A RANDOMISED CONTROLLED TRIAL TO COMPARE PULSE PRESSURE VARIANCE AND CENTRAL VENOUS PRESSURE AS GUIDE TO INTRAOPERATIVE FLUID MANAGEMENT IN NEUROSURGICAL PATIENTS

A dissertation submitted to the Tamil Nadu Dr. M.G.R.Medical university in partial fulfilment of the requirement for the award of M.D.Branch II (anaesthesia) degree March 2011

CERTIFICATE

This is to certify that this dissertation

"*A randomised controlled trial to compare pulse pressure variance and central venous pressure as guide to intraoperative fluid management in neurosurgical patients*"

Is an original work of research done by Dr. Shalini Cynthia,

Towards partial fulfilment of the requirements for the award of

MD Anaesthesia degree

Signature of the Guide

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Introduction:

Anaesthesia for neurosurgery has many challenges. The emphasis remains on the provision of good operative conditions, assessment and preservation of neurological function, and a rapid, high-quality recovery. Fluid management intraoperatively plays a major role in achieving these goals of neurosurgery. Candidates presenting for intracranial surgery may be at risk of hypovolaemia for different reasons, including insufficient fluid intake, physiological compensation for arterial hypertension, and osmotic diuretic therapy. Formula based fluid management is inappropriate in these situations and so therapy has to be individualised. Individualised 'Goal-directed fluid therapy' has been shown to improve outcome after surgery. Various indices have been derived to calculate fluid responsiveness and volemic status. These include O2 transport and hemodynamic variables such as mixed venous saturation, O2 delivery, stroke volume estimation, and pulmonary artery pressure which can be measured only with highly invasive monitoring. Dynamic indices such as pulse pressure variation, stroke volume variation and systolic pressure variation are considered reliable monitors for fluid responsiveness and are more practical. Among these, pulse pressure variation has been shown to have a high sensiivity and specificity. Our aim in this study was to see if fluid therapy guided by PPV variation is reliable in neurosurgical patients and to compare this with CVP guided therapy.

Aims and objectives:

To study the use of PPV as index of fluid management in neurosurgery and compare this with CVP

To assess the intraoperative hemodynamic stability using this therapy

To study the adequacy of tissue perfusion at the end of surgery as measured by acid base and lactate levels and post operative fluid management.

Review of literature

Fluid management in neurosurgery provides special challenges to the anaesthesia provider. The traditional approach to fluid management of patients with intracranial mass lesions or brain swelling often includes volume restriction to less than 1 litre/day. Though comfortable for the surgeon, the severe volume restriction leads to few major problems for the anesthesiologist e.g. hypovolaemia, electrolyte and acid base abnormalities and hypoxaemia. It has been shown that complete water restriction in dogs for 72 hours results in an 8.0% loss of body weight but only 1% decrease in brain water content (1).The modern approaches to management require that patient have reasonable circulating volumes to tolerate the changes induced by anaesthesia , surgery and other associated causes .(2)

Special considerations in neurosurgery:

The traditional approach for fluid management in patients with supratentorial masses and brain injury was to restrict fluids in an attempt to reduce brain volume and reduce cerebral edema. When used in conjunction with mechanical ventilation and osmotic dieresis it can produce a significant deficit in the functional circulating blood volume leading to hypotension, exaggerated circulatory responses to anaesthetic agents, hypoxemia and possible decrease in vertebral blood flow. Factors to be considered in fluid administration in neurosurgery are effects of fluids on intracranial volume, pressure and cerebral perfusion, the blood brain barrier and its role in fluid equilibrium, problems of hypo and hypervolemia in neurosurgery patients. (3)

Preservation of CPP (cerebral perfusion pressure)

Brain being encased within the skull increases in intracranial volume may produce deleterious increases in intracranial pressure. This can decrease cerebral perfusion resulting in ischemia and brain damage. Many mechanisms can increase the volume of the intracranial contents and ICP(intracranial pressure)

Brain mass may increase from the growth of tumours

Accumulation of blood either subdural, epidural or intracerebral

Increase in the volume of Cerebrospinal fluid

ICP can also increase secondary to vasodilation, which may be secondary to hypercapnea, hypoxemia, inhalation anaesthetics, intravenous anaesthetics like ketamine, direct acting vasodilators like nitroglycerine and nitroprusside or an initial effect of osmotic diuretics. Increase in central venous pressure by overhydration can also increase brain vascular volume and intracranial hypertension.

Preservation of CPP necessitates maintenance of normovolemia without adversely influencing intracranial pressure (ICP). Several physiologic principles underlie the relationship between fluid management, volume status and ICP. Cerebral blood volume (CBV) is a function of cerebral blood flow and cerebral venous volume, which in turn is a function of cerebral venous capacitance and cerebral venous pressure. Cerebral venous pressure is equal to central venous pressure in the supine position but is reduced as the head is elevated above the chest. Even though it was assumed that hypervolemia would be associated with greater central venous pressure, and, as a consequence, greater cerebral venous pressure and greater intracranial volume, few

clinical data support that assumption. Although relative fluid restriction has been associated with worse outcome in head-injured patients,(4) more aggressive fluid therapy has been associated with greater severity of pulmonary infiltrates. Brain tissue volume is a function of the integrity of the blood-brain barrier (BBB). In non-brain tissues, and in brain tissue in which the BBB has been damaged, the distribution of fluid between plasma volume and extracellular volume (ECV) is determined by capillary membrane permeability, transcapillary hydrostatic pressure gradients and transcapillary colloid osmotic (oncotic) pressure gradients as defined by the formula

Fluid movement = K(Pc+πi-Pi-πc)

K – filtration coefficient

Pc- hydrostatic pressure in the intravascular space

Pi- hydrostatic pressure in the interstitial space

Пc- colloid oncotic pressure in capillary

Пi- colloid oncotic pressure in interstitium.

In contrast to systemic capillary membranes, the cerebral capillary membranes that constitute the BBB are impermeable to most hydrophobic solutes, including sodium, but may become highly permeable if the BBB is disrupted. The terms hypotonic, isotonic and hypertonic refer to intravenous fluids in which the total osmolality is less than, roughly equal to, or greater than serum osmolality, with [Na+] in fluids relative to plasma [Na+] being the most important component of osmolality. Normal plasma osmolality averages 290mOsm/kg, of which 280mOsm/kg is attributable to sodium and its associated anions. The osmolalities of lactated Ringer's solution and 0.9% NaCl are

270mOsm/kg and 308mOsm/kg, respectively. Each mOsm/kg difference across a water-permeable membrane generates an osmotic pressure of 19.3 mmHg. Because each sodium ion is accompanied by an anion, an acute increase or decrease of plasma sodium of 1.0mEq/L generates an acute increase or decrease in osmolality of 2.0 mOsm/kg and an increase or decrease in osmotic pressure of 38.6 mmHg. Therefore, small acute differences in plasma sodium concentration ([Na+]) generate substantial osmotic pressure gradients across the intact BBB and may alter brain water to a clinically important extent.(5)

In summary blood brain barrier creates a semipermeable barrier between blood and brain. Administration of large quantities of water or glucose solutions will lead to an increase in brain water and ICP. Administration of isoosmotic saline or albumin have little effect on brain water and ICP while hyperosmotic solutions which do not cross blood brain barrier will decrease brain water content. With disruption of blood brain barrier the permeability to sodium, albumin and mannitol is increased.(5)

Hypertonic solutions:

Osmotic reduction of brain water and ICP is routinely accomplished with mannitol but hypertonic saline solutions are preferred by some clinicians.(6) Hypertonic saline solutions and mannitol solutions of similar osmolality have similar effects on brain water and intracranial pressure. Infusion of hypertonic saline, unlike mannitol, increases intravascular volume. While few complications relate specifically to osmotic therapy, acute severe hyperosmolality could theoretically precipitate BBB opening. Clinical use of hypertonic saline is associated, as is 0.9% saline, with hyperchloremic acidosis,

which usually requires no treatment, but must be differentiated from other causes of metabolic acidosis. (6)

Guidelines for fluid management in craniotomy:

As a general rule, isotonic crystalloid solutions should be used to replace preexisting deficits and blood loss. Transfusion may be indicated at a hemoglobin concentration ([Hgb]) of 8 g/dL, with a higher threshold being appropriate if there is evidence of tissue hypoxia or ongoing uncontrolled haemorrhage. Fresh frozen plasma may be infused if there is persistent haemorrhage despite adequate surgical hemostasis. There are few clear indications for the administration of albumin or synthetic colloids; they do not prevent the formation of brain edema. Hetastarch, in sufficient quantities, may be associated with coagulopathy. To reduce brain volume and improve operating conditions, hypertonic mannitol is frequently given, with hypertonic saline representing an alternative. In 238 neurosurgical patients randomized to receive either 160 mL of 3% saline or 15mL of 20% mannitol to induce brain relaxation during neurosurgery, brain relaxation was superior in the group receiving 3% saline, although there were no differences in major outcomes.8 Solutions containing dextrose are best avoided unless there is a specific indication for use (e.g., hypoglycemia).(4)

Restricted vs standard fluid management:

Optimal fluid management in high risk surgery has been shown to decrease post operative morbidity and decrease duration of hospital stay.(3)(7)(8)(9) The amount of

fluid and the type of fluid to be used has been a matter of debate and no single index has been suggested to define optimal fluid management. Studies comparing high and low volume loading of patients have been done and the post operative parameters like post operative complications and duration of hospital stay have been studied.(10)(11). *Brandstrup et al* (12)studied restricted Vs standard fluid therapy in patients posted for colorectal surgery. In the randomised control trial they found less complications and reduced hospital stay in the patients who received restricted fluid therapy.(13) However MacKay et al (14) found conflicting results in a similar randomised control trial done in patients undergoing colorectal surgery. The aim of this study was to compare outcome following administration of restricted or standard postoperative intravenous fluids and sodium in patients undergoing elective colorectal surgery. Eighty patients were randomized to restricted fluids (less than 2 litres water and 77 mmol sodium for 24 h after surgery) or a standard postoperative fluid regimen (3 litres water and 154 mmol sodium per day for as long as necessary). The primary endpoint was hospital stay. The median total intravenous fluid intake in the restricted group was 4.50 (4.00-5.62) litres compared with 8.75 (8.00-9.80) litres in the standard group ($P < 0.001$). Intravenous sodium intake was also significantly less in the restricted group; $P < 0.001$). There was no difference in median time to first flatus or first bowel motion ($P = 0.802$) between the restricted and standard groups, or in median hospital stay ($P = 0.902$). They concluded that restriction of intravenous fluids during surgery did not reduce post operative stay in hospital.(14) However there are studies to the contrary too(15)(16)

Various fluid indices have been used to direct fluid management . Static measurements include estimates of preload of the patient like central venous pressure (CVP) , capillary

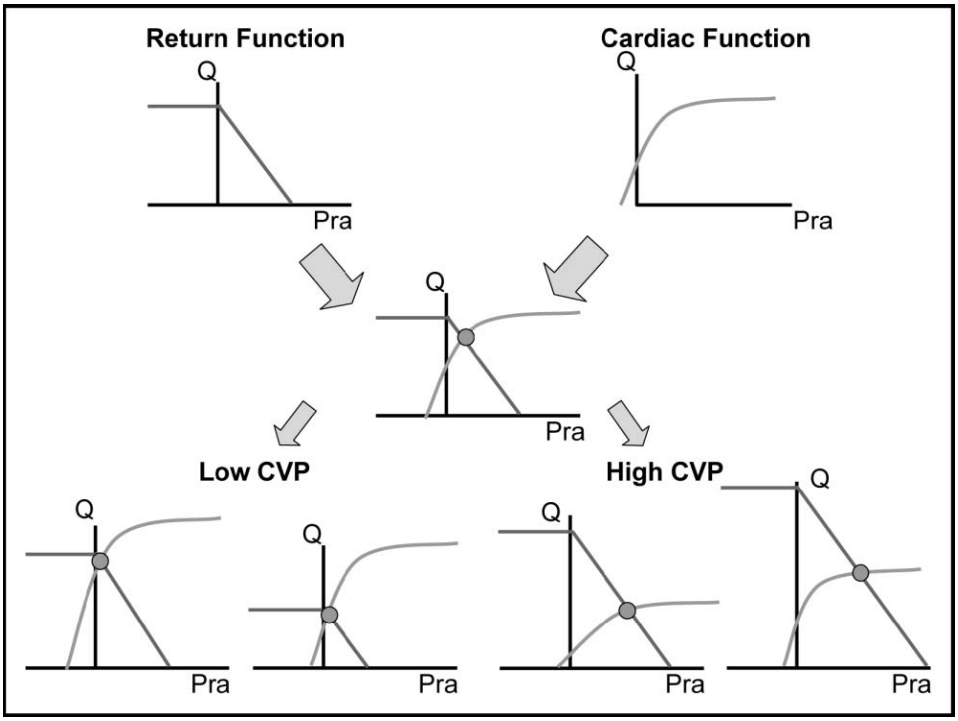
wedge pressure(PCWP)

Central venous pressure:

The measurement of central venous pressure (CVP) is very common in clinical practice. The CVP can be obtained with transducers and electronic monitors, witha simple water manometer, and even by simply measuring jugular venous distension (JVD) on physical examination. The origins of CVP monitoring can be traced back to Hughes and Macgovern who described a complicated technique for right atrial monitoring to guide fluid replacement (17)

Physiologic principles

Two reasons for measuring the CVP are assessment of volume status and assessment of the preload of the heart, but a measurement of CVP alone cannot achieve these objectives. This is because CVP and cardiac output are determined by the interaction of two function curves: the cardiac function curve and the return curves.(18). A value of CVP cannot be interpreted without some idea of cardiac output at the time of the measurement. This does not have to be an actual measurement of cardiac output and could include a clinical assessment of the patient's perfusion status (19)



The second physiological principle in CVP measurement is the concept of physiologic limits. The cardiac function curve has a steep ascending portion and then reaches a plateau (20) The plateau occurs because there is a limit to diastolic filling of the heart, which generally occurs first in the right ventricle. Under normal conditions, this limitation is due to constraint by the pericardium, but even in the absence of a pericardium, the cardiac cytoskeleton limits cardiac filling implying that the heart cannot be easily overfilled and there is no downward slope to the Starling curve. Limitation of filling in the right side of the heart also limits ejection from the right side of the heart, which thereby protects the left side of the heart and the lungs. Patients on the flat part of the curve will not have an increase in cardiac output with fluid boluses.(21)

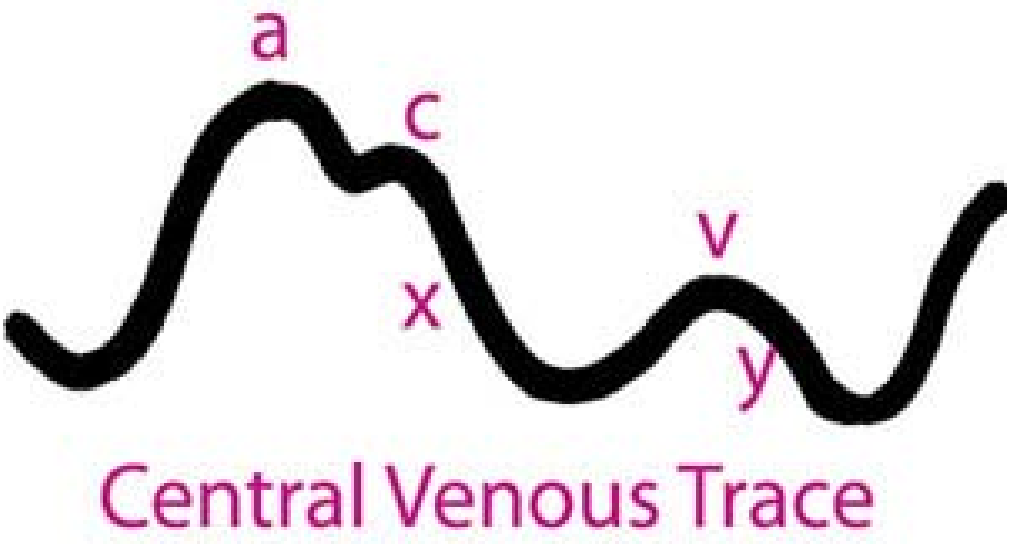
Principles of measurement:

