SVC CI | VTI Variability |
|---|---|---|---|---|---|
| VTI Variability | Pearson Correlation | .683** | .731** | .700** | 1 |
| | Sig. (2-tailed) | .005 | .002 | .004 | |
| | N | 15 | 15 | 15 | 15 |

*. Correlation is significant at the 0.05 level (2-tailed). **. Correlation is significant at the 0.01 level (2-tailed).

**Figure 15: Correlation of Aortic VTI variation and Cardiac Index Variation (Outcome Variable)**



Aortic VTI variability (VTIAoV) with a threshold value of >20% proved to be a good predictor in diagnosing the responders as well as the non responders accurately with a very high sensitivity and specificity [100%, 100%]. The two subgroups demonstrated a highly significant difference in the base line values ($p<0.01$) [Table 9].

The Ra subgroup exhibited significantly higher values above the threshold and the NRa group were found to have marginally lower cut-off values [Table 5]. The post FL VTIAoV value in the responder subgroup decreased sharply in contrast to the NRa group demonstrating that these subjects responded well to fluid therapy and were grossly fluid deficient at the beginning of the procedure [Figure 14].

VTIAoV also showed a good correlation to the CVI thereby establishing the fact that it is indeed a good predictor [Table 10, Figure 15]

**Table 11: Other Echo-derived Variables in SAH group**

| SAH | Responder (N=12) | | Non responder (N=3) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| VALVE AREA | 3.33 | 0.56 | 3.10 | 0.17 | .698 | .497 |
| SV Avg | 61.89 | 11.22 | 66.69 | 4.75 | -.708 | .492 |
| cardiac output | 5.47 | 1.37 | 5.82 | 1.03 | -.412 | .687 |
| Cardiac Index | 3.27 | 0.83 | 3.14 | 0.80 | .251 | .805 |
| SV Avg-PL | 78.30 | 13.91 | 76.93 | 6.14 | .163 | .873 |
| cardiac output-PL | 6.78 | 1.64 | 6.51 | 1.16 | .265 | .795 |
| Cardiac Index-PL | 4.05 | 0.99 | 3.51 | 0.91 | .855 | .408 |
| Cardiac Index Variation (%) | 24.08 | 6.79 | 11.68 | 1.64 | 3.061 | .009* |

* $p < 0.05$

**Figure 16: Comparison of Stroke Volume in SAH group**

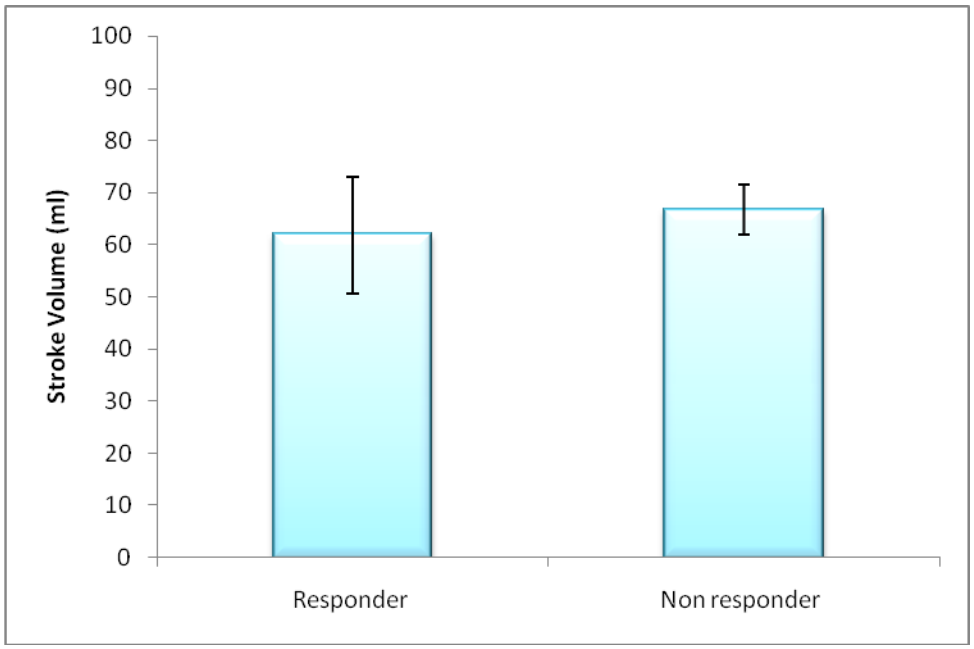
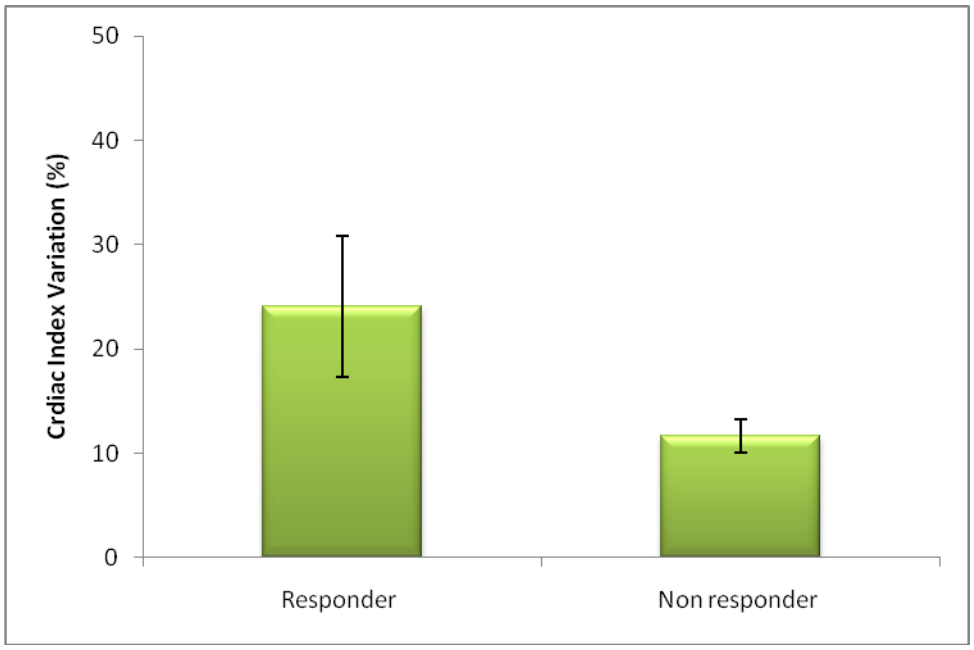


**Figure 17: Comparison of Cardiac Index Variation in SAH group**




The Stroke volume in both the subgroups were in the normal or high normal range and increased after fluid therapy in both the subgroups. Similarly the Cardiac output of the subjects in both the subgroups was within the normal range and there was no significant difference between the subgroups ($p > 0.05$) [Table 11, Figure 16].

There was a significant increase in the cardiac index post fluid loading in the responder group ($p < 0.05$) showing that this subset responded well to fluid therapy and thus were fluid deficient [Figure 17]. Whereas the NRa group demonstrated a very slight increase in the cardiac index which was not significant [Table 11].

## 2. Tumour Group

**Table 12: Sex distribution of Tumour Group**

| Sex | Responder | | Non responder | | **Total** | |
|---|---|---|---|---|---|---|
| | **N** | **%** | **N** | **%** | **N** | **%** |
| Male | 5 | 50.0 | 3 | 60.0 | 8 | 53.3 |
| Female | 5 | 50.0 | 2 | 40.0 | 7 | 46.7 |
| Total | 10 | 100.0 | 5 | 100.0 | 15 | 100.0 |

$\chi^2 = 0.134$ *df =1* *p=0.714*

**Figure 18 : Gender distribution in Tumour group**

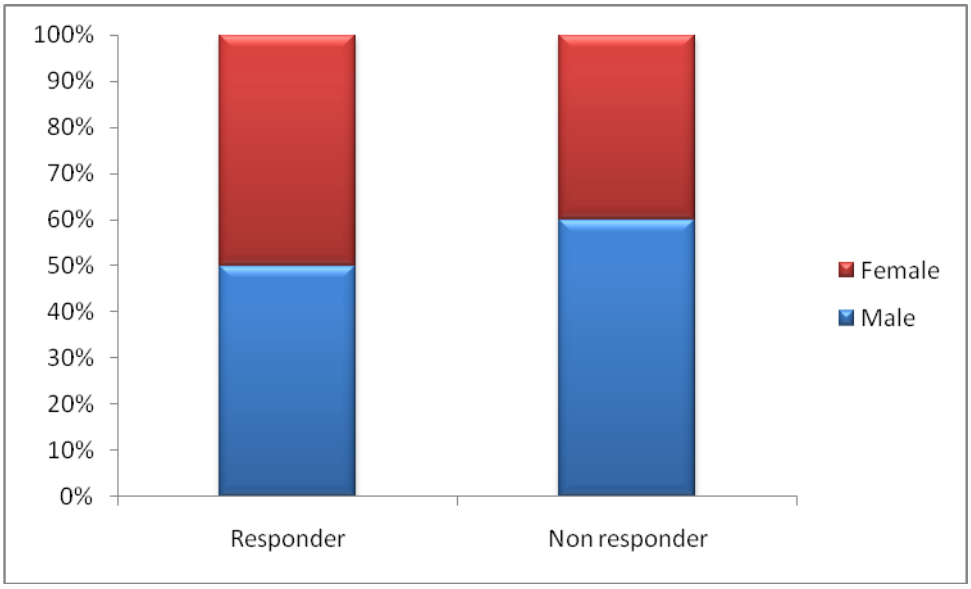


**Table 13: Demographic variables**

| **Tumour** | Responder (N=10) | | Non responder (N=5) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| Age | 43.60 | 10.88 | 46.40 | 3.36 | -.553 | .589 |
| height | 167.50 | 10.39 | 169.00 | 7.91 | -.282 | .782 |
| weight | 67.00 | 9.39 | 64.80 | 5.54 | .478 | .640 |
| BMI | 23.82 | 1.92 | 22.70 | 1.61 | 1.117 | .284 |
| BSA | 1.77 | 0.17 | 1.74 | 0.11 | .259 | .800 |

**Table 14: Intraoperative Anaesthetic Variables**

| **Tumour** | Responder (N=10) | | Non responder (N=5) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| EtCo2 | 36.80 | 2.62 | 36.20 | 2.95 | .402 | .694 |
| EtSevo | 1.65 | 0.10 | 1.63 | 0.10 | .298 | .771 |
| Temp | 36.07 | 0.36 | 36.16 | 0.38 | -.445 | .664 |
| PIP | 16.10 | 1.91 | 17.80 | 3.35 | -1.270 | .227 |

In the Tumour group presenting for surgical excision, we observed that 10 of the 15 subjects demonstrated an increase of > 15% in the cardiac index post fluid loading and thus were labeled as Responders in the Tumour (Rt) group. 5 subjects failed to respond positively to the fluid therapy and were labeled as Non responders in the Tumour group (NRt).

There was no male or female preponderance between the two groups [Table 12].There was statistically no significant difference ($p > 0.05$) between the Ra and NRa group in terms of demographic characteristics such as age, weight, height, Body Mass Index(BMI) and Body Surface Area(BSA)[Table 13].

The assessment of anaesthetic requirements showed that the end tidal sevoflurane (EtSevo) concentration was comparable between both the groups. Similarly there was no statistically significant difference ($p<0.05$) in terms of ventilatory parameters such as EtCo2 and PIP between the Rt and NRt population. The mean temperature of the subjects between the two groups were also within the similar range and were comparable [Table 14]

**Table 15: Intraoperative Hemodynamic Variables**

| Tumour | Responder (N=10) | | Non responder (N=5) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| HR | 77.40 | 8.02 | 68.20 | 7.60 | 2.129 | .053 |
| SBP | 116.40 | 12.14 | 117.00 | 9.85 | -.095 | .925 |
| HR-PL | 75.10 | 7.06 | 66.80 | 7.33 | 2.121 | .054 |
| SBP -PL | 127.20 | 7.98 | 125.80 | 12.77 | .263 | .797 |

**Figure 19: Comparison of Heart Rate in Tumour group**

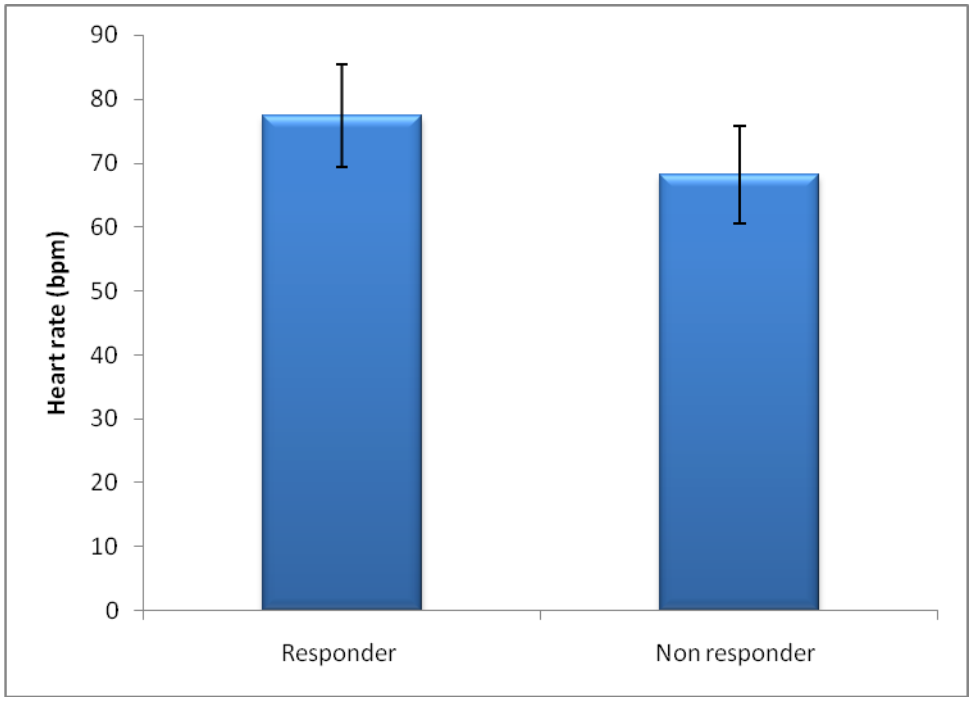
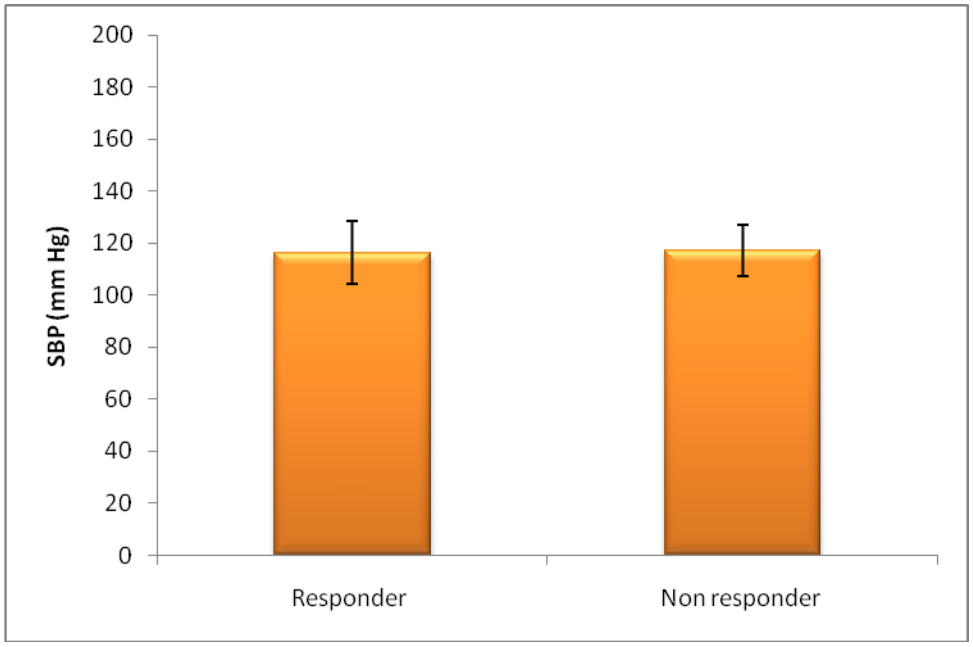



**Figure 20: Comparison of Systolic Blood Pressure in Tumour group**



Our observation in terms of hemodynamic variables like HR and SBP in the tumour population revealed that there was no significant difference in the baseline values between the Rt and NRt subsets [Tumour 15].

Both groups demonstrated an insignificant decrease in the HR post FL. Similarly SBP demonstrated a slight increase in both the subgroups post FL but this was not statistically significant [Figures 19, 20].

Both these variables had a poor correlation with the outcome predictor, Cardiac index variability, which was used to differentiate between the two subgroups.

