
SREE CHITRA TIRUNAL INSTITUTE FOR
MEDICAL SCIENCES & TECHNOLOGY
TRIVANDRUM

CORRELATION OF SYSTOLIC PRESSURE VARIATION, PULSE PRESSURE VARIATION AND STROKE VOLUME VARIATION IN DIFFERENT PRELOAD CONDITIONS FOLLOWING A SINGLE DOSE MANNITOL INFUSION IN ELECTIVE NEUROSURGICAL PATIENTS

Dissertation submitted for the partial fulfillment of the requirement for the degree of DM (Neuroanaesthesiology)

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DEPARTMENT OF ANAESTHESIOLOGY

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM, KERALA, 695011INDIA

DECLARATION

I hereby declare that this thesis entitled**"Correlation of systolic pressure variation, pulse pressure variation and stroke volume variation in different preload conditions following a single dose mannitol infusion in elective neurosurgical patients",** has been prepared by me under the capable supervision and guidance of Dr Manikandan S, Additional Professor, Department of Anesthesiology, SreeChitraTirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

Date:

Place: Thiruvananthapuram

Dr Arimanickam G

DM NeuroanesthesiaResident,

Department of Anesthesiology,

SCTIMST, Thiruvananthapuram.

CERTIFICATE

This is to certify that this thesis entitled**"Correlation of systolic pressure variation, pulse pressure variation and stroke volume variation in different preload conditions following a single dose mannitol infusion in elective neurosurgical patients",** is a bonafide work ofDrArimanickam G, DM Neuroanesthesia Resident, and has been done under my guidance and supervision at SreeChitraTirunal Institute for Medical Sciences & Technology, Thiruvananthapuram. He has shown keen interest in preparing this project.

Date

Place: Thiruvananthapuram

DrManikandan SMD., PDCC,
Additional Professor,
Department of Anesthesiology,
SCTIMST, Thiruvananthapuram.

CERTIFICATE

This is to certify that this thesis entitled, **"Correlation of systolic pressure variation, pulse pressure variation and stroke volume variation in different preload conditions following a single dose mannitol infusion in elective neurosurgical patients",** has been prepared by DrArimanickam G, DM Neuroanesthesia Resident, under the guidance of DrManikandan S, Additional Professor,Department of Anesthesiology at SreeChitraTirunal Institute for Medical Sciences & Technology, Thiruvananthapuram. He has shown keen interest in preparing this project.

Date

Place: Thiruvananthapuram

Prof. R C Rathod. MD.,
Professor & Head,
Department of Anesthesiology,
SCTIMST, Thiruvananthapuram.

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DrArimanickam G

CONTENTS

Introduction

Maintaining normovolemia in the perioperative period is very important for adequate tissue perfusion. Volume status of the patients can be assessed using static or dynamic indices. Static indices are filling pressures like central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP). An accurate measure of preload at a given point of time does not necessarily reflect preload responsiveness, which is more important for a clinician. It is universally accepted that these filling pressures have little correlation with fluid responsiveness.

Intermittent positive pressure ventilation of lung induces cyclic changes in left ventricular stroke volume. Positive pleural pressure during inspiration decreases right ventricular stroke volume. Corresponding change in left ventricular stroke volume is reflected during expiration due to delay of pulmonary transit time. During mechanical ventilation, left ventricular stroke volume decreases during expiration and increases during inspiration.

The magnitude of variation in left ventricular stroke volume within a respiratory cycle denotes preload dependency of the cardiovascular system. It is similar to application of ‘micro fluid challenge’ in a controlled and reversible manner and measuring the hemodynamic response. Based on this concept many dynamic indices indicating preload dependency of the cardiovascular system has been defined. Stroke volume variation, systolic pressure variation, delta down pressure and pulse pressure variation are the commonly used dynamic indices.

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. The PiCCO (Pulsion Medical Systems,

Munich, Germany), LiDCO (LiDCO Group PLC, London, England) and FloTrac (Edwards Lifesciences, Irvine, CA, USA) monitors use pulse contour analysis through a proprietary formula to measure cardiac output and stroke volume variation. Using echocardiography stroke volume variation is obtained from respiratory changes in velocity time integral (VTI) of aortic blood flow.

Recently various studies have demonstrated correlation between arterial pressure waveform derived indices and stroke volume variation. But in all these studies stroke volume is measured using pulse contour analysis. Recently transoesophageal echocardiography is being commonly used in neuroanaesthesia practice. We decided to study the correlation between arterial pressure waveform derived indices and echocardiography derived stroke volume variation in patients undergoing elective craniotomies. Repeated measurement of these variables following mannitol infusion can be done to assess their correlation at different preload conditions. In this echo era such a study will increase the confidence of physicians to use easily available arterial wave form derived indices when echocardiography is not available.

Review of literature

Dynamic indices

Dynamic indices apply a controlled and reversible preload variation and measure the hemodynamic response. This can be done by observing the cardiovascular response to positive pressure ventilation or to reversible preload-increasing manoeuvers such as passive leg rising. Cavallaro has proposed a classification of dynamic indices that predict volume responsiveness.(1) Group A consists of indices based on cyclic variation in SV or SV related hemodynamic parameters determined by mechanical ventilation induced cyclic variation in intrathoracic pressure (respiratory variations in stroke volume, systolic pressure, pulse pressure, aortic blood flow and pulse oximetry plethysmography). Group B is made up of indices based on cyclic variations of non stroke volume-related hemodynamic parameters determined by mechanical ventilation (vena cava diameter and ventricular preejection period). Group C consists of indices based on preload redistribution manoeuvers and mechanical ventilation is not required (passive leg raising and Valsalva maneuvers)

Heart lung interactions

In mechanically ventilated patients the magnitude of the respiratory changes in left ventricular (LV) stroke volume can be used to assess fluid responsiveness.(2) Intermittent positive-pressure ventilation induces cyclic changes in the loading conditions of right and left ventricles. Mechanical ventilation decreases preload and increases afterload of the right ventricle (RV).(3) The RV preload reduction is due to decrease in the venous return pressure gradient that is related to the inspiratory increase in pleural pressure.(4) The increase in RV afterload is related to the

inspiratory increase in transpulmonary pressure (alveolar minus pleural pressure).(5) The reduction in RV preload and increase in RV afterload both lead to a decrease in RV stroke volume, which is therefore at its minimum at the end of the inspiratory period.(6) The inspiratory impairment in venous return is assumed to be the main mechanism of the inspiratory reduction in RV ejection.(7) The inspiratory reduction in RV ejection leads to decrease in LV filling after a phase lag of two to three heart beats because of the long blood pulmonary transit time.(8) Thus LV preload reduction may induce a decrease in LV stroke volume, which is at its minimum during the expiratory period.(6)

Two other mechanisms may also occur. Mechanical ventilation may induce squeezing of blood out of alveolar vessels, and thus transiently increase LV preload.(9) The inspiratory increase in pleural pressure may decrease LV afterload and thus facilitate LV ejection.(10,11) The first mechanism in hypervolaemic conditions and the second mechanism in case of LV systolic dysfunction may induce a slight increase in LV stroke volume during the inspiratory period. However, experimental data suggest that these two mechanisms are only minor determinants of the respiratory changes in LV stroke volume.(12)

The commonly used indices representing heart lung interactions in day to day clinical practice are stroke volume variation (SVV), systolic pressure variation (SPV) and pulse pressure variation (PPV).

Systolic pressure variation

Because LV stroke volume is a major determinant of systolic arterial pressure, analysis of respiratory changes in systolic pressure has been proposed to assess the respiratory changes in LV stroke volume during mechanical ventilation.

Coyle et al proposed that the respiratory changes in systolic pressure could be analyzed by calculating the difference between the maximal and the minimal value of systolic pressure over a single respiratory cycle.(13)

SPV = (SBP max - SBP min) mm Hg

This difference is also expressed as the percentage of average between the maximal and minimal values.

SPV% = 100 x (SBP max - SBP min) / (SBP max +SBP min)/2 %

Systolic pressure variation is divided into two components (Δup and Δdown). These two components are calculated using a reference systolic pressure, which is the systolic pressure measured during an end-expiratory pause called apnoeic baseline.

Delta up represents the augmentation of systolic pressure due to the increase in Left Ventricular End Diastolic Volume (LVEDV) and the decrease in LV after load during inspiration.

Δup = SBP max – Apnoeic baseline

Delta down represents the fall in Left Ventricular End Diastolic Volume (LVEDV) and the increase in LV afterload during early expiration.

ΔDown = Apnoeic baseline – SBP min

The respiratory changes in systolic pressure result from changes in transmural pressure (mainly related to changes in LV stroke volume) and also from changes in extramural pressure (from changes in pleural pressure).(14) Denault et al had demonstrated in anaesthetized cardiac surgery patients, that changes in systolic pressure may reflect changes in airway pressure and pleural pressure better than they reflect concomitant changes in LV hemodynamics.(15) Therefore, respiratory

changes in systolic pressure may be observed despite no variation in LV stroke volume.

Pulse pressure variation

Pulse pressure is the difference between systolic and diastolic blood pressures. The arterial pulse pressure is directly proportional to stroke volume and inversely related to arterial compliance. Therefore, for a given arterial compliance, the amplitude of pulse pressure is directly related to LV stroke volume. In this regard, the respiratory variation in LV stroke volume has been shown to be the main determinant of the respiratory variation in pulse pressure.

Pulse pressure variation (PPV) is the maximal difference in pulse pressure seen within a respiratory cycle. PPV is also expressed as a percentage.