Two concepts are especially important: the concept that pressures are relative to an arbitrary reference point and the concept of transmural pressure. When a fluid filled catheter is used to measure central venous pressure it has to be referenced to an arbitrary point, the commonly accepted point of reference for hemodynamic measurements is the midpoint of the right atrium, where the heart interacts with the returning blood. This point in the supine position is referenced to the fifth intercostal space on a line from the midaxilla . The midaxilla measurement gives a CVP value that is approximately 3 mm Hg higher than measurements based on the sternal angle

Electronic measurement of central venous pressure

The CVP has three prominent positive waves: the ‘a,’ ‘c,’ and ‘v’ waves and two prominent negative waves, the ‘x’ and ‘y’ descents. The ‘a’ wave is due to atrial contraction, the ‘c’ wave is due to the backward buckling of the tricuspid valve at the onset of systole, and the ‘v’ wave is due to atrial filling during diastole. The ‘x’ descent is due to the fall in atrial pressure during relaxation of the atrial contraction. The ‘y’ descent is due to the sudden decrease in atrial pressure at the onset of diastole when the atrioventricular valve opens and allows the atrium to empty into the ventricle. The ‘y’ descent is affected by the relative filling of the atria and ventricles at the start of diastole, the compliance of the chambers, and the pressure outside the heart (22). This last factor can be useful for marking inspiration on the hemodynamic recording in patients with spontaneous breaths, for the ‘y’ descent increases during inspiration. Since the most common reason for assessing CVP is likely the assessment of cardiac preload the best place for the measurement is the ‘z’ point, which is at the leading edge of the ‘c’

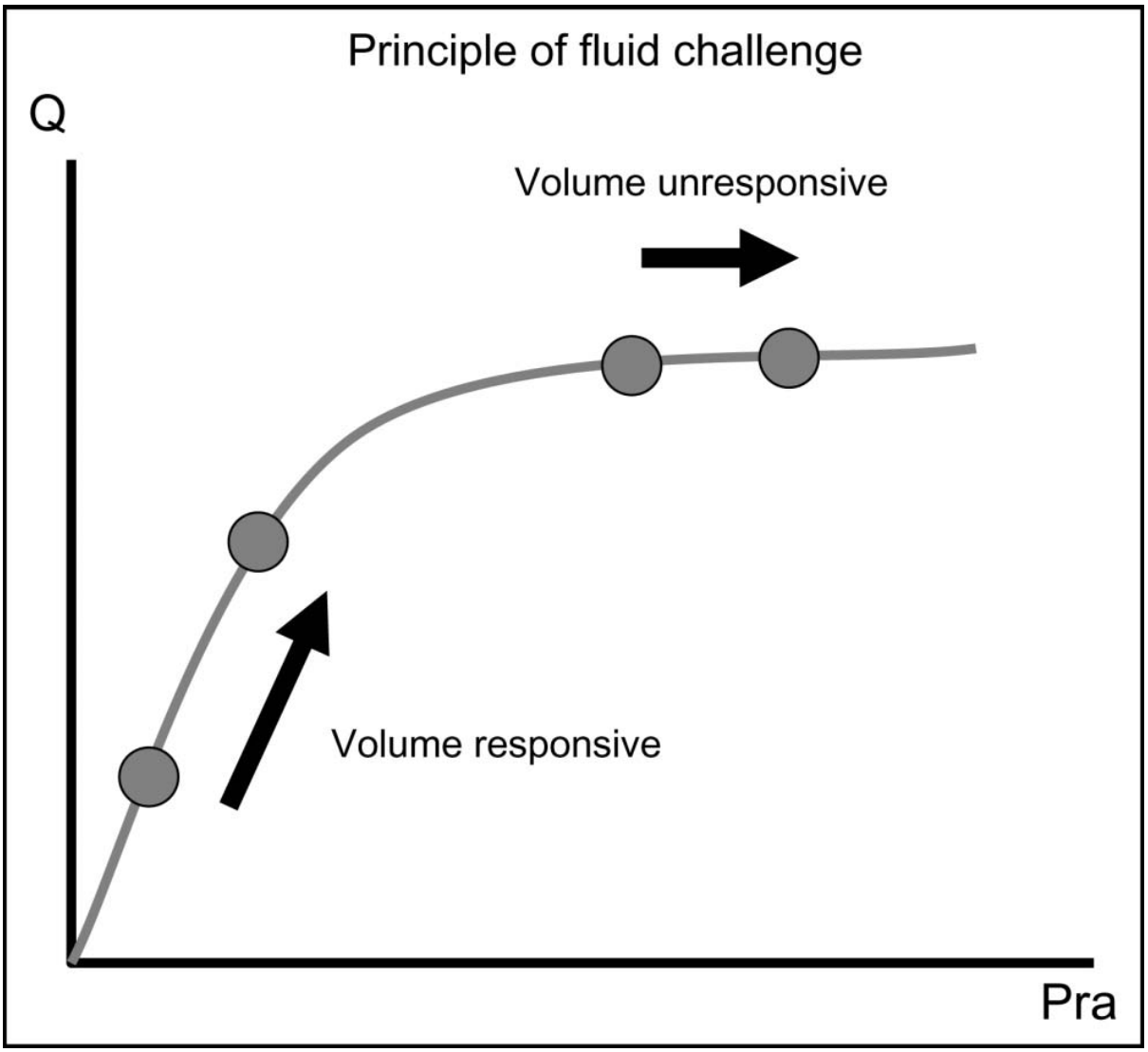
wave, which gives the final pressure in the atrium and thus the ventricle just before ventricular contraction



Fluid responsiveness

It is important to be able to recognize the plateau of the cardiac functions curve because it indicates the limits of volume responsiveness of the heart. The value at which this plateau occurs is highly variable among individuals. Patients can be volume limited at CVP values as low as 2 mm Hg , whereas others may respond at CVP values greater than 18 mm Hg. Magder et al found 40% of patients, with a CVP below 6 mm Hg did not respond to fluids . Most patients will be volume limited by a CVP of 10 to 12 mm Hg, and this range of CVP can be considered high. When giving volume challenges to patients with CVP values above this range, one should have some reason to expect that transmural right atrial pressure is less than is evident from the CVP relative to

atmosphere. Possibilities include patients with high positive end-expiratory pressure, thickened right ventricular walls, high abdominal pressure, and cardiac compression by the lungs or mediastinum. When possible, however, it is best not to use a single value of CVP to predict volume responsiveness, and some kind of dynamic test should be used. It also must be emphasized that just because a patient is fluid responsive does not mean that the patient needs fluid. Normal persons will usually have an increase in cardiac output in response to a fluid bolus.



Fluid challenge:

The gold standard for testing volume responsiveness is to give a fluid challenge fluid bolus is infuse rapidly to increase the CVP by 2 mm Hg and then determine whether there is an increase in cardiac output. (23) .The number of 2mm Hg is picked because a change of this magnitude can be identified with confidence on most monitors and recording devices. The change in cardiac output should be in the range of 300 ml/min. To minimize the amount of fluid needed, the fluid must be given quickly. If the fluid is given rapidly and the change in CVP is monitored continuously, the type of fluid does not matter.(19) The faster the fluid is given, the less is needed. When a measure of cardiac output is not available, other surrogate markers can be used. A change in arterial pressure does not correlate well with changes in cardiac output.(22)

'y' descent

Another indicator that there will not be an increase in cardiac output with a volume infusion is the magnitude of the 'y' descent. The presence of a large y descent indicates restriction of right ventricular filling (22) . This can be due to intrinsic stiffness of the ventricular wall or occur in a ventricle that is excessively volume-loaded. In either case, further volume loading is unlikely to change cardiac output. Madger et al found that when the y descent is >4mmHg the patient is unlikely to have a rise in cardiac output in response to a volume challenge .(24)

The magnitude of the Y descent is affected by the volume status, the magnitude and direction of the changes in pleural pressure, and the compliance of the pericardial

compartment. A large Y descent indicates a restrictive cardiac state, but a small Y descent does not rule out a restrictive condition because of the many interacting variables.

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Respiratory variation of CVP

The respiratory pattern in CVP can be used to predict fluid responsiveness (23)

Patients who have no inspiratory fall in CVP are on the flat part of their cardiac function curve and will not respond to fluids whereas patients who have an inspiratory fall in CVP are on the ascending part of the cardiac function curve and may or may not respond to fluids. Clinically useful information can also be obtained from the magnitude of the respiratory swings in CVP. In spontaneously breathing individuals a large fall inspiratory fall in CVP indicates that there was a large fall in pleural pressure.(23)

Placement of central venous catheter

CVP measurement requires placement of a central venous line. The following considerations need to be given in the placement of a line: Reliability of correct placement, prediction of the correct value, feasibility of line placement. Various methods and landmarks have been studied for measuring CVP.

Common sites for central line placement include internal jugular vein or subclavian vein on either side and femoral vein. Peripherally inserted central lines (PICC) can be inserted in the antecubital fossa through the median basilic or cephalic vein and are inserted till the catheter tip resides in a central vein. Comparison of CVP measurements

have been done from catheters placed in various positions and the accuracy determined.

Measurement of CVP:

CVP measurement can vary when measured by central line and PICC line .It was postulated that because of their longer length and narrower lumen, PICCs have a higher inherent resistance that makes them an inappropriate vehicle to measure central venous pressure without methodological modification.

Black et al studied the CVP measurement from central line and PICC line. They used a continuous infusion device to overcome the PICC's inherent resistance. A pressure difference of 3-4 mmHg was expected based on in vitro studies. However their study showed that the difference in measurement was only 1 mmHg.(25) PICC line can act as an additional tool for assessing patients' intravascular volume status, with a reported decrease in cost and risks (26)(27). Although PICCs are associated with decreased infection rates and a decreased incidence of pneumothorax,, PICCs may be associated with an increase in catheter malposition, inadvertent removal, and severed or leaking catheters, when compared with CICCs (27)(28).

Methods of central venous cathether placement:

Placement of a central line can be done using various methods. Anatomical landmarks can be used to decide site of puncture. Alternatively when the resources are available placement can be ultrasound guided and electrocardiogram guided. Studies have been done to compare efficacy of placement and the depth of placement.

The standard technique for placement of central venous catheters is by use of anatomical landmarks, which may not correlate with vessel location (29). The use of Doppler ultrasound to assist with catheter placement was first reported in 1984 (9). Ultrasonography for vessel location with subsequent catheter placement by landmark technique was later shown to have no effect on the complication or success rate of subclavian catheterization(16) (30) .Randolph et al (31) did a meta analysis of placement of central lines by various methods.

The outcomes assessed were the rapidity of placement, the number of attempts before successful placement, the success of placement, the rate of complications, and the rate of success after failure by the landmark method. From a pool of 208 randomized, controlled trials of venous and arterial catheters management, 12 randomized, controlled trials of ultrasound guidance or Doppler ultrasound guidance for placement of central venous or pulmonary artery occlusion pressure catheters in adult patients were identified. They found that compared with the landmark technique for placement of internal jugular and subclavian central venous catheters, ultrasound guidance significantly increases the probability of successful catheter placement, significantly reduces the number of complications encountered during catheter placement, and significantly decreases the need for multiple catheter placement attempts. However, the time it takes to successfully place a catheter may not be reduced using ultrasound guidance.

Unavailability of ultrasound device and lack of expertise limit the use of ultrasound.

However other methods can be used for placement as well.ECG controlled placement of central line was introduced in 1949.

Gebhard et al (21) conducted a trial to estimate accuracy of line placement by this method . Guidewire-ECG control resulted in more correctly positioned CVCs (96% vs 76%, $P < 0.001$) without increasing placement time. Significantly more CVCs were placed in the middle of the superior vena cava in group ECG (P _ 0.001), although placement into the right atrium or right ventricle and into other vessels occurred significantly more often in group NO-ECG (P _ 0.001)

They concluded that when available ECG should be used to position to avoid complications associated with line placement and to avoid costs of repositioning of central line.(32)

ECG guided placement of central line:

Cotrell described optimal positioning of central line for air aspiration (33)For introduction of catheter venipuncture is made by the modified Seldinger technique. The catheter is advanced alteast 20 cm via the arm or 15 cm via the neck. Specially adapted conducted connector for ECG attachment is placed on the guidewire . The monitor ECG is set for lead II and the right arm lead is connected to the connector. The ECG trace is observed on the monitor and the tip is manipulated until it lies in the right ventricle .The catheter is then withdrawn into the mid- right atrium to detect a biphasic P wave. The catheter is then withdrawn until the P wave is approximately the height of the QRS complex. It is then withdrawn some more till the P wave is smaller than the QRS complex and fixed at this point (34)(35)

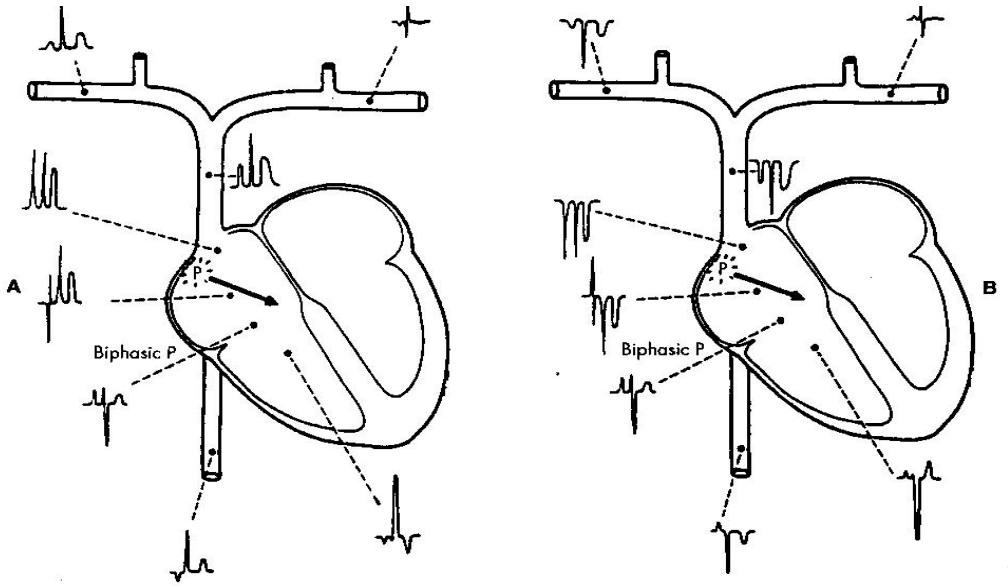
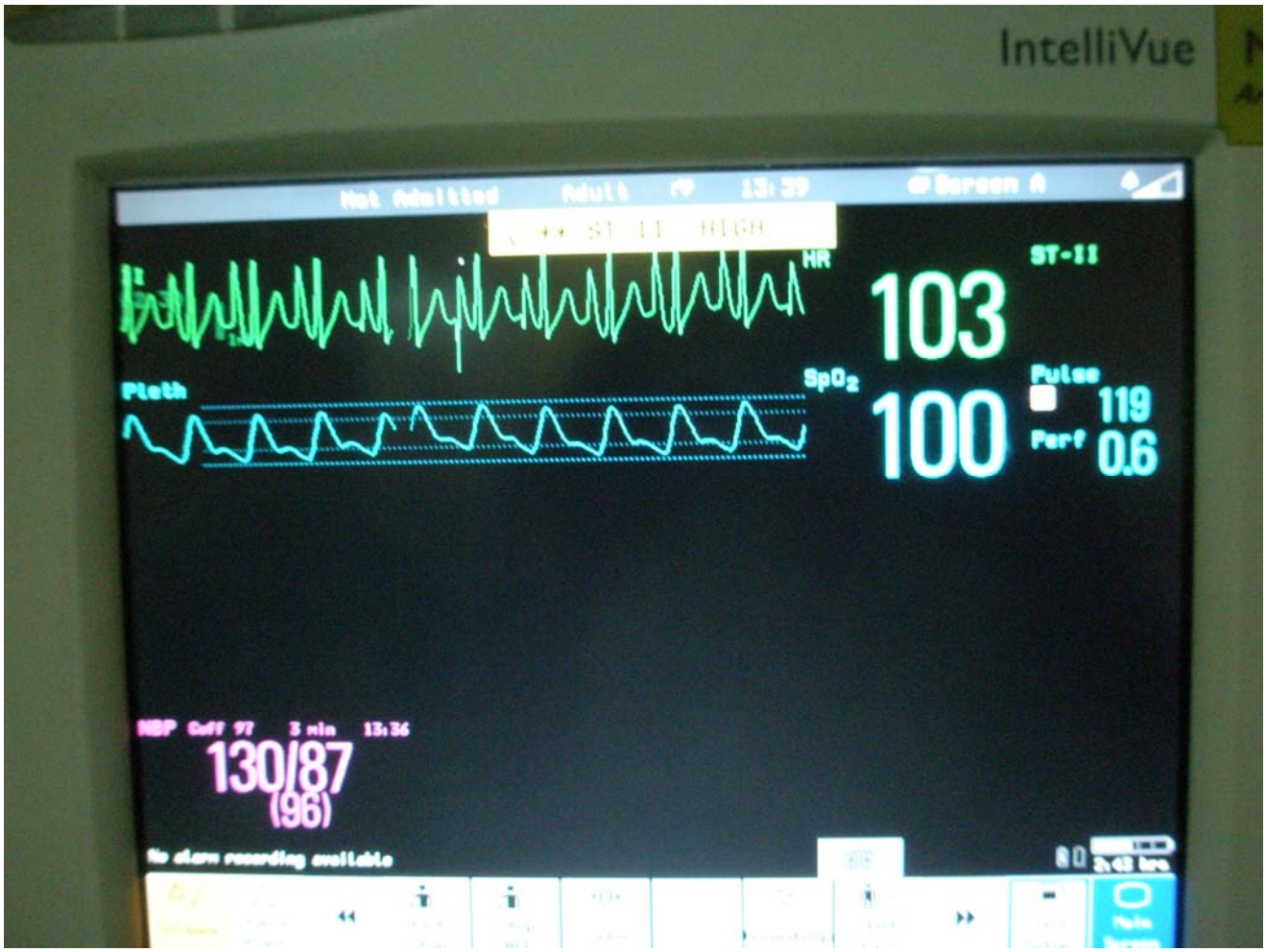


