TO STUDY THE HEMODYNAMIC CHANGES FROM SUPINE TO PRONE POSITION IN ASA II AND III PATIENTS UNDERGOING MAJOR SPINE SURGERY IN PRONE POSITION USING FLO TRAC SENSOR - AN OBSERVATIONAL STUDY.
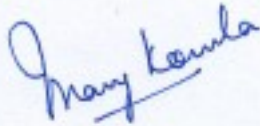
This Dissertation is in partial fulfillment of the requirement for the M.D. Degree (Branch X)

Anaesthesiology Examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai,

to be conducted in April 2015.

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CERTIFICATE

This is to certify that the dissertation entitled **'An observational study to study the hemodynamic changes from supine to prone position in ASA II and III   patients undergoing major spine surgery in prone position using FloTrac sensor'** is the bonafide original work of Dr. Nisha Sara Mundappallil Jacob, toward the M.D. Branch X (Anaesthesiology) Degree Examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, to be conducted in April 2015.

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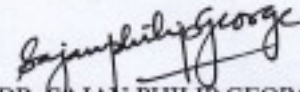VELLORE -632 004.

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TURNITIN ORIGINALITY REPORT

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AIM

To study hemodynamic changes from supine to prone position using Flo Trac sensor

INDEX

TITLE OF ABSTRACT:

HEMODYNAMIC CHANGES FROM SUPINE TO PRONE POSITION IN ASA II AND III PATIENTS UNDERGOING MAJOR SPINE SURGERY IN PRONE POSITION USING FLO TRAC SENSOR

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NAME OF CANDIDATE: Dr. Nisha Sara Mundappallil Jacob

DEGREE AND SUBJECT: M.D. Anaesthesia

NAME OF THE GUIDE: Dr. Sajan Philip George

OBJECTIVES:

This observational study assessed the hemodynamic changes that occurred in ASA II and III patients undergoing major elective spine surgery on changing position from supine to prone using the Flo Trac sensor. Additionally, it observed the effect of 10ml/kg of crystalloid fluid administered as a bolus before turning prone.

METHODS:

Twenty-nine patients were prospectively studied. Patients with valvular heart disease, chronic obstructive pulmonary disease, renal dysfunction and arrhythmia were excluded .After establishing venous access, radial arterial cannulation was undertaken and the Flotrac transducer was connected. Other routine monitors were connected. Induction was carried out with fentanyl , propofol and vecuronium; patients were intubated and mechanical ventilation established with tidal volumes of at least 8ml/kg. Anaesthesia was maintained with air /oxygen and Isoflurane titrated to a MAC of 0.8. Variables measured were heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), stroke volume variation (SVV), pulse pressure variation (PPV), cardiac output (CO) and cardiac index(CI).Variables were measured after induction in the supine position (T1) and every 5 minutes after turning prone up to 15 minutes (T2-T4). All patients received fluid bolus of 10ml/kg of crystalloids before change of position. A fall in cardiac index by more than 20% from baseline (T1) warranted treatment with crytalloids upto 10ml/kg and/or boluses of vasopressors. Failure to respond to these warranted starting inotropic agents.

Statistical analysis was performed using SPSS software. A General Estimating Equations (GEE) analysis was performed to analyze the change in variables across the time points (T2-T4) along with the significance of change (p value), with T1 as the reference. A paired t-test analysis was additionally done between time points T1 and T4. Correlation between variables (PPV and CO, SVV and CO and PPV and SVV) were assessed in the prone position at two time points using Pearson correlation test. Levene's test for Equality of Variance was used to analyse the difference in variables among patients on differing prone supports and among diabetic versus non-diabetic patients.

RESULTS:

There was a significant change in SBP (p=0.025), SVV (p=0.002) and PPV(p=0.02) 5 minutes after change of position to prone. However, there was no significant fall (p>0.05) in CO or CI during this time. There was a significant change in all hemodynamic variables (HR: p<0.001, SBP p<0.001, MAP p=0.014, PPV:p=0.024, SVV p=0.002, CO p<0.001, CI: p=0.003) except DBP 15 minutes after turning prone. A strong positive correlation was found to exist between SVV and PPV at T2 (r=0.835; p=<0.001) and T4 (r=0.75; p<0.001) while CO correlated weakly with SVV and PPV. Type of support (Relton-Hall vs. bolsters) and presence of diabetes did not significantly affect PPV and SVV. In conclusion, there was a statistically significant change in all hemodynamic variables 15 minutes after turning prone. There was no significant fall in CO or CI 5 minutes after turning prone; whether this can be attributed to the fluid bolus administered before change in position cannot be established at present.

KEY WORDS:

<u>AIM</u>

To study hemodynamic changes from supine to prone position using Flo Trac sensor.

OBJECTIVES

1. To observe the hemodynamic changes when turning from supine to prone position in ASA II and III patients undergoing major spine surgery using Flo Trac sensor.

2. To observe the response to a bolus of fluid (10ml/kg of crystalloid) before turning prone.

INTRODUCTION

Hemodynamic monitoring is an essential component of any form of anesthesia. Maintenance of optimum hemodynamics is important, especially in patients with disease processes. Hypotension and hypovolemia in these patients may lead to critical end-organ dysfunction. Over-hydration, on the other hand,leads to hemodilution, interstitial edema and has been implicated in increasing morbidity and prolonging hospital stay. It is therefore evident that optimum use of intravenous fluids is needed.

A variety of tools are available for monitoring intraoperative hemodynamics. Clinical signs such as pallor, pulse volume characterization and pattern of respiration have proved to be unreliable methods. For decades, static variables such as central venous pressure (CVP) and pulmonary capillary wedge pressure were used as standards for monitoring hemodynamic variables. In recent years, studies have shown that they cannot be relied upon. In addition to this, they require invasive procedures which carry inherent risks.