PPV %= 100 x (PP max – PP m in) / (PP max + PP min)/2 %

PPV %= 100 x [(SBP – DBP) max – (SBP – DBP) min]/

[(SBP – DBP) max + (SBP – DBP) min]/2 %

Calculation of PPV may be of particular help in the decision-making process regarding whether to institute volume expansion. Indeed, if PPV is low (<13%), then a beneficial haemodynamic effect of volume expansion is very unlikely to improve hemodynamics. In contrast, if PPV is high (>13%), then a significant increase in cardiac index in response to fluid infusion is very likely.

Interestingly, the assessment of cardiac preload dependence is not only useful in predicting volume expansion efficacy, but also in predicting the haemodynamic effects of any therapy that induces changes in cardiac preload conditions. In this regard, PPV has been shown to be useful in monitoring the haemodynamic effects of PEEP in mechanically ventilated patients with acute lung injury. Indeed, the decrease

in mean cardiac output induced by PEEP and the decrease in RV stroke volume induced by mechanical ventilation share the same mechanisms (the negative effects of increased pleural pressure on RV filling and of increased transpulmonary pressure on RV afterload). Thus, the magnitude of the expiratory decrease in LV stroke volume would correlate with the PEEP induced decrease in mean cardiac output.

In 14 mechanically ventilated patients with acute lung injury the following was demonstrated. PPV on zero end-expiratory pressure (ZEEP) was closely correlated with the PEEP-induced decrease in cardiac index; the higher PPV was on ZEEP, the greater the decrease in cardiac index when PEEP was applied. Also, the increase in PPV induced by PEEP was correlated with the decrease in cardiac index, such that changes in PPV from ZEEP to PEEP could be used to assess the haemodynamic effects of PEEP without the need for a pulmonary artery catheter. Finally, when cardiac index decreased with PEEP, volume expansion induced an increase in cardiac index that was proportional to PPV before fluid infusion.(16)

Limitations of SVV, SPV and PPV

Analysis of the respiratory changes in arterial pressure is not possible in patients with cardiac arrhythmias. Moreover, these parameters have been validated in sedated and mechanically ventilated patients. Therefore, whether the respiratory changes in LV stroke volume predict fluid responsiveness in spontaneously breathing patient remains to be evaluated. As mentioned above, the respiratory changes in LV stroke volume might also result from a decrease in LV afterload caused by the inspiratory increase in pleural pressure.(3) Thus, the respiratory changes in LV stroke volume could theoretically be an indicator of afterload dependence, rather than of preload dependence, for example in patients with congestive heart failure. In fact, it

is unlikely that the inspiratory increase in LV stroke volume can be responsible for large variations in LV stroke volume and hence in arterial pressure, even in the case of LV dysfunction.(12) In animals, induction of an experimental cardiac dysfunction was showed to result in a decrease rather than an increase in systolic pressure variation.(12)

Because the pulse pressure depends not only on stroke volume, but also on arterial compliance, large changes in pulse pressure could theoretically be observed despite small changes in LV stroke volume if arterial compliance is low (elderly patients with peripheral vascular disease). Similarly, small changes in pulse pressure could be observed despite large changes in LV stroke volume if arterial compliance is high (young patients without any vascular disease). In fact, a close relationship between baseline PPV and the changes in cardiac index induced by volume expansion was observed in a series of patients with a large range of ages and comorbidities, suggesting that the arterial compliance poorly affected the relationship between respiratory changes in LV stroke volume and PPV.(17)

Influence of tidal volume

Charron et al investigated the influence of tidal volume and adrenergic tone on these variables in mechanically ventilated patients. Cyclic changes in aortic velocity–time integrals (Δ%VTI, echocardiography) and Δ%PPV (catheter) were measured simultaneously before and after intravascular volume expansion and tidal volume was randomly varied below and above its basal value (5.9 to 9.2 ml/Kg). Intravascular volume expansion was performed by hydroxyethyl starch (100 ml in 60 s). Receiver operating characteristic curves were generated for Δ%VTI, Δ%PPV and left ventricle cross-sectional end-diastolic area

(echocardiography), considering the change in stroke volume after intravascular volume expansion (Δ15%) as the response criterion. Covariance analysis was used to test the influence of tidal volume on Δ%VTI and Δ%PPV. Twenty-one patients were prospectively included; 9 patients (43%) were responders to intravascular volume expansion. Δ%VTI and Δ%PPV values were higher in responders compared with non responders. Predictive values of Δ%VTI and Δ%PPV were similar (threshold: 20.4% and 10.0%, respectively) and higher than that of left ventricle cross-sectional end diastolic area at the appropriate level of tidal volume. Δ%PPV was slightly correlated with nor epinephrine dosage. Δ%PPV increased with the increase in the level of tidal volume both before and after intravascular volume expansion, contrasting with an unexpected stability of Δ%VTI. Authors concluded, Δ%VTI and Δ%PPV were good predictors of intravascular fluid responsiveness but the divergent evolution of these two variables when tidal volume was increased needs further explanation.(18)

De Backer et al evaluated the influence of tidal volume on the capacity of pulse pressure variation to predict fluid responsiveness. In their prospective interventional study conducted in a medico-surgical ICU, sixty mechanically ventilated critically ill patients requiring fluid challenge were separated according to their tidal volumes. Fluid challenge with either 1,000 ml crystalloids or 500 ml colloids was given. Complete hemodynamic measurements including pulse pressure variation were obtained before and after fluid challenge. Tidal volume was lower than 7 ml/kg in 26 patients, between 7– 8 ml/kg in 9 patients, and greater than 8 ml/kg in 27 patients. ROC curve analysis was used to evaluate the predictive value of pulse pressure variation at different tidal volume thresholds, and 8 ml/kg

best identified different behaviours. Overall, the cardiac index increased from 2.66 (2.00–3.47) to 3.04 (2.44– 3.96) l/min m^2. It increased by more than 15% in 33 patients (fluid responders). Pulmonary artery occluded pressure was lower and pulse pressure variation higher in responders than in non-responders, but fluid responsiveness was better predicted with pulse pressure variation than with pulmonary artery occluded pressure and right atrial pressures. Despite similar response to fluid challenge in low (<8 ml/kg) and high tidal volume groups, the percent of correct classification of a 12% pulse pressure variation was 51% in the low tidal volume group and 88% in the high tidal volume group. The authors concluded that pulse pressure variation was a reliable predictor of fluid responsiveness in mechanically ventilated patients only when tidal volume is at least 8 ml/kg.(19)

Vistisen et al studied eight prone, anesthetized piglets (23–27 kg) by subjecting to a sequence of 25% hypovolemia, normovolemia, and 25% and 50% hypervolemia. At each volemic level, tidal volumes were varied in three steps: 6, 9 and 12 ml/kg. Pulse-pressure variation (PPV) was measured during the three tidal volume steps at each volemic level. PPV increased significantly with increasing tidal volume at all volemic levels and was roughly proportional to the tidal volume at all volemic levels except in hypovolemia. They concluded that dynamic parameters are proportionally related to tidal volume and their predictability of fluid status may be improved by indexing to tidal volume.(20)

Influence of airway pressure

In 2008, Muller et al studied fifty seven mechanically ventilated and sedated patients with acute circulatory failure requiring cardiac output (CO) measurement.

Fluid challenge was given in patients with signs of hypoperfusion (oliguria <0.5 ml/kg/h, attempt to decrease vasopressor infusion rate). Fluid responsiveness was defined as an increase in the stroke index (SI) >15%. The stroke index was increased >15% in 41 patients (71%). At baseline, CVP was lower and PPV was higher in responders.

Receiver-operating characteristic (ROC) curves were generated for PPV and central venous pressure (CVP). The areas under the ROC curves of PPV and CVP were 0.77 (95% CI 0.65–0.90) and 0.76 (95% CI 0.64– 0.89), respectively (P = 0.93). The best cut off values of PPV and CVP were 7% and 9 mmHg, respectively.

In 30 out of 41 responders, PPV was <13%. The use of a low VT (< 8ml/kg IBW in 54 out of 57patients) was the main explanation given by the authors about the discrepancy between the findings of the that study. Using logistic regression, (Pplat- PEEP) was the sole independent factor associated with a PPV value <13% in responders. In these responders, (Pplat- PEEP) was less than 20 cm of H_2O. Authors concluded that in patients mechanically ventilated with low tidal volume, PPV values less than 13% do not rule out fluid responsiveness, especially when (Pplat- PEEP) is less than 20 cm of H_2O.(21)

Pulsed pressure variation is caused by the transmission of airway pressure to the pleural and pericardial spaces, which induces changes in venous return and cardiac preload. Therefore, PPV could be theoretically limited when the part of transmitted airway pressure to the pleural and pericardial spaces is low.(22) This could be due to the use of low tidal volume in normal lungs with high compliance or in ARDS patient's lungs with low compliance. In these conditions, the probability of

transmitting a sufficient pressure variation to the pleural and pericardial spaces to induce large PPV is low, thus it may not correctly predict stroke volume variation.

Influence of respiratory rate

In 17 hypovolemic patients, thermo dilution cardiac output and indices of fluid responsiveness were measured at a low RR (14-16 breaths/min) and at the highest RR (30 or 40 breaths/min) achievable without altering tidal volume. An increase in RR was accompanied by a decrease in pulse pressure variation from 21% (18-31%) to 4% (0-6%) ($P < 0.01$) and in respiratory variation in aortic flow from twenty three% (18-28%) to 6% (5-8%) ($P < 0.01$), whereas respiratory variations in superior vena cava diameter (caval index) were unaltered, i.e., from 38% (27-43%) to 32% (22-39%), P was not significant. Cardiac index was not affected by the changes in RR but did increase after fluids.(23)

Pulse pressure variation became negligible when the ratio between heart rate and RR decreased below 3.6. The authors concluded that respiratory variations in stroke volume and its derivates are affected by RR, but caval index was unaffected. They suggested that right and left indices of ventricular preload variation were dissociated. At high RRs the ability of stroke volume variations and its derivate, to predict the response to fluids might be limited, whereas caval index could still be used.