FIG. 17-1 Positioning right atrial catheter. A, P wave changes seen with lead II as the sensing lead. B, P wave changes seen with lead V as the sensing lead.

The use of ECG for central line placement has been supported by many studies. The use of this method has been proven to predictably improve aspiration of air from right atrium and decrease need for chest x ray for line placement.(36) (37)



As shown in figure catheter is withdrawn till p wave is biphasic and as tall as the QRS complex .

The catheter is further withdrawn till the height of the p wave is smaller than QRS and anchored at this point

Central venous pressure has been used to predict fluid responsiveness. However Marik et al (27) have done a systematic review to study the relationship between CVP and blood volume, the ability of CVP to predict fluid responsiveness, and the ability of the change in CVP to predict fluid responsiveness. Of the 24 studies included in this analysis, 5 studies compared CVP with the measured circulating blood volume while 19 studies determined the relationship between CVP and change in cardiac performance following a fluid challenge (generally defined as a _ 10 to 15% increase in stroke index/ cardiac index). In all, 830 patients across a spectrum of medical and surgical disciplines were studied.

The results of this systematic review are clear: (1) there is no association between CVP and circulating blood volume, and (2) CVP does not predict fluid responsiveness across a wide spectrum of clinical conditions. The likelihood that CVP can accurately predict fluid responsiveness is only 56% The results from this study therefore confirm that neither a high CVP, a normal CVP, a low CVP, nor the response of the CVP to fluid loading should be used in the fluid management strategy of any patient. None of the studies included in the analysis took the positive end-expiratory pressure levels or changes in intrathoracic pressure into account when measuring CVP. This is important because right ventricular filling is dependent on the transmural right atrial pressure gradient rather than the CVP alone. The practice parameters for hemodynamic support of sepsis in adult patients concludes that “fluid infusion should be titrated to a filling pressure” and that “pulmonary edema may occur as a complication of fluid resuscitation and necessitates monitoring of arterial oxygenation. This is clinically

important because a positive fluid balance in both ICU patients and those undergoing surgery has been associated with increased complications and a higher mortality. It is however equally likely that resuscitation guided by CVP will result in inadequate volume replacement. Furthermore, the use of diuretics based on CVP may result in intravascular volume depletion leading to poor organ perfusion and ultimately renal failure and multi organ failure because a “high” CVP does not necessarily reflect volume overload.(38)

The only reason to give a patient a fluid challenge is to increase the stroke volume. This assumes that the patient is on the ascending portion of the Frank-Starling curve and has “recruitable” cardiac output. Once the left ventricle is functioning near the “flat” part of the Frank-Starling curve, fluid loading has little effect on cardiac output and only serves to increase tissue edema and to promote tissue dysoxia. It is therefore crucial during the resuscitation phase of all critically ill patients to determine whether the patient is fluid responsive or not; this determines the optimal strategy of increasing cardiac output and oxygen delivery. Marik et al suggest clearly that CVP should not be used for this purpose .

In 1971, Forrester and colleagues, the pioneers of hemodynamic monitoring, concluded that “CVP monitoring in acute myocardial infarction is at best of limited value and at worst seriously misleading.” (39)In 1977, Dr. Burch, a well respected cardiologist, noted that “to accept non critically the level of central venous pressure as a quantitative index of blood volume can only lead to physiologic and/or therapeutic errors.”(40) The observations of Forrester et al, Baek and colleagues (41) , and Burch have now been

confirmed by 23 more recent studies. Magder reported that the respiratory variation in CVP in spontaneously breathing patients was predictive of fluid responsiveness. Additional studies are required to support using the respiratory variation in CVP to guide fluid management.

Hence it can be stated that CVP is a measure of right atrial pressure alone; and not a measure of blood volume or ventricular preload. However, measurement of the CVP may be useful in select circumstances, such as in patients who have undergone heart transplant, or in those who have suffered a right ventricular infarction or acute pulmonary embolism. In these cases, CVP may be used as a marker of right ventricular function rather than an indicator of volume status. This forms the basis to hemodynamic monitoring. (40)

Hemodynamic monitoring:

Measurements of indices like CVP and PAOP are not fully reliable with wide variations in intrathoracic pressures .They act as a poor estimate of preload as preload depends on ventricular volumes. To overcome the limitations of these static indices dynamic indices have been devised and used. These indices are based on the response of the circulatory system to a controlled preload variation by specific maneuvers redistributing blood volume (eg:mechanical ventilation, leg raising).(42)

Classification of dynamic indices:

Dynamic indices can be classified according the methodology used to predict preload variation. First group of indices are those which depend on cyclic variations of stroke volume or stroke volume related hemodynamic parameters like pulse pressure or aortic

blood flow determined by mechanical ventilation induced variations in intrathoracic pressure. Second group of indices are those based on cyclic variation of non stroke volume related hemodynamic parameters like vena cava diameter determined by mechanical ventilation. Third group are based on preload redistribution manoeuvres like passive leg raising.

Group A indices are the following:

Delta down: difference between apnoeic and tele expiratory systolic arterial pressure.(minimal value during mechanically ventilated cycle)

Delta Up: difference between tele inspiratory and apnoeic systolic arterial pressure (maximal value during mechanically ventilated cycle)

Systolic pressure variation: systolic arterial pressure variation during mechanically ventilatory cycle delta up+ delta down

Pulse pressure variation: arterial pulse pressure variation during mechanically ventilatory cycle.

Stroke volume variation: stroke volume variation during mechanically ventilatory cycle.

Peak aortic flow velocity variation: peak aortic blood flow velocity variation during mechanical ventilation.

Group B indices:

Left ventricle pre ejection period variation(delta PEP)

Ventilation induced variation of left ventricle pre ejection period or isovolumetric contraction time

Plethysmography delta PEP: calculated from plethysmography from R wave to the foot of plethysmographic wave.

Superior vena cava collapsibility index: ventilation induced variation of superior vena cava diameter.

Inferior vena cava distensibility index: ventilation induced variation in inferior vena cava diameter.

Group C indices:

Inspiratory right atrial pressure index:

Spontaneous inspiration induced right atrial pressure variation

Aortic blood flow variation due to passive leg raising:

Difference between aortic blood flow during passive leg raising and baseline aortic blood flow.

Respiratory systolic variation test:

Lungs are inflated with increasing airway pressures. systolic arterial pressure is measured after every inflation, so inflation induced variation in pressure can be calculated.

Physiological principles:

Effect of mechanical ventilation on right and left ventricular stroke volume

During mechanical ventilation the right ventricular stroke volume decreases and the left ventricular stroke volume increases with the opposite phenomenon happening during expiration. These physiological decreases are seen normally in patients but are

much wider when there is hypovolemia as their amplitude is predictive of fluid responsiveness.

Respiratory changes in right atrial pressure in spontaneously breathing patients

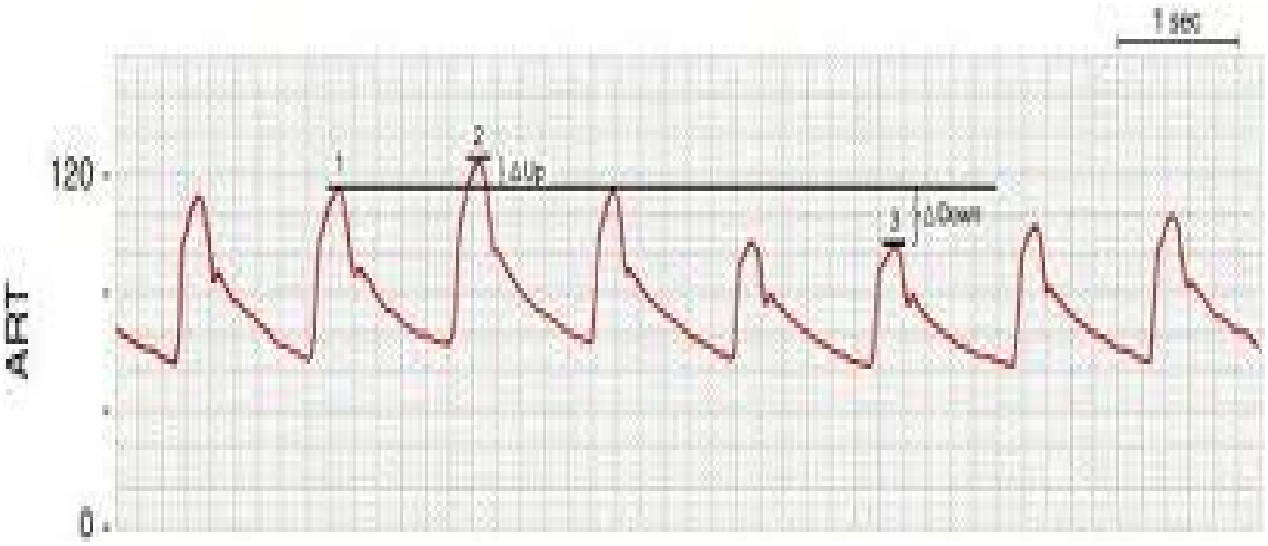
In patients with significant spontaneous breathing activity, the respiratory changes in right atrial pressure have been proposed to differentiate patients whose hearts are functioning on the flat part of the cardiac function curve from those who still have volume reserves and are on the ascending part of the curve. Unfortunately, many patients not have adequate inspiratory effort, and therefore do not have sufficient fall in pleural pressure to use this test to predict fluid responsiveness.

Respiratory changes in LV stroke volume in mechanically ventilated patients

In mechanically ventilated patients, the magnitude of the respiratory changes in LV stroke volume can be used to assess fluid responsiveness. Intermittent positive-pressure ventilation induces cyclic changes in the loading conditions of right and left ventricles. Mechanical insufflations decreases preload and increases afterload of the right ventricle . The inspiratory impairment in venous return is assumed to be the main mechanism of the inspiratory reduction in RV ejection (43). The inspiratory reduction in RV ejection leads to a decrease in LV filling after a phase lag of two to three heart beats because of the long blood pulmonary transit time . Thus, the LV preload reduction may induce a decrease in LV stroke volume, which is at its minimum during the expiratory period.

Respiratory changes in systolic pressure

In 1983, 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 .This difference was called 'systolic pressure variation' (SPV) and was divided into two components (delta up and delta down). These two components are calculated using a reference systolic pressure, which is the systolic pressure measured during an end-expiratory pause. Delta up is the difference between the maximal value of systolic pressure over a single respiratory cycle and the reference systolic pressure. It reflects the inspiratory increase in systolic pressure.Delta down is the difference between the reference systolic pressure and the minimal value of systolic pressure over a single respiratory cycle. It reflects the expiratory decrease in LV preload and stroke volume related to the inspiratory decrease in RV stroke volume.



Respiratory changes in pulse pressure

The pulse pressure (defined as the difference between the systolic and the diastolic pressure) is directly proportional to LV stroke volume and inversely related to arterial compliance . The pulse pressure is not directly influenced by the cyclic changes in pleural pressure, because the increase in pleural pressure induced by mechanical insufflation affect both diastolic and systolic pressures. In this regard, the respiratory changes in LV stroke volume have been shown to be reflected by changes in peripheral pulse pressure during the respiratory cycle [23]. Therefore,

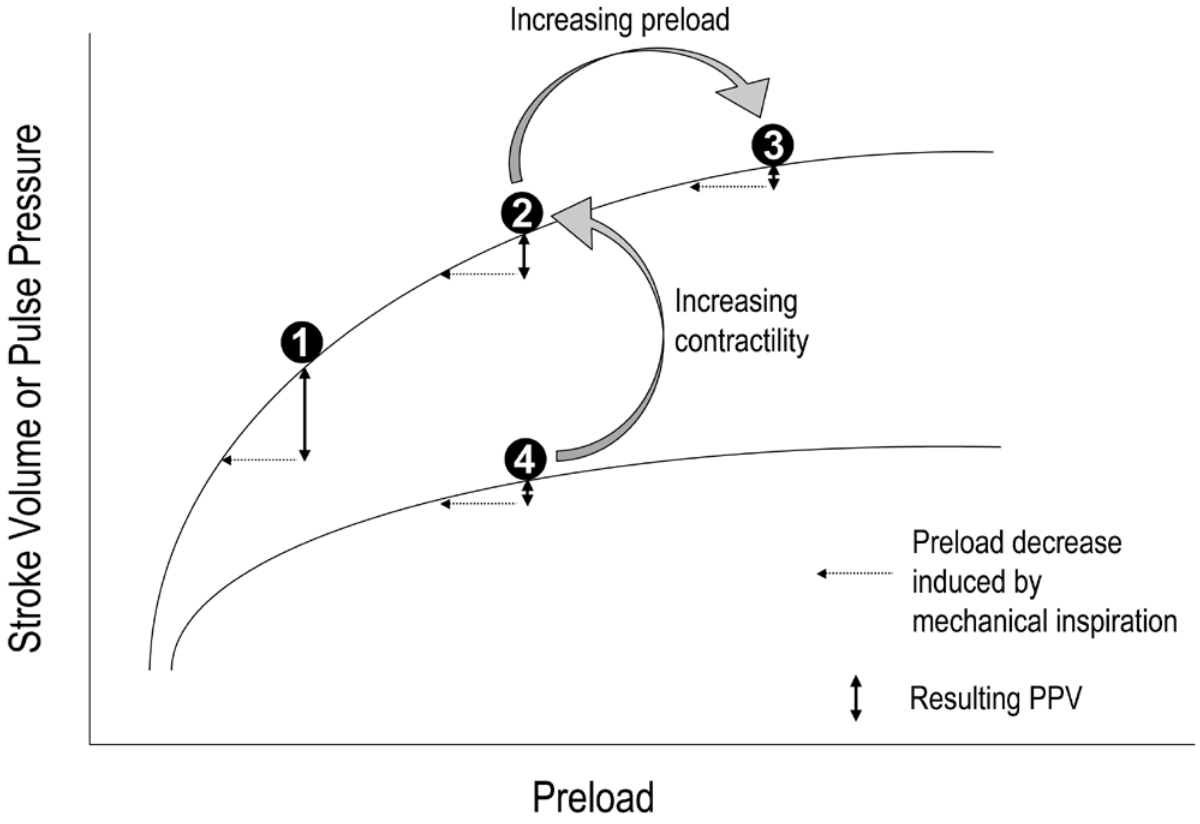
it was recently proposed that fluid responsiveness may be assessed by calculating the respiratory changes in pulse pressure (DPP) as follows:

(PPmax – PPmin)

DPP (%) = 100 × (PPmax + PPmin)/2

where PPmax and PPmin are the maximal and minimal values of pulse pressure over a single respiratory cycle.