**Table 16: Analysis of DD in Tumour group**

| Tumour | Responder (N=10) | | Non responder (N=5) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| DD | 7.70 | 1.34 | 3.80 | 2.17 | 4.346 | .001** |
| DD-PL | 4.10 | 1.20 | 2.00 | 0.71 | 3.581 | .003** |

* p< 0.05 , ** p< 0.01

**Figure 21: Comparison of Delta Down in Tumour group (Baseline vs Post loading)**

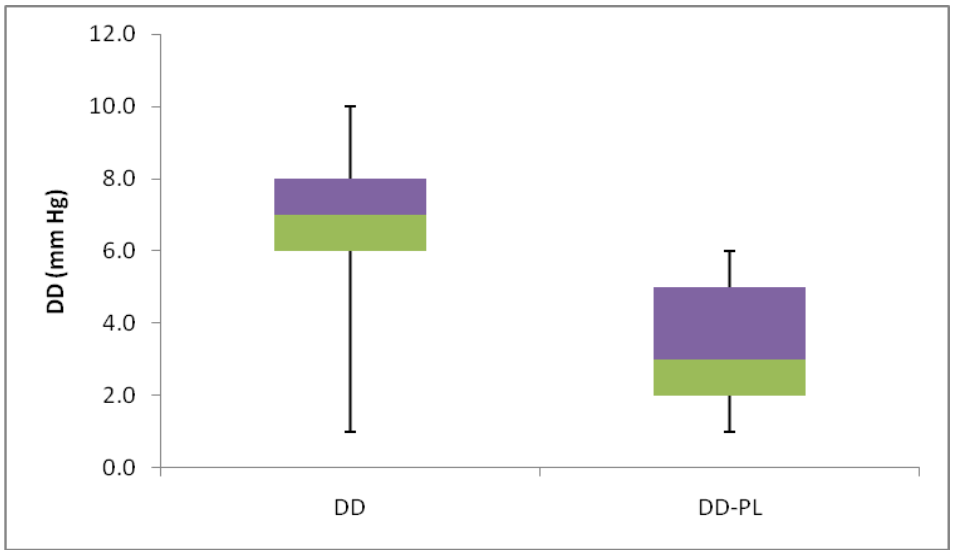
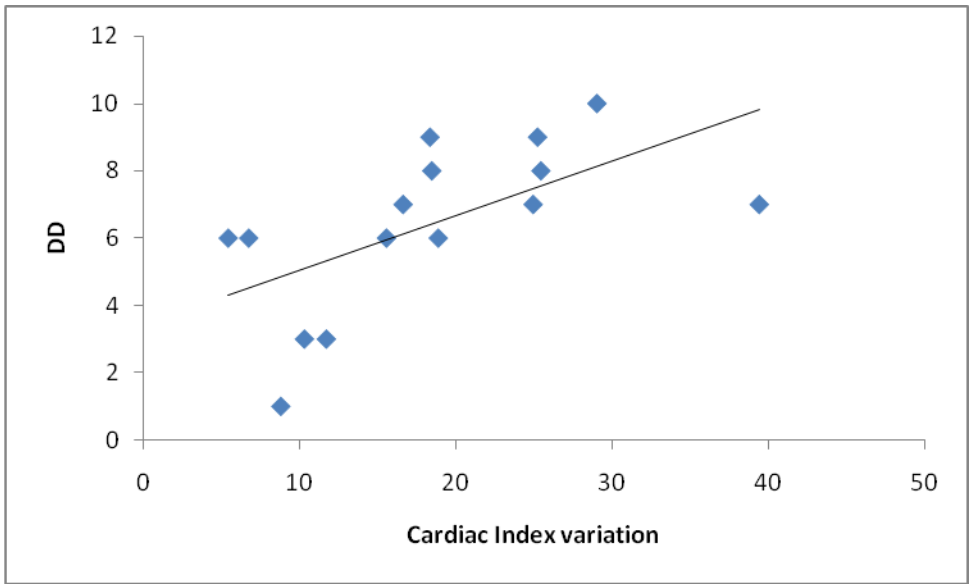


**Table 17: Correlation of DD & CIV (outcome variable) in Tumour group**

| Tumour Group | | Cardiac Index Variation (%) | DD | SVC CI | VTI Variability |
|---|---|---|---|---|---|
| DD | Pearson Correlation | .607* | 1 | .759** | .691** |
| | Sig. (2-tailed) | .016 | | .001 | .004 |
| | N | 15 | 15 | 15 | 15 |

*. Correlation is significant at the 0.05 level (2-tailed). **. Correlation is significant at the 0.01 level (2-tailed).

**Figure 22: Correlation of Delta Down and Cardiac Index Variation (Outcome Variable) in Tumour Group**



Delta down (DD) with the threshold of >5 mm Hg identified the subjects exhibiting a increase in cardiac index post FL from the ones who failed to do so thereby efficiently delineating the responders from the non responders. The mean DD in the Rt subgroup was significantly higher than that of NRt ($p<0.05$) [Table 16].

Similarly the non responder group demonstrated a mean which was lower than the cut-off value, but few subjects exhibited borderline high values (6mmHg) which resulted in false positives and thereby reducing the specificity (80%) of this index in differentiating between the two subgroups. In the responder population the DD decreased below the threshold post fluid loading which was consistent with a corresponding increase in CI thereby confirming that the subjects required the fluid therapy [Figure 21].The non responder population also exhibited a decrease in DD post fluid loading, but this was not statistically significant.

It exhibited fairly good correlation with the cardiac index variation ($r=0.607$) thereby demonstrating its efficacy as a predictor variable.

**Table 18: Analysis of SVC diameters and derived variables in Tumour group**

| Tumour | Responder (N=10) | | Non responder (N=5) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| SVC(Max) | 13.00 | 3.37 | 12.40 | 2.41 | .353 | .730 |
| SVC(min) | 5.30 | 2.31 | 8.60 | 1.95 | -2.730 | .017* |
| SVC CI | 59.05 | 16.64 | 30.94 | 5.20 | 3.629 | .003** |
| SVC(Max)-PL | 14.80 | 2.35 | 14.20 | 1.79 | .500 | .625 |
| SVC(min)-PL | 10.60 | 2.01 | 11.40 | 1.52 | -.780 | .449 |
| SVC CI-PL | 28.50 | 6.09 | 19.32 | 10.24 | 2.204 | .046 |

* $p< 0.05$ , ** $p< 0.01$

**Figure 23: Comparison of SVC collapsibility index in Tumour group (Baseline vs Post loading)**

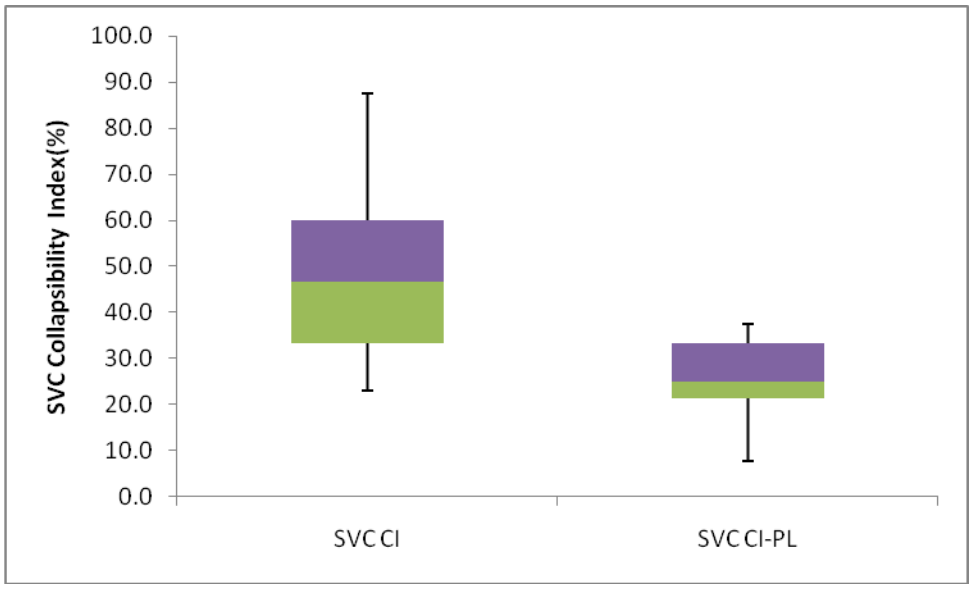
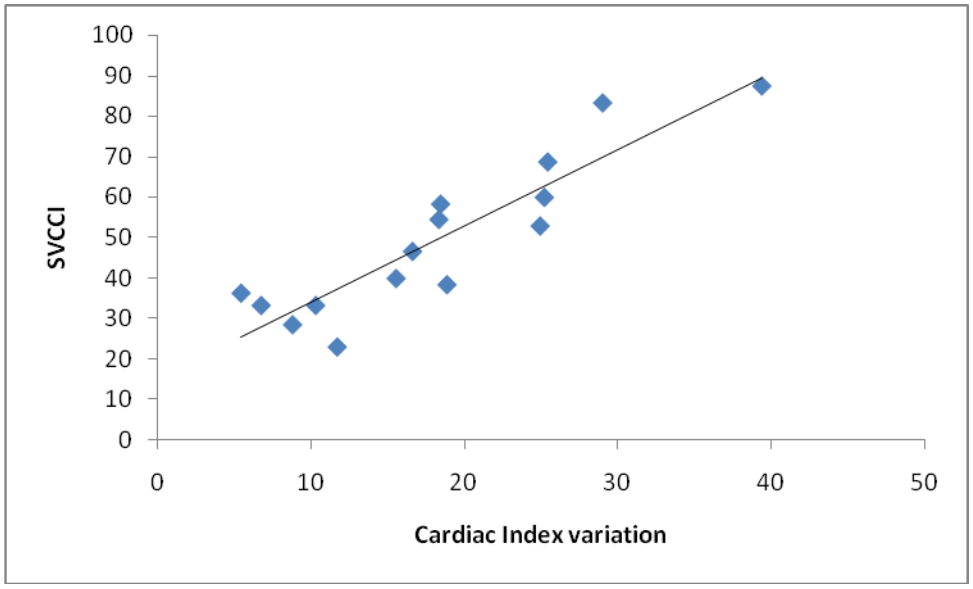



**Table 19: Correlation of predictor variables and the outcome variable**

| **Tumour Group** | | Cardiac Index Variation (%) | DD | SVC CI | VTI Variability |
|---|---|---|---|---|---|
| SVC CI | Pearson Correlation | .906** | .759** | 1 | .799** |
| | Sig. (2-tailed) | .000 | .001 | | .000 |
| | N | 15 | 15 | 15 | 15 |

*. Correlation is significant at the 0.05 level (2-tailed). **. Correlation is significant at the 0.01 level (2-tailed).

**Figure 24: Correlation of SVC Collapsibility Index and Cardiac Index Variation (Outcome Variable) in Tumour Group**




SVCCI in the tumour group proved to be an excellent predictor of fluid responsiveness. It was extremely sensitive and specific (100%, 100%) in differentiating the responders from the non responders. The baseline of SVCCI in Rt group was markedly increased above the threshold value of 38% which proved to be highly statistically significant ($p<0.01$) when compared to the mean baseline of the non responder group [Table18].

In the RT subgroup post fluid loading, the values significantly decreased from the baseline and correlated well with the increase in the Cardiac index, thereby proving that it has good utility as a predictor [Figure 24, Table19]. The NRt group also showed a non significant decrease in the post FL values compared to the baseline, thereby indicating the already filled status of the subjects in this subgroup [Figure 23].

**Table 20: Analysis of VTI & VTIAoV in Tumour group**

| Tumour | Responder (N=10) | | Non responder (N=5) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| VTI max | 20.69 | 1.47 | 22.22 | 1.49 | -1.890 | .081 |
| VTI min | 16.65 | 1.37 | 19.26 | 1.90 | -3.072 | .009** |
| VTI Avg | 18.67 | 1.38 | 20.74 | 1.69 | -2.554 | .024* |
| VTI Variability | 21.71 | 3.75 | 14.46 | 3.32 | 3.656 | .003** |
| VTI max-PL | 24.31 | 0.64 | 23.70 | 1.77 | .997 | .337 |
| VTI min-PL | 22.89 | 0.99 | 22.28 | 2.04 | .794 | .441 |
| VTI Avg-PL | 23.60 | 0.74 | 22.99 | 1.90 | .913 | .378 |
| VTIAoV-PL | 6.07 | 3.48 | 6.30 | 2.33 | -.130 | .899 |

* $p < 0.05$ , ** $p < 0.01$

**Figure 25: Comparison of Aortic VTI variation in Tumour group (Baseline vs Post loading)**

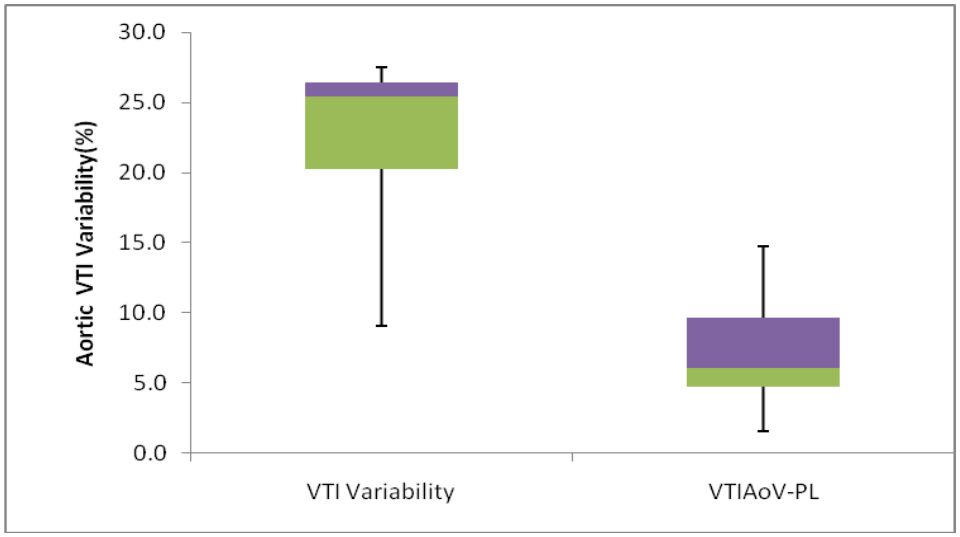
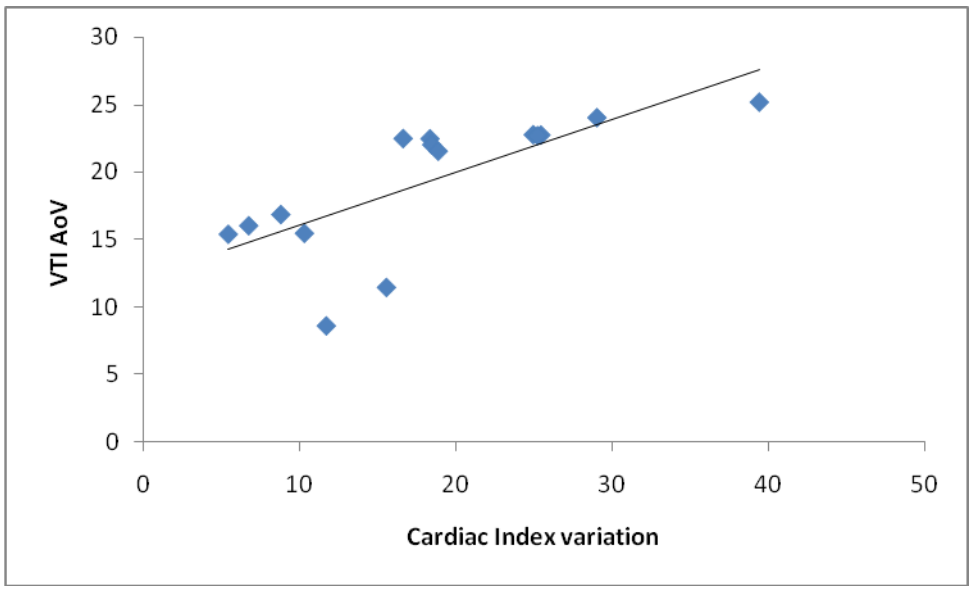


**Table 21: Correlation of predictor VTIAoV & CIV**

| Tumour Group | | Cardiac Index Variation (%) | DD | SVC CI | VTI Variability |
|---|---|---|---|---|---|
| VTI Variability | Pearson Correlation | .734** | .691** | .799** | 1 |
| | Sig. (2-tailed) | .002 | .004 | .000 | |
| | N | 15 | 15 | 15 | 15 |

*. Correlation is significant at the 0.05 level (2-tailed). **. Correlation is significant at the 0.01 level (2-tailed).

**Figure 26: Correlation of Aortic VTI variation and Cardiac Index Variation (Outcome Variable) in Tumour Group**



Similarly Aortic VTI variability also proved to be an excellent predictor in distinguishing between the subjects of both the subgroups. It showed a significant increase in the variability of >20% in the Rt group ($p<0.05$), which predicted the outcome variable, CIV of >15%, thereby diagnosing this subset to be hypovolemia [Table 20].

It also helped in positively delineating them from the non responders, who did not show significant variability. These non responders had values less than the threshold limit of 20%, which had a consistent correlation with a CIV of<15%, thus proving that these subjects had adequate volume reserve [Table 21, Figure 26].Variability significantly reduced below the cut-off value after the fluid bolus in the responder group which again reaffirmed the fact that these subjects required fluid therapy. [Figure 25]

Stroke volume significantly increased post fluid loading in the responder group which in turn resulted in an increased cardiac output and ultimately the cardiac index. This also affirms the findings that the predictors are indeed good in differentiating the subjects in need of fluid therapy from the ones who are not in need of it.

