HEMODYNAMIC CHANGES IN RESPONSE TO MANNITOL INFUSION IN NEUROSURGICAL PATIENTS UNDERGOING CRANIOTOMY: A TRANSESOPHAGEAL ECHOCARDIOGRAPHIC STUDY.

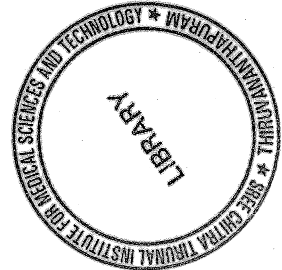
Thesis submitted for the partial fulfillment for the requirement

of

The degree of DM (Neuroanesthesiology)

of

SCTIMST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"Karmanye waadhikaraste maa phaleshu kadachana

Ma karma phalahetur bhurma te sango'stvakarmani"

"....Your right is to work only and never to the fruit thereof.
Be not instrumental in making your actions bear fruit,
nor let your attachment be to inaction...."

DECLARATION

I hereby declare that this thesis entitled **"Hemodynamic changes in response to mannitol infusion in neurosurgical patients undergoing craniotomy: A transesophageal echocardiographic study"**, has been prepared by me under the capable supervision and guidance Dr. Thomas Koshy, Professor, Department of Anesthesiology, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

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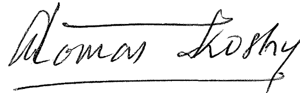
CERTIFICATE

This is to certify that this thesis entitled **"Hemodynamic changes in response to mannitol infusion in neurosurgical patients undergoing craniotomy: A transesophageal echocardiographic study"**, is a bonafide work of Dr Nilay Chatterjee, DM Neuroanesthesia Resident, and has been done under my direct guidance and supervision at Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram. He has shown keen interest in preparing this project.

Date: 4/10/2010

Place: Thiruvananthapuram



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CERTIFICATE

This is to certify that this thesis entitled **"Hemodynamic changes in response to mannitol infusion in neurosurgical patients undergoing craniotomy: A transesophageal echocardiographic study"**, has been prepared by Dr Nilay Chatterjee, DM Neuroanesthesia Resident, under the guidance of Dr. Thomas Koshy, MD, PDCC, Professor, Department of Anesthesiology at Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram. He has shown keen interest in preparing this project.

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INTRODUCTION

INTRODUCTION

Mannitol is the most commonly used osmotic diuretic to treat cerebral edema and to provide slack brain during craniotomy. Being a drug that increases the intravascular volume by drawing water from the intracellular compartment, it has a potential to significantly affect the hemodynamics. Apart from very few clinical studies measuring the hemodynamic variables, limited to heart rate and blood pressure, there is acute dearth of studies exclusively showing the hemodynamic effects of mannitol.[1] In fact a systemic search in PUBMED/MEDLINE could find very few substantiative articles on "mannitol" and "cardiac output".[2,3] One of these articles has shown the hemodynamic changes in response to a single dose of mannitol using non invasive cardiac output monitor based on thoracic electrical bioimpedance technique, in patients undergoing craniotomy.[3] By bioimpedance plethysmography they have shown that, stroke volume increased significantly for 15 minutes after the infusion of mannitol, but at 45 minutes it was significantly lower than that from 1 to 30 minutes. Cardiac index also showed similar changes. The rate of urine output was higher during first 10 minutes than during rest of the study period. A major limitation of the aforementioned study is that, the parameters could have correlated and confirmed in a far objective and specific manner with measurement of central venous pressure or by echocardiographic evaluation.[3]

Alfred and colleagues have shown that although osmotic agents are among the most fundamental tools to control intracranial pressure (ICP), prospective data to establish clear guidelines on their use are lacking.[4] Knapp has stated that intravenous bolus administration of mannitol lowers the ICP in 1 to 5 minutes; with a peak effect at 20 to 60 minutes. The effect of mannitol on ICP lasts 1.5 to 6 hours, depending on the clinical condition.[5] Muizelaar et al have shown that because of rheologic and osmotic

effects, infusion of mannitol is immediately followed by an expansion of plasma volume and a reduction in hematocrit and blood viscosity, which may increase cerebral blood flow (CBF).[6] The osmotic effect of mannitol increases serum tonicity and draws edema fluid from cerebral parenchyma. This process takes 15 to 30 minutes, until gradients are established. Bernard et al have described esophageal Doppler, a noninvasive, instantaneous cardiac output monitor and its reliability, which is comparable to that of other current techniques to measure cardiac output.[7] Schöber et al have illustrated in a review article that invasive cardiac output monitoring, traditionally performed with transpulmonary thermodilution techniques, is usually reserved for high risk critically ill patients because of the inherent risks of these methods. In contrast, transesophageal Doppler technology offers a safe, quick, and less invasive method for routine measurements of cardiac output.[8] Wakeling and colleagues have demonstrated improved patient outcome and reduced length of hospital stay when hemodynamic management is guided by transesophageal Doppler in major abdominal surgery.[9] Gan and colleagues have shown similar results in their study.[10]

In this background we proposed the present study to describe the hemodynamic changes in response to mannitol infusion with respect to time by transesophageal echocardiography (TEE), which is far more accurate, compared to any other non-invasive/lesser invasive methods, having extremely less inherent risk to the patient. We also intended to record blood pressure and central venous pressure from routinely placed invasive monitors in any major neurosurgery eg. radial artery catheter and central venous cannula inserted in internal jugular/subclavian vein. There is no single study till date, where the effects of mannitol infusion on hemodynamics have been studied with TEE derived measurements. TEE is far more specific and objective

compared to impedance plethysmography so far the measurements of stroke volume, cardiac output and cardiac index are concerned. TEE has got very little inherent risk, in comparison to invasive methods of measuring such indices eg. pulmonary artery catheter. Further as per ACC/AHA guidelines, TEE should be routinely used in neurosurgical procedures where there are anticipated risks of major fluid shifts, and hemodynamic perturbations (class IIa indication). The results of this study might throw more light on hemodynamic responses to mannitol infusion such as ejection fraction/fractional area of change, with respect to time in neurosurgical patients undergoing craniotomy.

AIMS

AND

OBJECTIVES

AIMS AND OBJECTIVES

1. To carry out an assessment of the extent and duration of hemodynamic changes (Arterial Blood Pressure, Central Venous Pressure, Heart rate, Stroke Volume, Cardiac Output, Cardiac Index, End Diastolic Area, End Systolic Area, Fractional Area of Change), with respect to time, in response to a single bolus dose of mannitol, in patients undergoing craniotomy for intracranial tumour surgery requiring intraoperative brain relaxation, using a non-invasive cardiac output monitor- TEE based on Doppler principles.
2. To correlate the changes of TEE derived parameters of hemodynamics with routinely monitored hemodynamic variables like Arterial Blood Pressure, Central Venous Pressure, Urine Output and Fluid Balance.

REVIEW OF LITERATURE

Review of Literature

Osmotherapy can be defined broadly as the use of osmotically active solutions to reduce the volume of the intracranial contents. The first description of the principles of osmotherapy as applied to the central nervous system (CNS) is often attributed to Weed and McKibben in 1919.[11] Their interpretation has formed the foundation of the concept of "osmotherapy" as it may be applied to treatment of space-occupying intracranial pathology.

In 1927, Fremont-Smith and Forbes formalized the intravenous delivery of osmotic agents for clinical practice, first making the use of concentrated urea.[12]

Hughes et al[13] were the first to demonstrate that concentrated solutions of human plasma proteins could effectively reduce raised intracranial pressure (ICP). However, concerns about allergic reactions and the cost of preparation of concentrated human plasma limited early interest in "oncotic therapy."

Wise and Chater[14] clearly demonstrated that the carbohydrate mannitol was a more practically useful agent. Unlike urea, mannitol was easy to prepare, chemically stable in solution, and did not produce vein irritation when infused, among other desirable properties that are discussed later. Intravenous mannitol infusions subsequently became a central modality in controlling of intracranial hypertension.

In the 1970s, the work of Little[15], Sundt[16], and Crowell and Olsson[17] identified the potentially beneficial rheologic effects of mannitol and other osmotic agents in the management of cerebral ischemia.

More recently, several investigators, most notably Rosner and Coley[18] and Muizelaar et al[19], have challenged the nostrum that osmotherapy is based on direct osmotic action and "shrinkage" of the brain parenchyma. Alternative theories that emphasize dynamic changes in cerebral blood volume (CBV) and CSF circulation have been put forth.[20] In general, these theories reflect a more differentiated view of the volume dynamics of the intracranial space.

Rosner has opined that in general, the ideal agent for use in osmotherapy is a rapidly excreted diuretic that establishes strong trans-endothelial osmotic gradients. Mannitol comes as close to this ideal as any agent currently available. An additional advantage of mannitol which is typically administered as a rapid intravenous infusion; is the potentially beneficial hemodynamic effects resulting from the bolus itself.[21]

As per Cote et al the effect of a mannitol bolus on systemic arterial pressure is variable. A slight increase in pulse pressure and mean arterial blood pressure is most commonly observed, but transient decreases in blood pressure secondary to decreases in systemic vascular resistance are not uncommon and have been described definitively in the literature.[1]

Findlay et al have tried to explain the mechanisms of vasodilatory effects of mannitol. As per their opinion the acute vasodilatory effect of mannitol is not well understood and has been related to mechanisms as diverse as decreases in plasma pH, release of atrial natriuretic factor, histamine release from basophils, and direct impairment of the contractile properties of vascular smooth muscle.[22,23,24]

Barry et al have looked at systematically administered mannitol boluses to patients with reduced left or right ventricular function.[25] Presumably because of the rapid clearance of mannitol from the plasma, signs and symptoms of congestive heart

failure were not observed in this series. According to them precaution must be taken in the case of patients with impaired renal clearance. If osmotherapy is used at all in this population, the dose and dosing interval should be decreased and increased, respectively. In addition, monitoring of pertinent hemodynamic variables that may guide the course of therapy should be considered.

Richard et al[26] have emphasized that an important practical point being the ratio of the volume of fluid diuresed to the volume of mannitol administered, which may be appreciably high, approaching five for a 25% solution of mannitol (the approximate ratio of the osmolality of mannitol to normal plasma osmolality). According to them, this fact readily explains the extent to which marked dehydration of the body can result from administration of osmotic diuretics. Hyperosmolar dehydration can be insidious. Unlike hemorrhage or relatively isotonic volume losses, which cause early clinical signs of impending hemodynamic instability, gradual hypertonic dehydration occurs in the presence of mounting osmotic and oncotic gradients favouring movement of fluid from the tissues into the vascular space. These forces tend to preserve circulating volume. Clinical signs of hemodynamic compromise therefore may not develop until quite late, when extravascular dehydration is severe.

Nikki et al et al have shown the hemodynamic changes in response to a single dose of mannitol using non invasive cardiac output monitor, in patients undergoing craniotomy.[3] They have measured blood pressure by non invasive means and cardiac output by bioimpedance plethysmography. They have shown that all post mannitol systolic blood pressure values were significantly lower than pre mannitol values, whereas stroke volume increased significantly for 15 minutes after the infusion of mannitol, but at 45 minutes it was significantly lower than that from 1 to 30 minutes.

Cardiac index also showed similar changes. The rate of urine output was higher during first 10 minutes than during rest of the study period.

Alfred and colleagues have shown that although osmotic agents are among the most fundamental tools to control ICP, prospective data to establish clear guidelines on their use are lacking.[4] Knapp has stated that intravenous bolus administration of mannitol lowers the ICP in 1 to 5 minutes; with a peak effect at 20 to 60 minutes. The effect of mannitol on ICP lasts 1.5 to 6 hours, depending on the clinical condition.[5] Muizelaar et al have shown that because of mannitol having rheologic and osmotic effects, infusion of mannitol is immediately followed by an expansion of plasma volume and a reduction in hematocrit and blood viscosity, which may increase CBF.[6] The osmotic effect of mannitol increases serum tonicity and draws edema fluid from cerebral parenchyma. This process takes 15 to 30 minutes, until gradients are established.

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MATERIALS

AND

METHODS

MATERIALS AND METHODS

METHODOLOGY:

A prospective, cross sectional, pilot study in neurosurgical patients undergoing craniotomy and requiring mannitol for intraoperative brain relaxation. The primary objective was to carry out an assessment of the hemodynamic changes, with respect to time, in response to a single dose of mannitol, in patients undergoing craniotomy for intracranial tumour surgery requiring intraoperative brain relaxation, using a non-invasive cardiac output monitor- TEE, based on Doppler principles.

TEE probe was placed after induction of anesthesia. A constant infusion of normal saline was maintained at the rate of 6 to 8 mL/kg/hr throughout the study period. Mannitol infusion was started 15 minutes before the dural opening at a dose of 1 gm/kg body weight and administered over 15 minutes.

Hemodynamic parameters eg. arterial blood pressure (ABP), central venous pressure (CVP), heart rate (HR), end diastolic area (EDA), end systolic area (ESA), fractional area of changes (FAC), stroke volume (SV), cardiac output (CO) were measured just before starting the mannitol infusion and after infusion is over, starting 5 minutes after infusion, then at every 10 minutes intervals up to 45 minutes. Recordings of systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were made by direct arterial blood pressure measured at radial artery. CVP was measured using CVP cannula placed in the internal jugular or in subclavian vein. UO was measured by urometer attached to urine bag; fluid was being administered by a measuring volumetric set. Amount of UO or fluid administered were noted at fixed time intervals. EDA and ESA were recorded by TEE, positioning the probe at transgastric (TG) mid-papillary short axis view, and drawing the endocardial border.

Diameter of LVOT was measured from mid-esophageal long axis view, and 'E', 'A' velocities were measured from mid esophageal long axis (MELAX) view by pulsed wave Doppler. SV was measured either from transgastric long axis or deep transgastric view, by using pulsed wave Doppler in LVOT, at the same site where LVOT diameter was recorded. For each time points 3 different recordings were made in close succession and loops were saved. Measurements of EDA, ESA, 'E', 'A' and SV were made from the saved loops when all the recordings were over. FAC, 'E/A' and CO were calculated using 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).