DPP accurately predicted the haemodynamic effects of volume expansion; a threshold value of 13% allowed discrimination between responder (defined as patients who experienced an increase in cardiac index ³15% in response to volume expansion) and non responder patients with a sensitivity and a specificity of 94 and 96%, respectively. Delta PP was a more reliable indicator of fluid responsiveness than the respiratory changes in systolic pressure(23) .The decrease in DPP induced by volume expansion was correlated with the increase in cardiac index, such that changes in DPP could be used to assess the haemodynamic effects of volume expansion.



Various studies have been done using these dynamic indices as markers of volume in patients.

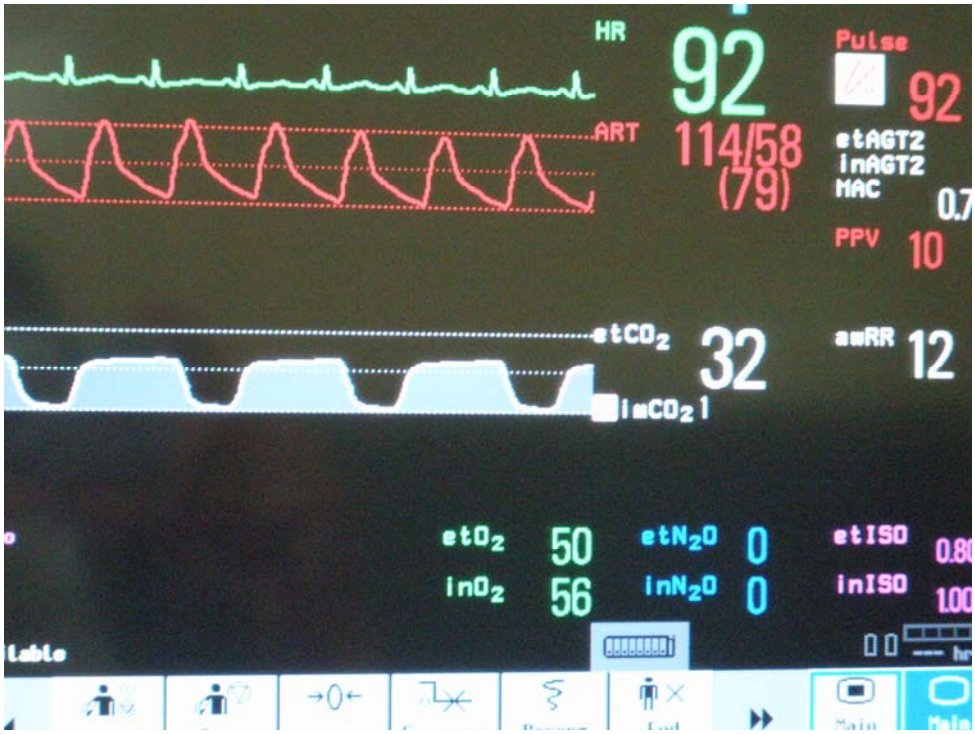
Until now, delta PP has had to be calculated offline (from a computer recording or a paper printing of the arterial pressure curve), or to be derived from specific cardiac output monitors, limiting the widespread use of this parameter. Recently, a method has been developed for the automatic calculation and real-time monitoring of deltaPP using standard bedside monitors. **Auler et al** (44) studied this method to predict if delta PP is

a reliable predictor of fluid responsiveness.They conducted a prospective clinical study in 59 mechanically ventilated patients in the postoperative period of cardiac surgery. Patients studied were considered at low risk for complications related to fluid administration (pulmonary artery occlusion pressure < 20 mm Hg, left ventricular ejection fraction > or = 40%). All patients were instrumented with an arterial line and a pulmonary artery catheter. Cardiac filling pressures and cardiac output were measured before and after intravascular fluid administration (20 mL/kg of lactated Ringer's solution over 20 min), whereas deltaPP was automatically calculated and continuously monitored.

Results of the study were as follows:

Fluid administration increased cardiac output by at least 15% in 39 patients (66% = responders). Before fluid administration, responders and nonresponders were comparable with regard to right atrial and pulmonary artery occlusion pressures. In contrast, deltaPP was significantly greater in responders than in nonresponders (17% +/- 3% vs 9% +/- 2%, P < 0.001). The deltaPP cut-off value of 12% allowed identification of responders with a sensitivity of 97% and a specificity of 95%.

They concluded that automatic real-time monitoring of deltaPP is possible using a standard bedside monitor and was found to be a reliable method to predict fluid responsiveness after cardiac surgery. (44)



As shown in the figure the PPV is displayed as a number calculated from the arterial pressure curve .

Bias et al (45)studied the abilities of pulse pressure variations and stroke volume variations to predict fluid responsiveness in prone position during scoliosis surgery . The aim of the study was to evaluate the ability of PPV and SVV to predict fluid responsiveness in mechanically ventilated patients in the prone position (PP) during scoliosis surgery.Thirty subjects were studied after the induction of anaesthesia in the supine position [before and after volume expansion (VE) with 500 ml of hetastarch 6%] and in PP (immediately after PP and before and after VE). PPV, SVV, cardiac output (CO), and static compliance of the respiratory system were recorded at each interval. Subjects were defined as responders (Rs) to VE if CO increased _15%.Results: Three

subjects were excluded. In the supine position, 16 subjects were Rs. PPV and16 subjects were Rs. PPV and SVV before VE were correlated with VE-induced changes in CO . Fluid responsiveness was predicted in PP by PPV .15% and by SVV .14% (45)

Kramer et al (46) studied PPV in post coronary artery bypass grafting and the ability to predict fluid responsiveness.The study was done to determine whether the degree of pulse pressure variation (PPV) and systolic pressure variation (SPV) predict an increase in cardiac output (CO) in response to volume challenge in postoperative patients who have undergone coronary artery bypass grafting (CABG), and to determine whether PPV is superior to SPV in this setting. It was a prospective clinical study conducted in the cardiovascular ICU of a university hospital. Twenty-one patients were studied immedVZDiately after arrival in the ICU following CABG .Intervention done was to administer a fluid bolus to all patients.

Hemodynamic measurements, including central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), CO (thermodilution), percentage of SPV (%SPV), and percentage of PPV (%PPV), were performed shortly after patient arrival in the ICU. Patients were given a rapid 500-mL fluid challenge, after which hemodynamic measurements were repeated. Patients whose CO increased by ≥ 12% were considered to be *fluid responders*. The ability of different parameters to distinguish between responders and nonresponders was compared.

Results: In response to the volume challenge, 6 patients were responders and 15 were nonresponders. Baseline CVP and PAOP were no different between these two groups. In contrast, the %SPV and the %PPV were significantly higher in responders than in

nonresponders. Receiver operating characteristic curve analysis suggested that the %PPV was the best predictor of fluid responsiveness. The ideal %PPV threshold for distinguishing responders from nonresponders was found to be 11. A PPV value of >11% predicted an increase in CO with 100% sensitivity and 93% specificity. They concluded that PPV and SPV can be used to predict whether or not volume expansion will increase CO in postoperative CABG patients. PPV was superior to SPV at predicting fluid responsiveness. Both of these measures were far superior to CVP and PAOP (21)

Similar results were found by Hofer et al who found that in contrast to standard preload indexes, SVV and PPV, comparably, showed a good performance in predicting fluid responsiveness in patients before off-pump coronary artery bypass grafting(46)

De Backer et al (47) studied the influence of tidal volume on PPV and its ability to predict fluid responsiveness. Fluid challenge with either 1,000 ml crystalloids or 500 ml colloids. Complete hemodynamic measurements including DeltaPP 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 DeltaPP at different tidal volume. Despite similar response to fluid challenge in low (<8 ml/kg) and high tidal volume groups, the percent of correct classification of a 12% DeltaPP was 51% in the low tidal volume group and 88% in the high tidal volume group. CONCLUSIONS: DeltaPP is a reliable predictor of fluid responsiveness in mechanically ventilated patients only when tidal volume is at least 8 ml/kg.(47) (48)

Benes et al(49) studied the use of stroke volume variation in patients coming for high risk major abdominal surgery

The aim of the study was to evaluate the influence of SVV guided fluid optimization on organ functions and postoperative morbidity in high risk patients undergoing major abdominal surgery. Fluid optimization guided by SVV during major abdominal surgery is associated with better intraoperative hemodynamic stability hypotensive episodes were less p=0.0001, decrease in serum lactate p=0.025 at the end of surgery and lower incidence of postoperative organ complication p= .0066(49)

Lopes et al(50) studied Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery in a prospective, randomized, single-centre study. The primary endpoint was the length of postoperative stay in hospital. Delta PP was monitored during the surgery and minimized to less than 10% by volume loading. They found that the study group received more fluids, had less complications in the post operative period $p<0.05$ and had shorter post operative stay in hospital $p<0.05$(51)

Mayer et al(52) studied goal-directed intraoperative therapy based on autocalibrated arterial pressure waveform analysis in patients coming for abdominal surgery.

The aim of this study was to perform intraoperative goal-directed therapy with a minimally invasive, easy to use device (FloTrac/Vigileo), and to evaluate possible improvements in patient outcome determined by the duration of hospital stay and the incidence of complications compared to a standard management protocol. In this randomized, controlled trial 60 high-risk patients scheduled for major abdominal surgery

were included. Patients were allocated into either an enhanced hemodynamic monitoring group using a cardiac index based intraoperative optimization protocol (FloTrac/Vigileo device, GDT-group, n = 30) or a standard management group (Control-group, n = 30), based on standard monitoring data. In high-risk patients undergoing major abdominal surgery, implementation of an intraoperative goal-directed hemodynamic optimization protocol using the FloTrac/Vigileo device was associated with a reduced length of hospital sta.(P=0.0006), and a lower incidence of complications compared to a standard management protocol(P = 0.001).(53)

Deflandre et al (53)compared delta down with delta pulse pressure as indicator of volemia in intracranial surgery.

Delta pulse pressure (DPP) and delta down (DD) are indicators of volaemia. The threshold value of DPP for discriminating between responders and non-responders to fluid loading (FL) is 13%. This study aimed at comparing DD with DPP during intracranial surgery.

Twenty-six adult patients undergoing scheduled intracranial surgery under general anaesthesia were enrolled. DD and DPP were simultaneously measured every 10 min. A DPP.13% on two consecutive occasions prompted a 250 ml FL. Pairs of data were analysed using regression analysis, receiver operating characteristics (ROC) curve, and prediction probability (Pk). significant correlation ws found between DD and DPP ($R^2$0.5431, P,0.001). 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).They concluded that DD is as efficient as DPP to assess hypovolaemia and predict responsiveness to FL in patients undergoing intracranial surgery. A 5 mm Hg DD value can be considered as a valuable threshold for initiating FL. These results support its use during intracranial surgery

MATERIALS AND METHODS

Type of study: A randomised controlled trial.

Inclusion criteria:

Patients planned for craniotomy between the ages of 18- 80 years.

Surgeries lasting more than two hours duration.

Patients planned for craniotomy for tumour excision

Surgery in Supine and lateral position

Exclusion criteria:

Patients with arrhythmia

Patients with chronic obstructive lung diseases and those with poor chest compliance.

Patients with raised intra abdominal pressures.

Patients who are not mechanically ventilated.

Patients on drugs producing lactic acidosis including metformin.

Patients in sepsis

Patient with baseline lactate more than 4

Patients undergoing surgery in prone and sitting position

Method of randomization

Block randomization

Method of allocation concealment:

Sequentially numbered, sealed, opaque envelopes

Methodology:

Clearance was obtained from the institutional review boards and the ethics committee to perform the study in its present format. Once the randomization was done the patient was met by the investigator and informed consent obtained. The patient was fasted minimum of six hours for solids and two hours for liquids. Anxiolytic premedication was avoided in patients with raised intracranial pressure.

Intravenous infusion was started using a wide bore cannula in a peripheral vein and direct arterial pressure monitoring established under local anaesthesia. A baseline arterial blood gas was taken with patient breathing room air. Other monitoring included pulse oximetry, capnography and electrocardiography. Anaesthesia was induced with thiopentone 5mg/kg, Fentanyl 2mcg/kg, and maintained on isoflurane end tidal concentration at 0.9% (MAC 0.8). in air and oxygen. Muscle relaxation was achieved using vecuronium 0.15mg/kg for endotracheal intubation and maintained with an infusion titrated to 2 twitches on neuromuscular monitoring. Patients were mechanically ventilated with a minimum of 8ml/kg of tidal volume and appropriate respiratory rate to achieve an ETCO2 between 30 and 35 mmHg.

Post induction, the right internal jugular vein was cannulated using a single lumen catheter (Arrow) in all patients guided by ECG. The catheter was advanced till a biphasic p wave was observed on the ECG and gradually withdrawn till peaked p waves were observed and the catheter was anchored at this depth. Baseline PPV was measured, once mechanical ventilation was ascertained and the tidal volume set at 8ml/Kg, in all patients. Simultaneously a baseline CVP was also measured. Based on the randomisation, CVP or PPV monitoring was used intra operatively to guide fluid management and the other monitor was discontinued till the end of surgery.

In the CVP group fluids were given to maintain the baseline value and all blood loss was promptly replaced. In the PPV group fluids were given to maintain the PPV less than 13% and fluid boluses were given when more than this number. Normal saline and ringer lactate was used alternatingly. If the estimation of blood loss exceeded 500ml , colloid or blood was infused depending on the patient's Hemoglobin with an aim to keep the Hemoglobin around 9 gm/dl. Forced air warming was used to maintain temperature which was measured with a probe in the nasopharynx. If hypotension persisted despite normal CVP or PPV, this was treated with a vasopressor viz. phenylephrine or ephedrine. A second reading of PPV and CVP were taken before discontinuing mechanical ventilation (Final PPV or CVP)

The total estimated blood loss was noted down at the end of surgery. Reversal of neuromuscular blockade was done with neostigmine and glycopyrolate. Patients were extubated when fully awake. Arterial blood gas was repeated when patients were maintaining saturation off oxygen and the vital signs were noted. Post operatively patients were shifted to the intensive care unit. The post operative follow up of the

patient was done after the first 24 hours. Fluid requirement and blood pressure fluctuations in the post operative period were recorded from the records of the patient.

Statistical analysis:

All baseline variables were summarized using descriptive statistical methods (Mean, Standard deviation, Frequencies and Percentages). The outcome variables were compared between the two groups using Independent two-sample t-test, if they are normally distributed. For variables which are not normally distributed, Mann-whitney U test was used to compare the medians between the groups. Paired t-test was used for within group comparisons. All statistical analyses was done using SPSS 11.0.