Influence of vasodilatation

Westphal et al studied 10 anesthetized and mechanically ventilated rabbits undergoing progressive hypotension by either controlled haemorrhage (Group1) or intravenous SNP infusion (Group 2). Animals in Group 1(n=5) had graded

haemorrhage induced at 10% steps until 50% of the total volume was bled. Mean arterial pressure (MAP) steps were registered and assumed as pressure targets to be reached in Group 2. Group 2 (n =5) was subjected to a progressive SNP infusion to reach similar pressure targets as those defined in Group 1. Heart rate (HR), systolic pressure variation (SPV) and PPV were measured at each MAP step, and the values were compared between the groups.

SPV and PPV were similar between the experimental models in all steps ($p > 0.16$). SPV increased earlier in Group 2. Both pharmacologic vasodilatation and graded haemorrhage induced PPV amplification similar to that observed in hypovolemia, reinforcing the idea that amplified arterial pressure variation does not necessarily represent hypovolemic status but rather potential cardiovascular responsiveness to fluid infusion.(24)

Hemodynamic monitoring using echocardiography

Trans-oesophageal echocardiography (TEE) allows direct visualization and assessment of left and right ventricular function and thus helps guide the decision between fluid challenge and use of vasopressors or/and inotropes. Visual estimates of euvolemia can be made with reasonable confidence, while numerical measures of fluid responsiveness depend upon computationally intensive serial measurements of two- and three-dimensional images. For example, large left ventricular volumes with minimal change between systolic and diastolic dimensions generally indicate a patient who will not increase CO with additional fluids. Patients with near obliteration of the ventricular cavity at end systole are generally fluid responsive. Fluid challenges in the latter cases, followed by inspection of ventricular filling by echocardiogram can be used to establish euvolemic ventricular filling. Additionally,

patients with empty left ventricles and full or enlarged right ventricles should entertain thoughts of high pulmonary artery pressures either from vascular disease or from thromboembolism.

Stroke volume and aortic blood flow velocity variation

In 19 mechanically ventilated septic shock patients, Feissel and co-workers analysed aortic blood flow velocities (V_{peak}) by trans-oesophageal echocardiography before and after volume expansion. Maximum values of V_{peak} (V_{peak} max) and minimum values of V_{peak} (V_{peak} min) were determined over one respiratory cycle. The respiratory changes in V_{peak} (ΔV_{peak}) were calculated as the difference between V_{peak} max and V_{peak} min divided by the mean of the two values and was expressed as a percentage. The indexed LV end-diastolic area (LVEDAI) and cardiac index (CI) were obtained at the end of the expiratory period. The volume expansion-induced increase in cardiac index was $\geq$ 15% in 10 patients (responders) and < 15% in 9 patients (non responders). Before volume expansion, ΔV_{peak} was higher in responders than in non responders (20 ± 6% vs 10 ± 3%), while LVEDAI was not significantly different between the two groups (9.7 ± 3.7 vs 9.7 ± 2.4 cm^2/m^2). Before volume expansion, a ΔV_{peak} threshold value of 12% allowed discrimination between responders and non responders with a sensitivity of 100% and a specificity of 89%. Volume expansion induced changes in cardiac index closely correlated with ΔV_{peak} before volume expansion.(25)

In 12 mechanically ventilated and anesthetized rabbits, Slama et al investigated whether the magnitude of respiratory changes in the aortic velocity time integral (VTI_{Ao}), recorded by transthoracic echocardiography (TTE) during a stepwise blood withdrawal and restitution, could be used as a reliable indicator of

volume depletion and responsiveness. At each step, left and right ventricular dimensions and the aortic diameter and VTI_{Ao} were recorded to calculate stroke volume (SV) and cardiac output (CO). Respiratory changes of VTI_{Ao} (maximal − minimal values divided by their respective means) were calculated. The amount of blood withdrawal correlated negatively with left and right ventricular diastolic diameters, VTI_{Ao}, SV, and CO and correlated directly with respiratory changes of VTI_{Ao}. Respiratory VTI_{Ao} variations (but not other parameters) at the last blood withdrawal step were also correlated with changes in SV after blood restitution. In conclusion, respiratory variations in VTI_{Ao} using TTE appear to be a sensitive index of blood volume depletion and restitution. (26)

Commonly used and reliable method for measuring stroke volume and cardiac output using an echocardiograph was to measure the velocity time integral (VTI) from the left ventricular outflow tract (LVOT).(27) The diameter of the aortic annulus was measured, and its area was calculated. Multiplying this area with the LVOT VTI gave the stroke volume, and multiplying stroke volume with heart rate gave the cardiac output.

Stroke volume variation (SVV) was one of the most extensively investigated dynamic parameters. The results of a recent systemic review by Zhang et al demonstrated that 1) the baseline SVV was correlated to the fluid responsiveness with pooled correlation coefficient of 0.718 and 2) SVV was able to predict fluid responsiveness across a wide spectrum of clinical settings, with a pooled diagnostic odds ratio of 18.4 (95% CI, 9.52–35.5). Most of the studies included in their analysis used PiCCO plus and FloTrac/Vigileo systems. This meta-analysis found SVV as a good predictor in patients ventilated with tidal volume of more than 8 ml/kg, whereas

its predictive value in patients with low tidal volume ventilation remained to be investigated. The presence of spontaneous breathing compromised the predictive value of SVV. In addition SVV could not be used in situations such as cardiac arrhythmia, valvular heart disease, intracardiac shunts, peripheral vascular disease and decreased ejection fraction.(28)

Offline measurement of SPV and PPV

The measurement of SPV and PPV using simple tools on the Datex Ohmeda S/5 had been described by Gouvea and Gouvea. It involved changing the ‘‘PA’’ and ‘‘wedge pressure’’ scales to record arterial pressure. In the wedge pressure menu, the screen would be frozen and a horizontal line would appear. It could now be freely moved to the uppermost point of the systolic pressure curve, and then down to the lowest systolic pressure. The difference between the maximum and minimum systolic pressure values in a single respiratory cycle was the systolic pressure variation. The corresponding diastolic pressures were also recorded. Pulse pressure values were calculated as the difference between systolic and diastolic pressures. ΔSPV as percent of the mean systolic pressure (SPV %) and ΔPPV as percent of the mean pulse pressure (PPV %) were then calculated using the following formulas:

SPV %=100 x (SBP max – SBP min) / (SBP max + SBP min)/2

PPV %=100 x (PP max – PP min) / (PP max + PP min)/2

SBP max, SBP min, PP max, and PP min were the maximal and minimal values within one respiratory cycle.(29)

Dynamic indices in Neuroanesthesiology

Berkenstadt et al studied 15 patients undergoing intracranial surgery using PiCCO continuous cardiac output monitor. During surgery, graded volume loading was performed with each volume loading step (VLS) consisting of 100 mL of 6% hydroxyethylstarch given for 2 min. Successive responsive VLSs were performed (increase in SV by 5% after a VLS) until a change in SV of less than 5% was reached (nonresponsive). A total of 140 VLSs were performed. Responsive and nonresponsive VLSs differed in their pre-VLS values of systolic blood pressure, SV, and SVV, but not in the values of heart rate and central venous pressure. By using receiver operating characteristic analysis, the area under the curve for SVV was statistically more than those for central venous pressure, heart rate and systolic blood pressure. Conclusion was SVV value of 9.5% or more would predict an increase in the SV of at least 5% in response to a 100-mL volume load, with a sensitivity of 99% and a specificity of 93%.(30)

Durga et al studied to quantify SPV during graded hypovolemia using the simple technique described by Gouvea and Gouvea and to compare its reliability relative to other hemodynamic indicators of hypovolemia. Twenty anesthetized neurosurgical patients of ASA grade I and II patients were administered a single dose of furosemide 0.5 mg/kg intravenously to obtain graded volume loss in the form of urine output. Invasive arterial pressure from radial artery and CVP were monitored using Datex OhmedaS/5. Heart rate, systolic blood pressure, diastolic blood pressure, CVP at zero end-expiratory pressure, SPV and PPV were measured at baseline and after a urine output of 200 and 500 mL. There was a significant correlation between volume loss and CVP, SPV, and PPV. The area under the curve of receiver operating

characteristic analysis was >0.75 for CVP, SPV, and PPV. SPV of 7.5mmHg and a change of SPV by 4.5mmHg, a PPV of 4.5 mmHg and change in PPV by 2.5mmHg were the best cut-off values that corresponded to a volume change of 500 mL. This simple method enabled calculation of SPV without the computerized modules and detected volume loss comparable to CVP.(31)