Dynamic variables are those that depend on the interaction between the heart and the lung. There are various indices used in modern-day practice. They are broadly categorized as non-invasive and invasive . The non-invasive indices include the plethysmography variability index and the ECG variability index. Indices derived from analysis of the arterial pressure waveform have proved to be reliable in assessing intravascular volume and in predicting responsiveness to fluid challenge. These include pulse pressure variation(PPV), systolic pressure variation (SPV) and stroke volume variation (SVV).

During mechanical ventilation, there are cyclical changes that occur in the arterial waveform. The increase in intrathoracic pressure due to the positive pressure ventilation results in a fall in right ventricular (RV) preload. Increase in the transpulmonary pressure which also occurs during positive pressure ventilation results in an increase in the RV afterload. Consequent to these effects, the RV stroke volume decreases. Fall in RV stroke volume subsequently leads to fall in the left ventricular (LV) preload and LV stroke volume. There is a fall in the left ventricular afterlaod and an increase in the left ventricular preload during inspiration. Thus, during mechanical ventilation, systolic pressure is maximal during inspiration . When positive pressure ventilation is released (that is, expiration), the venous return returns to baseline as do the systolic pressure and the stroke volume. Pulse pressure(PP) is the difference between the systolic and the diastolic pressure. PP is directly proportional to the systolic pressure and inversely proportional to the arterial compliance. If arterial compliance is assumed to be constant, then pulse pressure is directly related to left ventricular stroke volume. Pulse pressure variation (PPV) is used to quantify the change in pulse pressure with respiration and is expressed as a percentage.

Cardiac output monitoring is routinely not practiced in clinical anesthesia, except in patients with significant co-morbid illnesses who might benefit from its use or in patients in whom large fluid shifts are expected (eg. Liver transplantation).The invasive nature of the technology required for the traditional cardiac output monitoring precludes its use. It is also expensive. Techniques of monitoring cardiac output are broadly classified as non-invasive,

minimally invasive and invasive. The invasive method (thermodilution technique) requires the insertion of a pulmonary artery catheter. The minimally invasive techniques include transpulmonary thermodilution, the PiCCO system and the LiDCO system, all of which require the insertion of a central venous catheter. Doppler ultrasound and trans-esophageal echocardiography are operator-dependent. Waveform analysis of the Flo Trac system generates cardiac output in addition to dynamic variables and requires only a peripherally placed arterial line.

It is a routine practice to measure intraarterial blood pressure in major surgeries where significant blood loss or fluid shifts are expected and in patients with significant co-morbid illnesses. Attaching a Flo Trac sensor to the arterial line may provide valuable information which may prove essential in decision-making.

Change of position from supine to prone is associated with significant hemodynamic changes. These include fall in cardiac index (CI) and an increase in systemic vascular resistance (SVR). Fall in cardiac output occurs primarily as a result of decrease in stroke volume. In healthy individuals , however, blood pressure is invariably maintained due to the concomitant increase in systemic vascular resistance. In patients with significant co-morbid illnesses, a change in position from supine to prone may worsen hemodynamics significantly.

Thermodynamic variables other than cardiac output are also affected as a result of change in position. A fall in the stroke volume that results from the prone position occurs as a result of fall in right ventricular preload. This causes more pronounced cyclic variations produced by

mechanical ventilation and is manifest as an increase in the PPV and SVV.

Hemodynamic changes in the prone position may also be affected by the type of support used in positioning. Improper positioning of the prone support would cause abdominal compression which decreases lung compliance. This impedes the venous return to the right heart which results in a fall in the stroke volume and , as per Frank-Starling law, in the cardiac output. Moreover, an increase in the abdominal pressure would lead to an increase in the pressure in the epidural venous plexuses with resultant increased intra-operative blood loss.

Patients with conditions such as diabetes, hypertension and ischemic heart disease may be using a variety of drugs which include beta blockers, calcium channel blockers, angiotensin receptor blockers, ACE inhibitors and nitrates. They may also have varying degrees of autonomic dysfunction which may not have been diagnosed preoperatively. Anesthesia in these group of patients is fraught with the hazards of hypotension and resultant end-organ damage. These changes are often worsened when a change in position occurs.

This study aimed at determining the hemodynamic changes that occur with change in position as defined by the Flo Trac sensor. The Flo Trac sensor is a special transducer connected to a peripherally placed arterial line and measures hemodynamic variables over 20s intervals. Unlike previous studies in which majority of participants belonged to ASA I,the group of patients studied belonged to ASA Class II and II and underwent major spine procedures (Posterior Lumbar Intervertebral Fixation (PLIF), Transforaminal lumbar Intervertebral Fixation(TLIF), laminectomies in 3 or more levels with or without tumour

excision) in the prone position. The various variables studied included heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure,pulse pressure variation (PPV), stroke volume variation (SVV) , cardiac output (CO) ,cardiac index (CI).

REVIEW OF LITERATURE

In the peri-operative period, use of anesthetic agents, surgical interventions and positive pressure pressure ventilation all have a tremendous impact on the cardiovascular status of a patient. These changes are all the more important and potentially fatal if the patient has significant co-morbid illnesses. Hemodynamic monitoring during this crucial period aims at anticipating and preventing significant hemodynamic changes before irreversible damage occurs.