**Inter group Analysis – SAH Group vs Tumour Group**

**Responder population - SAH vs TUMOR**

**Table 21: Demographic data of the Responders**

| Responder | Tumour (N=10) | | SAH (N=12) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| Age | 43.60 | 10.88 | 46.50 | 7.70 | -.731 | .473 |
| Height | 167.50 | 10.39 | 162.25 | 8.04 | 1.337 | .196 |
| Weight | 67.00 | 9.39 | 63.42 | 8.53 | .937 | .360 |
| BMI | 23.82 | 1.92 | 24.04 | 2.30 | -.240 | .813 |
| BSA | 1.77 | 0.17 | 1.68 | 0.14 | 1.291 | .211 |
| EtCo2 | 36.80 | 2.62 | 36.75 | 1.86 | .052 | .959 |
| EtSevo | 1.65 | 0.10 | 1.65 | 0.08 | -.120 | .905 |
| Temp | 36.07 | 0.36 | 36.20 | 0.36 | -.845 | .408 |
| PIP | 16.10 | 1.91 | 16.08 | 1.73 | .021 | .983 |

**Table 22: Intraoperative Hemodynamic variables of Responder population**

| Responder | Tumour (N=10) | | SAH (N=12) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| HR | 77.40 | 8.02 | 88.08 | 10.31 | -2.669 | .015* |
| SBP | 116.40 | 12.14 | 137.42 | 11.56 | -4.152 | .000** |
| HR-PL | 75.10 | 7.06 | 86.33 | 10.61 | -2.856 | .010* |
| SBP -PL | 127.20 | 7.98 | 129.25 | 6.68 | -.656 | .519 |

* $p < 0.05$ , ** $p < 0.01$

**Figure 27: Comparison of Heart Rate in Responder Population (SAH vs Tumour)**

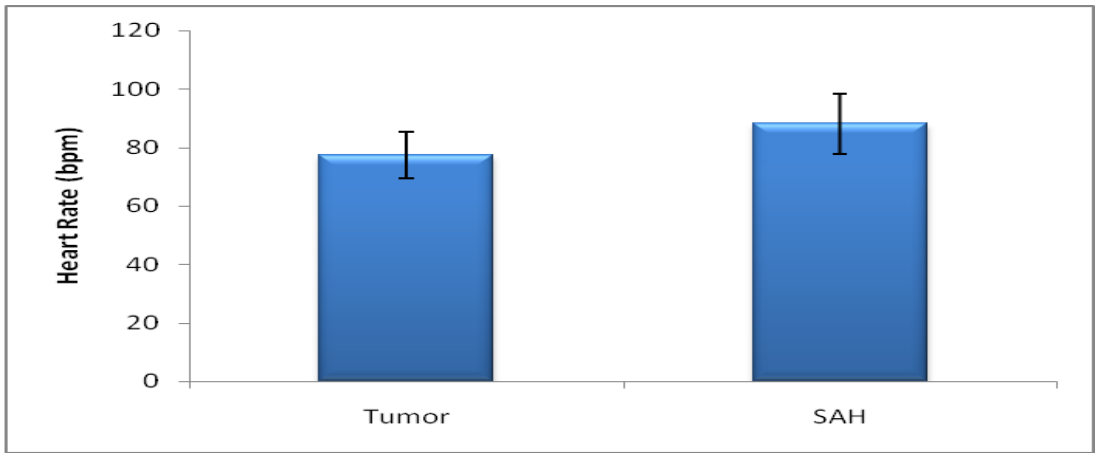
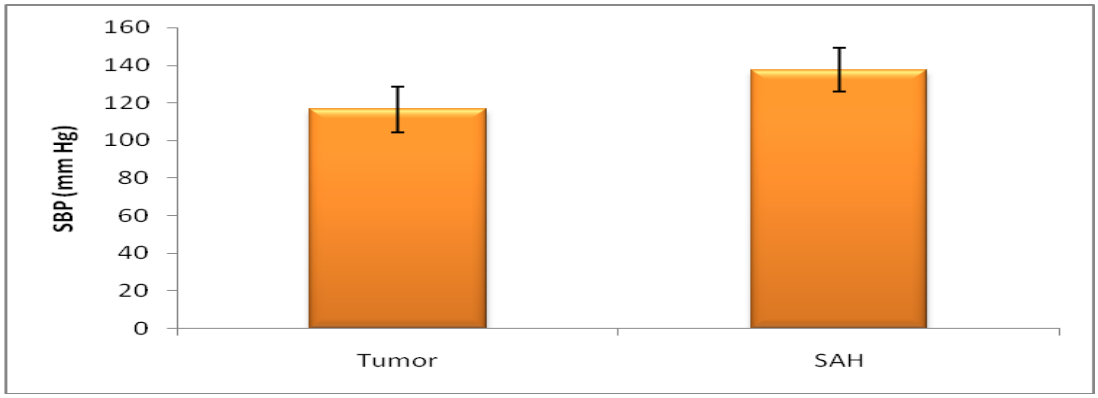



**Figure 28: Comparison of Systolic Blood Pressure in Responder Population (SAH vs Tumour)**




The groups, i.e. Ra (Responder in the aneurysm group) and Rt (Responder in the tumour group).

Our observations revealed that there was no statistically significant difference between the Ra and Rt population in terms of demographic characteristics such as age, weight, height, BSA and BMI [Table 21]. Similarly there was no difference in the anaesthetic requirement and the ventilatory settings between the two groups [Table 22].

The comparison of baseline HR between Ra and Rt showed a significant difference, with the HR of the Ra group being significantly higher than the Rt group ($p<0.05$) [Table 22]. In both the groups, the baseline HR showed a poor correlation with the outcome predictor variable, the cardiac index variation. Post fluid loading HR in both the groups showed a decrease from the baseline, but this was not found to be significant [Figure 27].

The baseline systolic blood pressure in the aneurysm group was higher than that of the tumour group. This difference was found to be statistically significant ($p<0.001$) [Table 22]. The SBP of both Ra and Rt exhibited poor correlation with CIV and proved to be a poor predictor of volume status. Post fluid loading there was a difference in the manner of response of this variable; SBP in Ra group showed a decrease from the baseline, which was not significant, whereas in the Rt group the SBP demonstrated an increase from the preloading baseline [Figure 28].

**Table 23: Analysis of DD in Responder Population**

| | Tumour (N=10) | | SAH (N=12) | | t | p |
|---|---|---|---|---|---|---|
| **Responder** | mean | sd | mean | sd | | |
| DD | 7.70 | 1.34 | 9.50 | 3.15 | 1.681 | .108 |
| DD-PL | 4.10 | 1.20 | 3.42 | 1.88 | .991 | .333 |

**Figure 29: Comparison of Delta Down in Responder Population (SAH vs Tumour)**

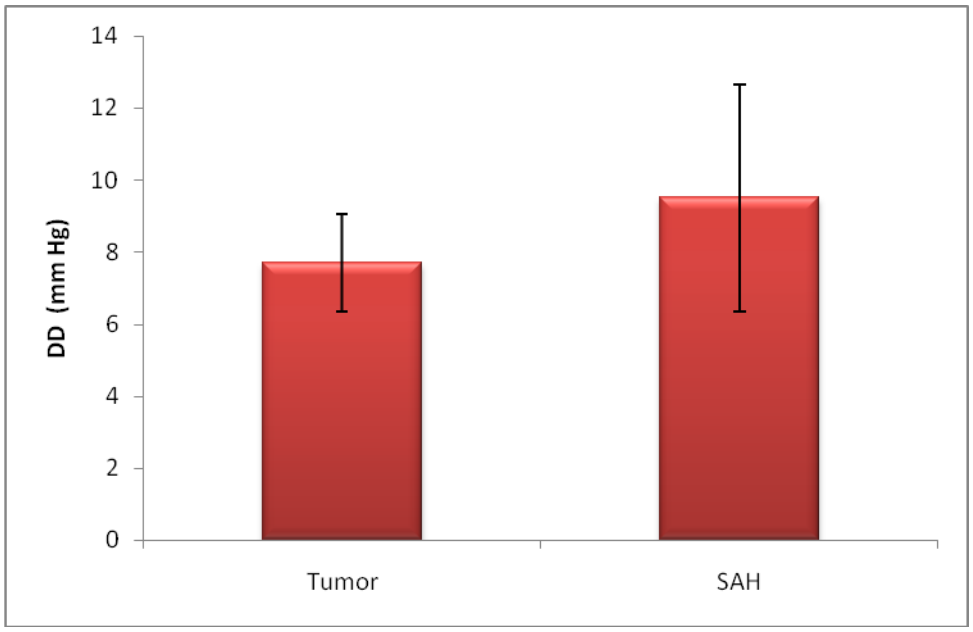
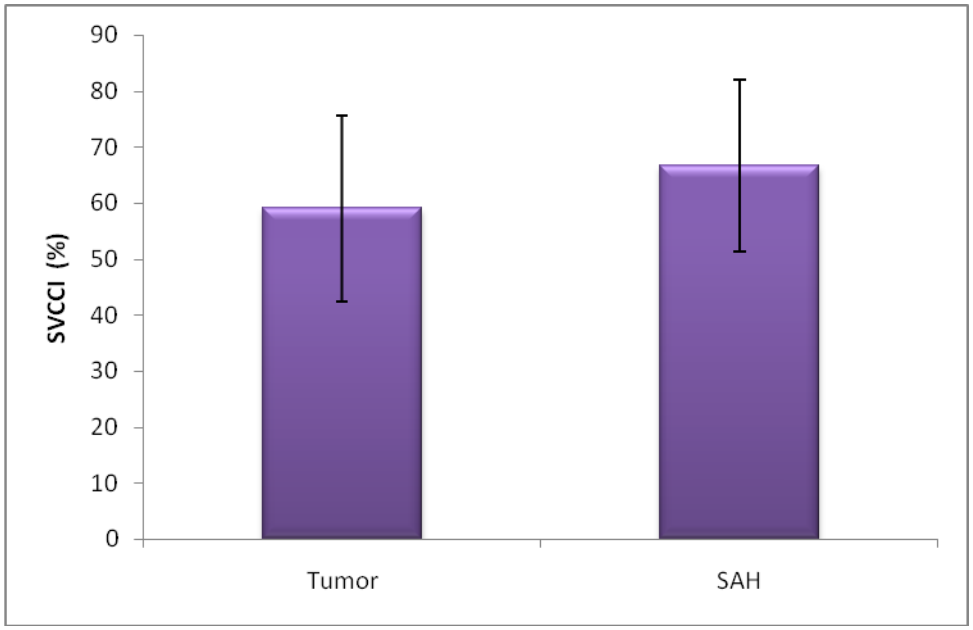



**Table 24: Analysis of SVC, SVCCI in Responder group**

| Responder | Tumour (N=10) | | SAH (N=12) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| SVC(Max) | 13.00 | 3.37 | 10.50 | 1.57 | 2.299 | .032* |
| SVC(min) | 5.30 | 2.31 | 3.67 | 2.10 | 1.734 | .098 |
| SVC CI | 59.05 | 16.64 | 66.71 | 15.29 | -1.124 | .274 |
| SVC(Max)-PL | 14.80 | 2.35 | 14.75 | 2.38 | .049 | .961 |
| SVC(min)-PL | 10.60 | 2.01 | 10.58 | 2.11 | .019 | .985 |
| SVC CI-PL | 28.50 | 6.09 | 28.24 | 7.81 | .086 | .932 |

**Figure 30: Comparison of SVC collapsibility index in Responder Population (SAH vs Tumour)**




The baseline DD in both the groups where higher than the threshold cut off value of 5 mm hg, but the DD of the Ra group was higher than Rt group even though it was not statistically significant[Table 23]. Both the groups behaved similarly post fluid loading showing a decrease from the baseline which was lower than the threshold cut-off limit of 5mm Hg, thereby demonstrating the volume responsiveness in both the groups [Figure 29]. The degree of decrease of DD in the Ra group was more than in the Rt group though it was not statistically significant ($p>0.05$). DD in both the population groups demonstrated good correlation with the outcome parameter CIV thereby proving its predictive value in both the groups [Tables 11, 22].

SVC diameters in the Ra and Rt were within the same range even though the Ra group had significant lower mean of SVC max ($p<0.05$). SVC min of Ra was also lower compared to the Rt group but this difference was not statistically significant [Table 24].

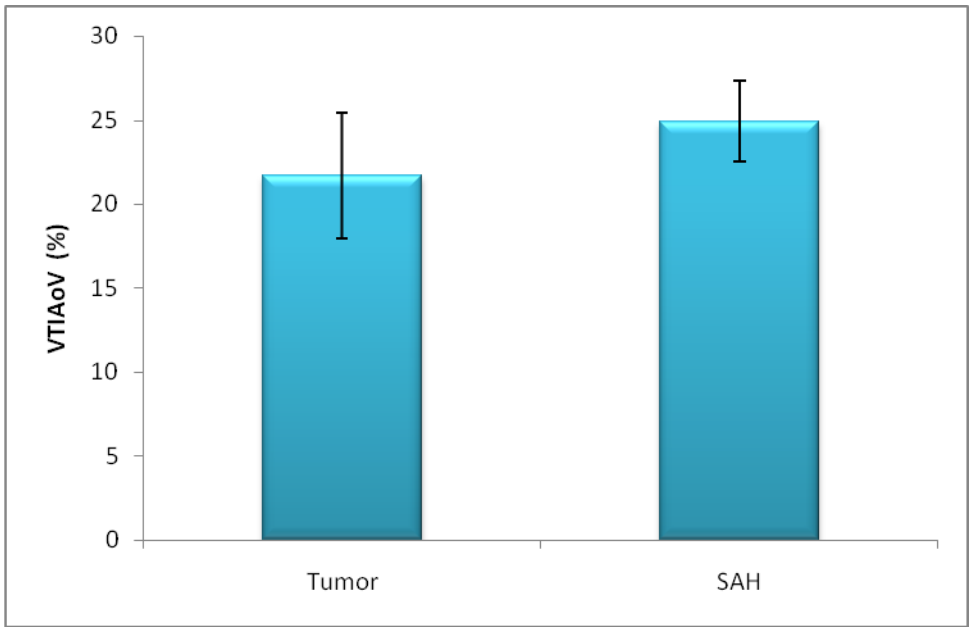
SVCCI in both Ra and Rt subjects were extremely good in predicting the responders. The degree of collapsibility index was same in both the population subsets indicating that this index is a reliable predictor in both the groups. Post FL SVCCI behaved in an identical pattern in both the groups showing decrease from the baseline value and which was lower than the threshold cut off value of 38% [Figure 30].

**Table 25: Analysis of VTI & VTIAoV in Responder population**

| | Tumour (N=10) | | SAH (N=12) | | t | p |
|---|---|---|---|---|---|---|
| **Responder** | mean | sd | mean | sd | | |
| VTI max | 20.69 | 1.47 | 20.87 | 0.94 | -.341 | .737 |
| VTI min | 16.65 | 1.37 | 16.25 | 0.92 | .818 | .423 |
| VTI Avg | 18.67 | 1.38 | 18.56 | 0.91 | .228 | .822 |
| VTI Variability | 21.71 | 3.75 | 24.93 | 2.43 | -2.425 | .025* |
| VTI max-PL | 24.31 | 0.64 | 24.24 | 1.12 | .187 | .853 |
| VTI min-PL | 22.89 | 0.99 | 22.32 | 1.24 | 1.179 | .252 |
| VTI Avg-PL | 23.60 | 0.74 | 23.48 | 0.98 | .329 | .746 |
| VTIAoV-PL | 6.07 | 3.48 | 8.21 | 3.71 | -1.384 | .182 |

* $p< 0.05$

**Figure 31: Comparison of Aortic VTI variation in Responder Population (SAH vs Tumour)**




Maximum and minimum Aortic VTI shared a similar pattern in both the groups, the degree of variation in the Ra group was significantly higher than the Rt population ($p<0.05$). Both the groups exhibited a similar response pattern post fluid loading. There was a decrease in the values below the baseline and also below the threshold cut-off value of 20% [Figure 31].

Even though the stroke volume in both the groups had no statistically significant difference ($p>0.05$) the significant higher HR in the Ra group resulted in higher CO [Table 19].This resulted in a statistically significant higher CI in the Ra group as compared to Rt group ($p<0.05$)[ Table 25]. Similarly, the Cardiac Index variation was slightly higher in Ra group as compared to the Rt group though not statistically significant.

**Table 26: Demographic Variables of Non responder population**

| Non responder | Tumour (N=5) | | SAH (N=3) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| Age | 46.40 | 3.36 | 39.67 | 8.02 | 1.713 | .138 |
| height | 169.00 | 7.91 | 175.00 | 5.57 | -1.139 | .298 |
| weight | 64.80 | 5.54 | 73.67 | 14.84 | -1.253 | .257 |
| BMI | 22.70 | 1.61 | 23.90 | 3.25 | -.714 | .502 |
| BSA | 1.74 | 0.11 | 1.89 | 0.22 | -1.288 | .245 |

**Table 27: Intraoperative Anaesthetic Variables**

| Non responder | Tumour (N=5) | | SAH (N=3) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| EtCo2 | 36.20 | 2.95 | 36.00 | 4.00 | .082 | .937 |
| EtSevo | 1.63 | 0.10 | 1.65 | 0.07 | -.265 | .800 |
| Temp | 36.16 | 0.38 | 35.67 | 0.50 | 1.579 | .165 |
| PIP | 17.80 | 3.35 | 18.00 | 1.00 | -.098 | .925 |

**Table 28: Intraoperative Hemodynamic Variables**

| Non responder | Tumour (N=5) | | SAH (N=3) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| HR | 68.20 | 7.60 | 87.00 | 11.14 | -2.882 | .028* |
| SBP | 117.00 | 9.85 | 139.00 | 8.54 | -3.193 | .019* |
| HR-PL | 66.80 | 7.33 | 84.33 | 11.68 | -2.664 | .037* |
| SBP -PL | 125.80 | 12.77 | 135.00 | 5.00 | -1.164 | .289 |

* $p < 0.05$

**Non Responder group – SAH group vs Tumour group**

Analysis of the Non responder subgroup of SAH (NRa) and Tumour (NRt) yielded the following observations.

There was no difference in terms of demographic variables between the two groups [Table 26]. Similarly the anaesthetic requirements and the ventilatory settings were within the similar range and were statistically insignificant [Table 27].