Twenty-six adult patients undergoing scheduled intracranial surgery under general anaesthesia were studied by Deflandre et al comparing delta pulse pressure (DPP) and delta down (DD) during intracranial surgery. DD and DPP were simultaneously measured every 10 min. A DPP >13% on two consecutive occasions prompted a 250 ml fluid bolus. Pairs of data were analysed using regression analysis, receiver operating characteristics (ROC) curve and prediction probability (Pk). A significant correlation between DD and DPP (R^2 =0.5431, P=0.001) was found. ROC curve analysis revealed an excellent accuracy of DD in predicting a DPP value higher or lower than 13% (area under the curve: 0.967, SE: 0.013). The DD threshold associated with the best sensitivity (0.90) and specificity (0.99) was 5 mm Hg. The Pk of DD to predict a DPP value higher or lower than 13% was 0.97 (SE: 0.01). A total of 41 fluid boluses performed in 19 patients resulted in a decrease of DD and DPP below 5 mm Hg and 13%, respectively, in all but one occasion. In this study DD was as efficient as DPP to assess hypovolemia and predict responsiveness to fluid bolus in patients undergoing intracranial surgery. A 5 mm Hg DD value could be considered as a valuable threshold for initiating fluid bolus. These results supported its use during intracranial surgery.(32)

In 26 patients undergoing scheduled craniotomy surgery, Qiao et al compared measurement of systolic pressure variation (SPV) (measured as both mm

Hg and %) and pulse pressure variation (PPV%) using the Ohmeda monitor method to simultaneously measured reference standard, stroke volume variation (SVV) determined with an Edwards FloTrac/Vigileo monitor, during volume loading. Variation in systolic pressure, pulse pressure, and stroke volume all decreased proportionally as fluid volume increased. The 3 test parameters, SPV (%), SPV (mm Hg), and PPV (%) were highly correlated to SVV with Pearson's correlation coefficients 0.894, 0.885 and 0.876 respectively. Bland- Altman plots comparing SPV (%) and PPV with SVV showed agreement with this standard. Receiver operating characteristic (ROC) curves showed no significant difference between the three test parameters for predicting the vascular response to fluid infusion. The authors concluded that there was no significant difference between SPV and PPV and the reference SVV measurement for predicting response to fluid loading. The Ohmeda monitor method requires less sophisticated technology and is much less expensive than other methods.(33)

Radhakrishnan et al studied forty one adult neurosurgical patients requiring mannitol infusion. Arterial line and plethysmographic probe were placed in the same limb. Digitized waveforms were collected before, at the end, and 15, 30 and 60 minutes after mannitol infusion. Using MATLAB, the following parameters were collected for three consecutive respiratory cycles,—systolic pressure variation (SPV), pulse pressure variation (PPV), plethysmographic peak variation (Pl-PV), plethysmographic amplitude variation (Pl-AV) and blood pressure-plethysmographic time lag (BP-Pleth time lag). Changes in above parameters over the study period were studied using repeated measure analysis of variance. Correlation between the parameters was analysed. SPV and Pl-PV showed significant increase at 15, 30

and 60 min compared to end of mannitol infusion ($P<0.01$ for SPV; $P<0.05$ for Pl-PV). PPV and Pl-AV showed significant increase only at 30 min ($P<0.05$). The correlation between DSPV–DPl-PV, DPPV–DPl-AV and DSPV–DBP-Pleth time lag were significant ($r = 0.3$;$P<0.01$). SPV and time lag had no significant interaction. Pl-PV correlates well with SPV following mannitol infusion and can be used as an alternative to SPV.(34)

Aims and objective

1. To assess the correlation of systolic pressure variation (SPV), pulse pressure variation (PPV) and stroke volume variation (SVV) in different preload conditions following a single dose mannitol infusion in neurosurgical patients undergoing elective supratentorial craniotomies.
2. To assess the correlation between these indices and volume loss in the form of urine output following mannitol infusion.

Methodology

Study design:

A prospective interventional study

Inclusion criteria:

1. Age greater than 16 years and lesser than 70 years
2. American society of anesthsiology (ASA) grade I and II
3. Elective supratentorial craniotomies

Exclusion criteria:

1. Cardiac rhythm other than sinus
2. Contraindications for trans oesophageal echocardiography (History of swallowing difficulty, oesophageal surgery, strictures, mass lesions or abnormalities)
3. Intra operative patient position other than supine
4. Cardiac (valvular heart disease, intracardiac shunts, peripheral vascular disease) or lung (like asthma, COPD and tuberculosis) pathologies

Materials:

Systolic pressure variation and pulse pressure variation values were measured from arterial wave form obtained in Philips V24E multi-parameter monitor. Stroke volume variation was measured by trans-oesophageal echocardiography, using multi-plane TEE probe (9T; 4.0 to 10.0MHz) in GE Vivid 7 machine.

Methods:

After obtaining approval from department review board and informed consent, fifty four consecutive patients undergoing elective craniotomies who satisfied inclusion and exclusion criteria were included in the study.

Anaesthesia management:

Patients received either no premedication or Glycopyrrolate 0.2 mg intramuscular injection on the morning of surgery according to treating consultant's discretion. Inside the operation theatre, non-invasive monitors like pulse oximetry (SPO_2), electro cardiogram (ECG) and non-invasive blood pressure (NIBP) were attached and baseline values were recorded. After securing intravenous access, anaesthesia was induced with Sodium thiopentone 5 mg/Kg intravenously. For facilitating endotracheal intubation Vecuronium 0.12 mg/Kg and Fentanyl 2 μg/Kg were administered. Airway was secured using appropriate size endotracheal tube.

Anaesthesia was maintained with air-oxygen mixture and 1% isoflurane. All patients were control ventilated with a fixed tidal volume of 8 mL/Kg and positive end expiratory pressure (PEEP) of zero. End tidal carbon-dioxide was monitored and maintained between 30 to 35 mm Hg by adjusting respiratory rate. In all patients radial artery cannulation was done for invasive blood pressure monitoring (using a 20 G BD Insite W^{TM} cannula). After securing all invasive lines and before positioning patients using clamps, TEE probe was inserted and baseline cardiac status was assessed. Once the patients were positioned, crystalloid intravenous fluids (normal saline and lactated Ringer's solution) were given at the

rate of 4 to 6 mL/Kg/h. Fluid boluses of 100 ml were given if mean arterial pressure (MAP) decreased ≤ 60 mmHg or ≥20% from the baseline value. Fentanyl at the dose of one μg/Kg/h was given as infusion. Stable anaesthetic depth was established by maintaining constant MAC value.

Observations:

Measurements of baseline values for systolic pressure variation (SPV), pulse pressure variation (PPV) and stroke volume variation (SVV) were done. Mannitol infusion (20%) at the dose of 1 g/Kg was started during first burr hole placement and it was given over 15 to 20 minutes.

Repeated measurements of SPV, PPV, SVV, urine output and peak airway pressure were done at the interval of 15, 30, 60, 90 and 120 minutes after stopping mannitol infusion.

Measurement of systolic pressure variation (SPV) and pulse pressure variation (PPV):

To measure SPV and PPV, arterial pressure wave form label in the monitor was changed to PAP (pulmonary artery pressure). (Figure 1) After optimising the scale, "Procedure" option was selected from menu. Among various procedures, "Wedge" option was selected. (Figure 2) Once arterial pressure wave forms corresponding to consecutive three respiratory cycles were obtained in procedure screen, tracing was stopped by selecting "stop trace" option. (Figure 3) In this monitor simultaneous respiratory wave forms were obtained from ECG electrodes. Next "edit wedge" option was selected. A cursor (horizontal line) appeared in procedure screen which can be moved up and down and pressure value corresponding to cursor position would be shown. (Figure 4) This was used to obtain maximum and minimum values for systolic and diastolic pressure in a single respiratory cycle. Systolic pressure variation and pulse pressure variation were calculated using following formulae.

SPV% = 100 x (SBP max - SBP min) / (SBP max +SBP min)/2 %

PPV %= 100 x (PP max – PP min)/ (PP max + PP min)/2 %

PPV %= 100 x [(SBP – DBP) max – (SBP – DBP) min] / [(SBP – DBP) max + (SBP – DBP) min]/2 %

Figure 1: Labelling arterial wave form as pulmonary artery pressure (PAP)

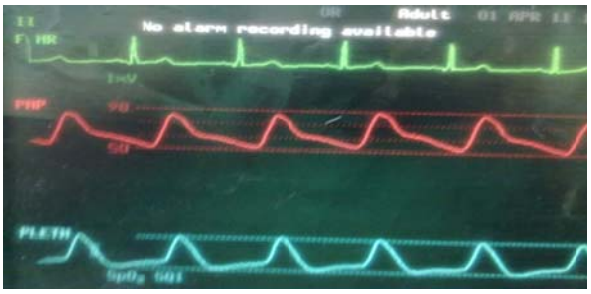


Figure 2: Selecting "Wedge" option from the menu at the bottom of the screen

Figure 3: Selecting "Stop Trace" option

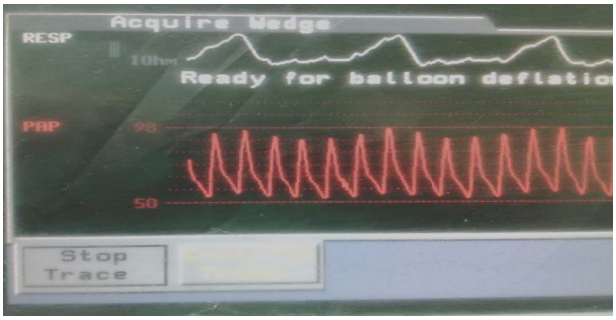
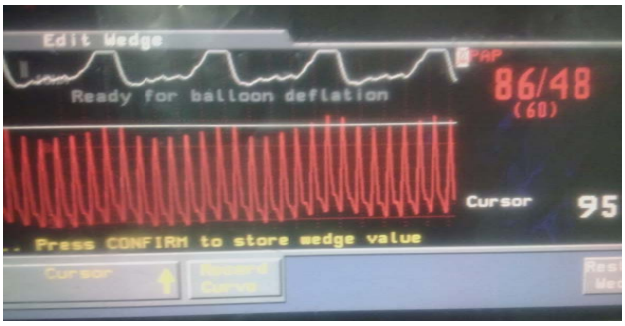


Figure 4: Cursor (white horizontal line) and corresponding pressure value (number in white colour)



Measurement of stroke volume variation (SVV):

Measurement of SVV was done using trans-aortic Doppler flow velocities. For obtaining this, the multi-plane probe was positioned in deep transgastric aortic long axis view. After ruling out stenosis or regurgitation at aortic valve, screen was frozen at aortic valve opening and aortic valve (AV) diameter was measured. (Figure 5) Then cursor for pulse wave Doppler was placed on aortic side of AV valve and tracing obtained. Baseline and horizontal sweep speed were adjusted and VTI (velocity time integral) wave form trace, corresponding to 3 or 4 respiratory cycles was obtained and the screen was frozen. (Figure 6) Maximum and minimum stroke volume values in each respiratory cycle were measured. (Figure 7) Stroke volume variation was calculated using following formulae.

$$SVV\ \% = 100 \times (SV\ max - SV\ min) / (SV\ max + SV\ min)/2\ \%$$

Once the appropriate wave forms were obtained, both the monitors' screens were frozen at the same time and the values were noted.