Almost all anesthetic agents have a depressant effect on the cardiovascular system. Induction and maintenance of anesthesia is associated with attenuation of cardiovascular reflexes, peripheral vasodilation, fall in cardiac output and blood pressure. Establishment of positive pressure ventilation is further associated with a decrease in systemic venous return as a result of the rise in intrathoracic pressure. A combination of these factors, together with disease characteristics of the patient, such as a 'fixed-output' state , can result in profound cardiovascular depression during general anesthesia.

Hemodynamic monitoring is an integral part of intraoperative monitoring. It enables the clinician to ascertain the adequacy of circulatory function of the patient. Monitoring the circulation is included as one of the 'Standards for Basic Anesthetic Monitoring' as described by the American Society of Anesthesiologists(ASA).(1)

Modalities of hemodynamic monitoring are numerous and varied. They range from as simple a maneuver as 'finger on the pulse' to the many sophisticated technologies available today that allow determination of beat to beat variables which enable better management of hemodynamics in high risk patients. Historically, the techniques available for monitoring the circulatory status of the patient under anaesthesia included crude methods such as placing a finger on the pulse for characterization of pulse volume, determining the color of skin and mucosal membranes, assessment of the pattern of ventilation and capillary refill time. The advent of electronic monitoring has freed the clinician from clerical tasks and enabled him to fine-tune his clinical judgment and skills. They allow for 'continual' as well as 'continuous' monitoring of different variables.

One of the most important therapeutic and earliest interventions in the event of circulatory instability is volume expansion. The physiological basis of this intervention is the Frank-Starling law. An increase in the preload of the heart (the end-diastolic volume) is expected to cause an increase in the stroke volume and hence the cardiac output. However, the stroke volume also depends on the ventricular contractility. A decrease in the ventricular contractility would result in a decrease in the slope of the relationship between stroke volume and end-diastolic volume. Studies have shown that only 40-72% of patients who are critically ill and who have been treated with fluid challenge respond with a significant increase in stroke volume and cardiac output.(2) It is evident that administration of intravascular fluids needs to carried out judiciously. Over- zealous administration would

result in pulmonary , hemodilution and peripheral edema; whereas under-filling the patient would result in inadequate oxygen delivery to the tissues. (3) Goal directed use of fluids intraoperatively has been shown to decrease the length of hospital stay in the post-operative period as well as result in earlier return of bowel function and reduce the incidence of nausea and vomiting. (4)Optimum use of fluids is enabled through the measurement of different variables.

Modalities of assessment of intravascular fluid status can be broadly divided as those derived from clinical assessment of the patient, measurement of static variables and dynamic variables.

CLINICAL SIGNS

In the past, clinical signs were used to assess fluid status and evaluate response to resuscitation with intravenous fluids. These included techniques such as assessment of skin turgor, chest movement, pattern of respiration, characterization of the volume of palpated pulse and urine output.(5)

STATIC VARIABLES

Since clinical signs were found to be unreliable, static variables were used to monitor intraoperative and postoperative hemodynamics. These included variables such as central venous pressure(CVP) and pulmonary capillary wedge pressure(PCWP).

CENTRAL VENOUS PRESSURE (CVP)

For decades, CVP has been used as a tool to monitor intravascular volume and response to fluid challenge. A CVP of 8-12mmHG for non-ventilated and 12-15mmHg for mechanically ventilated patients has been set as one of the targets to be achieved in early resuscitation of patients with sepsis.(6) Literature in recent years suggests that CVP is neither reflective of the circulating blood volume, nor can it be used to assess response to fluid challenge.(7,8) Similarly, pulmonary capillary wedge pressure has also been shown to be unreliable in determining response to fluids. (9,10)

RIGHT VENREICULAR END-DIASTOLIC VOLUME (RVEDV) AND LEFT VENTRICULAR END-DIASTOLIC AREA (LVEDA)

Other static variables that have been studied include right ventricular end-diastolic volume (RVEDV) and left ventricular end-diastolic area (LVEDA). While the former required insertion of a pulmonary artery catheter, the latter is measured by transesophageal echocardiography using the trans-gastric short-axis view of the left ventricle. Neither has been found to be reliable predictors of fluid responsiveness.(2)

DYNAMIC VARIABLES

Dynamic variables are those variables that are derived from the interaction between the heart and the lungs during mechanical ventilation. Prerequisites for accuracy of hemodynamic monitoring using most dynamic variables include that

- the patient be mechanically ventilated with tidal volumes of at least 8ml/kg

- the patient not have spontaneous breaths

- the patient not have arrhythmia.(5,11,12)

Some of the dynamic indices in clinical practice include the following

cardiac output and cardiac index

pulse pressure variation

stroke volume variation.

Many of the dynamic variables are measured using invasive arterial blood pressure monitoring which involves cannulation of one of the arteries in the body. The artery cannulated may be the radial artery, brachial artery, axillary artery or the femoral artery.

INDICATIONS FOR PLACEMENT OF ARTERIAL LINE

Indications for placement of an arterial line include the following:(13)

-Patients with conditions which warrant beat-to-beat assessment of the blood pressure and in whom close monitoring of blood pressure is required.

-Patients who require repeated sampling of arterial blood gas.

-Patients who are receiving vasoactive agents.

-Patients in whom assessment of non-invasive blood pressure may not be possible or accurate. Eg: burns, obese patients.

-Patients who require frequent and prolonged blood pressure monitoring and may develop neuropraxia or tissue injury as a result of repetitive inflation of the blood pressure cuff.

-Patients who require monitoring of cardiac output – analysis of waveform gives information   about the cardiovascular status.

PRINCIPLES BEHIND INVASIVE ARTERIAL MONITORING

HYDRAULIC COUPLING

The basic principle of invasive arterial blood pressure monitoring is to provide a column of

fluid that connects the arterial blood to a transducer. It requires the following components:

- – intra-arterial cannula

- – tubing with liquid column

- – pressure transducer

- – microprocessor with display screen

- – mechanism for calibration and zeroing.