Analysis of basic hemodynamic parameters like HR and BP showed a significant difference between the two groups ($p<0.05$)[Table 28].The aneurysm group had a significantly higher baseline as compared to the tumour group .Both NRa and NRt subjects showed a decline in the HR post fluid loading which was not statistically significant. In both the groups it showed poor correlation with the outcome predictor, cardiac index variability, there by conveying the message that it is a poor predictor of fluid responsiveness in both the non responder groups[Table 29].

Comparison of SBP in both NRa and NRt groups revealed a significantly higher BP in the NRa group ($p<0.05$). The NRa group showed a small decline in the post fluid loading state compared to the baseline and the NRt group demonstrated an increase in the post loading SBP compared to the baseline but both these findings were not statistically significant [Table 29]. In both the groups it demonstrated a poor correlation with change in the cardiac index.

**Table 29: Analysis of DD, SVC & SVCCI in Non responder population**

| | Tumour (N=5) | | SAH (N=3) | | T | p |
|---|---|---|---|---|---|---|
| **Non responder** | mean | sd | mean | sd | | |
| DD | 3.80 | 2.17 | 4.33 | 1.53 | -.369 | .725 |
| SVC(Max) | 12.40 | 2.41 | 10.33 | 2.31 | 1.191 | .279 |
| SVC(min) | 8.60 | 1.95 | 6.67 | 2.08 | 1.327 | .233 |
| SVC CI | 30.94 | 5.20 | 36.18 | 7.27 | -1.203 | .274 |
| DD-PL | 2.00 | 0.71 | 3.00 | 2.00 | -1.061 | .330 |
| SVC(Max)-PL | 14.20 | 1.79 | 15.67 | 2.08 | -1.062 | .329 |
| SVC(min)-PL | 11.40 | 1.52 | 12.00 | 3.61 | -.339 | .746 |
| SVC CI-PL | 19.32 | 10.24 | 24.50 | 12.44 | -.643 | .544 |

**Figure 32: Comparison of Delta Down in Non Responder Population (SAH vs Tumour)**

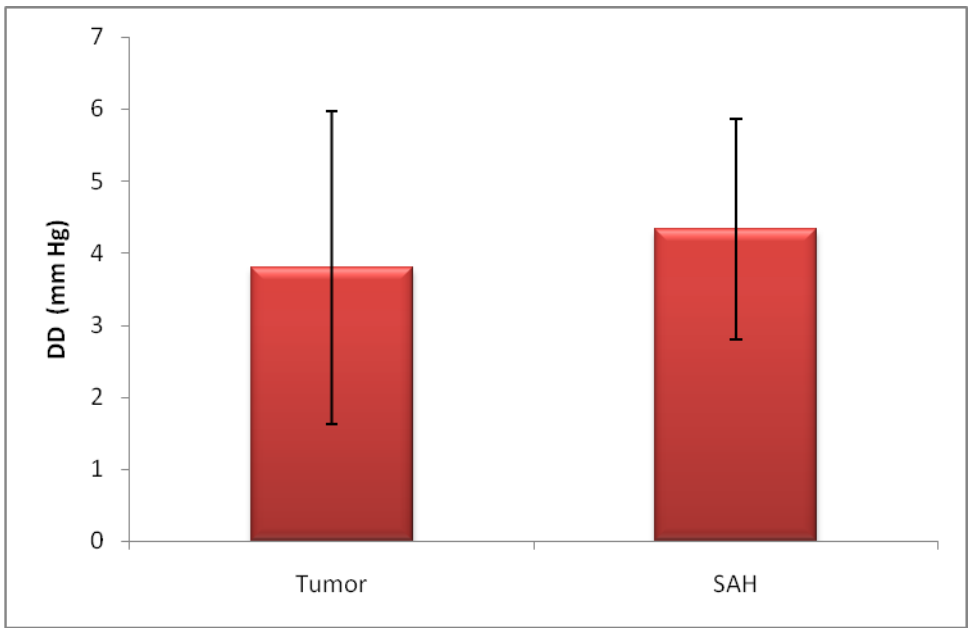
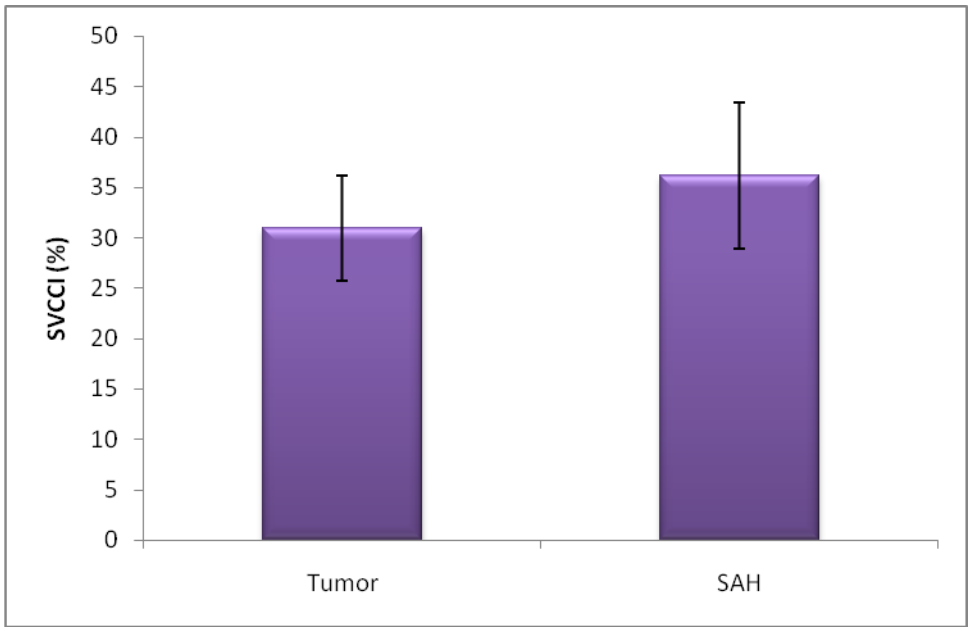



**Figure 33: Comparison of SVC collapsibility index in Non Responder Population (SAH vs Tumour)**



The analysis of DD between the two groups revealed that in both the groups the values were below the threshold cut-off demonstrating the efficacy in detecting the subjects who will not benefit from fluid therapy [Table 29].

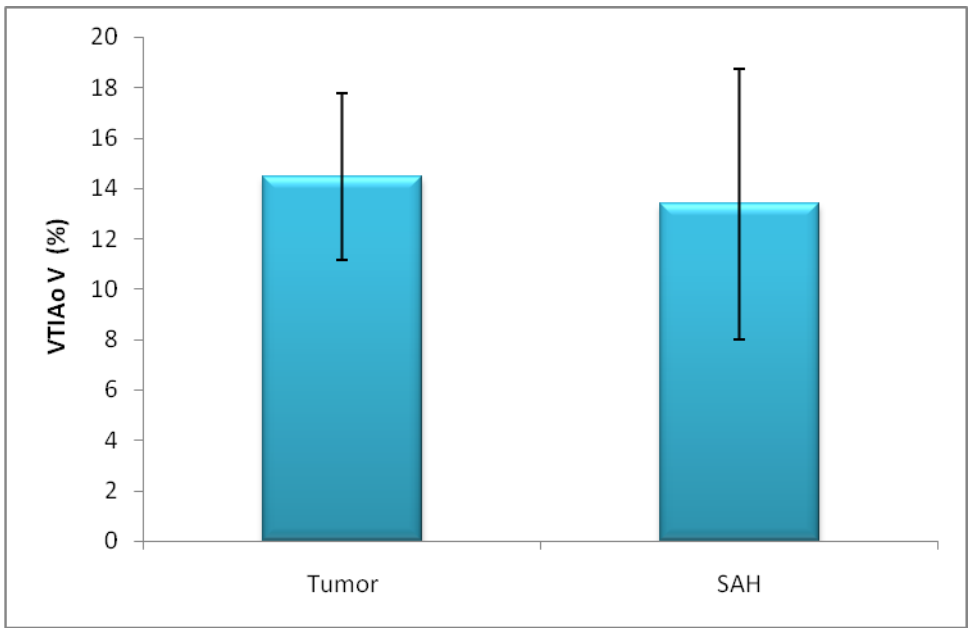
There was no statistically significant difference between the two groups ($p>0.05$) and in both the groups, DD showed a decline after fluid loading reflecting the intra-vascular status [Table 29]. Both the population subsets also demonstrated a significant correlation with the changes in the cardiac index [Tables 6 & 17]

Similarly the SVC Collapsibility Index in both the groups were comparable and had a high sensitivity and specificity in detecting the Non-responders in both the groups, demonstrating a good correlation with the outcome thereby proving that it is indeed a good index to predict fluid responsiveness in the population studied[Figure 33].

**Table 30: Analysis of VTI & VTIAoV in Nonresponder population**

| | Tumour (N=5) | | SAH (N=3) | | t | p |
|---|---|---|---|---|---|---|
| **Non responder** | mean | sd | mean | sd | | |
| VTI max | 22.22 | 1.49 | 23.67 | 0.50 | -1.580 | .165 |
| VTI min | 19.26 | 1.90 | 20.73 | 1.52 | -1.133 | .301 |
| VTI Avg | 20.74 | 1.69 | 22.20 | 1.00 | -1.338 | .229 |
| VTI Variability | 14.46 | 3.32 | 13.37 | 5.37 | .364 | .729 |
| VTI max-PL | 23.70 | 1.77 | 25.37 | 0.64 | -1.529 | .177 |
| VTI min-PL | 22.28 | 2.04 | 24.23 | 1.31 | -1.463 | .194 |
| VTI Avg-PL | 22.99 | 1.90 | 24.80 | 0.96 | -1.505 | .183 |
| VTIAoV-PL | 6.30 | 2.33 | 4.64 | 3.16 | .858 | .424 |

**Figure 34: Comparison of Aortic VTI variation in Non Responder Population (SAH vs Tumour)**




Aortic VTI variability also showed consistency in both the groups and were comparable even though the NRa group had a slightly higher mean value compared to NRt group [Table 30, Figure 34].It showed good sensitivity and specificity in diagnosing the Non responders of both the subsets studied. The Aortic VTI variability also demonstrated a good correlation with the variation in the cardiac index post fluid loading [Tables 15, 21]

**Table 31: Echo-derived Variables in Non responder population**

| Non responder | Tumour (N=5) | | SAH (N=3) | | t | p |
|---|---|---|---|---|---|---|
| | mean | sd | mean | sd | | |
| VALVE AREA | 3.28 | 0.62 | 3.10 | 0.17 | .479 | .649 |
| SV Avg | 68.32 | 15.70 | 66.69 | 4.75 | .171 | .870 |
| cardiac output | 4.63 | 0.96 | 5.82 | 1.03 | -1.668 | .146 |
| BSA | 1.74 | 0.11 | 1.89 | 0.22 | -1.288 | .245 |
| Cardiac Index | 2.67 | 0.62 | 3.14 | 0.80 | -.924 | .391 |
| SV Avg-PL | 75.48 | 16.26 | 76.93 | 6.14 | -.144 | .890 |
| cardiac output-PL | 5.04 | 1.14 | 6.51 | 1.16 | -1.751 | .131 |
| Cardiac Index-PL | 2.91 | 0.73 | 3.51 | 0.91 | -1.026 | .345 |
| Cardiac Index Variation (%) | 8.61 | 2.55 | 11.68 | 1.64 | -1.840 | .115 |

The SV, the CO and the CI were comparable between the two groups and tough the NRa group revealed a slightly higher mean for these variables than those in NRt it was of no statistical significance [Table 31].

# DISCUSSION

# DISCUSSION

Predicting fluid responsiveness in patients has always been a great challenge to anesthesiologists and intensivists for many decades. Since it is quite difficult to actually measure the intravascular volume, various static and dynamic variables are used indirectly to identify the fluid status of the patient.

Here we studied three of these variables namely Delta Down (DD), Superior Vena Cava Collapsibility Index (SVCCI) and Aortic Velocity Time Integral (VTIAo) Variability. This study was conducted to identify which among the three variables studied was the best predictor of fluid responsiveness in patients with aneurysmal SAH as well in patients with supratentorial tumours undergoing neurosurgery and also to note any differences between the two pathological conditions that neuro-anesthesiologist commonly encounter in practice. To the best of our knowledge there have been no studies which have compared the fluid responsiveness between the above mentioned neuropathological states.

**Brief summary of the results:**

Our study consisted of two groups, one with aneurysmal Sub Arachnoid Hemorrhage (SAH group) and the other with supratentorial tumours (tumour group). These groups were further categorized as those who responded to the fluid challenge as responders (R) and those who did not respond to the fluid challenge as Non-Responders (NR). Our analysis revealed that there was no significant difference ($p > 0.05$) between the groups and intra group(R vs NR)

as well as between the SAH group vs tumour group in terms of demographic characteristics.

We observed that there was no statistical difference between the groups (R vs NR and SAH vs Tumour) in terms of anesthetic requirement or ventilatory parameters.

Hemodynamic variables such as the baseline Heart Rate (HR) and Systolic Blood Pressure (SBP) values between responders and non responders of individual groups were comparable with no significant difference between the two groups. Post fluid loading HR did not vary much from the baseline. There was no significant decrease in the heart rate from the baseline values in either subset of patients.

SBP initially increased from baseline values post Fluid Loading (FL) thereafter it remained almost similar to baseline. But the increase seen was not clinically relevant nor was it statistically significant. Both these parameters showed poor correlation with the outcome predictor i.e. Cardiac Index Variability (CIV) thereby revealing that they were poor predictors of volume responsiveness and could not differentiate the responders from the non responders effectively.

The intergroup analysis between the SAH group and the tumour group revealed a significantly higher HR and SBP ($p < 0.05$) in the SAH group when compared to the tumour population in case of both responders and non responders. It was also observed that the HR and SBP in the SAH group did not show the expected response post FL. That is, the HR did not reduce nor did

the SBP increase after the fluid loading which is the conventional response observed in normal population.

Our results showed that DD with a cut-off of 5mm Hg was very efficient in predicting Cardiac Index variation (post fluid loading) higher or lower than 15% in both the SAH and Tumour population .There was significant correlation between DD and the outcome variable, CI variability ($r = 0.716$) which was considered as the gold standard in predicting the volume status of the patients thereby differentiating the responders from the non responders.

Fluid loading in patients suspected to be hypovolemic and who were later diagnosed as responders showed a significant decrease of DD below the threshold value of 5 mm Hg, post fluid loading [Table 23]. In the Non responder group also, DD reduced below the baseline value post FL but this was not significant. Thus DD with a threshold of 5 mm Hg is an excellent predictor of fluid status in these subjects, in both groups, with high index of sensitivity and specificity (90% & 85%) in differentiating the responders from non responders.

SVCCI with a threshold value of 38% was extremely efficient in differentiating the responders from the non responders in both the groups. The mean value of SVCCI was significantly elevated above the of 38 % cut-off ($p<0.05$) in the responder group where as the mean value in the non responder population was below the threshold value. Responders of both groups showed significant decrease in the post fluid loading value from the baseline which

demonstrated the positive response of the subjects to fluid therapy [Tables 24, 29].

Similarly the post FL mean value was significantly lower than the threshold conveying the inference that the subjects have been adequately resuscitated with fluid therapy. The statistically significant difference ($p<0.05$) exhibited by this variable pre and post fluid loading is associated with very high sensitivity (100%) and specificity(95%) in detecting the volume status of the subjects as well as in differentiating the R subgroup from the NR subgroup .

SVCCI also showed excellent correlation with the outcome predictor CIV , thereby positively predicting the variation of CI in these subjects which in turn helps in distinguishing between the responders (R) from Non responders (NR),($r=0.906$) .

VTIAo Variability with a threshold value of > 20% proved to be a good predictor in diagnosing the R subgroup as well as the NR subgroup accurately in both the groups analyzed. The two subgroups(R vs NR) demonstrated a significant difference in the pre fluid loading base line values ($p<0.05$). The R subgroup exhibited a significantly higher value ($p<0.05$) well above 20% and the NR group had a marginally lower value than the cut-off [Figures: 14, 25].

This demonstrates that VTIAo V can identify the responders and the non responders with good sensitivity and specificity (100%, 90%) The post Fluid Loading values in the R subgroup decreased sharply in contrast to the NR group demonstrating that the subjects were grossly fluid deficient at the

beginning of the procedure and thus showed good response to the fluid therapy**.**VTIAoV also had good correlation to the Cardiac index Variations thereby establishing the fact that it is indeed a good predictor of fluid responsiveness(r=0.732).

The baseline stroke volume (SV) measurements in both the subgroups, R vs NR, of both the population groups studied were in the normal or high normal range, and they all responded with an increase in SV after fluid loading[Table :31].Next we measured the cardiac output (CO) of the subjects in both the subgroups, and found that they were within the normal range and there was no significant difference between the subgroups (R vs NR). But there was a significant increase in the cardiac output post fluid loading in the responder group ($p>0.05$) showing that this subset responded well to fluid therapy and were indeed fluid deficient. Whereas the NR group demonstrated an increase in the Cardiac output which was statistically not significant [Table: 31].

It was also noted that even though the Stroke volume in both the groups (SAH vs Tumour) had no statistically significant difference, the higher HR in the SAH group resulted in a higher CO measurement. This resulted in a statistically significant higher CI in the SAH group as compared to the tumour group. The SAH group showed a higher degree of variability in the cardiac index compared to the tumour group, but this was found to be statistically not significant.