Results:

Total number of patients enrolled were 60. 3 patients were excluded as they required post operative ventilation. In the final analysis there were 29 patients in the CVP group and 28 in the PPV group

Table 1 shows the patient characteristics, the two groups were similar with regard to age sex and ASA grading

Table 1:Demography

	CVP group	**PPV group**
	Mean (SD)	Mean(SD)
Height	158.76(6.4)	156.93(5.9)
Weight	57.55(9.7)	58.85(10.8)
Age	43.44(10.26)	39.96(13.98)
BMI	22.78(2.98)	23.83(3.75)
Sex(M:F)	12:17	11:17
ASA grade 1:2	21:8	21:7

The distribution of the various medications the patients were on is shown in table 2

Table 2:Medications:

	CVP group		PPV group		
Medications	Number	%	Number	%	P
nil	1	3.45	0	0.00	
Antiepileptics	23	79.31	26	92.86	2.1
Steroids	22	75.86	24	85.71	0.8
OHA s	3	10.34	3	10.71	5.8
Insulin	0	0.00	1	3.57	
Antihypertensive	7	24.14	2	7.14	
lipid lowering drug	1	3.45	0	0.00	
aspirin	0	0.00	1	3.57	

Distribution of comorbid illness in both groups were as described in table 3

Table 3: Distribution of comorbid illness in both groups

Comorbidity	CVP group	PPV group
Nil	20	22
DM	2	4
HT	8	3
CAD	1	0
Thyroid	1	1

The groups were comparable with regards to the baseline investigations. Mean size of tumour was similar in both groups. The baseline pH, baseline lactate were also not different significantly.

Table 3: Baseline characteristics

	CVP group	PPV group
PCV	37.53 (4.89)	37.49 (4.75)
S.Creatinine	0.878 (.158)	0.89 (0.15)
Size of tumour	5.07 (1.4)	5.00 (1.79)
Systolic pressure mmHg	122.38 (26.81)	129.0 (25.94)
Diastolic Pressure mmHg	73.06 (10.25)	73.28 (11.3)
Heart Rate /min	83.89 (14.27)	83.93 (13.8)
pH	7.45 (0 .05)	7.44 (0.03)
HCO3	25.63(2.30)	24.16 (2.67)
Lactate	1.95 (0.67)	2.40 (1.65)
Na	134.76 (3.0)	135.43(2.7)
K	3.81(1.1)	3.78(0 .33)
Ca	1.09(.07)	1.11(0 .044)
Cl	107.9(4.65)	107.88(2.91)
Hb	12.41(1.79)	12.71(1.97)

Analysis of hemodynamic parameters

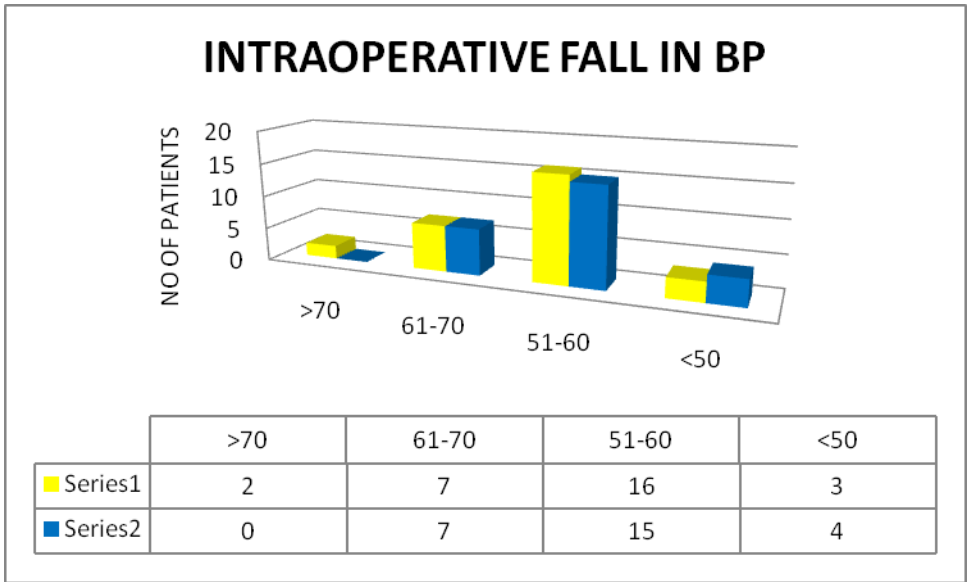
The hemodynamic parameters intraop and postoperatively were analysed. Table 4 shows the mean fall in blood pressure. The fall in mean between the groups was not statistically significant.

Table 4: Maximum Fall in intraoperative blood pressure and postoperative blood pressure

Group	N	lowest intraop mean	SD	Lowest post op mean	SD	Sig
CVP group	29	57.9	6.65	73.5	6.6	.063
PPV group	28	54.6	8.2	76.2	7.7	.179

The distribution of lowest blood pressures were as shown in the figure 1

Fig 1: Distribution of lowest intraoperative blood pressure in both groups



Series 1: CVP group Series 2: PPV group

Analysis of acid base status

The change in the pH was analysed. The distribution of pH between the groups is as shown in figure 2. Most patients n=36 had a pH in the normal range .

Fig 2: Distribution of post op pH between CVP and PPV groups

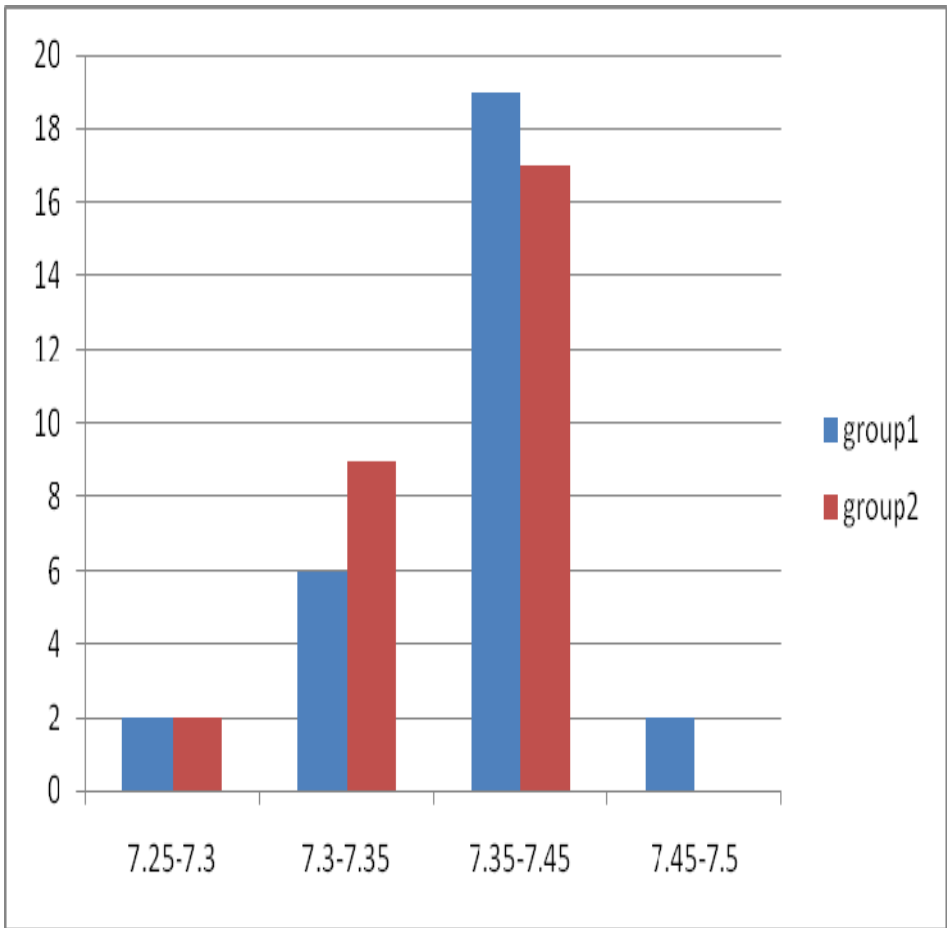


Figure 2: comparison of post operative pH in both groups

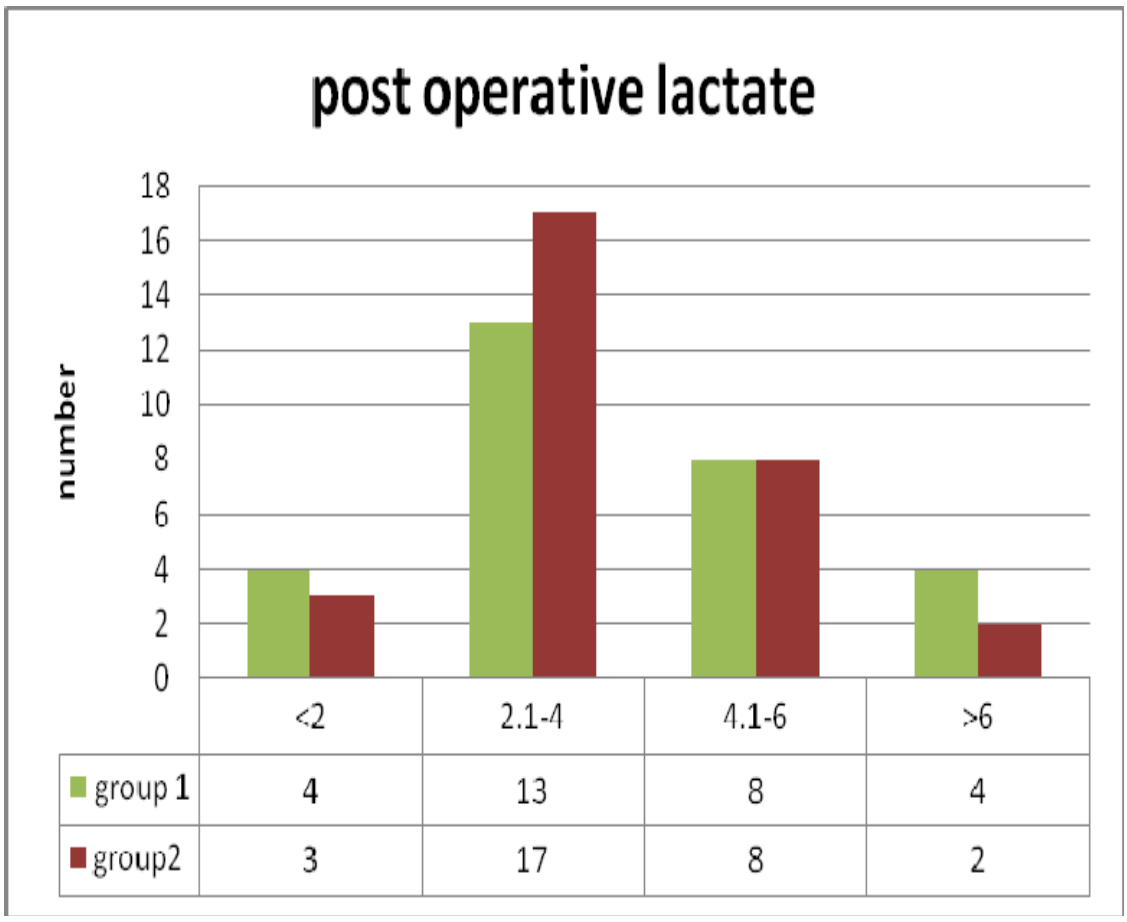
Group1:CVP Group2: PPV

20% of patients had mild acidosis and the difference between the groups was not statistically significant.

Analysis of tissue perfusion

The serum lactate at the end of surgery was analysed in the groups. We found that 30 patients had lactate value between 2.1- 4, at the end of surgery. The distribution of the values between the groups were as shown in figure 3

Fig 3 **Distribution of lactate values between the two groups**



Group 1-CVP Group 2-PPV

The data was stratified based on the lactate values into 2 groups as less than 4 and more than 4

Considering that lactate values depend on the total fluid used and hypothermia and estimated blood loss we compared these variables between the two groups as shown in table 5

Table 5: Distribution of serum lactate values and the variables influencing it

Lactate <4						Lactate>4				
	Cvp group		PPV group		P	CVP group		PPV group		P
	Mean	SD	Mean	SD		mean	SD	Mean	SD	
Estimatedloss	659.5	378.4	1129.4	854.9	**0.27**	956.2	1128	1154	962	**0.26**
Total fluids	2545.2	893.	3041.1	1719.2	**0.63**	3500	3186.24	3459.09	1771.414	**0.39**
Change in pH	-.06	.069	-.076	.0526	**0.5**	-.078	.0570557	-.07	.0536656	**0.8**

We found no significant difference between the two groups with regard to these variables.

Table 6: Estimation of blood loss in both groups and comparison of pre and post op Hb.

Group	Number	Mean blood loss	SD	Hbpre	Hbpost
CVP	29	777.5	665	12.4	9.9
PPV group	28	1101.7	913	12.7	9.7
Significance		0.00		0.41	0.71

We found a significant difference in the total estimated blood loss between both groups. However the preoperative and post operative haemoglobin was comparable in both groups.

Amount of fluids used:

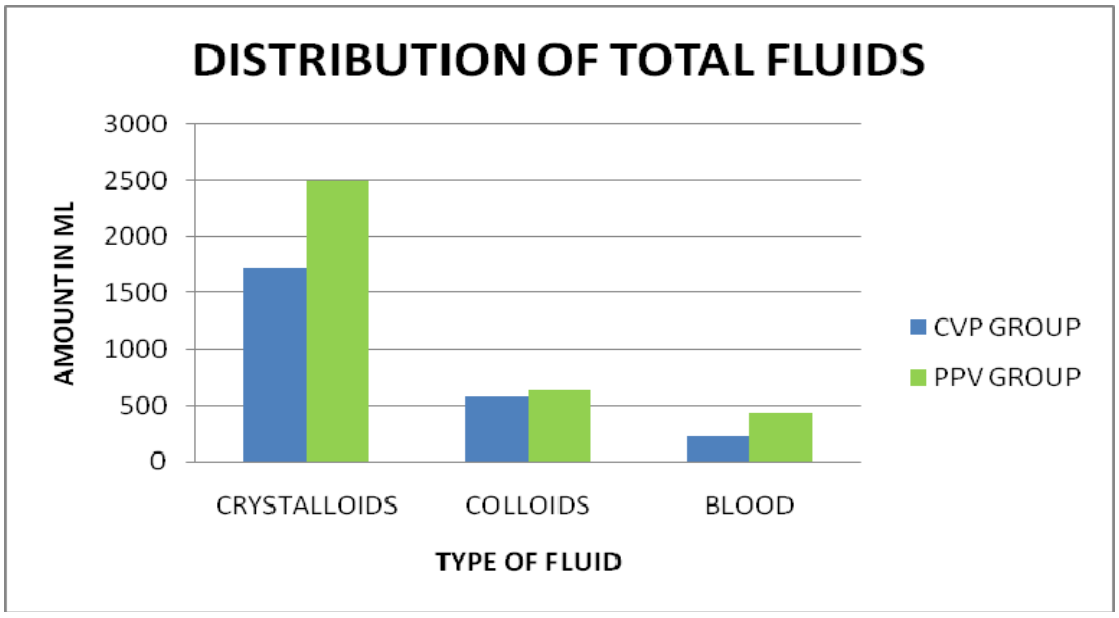
The amount of fluid used in the intraoperative period was compared between the two groups. The fluids were categorised as crystalloids , colloids and blood .The distribution was as shown in table 7.

Table 7:Intra operative fluid management

Group	Crystalloids			Colloids			Blood		
	Median	P25	P75	median	P25	P75	Median	P25	P75
CVP	1500	1200	2000	500	500	500	0	0	350
PPV	2250	1500	3000	500	250	1000	175	0	550
P value	.002			0.57			.142		

As shown in the table the median value for colloid use was similar in both groups. The p value was significantly different for the use of crystalloids between both groups. This was probably secondary to the increased blood loss in the PPV group. This is graphically represented in figure 4

Fig 4: Distribution of total fluids between both groups



In patients from the groups with post operative lactate more than 4 we analysed the total amount of fluid used and the factors influencing fluid management namely the estimated blood loss, size of the tumour and the duration of surgery.