The pressure waveform of the arterial pulse is transmitted across the fluid column to the transducer where it is converted into an electrical signal. The microprocessor then processes the signal, amplifies it and converts it so that it is visible on the display screen. The information is displayed on the screen graphically and numerically.

ARTERIAL CANNULATION

Ideally, the ascending aorta is the place to monitor arterial waveform. As this is impractical, other sites are used for intra-arterial cannulation. Commonly used sites include the radial artery, femoral artery, brachial artery and the axillary artery. The arterial waveform will differ in morphology depending on where the cannula is placed. As the distance from the aorta increases there is a decrease in the compliance , oscillation and reflection of the blood pressure waves. This is reflected in the deformed morphology of a peripherally placed

arterial waveform as compared to the aortic waveform. The systolic blood pressure is typically higher and the diastolic pressure lower in the peripheral arterial waveform; (**Fig: 1**) the mean pressures, however, are similar.(14)
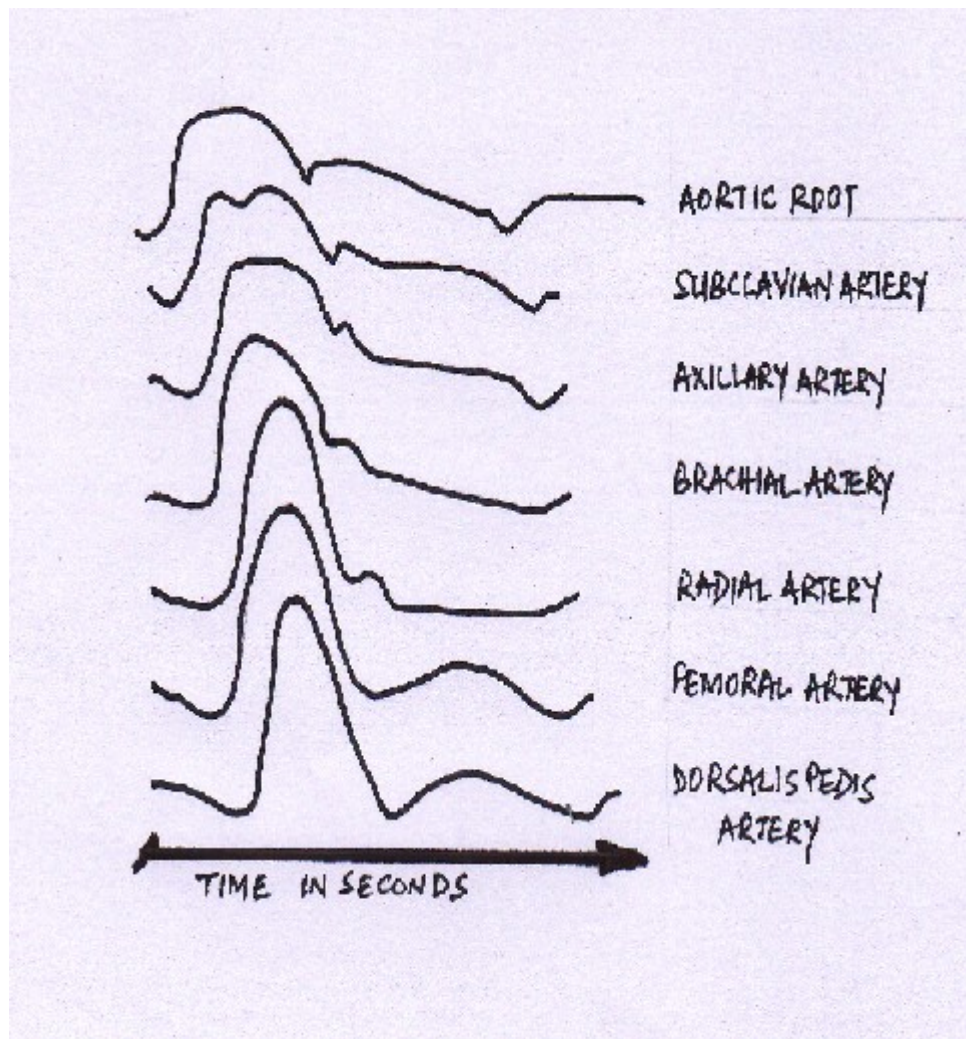
Figure 1: Variation in morphology of the arterial waveform from the aortic root to dorsalis pedis artery. As the distance from the aorta increases, systolic pressure increases , the upstroke is steeper, the dicrotic notch appears later and the diastolic pressure decreases. The mean arterial pressure remains constant.

The radial artery is the most commonly catheterised artery. The Allen test was originally described by E. V. Allen in 1929 to assess the collateral blood flow from the ulnar artery to the hand. The radial and ulnar arteries are compressed by the examiner and the patient is asked to make a tight fist so as to exsanguinate the palm. The fist is then opened,the pressure over the ulnar artery released and the color of the palm is observed. Normally, a flush should appear over the hand; pallor of the hand lasting more than 10 seconds is indicative of reduced ulnar collateral supply.

A normal or negative Allen test, however, does not guarantee against digital ischemia.(15–17) Conversely, patients with a positive Allen's test have had radial artery catheterisation without incident. (18,19) The Allen test, therefore, cannot be relied on to avoid digital ischemia following radial arterial cannulation.