Figure 5: Measurement of aortic valve (AV) diameter

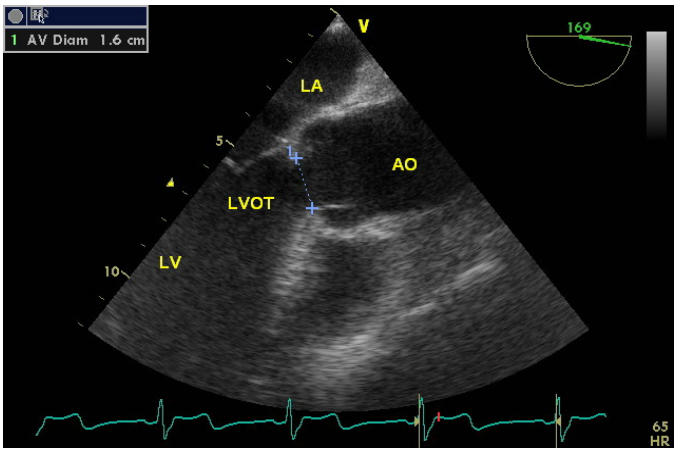


Figure 6: Obtaining aortic blood flow (VTI) and identifying maximum and minimum stroke volume within a respiratory cycle

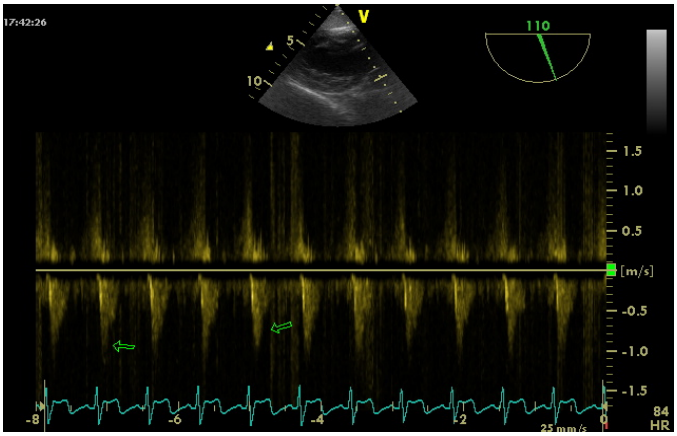
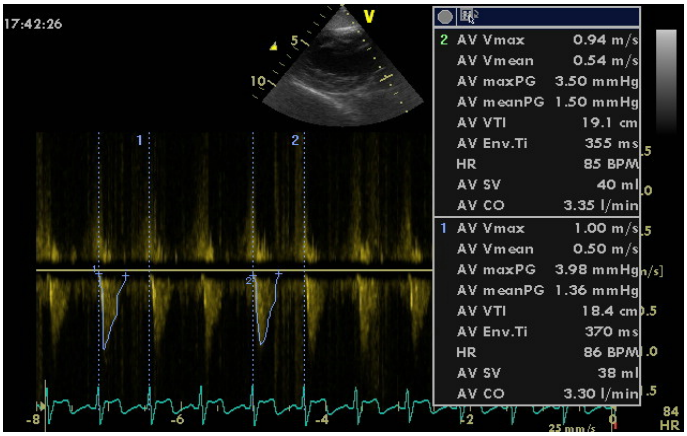


Figure 7: Measurement of maximum and minimum stroke volume



Observations and results

Demographic data of the study population is given below (Table 1).

Table 1: Demographic data

Parameters	Values
Age (%)	
16-20	2(3.7%)
21-30	8(14.8%)
31-40	11(20.4%)
41-50	17(31.5%)
51-60	12(22.2%)
61-70	4(7.4%)
Gender	
Male:female	24:30
Weight (in Kg, mean±SD)	64±10.11
Surgery (%)	
Aneurysm	22(40.7%)
AVM	2(3.7%)
Gliomas	14(26%)
Meningiomas	7(13%)
Epilepsy	3(5.5%)
Others	6(11.1%)

The mean and standard deviation for systolic pressure variation (SPV), pulse pressure variation (PPV), stroke volume variation (SVP) at different time intervals are given below (Table 2).

Table 2: SPV, PPV, SVV (Mean ± SD) at different time intervals

Variables	Time intervals						P value*
	Baseline	Fifteen minutes	Thirty minutes	Sixty minutes	Ninety minutes	Two hours	
SPV (%)	9.0264± 2.2107	8.4449± 2.1934	9.7898± 2.9735	12.1827± 3.9204	13.1006± 3.5201	15.0353± 4.2133	0.0001
PPV (%)	5.8182± 1.4438	5.9763± 1.6471	7.5507± 2.2164	8.8079± 2.2224	10.6443± 3.6500	11.1445± 4.5407	0.0001
SVV (%)	17.5162± 9.1286	15.6115± 7.8832	20.1618± 9.1245	21.1314± 10.6392	23.8831± 9.3280	24.7750± 14.7624	0.0001

* One way ANOVA

Systolic pressure variation (SPV) slightly decreased initially at 15 minutes after stopping mannitol infusion. Following that there was a continuing increase till two hours (Graph 1). Pulse pressure variation (PPV) did not changed during 15 minutes, but there after started increasing similar to systolic pressure variation (Graph 2). Stroke volume variation (SVV) behaved similar to systolic pressure variation. There was an initial decrease at 15 minutes followed by continuous increase later throughout the study period. (Graph 3)

The mean and standard division for cumulative urine output, urine output per Kg body weight and urine flow rate at different time intervals are given in the table below (Table 3).

Table 3: Urine output, urine output per Kg body weight and urine flow rate (Mean ± SD) at different time intervals

Variables	Time intervals					P value*
	Fifteen minutes	Thirty minutes	Sixty minutes	Ninety minutes	Two hours	
Cumulative urine output(mL)	287.04 ± 185.86	517.59 ± 286.30	955.56 ± 522.30	1355.56 ± 602.01	1721.30 ± 676.18	0.0001
Cumulative urine output per Kg(mL/Kg)	4.53 ± 2.94	8.15 ± 4.39	15.06 ± 8.05	21.54 ± 9.57	27.54 ± 10.91	0.0001
Urine flow rate (mL/Kg/h)	18.12 ± 11.77	14.50 ± 10.01	13.84 ± 7.34	12.92 ± 6.66	11.23 ± 6.02	0.001
Urine output per Kg at each time interval	4.53± 2.94	3.62± 2.50	6.90± 3.69	6.48± 3.32	5.82± 3.56	0.0001

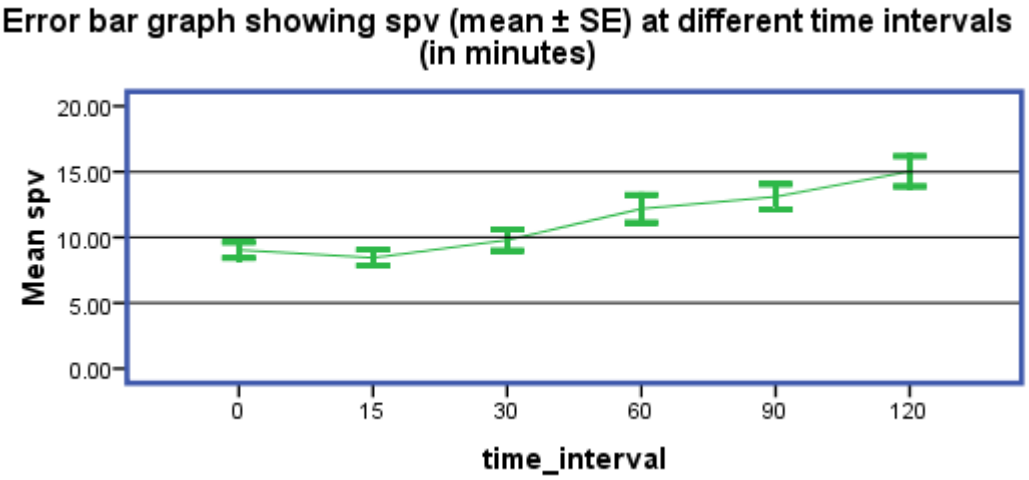
* One way ANOVA

Urine flow rate was highest during the first fifteen minutes and then gradually decreased till two hours. (Graph 5)