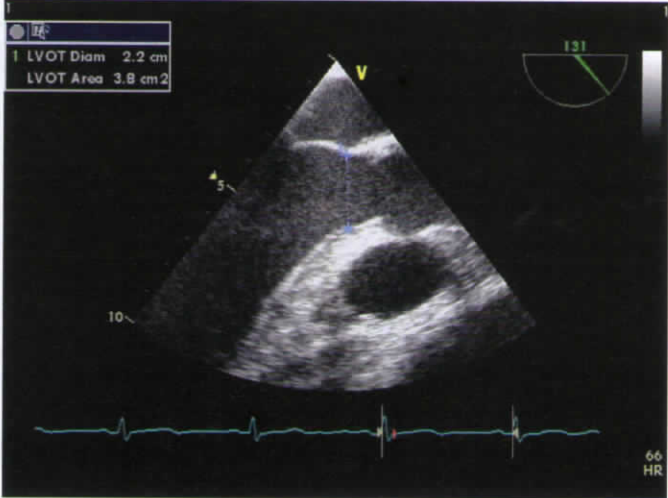


Figure E1: Measurement of LVOT diameter

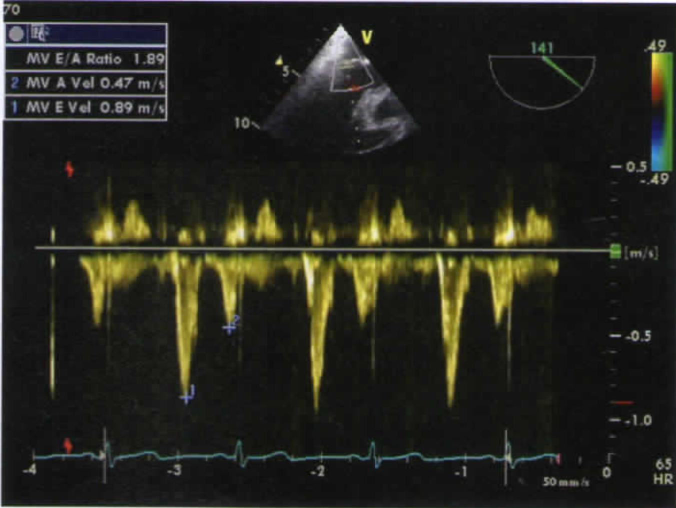


Figure E2: Measurement of 'E' 'A' and 'E/A' ratio

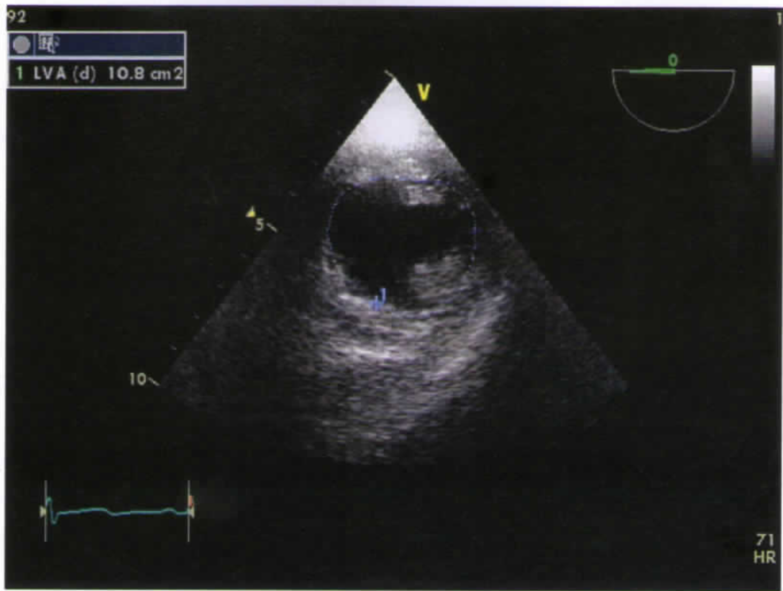


Figure E3: Measurement of EDA

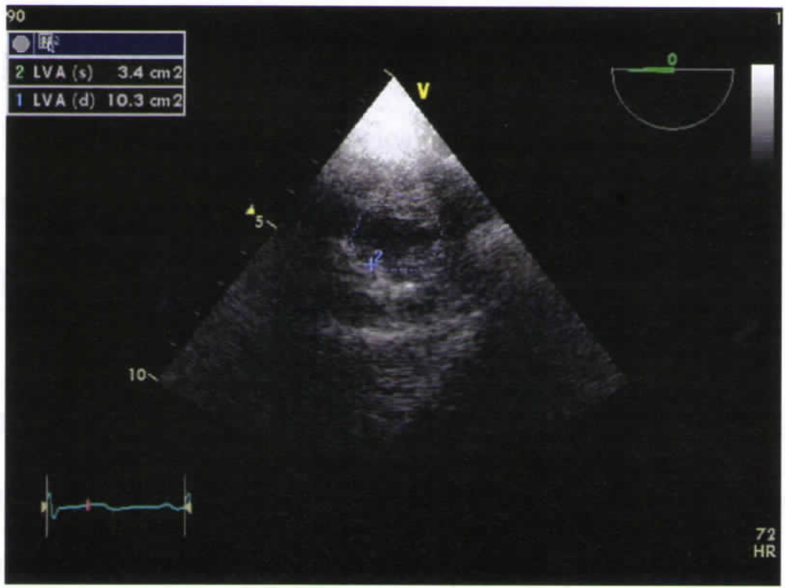


Figure E4: Measurement of ESA

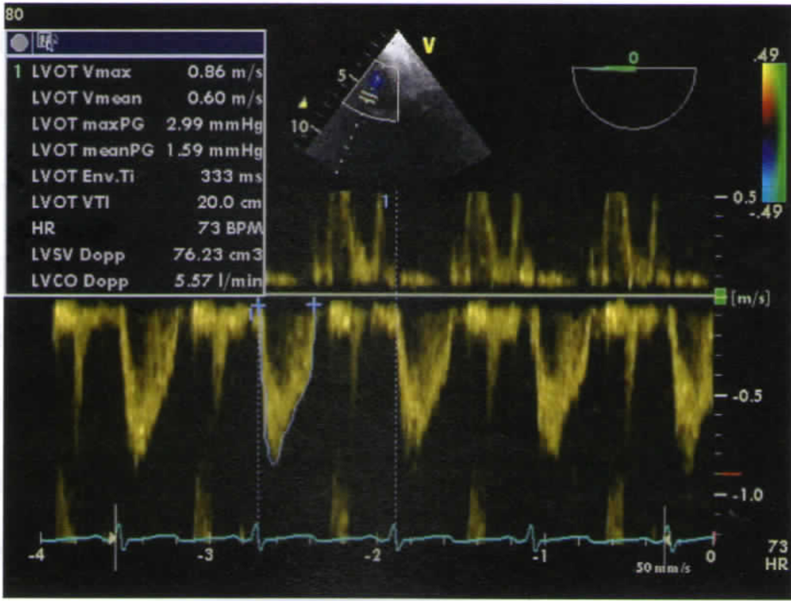


Figure E5: Measurement of $LVOT_{VTI}$

A standardized general anesthetic technique consisting of induction with propofol, tracheal intubation after muscle paralysis with vecuronium and maintenance with air, oxygen and sevoflurane was used in all the patients. Analgesia was provided with fentanyl 4 mcg/kg at the induction of anesthesia, followed by 2 mcg/kg just before skull pin application and thereafter 2 mcg/kg/hour throughout the surgery. Isotonic intravenous fluids were administered at a rate of 6-8 ml/hour. Throughout the study period sevoflurane was maintained between 0.5 to 0.7 minimum alveolar concentration (MAC).

SUBJECT/PARTICIPANT SELECTION

TYPE: All adult neurosurgical patients undergoing craniotomy for supra-tentorial large brain tumours, requiring mannitol infusion for intraoperative brain relaxation.

NUMBER: 15 adult patients undergoing surgery for brain tumour.

INCLUSION CRITERIA: Patients undergoing elective neurosurgical procedures (craniotomy) due to presence of tumors of considerable size [exceeding 2.5 cm, at least in 2 dimensions], aged between 18-50 years.

EXCLUSION CRITERIA: Patients with known relative or absolute contraindication to placement of TEE probe (esophageal stricture, esophagitis, gastritis/gastric ulcer, restricted mouth opening), surgical positioning requiring extreme flexion of the neck, patient's refusal, pregnant women, persons incompetent to give consent.

STATISTICAL ANALYSIS:

Results obtained from the study were expressed in mean +/- SD, for non parametric data chi square test was applied and for numeric data with continuous variables ANOVA for repeated measures followed by post hoc analysis with least significance

difference (LSD) was performed. A “p” value less than 0.05 was considered as statistically significant and less than 0.01 as highly significant. The software SPSS 17.0 had been used for analysis.

OBSERVATIONS AND RESULTS

OBSERVATIONS AND RESULTS

Results obtained from the study were expressed in tabular format. Continuous numeric variables were expressed as Mean (SD). Binary or ordinal data were expressed as number (%). Qualitative data was analyzed by Pearson's chi square test, fisher exact test was employed when the number in individual cell was </=5. Quantitative data was expressed as mean (SD or SEM). Analysis of variance was done for repeated measures of continuous variables by 1 way ANOVA, for post hoc analysis LSD test was applied. Software used for the analysis was SPSS version 17.0 [SPSS; Chicago IL].

Table A: Demographic Data

Age of the subjects	31 +/- 10 years
M:F	9:6
Body weight	58 +/- 16 kg

Table 1: Changes of different hemodynamic parameters e.g. Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), Heart Rate (HR) and Central Venous Pressure (CVP), with respect to time

*(corresponding p values, at each time points, compared to baseline, are given in brackets; * indicates p is statistically significant i.e. <0.05 and ** indicates p is highly significant, <0.01)*

Parameter	Baseline; before mannitol infusion	5 mins after mannitol	15 mins after mannitol	25 mins after mannitol	35 mins after mannitol	45 mins after mannitol
SBP (mm Hg)	124 +/- 19	134 +/- 14 (0.138)	125 +/- 14 (0.881)	125 +/- 18 (0.898)	122 +/- 18 (0.733)	118 +/- 19 (0.317)
DBP (mm Hg)	71 +/- 11	70 +/- 8 (0.854)	69 +/- 9 (0.580)	71 +/- 9 (0.941)	69 +/- 11 (0.685)	68 +/- 10 (0.507)
MAP (mm Hg)	89 +/- 13	91 +/- 10 (0.664)	87 +/- 12 (0.675)	89 +/- 13 (0.919)	87 +/- 13 (0.572)	85 +/- 13 (0.410)
HR (beats/min)	72 +/- 12	77 +/- 12 (0.276)	75 +/- 14 (0.529)	77 +/- 14 (0.529)	76 +/- 13 (0.425)	76 +/- 13 (0.401)
CVP (mm Hg)	6 +/- 1	9 +/- 2 (0.0001)**	7 +/- 2 (0.105)	7 +/- 2 (0.370)	6 +/- 2 (0.806)	5 +/- 2 (0.254)

ANOVA followed by post hoc analysis by LSD showed SBP increased from baseline values to 5 minutes post mannitol, however this was non-significant (p=0.138), thereafter SBP remained almost similar to baseline across all other time points, without much variation from its baseline value.

Both in DBP and MAP values changed very little from baseline across different time points post mannitol and these small variations were statistically non significant.

Heart rate changes were not appreciable across different time points, although there was a general trend for non significant increase in HR at 5 minutes post mannitol, but thereafter quickly it returned to baseline at maintained at that level.

CVP increased from its baseline value after mannitol infusion is over and reached to its maximum level at 5 minutes post mannitol (6+/-1 at baseline to 9+/-2 at 5 minutes post mannitol; $p<0.001$), it remained elevated, although non significantly till 15 minutes post mannitol (7+/-2; $p=0.1$), then came down, starting at 25 minutes onwards and reached below baseline levels at 45 minutes post mannitol, however this decrease was statistically not significant (5+/-2; $p=0.25$).

Table 2: Changes of Left Ventricular End Diastolic Area (EDA), End Diastolic Area index (EDAi), End Systolic Area (ESA), End Systolic Area index (ESAi) and Fractional Area Change (FAC) with respect to time

Parameter	Baseline; before mannitol infusion	5 mins after mannitol	15 mins after mannitol	25 mins after mannitol	35 mins after mannitol	45 mins after mannitol
EDA (cm^2)	11.9 +/- 2.2	15 +/- 3 (0.002)**	13.5 +/- 3.3 (0.118)	12.5 +/- 2.6 (0.572)	11.6 +/- 2.5 (0.748)	11.8 +/- 2.2 (0.921)
EDAi (cm^2/m^2 BSA)	7.2 +/- 1.4	9.2 +/- 1.8 (0.002)**	8.2 +/- 2 (0.119)	7.6 +/- 1.7 (0.563)	7 +/- 1.5 (0.737)	7.2 +/- 1.4 (0.932)
ESA (cm^2)	4.9 +/- 1.3	5.5 +/- 1.6 (0.310)	4.9 +/- 1.5 (0.928)	4.7 +/- 1.4 (0.773)	4.4 +/- 1.5 (0.359)	4.9 +/- 1.5 (0.975)
ESAi (cm^2/m^2 BSA)	2.9 +/- 0.8	3.3 +/- 0.9 (0.239)	3 +/- 0.9 (0.919)	2.9 +/- 0.8 (0.786)	2.7 +/- 0.8 (0.338)	2.9 +/- 0.8 (0.977)
FAC (%)	58.8 +/- 7.2	64 +/- 6.2 (0.06)	63 +/- 6.8 (0.137)	61.7 +/- 7.7 (0.301)	62 +/- 9.5 (0.261)	58.9 +/- 7.5 (0.994)

EDA: ANOVA followed by Post hoc analysis (by least significant difference- LSD) showed EDA increased significantly after mannitol infusion and this increase was statistically significant at 5 minutes after mannitol infusion was over with respect to baseline (from 11.9+/-2.2 at baseline to 15+/-3 at 5 minutes; p=0.002), then it remained non significantly elevated till 25 minutes following which it came down gradually, reached the baseline levels at 45 minutes post infusion.