Technique of percutaneous intra-arterial cannula placement

Radial artery is the most popular choice for cannulation due to the easy accessibility and good collateral circulation available to the hand. The hand is positioned for cannulation by ensuring gentle dorsiflexion at the wrist and the artery is palpated along its course. After preparing the skin with an antiseptic solution, local anesthetic is injected (1% lignocaine). Local anesthetic not only ensures analgesia during the procedure and thus patient cooperation, but, if applied appropriately in the subcutaneous plane, prevents vessel spasm

and enables better control of the catheter in this plane.(20)

A 20 gauge catheter-over- needle assembly is introduced at an angle of 30-45 degrees to the skin until blood from the artery is visualized as a 'flash' in the hub of the needle. The catheter-needle assembly is then flattened and introduced a few millimeters into the artery, all the time ensuring that backflow of blood is present. This ensures that the catheter tip, which is slightly proximal to the needle tip, is now within the vessel lumen. The catheter is then threaded into the vessel. (**Fig: 2**) Proximal pressure is applied to occlude the vessel, the needle is removed and the pressure tubing attached to the catheter. A sterile dressing is applied, and the catheter is secured in place with either sutures or tapes.

In the transfixion technique, the anterior and posterior walls of the vessel are punctured intentionally and the needle is removed. The catheter is removed till the tip is within the lumen and then it is threaded. (**Fig: 3**)