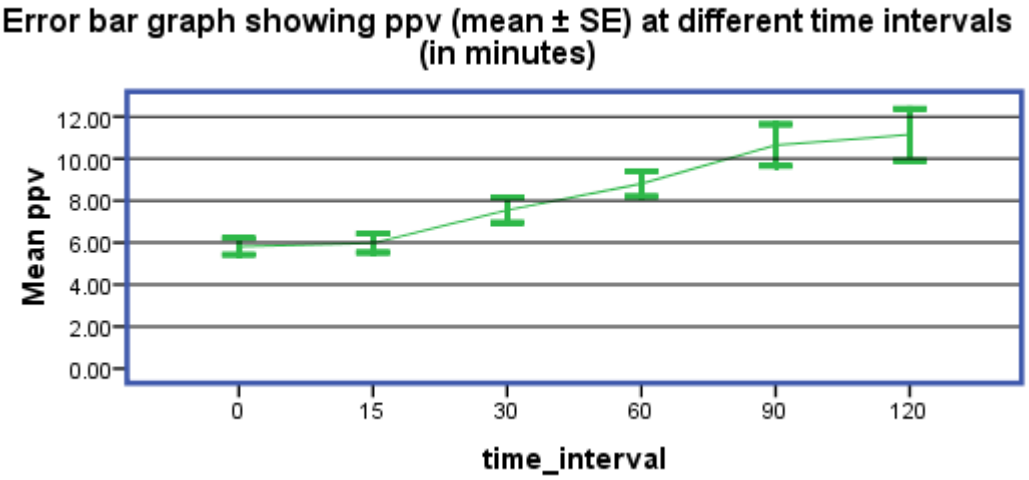
Change in peak airway pressure during the study period was less than 2 cm H_20. Mean and standard deviation values were 20.01 and 2.33 respectively.

Graphs

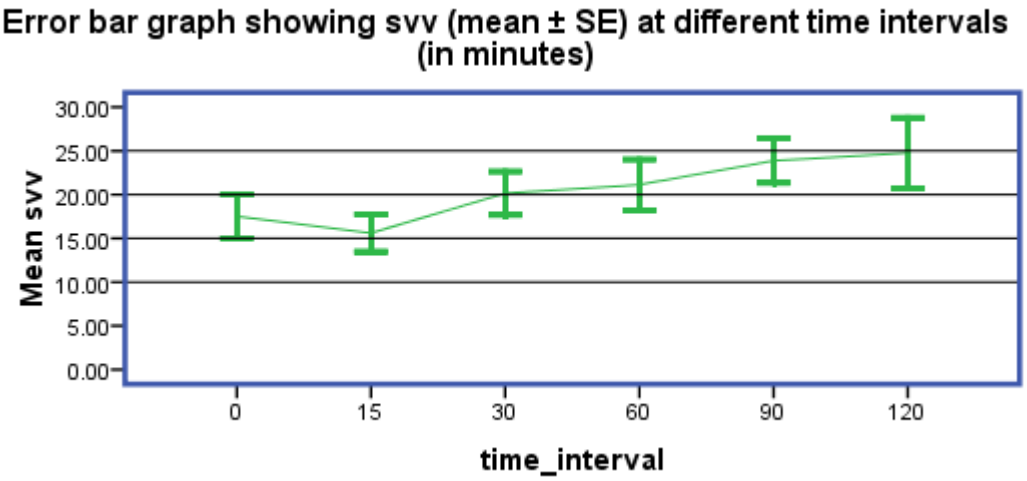
Graph 1



Graph 2

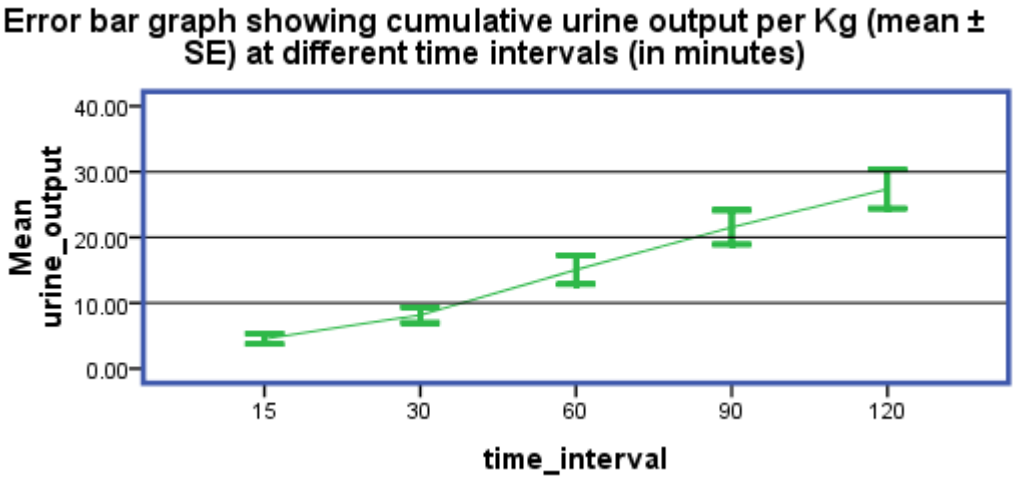


Graph 3

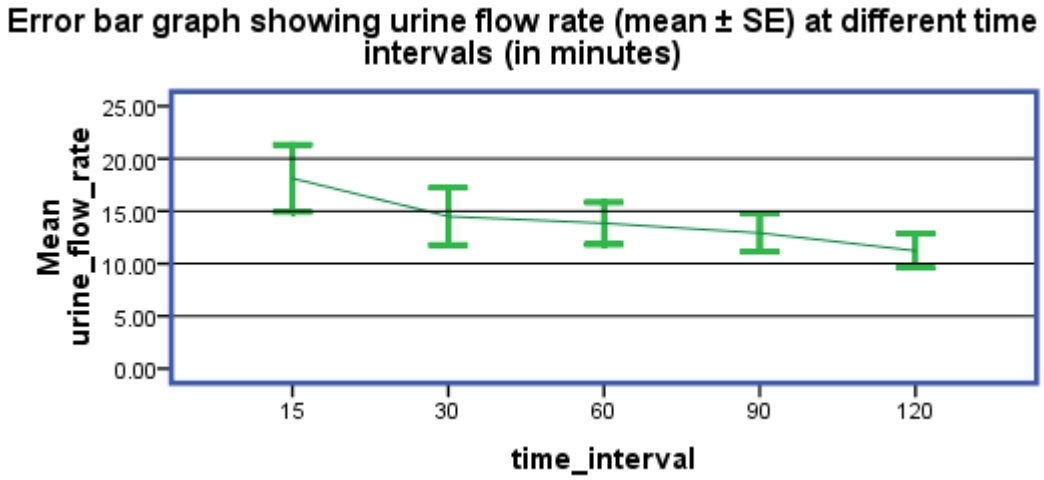


Graphs

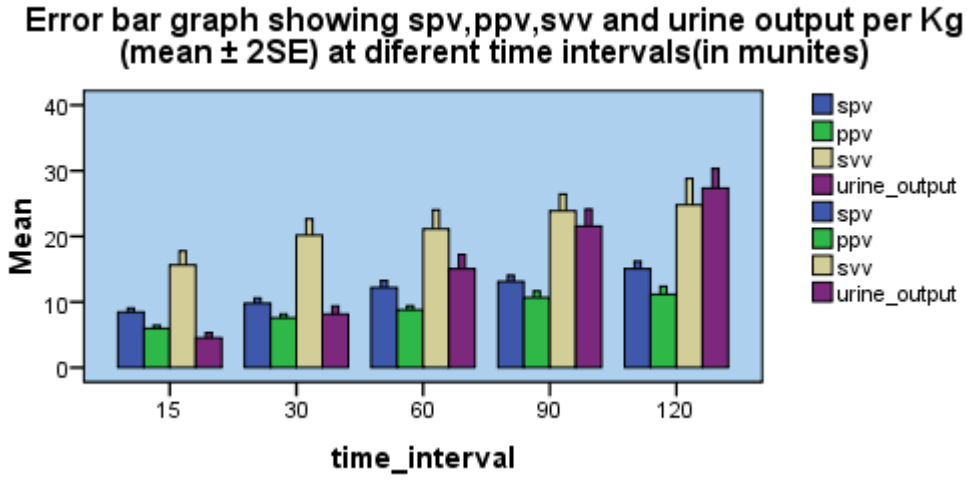
Graph 4



Graph 5



Graph 6



Statistical analysis

Sample size calculation

A pilot study consisting of eleven patients was conducted. Baseline values of systolic pressure variation, pulse pressure variation and stroke volume variation were measured.

Table 4: SPV, PPV and SVV (Mean ± S.D) at baseline in pilot study

SPV	PPV	SVV
7±1.7564	4±1.20511	13±4.8382

Pearson correlation coefficient between SPV and SVV was 0.36973 and between PPV and SVV was 0.37342. Correlation table was referred to find out the appropriate sample size.(35) After fixing the level of significance at 0.01, for the two tailed Pearson correlation coefficient of 0.35, sample size was found to be 52.

Correlations among dynamic indices at different time intervals are shown in the following table (Table 5). Significant correlation was present between SPV and SVV throughout the study period. Significant correlation between SPV and PPV was present only at 90 minutes and two hours after mannitol. PPV was poorly correlating with SVV at all time intervals.