EDAi: EDAi increased significantly after mannitol infusion at 5 minutes with respect to baseline (7.2+/-1.4 at baseline to 9.2+/-1.8 at 5 minutes post mannitol, p=0.002), then it remained non significantly elevated till 15 minutes post mannitol infusion, then gradually came down and reached the baseline levels at 45 minutes post infusion.

ESA: ESA increased non-significantly after mannitol infusion at 5 minutes (p>0.05) with respect to baseline, then it remained almost similar to the baseline values across all the time points.

ESAi: ESAi increased non-significantly after mannitol infusion at 5 and at 15 minutes with respect to baseline (p>0.05), then gradually came down and reached almost similar to baseline values at 45 minutes.

FAC: FAC increased non-significantly after mannitol infusion with respect to baseline, achieved its maximum value at 5 minutes post mannitol and remained elevated till 35 minutes, then gradually came down reached almost similar to the baseline values at 45 minutes.

Table 3: Changes of Left Ventricular Outflow Tract-Velocity Time Integral ($LVOT_{VTI}$), Stroke Volume of Left Ventricle (SV), Cardiac Output (CO) and Cardiac Index (CI), with respect to time

Parameter	Baseline; before mannitol infusion	5 mins after mannitol	15 mins after mannitol	25 mins after mannitol	35 mins after mannitol	45 mins after mannitol
$LVOT_{VTI}$ (cm)	14.2 +/- 2.2	18.6 +/- 2.2 (0.0001)**	17.6 +/- 1.9 (0.0001)**	15.5 +/- 2.4 (0.084)	14.4 +/- 2 (0.807)	13.4 +/- 1.6 (0.301)
SV (ml/beat)	46.4 +/- 10.1	61.2 +/- 13.2 (0.0001)**	58 +/- 12.7 (0.005)**	50.8 +/- 11.8 (0.276)	46.8 +/- 9.3 (0.9)	43.8 +/- 8.9 (0.536)
CO (liter/min)	3.4 +/- 0.9	4.7 +/- 1.3 (0.001)**	4.4 +/- 1.2 (0.013)*	3.8 +/- 1.1 (0.252)	3.6 +/- 0.9 (0.627)	3.3 +/- 0.8 (0.909)
CI (litre/min/m^2BSA)	2 +/- 0.7	2.9 +/- 0.9 (0.002)**	2.7 +/- 0.8 (0.026)*	2.3 +/- 0.7 (0.308)	2.2 +/- 0.6 (0.694)	2 +/- 0.5 (0.893)

$LVOT_{VTI}$ values consistently increased from its baseline values after mannitol infusion and reached highly significant levels at 5 and 15 minutes post infusion (14.2+/-2.2 at baseline to 18.6+/-2.2 at 5 minutes post infusion; $p<0.001$, and 17.6+/-1.9 at 15 minutes post infusion; $p<0.001$). $LVOT_{VTI}$ remained elevated, although non significantly till 25 minutes post mannitol, then gradually decreased and reached below baseline levels at 45 minutes post infusion; however this decrease was statistically non-significant ($p=0.3$).

SV values also followed similar pattern. It increased from its baseline values after mannitol infusion and reached highly significant levels at 5 and 15 minutes post infusion (46.4+/-10.1 at baseline to 61.2+/-13.2 at 5 minutes post infusion; $p<0.001$, and 58+/-12.7 at 15 minutes post infusion; $p=0.005$). Thereafter SV gradually decreased and reached below baseline levels at 45 minutes post infusion; however this decrease was statistically non-significant ($p=0.53$).

CO significantly increased from baseline to 5 and 15 minutes post mannitol (3.4+/-0.9 at baseline, 4.7+/-1.3 at 5 minutes; p=0.001, and 4.4+/-1.2 at 15 minutes; p=0.013) there after CO gradually came down and reached almost baseline levels at 45 minutes post mannitol.

Similar trends were observed in CI, which significantly increased from baseline to 5 and 15 minutes post mannitol (2+/-0.7 at baseline, 2.9+/-0.9 at 5 minutes; p=0.002, and 2.7+/-0.8 at 15 minutes; p=0.026) there after CI came down and reached almost baseline levels at 45 minutes post mannitol.

Table 4: Changes of indices of Left Ventricular Diastolic Function in terms of changes in Mitral Inflow Velocities E, A and E/A, with respect to time

Parameter	Baseline; before mannitol infusion	5 mins after mannitol	15 mins after mannitol	25 mins after mannitol	35 mins after mannitol	45 mins after mannitol
E (m/sec)	0.79 +/- 0.17	0.91 +/- 0.14 (0.032)*	0.76 +/- 0.16 (0.635)	0.75 +/- 0.16 (0.459)	0.68 +/- 0.13 (0.054)	0.71 +/- 0.16 (0.192)
A (m/sec)	0.45 +/- 0.16	0.51 +/- 0.16 (0.279)	0.44 +/- 0.14 (0.756)	0.41 +/- 0.12 (0.387)	0.41 +/- 0.11 (0.416)	0.43 +/- 0.12 (0.642)
E/A	1.8 +/- 0.39	1.93 +/- 0.55 (0.632)	1.88 +/- 0.65 (0.816)	1.95 +/- 0.65 (0.546)	1.75 +/- 0.52 (0.673)	1.75 +/- 0.53 (0.704)

Mitral valve inflow velocity showed the following changes: ‘E’ velocity increased from baseline values to 5 minutes post mannitol (0.79+/-0.17 at baseline to 0.91+/-0.14 at 5 minutes post mannitol; p=0.03) but thereafter returned to almost similar to baseline values

and remained at that level across all other time points. 'A' velocity increased non-significantly at 5 minutes post mannitol then returned to almost similar to baseline values and maintained at that level across all other time points. 'E/A' ratio also increased from baseline values to non-significantly increased levels at 5 minutes (1.83+/-0.39 at baseline to 1.93+/-0.54 at 5 minutes post mannitol; p=0.63), then returned to baseline values and remained at that level throughout all other time points.

Table 5: Changes in Systemic Vascular Resistance (SVR) with respect to time

Parameter	Baseline; before mannitol infusion	5 mins after mannitol	15 mins after mannitol	25 mins after mannitol	35 mins after mannitol	45 mins after mannitol
SVR (dynes * sec * cm^{-5})	2147 +/- 756	1463 +/- 380 (0.002)**	1571 +/- 513 (0.008)**	1859 +/- 619 (0.175)	1915 +/- 567 (0.273)	2032 +/- 555 (0.586)

Systemic Vascular Resistance decreased significantly from baseline levels at 5 and 15 minutes post mannitol (2147.46+/-756.47 at baseline to 1463.1+/-380.7 at 5 minutes post infusion; p=0.002, and 1571.42+/-513.5 at 15 minutes post infusion; p=0.008), thereafter it gradually increased towards baseline levels, starting at 25 minutes post mannitol onwards, and almost reached baseline levels at 45 minutes after mannitol infusion was over.

Table 6: Details of Fluid Intake (FI) and Output, in terms of Urine Output (UO), Fluid Intake (FI) and Fluid Balance (FB) with respect to time

Parameter	From induction of anesthesia to the time of mannitol infusion	0 to 5 mins after mannitol	6 to15 mins after mannitol	16 to25 mins after mannitol	26 to35 mins after mannitol	36 to 45 mins after mannitol
UO (ml)	176 +/- 76 [0.685]	185 +/- 93 (0.728)	110 +/- 30 (0.003)** [0.001]##	104 +/- 22 (0.0001)** [0.0001]##	103 +/- 22 (0.0001)** [0.0001]##	84 +/- 13 (0.0001)** [0.0001]##
FI (ml)	239 +/- 87 [0.0001]##	101 +/- 92 (0.0001)**	86 +/- 21 (0.0001)** [0.455]	71 +/- 16 (0.0001)** [0.129]	68 +/- 12 (0.0001)** [0.99]	62 +/- 11 (0.0001)** [0.051]
FB (ml)	76 +/- 111 [0.0001]##	-84 +/- 72 (0.0001)**	-24 +/- 25 (0.001)** [0.004]##	-34 +/- 22 (0.0001)** [0.016]#	-35 +/- 14 (0.0001)** [0.020]#	-22 +/- 14 (0.001)** [0.003]##

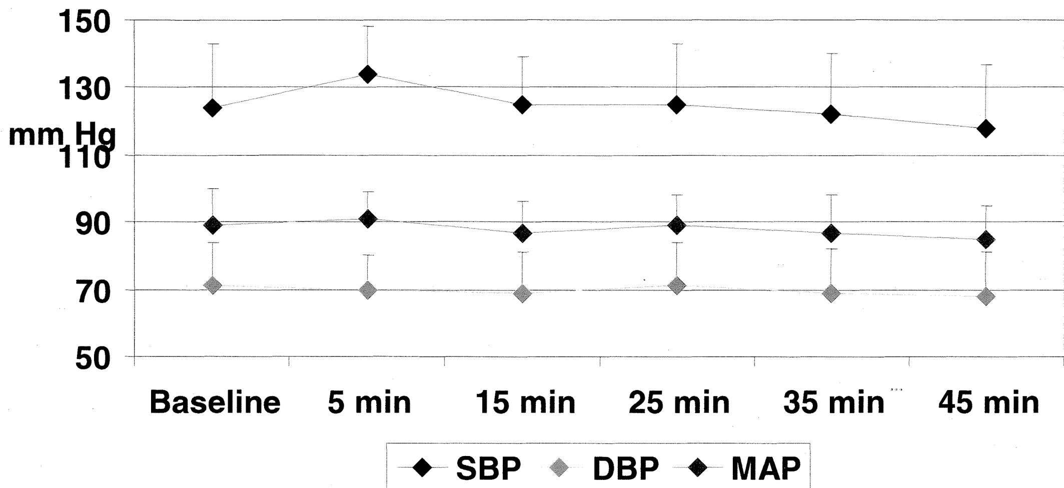
*p values when baseline compared to different time intervals, post mannitol, are given within ( ), */** indicating significant or highly significant differences from baseline. Again, p values, when 0-5 minutes post mannitol compared to all other time intervals are given within [ ], #/## indicates significant or highly significant difference from 0-5 minutes values.*

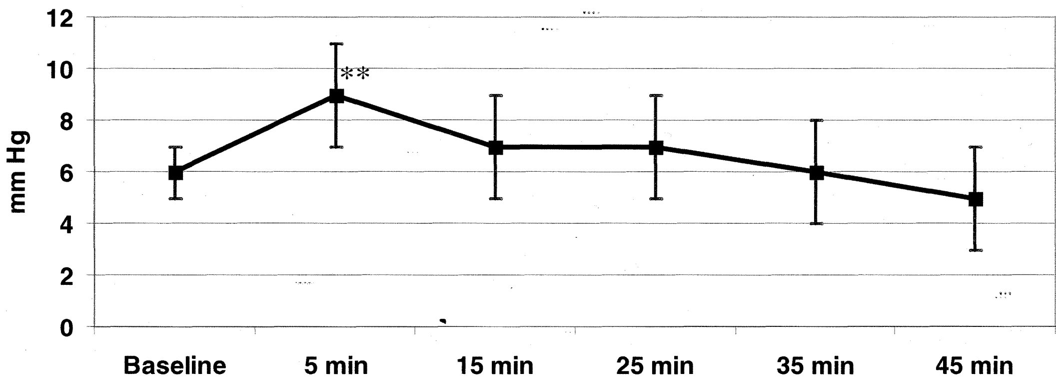
Urine output increased after mannitol infusion was over and it was maximum within 0-5 minutes post mannitol, although not reached to the level of statistical significance (176+/-76 at baseline and 185+/-93 at 0-5 minutes post infusion; p=0.728), thereafter UO was significantly low compared to its volume at 0-5 minutes post mannitol, at all the subsequent time intervals thereafter, and this difference was statistically highly significant (p<0.01 at 6-15, 16-25, 26-35 and 36-45 minutes post mannitol).

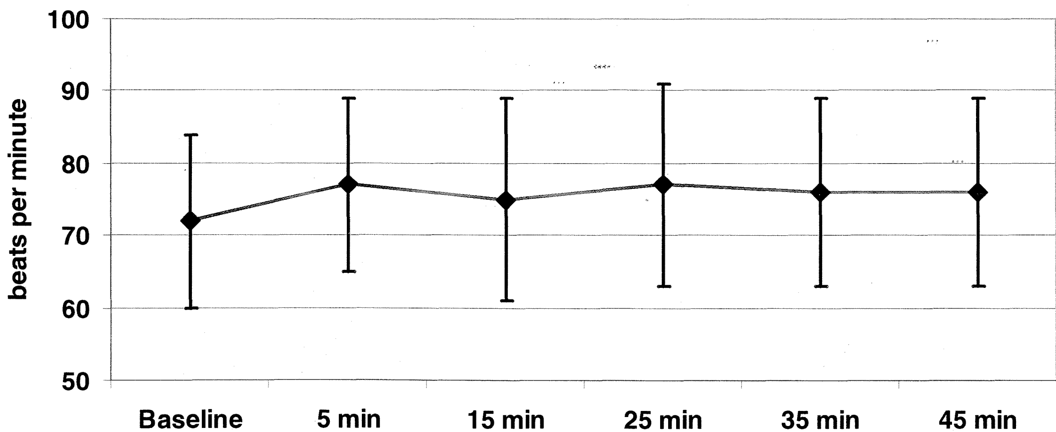
Fluid Balance (calculated as FI-UO) was negative at all time intervals following mannitol infusion. It was maximally negative at 0-5 minutes post mannitol compared to baseline (76+/-111 at baseline and -84+72 at 0-5 minutes post mannitol; p=0.0001), following this, even though FB remained consistently negative at all subsequent time intervals, but it maintained at significantly less negative values compared to that at 0-5 minute time interval.