**Justification for choosing dynamic indices like DD, SVCCI and Aortic VTI variability as predictors in this study and a brief appraisal of prior studies on predictors of fluid responsiveness :**

As clearly mentioned earlier, we re-emphasize the need for dynamic indices for predicting volume responsiveness in neurosurgical patients because of the following reasons:

It is now proved beyond doubt that, static indices like CVP, PAOP and variables obtained from echocardiographic evaluation such as RAP, RVEDV and LVEDA cannot accurately sense the changes in ventricular preload and are therefore not good predictors of fluid responsiveness [48, 51, 60, 84] It has been shown that both RAP and PAOP tend to erroneously estimate the transmural pressures in subjects with PEEP (extrinsic or intrinsic). It has also been seen that PAOP is majorly dependent on the left ventricle compliance which in SAH patients can be reduced due to multiple reasons such as a neuroendocrine response, high sympathetic surge and associated cardiomyopathies e.g.: Takotsubo cardiomyopathy[1, 108-110].

Since it is the transmural pressures and not the intra-cavitary pressures like RAP and PAOP that reflects the end-diastolic volume via the chamber compliance, these surrogates too are poor predictors of fluid responsiveness.

Similarly estimation of the RVEDV, LVEDA by echocardiography does not reflect LVEDV accurately and hence does not reflect the LV preload in most of the patients.[20, 21, 51, 52]. For example, in scenarios where there is associated right ventricular dysfunction there is no beneficial hemodynamic outcome offered by volume expansion even though it will exhibit low LVEDV

and significant hypovolemia. Also evaluation of pre-fluid loading LVEDV gives little knowledge about the compliance of the diastolic chamber which is an important determinant of the fluid responsive status of the patient. For example, hypovolemia can be present in patients with dilated cardiomyopathy even though they will present with a normal or high LVEDA value.

It should be understood that the post fluid therapy increase in end diastolic volume depends mainly on how the partitioning of the fluid happens into the different zones of cardiovascular compliances organized in series [Right Atrium-Right Ventricle-Pulmonary circulation-Left Atrium-Left Ventricle]. It should also be noted that rise in stroke volume as a result of increase in LVEDV mainly depends on the ventricular function because a decrease in contractility of the ventricles will decrease the relationship slope between LVEDV and SV.

Because of the foresaid reasons, a patient can get diagnosed as a non-responder to fluid loading because of high venous compliance or low ventricular compliance which may or may not be associated with ventricular dysfunction. It is due to this fact that bedside indicators, though they have the attraction of widespread availability, low cost, ease of recording and are non-invasive, they lack the accuracy as predictors of fluid responsiveness in neurosurgical patients especially those with aneurysmal SAH in whom various factors such as the venous capacitance, compliance of the left ventricle and ventricular contractility are frequently altered.

**Why was Delta Down chosen?**

Standard methods usually used to analyze fluid responsiveness in critically ill patients is based on the measurement of Cardiac output or Stroke volume and its variation. But evaluation of data offered by recent studies suggest that inspite of minor limitations, changes in arterial pressure track blood flow changes accurately ,following a fluid challenge.[22, 94, 98] Thus, we opted to use an arterial pressure-based variable for determining fluid responsiveness.

The physiological rationale is that positive pressure inspiration during mechanical ventilation impedes venous return thereby increasing the RV after load. This in turn results in a decrease of the LV preload few heart beats later. Meanwhile inspiratory pressure also purges blood from pulmonary vasculature into the left ventricle, and simultaneously decrease LV after load by reducing the aortic transmural pressure [90].The combination of these events results in an early inspiratory increase in left ventricular SV and ABP, which is defined as delta up which is followed by an decrease in SV a few heart beats later, which is called delta down.

Vice versa happens during expiration where there is an increase in the right ventricular preload as well as decrease in afterload thereby increasing RV SV. Meanwhile in left side, these effects are the opposite as demonstrated by the preload decrease and after load increase resulting in lower Left Ventricular SV and arterial blood pressure. Thus delta up is mainly due to increase in LV preload and simultaneous decrease of after load, whereas delta down is attributed to decreased venous return to the right side of the heart.

De Backer et al concluded that the influence of RV changes on the LV output is majorly dependent on the HR as well as respiratory rate and their timing to each other as well [86]. They proved that the variation of respiration and its impact on the heart disappeared with higher RR or when ratio of HR/RR is less than 3.6. This can also happen when the patient triggers the ventilator and or takes a spontaneous breath. This is why it is mandatory to use lower respiratory rates while recording this variable, making sure no spontaneous breaths are taken by the subject during the recording of the values.

Prior studies in perioperative and ICU population done using DD showed that a cut-off of 5 mm Hg can be used for differentiating fluid responders from non responders and as well as to diagnose hypovolemia and initiate Fluid loading [ 22,23]. DD has shown excellent correlation with Delta Pulse Pressure(DPP) which is a widely used dynamic index derived from the arterial trace, that has gained widespread acceptance due to its non invasiveness and its good predictor power.

The calculation of DD compared with DPP is easier and does not require specialized software or the cumbersome use of algorithms as for Pulse Pressure Variation (PPV) and DPP. DD can be easily calculated from the bedside monitors. Another reason being, as proven already “delta up” reflects sequestrated amount of blood in the lungs which is driven out during mechanical inspiration. This sequestered blood, does not effectively contribute to the circulating blood volume thereby influences the calculation of the DPP / PPV but not that of the DD [22].

This attraction of DD kindled our interest in further evaluation of this variable in the neurosurgical population.

**Why TEE based variables?**

In our study we have used TEE to obtain dynamic variables such as, SVC diameters, Aortic VTI, LVOT/aortic orifice diameter and based on these variables, we calculated the SVC collapsibility index and Aortic VTI variability in mechanically ventilated patients. We considered Aortic VTI variation as a surrogate measure of changes in preload and contractile function of the left ventricle. SV and CO were also recorded from TEE. It is proven that SV and CO calculated with TEE is more definitive when compared to bio impedance plethysmogram [59].

TEE also helps in simultaneous quantification of changes in loading conditions, cardiac output and diastolic function of the subject being evaluated, especially since the neurosurgical population, particularly SAH patients who show dynamic variability in their cardiac compliance and mechanical properties. Cardiac output measured by TEE have been shown to correlate well with measurements of CO obtained using thermo dilution technique with Pulmonary Artery Catheter(PAC) which is considered as the gold standard, but is far more invasive and when compared to TEE had greater degree of complications[59,68]. The incidence of arrhythmias and adverse cardiac events is higher with the use of PAC, which will be detrimental in a situation where there are high levels of circulating catecholamines as in patients with SAH [24].

TEE is now considered to be relatively safe and non-invasive. However insertion and manipulation of the TEE probe may cause oropharyngeal, esophageal and gastric trauma. The occurrences of TEE associated complications are in the range of 0%-0.5%, which is minimal when compared to the benefits offered by it in terms of cardiac status evaluation [59,106].

Even otherwise TEE is now being routinely used in the management of neurosurgical patients during the perioperative period, as there exists a class II a recommendation for its use especially in the assessment of PFO, sitting position and maintenance of perioperative hemodynamics.

**What was missing in the earlier studies that we tried to address?**

We decided to study the correlation between arterial pressure waveform derived indices and echocardiography derived indices such as aortic VTI variation , SVC collapsibility index and the outcome predictor cardiac index variation (pre vs post FL) in SAH patients undergoing elective craniotomies for aneurysm clipping. Measurement of these variables at baseline and following crystalloid bolus infusion can be done to assess their correlation at different fluid status conditions. Our aim was to find out the reliability of these variables in predicting volume status of patients with SAH who are mechanically ventilated in whom there is a complex homeostasis due to coexistence of cardiac dysfunction, neuroendocrine disturbances, hypovolemia and diuretic therapy.

At the bedside, the respiratory variations in left ventricular stroke volume can be assessed by analysis of arterial pressure (arterial catheter) or aortic blood flow velocity (echocardiography) waveforms. Similarly respiratory variations in SVC diameter (echocardiography) and the SVC collapsibility index are reliable indicators of fluid responsiveness .Using echocardiography, respiratory changes in velocity time integral (VTI) of aortic blood flow and SVC variation is studied. Various studies have demonstrated a correlation between arterial pressure waveform derived indices and VTI Ao and SVC variation.

There is 30- 35 % incidence of cardiac dysfunction in post SAH patients.[1, 108] In animals, inducing cardiac dysfunction experimentally revealed a decrease rather than an increase in Systolic Pressure Variation [24]. The SPV depends not only on stroke volume, but also on arterial compliance. It is shown that arterial compliance poorly affects the relationship between respiratory changes in LV stroke volume and delta down [24].

Dynamic parameters are proportionally related to tidal volume and their predictability of fluid status may be improved by indexing to tidal volume [23]. At high respiratory rates the ability of stroke volume variations and its derivatives, to predict the response to fluids might be limited, whereas caval indices could still be used [26].

Trans-oesophageal echocardiography (TEE) allows direct visualization and evaluation of left as well as right ventricular function and thus helps guide the decision between fluid challenge and use of vasopressors or/and inotropes. It has been proved that respiratory variations in VTI Ao using

TTE appear to be a sensitive index of blood volume depletion and restitution [26].

The tumour population was included with the intend that it will act as a control group i.e.; similar operative and anesthetic settings but with the absence of neuroendocrine response and sympathetic storm. Furthermore this will also help in further validation of these variables across the spectrum of neurosurgical patients.

The results of the study will help in planning a careful fluid management strategy that will improve the outcome in patients with SAH by preventing the incidence of vasospasm, pulmonary oedema and associated perioperative complications. In this echo era such a study will boost the confidence of physicians to use the easily available arterial wave form derived indices when echocardiography is not available.

**The clinical consequences of our findings:**

The result of this study throws light on some of the very important aspects of fluid therapy in SAH patients as well as patients with supratentorial tumours presenting for surgical management of the same.

Analysis of our observations showed that there was no difference in basic hemodynamic parameters like the HR and SBP, between the responders as well as the non responders. It was noted that in the SAH group the patients who were grossly fluid deficient had a higher baseline HR and SBP more likely due to the underlying sympathetic surge secondary to the neuroendocrine response, post SAH, resulting in high levels of circulating catecholamines. Even after fluid loading, these indices remained high showing its poor correlation with the volume status of the subjects. Thus these variables are poor indices to assess the volume status of the patients with SAH as well as with supratentorial tumours.

DD with a threshold of 5 mm of Hg proved to be a good and reliable predictor in assessing the volume status of subjects in both the groups and showed excellent sensitivity and specificity in differentiating the responders from the non responders in the SAH as well as tumour population. It also showed good correlation with the changes in the cardiac index post loading thereby accurately predicting the responsiveness of the subjects in the responder group.

This was similar to the findings observed by Deflandre et al, who came to the conclusion that a DD value of > 5 mm Hg could be used to differentiate

responders from non responders in neurosurgical patients [22]. They also observed that Fluid Loading (FL) in patients suspected to be hypovolemic resulted in a consistent decrease of DD below their threshold values which was observed in our study as well.

Our findings were also consistent with the meta analysis performed by Michard F and Teboul JL, who came to the conclusion that before fluid administration, the Delta Down (DD) and Delta Vpeak were significantly higher in responders, and the cutoff value accurately predicted fluid responsiveness with high positive (77 to 95%) and negative (81 to 100%) predictive values[23].Our study also showed DD had a good sensitivity and specificity (95% & 85%) in SAH as well as tumor patients.

Evaluation of the SVC diameters and the derived variable of SVCCI revealed that this index is an excellent predictor of the fluid status of the subjects of both populations. The responders as well as the non responders showed smaller SVC diameters prior to the fluid loading which increased after the fluid therapy. The SVCCI demonstrated high sensitivity and specificity (100,100) in both groups in discriminating the responder population from the non responders.

The mean value of the responder group in both populations were significantly above the cut-off threshold of 38 % and post fluid loading these values reduced below the threshold, thereby demonstrating its efficacy and high level of correlation with other outcome parameters like SV and CI variability. Even in the non responder population of both groups, it showed excellent correlation with the outcome determining parameter; CIV. Our

analysis also showed that this variable behaved in a comparable manner in Aneurysmal group as well as in the tumour population, thereby showing that it is not affected by the neuroendocrine effects often seen in the SAH population.

Our findings were concurrent with that of Vieillard-Baron et al who studied superior vena caval collapsibility as an indicator of volume status in patients with sepsis and concluded that threshold superior vena caval collapsibility of 38%, allowed discrimination between responders and non-responders, with a sensitivity of 90% and a specificity of 100%[79]. They also concluded that the superior vena cava measurement should be routinely and systematically performed during echocardiography in septic shock as it gives an accurate index of fluid responsiveness.

Our findings were further supported by the findings of Charron et al who proved echocardiographic measurements of fluid responsiveness and found that the superior vena cava (SVC) diameter changes during mechanical ventilation could be used as a measure of fluid responsiveness[26, 66].

Our study showed that VTIAo variability of > 20% demonstrated high sensitivity and specificity (100%, 95%) in both the groups, discriminating the responders from the non responders. The mean value of the responder group in both population were significantly above the cut-off threshold of 20 % and post fluid loading these values reduced below the threshold thereby demonstrating its ability as a predictor of fluid status of subjects in both the groups. It further exhibited a high level of correlation with Cardiac index variability thereby proving the fact that this is indeed a very sensitive predictor.

Even in the non responder population of both groups it showed an excellent correlation when evaluated against the outcome variable .Thus our analysis revealed that VTIAo variability behaved in a comparable manner in SAH as well as in the tumour population, thereby showing that it is not affected by the neuroendocrine effects present in aneurysmal SAH population. Our analysis revealed that even though it was slightly increased in the SAH group, it was statistically not significant ($p>0.05$). This proves its credibility as an excellent predictor in both the sets of population.

Our observations were comparable with the results obtained by Feissel et al in patients with septic shock who were being mechanically ventilated[24]. They had concluded that Vpeak was significantly greater ($20^{+}/-$ 6% vs $10^{+}/-$ 3%, $p < 0.01$) in responder patients than in patients who were non-responders. They also demonstrated that a Vpeak threshold of 12% allowed good differentiation of responders and non-responders, having a positive predictive value of 91% and a negative predictive value of 100%.

Similarly Byon et al also proved that DV peak >11% identified responders with good sensitivity and acceptable specificity in pediatric patients undergoing neurosurgery [54].

Though the above mentioned studies assessed the peak velocities, its variation VTI is a variable derived from the aortic velocity and is thus comparable to this parameter.

**Why our study outcome has differences with some prior studies?**

It should be noted that in prior studies various types/ volumes of IV fluids has been used with various speed of fluid infusion, and there has also been a variation in defining the responders to volume expansion. This might have a significant influence on our observed data and thus in turn may affect the results and conclusions of the study. Certain studies already done e.g.: by Levitov et al, Poelaert et al, used transthoracic echocardiography, and since evaluation of echocardiographic variables is highly operator dependent with high inter operator variability, the values may not be reproducible [25, 100].

Also due to intravascular- extravascular equilibration, the speed of volume infusion will also drastically influence the hemodynamic response, particularly in SAH patients who can present with leaky systemic capillaries. Various studies have used different definitions of responders, so some patients considered as responders in these previous studies, will be considered as non-responders in other studies [25, 52, 85, 100, 107].

In studies using the same definition of responders as ours, since the individual data is not freely available a comparison of each of the parameters and its predictive value is not possible. Also most importantly, the predictive value of these dynamic parameters has never been evaluated in neurosurgical patients and especially in patients with aneurysmal SAH; thereby we do not have any comparative analysis of assessment of these variables in similar settings.

Therefore further research into this area is required to evaluate the predictive power of these parameters in discriminating responders from non-responders prior to fluid loading.

**Limitations of this study**

Firstly, this is a pilot study with 15 subjects in each group. An adequately powered study with a larger study population is needed to generalise the results obtained from this study. The results obtained by us are limited to a subset of patients having apparently no cardiovascular dysfunction which may not be representative of the general set of subjects presenting for surgery in both the groups. None of these patients received any osmotic agents before surgery.

We have not recorded nor commented on other echo derived parameters of volume responsiveness e.g.: LVEDV status. These are not contemplated in the present study as more recordings would have been time consuming and hence not possible within the specified time period allotted for the acquisition of data. A comparison group with higher grades of SAH (III and IV) as well as tumour group with associated cardiac comorbidities would have better demonstrated the efficacy of these parameters in situations where their abilities will be better appreciated.

Secondly, in patients with cardiac arrhythmias analysis of the ABP waveform is not possible and in this situation, the arterial pressure changes will not reflect the effects implicated by mechanical ventilation on LV stroke volume. Around 30- 50% of SAH patients and even patients presenting for neurosurgery can present with arrthymias where the credibility of DD will be of question.

Thirdly, an important limitation of Aortic VTI variability and SVCCI is that its value depends on the skill of the echo cardiographer and the evaluator of the recorded signals. It should be kept in mind that Aortic VTIV can be affected by cardiac rhythm, ratio of HR/RR and the tidal volume.

Finally, another important limitation of this study is that SV and in turn the cardiac output and the Cardiac index were determined from the Aortic VTI by Doppler echocardiography. It should be realized that both these measurements share similar methodological properties which may be more closely related, thus resulting in uncontrolled bias.

A future study with a larger sample size and adequate power, including patients with known mild to moderate cardiac risk could help in generalizing the results obtained in this study. It will also be interesting to observe the pattern of alterations in the systolic as well as diastolic functions of the heart in response to fluid loading, in this subgroup of patients who often present with associated cardiac dysfunction.

# CONCLUSION

# CONCLUSION

Aortic VTI Variation (VTIAoV) >20% and SVC Collapsibility Index (SVCCI)>38 % appears to be the more "reliable index of fluid responsiveness" as compared to Delta Down (DD) and will have greater role for the predicting fluid responsiveness in neurosurgical scenarios.

SVC Collapsibility Index is a strong predictor of Fluid responsiveness and can be obtained easily from basic TEE view (Mid-oesophageal Bicaval View) which is used commonly in Neuroanesthesia practice with a M mode and the calculation is simple.