Table 5: Pearson correlation co-efficient (level of significance) among dynamic indices at different time intervals

Variables	Baseline r (P)	15 minutes r (P)	30 minutes r (P)	60 minutes r (P)	90 minutes r (P)	Two hours r (P)
SPV and PPV	0.238 (0.083)	0.063 (0.651)	0.111 (0.426)	0.101 (0.468)	0.481** (0.000)	0.631** (0.000)
SPV and SVV	0.344* (0.011)	0.371** (0.006)	0.179 (0.196)	0.525** (0.000)	0.447** (0.001)	0.242 (0.078)
PPV and SVV	0.201 (0.144)	0.178 (0.198)	0.177 (0.199)	0.092 (0.509)	0.156 (0.261)	0.162 (0.243)

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

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

Correlations between each dynamic index and corresponding cumulative urine output at different time intervals are shown in table below (Table 6). SPV and SVV correlated with urine output at 15 and 30 minutes, but not later. PPV had weak correlation with urine output.

Table 6: Pearson correlation co-efficient (level of significance) between dynamic indices and urine output at different time intervals

Variables	Urine output per Kg				
	15 minutes r (P)	30 minutes r (P)	60 minutes r (P)	90 minutes r (P)	Two hours r (P)
SPV	0.331* (0.014)	0.302* (0.027)	0.036 (0.797)	0.149 (0.281)	0.267 (0.051)
PPV	0.133 (0.339)	0.165 (0.233)	0.157 (0.258)	0.249 (0.070)	0.175 (0.206)
SVV	0.854** (0.000)	0.346* (0.010)	0.252 (0.066)	0.012 (0.933)	0.235 (0.087)

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

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

Correlations between values of dynamic indices and corresponding urine flow rate at different time intervals are shown in following table (Table 7). Values of SVV and SPV correlated significantly with urine flow rate during first fifteen minutes. After 60 minutes correlation is not strong. Values of PPV correlated significantly with urine flow rate at 30 and 90 minutes.

Table 7: Pearson correlation co-efficient (level of significance) between dynamic indices and urine flow rate at different time intervals

Variables	Urine flow rate				
	15 minutes r (P)	30 minutes r (P)	60 minutes r (P)	90 minutes r (P)	Two hours r (P)
SPV	0.331* (0.014)	0.200 (0.148)	0.051 (0.714)	0.079 (0.568)	0.149 (0.283)
PPV	0.133 (0.133)	0.293* (0.032)	0.146 (0.293)	0.269* (0.049)	0.097 (0.485)
SVV	0.854** (0.000)	0.456** (0.001)	0.248 (0.071)	0.020 (0.887)	0.083 (0.550)

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

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

Correlations between baseline values of dynamic indices and urine flow rate at different time intervals are shown in following table (Table 8). Baseline values of SPV and SVV were positively correlated with urine flow rate at 15 minutes and one hour after mannitol.

Table 8: Pearson correlation co-efficient (level of significance) between baseline dynamic indices and urine flow rate at different time intervals

	Urine flow rate		
Baseline values	15 minutes r (P)	30 minutes r (P)	60 minutes r (P)
SPV	0.312* (0.022)	0.109 (0.432)	0.301* (0.027)
PPV	0.228 (0.097)	0.071 (0.609)	0.186 (0.177)
SVV	0.467** (0.000)	0.185 (0.181)	0.447** (0.001)

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

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

When the values of SPV, PPV and SVV at different time intervals were pooled together, they had significant correlation with each other, in the order of between SPV and PPV > SPV and SVV > PPV and SVV. (Table 9)

Same interaction can be graphically represented using scatter plot and line of fit. (Graphs 7, 8, 9)

Table 9: Pearson correlation coefficient between pooled values of dynamic indices

Variables	SPV and PPV	SPV and SVV	PPV and SVV
r (P)	0.584** (0.000)	0.434** (0.000)	0.290** (0.000)

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

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

The pooled values of SPV, PPV and SVV had significant correlation with urine output, in the order of SPV>PPV>SVV. (Table 10)

Table 10: Pearson correlation coefficient between pooled values of dynamic indices and urine output per Kg

Variables	SPV r (P)	PPV r (P)	SVV r (P)
Urine output per Kg	0.516** (0.000)	0.496** (0.000)	0.351** (0.000)

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

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

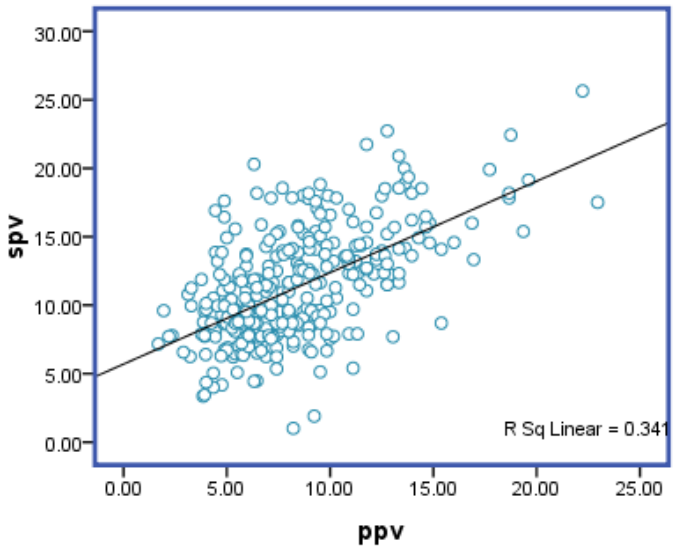
Receiver operating characteristics analysis of SPV, PPV and SVV values considering urine output ≥15mL/Kg as the response criteria (which corresponds to 10 mL/Kg volume loss) are shown in table below (Table 11). Predictive effect of SPV and PPV in differentiating a volume loss ≥ 10 mL/Kg was better than SVV. (Graph10). The best cut-off values for SPV, PPV and SVV were 12%, 9%and 20% respectively.

Table 11: Receiver operating characteristics of SPV, PPV and SVV considering urine output ≥15mL/Kg as the response criteria

Variables	AUC(95%CI)	Std. Error	Cut off values	Sensitivity	Specificity
SPV	0.762 (0.702 – 0.823)	0.031	12%	0.717	0.726
PPV	0.755 (0.695 – 0.816)	0.031	9%	0.655	0.758
SVV	0.651 (0.585 – 0.717)	0.034	20%	0.558	0.637