GRAPHS AND CHARTS

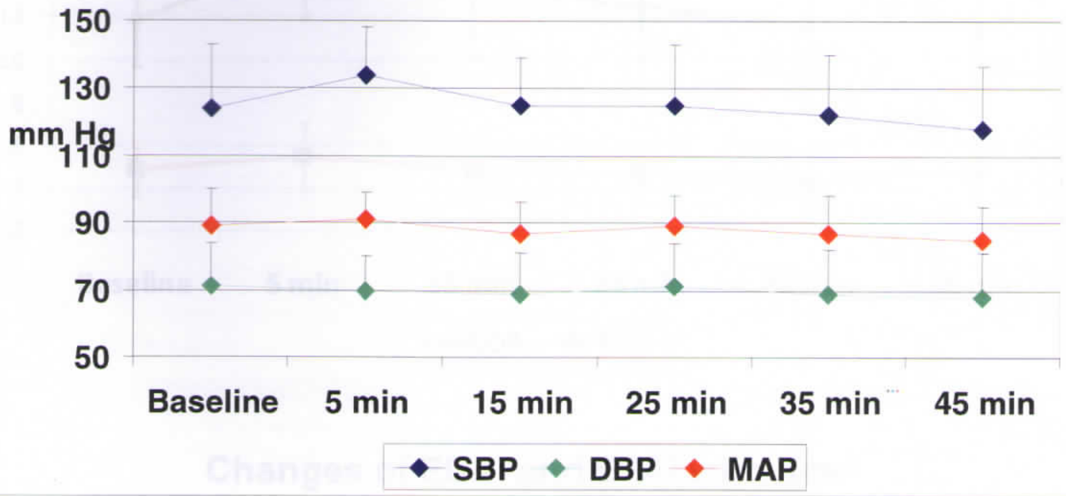
GRAPHS AND CHARTS

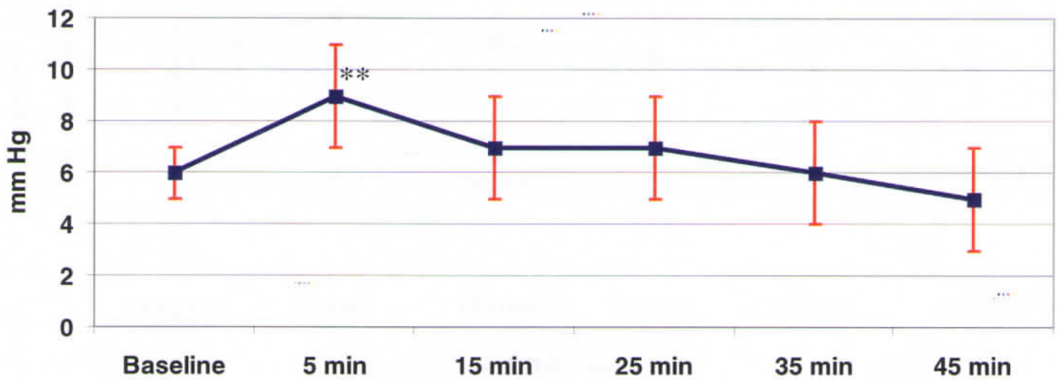


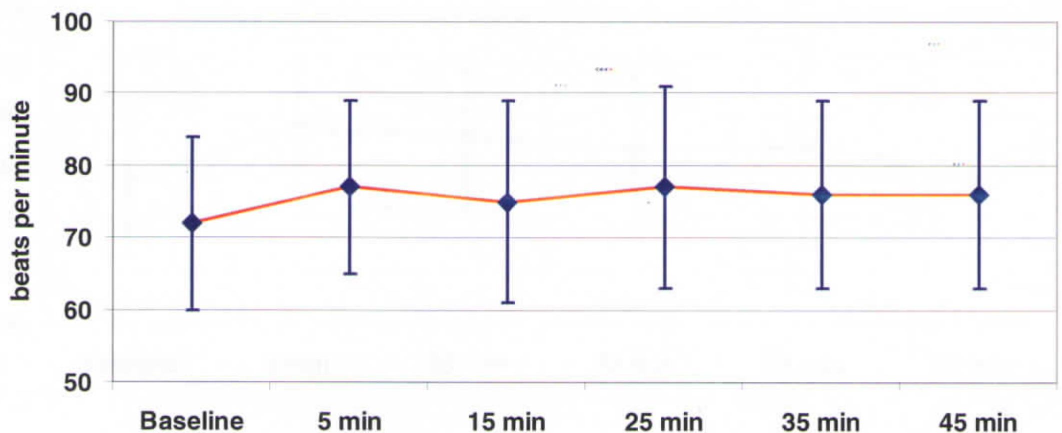


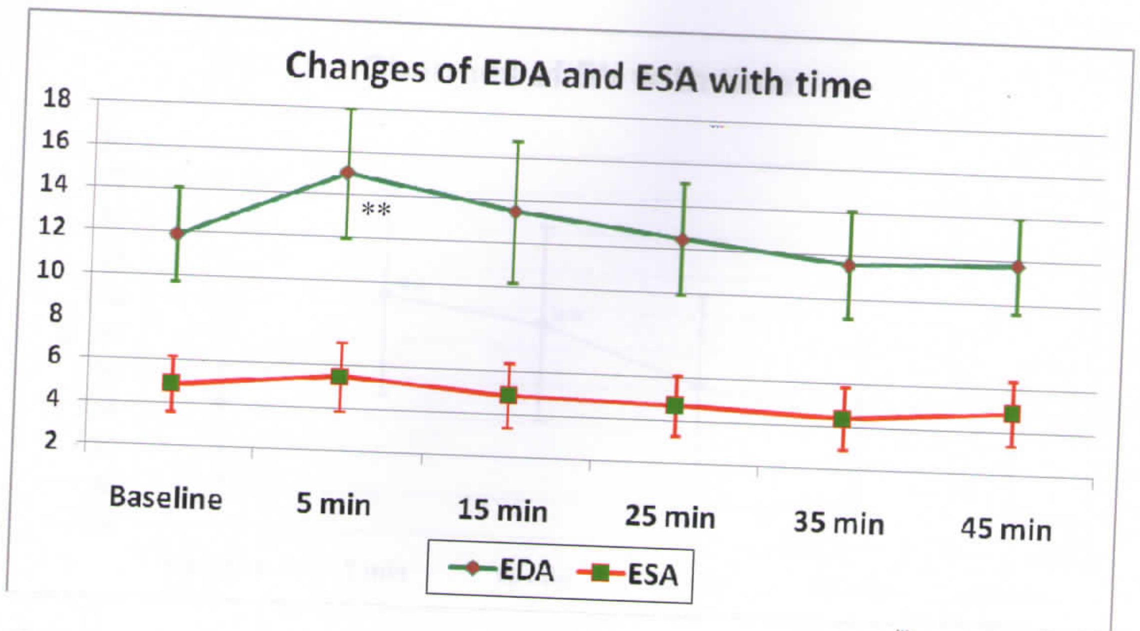


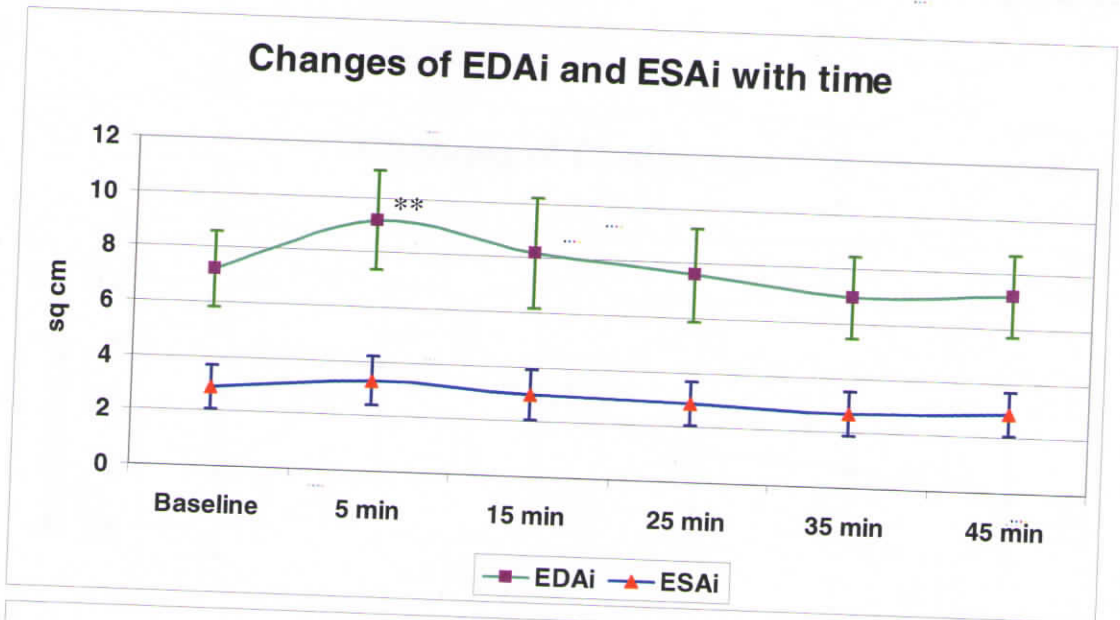
GRAPHS AND CHARTS

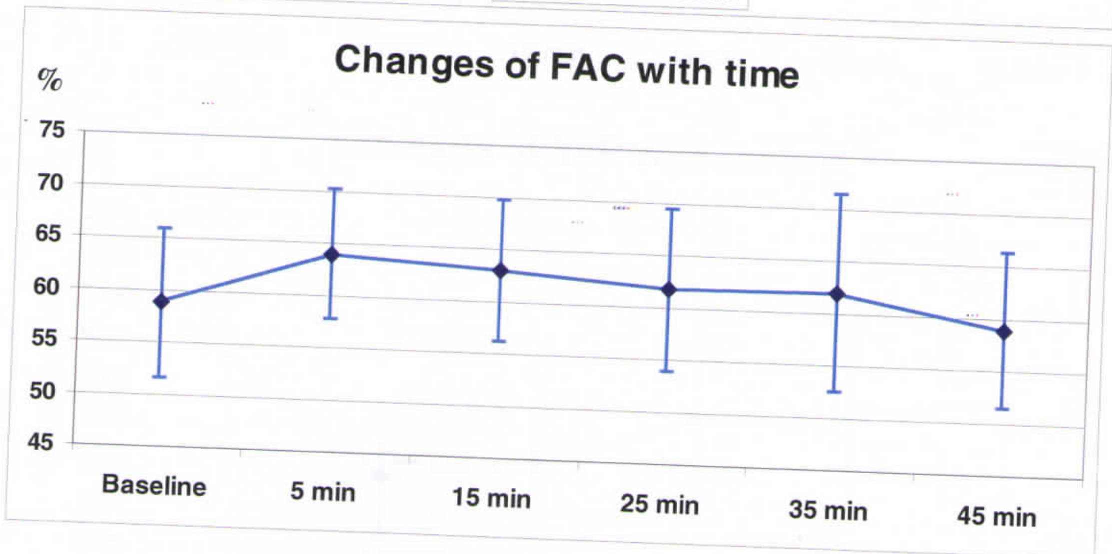


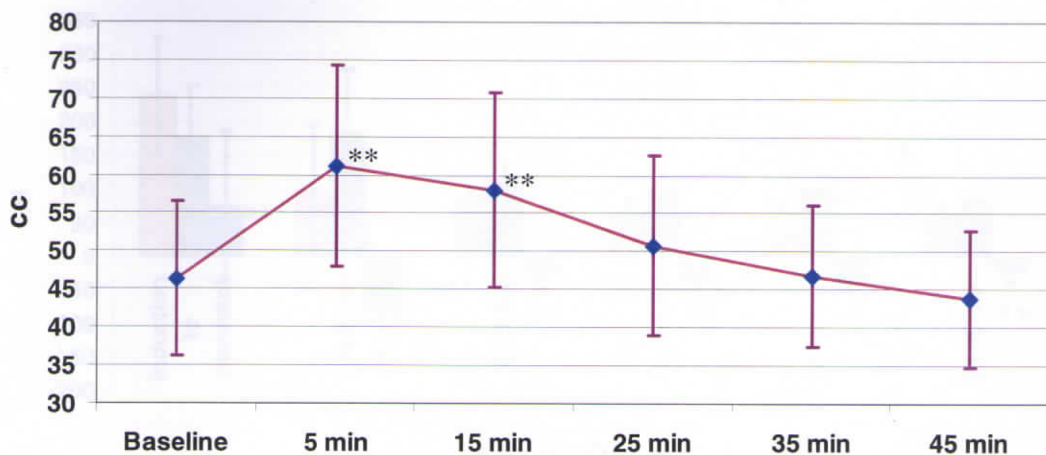


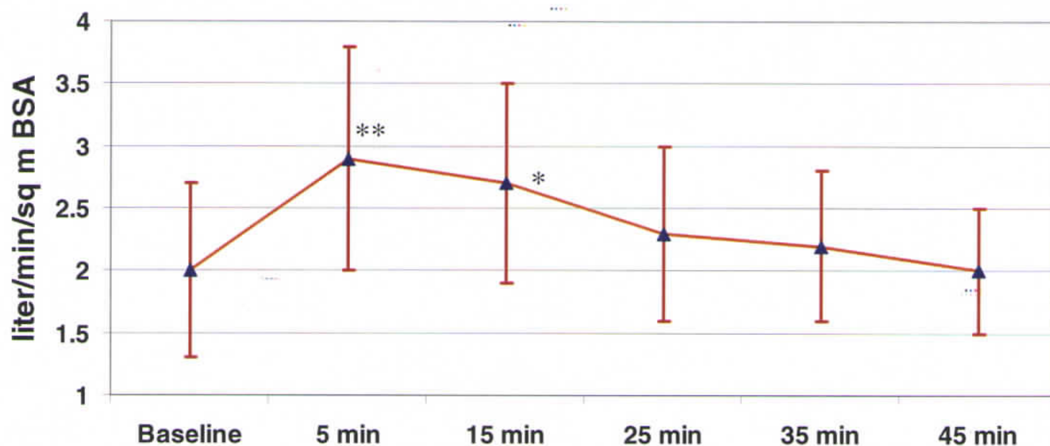


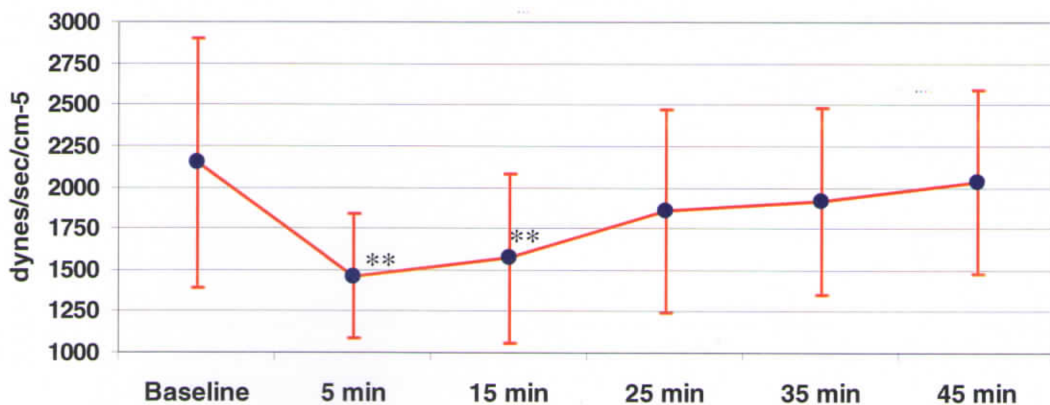

Changes of EDA and ESA with time
18
16
14
12
10
8
6
4
2
**
Baseline
5 min
15 min
25 min
35 min
45 min
EDA
ESA