Aortic VTI Variation is a good predictor but requires the skill of the echographer to obtain the proper window (Deep Trangastric LAX) and involves the use of Doppler thus the angle of interrogation plays a major role.

Delta Down with a cut-off of 5 mm Hg DD value can be considered as a threshold for initiating Fluid loading. Caution should be exercised in view of relatively lower specificity and predictivity which may result in erroneous over loading of patients who are actually not fluid deficient.

# BIBLIOGRAPHY

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1. Lerch, C., et al., *Specialized neurocritical care, severity grade, and outcome of patients with aneurysmal subarachnoid hemorrhage.* Neurocrit Care, 2006. **5**(2): p. 85-92.
2. Goto, Y. and S. Yamagata, *[Deteriorating factors on the outcome in patients with fair grade of subarachnoid hemorrhage (WFNS grade I and II)].* No Shinkei Geka, 2006. **34**(6): p. 577-82.
3. Espiner, E.A., et al., *The neuro-cardio-endocrine response to acute subarachnoid haemorrhage.* Clin Endocrinol (Oxf), 2002. **56**(5): p. 629-35.
4. Manea, M.M., et al., *Brain-heart axis - Review Article.* J Med Life, 2015. **8**(3): p. 266-71.
5. Salem, R., et al., *Subarachnoid hemorrhage induces an early and reversible cardiac injury associated with catecholamine release: one-week follow-up study.* Crit Care, 2014. **18**(5): p. 558.
6. McLaughlin, N., et al., *Pulmonary edema and cardiac dysfunction following subarachnoid hemorrhage.* Can J Neurol Sci, 2005. **32**(2): p. 178-85.
7. Lennihan, L., et al., *Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage : a randomized controlled trial.* Stroke, 2000. **31**(2): p. 383-91.
8. Mutoh, T., et al., *Goal-directed fluid management by bedside transpulmonary hemodynamic monitoring after subarachnoid hemorrhage.* Stroke, 2007. **38**(12): p. 3218-3224.
9. Mori, K., et al., *Hemorheological and hemodynamic analysis of hypervolemic hemodilution therapy for cerebral vasospasm after aneurysmal subarachnoid hemorrhage.* Stroke; a journal of cerebral circulation, 1995. **26**(9): p. 1620-6.

10. Sen, J., et al., *Triple-H therapy in the management of aneurysmal subarachnoid haemorrhage.* The Lancet Neurology, 2003. **2**(10): p. 614-21.
11. Reynolds, M.R., et al., *The safety of vasopressor-induced hypertension in subarachnoid hemorrhage patients with coexisting unruptured, unprotected intracranial aneurysms.* J Neurosurg, 2015: p. 1-10.
12. Rivers, E., et al., *Early goal-directed therapy in the treatment of severe sepsis and septic shock.* N Engl J Med, 2001. **345**(19): p. 1368-77.
13. Bundgaard-Nielsen, M., N.H. Secher, and H. Kehlet, *'Liberal' vs. 'restrictive' perioperative fluid therapy--a critical assessment of the evidence.* Acta Anaesthesiol Scand, 2009. **53**(7): p. 843-51.
14. Doherty, M. and D.J. Buggy, *Intraoperative fluids: how much is too much?* British journal of anaesthesia, 2012. **109**(1): p. 69-79.
15. Lenkin, A.I., et al., *Comparison of goal-directed hemodynamic optimization using pulmonary artery catheter and transpulmonary thermodilution in combined valve repair: a randomized clinical trial.* Crit Care Res Pract, 2012. **2012**: p. 821218.
16. Lichtwarck-Aschoff, M., R. Beale, and U.J. Pfeiffer, *Central venous pressure, pulmonary artery occlusion pressure, intrathoracic blood volume, and right ventricular end-diastolic volume as indicators of cardiac preload.* J Crit Care, 1996. **11**(4): p. 180-8.
17. Levin, A., J. Klassen, and M.L. Halperin, *Challenging consults: application of principles of physiology and biochemistry to the bedside. Osmotic diuresis: the importance of counting the number of osmoles excreted.* Clin Invest Med, 1995. **18**(5): p. 401-5.

18. Preisman, S., et al., *New monitors of intravascular volume: a comparison of arterial pressure waveform analysis and the intrathoracic blood volume.* Intensive Care Med, 1997. **23**(6): p. 651-7.
19. Singh, S., W.G. Kuschner, and G. Lighthall, *Perioperative intravascular fluid assessment and monitoring: a narrative review of established and emerging techniques.* Anesthesiol Res Pract, 2011. **2011**: p. 231493.
20. Della Rocca, G. and M.G. Costa, *Preload index and fluid responsiveness: different aspects of the new concept of functional hemodynamic monitoring.* Minerva Anestesiol, 2008. **74**(7-8): p. 349-51.
21. Hofer, C.K. and M. Cannesson, *Monitoring fluid responsiveness.* Acta Anaesthesiol Taiwan, 2011. **49**(2): p. 59-65.
22. Deflandre, E., V. Bonhomme, and P. Hans, *Delta down compared with delta pulse pressure as an indicator of volaemia during intracranial surgery.* British journal of anaesthesia, 2008. **100**(2): p. 245-50.
23. Michard, F., *Changes in arterial pressure during mechanical ventilation.* Anesthesiology, 2005. **103**(2): p. 419-28; quiz 449-5.
24. Feissel, M., et al., *Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock.* Chest, 2001. **119**(3): p. 867-73.
25. Levitov, A. and P.E. Marik, *Echocardiographic assessment of preload responsiveness in critically ill patients.* Cardiology research and practice, 2012. **2012**: p. 819696.

26. Charron, C., et al., *Echocardiographic measurement of fluid responsiveness.* Current opinion in critical care, 2006. **12**(3): p. 249-54.
27. Sarrafzadeh, A.S., et al., *Monitoring in Neurointensive Care - The Challenge to Detect Delayed Cerebral Ischemia in High-Grade Aneurysmal SAH.* Front Neurol, 2014. **5**: p. 134.
28. de Rooij, N.K., et al., *Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends.* J Neurol Neurosurg Psychiatry, 2007. **78**(12): p. 1365-72.
29. Ingall, T., et al., *A multinational comparison of subarachnoid hemorrhage epidemiology in the WHO MONICA stroke study.* Stroke, 2000. **31**(5): p. 1054-61.
30. Sherlock, M., et al., *The incidence and pathophysiology of hyponatraemia after subarachnoid haemorrhage.* Clin Endocrinol (Oxf), 2006. **64**(3): p. 250-4.
31. Audibert, G., et al., *Endocrine response after severe subarachnoid hemorrhage related to sodium and blood volume regulation.* Anesth Analg, 2009. **108**(6): p. 1922-8.
32. Palmer, B.F., *Hyponatremia in patients with central nervous system disease: SIADH versus CSW.* Trends Endocrinol Metab, 2003. **14**(4): p. 182-7.
33. Pereira, J.L., et al., *Pituitary deficiency after aneurysmal subarachnoid hemorrhage.* Clinics (Sao Paulo), 2013. **68**(6): p. 745-9.
34. Jeon, I.C., et al., *Cardiac troponin I elevation in patients with aneurysmal subarachnoid hemorrhage.* J Korean Neurosurg Soc, 2009. **46**(2): p. 99-102.

35. Berendes, E., et al., *Differential secretion of atrial and brain natriuretic peptide in critically ill patients.* Anesth Analg, 2001. **93**(3): p. 676-82.

36. Dorsch, N.W., *The effect and management of delayed vasospasm after aneurysmal subarachnoid hemorrhage.* Neurol Med Chir (Tokyo), 1998. **38 Suppl**: p. 156-60.

37. Findlay, J.M., J. Nisar, and T. Darsaut, *Cerebral Vasospasm: A Review.* Can J Neurol Sci, 2015: p. 1-18.

38. Rowland, M.J., et al., *Delayed cerebral ischaemia after subarachnoid haemorrhage: looking beyond vasospasm.* British journal of anaesthesia, 2012. **109**(3): p. 315-29.

39. Keyrouz, S.G. and M.N. Diringer, *Clinical review: Prevention and therapy of vasospasm in subarachnoid hemorrhage.* Crit Care, 2007. **11**(4): p. 220.

40. Stachura, K. and B. Danilewicz, *[Cerebral vasospasm after subarachnoid hemorrhage. Current possibilities of prevention and treatment].* Przegl Lek, 2002. **59**(1): p. 46-8.

41. Hunt, M.A. and A. Bhardwaj, *Caveats for triple-H therapy in the management of vasospasm after aneurysmal subarachnoid hemorrhage.* Crit Care Med, 2007. **35**(8): p. 1985-6.

42. Lee, K.H., T. Lukovits, and J.A. Friedman, *"Triple-H" therapy for cerebral vasospasm following subarachnoid hemorrhage.* Neurocrit Care, 2006. **4**(1): p. 68-76.

43. Rothberg, C., et al., *Responses to experimental subarachnoid hemorrhage in the spontaneously breathing primate.* J Neurosurg, 1980. **52**(3): p. 302-8.

44. de Rooij, N.K., et al., *Early prediction of delayed cerebral ischemia after subarachnoid hemorrhage: development and validation of a practical risk chart.* Stroke, 2013. **44**(5): p. 1288-94.

45. Kasuya, H., et al., *Bedside monitoring of circulating blood volume after subarachnoid hemorrhage.* Stroke, 2003. **34**(4): p. 956-60.

46. Hofer, C.K., et al., *Volumetric preload measurement by thermodilution: a comparison with transoesophageal echocardiography.* British journal of anaesthesia, 2005. **94**(6): p. 748-55.

47. Gan, H., et al., *Predicting fluid responsiveness in children: a systematic review.* Anesth Analg, 2013. **117**(6): p. 1380-92.

48. Sabatier, C., et al., *[Assessment of cardiovascular preload and response to volume expansion].* Med Intensiva, 2012. **36**(1): p. 45-55.

49. Lopes, M.R., J.O. Auler, Jr., and F. Michard, *Volume management in critically ill patients: New insights.* Clinics (Sao Paulo), 2006. **61**(4): p. 345-50.

50. Coudray, A., et al., *Fluid responsiveness in spontaneously breathing patients: a review of indexes used in intensive care.* Crit Care Med, 2005. **33**(12): p. 2757-62.

51. Diebel, L.N., et al., *End-diastolic volume. A better indicator of preload in the critically ill.* Arch Surg, 1992. **127**(7): p. 817-21; discussion 821-2.

52. Ishihara, H., et al., *Neither dynamic, static, nor volumetric variables can accurately predict fluid responsiveness early after abdominothoracic esophagectomy.* Perioper Med (Lond), 2013. **2**(1): p. 3.

53. Hu, B., et al., *Assessment effect of central venous pressure in fluid resuscitation in the patients with shock: a multi-center retrospective research.* Chin Med J (Engl), 2013. **126**(10): p. 1844-9.

54. Byon, H.J., et al., *Prediction of fluid responsiveness in mechanically ventilated children undergoing neurosurgery.* British journal of anaesthesia, 2013. **110**(4): p. 586-91.

55. Lakhal, K., et al., *Central venous pressure measurements improve the accuracy of leg raising-induced change in pulse pressure to predict fluid responsiveness.* Intensive Care Med, 2010. **36**(6): p. 940-8.

56. Weyland, A. and F. Grune, *[Cardiac preload and central venous pressure].* Anaesthesist, 2009. **58**(5): p. 506-12.

57. Calvin, J.E., A.A. Driedger, and W.J. Sibbald, *The hemodynamic effect of rapid fluid infusion in critically ill patients.* Surgery, 1981. **90**(1): p. 61-76.

58. Wagner, J.G. and J.W. Leatherman, *Right ventricular end-diastolic volume as a predictor of the hemodynamic response to a fluid challenge.* Chest, 1998. **113**(4): p. 1048-54.

59. Tousignant, C.P., F. Walsh, and C.D. Mazer, *The use of transesophageal echocardiography for preload assessment in critically ill patients.* Anesth Analg, 2000. **90**(2): p. 351-5.

60. van Lavieren, M., et al., *Dynamic preload indicators decrease when the abdomen is opened.* BMC Anesthesiol, 2014. **14**: p. 90.

61. Wilkman, E., et al., *Fluid responsiveness predicted by elevation of PEEP in patients with septic shock.* Acta Anaesthesiol Scand, 2014. **58**(1): p. 27-35.

62. Kim, S.H., 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**(1): p. 19-32.

63. Melot, J., et al., *[Use of indicators of fluid responsiveness in septic shock: a survey in public emergency departments].* Ann Fr Anesth Reanim, 2012. **31**(7-8): p. 583-90.
64. Nordstrom, L., *Haemodynamic effects of intermittent positive-pressure ventilation with and without an end-inspiratory pause.* Acta anaesthesiologica Scandinavica Supplementum, 1972. **47**: p. 29-56.
65. Beaussier, M., et al., *Determinants of systolic pressure variation in patients ventilated after vascular surgery.* J Cardiothorac Vasc Anesth, 1995. **9**(5): p. 547-51.
66. Charron, C., et al., *The influence of tidal volume on the dynamic variables of fluid responsiveness in critically ill patients.* Anesth Analg, 2006. **102**(5): p. 1511-7.
67. Hofer, C.K., et al., *Stroke volume and pulse pressure variation for prediction of fluid responsiveness in patients undergoing off-pump coronary artery bypass grafting.* Chest, 2005. **128**(2): p. 848-54.
68. Kutty, S., et al., *Systemic venous diameters, collapsibility indices, and right atrial measurements in normal pediatric subjects.* J Am Soc Echocardiogr, 2014. **27**(2): p. 155-62.
69. Belloni, L., et al., *Assessment of fluid-responsiveness parameters for off-pump coronary artery bypass surgery: a comparison among LiDCO, transesophageal echochardiography, and pulmonary artery catheter.* J Cardiothorac Vasc Anesth, 2008. **22**(2): p. 243-8.
70. Drvar, Z., et al., *[Stroke volume and pulse pressure variation are good predictors of fluid responsiveness in sepsis patients].* Acta Med Croatica, 2013. **67**(5): p. 407-14.

71. Huang, C.C., 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**(10): p. 2810-6.

72. Kim, S.H., et al., *Is stroke volume variation a useful preload index in liver transplant recipients? A retrospective analysis.* Int J Med Sci, 2013. **10**(6): p. 751-7.

73. Cannesson, M., et al., *Pleth variability index to monitor the respiratory variations in the pulse oximeter plethysmographic waveform amplitude and predict fluid responsiveness in the operating theatre.* British journal of anaesthesia, 2008. **101**(2): p. 200-6.

74. Chu, H., et al., *Accuracy of pleth variability index to predict fluid responsiveness in mechanically ventilated patients: a systematic review and meta-analysis.* J Clin Monit Comput, 2015.

75. Muller, L., et al., *An increase in aortic blood flow after an infusion of 100 ml colloid over 1 minute can predict fluid responsiveness: the mini-fluid challenge study.* Anesthesiology, 2011. **115**(3): p. 541-7.

76. Reuter, D.A., et al., *Usefulness of left ventricular stroke volume variation to assess fluid responsiveness in patients with reduced cardiac function.* Crit Care Med, 2003. **31**(5): p. 1399-404.

77. Sondergaard, S., *Pavane for a pulse pressure variation defunct.* Crit Care, 2013. **17**(6): p. 327.

78. Tran, H., et al., *Variation in blood pressure as a guide to volume loading in children following cardiopulmonary bypass.* J Clin Monit Comput, 2007. **21**(1): p. 1-6.

79. Vieillard-Baron, A., et al., *Influence of superior vena caval zone condition on cyclic changes in right ventricular outflow during respiratory support.* Anesthesiology, 2001. **95**(5): p. 1083-8.

80. Sandroni, C., et al., *Accuracy of plethysmographic indices as predictors of fluid responsiveness in mechanically ventilated adults: a systematic review and meta-analysis.* Intensive Care Med, 2012. **38**(9): p. 1429-37.

81. Forget, P., F. Lois, and M. de Kock, *Goal-directed fluid management based on the pulse oximeter-derived pleth variability index reduces lactate levels and improves fluid management.* Anesth Analg, 2010. **111**(4): p. 910-4.

82. Zimmermann, M., et al., *Accuracy of stroke volume variation compared with pleth variability index to predict fluid responsiveness in mechanically ventilated patients undergoing major surgery.* Eur J Anaesthesiol, 2010. **27**(6): p. 555-61.

83. Cecconi, M., et al., *Efficacy of functional hemodynamic parameters in predicting fluid responsiveness with pulse power analysis in surgical patients.* Minerva Anestesiol, 2012. **78**(5): p. 527-33.

84. Renner, J., et al., *Global end-diastolic volume during different loading conditions in a pediatric animal model.* Anesth Analg, 2007. **105**(5): p. 1243-9, table of contents.

85. Michard, F. and J.L. Teboul, *Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence.* Chest, 2002. **121**(6): p. 2000-8.

86. Jardin, F., *Cyclic changes in arterial pressure during mechanical ventilation.* Intensive care medicine, 2004. **30**(6): p. 1047-50.

87. Robotham, J.L., et al., *Ejection fraction revisited.* Anesthesiology, 1991. **74**(1): p. 172-83.

88. Pizov, R., Y. Ya'ari, and A. Perel, *The arterial pressure waveform during acute ventricular failure and synchronized external chest compression.* Anesth Analg, 1989. **68**(2): p. 150-6.

89. Coriat, P., et al., *A comparison of systolic blood pressure variations and echocardiographic estimates of end-diastolic left ventricular size in patients after aortic surgery.* Anesth Analg, 1994. **78**(1): p. 46-53.

90. Perel, A., *Assessing fluid responsiveness by the systolic pressure variation in mechanically ventilated patients. Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension.* Anesthesiology, 1998. **89**(6): p. 1309-10.