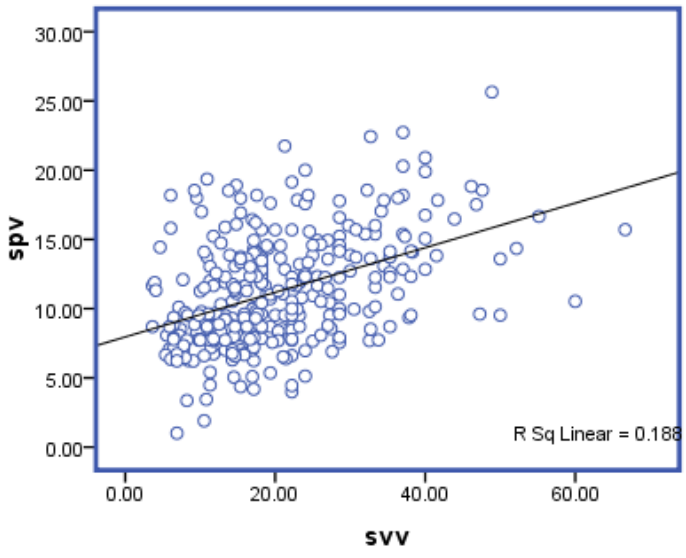
Graph 7

Scatter plot for SPV and PPV



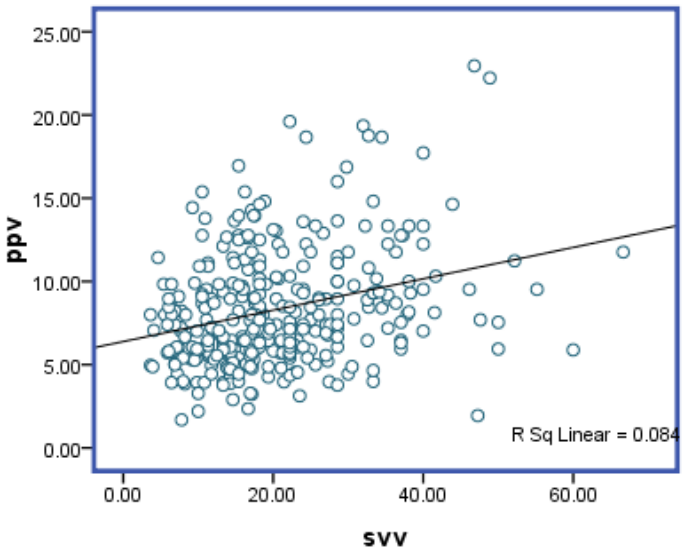
Graph 8

Scatter plot for SPV and SVV



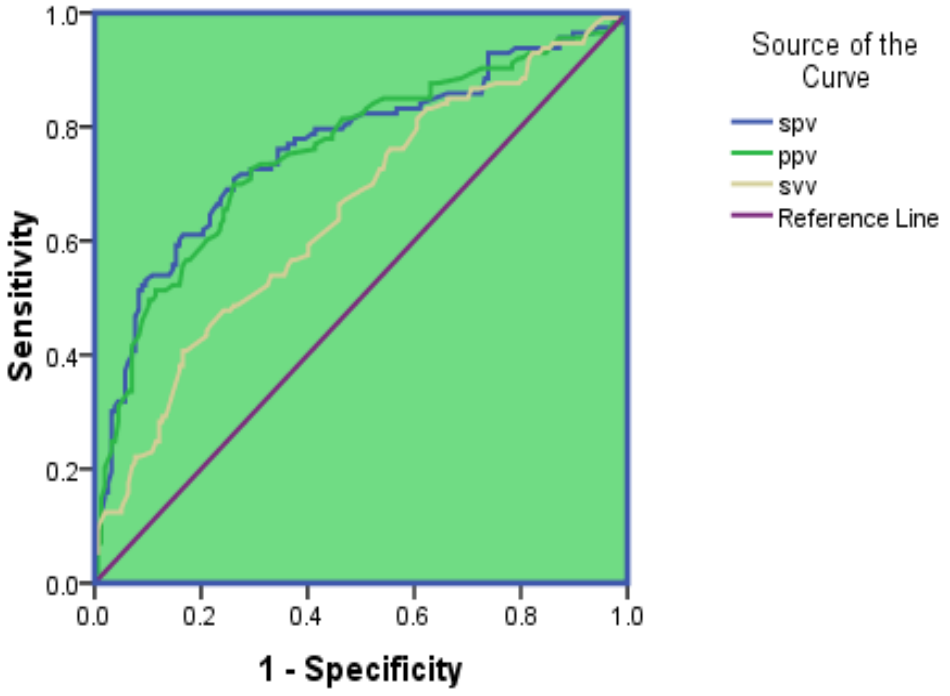
Graph 9

Scatter plot for PPV and SVV



Graph 10

ROC Curve for SPV, PPV and SVV with urine output ≥ 15 mL/Kg as response criteria



Diagonal segments are produced by ties.

Discussion

Brief summary of the results

In this study following a single dose of mannitol infusion urine flow rate was highest during the first fifteen minutes, similar to previous reports. (37, 38)

Systolic pressure and stroke volumevariationdecreased initiallyprobably due to intravascular volume expansion but then increased significantlytill the end of study indicating volume loss due todiuresis and these changes following mannitol have been reported earlier. (34) Similar changes were not found in pulse pressure variation.

As the aim of the study was to find correlation among these dynamic indices at different loading conditions, establishing a significant change in preload at different time intervals would be a prerequisite. Average urine output at the end of two hours following mannitol infusion was 1720mL (27 mL/Kg). Considering a constant fluid intake of 4 to 6 mL/Kg/h during this study periodand a significant difference in urine output at different time intervals ($P<0.0001$), different preload condition at each stage can be ascertained.

SVV and SPV values correlated with urine output per Kg body weight in the first 30 minutes following mannitol infusion. PPV values correlated poorly with urine output at all time intervals.

Significant correlation was present between SPV and SVV values throughout the study period.Although SPV and PPVvalues increased as the negative fluid balance increased, a significant correlation between the valuescould be demonstrated

only during 90 minutes and two hours following mannitol. SVV and PPV values correlated poorly throughout the study period.

But when data at different time intervals were pooled, all three indices correlated significantly with each other and also with urine output per Kg.

ROC curve analysis revealed better predictability of volume loss by SPV and PPV when compared to SVV.

Cardiovascular effects of mannitol

Mannitol given in the dose of 1 g/Kg over 15 to 20 minutes produces predictable changes in hemodynamic status.(36,37,38) An immediate cardiovascular effect of mannitol is a transient increase in cardiac output (CO) due to its direct effect on vascular tone.(36) Mannitol has also been found to release histamine from basophils, which in turn causes a decline in systemic vascular resistance (SVR).(39)Central venous pressure initially increases (within 15 minutes) and starts to fall thirty minutes after administration of mannitol.(36) After 45 minutes, the cardiovascular statusfollowing mannitol infusion isdictated by the balance between amount of intravascular volume contraction caused by diuresis and the amount of fluid intake.Such predictablechanges in hemodynamic status in the first hourfollowing infusion, render mannitol-induced intravascularchanges ‘a model for studying clinical situationswith varying intravascular volume’.(34)

What was the earlier literature on the issue?

Offline measurement of SPV and PPV as described by Gouvea and Gouvea had been validated by more than one study. (31,32,33)SPV and PPV values expressed in mm Hg had been shown to correlate significantly with amount of volume loss following furosemide.(31) SPV and PPV values expressed inpercentage had been shown to correlate strongly with SVV measured using FloTrac/Vigileo monitor.(33) Systolic pressure variationhas been found to correlate well with echocardiographicestimate of left ventricular end diastolic volume.(40)SVV derived from FloTrac and Doppler measurements had been shownto have acceptable bias and limits of agreement and similar performance in terms of fluid responsiveness in patients undergoing liver transplantation.(41)

Rational for the present study

Although previous studies had found strong correlation among SPV, PPV and SVV, unlike in this study they all had used either PiCCO or FloTrac/Vigileo systems to determine SVV.(30,33) These monitoring systems use pulse contour analysis to derive stroke volume variation and cardiac output. Till now correlation among SPV, PPV and Doppler blood flow velocity derived SVV has not been studied.

Calculation of stroke volume variation using echocardiography

In transoesophageal echocardiography, deep transgastric aortic long axis view provides optimal alignment of aortic blood flow and probe and it is considered as the ideal view for stroke volume and cardiac output measurements. (42,43) Though there may be under estimation of absolute stroke volume using transoesophageal

echocardiography,(44) the proportionate variation in stroke volume during each respiratory cycle may be preserved. Greatest limiting factor in using TEE for measuring stroke volume is the high influence of angle between the ultrasound beam and direction of blood flow. We avoided any probe manipulation during the study period. But displacement of heart due to respiratory movements itself might change the angle of insonation within a respiratory cycle. This can introduce an error in the measurement of stroke volume variation using TEE.

Clinical consequences of this study

Lack of correlation among these dynamic variables at some time intervals could be due to variation in influence of SVR on these parameters. While SVV measured by echocardiography could be the least affected, PPV measured from arterial pressure trace could be the most affected one. Though affected by changes in SVR, SPV and PPV could still predict fluid responsiveness, as fall in SVR could be considered as 'relative hypovolemia' of the expanded intravascular space and those patients also respond to fluid challenges. Furthermore a volume loss of 10 mL/Kg or more in the form of urine output was better predicted by SPV and PPV values than that of SVV values.

In contrast to normal expectation, positive correlation between baseline values of dynamic indices and urine output in first half an hour, suggests that hypovolemic patients might continue to void large amount of urine and become more hypovolemic. More urine output in these hypovolemic patients could be possible because of additional intravenous fluids infused (within the accepted 4 to 6 ml/Kg/h range) by treating anaesthesiologist, to negate the development of overwhelming

hypovolemia. All the patients in this study received mannitol for the first time in operation theatre and the above finding cannot be generalised for patients on chronic mannitol therapy. The importance of replacing the urine output over time to avoid severe hypovolemia cannot be underestimated.

Possible limitations of the present study

Using a low tidal volume (8 mL/Kg) can be considered as the possible limitationof the present study.The rationale for choosing 8mL/Kg tidal volume in our study was, with 10mL/Kg tidal volume, in few patients transoesophageal echocardiographic view was not stable. It changed considerably within each respiratory cycle and pulse wave Doppler waveform was not obtained continuously. This may be because of small size of thoracic cavity or more compliant lung resulting in more displacement of heart. Further De Backer and co-workers showed that pulse pressure variation was a reliable predictor of fluid responsiveness only if tidal volume was more than 8 ml/kg. (19) With 8mL/Kg tidal volume we were able to get stable echocardiographic view throughout each respiratory cycle in all patients. SPV and PPV values had significant correlation in 90 minutes and two hours after mannitol.As correlation was getting stronger with increasing hypovolemia,choosing a lesser tidal volume could be put forward as the reason for absence of correlation among these dynamic indices at some point of time.

Conclusion

1. During mechanical ventilation with a tidal volume of 8 mL/Kg, systolic pressure variation correlated significantly with stroke volume variation at different preload conditions following mannitol infusion. Pulse pressure variation correlated poorly with stroke volume variation. Systolic pressure variation and pulse pressure variation correlated only in the presence of hypovolemia, when a low tidal volume (8 mL/Kg) is being used.
2. Stroke volume variation and systolic pressure variation correlated significantly with amount of volume loss in the form of urine output for the first hour following mannitol infusion.
3. Systolic and pulse pressure variations predict a concomitant volume loss of 10mL/Kg or more, better than stroke volume variation.

Though in general all three dynamic indices correlated with each other and the degree of volume loss, at different preload conditions, the strength of correlation varied. This may be because of variation in influence of factors like systemic vascular resistance and tidal volume on these indices. Physicians should be aware of these limitations while employing these clinically useful indices.

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Annexure A - PROFORMA

Correlation of systolic pressure variation, pulse pressure variation and stroke volume variation in different preload conditions following a single dose mannitol infusion in elective neurosurgical patients

Name: IP no.:

Age/sex: Weight/Height

Diagnosis: Procedure:

Variables	Base line	After 15 mins	After 30 mins	After 60 mins	After 90 mins	After 120 mins
Max SBP						
Min SBP						
Max DBP						
Min DBP						
Max SV						
Min SV						
U/O (after mannitol)						
Peak airway Pressure						
MAC						
HR						

Protocol:

1. Induction agent: Sodium thiopental 5 mg/Kg
2. Opioid: Fentanyl infusion 1 mic/Kg/h
3. MAC value within ± 0.2
4. Tidal volume 8ml/Kg
5. Adjust respiratory rate to maintain $ETCO_2$
6. After starting mannitol, intravenous crystalloid infusion 4 to 6 ml/Kg/h
7. Fluid boluses of 100 ml were given if mean arterial pressure (MAP) decreased ≤ 60 mmHg or ≥20% from the baseline value.