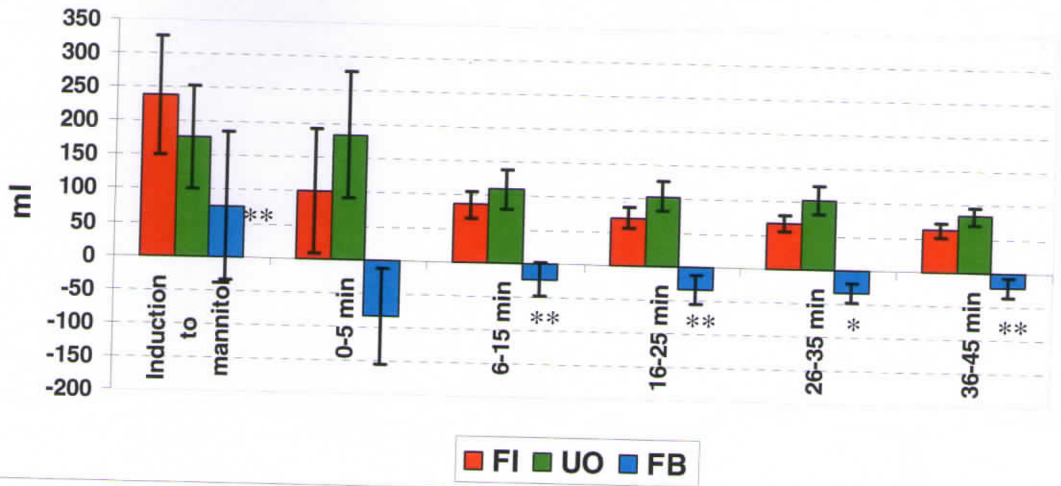

Changes of EDAi and ESAi with time
sq cm
12
10
8
6
4
2
0
**
Baseline
5 min
15 min
25 min
35 min
45 min
EDAi
ESAi


Changes of FAC with time
%
75
70
65
60
55
50
45
Baseline
5 min
15 min
25 min
35 min
45 min


Changes of SV with time
cc
80
75
70
65
60
55
50
45
40
35
30
**
**
Baseline
5 min
15 min
25 min
35 min
45 min


Changes of CI with time
liter/min/sq m BSA
4
3.5
3
2.5
2
1.5
1
**
*
Baseline
5 min
15 min
25 min
35 min
45 min


Changes of SVR with time
dynes/sec/cm-5
3000
2750
2500
2250
2000
1750
1500
1250
1000
**
**
Baseline
5 min
15 min
25 min
35 min
45 min



Changes of FI, UO and FB with time
ml
350
300
250
200
150
100
50
0
-50
-100
-150
-200
Induction to mannitol
0-5 min
6-15 min
16-25 min
26-35 min
36-45 min
**
**
**
*
**
FI
UO
FB

DISCUSSION

DISCUSSION

Brief summary of the results (salient points):

The results of this prospective observational study have shown the following hemodynamic changes following mannitol infusion with respect to time. Systolic Blood Pressure (SBP) initially non-significantly increased from baseline values to 5 minutes post mannitol, thereafter it remained almost similar to baseline. Values for Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP) and Heart Rate (HR) did not change much. Central Venous Pressure (CVP) significantly increased following mannitol infusion, reached maximum value at 5 minutes post mannitol, thereafter it remained non-significantly elevated, till 15 minutes, subsequently remained close to baseline till 45 minutes.

End Diastolic Area (EDA) and End Diastolic Area index (EDAi) increased significantly at 5 minutes following mannitol infusion compared to baseline, then they remained non-significantly elevated till 25 (EDA) and 15 minutes (EDAi), subsequently decreased gradually and reached the baseline levels at 45 minutes post infusion. End Systolic Area (ESA) and End Systolic Area index (ESAi) and Fractional area changes (FAC) did not alter much. Left Ventricular Outflow Tract-Velocity time integral ($LVOT_{VTI}$), Stroke Volume (SV), Cardiac Output (CO) and Cardiac Index (CI) followed similar type of trends. Their value consistently increased from baseline following mannitol infusion, attained highly significant levels at 5 and 15 minutes post infusion. Subsequently their values remained non-significantly elevated till 25 minutes, following which they gradually decreased and arrived to non-significantly below baseline levels at 45 minutes post infusion.

Changes of mitral inflow velocity showed following patterns. 'E' velocity significantly increased from baseline values to 5 minutes post mannitol, thereafter returned almost similar to baseline and remained at that level across all other time points. Both 'A' velocity and 'E/A' ratio did not change much across different time points. Systemic Vascular Resistance (SVR) decreased in a highly significant manner, from baseline, at 5 and 15 minutes post mannitol, thereafter gradually moved upwards, towards baseline levels, starting at 25 minutes onwards, and almost reached baseline levels at 45 minutes.

Urine output (UO) was maximum at 0-5 minutes time interval following mannitol, thereafter UO was significantly low compared to 0-5 minutes post mannitol, at all the subsequent time intervals (e.g. 6-15, 16-25, 26-35 and 36-45 minutes post mannitol, when compared to 0-5 minutes time interval). Fluid Balance (FB, calculated as Fluid Intake-Urine Output) was negative at all time intervals following mannitol infusion, being maximally negative at 0-5 minutes post mannitol compared to baseline, following which, although FB remained consistently negative at all subsequent time intervals, but maintained at significantly less negative levels, compared to that at 0-5 minute time interval.

<u>Rational of the present study: what we intended to know?</u>

We have undertaken this study primarily to observe the extent of hemodynamic changes with respect to time following a bolus dose of mannitol infusion. Subsequently, we tried to figure out to what degree these hemodynamic variables are interrelated, and how the changes of one affects the other, or the extent of alterations of one set of similar variables with another set. For example if mannitol has caused an increase in SV and CO, then it has to be coupled with an increased MAP, HR or a

decrease in SVR. Again if a significant increase in preload following mannitol has been reflected by an augmented CVP, it has to be matched by increased EDA at the corresponding time points. These interrelationships could be explored from the results as discussed in the subsequent sections.

Cerebrovascular and Cardiovascular effects of mannitol

Mannitol, a six carbon sugar, with a molecular weight of 182, is the most commonly used hyperosmolar solution, administered during craniotomy to reduce brain bulk. Usual concentration of mannitol is 20%, dosage ranging from 0.5 to 2 gm/kg (commonly used at 1gm/kg), and generally administered over 15 minutes. Action of mannitol begins within 4-5 minutes of administration and peaks at about 30-45 minutes. Classic mechanism of action of mannitol is the movement of intracellular water into intravascular compartment along the osmotic gradient across an intact blood brain barrier (BBB). As 20% mannitol is having an osmolarity of 1098 mOsm/l it can easily develop a gradient across which intracellular water is drawn to intravascular spaces. Although this is the main mechanism of action, there exists some evidence that the rapid action of mannitol can be mediated by decreased production of CSF.[27]

Cerebrovascular actions of mannitol can be considered triphasic: transient, delayed and late. Because of high osmolarity initially mannitol transiently increases Cerebral Blood Flow (CBF), Cerebral Blood Volume (CBV) and Intra Cranial Pressure (ICP), which is followed by decrease in CBV and ICP[28] with the onset of diuresis. Mannitol increases CBF by decreasing blood viscosity.[29,30,31] Hematocrit determines blood flow, especially for the narrow vessels. Hemodilution leads to increased blood flow by two mechanisms. Reduction of hematocrit leads to less erythrocyte aggregation

and improved laminar flow. Mannitol also reduces rigidity of erythrocytes and enhances passage through small blood vessels.[32] Sulpicio et al have shown that mannitol briefly increases cerebrovascular resistance and thereby diminishes CBV.[33] Ravussin et al have shown by positron tomographic study in dogs and human subjects that rapid infusion of mannitol increases CBV upto 3 minutes after infusion.[34]

Cardiovascular effects of mannitol infusion include marked changes of blood rheology, a transient and direct effect on vascular tone and increase in CO.[32,35,36] Mannitol reduces viscosity of blood by decreasing hematocrit and also by decreasing volume, rigidity and cohesiveness of red blood cell membranes.[37] Mannitol has also been found to release histamine from basophils from circulation. Histamine in turn causes fall in SVR.[38] Mannitol infusion may temporarily exert a mild inotropic effect by decreasing afterload and augmenting preload. Systematically there occurs an acute drop in SVR (because of reduced SVR and increased preload), particularly when mannitol is infused quickly (<10 min), resulting transient hypotension, followed by marked rise in CVP, Pulmonary Capillary Wedge Pressure (PCWP) and CO. Potential complications from the delayed effects therefore include fluid overload and pulmonary edema in patients having poor cardiac function. Within 45 minutes the cardiovascular effects get dissipated and intravascular volume starts contracting with the onset of full diuresis.

Hence the combined cerebrovascular and cardiovascular effects potentially improve blood flow and substrate delivery to the organs.

What was the earlier literature on the issue? What was missing in the earlier studies that we tried to address?

There are very few studies exclusively dedicated to the hemodynamic effects of mannitol. In a recent study Nikki et al have shown the hemodynamic changes after administration of mannitol, measured by a non-invasive cardiac output monitor, the bioimpedance plethysmogram.[3] They have not used TEE or recorded CVP which could have confirmed their results in a more definitive way. Lin et al have shown early increase in CVP values following mannitol infusion in traumatic brain injury.[39] Charles et al has postulated in a study that the mechanism of transient hypotension following hyperosmolar solutions is primarily the vaodilation in skeletal muscle.[1] Lavy and Giannota have evaluated the changes of CVP and Left Ventricular Stroke Volume index (LV_{SVi}) with increasing PCWP.[40] They observed no correlation between CVP and PCWP during volume expansion. After an extensive and thorough search of the available literature we are unable find even a single study that has exclusively dealt with the hemodynamic changes in response to a single dose bolus of mannitol infusion, recorded with TEE, in terms of changes of preload, SV, CO and SVR with respect to time.

Hypertonic saline (HTS) solutions have evolved as a reasonable alternative to mannitol for reduction of brain bulk or they may be used to manage otherwise refractory intracranial hypertension. Ching-Tang Wu et al have compared 3% hypertonic saline and mannitol for brain relaxation during elective supratentorial brain tumor surgery.[41] Their results suggest that HTS provided better brain relaxation than did mannitol during elective supratentorial brain tumor surgery, whereas it did not affect ICU stays or hospital days. Another investigation comparing 20% mannitol and

3% HTS in equimolar dosage have found no difference between them in the extent of brain relaxation.[42] Goertz et al has shown increased Left Ventricular (LV) preload and decreased LV afterload in a study on the effects of 7.2% HTS / 6% hetastarch on LV contractility in anesthetized humans following HTS infusion.[43] Caution is advised for high osmolar fluid loads because they are associated with an increased risk of the potentially deleterious consequences of hypernatremia or may induce osmotic BBB opening, with possible harmful extravasations of the hypertonic solution into the brain tissue,[44] and rarely, they might even cause coagulopathy.[45]

Justification: why TEE and not other methods?

In the present study we have used TEE to obtain hemodynamic variables (EDA, ESA, FAC, $LVOT_{VTI}$, SV and CO). We have considered EDA, ESA and FAC as a surrogate measure of changes in preload and contractile function of the left ventricle. SV and CO were also recorded from TEE. Compared to bioimpedance plethysmogram such recordings (SV, CO) are more definitive with TEE.[3] Moreover simultaneous quantification of changes in loading conditions, cardiac output and diastolic function is only possible with TEE.