Needle-guidewire-catheter assemblies are available where a sterile guidewire may be introduced through the catheter to aid insertion using the modified Seldinger technique. (13,20) Alternatively, ultrasound guided catheterisation of the artery may be carried out.(21) The femoral artery is catheterised using the modified Seldinger technique. (**Fig: 4**)
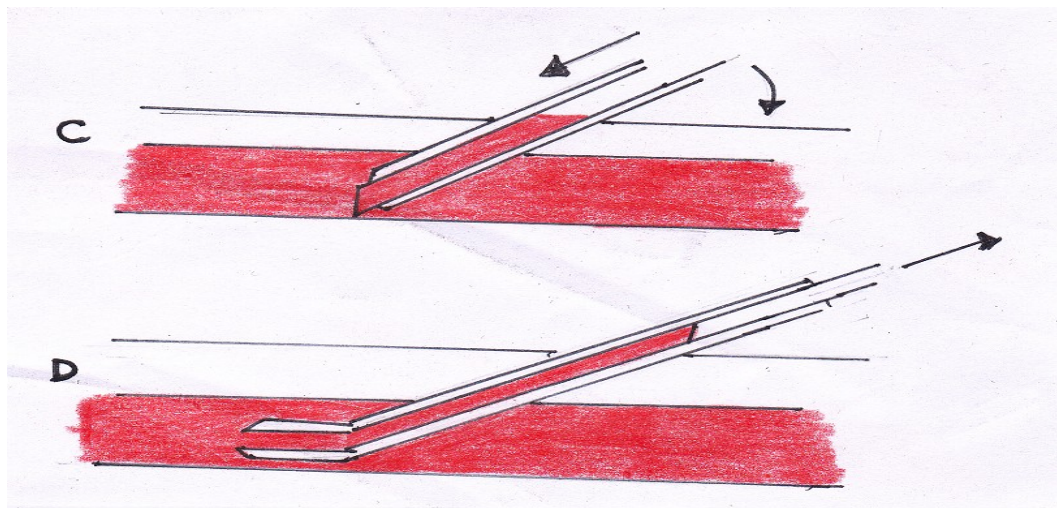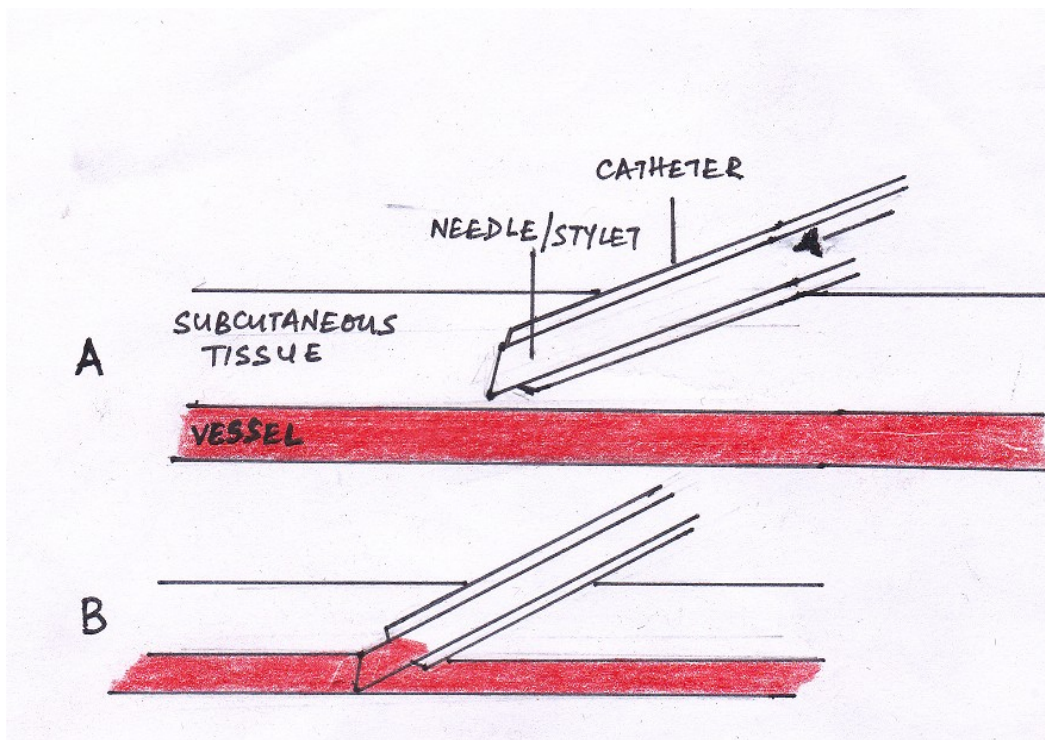
Figure 2: Direct technique of percutaneous arterial cannulation. A- The catheter with the stylet is passed through the skin and subcutaneous plane. B- Once the stylet is within the artery and 'flash' of blood is seen, it is halted. C- The assembly is flattened and introduced a few more millimeters to ensure catheter tip is within the vessel. D- The catheter is threaded into the vessel and the stylet is removed.