Table 9 shows the factors influencing fluid management in both groups.

Table 9: Factors influencing fluid management in CVP and PPV group in patients with post op lactate >4

	CVP group		PPV group		P value
	MEAN	SD	MEAN	SD	
Estimated loss	741.3793	685.704	1139.286	881.9546	**0.10**
Duration	303.1034	71.65659	314.2857	120.4983	**0.97**
Tumour size	5.072414	1.422246	5.003571	1.795979	**0.83**

As seen from the table there was no significant difference between the variables .

Chloride and abnormal pH

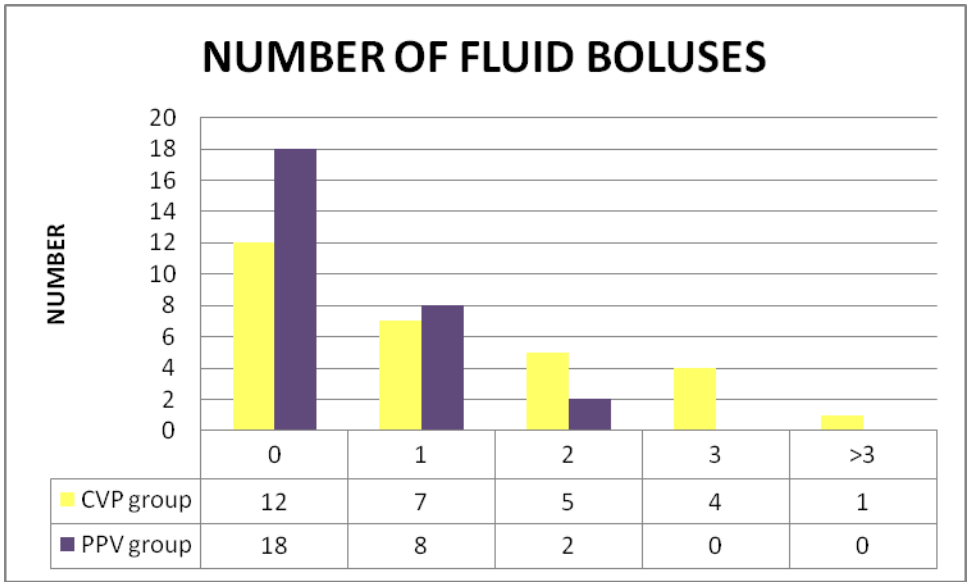
Chloride value was available in 31 cases. The arterial blood gas we used did not provide chloride value.random sampling of chloride was done in few patients to ensure that acidosis was not due to hyperchloremia.

We found no correlation between the change in chloride levels and abnormal pH in these patients in both groups

Post operative fluid boluses and fluid management

The postoperative hemodynamics as mentioned earlier and the amount of fluid boluses required were documented. The number requiring fluid boluses were almost equally distributed between the groups as shown in figure 4

Fig 4: **Distribution of number of fluid boluses in the post operative period**



Discussion

Fluid management in neurosurgery is specially challenging to the anaesthesiologist as the indices commonly used to guide fluid replacement is inappropriate in these patients. Blood loss estimation is erroneous in view of the use of fluid for irrigation and the concealed loss under the drapes. Urine output cannot be used as an index due to the use of osmotic diuretic like mannitol. The use of central venous pressure may not be reliable in the different positions patients are operated upon. Direct arterial pressure monitoring is routinely done in neurosurgery and if cardiovascular monitors used in the OR have the facility to measure PPV, this monitoring is easily achieved in most patients. Our aim in this study was to see if PPV can be used as an index to predict fluid requirement in neurosurgery. We also compared fluid therapy using PPV against CVP guided fluid therapy as control which is commonly used during major operations. Studies have favoured the use of PPV in high risk bowel surgery and in coronary artery bypass grafting over CVP. (44)(54)

We enrolled 60 patients but analysed the results in 57 patients. 3 patients were excluded due to the need for post operative elective mechanical ventilation. Both patient groups were comparable with regard to the demography and co- morbid illnesses. All patients belonged to ASA grade 1&II. Our study showed that PPV is a good index of fluid management in neurosurgical patients, based on the intraoperative hemodynamics and the acid base status and lactate levels. We compared this therapy with CVP guided fluid therapy and found that hemodynamic parameters, acid base status and lactate were comparable in both groups. Though there is a significant difference in the amount

of crystalloid used in the PPV group, we attribute it to the larger blood loss (mean 1129 Vs 659 in the CVP group) .While using PPV we aimed to achieve a value of < 13%. However when using CVP, it is a trend that we follow and not absolute numbers. In dehydrated patients such as neurosurgical patients on osmotic diuretic fluid therapy, following a trend may not be safe as the baseline reading may not be optimum. Besides, in patients with cardiac dysfunction, fluid therapy with CVP may not be advisable. Since all our patients belonged to ASA Class I&II, we considered CVP to be representative of left sided pressures. We used ECG guided internal jugular cannulation for all patients and positioned the tip at the atrio-caval junction for standardisation. We routinely use peripherally inserted central venous catheterisation via the brachial vein for neurosurgical procedures, so the correct position of the catheter cannot be ascertained without the use of radiology, echocardiography etc., which may not be feasible on a routine basis. Measuring PPV is much simpler if the facility is available in the OR. Our study proved that PPV is a reliable monitor for intraoperative use, this being a dynamic index measuring fluid responsiveness. Our study included mostly patients in supine position and lateral positions, and we found PPV to be consistent in these positions. More study needs to be done to ascertain the reliability in other positions such as prone and sitting. Among the other dynamic indices of hemodynamic variables, PPV has been found to be better than systolic pressure variation.

The fall in mean blood pressure in both groups were compared. We found that 38 patients had a mean BP less than 60. The drop in blood pressure was mostly found in the considerable long period between induction and incision. There was no significant difference between the groups.

The fluid requirement in both cases was evaluated taking into consideration the variables controlling fluid management. Fluids given depend on the duration of surgery , estimated blood loss and the size of the tumour. The duration of surgery and the size of tumour were comparable. Estimated blood loss was significantly more in the PPV group explaining the significantly larger crystalloid use in the PPV group. Though patients received larger volume no patients had symptoms and signs of fluid overload.

Another aim of our study was also to evaluate adequacy of tissue perfusion as evaluated by serum lactate levels. We tried to control the factors influencing lactate levels and thus excluded patients with sepsis, high baseline lactate, patients on lactic acidosis producing drugs. Intraoperatively we tried to avoid hypothermia. The temperature was in the range of 35-36 degrees intraoperatively. The data was categorised into 2 groups based on lactate as <4 and >4. We analysed the factors influencing serum lactate in both groups like change in pH, estimated blood loss and the amount of fluid required to restore perfusion. Though 24 of 57 patients had a lactate value above 4 we found no statistical difference between the two groups (p value 0.26, 0.38,0.8) despite the larger blood loss and fluid requirement in the PPV group. The probable explanation for the increase in lactate could be hypothermia which is normally found in these patients with the large volume of fluid used for irrigation and the temperature in the OR. Many patients had an initial lower temperature though by the end of surgery the temperature had come up to 36 in most patients. Interestingly, there were quite a number of patients who had baseline lactate above normal range.

Post operative fluid management was left to the intensivist who had no idea of which group the patient belonged. The amount of fluid infused has a reflection on the intraoperative management as postoperative blood loss in neurosurgical patients is minimal unless they develop haematoma. No patient required rexploration. The protocol for fluid administration in the ICU is to give boluses of 500 ml of fluid if there is a trend in drop of blood pressure. 30 out of 57 patients did not require any boluses. The lowest blood pressure and the number of fluid boluses used were analysed between the groups. The number of patients who required boluses were more in the CVP group. There were no patients in the PPV group who required more than 2 boluses. The reason for the lack of statistically significant difference in the two groups could be the small number of patients.

Conclusion:

1. Our study proves that pulse pressure variation (PPV) is a reliable and easily monitored index for fluid therapy in neurosurgical patients undergoing craniotomies in supine and lateral position.

2. Fluid management using PPV is as efficacious as using CVP as a guide for fluid management in patients with normal cardiac function. Despite a significantly larger blood loss in the PPV group, intraoperative hemodynamic stability and postoperative acid base and lactate level were comparable in the two groups.

3. No patient had signs of fluid overload in either group.

4. The acid base status was acceptable in both groups. Though PH were within normal limits, both groups had patients with higher than normal lactate levels. The cause for lactate cannot not be explained on the blood loss, change in pH, volume of fluid infused, duration of surgery or size of tumour.

5. There was no significant hemodynamic instability in any patient in the postoperative period.

Recommendation:

1. We recommend the use of PPV as a guide to fluid management in all neurosurgical patients especially when significant blood loss is expected.

2. We recommend more studies comparing PPV and CVP in patients requiring surgery in various positions such as prone, sitting, concorde and in high risk patients to establish the usefulness of PPV and perhaps the superiority of PPV in these situations.

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Annexures:

Patient information sheet and consent form:

The study in which you will be participating is a research project to compare two methods of administering intravenous fluids during the surgery that you are about to undergo; i.e craniotomy.(in neurosurgery wher e the skull bone is opened). At the end of the study we hope to evaluate if one method of giving fluids is better than the other in terms of any increased requirement of fluids after the operation, stability of blood pressure after the surgery, accumulation of acid in the blood which occurs with inadequate fluids. If we can validate this method of giving fluids we will be able to avoid post operative problems in such patients.

You will be enrolled in this trial when you undergo the operation. You will not be subject to any new procedures apart from those done normally for this kind of surgery. You will be given general anesthesia and all intervention will be done during the surgery based on the two methods of giving fluids.allthe measurements are done electronically and you will not be subject to any discomfort. We do not anticipate any major side effects due to the two methods because both are used commonly in such operations . Your blood pressure readings and amount of fluid given to you will be recorded by us during the operation. After the operation you will be observed in the intensive care unit as is the routine in such cases.

In case of any queries related to the trial you can contact Dr.Shalini Cynthia, Dr, Amar, Dr. Grace Korula from the department of anaesthesia. Your participation is entirely voluntary and you are free to opt out of the study at any time you feel inconvenienced by it. Opting out entails no penalties in any form.

There will be approximately 60 patients involved in the study.

INFORMED CONSENT

Study Title:

Study Number:

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age:_____

Please initial box

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am

free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date:_____/_____/_____

Name of the Witness: _____

Consent will be obtained by the principal investigator performing the study before the patient is subjected to the surgery in the ward.The information sheet has been made

available in the vernacular spoken by the patient and the patient will also be explained the process in his vernacular language by persons competent in that language. The consent will be obtained at the bed side in the ward for patients who are admitted

The patient will not be required to incur any expense for the study. The information gathered from the study will be maintained in strict confidentiality and will be known only to the investigator. It will not be disclosed or used for any purpose other than this study.

Study protocol and data entry sheet:

Data entry sheet :

Roll No: Sex: Age:

ASA grade:

Height : Weight : BMI:

Co morbidities:

Medications:

Preoperative investigations:

Hb/PCV Creat Platelets:

Tumour histology:

Tumour size from MRI scan:

Type of surgery:

Parameters:

	Preinduction	Post induction	End of surgery
Heart rate			
Blood pressure			
Mean art pressure			
CVP			
PPV			

Lowest blood pressure recorded:

ABG recording	At start of surgery	At end of surgery
pH		
pCO2		
paO2		
Sao2		
Lactate		
Na		
K		
Calcium		
Hemoglobin		
ABE		

Fluids given: (in ml)

Normal saline	
Ringer lactate	
Colloid (please specify)	
Whole blood	
Packed cells	
FFP's	
Other	

Post operative period:

Lowest blood pressure recorded

Total fluids given post operatively

Blood transfused

Post op PCV

THESIS PROTOCOL:

Comparison of CVP and PPV guided fluid therapy in patients planned for supine and lateral position craniotomy surgery.

Patients planned for tumour excision in supine and lateral position:

Preinduction :

Large bore intravenous cannula under LA

Arterial line to be established under LA

Arterial blood gas to be done with patient breathing room air.

Monitoring ECG, Arterial BP, EtCO2, Pulse oximeter

Induction:

fentanyl upto 2 mcg/kg, thiopentone 5 mc/kg, vecuronium 0.1mg/kg.

Isoflurane at 1-5-2% to maintain endtidal concentration at 0.9-1

Intraoperative period:

Single lumen central venous cathether to be put into right internal jugular vein using ECG control and fixed at the point where the p wave decreases in amplitude after becoming biphasic.

Mechanical ventilation with tidal volume of 8ml/kg and appropriate rate.

Baseline PPV and CVP to be noted down. In PPV group fluids to be given every time PPV value was more than 13

In CVP group fluids to be given to maintain baseline CVP.

Temperature to be maintained between 36-37degree Celsius

Vecuronium infusion to be started and titrated to get 2 twitches on neuromuscular monitoring.

Normal saline and ringer lactate to be used alternatingly and blood loss replaced with colloid or blood depending on the Hb .

If BP is unstable inspite of adequate fluid therapy and normal PPV and CVP values vasoconstrictor like Phenylephrine or ephedrine to be used.

PPV and CVP reading at the end of surgery to be noted before discontinuing mechanical ventilation

Extubation:

Reversal with neostigmine and glycopyrollate. Extubate when fully awake.

Arterial blood gas to be repeated when patient maintains saturation on room air.

group	no	hospitalno	duration	sex	age	asagrade	weight	height
1	1	523159	210	2	40	1	47	160
1	3	519438	300	2	33	1	55	155
1	5	494273	300	1	49	1	64	154
1	8	584309	230	2	35	1	45	150
1	9	533207	210	2	42	2	66	155
1	10	556539	300	2	36	1	44	160
1	13	615546	240	1	63	2	74	164
1	14	622646	330	2	48	3	64	154
1	16	663186	390	2	43	1	44	155
1	18	629080	240	2	55	2	61	160
1	21	675398	270	1	61	2	75	165
1	22	676127	330	1	51	1	60	168
1	26	683463	300	1	27	1	73	167
1	28	680442	330	2	33	1	63	160
1	32	756271	420	2	45	1	50	150
1	33	716692	310	2	40	1	57	153
1	35	696628	420	2	55	2	55	155
1	40	637142	300	2	25	1	52	152
1	43	704525	360	1	66	1	44	160
1	44	731814	240	1	47	1	75	179
1	47	734251	285	1	38	1	61	164
1	48	974698	300	2	39	1	42	155
1	51	714043	180	2	48	1	57	155
1	52	709050	225	1	29	1	53	154
1	54	700772	420	2	41	1	55	156
1	56	752106	300	1	40	1	52	163
1	58	735635	300	2	51	2	53	155
1	59	757588	270	1	39	2	67	166
1	60	732860	480	1	41	1	61	160
2	2	524538	120	1	25	1	45	155
2	4	524927	420	2	45	1	50	160
2	6	560052	240	2	27	1	80	158
2	7	454249	195	2	58	2	69	155
2	11	584536	90	1	60	1	50	150
2	12	593582	300	2	49	1	51	152
2	15	386942	280	2	69	2	57	152
2	17	654767	480	2	30	1	58	154
2	19	641997	405	2	29	1	80	164
2	20	681901	420	1	61	2	61	160
2	23	710736	240	2	37	2	49	150
2	24	659086d	330	1	36	1	57	157
2	25	681821d	420	1	63	2	60	165
2	30	675518	270	2	44	1	46	152
2	31	682973	630	2	30	1	54	160
2	34	725236	240	1	28	1	63	165
2	36	707871	210	2	45	2	45	144