Cardiac output measurements performed by TEE, measured at the LVOT or aortic valve in the absence of aortic regurgitation, have been shown to correlate well with measurements made by thermodilution, using a Pulmonary Artery Catheter (PAC).[46-50] Although PAC is considered the gold standard for measuring cardiac output, it is far more invasive compared to TEE. A growing number of studies have observed increasing number of complication rates, without any improvement in outcome, with the use of pulmonary artery catheter. In a review of pulmonary artery cauterization for perioperative monitoring in a series of 6245 patients undergoing cardiac and non

cardiac surgery, Kamlesh et al[51] have reported the following complications: persistent premature ventricular complexes requiring therapy in 3.1%, right bundle branch block (RBBB) in 0.05%, left bundle branch and complete heart block in 0.016%, intrapulmonary hemorrhage in 0.064%, pulmonary infarcts in 0.064% and perforation in RV in 0.016% of the patients. Sandham et al have shown that incidence of pulmonary embolism is significantly high with PAC in elderly high risk surgical patients requiring intensive care.[52] They concluded that no benefit to therapy was directed by PAC in such patients. TEE is considered to be relatively safe and noninvasive. 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%.[53-55] Daniel et al[54] have described a complication rate of 0.18% in a multicenter survey of 10,419 adult patients undergoing TEE. Kallmeyer et al have found the overall TEE associated morbidity and mortality were 0.2% and 0% respectively in a single centre series of 7200 adult cardiac surgical patients.[56] The commonest TEE associated complication was odynophagia (0.1%) in their study population.

Numerous studies have validated the use of these surrogate measures reflective of the true changes in LV function. Clements et al evaluated ventricular area as a surrogate for volume; [57] they used transgastric mid papillary short axis view to measure EDA, ESA and calculated FAC. They validated TEE derived measurements with simultaneous radionucleotide imaging and found a correlation r=0.86 with TEE derived EDA. TEE derived ESA also correlated with radionucleotide ESA (r=0.92) as did the FAC (r=0.96). This validation study supports the use of LV_{EDA} as a surrogate for preload. In patients with normal and abnormal LV function and graded hypovolemia, acute blood loss caused directional changes of LV_{EDA}. Two

dimensional (2-D) TEE detected a change in LV_{EDA} with as little as 2.5% estimated blood volume deficit, which is approximately 1.75ml/kg. The mean change in LV_{EDA} was 0.3 cm^2/% estimated blood volume deficit.[58] Reich et al in their study found mild reduction of blood volume with high sensitivity (80-95%) and specificity (80%) in predicting pediatric patients following sternal closure who underwent repair of congenital heart lesions.[59]

EDA is measured by acquiring mid papillary short axis view and scrolling to the largest image frame corresponding to the peak of the QRS complex. Then with planimetry the borders of the endocardium are traced using the leading edge method and including the papillary muscles in the measurement. Similarly ESA can be measured either coinciding with end of T wave in ECG or the image frame on which LV cavity is smallest and thereafter tracing the endocardial borders in a similar manner. If the BSA is known, then EDA index can be calculated, which if less than 5.5cm^2/m^2 defines hypovolemia.[60] With the decrease in preload, linear decrease in LV_{EDA}, LV_{ESA} and end systolic cavity obliteration ('kissing ventricle') is a potential alarm for hypovolemia. Such obliteration can also reflect increased inotropic state and decreased SVR. Leung and Levine have found that although end systolic cavity obliteration detected by TEE is frequently associated with decreased LV preload, 10% of the time it reflects only an increase in EF.[61] End systolic cavity obliteration is very sensitive in predicting decrease in ESA (100%), but the specificity for decrease in preload is low (10% to 30%).

Calculation of the stroke volume by Doppler:

Flow rate of a fluid through fixed orifice is directly proportional to the cross sectional area (CSA) of the orifice and the flow velocity of the fluid, within the orifice, given by the formula: Flow rate (cm^3/s) = CSA (cm^2) X flow velocity (cm/s)

Instantaneous flow rate of blood going through an orifice or blood vessel of constant CSA is directly proportional to the product of CSA of the orifice or blood vessel and the instantaneous blood flow velocity. The acceleration and deceleration of blood flow velocity during the ejection period (or filling period) provides a distinct Doppler profile for a given orifice. The summation of velocities over the entire flow period is called velocity time integral (VTI), which is equal to the area bounded by the Doppler flow velocity profile and the zero velocity baseline, and measured by tracing Doppler signal using the software package of the echo machine for the required calculation. Conceptually VTI is thought to be the distance that blood travels with each beat of heart, therefore this is also called as stroke distance.

Stroke volume (SV) can be calculated as the product of CSA and VTI by the formula: SV (cm^3) = CSA (cm^2) X VTI (cm). Stroke volume can be calculated at many different locations within the heart or great vessels by using appropriate Doppler velocity signal to determine VTI at the same location that has been used while 2-D imaging, to determine CSA. VTI is usually measured with pulsed wave Doppler. Most commonly CSA of the orifice to be measured is assumed to be circular. Hence, can be calculated using the formula for the area of the circle after measuring the orifice diameter (D) in cm. Thus CSA (cm^2) = $\pi\ (D/2)^2$. The Doppler method for determining SV at a particular site is based on the following assumptions 1. Blood flow is assumed to be laminar, with flat spatial flow velocity profile, as in generally the case in LVOT. 2. Measurements of the VTI and CSA (i.e. diameter) are made at the same time and the same anatomic location. 3. VTI measurement represents the average VTI (about 3-5 measurements are averaged for a normal patient with sinus rhythm, whereas 8-10 should be averaged for a patient with atrial fibrillation). 4. CSA

(i.e. diameter) measurement is accurate and 5. The VTI is measured with Doppler beam parallel to the blood flow ($\theta=0^0$ in the Doppler equation) in order to avoid underestimation. The highest velocity signal obtained or the loudest audio signal generated, will correlate with the most parallel alignment of the Doppler beam with the blood flow. In the present study we have consistently measured CSA of LVOT in mid-esophageal long axis view within 1 cm from the aortic valve, and averaged 3 measurements taken at the same site. VTI of LVOT has been taken mostly in deep transgastric view at the same site where CSA was measured, or sometimes from transgastric long axis view, when proper imaging window was not available from deep transgastric imaging plane. All measurements were made at end-expiration. Since all of our patients are having sinus rhythm, we have taken three measurements, at each time point, and saved the loops. Subsequently, from them average value of VTI was taken.

Calculation of cardiac output by Doppler:

CO can be calculated by 2-D Doppler after determining a Doppler SV and measuring heart rate.[62] CO is calculated as product of SV and the HR. Cardiac index (CI) is calculated by dividing CO by BSA.

$$\text{CO (l/min)} = \text{SV (cm}^3\text{) X (1 liter/1000 cm}^3\text{) X HR (bpm)}$$

$$\text{CI (l/min/m}^2\text{)} = \text{CO (l/min)/BSA (m}^2\text{)}$$

An accurate estimation of CO depends on precise determinations of the VTI and CSA. SV calculations for the estimation of CO are preferably made with multiplane TEE at the LVOT or aortic valve for the following reasons: 1. the acceleration of blood through the LVOT or aortic valve during systole favours laminar flow with a flat flow velocity profile, in contrast to parabolic flow velocity profile present in ascending aorta or pulmonary artery. 2. Multiplane TEE provides excellent views of LVOT and

Aortic Valve (AV), therefore measurements of LVOT diameter and aortic valve CSA are more accurate. 3. LVOT is more circular and changes shape very little during the cardiac cycle when compared to Main Pulmonary Artery (MPA) or Mitral Valve (MV). Measurement made at MPA or MV is less reliable than those made at LVOT and AV.[63] Although CSA of the aortic valve orifice changes dramatically throughout systole, the CSA of the AV during mid systole can be used to provide a good estimate of transaortic stroke volume by Doppler.

Data for LVOT SV calculation:

The pulsed wave sample volume is placed in the LVOT just proximal to the AV (within 1 cm) using either the transgastric long axis view or the deep transgastric view for determination of $LVOT_{VTI}$. The diameter (cm) of the LVOT is best obtained from the mid esophageal long axis view of the aortic valve (approximately 1 cm proximal to the valve) for determination of CSA using the formula for the area of a circle.

$CSA_{LVOT} = 0.785\ D_{LVOT}^2$

SVR is calculated by the formula: SVR = [(MAP-CVP)/CO] X 80

The clinical consequences of our findings:

The results of this study throw lights to some of the very important aspects of hemodynamic changes following mannitol infusion in neurosurgical patients undergoing craniotomy. It is observed from the results that following mannitol infusion there is hardly any remarkable change in SBP, DBP, MAP and HR, whereas CVP increases significantly till 5 minutes, and non-significantly remains elevated till 15 minutes, following which CVP comes down to baseline levels at 45 minutes. Again EDA and EDAi remains significantly elevated till 5 minutes and non-significantly till 25 and 15 minutes following mannitol respectively, whereas ESA and

ESAi values maintain close to baseline. These findings could be explained in terms of transient vasodilatation caused by mannitol, as it draws water from extravascular to intravascular compartment. As a consequence, it increases preload, as observed by increased EDA along with almost unchanged ESA, immediately following mannitol infusion. But as per Frank Sterling mechanism an augmented preload should be matched with an increased SV, which subsequently reflect an enhanced CO and CI, as HR is almost unaltered across different time points. Likewise our results show a highly significant rise in SV, CO and CI both at 5 and 15 minutes following mannitol, even a trend towards non-significant elevation of all those parameters till 25 minutes following which they approach baseline.

But although there is significantly augmented SV and CI till 15 minutes following mannitol infusion, due to mannitol induced vasodilatation (reduced afterload) and enhanced preload, this not exactly matched with an increased MAP, which is indeed surprising. But this relatively stationary MAP with a heightened SV and CI can be explained in terms of changes in SVR. It is noticed from the results that SVR decreases very significantly at 5 and 15 minutes following mannitol infusion, subsequently it starts increasing and reaching almost similar to baseline at 45 minutes. This fall in SVR, which is initiated due to peripheral vasodilatation caused by mannitol and thereafter supplemented and maintained with the onset of mannitol induced diuresis, keeps fluid balance negative, starting at 15 minutes post mannitol, till 45 minutes, compared to fluid balance at 5 minutes following mannitol infusion. This maintains MAP at almost stationary levels in spite of an augmented SV and CI. Afterwards, at 25 minutes onwards, when SVR starts increasing in the direction of baseline, accompanied with a parallel fall in CVP, EDAi, SV and CI: all towards

baseline; keeps MAP maintained almost at the similar level like the first 25 minutes following mannitol.

Nikki et al in their study on hemodynamic changes after administration of mannitol have found that SV has increased significantly for 15 minutes,[3] which is similar to the our results, again like their study we have also observed similar increase in CI till 15 minutes. However in their study SV and CI was significantly low at 45 minutes compared to baseline, whereas in the present study these parameters were almost similar to baseline values. This could be due to relatively longer duration of infusion of mannitol, 15 minutes in the present study, compared to 10 minutes in the study by Nikki et al, or because of better overall hemodynamic/fluid management guided by TEE. The relatively stationary values of MAP and HR following mannitol infusion in our study corroborates to the findings of earlier studies by Sulpicio et al.[33]

Indices of left ventricular diastolic function as recorded in our study in terms of changes in 'E', 'A' velocities and 'E/A' ratio, do not change much from baseline values, although 'E' velocity has increased significantly at 5 minute post mannitol, without a proportionate change in 'E/A' does not imply much about any impending diastolic dysfunction, developing in response to increased preload and contractility. The reason could be because of our exclusion of patients with known cardiac ailments. Moreover 'E/A', as a sole measure of diastolic function, may not be accurate in a background of continuously changing loading conditions.[64]

The patterns of the changes of the recorded parameters, with respect to time, in the present study raise some important issues. It is postulated that mannitol decreases brain water content by the movement of water from extravascular to intravascular compartment across the osmotic gradient. But this mechanism holds true only in presence of an intact BBB. Then what would be the effect of mannitol infusion, even

in standard dosage, in patients with breached BBB, as commonly found in patients with considerably large brain tumours? Does the rate of reduction in brain water content correlates with the increase in CO? An objective way of establishing a relationship between these two parameters needs to be addressed. Similar to the results of the study by Lin et al,[38] we have also found significant increase in CVP immediately following mannitol infusion, which should theoretically correlate with an augmented Right Ventricular End Diastolic Pressure (RV_{EDP}). Therefore patients with right coronary artery disease will be at risk for impending ischemia and its consequences. Willerson et al have shown that mannitol increases coronary blood flow up to an extent of 39% accompanied by a small but consistent increase in LV systolic index of contractility ($LV_{dp/dt}$).[65] They have commented that the combination of increased myocardial contractility with an even greater increase in coronary perfusion may be of value in patients with coronary atherosclerosis. The apparently harmful effects of mannitol, due to hypervolemia, on cardiovascular system last for about 20 minutes but thereafter hypovolemia predominates, hence unless the preload is optimised by adequate volume infusion under precise monitoring conditions (preferably by changes in EDA, ESA and CI), there lies every possibility of manifestations of late deleterious systemic effects of mannitol. Elevated Left Ventricular End Diastolic Pressure (LV_{EDP}) is an independent predictor of mortality and this variable is independent of Left Ventricular Ejection Fraction (LV_{EF}), as shown by Salem et al in cardiac surgical patients.[66] It is possible to predict LV_{EDP}, non-invasively from Left Ventricular Volume (LV_{EDV}) but this method can be misleading in patients with advanced diastolic dysfunction.[67] How to predict LV_{EDP} with reasonable accuracy from EDA (in patients without having significant aortic

regurgitation jet), requires attention, as TEE derived EDA is extremely sensitive to changes in volume status.

Limitations of the present study: Does our methodology limit the application of the results to only a limited set of patients or clinical conditions?