91. Tavernier, B., et al., *Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension.* Anesthesiology, 1998. **89**(6): p. 1313-21.

92. Slama, M., et al., *Respiratory variations of aortic VTI: a new index of hypovolemia and fluid responsiveness.* American journal of physiology Heart and circulatory physiology, 2002. **283**(4): p. H1729-33.

93. Caille, V., et al., *Hemodynamic effects of passive leg raising: an echocardiographic study in patients with shock.* Intensive Care Med, 2008. **34**(7): p. 1239-45.

94. Marik, P.E., et al., *Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature.* Crit Care Med, 2009. **37**(9): p. 2642-7.

95. Solus-Biguenet, H., et al., *Non-invasive prediction of fluid responsiveness during major hepatic surgery.* British journal of anaesthesia, 2006. **97**(6): p. 808-16.

96. Wu, Y., et al., *A 10-second fluid challenge guided by transthoracic echocardiography can predict fluid responsiveness.* Crit Care, 2014. **18**(3): p. R108.

97. Zhang, Z., et al., *Changes in brain natriuretic peptide are correlated with changes in global end-diastolic volume index.* J Thorac Dis, 2013. **5**(2): p. 156-60.

98. Gruenewald, M., et al., *Dynamic and volumetric variables of fluid responsiveness fail during immediate postresuscitation period.* Critical care medicine, 2011. **39**(8): p. 1953-9.

99. Monnet, X., et al., *Measuring aortic diameter improves accuracy of esophageal Doppler in assessing fluid responsiveness.* Critical care medicine, 2007. **35**(2): p. 477-82.

100. Poelaert, J. and C. Roosens, *Echocardiography and assessing fluid responsiveness: acoustic quantification again into the picture?* Critical care (London, England), 2007. **11**(1): p. 105.

101. Wiesenack, C., et al., *Assessment of fluid responsiveness in mechanically ventilated cardiac surgical patients.* European journal of anaesthesiology, 2005. **22**(9): p. 658-65.

102. Choi, D.Y., et al., *Respiratory variation in aortic blood flow velocity as a predictor of fluid responsiveness in children after repair of ventricular septal defect.* Pediatr Cardiol, 2010. **31**(8): p. 1166-70.

103. Durand, P., et al., *Respiratory variations in aortic blood flow predict fluid responsiveness in ventilated children.* Intensive Care Med, 2008. **34**(5): p. 888-94.

104. Poelaert, J.I., et al., *Evaluation of transesophageal echocardiography as a diagnostic and therapeutic aid in a critical care setting.* Chest, 1995. **107**(3): p. 774-9.

105. Corte-Real, H. and C. Franca, *[The transoesophageal echocardiography in the general intensive care: its utility in the ventilated critically ill patient].* Acta Med Port, 2011. **24 Suppl 4**: p. 747-54.

106. Poelaert, J., C. Schmidt, and F. Colardyn, *Transoesophageal echocardiography in the critically ill.* Anaesthesia, 1998. **53**(1): p. 55-68.

107. Poelaert, J., et al., *Transoesophageal echocardiography in critically ill patients. A comprehensive approach.* Eur J Anaesthesiol, 1997. **14**(4): p. 350-8.

108. D'Souza, S., *Aneurysmal Subarachnoid Hemorrhage.* J Neurosurg Anesthesiol, 2015. **27**(3): p. 222-40.

109. Iijima, T., et al., *The maintenance and monitoring of perioperative blood volume.* Perioper Med (Lond), 2013. **2**(1): p. 9.

110. Lagares, A., et al., *[Idiopathic subarachnoid hemorrhage; comparison of different bleeding patterns and long-term outcome].* Neurocirugia (Astur), 2002. **13**(2): p. 110-9.

# ANNEXURE

# Technical Advisory Committee (Clinical Studies)

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
THIRUVANANTHAPURAM – 695011, INDIA

**TAC Registration No: SCT-/S/2013/204** **Date:20.01.2014**

**Project title:** Comparison of Delta Down, Superior Vena Cava Collapisibilty Index and Aortic Velocity Time Integral(VTI)Ao variability as predictors of fluid responsiveness in patients with SAH.

| |
|---|
| Principal Investigator: |
| Name: Dr. Ajay Prasad Hrishi .P Degree: MBBS, MD( Anaesthesiology),DNB (Anaesthesiology) DM Neuroanesthesia Resident, Department of Anaesthesiology, SCTIMST |
| Co-Principal Investigator(s) |
| (1)Name : Dr.Manikandan.S Degree: MBBS, MD(Anesthesiology), PDCC (Neuro anaesthesiology) Additional professor, Department of Anaesthesiology, Neuroanaesthesiology division, SCTIMST |
| (2) Name : Dr. Girish Menon.R Degree: MBBS,MCh (Neurosurgery) Professor, Department of Neurosurgery, SCTIMST |

**Members who participated in the TAC meeting on 4/01/2014**

Dr. Sanjeev V Thomas (Chairman)

Dr. Asha Kishore

Dr. Lissy K Krishnan

Dr. Thomas Koshy

Dr. Krishnamoorthy.K.M

Dr. Biju Soman

Dr. Easwer. H.V

Dr. K. Shivakumar (Member Secretary)

**Risk Classification of the project (Minimum/ Moderate/ High):** Minimum

**Requirement of DSMB:** No

**Recommended members of DSMB:** Not applicable

**Recommendations of TAC:**
Recommended for consideration of IEC in the light of the responses received from the investigator.

The PI may note that there can be no additions / alterations in the documents approved by TAC when they are submitted to the IEC.

**Signature of the Member Secretary, TAC (Clinical Studies)**

**Note for IEC**

Copy of the investigator's responses to questions/suggestions from TAC is attached (Appendix-1).

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान
तिरुवनन्तपुरम - 695 011, केरल, भारत
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
THIRUVANANTHAPURAM - 695 011, INDIA
(An Institute of National importance under Govt. of India)

**Institutional Ethics Committee (IEC)**
**(IEC Regn No. ECR/189/Inst/KL/2013)**

SCT / IEC- 559 / FEBRUARY-2014 03-03-2014

Dr. Ajay Prasad Hrishi. P
Resident
Department of Anesthesiology
SCTIMST.

Dear Dr. Ajay Prasad Hrishi,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study titled "COMPARISON OF DELTA DOWN, SUPERIOR VENA CAVA COLLAPISIBILTY INDEX AND AORTIC VELOCITY TIME INTEGRAL (VTI) AO VARIABILITY AS PREDICTORS OF FLUID RESPONSIVENESS IN PATIENTS WITH SAH. (IEC-559)" on 14th February, 2014.

**The following documents were reviewed:**

1. *Covering letter dated 22.01.2014 addressed to the Chairperson, IEC, SCTIMST.*
2. *Technical Advisory Committee's Approval Letter.*
3. *TAC Application form.*
4. *IEC Application form .*
5. *Project proposal.*

**IEC Decision**

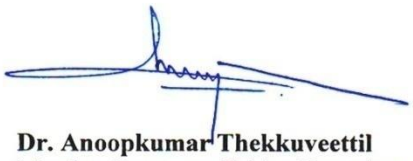
Approved the conduct of the study in the present form.

**Remarks:**

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Yours Sincerely



**Dr. Anoopkumar Thekkuveettil**
Member Secretary, Ethics Committee.

# CONSENT FORM

**Title of the study:**

Comparison of Delta Down, Superior Vena Cava Collapsibility Index and Aortic Velocity Time Integral(VTI) Ao variability as predictors of fluid responsiveness in patients with SAH**.**

**Name of the Investigators:**

Dr Ajay Prasad Hrishi.P ,Dr.Manikandan.S, Dr Girish Menon .R.

You are being requested to participate in this study which compares different parameters which detect hemodynamic changes in response to fluid therapy. This study will require placement of invasive arterial cannula and use of Transesophageal echocardiography .Both these tools are used routinely as part of Anaesthesia in this institute and worldwide. We have planned to include about 30 people from this hospital in this study.

**What is TEE?**

TEE is an ultrasound of your heart. During TEE an ultrasound probe is inserted through your mouth into the oesophagus. Ultrasound shows the structure and functions of the heart muscles and valves from different angles. This tool has been used all over the world in neurosurgical patients undergoing major surgeries and found to be safe.

**What is invasive arterial BP?**

Invasive arterial BP is the monitoring of blood pressure of the patient after placing an arterial cannula in the peripheral artery of your hand/leg. This method of BP monitoring is a part of standard anaesthesia monitoring and has been used all over the world in neurosurgical patients and found to be safe.

**If you take part what will you have to do?**

On the day of surgery you will be taken inside the Operation Theatre. Monitors to check your heart beat, blood pressure and oxygen saturation level will be attached. A small venous will be inserted under local anaesthesia in the hand for fluid and drug administration.

Arterial cannula also will be inserted under local anaesthesia for monitoring the blood pressure. General Anaesthesia will be induced as per the routine anaesthesia practice in the hospital. After the patient is fully sedated, and paralyzed and connected to ventilator, a TEE probe will be inserted through the mouth into the oesophagus. After this the parameters to be studied are recorded. Following this IV fluid bolus as per the study requirement will be given to the patient and again the parameters are recorded. After recording the parameters the surgery continues as planned by the neurosurgical team. Both the tools will be used to monitor the hemodynamic changes throughout the surgery as per routine. At the end of surgery TEE probe will be removed. Arterial line will be retained for post operative monitoring in ICU.

**What is IV fluid bolus?**

I V fluids are routinely used intraoperatively to maintain the hemodynamics intraoperatively . In this study a measured amount of i.v fluid (15ml/kg) is given over a period of 30 minutes to study its effect on the patient's hemodynamics.

Does IV fluid Bolus have adverse effects?

Majority of patients will not have any side effects as the bolus is given under controlled conditions under anaesthesia. Reported side effects are mainly worsening of the existing cardiac failure, flooding of the lung tissue by the fluid.

**Does TEE use have any side effects?**

The majority of people have not had any side effects. The reported side effects are sore throat and numbness of throat when used in awake patients but the incidence of this complication in our study will be remote as the patient is in general anaesthesia. Other reported complications are very rare and include injuries to teeth, oesophagus. Oesophageal intubation can induce vagal and sympathetic reflexes such as hypertension or hypotension, tachy arrhythmias or bradycardia.These complications are very rare in patients under general anaesthesia as they are in deep sedation and paralysed and anaesthesia mostly blunts the hemodynamic effects of TEE.Futhermore the patients with risk of getting injured are excluded by the exclusion criteria.

**Does invasive arterial line use have any side effects?**

The majority of people have not had side effects. The reported side effects are haemorrhage, infection, vascular insufficiency, ischemia, thrombosis, embolization, and neuronal or adjacent structure injury. These are very rare complications and are prevented by preoperative testing for good collateral circulation and avoiding long term cannulation.

**Can you withdraw from this study after it starts?**

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way. In addition, if you experience any side effects, the study will be stopped and you will be given additional treatment.

**What will happen if you develop any study related injury?**

We do not expect any injury to happen to you since the anaesthesia technique and monitoring tools would be same even if you were not part of the study. But if you do develop any side effects or problems due to the study, these will be treated at no cost to you. We are unable to provide any monetary compensation, however.

**Will you have to pay for the cost of using the devices?**

Arterial BP monitoring and TEE are used as a part of routine anaesthesia procedures for surgery. Any extra charge for monitoring purpose will be borne by the Principal Investigator.

**What happens after the study is over?**

Arterial BP, Transesophageal Echocardiography is a routinely used tool for monitoring heart and circulation during major neurosurgery. After the study is over the same tools will be used to monitor hemodynamics throughout the length of the surgery. After surgery is over the TEE probe will be removed before shifting the patient to ICU

**Will your personal details be kept confidential?**

The results of this study will be used for thesis submission as a part of academic research and will be submitted to a medical journal for publication, but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask Dr Ajay Prasad Hrishi.P (Principal investigator) mobile number: 9495239765. Email: drajayprasadhrishi@sctimst.ac.in

**Inclusion /exclusion criteria to be part of this study**

| **Factors** | **Include** | **Exclude** | **Factors** | **Include** | **Exclude** |
|---|---|---|---|---|---|
| Patient consent | Yes | No | Abnormal blood clotting problem | No | Yes |
| Nature of procedure | Elective | Emergency | | | |
| Age | 18-60 | < 18, >60 | Presence of oesophageal pathologies (oesophageal mass , stricture , tracheo-esophageal fistula , oesophageal varices,peptic ulcer, scleroderma) | No | Yes |
| Pre OP ECG normal | Yes | No | | | |
| Pre OP Echocardiography | Yes | No | | | |
| h/cardiac Pathologies (valvular heart disease, intracardiac shunts, peripheral vascular disease) or | No | Yes | History of active upper GI bleed/recent upper GI bleed. | No | Yes |
| Pre op Heart rate | > 50 | < 50 | History of previous oesophageal/upper GI surgery | No | Yes |
| h/o Lung Pathologies (like asthma, COPD and tuberculosis) pathologies | No | Yes | | | |
| Uncontrolled hypertension | No | Yes | | | |
| Presently Pregnant. | No | Yes | | | |
| | | | Supine position intraoperatively | Yes | No |

**Participant's name:** **Date of Birth / Age (in years)**:

I_____, son/daughter of _____

Declare that (Please tick boxes)

- I have read the above information provided to me regarding the study: A study on the ***Comparison of Delta Down, Superior Vena Cava Collapsibility Index and Velocity Time Integral(VTI) Ao variability as predictors of fluid responsiveness in patients with SAH*** **[ ]**
- I have clarified any doubts that I had. [ ]
- I also understand that my participation in this study is entirely voluntary And that I am free to withdraw permission to continue to participate at Any time without affecting my usual treatment or my legal rights [ ]
- I understand that the study staff and institutional ethics committee Members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access [ ]
- I understand that my identity will not be revealed in any information released to third parties or published [ ]
- I voluntarily agree to take part in this study [ ]
- I have been provided with the contact numbers of the principle investigator, in case I want to know more about the study and participants rights [ ].
- I received a copy of this signed consent form [ ]

Name: Name of witness:
Signature: Signature:

Date:

**Person Obtaining Consent**

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

Name:

Signature: Date:

# Comparison of Delta Down(DD), Superior Vena Cava Collapsibility Index(SVCCI) and Aortic Velocity Time Integral(VTI Ao) variability as predictors of fluid responsiveness in patients with SAH.

**PROFORMA :** **serial number :** **/ 30**

Group : 1/ 2

Name : Weight: Diagnosis :

Age : Height: Proposed surgery :

Sex: Date of surgery :

I.P number : Aneuyrsm/Tumor site :

**Check list :**

| Factors | Include | Exclude | Factors | Include | Exclude |
|---|---|---|---|---|---|
| Patient consent | Yes | No | Abnormal coagulation profile. | No | Yes |
| Nature of procedure | Elective | Emergency | | | |
| Age | 18-60 | < 18, >60 | Presence of esophageal pathologies ( esophageal mass , stricture , tracheo-esophageal fistula , esophageal varices,peptic ulcer,scleroderma) . | No | Yes |
| Sinus Rhythm | Yes | No | | | |
| Pre OP Echocardiography | Yes | No | | | |
| Cardiac Pathologies (valvular heart disease, intracardiac shunts, peripheral vascular disease) or | No | Yes | History of active upper GI bleed/recent upper GI bleed. | No | Yes |
| Pre op Heart rate | > 50 | < 50 | History of previous esophageal/upper GI surgery | No | Yes |
| Lung Pathologies (like asthma, COPD and tuberculosis) pathologies | No | Yes | | | |
| Systemic HT stage III & above | No | Yes | | | |
| Heart block | No | Yes | | | |
| Pregnancy , Nursing | No | Yes | | | |
| | | | Supine position intraoperatively | Yes | No |

**Baseline Parameters**

| Parameters | Temp(*C) | Etsevo | EtCo2 | HR | PIP | SBP(Apneic) | SBP(max) | SBP (Min) | SVC diameter | LVOT Diameter | Aortic VTI (max,min) | SV | CO | CI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Values** | | | | | | | | | | | | | | |

Patient weight : Kg IV fluid dose : Infusion started time : Infusion completed time :

**Post Fluid Loading Parameters**

| Parameters | Temp(*C) | Etsevo | EtCo2 | HR(bpm) | PIP | SBP(Apneic) | SBP(max) | SBP (Min) | SVC diameter | LVOT Diameter | Aortic VTI | SV | CO | CI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Values** | | | | | | | | | | | | | | |

| Adverse events | Treatment | Further Intervention |
|---|---|---|
| Sore throat | | |
| Arrthymias | | |
| Esophageal injury | | |
| Others | | |