2	38	722927	300	2	37	1	62	149
2	39	725314	315	1	36	1	60	165
2	41	695142	270	2	34	1	46	156
2	42	678246	300	2	45	2	74	155
2	45	730190	255	2	27	1	50	156
2	46	739878	570	1	20	1	54	164
2	49	728685	300	2	35	1	51	148
2	50	744977	225	2	37	1	62	160
2	53	735694	405	1	22	1	75	164
2	55	723914	300	1	63	1	60	160
2	57	679875	270	1	27	1	79	164

bmi	comorbid1	comorbid2	antiepilept	steroid	medication	medication	pcv	creat
18.3	0	0	1	1	0	0	34	0.7
22.9	0	0	1	1	0	0	30	0.8
27	0	0	1	1	0	0	35	0.7
20	2	0	0	0	5	0	35	0.7
27.5	4	0	1	0	0	0	36.9	0.7
17.1	0	0	1	0	0	0	32.3	0.7
27.6	2	3	0	0	7	3	40.9	0.9
27	2	0	0	0	5	0	37.5	0.6
18.3	0	0	1	1	0	0	30.4	0.8
23.8	2	0	1	1	5	0	36	0.9
27.5	1	2	1	1	3	5	42.5	1.1
21.3	0	0	0	0	0	0	43.5	1
23.7	0	0	1	1	0	0	48	1
24.6	0	0	1	1	0	0	29.9	1
22.2	0	0	1	1	0	0	36.8	0.8
24.3	0	0	0	1	0	0	35.7	0.8
22.9	1	2	1	1	3	5	37.3	0.9
22.5	0	0	1	1	0	0	36	0.8
17.1	0	0	1	1	0	0	39	1.2
23.4	0	0	1	1	0	0	39.9	0.9
22.7	0	0	1	1	0	0	40.3	1
20	0	0	1	1	0	0	36.9	0.8
23	0	0	1	1	0	0	34.7	1
23.3	0	0	1	1	0	0	42	1
23	0	0	1	0	0	0	37.8	0.8
19.6	0	0	1	1	0	0	49.5	1.1
22.1	2	0	0	1	5	0	30.1	0.7
24.3	2	0	1	1	5	0	38.6	1.2
23.8	0	0	1	1	0	0	41.8	0.9
18.7	0	0	1	1	0	0	45	0.8
19.5	0	0	0	1	0	0	38	0.7
32.1	0	0	1	0	0	0	40	0.8
28.7	1	2	1	1	4	0	38	1.1
22.2	0	0	1	1	0	0	30.2	1.1
22	0	0	0	1	0	0	36.1	0.7
24.6	2	0	1	0	5	0	32.7	1.1
24.4	0	0	1	0	0	0	37.5	0.9
29.7	0	0	1	1	0	0	38.3	0.9
23.7	0	0	1	1	0	0	40.8	0.9
21.8	1	0	1	1	3	0	33.2	0.7
23.1	0	0	1	1	0	0	40.8	1
22	1	2	1	1	3	5	45.1	1.3
19.9	0	0	1	1	0	0	37.8	0.8
21	0	0	1	1	0	0	33.1	0.9
23.1	0	0	1	1	0	0	42.5	1
21.7	1	0	1	1	3	0	36	0.7

27.9	0	0	1	1	0	0	35.8	0.8
22	0	0	1	1	0	0	44.5	1
18.9	0	0	1	1	0	0	29.8	0.7
30.8	4	0	1	1	8	0	37.7	0.7
22.2	0	0	1	1	0	0	31	0.9
19.3	0	0	1	1	0	0	38.4	0.9
23.3	0	0	1	1	0	1	38.7	0.8
24.2	0	0	1	1	0	1	26.7	0.9
27.9	0	0	1	1	0	0	42.2	0.9
23.4	0	0	1	0	0	0	37.2	1.1
29.4	0	0	1	1	0	0	42.8	0.9

histology	sizeoftumo	typeofsurg	syspre	diaspre	meanpre	deltasys	syspost	diaspost	meanpost
1	7	2	129	76	93	-7	122	78	93
1	5	2	109	74	86	2	141	90	107
1	4.5	5	116	78	91	-1	110	70	83
1	5	7	146	65	92	2	130	80	96
2	5	1	143	70	94	8	127	71	90
1	5.7	6	127	76	93	-7	110	82	91
1	5	7	111	77	88	-10	160	80	106
2	8.2	7	153	83	106	-11	135	65	88
1	4.5	5	112	64	80	-6	137	81	99
1	3.2	1	150	73	98	-11	116	70	85
1	3	6	164	76	105	-24	130	80	96
1	5.9	4	140	89	105	-23	125	80	95
1	8	5	120	70	86	22	133	82	99
1	5	2	132	80	97	-10	163	88	113
1	5.3	2	120	84	96	-21	123	72	89
1	4.5	4	137	78	97	8	120	70	87
1	5.7	1	150	86	107	10	115	66	82
2	3	3	118	64	82	-3	147	67	94
1	4.5	2	91	59	70	4	105	55	79
	4.4	7	118	89	98	-4	110	63	79
1	4.2	1	104	47	66	-28	132	62	85
6	7.3	3	110	54	73	20	160	95	116
1	2.5	2	100	59	73	-10	120	70	87
3	4.5	3	117	79	91	32	146	70	95
1	4	5	125	71	89	7	155	88	110
1	5	1	110	72	85	18	138	66	90
1	4.2	4	130	70	90	-2	130	78	95
1	6	2	137	86	103	-18	122	78	93
1	7	1	130	70	90	44	144	76	99
4	6	1	139	73	95	20	140	76	97
1	4	4	128	74	92	13	150	80	103
1	2.3	2	117	63	81	-1	130	70	90
1	2	6	170	82	111	-10	140	81	100
2	6	2	154	75	101	-30	190	104	130
1	5	4	148	87	107	7	120	76	90
1	2	1	154	84	107	11	126	82	97
1	5.1	7	105	65	78	8	126	62	83
1	5	1	101	65	77	-15	125	75	91
1	3	1	114	68	83	10	135	71	92
1	4	1	130	76	94	8	99	60	73
1	8.5	7	114	63	80	6	124	70	89
1	8	1	148	81	103	-10	100	58	72
1	5	1	140	71	94	0	120	70	87
1	4.4	1	100	60	73	15	119	60	80
5	6	1	131	95	107	8	118	52	74
1	4.6	2	220	110	146	28	120	84	99

1	3	7	113	63	80	14	120	70	86
1	4.2	6	115	69	85	9	109	56	74
1	6	6	140	64	89	21	138	90	91
1	2	1	125	69	88	5	125	60	82
1	7	5	110	62	78	-10	115	57	76
	7.5	1	120	76	90	10	130	90	103
1	7	7	92	60	71	2	112	76	88
1	6	1	106	67	80	-14	126	78	94
1	6	6	120	70	87	20	150	70	96
1	5.2	1	120	80	93	3	140	77	98
1	5.3	6	140	80	100	-25	105	66	79

hrpre	hrpost	deltahr	cv pre	cvp post	deltacvp	ppv pre	ppvpost	deltappv
79	110	31	4	3	-1	12	15	3
58	109	51	5	4	-1	6	7	1
65	76	10	8	9	1	13	12	-1
92	78	-14	8	4	-4	8	8	0
108	87	-21	12	11	-1	9	10	1
103	106	3	7	10	3	9	10	1
87	92	5	7	8	1	10	8	-2
62	80	18	9	9	0	10	6	-4
73	105	32	7	6	-1	12	19	7
84	113	92	9	8	-1	10	11	1
114	130	16	3	0	-3	10	8	-2
113	103	-10	6	12	6	17	8	-9
87	104	14	10	10	0	8	4	-4
70	90	20	1	1	0	6	4	-2
99	120	21	9	5	-4	10	4	-6
98	104	6	10	15	5	10	13	3
79	108	29	8	8	0	13	8	-5
78	89	11	9	10	1	7	7	0
87	96	9	7	8	1	10	5	-5
76	123	47	11	13	2	6	10	4
76	89	13	10	13	3	12	7	-5
82	90	8	5	9	4	5	11	6
94	86	-8	10	9	-1	6	7	1
84	116	32	6	9	3	13	6	-7
80	88	8	7	4	-3	13	13	0
74	88	14	8	6	-2	18	6	-12
92	90	-2	10	9	-1	5	5	0
81	88	7	8	9	1	5	5	0
80	112	32	7	9	2	13	12	-1
82	82	0	9	11	2	10	7	-3
96	120	24	6	6	0	18	11	-7
73	104	31	6	4	-2	8	12	4
114	120	6	6	10	4	7	9	2
58	90	32	6	6	0	8	10	2
85	95	10	5	6	1	9	8	-1
77	92	15	6	8	2	11	15	4
91	104	13	6	4	-2	10	10	0
94	90	-4	8	11	3	8	16	8
79	86	7	9	10	1	4	10	6
78	88	10	9	14	5	9	10	1
95	98	3	5	6	1	10	6	-4
64	72	8	3	3	0	9	13	4
73	130	57	7	2	-5	10	10	0
78	89	11	4	6	2	11	7	-4
87	110	23	1	4	3	11	7	-4
96	100	4	6	5	-1	13	5	-8

90	100	10	8	8	0	9	12	3
97	104	7	7	6	-1	9	9	0
98	108	10	4	5	1	8	8	0
72	87	15	6	7	1	10	11	1
103	82	-21	4	5	1	6	6	0
80	85	5	6	3	-3	6	7	1
82	108	26	7	9	2	12	11	-1
82	72	-10	10	10	0	12	8	-4
55	80	25	9	8	-1	14	7	-7
89	98	9	8	8	0	11	14	3
60	84	24	12	14	2	4	25	21

lowestsys	lowestdias	meanpre	meanlowes	fallinmean	tempext	lowesttem	pre_ph	pH_ post
92	54	93	66	27	36.1	35.8	7.42	7.28
82	46	95	58	37	34.5	33.9	7.43	7.33
80	48	86	59	27	37	35.6	7.48	7.38
76	40	92	52	40	35.5	35.5	7.4	7.35
97	59	91	72	19	37.7	36.8	7.43	7.39
83	46	81	58	23	36.3	36.5	7.42	7.35
92	45	111	60	51	36.2	35.9	7.4	7.32
78	46	92	56	36	36.5	36	7.46	7.42
79	52	94	61	33	35.6	35.4	7.47	7.37
83	42	93	55	38	35	34.7	7.47	7.29
78	42	101	54	47	36.4	36	7.49	7.33
63	41	107	48	59	35.5	34.5	7.47	7.34
66	44	88	51	37	35.5	35.2	7.46	7.32
72	35	106	47	59	35.9	35	7.42	7.44
86	41	107	56	51	35.8	35.4	7.43	7.27
85	45	80	58	22	36.5	36.2	7.5	7.41
77	41	78	53	22	36	35.3	7.48	7.43
84	45	98	58	40	36.4	35.9	7.46	7.33
80	44	77	56	21	36.6	35.4	7.39	7.42
68	40	83	49	34	36.3	35.9	7.44	7.39
81	44	105	56	49	36.5	36.1	7.45	7.38
90	59	105	69	36	36.6	35.6	7.46	7.45
105	50	94	68	26	37.6	37.1	7.43	7.4
85	39	80	54	26	35.6	35	7.38	7.29
88	55	103	66	37	36.3	35.8	7.45	7.44
79	52	86	61	25	36.6	36.2	7.5	7.4
90	60	97	70	27	36.9	35.7	7.44	7.44
69	44	94	52	42	37	35.8	7.46	7.38
87	52	73	63	10	36.9	35.7	7.44	7.39
70	40	96	50	46	36.2	36.6	7.49	7.43
82	46	97	58	39	35.9	34.9	7.44	7.4
83	51	107	61	46	36.7	36.2	7.43	7.37
75	31	107	46	61	36.4	35.3	7.41	7.32
84	60	146	68	78	36.2	35.9	7.46	7.32
84	44	80	53	27	36.8	36.5	7.46	7.425
82	54	85	63	22	36.5	35.9	7.47	7.31
66	36	82	46	36	36.9	36.9	7.39	7.3
76	41	89	53	36	35.5	35	7.45	7.36
96	50	88	61	27	36	35.7	7.39	7.35
80	53	70	64	14	36.4	36.2	7.64	7.37
84	51	98	64	34	36.1	35.5	7.46	7.36
43	21	78	28	50	36	35.7	7.46	7.35
80	47	90	58	32	37.3	36.3	7.36	7.41
75	42	66	53	13	36.1	35.7	7.43	7.35
84	44	73	53	20	35.5	35	7.34	7.37
73	40	71	53	18	36	35.1	7.5	7.45

88	48	80	53	27	36	35.9	7.45	7.4
77	44	73	55	18	36	35.6	7.41	7.31
74	42	91	53	38	35.8	35.3	7.46	7.45
86	48	87	60	27	36.8	35.6	7.4	7.31
81	43	89	56	33	37.6	36.3	7.46	7.47
80	40	93	53	40	36.2	36.2	7.43	7.34
80	49	85	59	26	37.3	35.5	7.4	7.4
77	50	100	59	41	36.5	36.1	7.45	7.33
74	41	90	52	38	35.4	36.1	7.45	7.41
78	52	103	61	42	37.1	36.1	7.4	7.37
59	27	90	38	52	35.4	36.1	7.39	7.37

pCO2_pre	pCO2_ pst	fiO2	paO2pre	paO2post	saO2pre	saO2post	HCo3pre	HCO3post
41	43	60	516	366	100	100	25.6	18.7
43	43	21	102	136	98	99	27.4	21.1
36	35	60	372	160	100	99	25.7	19.7
30	27	21	84	81	97	95	18	14
43	46	21	86	90	97	97	27.4	26.7
34	38	21	91	90	97	96	21.25	19.7
35	51	21	84	76	96	94	26	24
42	39	21	81	109	96	98	29	25.3
40	44	21	87	132	97	99	29	25
33	35	21	102	123	99	98	24	16.8
30	46	21	109	144	99	99	22.9	24.3
34	40	21	88	95	97	97	24.7	21.6
36	45	21	111	211	99	100	25.5	23.2
41	38	40	156	204	99	100	26.6	25.8
29	41	21	76	83	95	94	19.2	18.8
33	35	21	107	98	99	98	25.2	22.2
35	36	21	97	114	98	99	26.1	23.9
41	53	21	62	74	93	94	29.2	27.9
37	34	21	91	80	97	96	22.4	22.3
38.5	36.1	60	224	236	97.4	97.5	26.5	22.3
39	42	21	70	73	95	94	27.1	24.8
37	33	21	96	124	98	99	26.3	22.9
37.6	37.7	21	71	113	94.7	97.7	25.3	23.9
39	32	21	80	100	95	97	23	15
39	37	21	114	93	99	98	27.1	25.1
36	38	21	87	84.8	97	96	28	24
34	31	21	81	115	96	99	23.1	21.1
25.7	31.2	21	114	91	98	97	21.3	20.1
30.9	29.6	40	134	112	98.3	98.4	22.8	19.6
35.3	36.1	21	96.9	85.4	98	97	27.8	24.5
39	39	100	324	313	97	100	26.5	24.2
38.8	40.5	21	94	112	97.8	98	26.1	23.2
44	46	60	239	209	97.3	99	27.1	22.8
35.8	**46.8**	**21**	**90**	**82**	**97**	95	26.1	23.8
32.2	30.3	21	80	91	96	99.6	23	20.2
33.6	43.8	40	134	130	98.4	98.9	24.5	21.6
36.8	38.3	21	106	102	97	99	22.9	18.8
26.7	31.8	21	88	139	97	98.8	20.8	27.7
34.5	39.7	21	60.7	88	90	98	21	22
34.6	37.1	21	86	98	96.6	97.2	25.8	21.8
30.4	40.1	60	311	234	99	99	21.3	22.7
33	43	21	83	119	96	97	25	23
47	42	60	172	250	99	100	25.6	25.5
39.2	37.5	21	86	102	96.7	97.2	25.9	20.9
53.5	40.1	21	73.5	126	94	98	26.5	23.2
36.8	39.4	21	96	122	98	99.8	29.4	27.5