There are some limitations of this study. First of all this is a pilot study with 15 subjects. A larger study with adequate power is needed to generalise the results obtained from this study. The results are limited to a subset of patients having apparently no cardiovascular dysfunction and receiving a single bolus dose of mannitol during craniotomy. None of these patients have received mannitol before surgery. The findings would have been more definitive, if we had simultaneously recorded the so called "dynamic" hemodynamic parameters like delta pulse pressure (DPP) or delta down, which are more accurate in predicting volume status and fluid responsiveness, compared to static hemodynamic parameters (eg. right atrial pressure, PCWP, LV_{EDA}).[68,69,70] Changes of mitral inflow pattern, as an indicator for diastolic function, as illustrated in the study by recording the changes in 'A', 'E' and 'A/E', are known to be unreliable in a background of changing loading conditions as happens with mannitol infusion. Hence recording of colour M mode flow propagation velocity (V_p) or mitral annular tissue Doppler (TDI) would have been better as they are least affected by such changes in preload.[63] These are not contemplated in the present study as more recordings would have been further time consuming and may not be possible within the specified time period in between the two consecutive recordings. A comparison group with equiosmolar amount of hypertonic saline would have better demonstrated the extent and duration of changes of same hemodynamic parameters in contrast to mannitol. Considerable variation in the extent of blood loss during

craniotomy before dural opening may influence the loading condition. Finally although from a practical standpoint the transient increase in EDA, CVP, SV and CI may not have much implication in patients with normal cardiovascular status but same may not hold true for patients with borderline cardiac function. The duration and extent of change of these hemodynamic variables need to be evaluated in that particular subset of patients who might develop considerable hemodynamic alterations.

What future studies are necessary to complete the understanding that is lacking in this study?

A future study with a larger sample size and adequate power, including patients with known mild cardiac risk and with a comparable group receiving some other type of hyperosmolar infusion like hypertonic saline could help in generalizing the results obtained this study. It will be interesting to observe the pattern of alterations in diastolic function in response to hyperosmolar solutions in patients with borderline cardiac function, recorded by TEE using more specific and reliable method e.g. tissue Doppler or propagation velocity.

CONCLUSION

CONCLUSION

In conclusion, we can state that a single bolus dose of mannitol caused a significant increase in EDA, SV and CI along with a significant increase in CVP. A concomitant significant fall in SVR took place along with, but these were not associated with a change in either in HR or in SBP, DBP or MAP. These effects were most pronounced at 5 minutes, but remained prevalent till 15 minutes following mannitol infusion. Following which they approached their respective baseline values and remained comparable to baseline till 45 minutes post mannitol. This study is limited only to a single dose of mannitol in a group of neurosurgical patients, with normal cardiovascular function, who were not under mannitol therapy earlier. It would be interesting to study the hemodynamic response to repeated doses in patients on prolonged mannitol therapy and extent of changes in patients with borderline cardiovascular function, elderly patients and diabetic patients who may have occult coronary artery disease.

Proforma

Age		Sex		Weight		Height		BSA	

Diagnosis:		Surgery	

Mannitol started at: Mannitol over at:

Time						
Parameter	Before mannitol	5 min	15 min	25 min	35 min	45 min
SBP						
DBP						
MAP						
HR						
CVP						
MAC						
BIS/ENTROPY						
$LVOT_{diameter}$						
$LVOT_{area}$						
$E_{velocity}$						
$A_{velocity}$						
E/A						
EDA						
EDA_{index}						
ESA						
ESA_{index}						
FAC						
EF						
$LVOT_{VTI}$						
SV						
CO						
CI						
UO						

Total amount of fluid infused [upto 45 minutes after mannitol]	

Fluid balance at 45 min:	
Urine output	
Blood Loss	
Rescue fentanyl [mcg]	Dose: mcg, No of times:

Standardised anaesthesia protocol: Fentanyl 4cg/kg at induction, 2 mcg/kg before pin application, thereafter infusion 2mcg/kg/hour, O_2/Air, Midazolam 1 mg, Sevoflurane 0.5-0.7 MAC, Fluid 6-8 ml/kg/hour

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Abbreviations

ABBREVIATIONS USED

ABP	Arterial blood pressure
AV	Aortic valve
BBB	Blood brain barrier
BSA	Body surface area
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CI	Cardiac index
CO	Cardiac output
CPP	Cerebral perfusion pressure
CSA	Cross sectional area
CSF	Cerebro spinal fluid
CVP	Central Venous pressure
CWD	Continuous Doppler
DBP	Diastolic blood pressure
DPP	Delta pulse pressure
EDA	End diastolic area of left ventricle
EDA_i	Indexed end diastolic area of left ventricle
EF	Ejection fraction
ESA	End systolic area of left ventricle
ESA_i	Indexed end systolic area of left ventricle
FAC	Fractional area changes
FB	Fluid balance
FI	Fluid intake
HR	Heart rate
ICP	Intra cranial pressure
LAP	Left atrial pressure
LV	Left ventricle
LVOT	Left ventricular outflow tract
$LVOT_a$	Left ventricular outflow tract area
$LVOT_d$	Left ventricular outflow tract diameter
LV_{Svi}	Left ventricular stroke volume index
MAP	Mean arterial pressure
MPA	Main pulmonary artery
MV	Mitral valve
PAC	Pulmonary artery catheter
PAP	Pulmonary artery pressure
PCWP	Pulmonary capillary wedge pressure
PWD	Pulsed wave Doppler
RAP	Right atrial pressure
RV	Right ventricle
RV_{EDP}	Right ventricular end diastolic pressure
RV_{EDV}	Right ventricular end diastolic volume

SBP	Systolic blood pressure
SV	Stroke volume
SVR	Systemic vascular resistance
TEE	Transesophageal Echocardiography
TDI	Tissue Doppler imaging
TTE	Transthoracic Echocardiography
UO	Urine output
Vp	Mitral inflow propagation velocity
VTI	Velocity time integral

Master Chart

MASTER CHART

No.	IP#	Age (yrs)	Sex	Body wt (kg)	Height (cm)	BSA (sqm)
1	191421	20	M	62	164	1.68
2	278978	32	M	62	163	1.68
3	308133	31	F	61	162	1.66
4	305455	59	M	54	167	1.58
5	308655	29	F	48	157	1.45
6	307948	47	M	68	159	1.73
7	309608	49	F	65	156	1.68
8	308428	29	F	50	161	1.5
9	271887	32	M	68	160	1.74
10	279193	24	M	55	156	1.54
11	300765	30	M	65	170	1.75
12	300211	18	F	47	157	1.43
13	308064	54	M	68	164	1.76
14	267355	17	M	64	163	1.7
15	308995	33	F	78	152	1.81

No.	Diagnosis	Surgery
1	Recurrent craniopharyngoma	Reexploration & decompression
2	Recurrent pituitary adenoma	Transcranial decompression
3	Right frontal glioma	Frontal craniotomy and decompression
4	Right frontal meningioma	Right frontal craniotomy and decompression
5	Right temporal glioma	Right temporal craniotomy and decompression
6	Suprasellar Lesion	Right pterional craniotomy and decompression
7	Sphenoid wing meningioma	Right pterional craniotomy and decompression
8	Left temporal glioma	Left temporal cranitomy and decompression
9	Right frontal glioma	Right frontal craniotomy and decompression
10	Frontal convexity meningioma	Bicoronal craniotomy and decompression
11	Parasaggital meningioma (left)	Right parietal craniotomy and decompression
12	Left parietal glioma	Left parietal craniotomy and decompression
13	Left Insular glioma	Left temporal cranitomy and decompression
14	Right frontal Lesion	Right frontal eraniotomy and excesion
15	Pituitary macroadenoma	Transcranial excision

No.	Mannitol (ml)	SBP baseline	SBP 5 min	SBP 15 min	SBP 25 min	SBP 35 min	SBP 45 min
1	300	88	109	95	96	75	83
2	300	107	114	119	104	106	98
3	300	118	125	121	127	127	125
4	250	168	156	140	135	135	128
5	250	119	140	135	143	135	137
6	300	135	140	129	130	128	140
7	300	113	120	103	96	98	90
8	250	110	126	118	113	114	107
9	350	150	135	129	138	137	136
10	300	127	138	142	139	138	131
11	300	118	148	144	161	145	143
12	250	121	128	124	121	121	119
13	350	134	155	119	119	123	106
14	300	126	130	120	129	119	103
15	350	130	140	140	125	131	124

No.	DBP b/l	DBP 5	DBP 15	DBP 25	DBP 35	DBP 45	MAP b/l	MAP 5	MAP 15	MAP 25	MAP 35	MA 45
1	55	63	55	56	43	49	67	78	67	68	54	
2	69	73	73	68	69	68	82	86	90	80	81	
3	68	57	58	62	62	62	83	76	75	79	80	
4	80	71	71	76	76	76	110	98	90	94	94	
5	63	82	75	75	68	71	85	101	95	101	91	
6	75	73	73	73	75	81	101	99	94	95	95	1
7	65	66	58	57	59	56	81	84	73	69	72	
8	62	74	71	70	71	64	80	93	89	85	87	
9	93	77	77	85	85	86	114	94	93	101	101	1
10	73	68	73	72	69	68	91	95	99	98	93	
11	76	77	84	88	89	78	94	106	109	117	110	1
12	63	60	65	65	65	64	83	81	83	82	83	
13	86	81	67	68	72	63	99	105	83	84	89	
14	56	57	54	67	58	63	73	76	71	85	74	
15	80	75	80	78	81	79	97	98	100	95	97	

No.	HR b/l	HR 5	HR 15	HR 25	HR 35	HR 45	CVP b/l	CVP 5	CVP 15	CVP 25	CVP 35	CVP 45
1	75	77	71	68	72	71	7	11	7	7	6	
2	65	63	60	65	66	68	7	10	7	5	5	
3	57	65	64	65	64	66	5	12	11	9	9	
4	84	89	90	89	90	96	6	9	6	4	4	
5	69	72	67	66	67	66	5	9	6	4	6	
6	64	75	75	73	73	65	8	13	9	7	6	
7	74	80	83	82	80	82	5	6	4	4	4	
8	89	94	98	93	99	94	4	6	2	3	1	
9	50	58	56	57	59	59	6	9	5	7	6	
10	80	86	79	79	84	82	4	7	7	8	5	
11	56	59	58	58	58	59	6	8	9	10	8	
12	84	91	89	90	83	89	6	8	9	6	8	
13	78	90	93	88	89	83	5	7	9	10	10	
14	77	75	60	60	64	69	9	11	10	8	9	
15	82	88	86	96	93	95	7	10	9	9	6	

No.	MACb/l	MAC 5	MAC 15	MAC 25	MAC 35	MAC 45	LVOTd bm	LVOTd 5	LVOTd 15	LVOTd 25	LVOTd 35	LVOTd 45
1	0.7	0.6	0.6	0.6	0.6	0.5	2	2	2	2	2	2
2	0.7	0.6	0.6	0.6	0.6	0.6	1.9	1.9	1.9	1.9	1.9	1.
3	0.7	0.6	0.6	0.6	0.6	0.6	2	2	2	2	2	2
4	0.7	0.6	0.6	0.6	0.6	0.6	2.1	2.1	2.1	2.1	2.1	2.
5	0.7	0.7	0.7	0.7	0.7	0.7	2.2	2.2	2.2	2.2	2.2	2.
6	0.7	0.7	0.7	0.7	0.6	0.7	2.2	2.2	2.2	2.2	2.2	2.
7	0.7	0.7	0.7	0.7	0.7	0.7	2	2	2	2	2	2
8	0.5	0.6	0.6	0.7	0.6	0.6	1.9	1.9	1.9	1.9	1.9	1.
9	0.7	0.8	0.8	0.9	0.9	0.8	2.2	2.2	2.2	2.2	2.2	2.
10	0.6	0.6	0.5	0.6	0.7	0.6	2.3	2.3	2.3	2.3	2.3	2.
11	0.7	0.7	0.7	0.7	0.7	0.7	2.2	2.2	2.2	2.2	2.2	2.
12	0.6	0.6	0.6	0.6	0.6	0.6	1.7	1.7	1.7	1.7	1.7	1.
13	0.6	0.6	0.6	0.6	0.6	0.6	2.2	2.2	2.2	2.2	2.2	2.
14	0.5	0.6	0.6	0.6	0.6	0.7	1.9	1.9	1.9	1.9	1.9	1.
15	0.6	0.6	0.6	0.6	0.6	0.6	1.8	1.8	1.8	1.8	1.8	1.

No.	LVOTa bm	LVOTa 5	LVOTa 15	LVOTa 25	LVOTa 35	LVOTa 45	E b/l	E 5	E 15	E 25	E 35	E 45
1	3.3	3.3	3.3	3.3	3.3	3.3	0.92	0.91	0.88	0.94	0.81	0.82
2	2.7	2.7	2.7	2.7	2.7	2.7	0.8	0.8	0.88	0.79	0.66	0.66
3	3.1	3.1	3.1	3.1	3.1	3.1	0.58	0.81	0.78	0.75	0.7	0.75
4	3.4	3.4	3.4	3.4	3.4	3.4	0.83	0.85	0.56	0.5	0.5	0.51
5	3.8	3.8	3.8	3.8	3.8	3.8	0.73	1.1	0.85	0.91	0.81	0.83
6	3.8	3.8	3.8	3.8	3.8	3.8	0.88	1.03	0.89	0.88	0.82	0.79
7	3.1	3.1	3.1	3.1	3.1	3.1	0.7	0.77	0.68	0.62	0.64	0.61
8	2.8	2.8	2.8	2.8	2.8	2.8	0.96	0.86	0.6	0.55	0.51	0.58
9	3.7	3.7	3.7	3.7	3.7	3.7	0.66	0.73	0.67	0.62	0.62	0.6
10	4.2	4.2	4.2	4.2	4.2	4.2	0.86	1.2	0.87	0.76	0.74	1.02
11	3.8	3.8	3.8	3.8	3.8	3.8	0.51	0.71	0.52	0.45	0.44	0.41
12	2.3	2.3	2.3	2.3	2.3	2.3	1.1	1.1	0.87	0.87	0.81	0.77
13	3.8	3.8	3.8	3.8	3.8	3.8	0.53	0.95	0.53	0.78	0.61	0.83
14	2.9	2.9	2.9	2.9	2.9	2.9	1.02	0.95	1.02	0.99	0.85	0.9
15	2.5	2.5	2.5	2.5	2.5	2.5	0.83	1.02	0.9	0.86	0.71	0.7