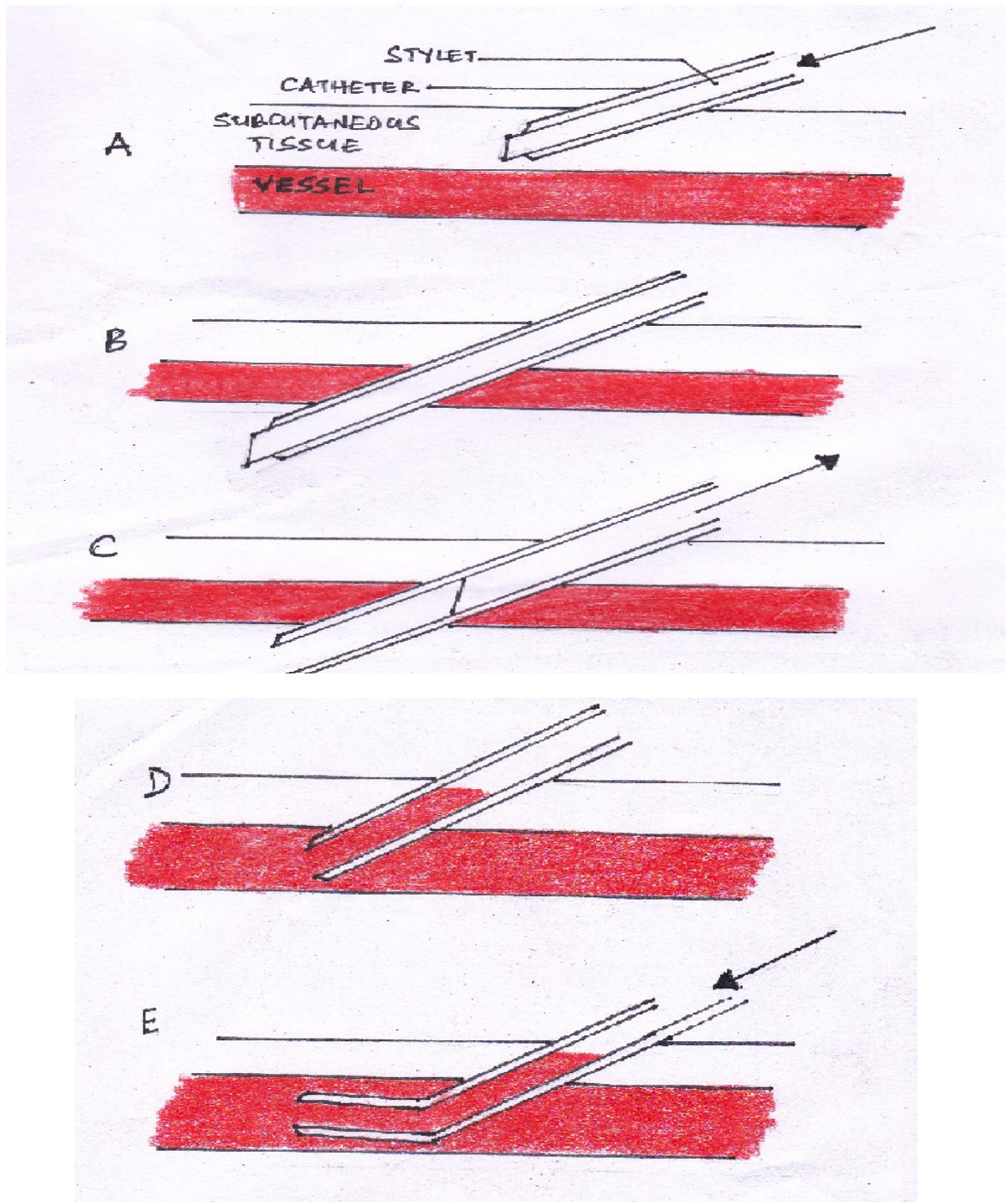
Figure 3: Transfixion technique. A- The catheter with the stylet is passed through the skin and subcutaneous plane. B- The assembly is passed through the artery. C- The stylet is removed. D- The catheter is withdrawn until blood is visualised. E- The catheter is advanced into the vessel.
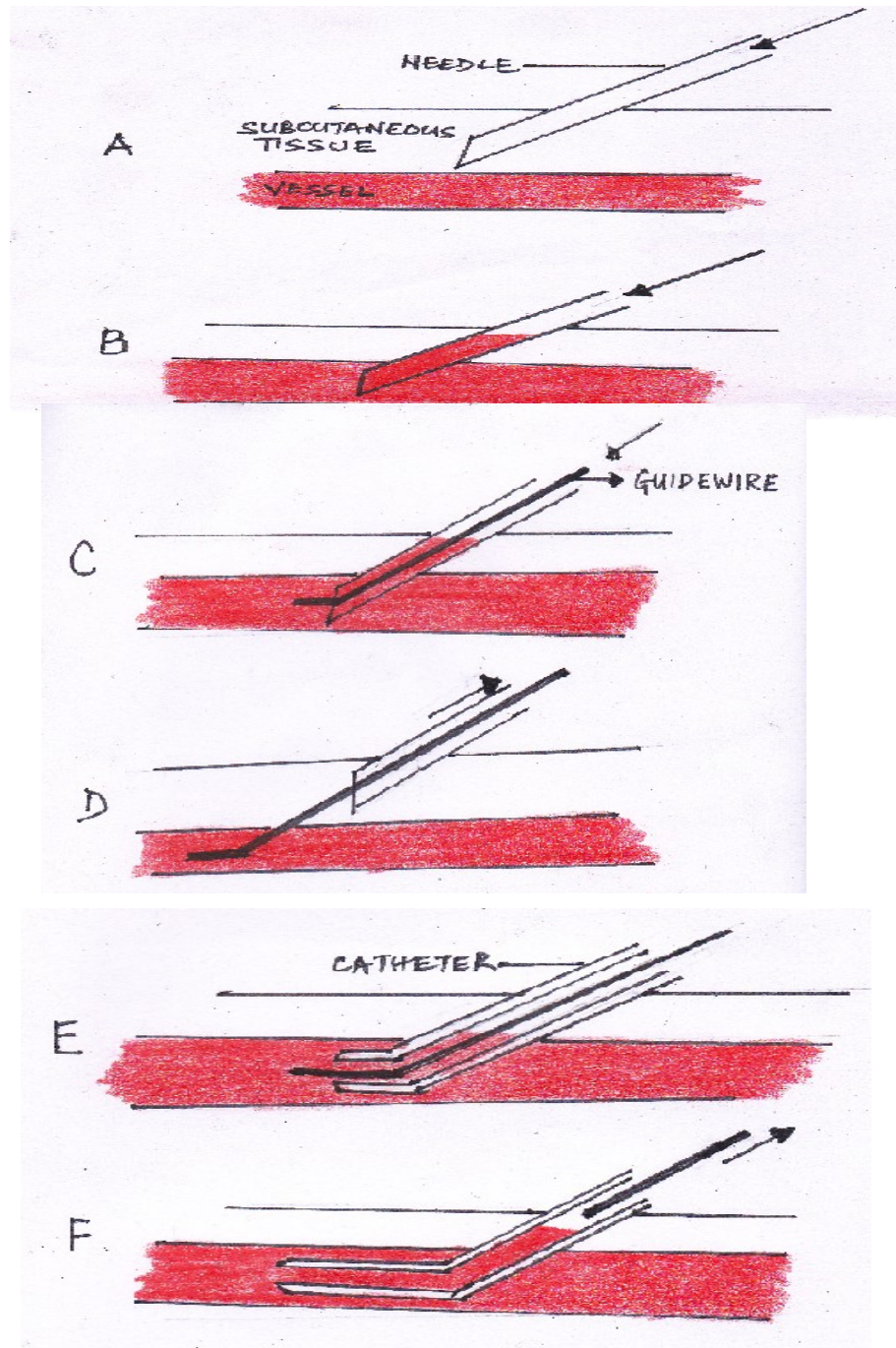
Figure 4:The Seldinger technique. A- The needle is passed through the skin and subcutaneous plane. B- When blood appears in the needle, it is held steady. C- The guidewire is passed through. D- The needle is removed. E- The catheter is passed over the guidewire while maintaining control of the guidewire. F- The guidewire is removed as the catheter is advanced into the vessel.