**Name & Signature of Investigator :**

# MASTER CHART

# KEY TO MASTER CHART

BMI-BODY MASS INDEX

BSA-BODY SURFACE AREA

HR-HEART RATE

SBP-SYSTOLIC BLOOD PRESSURE

EtCO2-END TIDAL CARBON DIOXIDE

EtSevo-END TIDAL SEVOFLURANE

TEMP-TEMPERATURE

PIP-PEAK INSPIRATORY PRESSSURE

DD-DELTA DOWN

SVC-SUPERIOR VENA CAVA

VTI-Aortic VELOCITY TIME INTEGRAL

VTIAoV-AORTIC VTI VARIATION

VA-VALVE AREA

VA-VALVE AREA

SV-STROKE VOLUME

CO-CARDIAC OUTPUT

CI-CARDIAC INDEX

PL-POST LOADING

MIN-MINIMUM

Max-MAXIMUM

Avg-AVERAGE

CIV-CARDIAC INDEX VARIATION

# MASTER CHART

| | NO | Age (yrs) | Sex | Height | Weight(Kg) | BMI (kg/m2) | BSA (m2) | HR (bpm) | SBP (mm Hg) | EtCo2 (mm Hg) | EtSevo (mm Hg) | Temp (°C) | PIP (cm H20) | DD (mm Hg) | SVC Max (mm) | SVC min (mm) | SVC CI (%) | VTI max (cm) | VTI min (cm) | VTI Avg (cm) | VTIAoV (%) | VA (cm) | SV Avg (ml) | CO (L) | CI (L/min/m2) | HR-PL | SBP -PL | DD-PL | SVC (Max)-PL | SVC (min)-PL | SVC CI-PL | VTI max-PL | VTI min-PL | VTI Avg-PL | VTIAoV-PL | SV Avg-PL | CO-PL | CI-PL | CIV(%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tumor | 1 | 45 | M | 175 | 68 | 22.204082 | 1.82 | 61 | 122 | 36 | 1.66 | 36.8 | 18 | 3 | 13 | 10 | 23.076923 | 24.2 | 22.2 | 23.2 | 8.6206897 | 3.9 | 90.48 | 5.51928 | 3.0325714 | 62 | 130 | 2 | 13 | 12 | 7.6923077 | 26.1 | 24.9 | 25.5 | 4.7058824 | 99.45 | 6.1659 | 3.3878571 | 11.715659 |
| Tumor | 2 | 54 | F | 166 | 61 | 22.13674 | 1.68 | 77 | 113 | 37 | 1.77 | 36.1 | 14 | 9 | 11 | 5 | 54.545455 | 22.8 | 18.2 | 20.5 | 22.439024 | 2.7 | 55.35 | 4.26195 | 2.536875 | 78 | 118 | 5 | 14 | 11 | 21.428571 | 25.1 | 22.8 | 23.95 | 9.6033403 | 64.665 | 5.04387 | 3.0023036 | 18.346532 |
| Tumor | 3 | 37 | M | 180 | 76 | 23.45679 | 1.95 | 81 | 107 | 32 | 1.52 | 36.3 | 16 | 7 | 15 | 8 | 46.666667 | 21.3 | 17 | 19.15 | 22.454308 | 3.2 | 61.28 | 4.96368 | 2.5454769 | 79 | 121 | 4 | 16 | 12 | 25 | 23.7 | 22.1 | 22.9 | 6.9868996 | 73.28 | 5.78912 | 2.9687795 | 16.629597 |
| Tumor | 4 | 32 | M | 169 | 71 | 24.859074 | 1.83 | 69 | 130 | 36 | 1.62 | 35.9 | 15 | 6 | 10 | 6 | 40 | 20.3 | 18.1 | 19.2 | 11.458333 | 4.1 | 78.72 | 5.43168 | 2.9681311 | 67 | 125 | 4 | 13 | 10 | 23.076923 | 23.9 | 21.8 | 22.85 | 9.190372 | 93.685 | 6.276895 | 3.4299973 | 15.560839 |
| Tumor | 5 | 34 | F | 153 | 57 | 24.349609 | 1.56 | 74 | 119 | 39 | 1.48 | 36.1 | 18 | 8 | 12 | 5 | 58.333333 | 22.2 | 17.8 | 20 | 22 | 3 | 60 | 4.44 | 2.8461538 | 72 | 138 | 3 | 15 | 10 | 33.333333 | 24.8 | 23.9 | 24.35 | 3.6960986 | 73.05 | 5.2596 | 3.3715385 | 18.459459 |
| Tumor | 6 | 45 | F | 160 | 54 | 21.09375 | 1.55 | 79 | 103 | 38 | 1.71 | 36.5 | 19 | 8 | 16 | 5 | 68.75 | 20.1 | 16 | 18.05 | 22.714681 | 2.9 | 52.345 | 4.135255 | 2.6679065 | 75 | 119 | 5 | 16 | 10 | 37.5 | 24.6 | 23.1 | 23.85 | 6.2893082 | 69.165 | 5.187375 | 3.3466935 | 25.442687 |
| Tumor | 7 | 59 | M | 174 | 66 | 21.799445 | 1.79 | 65 | 138 | 41 | 1.66 | 36.2 | 13 | 6 | 13 | 8 | 38.461538 | 21.1 | 17 | 19.05 | 21.52231 | 3.6 | 68.58 | 4.4577 | 2.4903352 | 64 | 142 | 2 | 15 | 10 | 33.333333 | 23.2 | 22.8 | 23 | 1.7391304 | 82.8 | 5.2992 | 2.9604469 | 18.877448 |
| Tumor | 8 | 42 | F | 164 | 56 | 20.82094 | 1.6 | 63 | 125 | 35 | 1.53 | 36 | 15 | 1 | 14 | 10 | 28.571429 | 20.6 | 17.4 | 19 | 16.842105 | 3.9 | 74.1 | 4.6683 | 2.9176875 | 64 | 115 | 2 | 15 | 13 | 13.333333 | 21.4 | 19.3 | 20.35 | 10.31941 | 79.365 | 5.07936 | 3.1746 | 8.8053467 |
| Tumor | 9 | 30 | M | 182 | 80 | 24.151673 | 2.01 | 84 | 128 | 38 | 1.67 | 36.1 | 16 | 7 | 17 | 8 | 52.941176 | 19.1 | 15.2 | 17.15 | 22.740525 | 2.8 | 48.02 | 4.03368 | 2.006806 | 80 | 130 | 4 | 18 | 13 | 27.777778 | 23.9 | 21.1 | 22.5 | 12.444444 | 63 | 5.04 | 2.5074627 | 24.947938 |
| Tumor | 10 | 46 | M | 177 | 70 | 22.343516 | 1.86 | 66 | 100 | 33 | 1.75 | 35.8 | 14 | 6 | 15 | 10 | 33.333333 | 20.9 | 17.8 | 19.35 | 16.020672 | 2.5 | 48.375 | 3.19275 | 1.7165323 | 61 | 110 | 3 | 17 | 12 | 29.411765 | 22.9 | 21.8 | 22.35 | 4.9217002 | 55.875 | 3.408375 | 1.8324597 | 6.7535823 |
| Tumor | 11 | 37 | F | 151 | 60 | 26.314635 | 1.59 | 91 | 102 | 35 | 1.78 | 35.2 | 18 | 10 | 18 | 3 | 83.333333 | 18.2 | 14.3 | 16.25 | 24 | 3.4 | 55.25 | 5.02775 | 3.1621069 | 80 | 130 | 3 | 18 | 14 | 22.222222 | 24.4 | 23.3 | 23.85 | 4.6121593 | 81.09 | 6.4872 | 4.08 | 29.027895 |
| Tumor | 12 | 55 | M | 172 | 80 | 27.041644 | 1.96 | 70 | 110 | 38 | 1.65 | 35.9 | 15 | 7 | 8 | 1 | 87.5 | 19.7 | 15.3 | 17.5 | 25.142857 | 3.7 | 64.75 | 4.5325 | 2.3125 | 69 | 127 | 6 | 11 | 7 | 36.363636 | 25.2 | 24.3 | 24.75 | 3.6363636 | 91.575 | 6.318675 | 3.2238138 | 39.408163 |
| Tumor | 13 | 53 | F | 168 | 65 | 23.030045 | 1.74 | 84 | 114 | 34 | 1.62 | 36.4 | 17 | 9 | 10 | 4 | 60 | 22.1 | 17.6 | 19.85 | 22.670025 | 3 | 59.55 | 5.0022 | 2.8748276 | 87 | 122 | 5 | 12 | 9 | 25 | 24.3 | 23.7 | 24 | 2.5 | 72 | 6.264 | 3.6 | 25.224901 |
| Tumor | 14 | 48 | F | 158 | 63 | 25.23634 | 1.66 | 80 | 120 | 36 | 1.7 | 36.2 | 20 | 3 | 9 | 6 | 33.333333 | 23 | 19.7 | 21.35 | 15.456674 | 3.2 | 68.32 | 5.4656 | 3.2925301 | 79 | 134 | 2 | 13 | 11 | 15.384615 | 24.6 | 23.1 | 23.85 | 6.2893082 | 76.32 | 6.02928 | 3.6320964 | 10.313232 |
| Tumor | 15 | 51 | M | 171 | 67 | 22.913033 | 1.78 | 71 | 118 | 41 | 1.52 | 36 | 22 | 6 | 11 | 7 | 36.363636 | 22.4 | 19.2 | 20.8 | 15.384615 | 2.9 | 60.32 | 4.28272 | 2.4060225 | 68 | 140 | 1 | 13 | 9 | 30.769231 | 23.5 | 22.3 | 22.9 | 5.2401747 | 66.41 | 4.51588 | 2.5370112 | 5.4442037 |
| Anuerysm | 1 | 54 | M | 173 | 72 | 24.056935 | 1.7 | 92 | 150 | 40 | 1.58 | 36.5 | 16 | 14 | 10 | 2 | 80 | 19.9 | 15.2 | 17.55 | 26.780627 | 3 | 52.65 | 4.8438 | 2.8492941 | 90 | 132 | 4 | 18 | 12 | 33.333333 | 25.4 | 23.9 | 24.65 | 6.0851927 | 73.95 | 6.6555 | 3.915 | 37.402453 |
| Anuerysm | 2 | 39 | F | 158 | 66 | 26.438071 | 1.7 | 88 | 144 | 34 | 1.65 | 36.1 | 15 | 5 | 9 | 3 | 66.666667 | 21.1 | 17 | 19.05 | 21.52231 | 2.8 | 53.34 | 4.69392 | 2.7611294 | 87 | 125 | 1 | 10 | 8 | 20 | 24.1 | 22.9 | 23.5 | 5.106383 | 65.8 | 5.7246 | 3.3674118 | 21.957767 |
| Anuerysm | 3 | 53 | F | 152 | 57 | 24.671053 | 1.57 | 84 | 139 | 36 | 1.71 | 36.8 | 17 | 8 | 11 | 5 | 54.545455 | 21.5 | 17.2 | 19.35 | 22.222222 | 3.3 | 63.855 | 5.36382 | 3.4164459 | 83 | 130 | 5 | 14 | 11 | 21.428571 | 24.6 | 23.7 | 24.15 | 3.7267081 | 79.695 | 6.614685 | 4.2131752 | 23.320413 |
| Anuerysm | 4 | 49 | F | 165 | 78 | 28.650138 | 1.93 | 90 | 128 | 39 | 1.66 | 36 | 14 | 6 | 12 | 5 | 58.333333 | 21.2 | 17.3 | 19.25 | 20.25974 | 2.4 | 46.2 | 4.158 | 2.1544041 | 90 | 135 | 1 | 17 | 13 | 23.529412 | 22.4 | 21 | 23.1 | 6.0606061 | 55.44 | 4.9896 | 2.585285 | 20 |
| Anuerysm | 5 | 39 | M | 176 | 72 | 23.243802 | 1.88 | 96 | 144 | 35 | 1.65 | 35.7 | 18 | 9 | 11 | 4 | 63.636364 | 20.4 | 15.8 | 18.1 | 25.414365 | 4.1 | 74.21 | 7.12416 | 3.7894468 | 88 | 124 | 6 | 13 | 8 | 38.461538 | 24.1 | 22.3 | 23.2 | 7.7586207 | 95.12 | 8.37056 | 4.4524255 | 17.495396 |
| Anuerysm | 6 | 55 | M | 169 | 64 | 22.408179 | 1.73 | 79 | 140 | 38 | 1.59 | 36.2 | 15 | 12 | 8 | 1 | 87.5 | 19.3 | 14.9 | 17.1 | 25.730994 | 3.9 | 66.69 | 5.26851 | 3.0453815 | 74 | 138 | 5 | 15 | 10 | 33.333333 | 22.8 | 20.7 | 21.75 | 9.6551724 | 84.825 | 6.27705 | 3.6283526 | 19.142794 |
| Anuerysm | 7 | 34 | F | 150 | 52 | 23.111111 | 1.47 | 81 | 139 | 35 | 1.6 | 36.5 | 14 | 10 | 8 | 2 | 75 | 21.1 | 16.2 | 18.65 | 26.273458 | 3.4 | 63.41 | 5.13621 | 3.4940204 | 80 | 122 | 4 | 18 | 14 | 22.222222 | 25 | 21.6 | 23.3 | 14.592275 | 79.22 | 6.3376 | 4.3112925 | 23.390593 |
| Anuerysm | 8 | 39 | M | 181 | 90 | 27.471689 | 2.13 | 77 | 130 | 32 | 1.57 | 35.6 | 19 | 4 | 9 | 6 | 33.333333 | 23.2 | 19.1 | 21.15 | 19.385343 | 2.9 | 61.335 | 4.722795 | 2.2172746 | 74 | 140 | 3 | 15 | 11 | 26.666667 | 24.9 | 23.8 | 24.35 | 4.5174538 | 70.615 | 5.22551 | 2.4532911 | 10.644438 |
| Anuerysm | 9 | 57 | F | 163 | 67 | 25.217359 | 1.74 | 87 | 150 | 37 | 1.5 | 36.3 | 16 | 13 | 11 | 4 | 63.636364 | 21.1 | 16 | 18.55 | 27.493261 | 3 | 55.65 | 4.84155 | 2.7825 | 92 | 133 | 6 | 14 | 8 | 42.857143 | 25.62 | 22.1 | 23.86 | 14.752724 | 71.58 | 6.58536 | 3.7846897 | 36.017598 |
| Anuerysm | 10 | 48 | F | 174 | 70 | 23.120624 | 1.84 | 99 | 147 | 36 | 1.7 | 35.2 | 17 | 6 | 9 | 5 | 44.444444 | 23.6 | 21 | 22.3 | 11.659193 | 3.2 | 68.32 | 6.76368 | 3.675913 | 97 | 130 | 5 | 14 | 9 | 35.714286 | 25.1 | 23.2 | 24.15 | 7.8674948 | 77.28 | 7.49616 | 4.074 | 10.829608 |
| Anuerysm | 11 | 38 | M | 159 | 55 | 21.755469 | 1.56 | 86 | 109 | 38 | 1.72 | 36.3 | 15 | 8 | 10 | 1 | 90 | 19.9 | 15.1 | 17.5 | 27.428571 | 2.8 | 49 | 4.214 | 2.7012821 | 85 | 119 | 3 | 12 | 9 | 25 | 23.5 | 21.4 | 22.45 | 9.3541203 | 62.86 | 5.3431 | 3.4250641 | 26.79402 |
| Anuerysm | 12 | 47 | M | 166 | 67 | 24.314124 | 1.76 | 106 | 145 | 35 | 1.64 | 35.9 | 16 | 9 | 12 | 6 | 50 | 21 | 16.1 | 18.55 | 26.415094 | 3.5 | 64.925 | 6.88205 | 3.9102557 | 104 | 123 | 1 | 16 | 13 | 18.75 | 24.2 | 21.6 | 23.9 | 10.878661 | 83.65 | 8.6996 | 4.9429545 | 26.410009 |
| Anuerysm | 13 | 32 | F | 170 | 61 | 21.107266 | 1.7 | 85 | 140 | 40 | 1.68 | 36.2 | 18 | 3 | 13 | 9 | 30.769231 | 24.2 | 22.1 | 23.15 | 9.0712743 | 3.2 | 70.4 | 5.984 | 3.52 | 82 | 135 | 1 | 18 | 16 | 11.111111 | 26.1 | 25.7 | 25.9 | 1.5444015 | 82.88 | 6.79616 | 3.9977412 | 13.572193 |
| Anuerysm | 14 | 43 | F | 155 | 60 | 24.973985 | 1.61 | 101 | 132 | 38 | 1.74 | 36.5 | 20 | 14 | 11 | 3 | 72.727273 | 23 | 17.7 | 20.35 | 26.044226 | 4.2 | 85.47 | 8.63247 | 5.3617826 | 99 | 130 | 3 | 15 | 11 | 26.666667 | 25.9 | 24.7 | 25.3 | 4.743083 | 106.26 | 10.51974 | 6.534 | 21.862457 |
| Anuerysm | 15 | 50 | F | 161 | 51 | 19.675167 | 1.51 | 67 | 129 | 36 | 1.79 | 35.6 | 17 | 6 | 13 | 8 | 38.461538 | 20.9 | 16.5 | 18.7 | 23.529412 | 3.6 | 67.32 | 4.51044 | 2.9870464 | 64 | 140 | 2 | 15 | 10 | 33.333333 | 23.2 | 21.9 | 22.55 | 5.7649667 | 81.18 | 5.19552 | 3.4407417 | 15.188762 |

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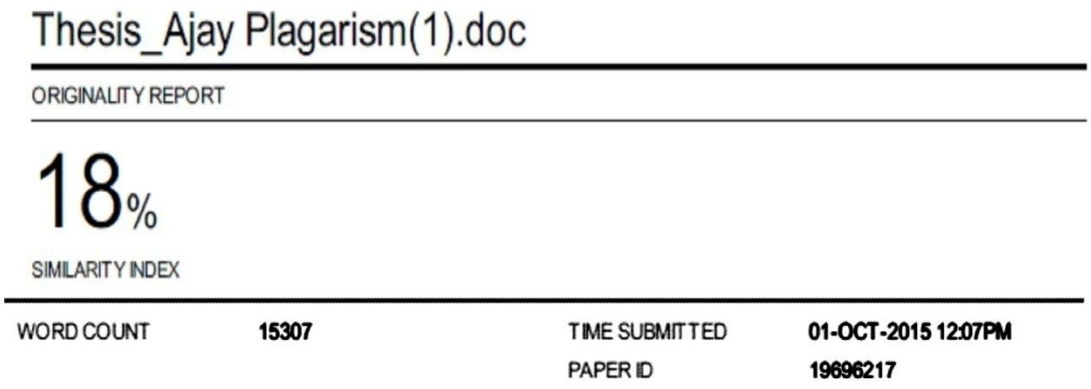
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