No.	A b/l	A 5	A 15	A 25	A 35	A 45	E/A b/l	E/A 5	E/A 15	E/A 25	E/A 35	E/A 45
1	0.47	0.37	0.45	0.39	0.36	0.33	1.96	2.46	1.96	2.41	2.25	2.48
2	0.4	0.46	0.4	0.36	0.33	0.31	2.00	1.74	2.20	2.19	2.00	2.13
3	0.24	0.31	0.33	0.34	0.27	0.27	2.42	2.61	2.36	2.21	2.59	2.78
4	0.74	0.74	0.61	0.53	0.57	0.45	1.12	1.15	0.92	0.94	0.88	1.13
5	0.39	0.58	0.47	0.37	0.41	0.37	1.87	1.90	1.81	2.46	1.98	2.24
6	47	0.46	0.49	0.47	0.47	0.46	0.02	2.24	1.82	1.87	1.74	1.72
7	0.51	0.58	0.32	0.32	0.43	0.43	1.37	1.33	2.13	1.94	1.49	1.42
8	0.75	0.78	0.83	0.68	0.66	0.74	1.28	1.10	0.72	0.81	0.77	0.78
9	0.27	0.33	0.28	0.25	0.3	0.3	2.44	2.21	2.39	2.48	2.07	2.00
10	0.47	0.53	0.36	0.43	0.51	0.6	1.83	2.26	2.42	1.77	1.45	1.70
11	0.32	0.41	0.39	0.31	0.36	0.33	1.59	1.73	1.33	1.45	1.22	1.24
12	0.65	0.83	0.57	0.65	0.53	0.5	1.69	1.33	1.53	1.34	1.53	1.54
13	0.25	0.41	0.35	0.33	0.31	0.44	2.12	2.32	1.51	2.36	1.97	1.89
14	0.45	0.33	0.32	0.3	0.42	0.45	2.27	2.88	3.19	3.30	2.02	2.00
15	0.49	0.59	0.46	0.47	0.31	0.53	1.69	1.73	1.96	1.83	2.29	1.32

No.	EDA b/l	EDA 5	EDA 15	EDA 25	EDA 35	EDA 45	EDAi b/l	EDAi 5	EDAi 15	EDAi 25	EDAi 35	EDAi 45
1	9.1	12.2	10.4	9.8	8.8	8.4	5.4	7.3	6.2	5.8	5.2	5.0
2	10.9	13.7	11.5	10.4	10.4	9.9	6.5	8.1	6.8	6.2	6.2	5.9
3	10.1	12.7	11.2	10.5	10.3	9.5	6.1	7.6	6.7	6.3	6.2	5.7
4	12.2	13.4	10.9	11.3	11.1	11.4	7.7	8.5	6.9	7.2	7.0	7.2
5	12.1	15.4	15.1	13.5	10.3	13.2	8.4	10.6	10.4	9.3	7.1	9.1
6	10.6	11.7	10.6	10.9	10.5	9.9	6.1	6.8	6.1	6.3	6.1	5.7
7	9.9	12.8	12.6	10.9	10.5	11.3	5.9	7.6	7.5	6.5	6.3	6.7
8	9.6	12.1	12.3	9.5	9.2	10.6	6.4	8.1	8.2	6.3	6.1	7.1
9	14.7	18.6	16.5	15.5	15.3	13.6	8.4	10.7	9.5	8.9	8.8	7.8
10	15.6	19.5	19.6	18.3	16.6	14.7	10.1	12.7	12.7	11.9	10.8	9.5
11	14.8	20.2	18.5	15.9	14.4	16.5	8.5	11.5	10.6	9.1	8.2	9.4
12	10.4	12.4	10.7	11.6	9.3	10.5	7.3	8.7	7.5	8.1	6.5	7.3
13	11.8	16.2	12.1	11.9	11.3	11.1	6.7	9.2	6.9	6.8	6.4	6.3
14	15.3	19.4	18.6	15.8	15.2	14.1	9.0	11.4	10.9	9.3	8.9	8.3
15	11.7	15.7	11.4	11.3	10.8	12.6	6.5	8.7	6.3	6.2	5.9	6.9

No.	ESA b/l	ESA 5	ESA 15	ESA 25	ESA 35	ESA 45	ESAi b/l	ESAi 5	ESAi 15	ESAi 25	ESAi 35	ESAi 45
1	3.7	2.9	3.2	3.5	2.6	3.0	2.2	1.7	1.9	2.1	1.5	1.8
2	4.8	4.4	4.6	4.2	4.1	4.6	2.9	2.6	2.7	2.5	2.4	2.7
3	4.2	5.5	4.5	4.7	3.7	4.5	2.5	3.3	2.7	2.8	2.2	2.7
4	5.2	5.2	5.5	5.4	5.5	5.7	3.3	3.3	3.5	3.4	3.5	3.6
5	7.0	7.1	6.6	6.6	4.9	6.0	4.8	4.9	4.6	4.6	3.4	4.1
6	4.0	3.0	3.5	3.2	3.1	2.6	2.3	1.7	2.0	1.8	1.8	1.5
7	3.8	4.0	4.1	4.1	4.0	4.3	2.3	2.4	2.4	2.5	2.4	2.6
8	3.6	4.3	3.9	3.2	2.4	4.1	2.4	2.8	2.6	2.1	1.6	2.7
9	6.5	7.3	6.7	5.6	5.0	5.5	3.7	4.2	3.9	3.2	2.9	3.2
10	5.8	6.3	5.9	6.0	4.8	5.6	3.8	4.1	3.8	3.9	3.1	3.6
11	6.3	7.1	6.5	6.1	7.4	7.6	3.6	4.1	3.7	3.5	4.2	4.3
12	2.3	4.7	2.6	2.6	2.5	2.8	1.6	3.3	1.8	1.8	1.7	2.0
13	5.1	5.8	4.4	3.8	4.2	4.6	2.9	3.3	2.5	2.2	2.4	2.6
14	6.5	8.4	7.6	7.2	6.5	7.1	3.8	4.9	4.5	4.2	3.8	4.2
15	5.3	6.2	5.1	5.4	5.9	5.8	2.9	3.4	2.8	3.0	3.3	3.2

No.	FAC b/l	FAC 5	FAC 15	FAC 25	FAC 35	FAC 45	LVOTvti b/l	LVOTvti 5	LVOTvti 15	LVOTvti 25	LVOTvti 35	LVOTvti 45
1	58.8	76.2	69.2	64.3	70.8	64.9	13.2	16.2	15.3	15.7	14.0	12.6
2	55.8	67.8	60.2	59.4	60.6	53.8	10.4	14.5	13.4	11.8	12.3	10.9
3	58.6	56.9	59.6	55.2	64.1	52.4	11.2	16.4	16.3	12.7	13.2	11.8
4	57.7	61.0	49.5	52.2	50.5	50.4	14.9	17.9	15.9	12.8	11.6	12.2
5	42.6	53.9	56.0	50.9	52.1	54.5	14.3	18.8	18.3	17.7	13.6	13.8
6	62.1	74.4	67.0	70.6	70.5	73.7	14.9	21.4	18.9	17.8	17.2	16.1
7	61.6	68.5	67.5	62.1	62.3	61.7	15.3	20.7	17.6	16.7	16.9	13.7
8	62.8	64.8	68.2	66.6	74.3	61.3	18.8	21.4	19.8	16.7	15.5	15.4
9	55.8	60.8	59.4	63.9	67.3	59.6	12.2	17.2	16.3	12.1	12.6	11.9
10	62.8	67.7	69.9	67.2	71.1	61.9	16.4	20.7	19.4	17.2	13.8	14.1
11	57.4	64.9	64.9	61.6	48.6	53.9	12.5	18.4	19.6	14.7	13.2	11.8
12	77.9	62.1	76.2	77.6	73.1	73.3	16.3	22.1	20.1	20.1	18.8	15.8
13	56.8	64.2	63.6	68.1	62.8	58.6	13.4	18.3	18.5	16.2	15.6	13.8
14	57.8	56.7	59.1	54.4	57.2	49.6	13.1	16.7	17.1	14.7	13.7	12.8
15	54.7	60.8	55.4	52.2	44.9	53.8	15.7	19.3	18.5	15.7	13.6	14.3

No.	SV b/l	SV 5	SV 15	SV 25	SV 35	SV 45	CO b/l	CO 5	CO 15	CO 25	CO 35	CO 45
1	43.6	53.5	50.3	51.8	46.1	41.7	3.27	4.12	3.57	3.52	3.32	2.96
2	28.1	39.0	36.1	31.7	33.3	29.3	1.83	2.46	2.16	2.06	2.20	1.99
3	34.8	50.7	50.4	39.5	40.8	36.6	1.98	3.30	3.23	2.57	2.61	2.41
4	50.7	60.9	54.1	43.5	39.4	41.3	4.26	5.42	4.87	3.87	3.55	3.97
5	54.5	71.4	69.5	67.3	51.5	52.4	3.76	5.14	4.66	4.44	3.45	3.46
6	56.6	81.3	71.8	67.6	65.4	61.2	3.62	6.10	5.39	4.94	4.77	3.98
7	47.4	64.2	54.4	51.9	52.4	42.3	3.51	5.13	4.52	4.25	4.19	3.47
8	52.5	59.8	55.4	46.8	43.3	43.0	4.67	5.62	5.43	4.35	4.29	4.04
9	45.1	63.6	60.3	44.8	46.6	43.9	2.26	3.69	3.38	2.55	2.75	2.59
10	68.9	86.9	81.5	72.2	58.0	59.2	5.51	7.48	6.44	5.71	4.87	4.86
11	47.5	69.9	74.5	55.9	50.2	44.8	2.66	4.13	4.32	3.24	2.91	2.65
12	37.5	50.8	46.2	46.2	43.2	36.3	3.15	4.63	4.11	4.16	3.59	3.23
13	50.9	69.5	70.3	61.6	59.3	52.4	3.97	6.26	6.54	5.42	5.28	4.35
14	38.1	48.3	49.6	42.5	39.7	37.1	2.93	3.62	2.98	2.55	2.54	2.56
15	39.3	48.3	46.2	39.3	34.0	35.8	3.22	4.25	3.97	3.77	3.16	3.40

No.	CI b/l	CI 5	CI 15	CI 25	CI 35	CI 45	UO b/l	UO 5	UO 15	UO 25	UO 35	UO 45	UO tot
1	1.94	2.45	2.13	2.10	1.97	1.76	200	400	150	100	120	110	1080
2	1.09	1.46	1.29	1.23	1.31	1.19	150	180	75	120	100	70	695
3	1.20	1.99	1.94	1.55	1.57	1.45	250	150	60	70	60	90	680
4	2.69	3.43	3.08	2.45	2.25	2.51	100	120	110	80	100	80	590
5	2.59	3.55	3.21	3.06	2.38	2.39	150	200	150	125	130	80	835
6	2.09	3.53	3.11	2.85	2.76	2.30	80	80	120	100	80	90	550
7	2.09	3.06	2.69	2.53	2.49	2.07	300	150	90	120	130	100	890
8	3.12	3.75	3.62	2.90	2.86	2.70	250	100	130	110	110	90	790
9	1.30	2.12	1.94	1.47	1.58	1.49	100	240	120	90	120	70	740
10	3.58	4.86	4.18	3.71	3.16	3.15	180	350	140	120	130	60	980
11	1.52	2.36	2.47	1.85	1.66	1.51	150	160	80	130	110	80	710
12	2.20	3.23	2.88	2.91	2.51	2.26	310	170	70	60	70	90	770
13	2.26	3.56	3.71	3.08	3.00	2.47	90	110	100	90	90	70	550
14	1.72	2.13	1.75	1.50	1.50	1.51	220	240	140	130	110	100	940
15	1.78	2.35	2.19	2.08	1.75	1.88	110	90	110	120	90	80	600

No.	FI b/l	FI 5	FI 15	FI 25	FI 35	FI 45	FI tot	FB b/l	FB 5	FB 15	FB 25	FB 35	FB 45	FB tot
1	400	90	70	60	80	70	980	200	-220	-80	-40	-40	-40	-100
2	300	110	50	70	60	50	1130	150	-70	-25	-50	-40	-20	435
3	150	100	70	60	50	60	790	-100	-50	10	-10	-10	-30	110
4	200	60	80	70	60	60	670	100	-60	-30	-10	-40	-20	80
5	250	50	100	80	90	80	900	100	-110	-50	-45	-40	0	65
6	250	100	100	70	60	60	940	170	20	-20	-30	-20	-30	390
7	330	40	100	120	80	70	1040	30	-110	10	0	-50	-30	150
8	180	110	130	80	60	80	920	-70	10	0	-30	-50	-10	130
9	190	50	90	60	80	50	830	90	-190	-30	-30	-40	-20	90
10	380	70	80	70	70	60	940	200	-110	-60	-50	-60	0	-40
11	290	130	60	60	70	40	1070	140	-30	-20	-70	-40	-40	360
12	160	90	70	50	60	60	830	-150	-80	0	-10	-10	-30	60
13	180	60	90	80	70	70	720	90	-50	-10	-10	-20	0	170
14	230	50	110	70	80	60	840	10	-190	-30	-60	-30	-40	-100
15	290	70	90	60	50	60	970	180	-20	-20	-60	-40	-20	370

No.	SVR b/l	SVR 5	SVR 15	SVR 25	SVR 35	SVR 45
1	1469	1302	1343	1385	1158	1568
2	3287	2472	3068	2910	2767	2889
3	3145	1553	1587	2183	2175	2386
4	1955	1314	1381	1859	2028	1774
5	1703	1431	1528	1748	1970	2080
6	2053	1128	1262	1426	1492	2032
7	1732	1216	1222	1223	1298	1498
8	1301	1238	1281	1509	1605	1583
9	3828	1842	2084	2947	2763	2997
10	1263	942	1143	1262	1446	1450
11	2647	1900	1852	2642	2805	2903
12	1956	1263	1439	1461	1672	1756
13	1893	1253	905	1093	1198	1287
14	1746	1435	1640	2415	2045	2186
15	2233	1658	1834	1826	2302	2096