32.5	33.6	60	228	263	99	99	23.8	21.8
31.8	38	60	282	266	99.7	99.5	21.4	19.1
34.8	36.9	21	83	97	96.9	95.9	25.8	24.5
45	47.4	21	93	98	97	99	27.5	24.5
20.9	29	21	99	93	98	98	19.6	23.1
36.6	42	21	71	96	95	98	24.8	22.4
43.5	36.7	21	75.5	101	95	97.9	26.4	23.3
34.4	39.7	21	87.9	89	96.6	95.8	25	20.5
33.2	35	21	81	114	96.1	98	24.8	22.9
41.3	36.8	21	87.4	91.3	96.6	97	25.3	21.5
41	36.7	21	85	95.4	97	98	24.5	21.8

lactatepre	lactatepost	deltalactat	ABEpre	ABEpost	Na _pre	Na_post	K_pre	K_ post
1.3	3.8	2.5	1.9	-6.5	133	141	3.3	3.4
1.6	2.8	1.2	4.2	-3.2	140	143	3.2	3.7
1.6	2.9	1.3	3.2	-3.4	132	136	4.1	3.5
3.8	5.7	1.9	-3.8	-10.7	143	147	3.7	3.4
2.4	3.2	0.8	3.7	2.3	137	141	3.8	3.8
2	3.1	1.1	-2.4	-4.6	138	139	3.4	3.9
1	1.8	0.8	1.2	0.2	135	136	3.9	4.5
1.5	2.4	0.9	6.1	0.8	138	142	3.6	3.3
1.8	3.4	1.6	5.4	0.1	139	138	3.8	3.5
3.2	5.8	1.4	0.7	-9.8	133	142	3.6	4.6
8.8	8.5	-0.3	-0.4	-1.6	130	129	3.9	3.8
0.5	1.2	0.7	1	-4.2	135	139	3.8	3.9
2.2	4	1.8	1.8	-2.9	134	132	4.5	4.8
1.7	3.5	1.8	1.9	1.6	131	134	3.7	4
3.7	4.8	1.1	-4.1	-7.6	135	135	4	5
2.2	6.4	4.2	2.5	-2.4	136	137	3.5	3.8
2.6	4.8	2.2	2.6	-0.4	136	137	4	3.8
2.7	2.5	-0.2	5.4	2	131	130	4	3.9
3.8	4.7	0.9	-2.6	-2.4	132	136	3.7	3.8
1.6	6.5	4.9	2.3	-2.5	132	139	3.8	3.4
1.4	2.9	1.5	3.1	-0.3	139	140	3.5	3.6
1.3	1.8	0.5	2.5	-1.1	139	145	2.8	3.1
1.3	3.5	2.2	1	-0.7	135	135	3.6	3.7
4	7.2	3.2	-2	-11	134	138	4.2	4.2
0.8	1.8	1	3.1	0.9	131	136	4.8	3.7
2.9	3.1	0.2	4.9	-0.4	133	140	4.1	4.1
2.4	4.3	1.9	-1.1	-3.1	135	138	4	4
4	6	2	-4.9	-5.3	137	139	3.6	4.2
2.2	5	2.8	-2	-5.9	131	137	3.8	3.8
2.1	3.3	1.2	3.8	-0.1	130	136	3.9	3.8
0.9	2.7	1.8	2.3	-0.6	131	131	3.4	3.7
2.1	5	2.9	1.9	-1.5	136	135	4.1	4.3
3.2	3.1	0.1	3	-1.9	134	140	3.6	3.3
2.1	1.9	-0.2	1.9	-1.7	137	139	3.6	3.6
2	2.6	0.6	0	-3.8	136	141	3.6	3.7
1.2	3.4	2.2	2.1	-3.8	133	135	3.7	4.3
1.9	4.8	2.9	-1.8	-7	135	137	3.6	3.6
3.3	3.5	0.2	-4.3	-6.5	137	141	3.3	3.6
3.2	3.5	0.3	-2.9	-2.8	136	140	3.6	3.4
1.1	2.1	1	1.6	-3.1	132	136	3.6	3.6
1	2.9	1.8	-1.3	12	134	135	3.2	4.4
1.5	2.5	1	0.8	-1.5	135	140	3.6	3.5
1.8	1.2	-0.6	1.3	0.9	138	146	3.5	3.5
2.4	4.4	2	1.8	-4.4	137	140	3.8	3.9
1.1	3.6	2.5	2.5	-1.4	130	135	9.2	4
3.1	4.8	1.7	5.5	3.4	135	140	3.7	3.5

0.7	2.5	1.8	-0.8	-3.1	137	137	3.9	4.4
2.8	4.5	1.7	-3.7	-6.5	137	136	4	4.7
0.9	1.8	0.9	1.6	0.1	135	136	2.7	3.2
1.6	3.6	2	3.5	-2	136	136	3.9	3.9
2.6	3.4	0.8	-5.9	-1.6	138	136	2.6	4.1
0.8	2.8	2	0.5	-2.4	136	137	4.4	3.7
2	3.3	1.3	2.4	-1.4	136	137	3.8	4.6
2	2.4	0.4	0.8	2.9	136	137	3.4	3.8
1.8	4	2.2	0.2	-1.8	140	139	3.4	3.6
2.3	6.3	4	1.1	-3.5	131	132	3.7	4.1
1.8	6.9	5.1	0.1	-3.1	138	144	3.7	3.6

Ca_pre	Ca_ post	cl_pre	cl_post	Hb_pre	Hb_post	Fluid _NS	RL	Colloid
1.11	0.4			12	8.9	1500	0	500
1.07	1.04			14.7	10.9	1200	0	500
1.05	1.01			10.2	6.5	1100	1100	500
1.11	0.79			12.6	6	2500	500	1000
1.16	1.08			12.2	10.5	1000	0	500
1.11	1.08			12.5	10.5	1300	0	500
1.1	1.1			12.4	12.4	1000	0	0
1.12	1.07			11.5	9.9	1500	500	0
1.18	1.09			12.7	10.5	1000	500	0
1.05	0.9			11	8	1500	0	2000
1.08	1.04			10.2	8.4	1000	0	0
1.14	1.03			14.4	11.6	2000	0	1500
1.15	0.98			12.1	9.9	1600	0	500
1.09	1.07			9.9	9	500	700	500
1.09	1.1			12.3	9.3	1500	0	500
1.07	0.9			11	10.3	1500	0	400
1.14	1.07			14.3	10	1500	100	500
1.07	1.01			13	10	1000	0	500
1.16	1.01			14	10.5	2000	0	500
1.15	1.07	101	112	13.6	6.8	2500	1000	2000
1.14	1.05			15.3	11.5	1500	0	500
1.16	1.12			15.4	13	2250	0	0
1.13	1.06			10.5	9.3	650	500	0
1.15	1.05			15.8	12.3	3000	0	500
1.01	1			13.7	8.4	1500	0	500
1.12	1.2	103	106	16.5	13.1	2000	0	1000
1.14	1.09			11.9	10.9	1000	0	500
1.1	1.05	111	113	13	10.7	1000	500	500
1.16	1.12	107	113	10.5	9.3	2500	500	1000
1.02	1.01	102	110	11.6	8.5	2000	1000	1000
1.07	1.09			11.8	9	1500	0	500
1.14	1.08	107	112	13.5	11.7	1500	500	1000
1.07	0.93	103	115	12.8	9	2000	500	0
1.1	0.99	107	112	12.8	9.6	1000	0	500
1.1	0.95	107	113	11	8	1500	500	500
1.08	0.97	107	114	16.8	10.3	2000	1000	1000
1.15	1.1	107	111	12	10.8	1500	1000	500
1.13	0.94	111	118	9.9	8.9	2500	500	500
1.13	1.17	112	115	11.9	11.7	2000	1000	0
1.12	1.03	108	114	14.2	9.3	1500	0	700
0.98	1.05	111	111	11.7	11.6	1500	500	0
1.13	1.1	109	115	10.1	8.9	2500	1500	1000
1.18	1.1	109	120	13.7	10.1	2500	1500	1500
1.12	1.02	110	115	12.6	11.8	2000	200	0
1.15	1.14	106	111	12.3	9.2	1000	500	500
1.04	0.96	104	112	11.7	7.8	2500	1000	500

1.05	0.98	110	113	8.8	9	1000	500	0
1.09	1.1	113	113	10.3	9.6	1500	500	0
1.08	1.08	108	110	12.5	10.2	1500	1000	500
1.19	0.8	105	107	14.7	8.9	1000	500	1500
0.8	0.9	118	112	10.9	8.1	2100	700	1000
1.03	1.07	111	111	11.2	9.2	1000	1000	500
1.1	1.02	108	117	16.7	11.9	2000	1000	1000
1.07	0.95	108	113	15.4	12.4	1500	500	0
1.01	1.07	113	113	9.6	9	1000	500	500
1.13	1.05	101	107	12.9	10.1	1000	250	500
1.22	0.9	108	114	13.2	9.7	3000	2500	2500

type _of_ f	Wholebloo	Packedcells	FFP	totalfluids	estimatedl	lowestsys_	lowestdias_	meanpostc
1	350	0	0	2350	1100	90	60	70
1	0	0	0	1700	400	100	60	73
1	0	350	0	3050	800	80	60	66
1	0	0	0	4000	1200	84	50	61
1	850	0	0	2350	1600	100	60	73
1	0	0	0	1800	600	97	70	77
0	0	0	0	1000	400	110	70	83
0	0	0	0	2000	400	100	70	80
0	0	0	0	1500	200	100	70	80
1	700	0	0	4200	1000	90	60	70
0	0	0	0	1000	150	100	60	73
1	350	700	0	4550	1600	100	70	80
1	0	0	0	2100	100	110	70	83
1	0	0	0	1700	500	95	47	63
1	0	0	0	2000	500	110	70	83
1	350	0	0	2250	800	100	60	73
1	0	0	0	2100	550	100	60	73
1	0	0	0	1500	500	90	60	70
1	0	0	0	2500	800	90	60	70
1	1700	0	0	7200	3500	100	60	73
1	0	0	0	2000	400	100	60	73
0	0	0	0	2250	500	110	65	80
0	0	0	0	1150	300	100	70	83
1	0	0	0	3500	400	90	60	70
1	0	0	0	2000	800	86	42	57
1	0	0	0	3000	750	100	60	73
1	0	0	0	1500	300	108	60	76
1	350	0	0	2350	900	100	60	73
1	1000	0	0	5000	1500	100	60	73
1	700	0	0	4700	1500	100	70	80
1	0	0	0	2000	500	110	60	77
1	0	350	0	3350	1000	90	60	70
0	500	0	0	3000	1000	80	60	66
0	0	0	0	1500	250	130	80	97
1	0	0	0	2500	900	120	60	80
1	350	0	0	4350	2000	74	56	62
1	0	0	0	3000	300	100	60	73
1	1400	0	0	4900	2500	90	50	63
0	0	0	0	3000	400	90	50	63
1	0	0	0	2200	600	110	70	83
0	0	0	0	2000	300	100	70	80
1	1400	0	0	6400	2800	100	60	73
1	1000	0	0	6500	1800	100	70	80
0	0	0	0	2200	350	100	70	80
1	0	0	0	2000	500	110	70	83
1	1050	0	0	5050	2200	100	70	80

0	500	0	0	2000	450	100	60	73
0	0	0	0	2000	300	100	60	73
1	0	0	0	3000	600	100	70	80
1	0	350	0	3350	2000	90	60	70
1	600	0	0	4400	600	100	70	80
1	0	0	0	2500	350	90	70	77
1	0	0	0	4000	700	100	60	73
0	500	0	0	2500	1650	98	70	79
1	350	0	0	2350	700	110	60	77
1	0	0	0	1750	800	100	60	73
1	1000	2100	0	11100	3800	110	16.5	90

fallinmean	fluidbolus	totalfluids	bloodtrans	packedcell	wholeblood	ffp	prc	CRYO
23	1	1750	0	0	0	0	0	0
22	0	1400	0	0	0	0	0	0
20	3	3900	1	350	0	0	0	0
31	1	2400	2	700	850	0	0	0
18	1	2625	0	0	0	0	0	0
4	2	3600	0	0	0	0	0	0
28	0	1700	0	0	0	0	0	0
12	0	1850	0	0	0	0	0	0
14	0	1750	0	0	0	0	0	0
73	2	1900	1	0	700	0	0	0
28	0	2100	0	0	0	0	0	0
27	0	1700	0	0	0	0	0	0
5	0	1350	0	0	0	0	0	0
43	3	3600	0	0	0	0	0	0
24	0	2300	0	0	0	0	0	0
7	1	3200	0	0	0	0	0	0
5	4	3900	0	0	0	0	0	0
28	1	3050	1	0	350	0	0	0
7	3	3100	0	0	0	0	0	0
10	2	2900	1	0	500	0	2	0
32	0	2150	0	0	0	0	0	0
25	2	2300	0	0	0	0	0	0
11	2	2250	0	0	0	0	0	0
10	1	2575	0	0	0	0	0	0
46	3	3100	1	0	350	0	0	0
13	0	1500	0	0	0	0	0	0
21	0	3500	0	0	0	0	0	0
21	0	2400	0	0	0	0	0	0
0	1	2800	0	0	0	0	0	0
16	0	1250	0	0	0	0	0	0
20	0	2150	0	0	0	0	0	0
37	0	1350	0	0	0	0	0	0
41	2	2900	1	0	500	0	0	0
49	1	2200	0	0	0	0	0	0
0	1	1750	0	0	0	0	0	0
23	2	3600	1	350	0	0	0	0
9	0	2100	0	0	0	0	0	0
23	0	2120	0	0	0	0	0	4
25	0	1350	0	0	0	0	0	0
-13	0	2100	0	0	0	0	0	0
18	1	1850	0	0	0	0	0	0
5	1	2200	1	350	0	0	0	0
10	0	2500	0	0	0	0	0	0
-14	1	2350	0	0	0	0	0	0
-10	0	1350	0	11.5	0	0	0	0
-9	0	4650	0	0	0	0	4	5

7	1	1900	0	0	0	0	0	0
0	0	2300	0	0	0	0	0	0
11	0	1800	0	0	0	0	0	0
17	0	2120	0	0	0	0	0	0
9	0	1350	0	0	0	0	0	0
16	0	2050	0	0	0	0	0	0
12	1	1750	0	0	0	0	0	0
21	1	2000	0	0	0	0	0	0
13	0	2160	0	0	0	0	0	0
30	0	1750	0	0	0	0	0	0
0	0	1870	0	0	0	0	8	4

postop_pc	postopdura	hospitalno
27.2	12	523159
34	20	524538
25.2	18	519438
22.2	10	524927
30.2	18	494273
29.8	18	560052
34.5	13	454249
29.4	14.5	584309
34.2	15	533207
37.6	12	556539
31.6	20	584536
39.5	15	593582
39.2	14.5	615546
27.7	16	622646
30.2	18	386942
27.3	12	663186
29.6	14.5	654767
26.8	15	629080
30.1	15.5	641997
30.8	10	681901
37.6	15	675398
34.4	16.5	676127
25		710736
32	17	659086d
27.6	15	681821d
40.8	11.5	683463
26.5	16	680442
28.7	18	675518
28.8	12	682973
26.7	9.5	756271
30.3	17	716692
36	11.5	725236
35.3	10	696628
34.2	10.5	707871
28.8	11.5	722927
35.7	12	725314
32.4	17	637142
27.7	12	695142
33.5	11.59	678246
35.7	9	704525
32.6	17	731814
21.5	10	730190
30.1	10.5	739878
36.7	17.5	734251
29	10	974698
29.4	11.5	728685

30.9	18.5	744977
27.4	19	714043
36	11	709050
30.6	16.5	735694
27.7	11	700772
25.7	17	723914
38.9	11	752106
37	11.5	679875
25.5	18	735635
32.7	15	757588
25.5	14.5	732860