PRESSURE TRANSDUCER

Typical pressure transducers contain strain gauges made of silicone crystals that distort with changes in blood pressure. A diaphragm and a variable resistance transducer contained within the strain gauge connects the fluid wave to an electric signal. When the diaphragm is distorted, a change in voltage occurs across a Wheatstone bridge circuit; this voltage change can be calibrated accurately to reflect the arterial pressure. (14)

ARTERIAL WAVEFORM ANALYSIS

A wide variety of information can be obtained from the analysis of the waveform that is derived following arterial cannulation.   The morphology of the arterial wave differs depending on the site of cannulation.

A typical arterial waveform **(Fig:5)** has the following points:(22)

    a) Systolic upstroke – a sharp up-stroke associated with left ventricular ejection and opening of the aortic valve.

    b) Systolic peak

    c) Systolic decline – decline in the waveform as the ventricular flow is dispersed

peripherally. Isovolumetric relaxation and diastolic filling of the heart occurs during t his time

d)Dicrotic notch – as a result of isovolumetric relaxation, there is slight fall in pressure just before closure of the aortic valve. It is also called the incisura.

e) Diastolic run-off – run-off to distal arterioles reflected by further fall in pressure

f) End-diastole

Stroke work is represented by the area under the systolic portion of the waveform.
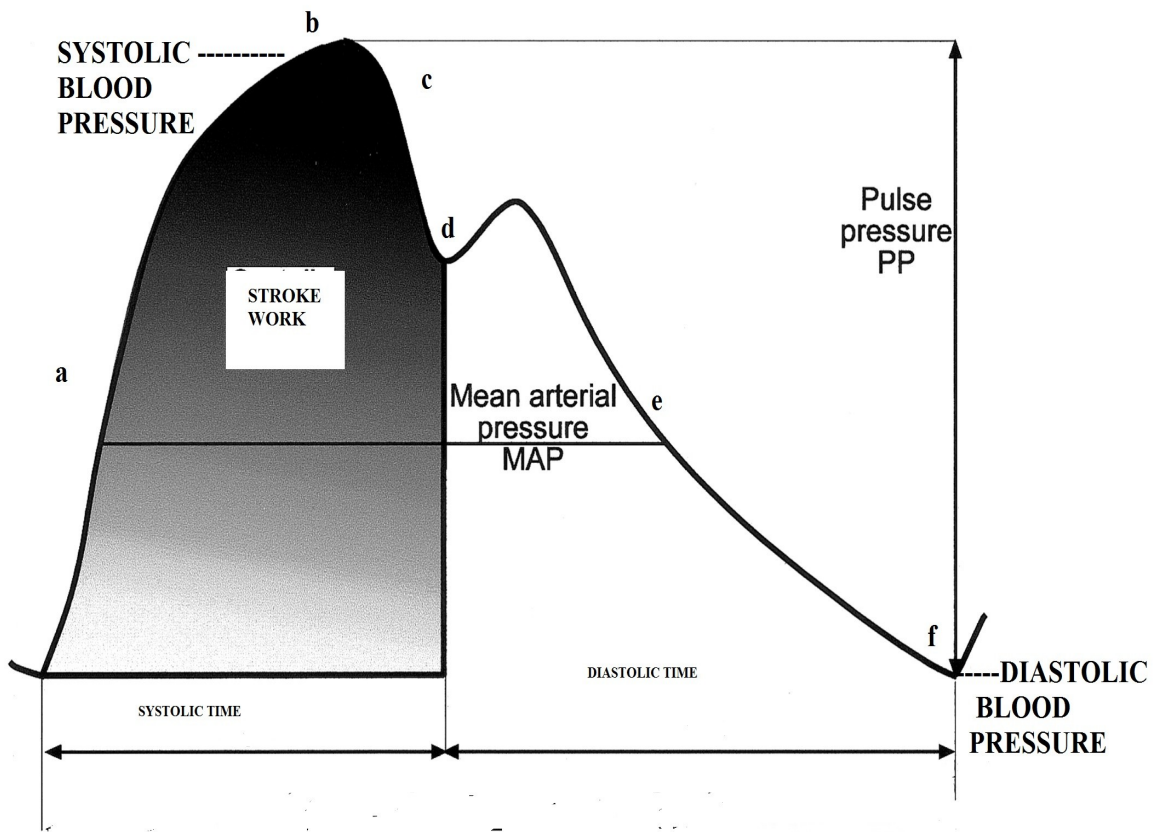
Figure 5: Arterial pressure waveform. a- systolic upstroke, b- systolic peak, c- systolic decline, d- dicrotic notch, e- diastolic run-off, f- end-diastole.

The morphology of the arterial wave differs depending on the site of cannulation. (**Fig:1**) A peripheral arterial waveform will have a steeper upstroke, higher peak systolic pressure, a lower end-diastolic pressure and a later dicrotic notch. This phenomenon is called pulse amplification. The mean pressure,however, is similar to a centrally placed arterial waveform. This difference can be attributed to differences in amplification elasticity and distortion in the smaller vessels.(22,23)

CARDIAC OUTPUT MONITORING

PHYSIOLOGY OF CARDIAC OUTPUT

Cardiac output (CO) is the volume of blood flow from the heart in a minute. It is measured in liters per minute. In average adult male, the cardiac output averages 5-6l/min. An increase in the oxygen demand in the body is met by an increase in the cardiac output. Although numerous factors that determine the oxygen delivery to the tissues (hemoglobin, partial pressure of arterial oxygen and saturation), cardiac output remains the most important one.

Cardiac output is dependent on the stroke volume (SV) and the heart rate (HR). **Stroke volume** is the volume of blood pumped out of the heart during each ventricular contraction or heart beat. Normal stroke volume in an adult ranges from 60-100ml/beat.

$$CO = SV \times HR$$

HEART RATE

Cardiac output is a product of stroke volume and heart rate. A decrease in stroke volume as would occur in a failing heart would cause in a compensatory rise in the heart rate as a result of neurochemical mechanisms that come into play. This maintains a normal cardiac output up to such a point where a rise is in heart rate is so high that diastolic filling of the ventricles

is compromised resulting in lower end-diastolic volume and stroke volume. In addition to this, myocardial perfusion is compromised as the time for diastole, when myocardial perfusion occurs, is critically diminished; this may result in myocardial ischemia or infarction. On the other hand, too slow a heart rate may be inadequate to meet the oxygen demands of the body.

STROKE VOLUME

The following factors determine stroke volume -

preload

afterload

cardiac contractility.

Each of the above factors, will, therefore, affect the cardiac output.

PRELOAD

Preload refers to the degree of ventricular muscle stretching that occurs at end-diastole. It is influenced by

the compliance of the ventricle

the volume and pressure of the blood within the ventricles.

THE FRANK-STARLING LAW

The Frank-Starling law conceptualizes the effect of preload on stroke volume. It was described by Starling in 1914, where the muscle fiber length determined the cardiac muscle work and the force of contraction. The intra-ventricular volume at the end of diastole (left ventricular end-diastolic volume LVEDV) represent the myofilament length which is difficult to measure directly. The venous return to the heart determines the end-diastolic volume. The more the ventricle is stretched, the greater the stroke volume until the cardiac muscle fibers are stretched beyond their limit.**(Fig: 6)** At this point, the stroke volume begins to decline, as is seen in a failing heart.

AFTERLOAD

Afterload is the resistance that the heart must overcome so as to eject blood. It is the systolic load on the left ventricle after contraction begins. Compliance of the aorta, which is the ability of the aorta to give way to ventricular systolic forces, determines afterlaod.

CONTRACTILITY

It is the intrinsic contractile performance of the heart independent of the loading conditions. It is difficult to describe the contractile performance independent of the preload and afterload. It is difficult to estimate contractility clinically. Ejection fraction, which is the most common surrogate used, is load-dependent. (24)
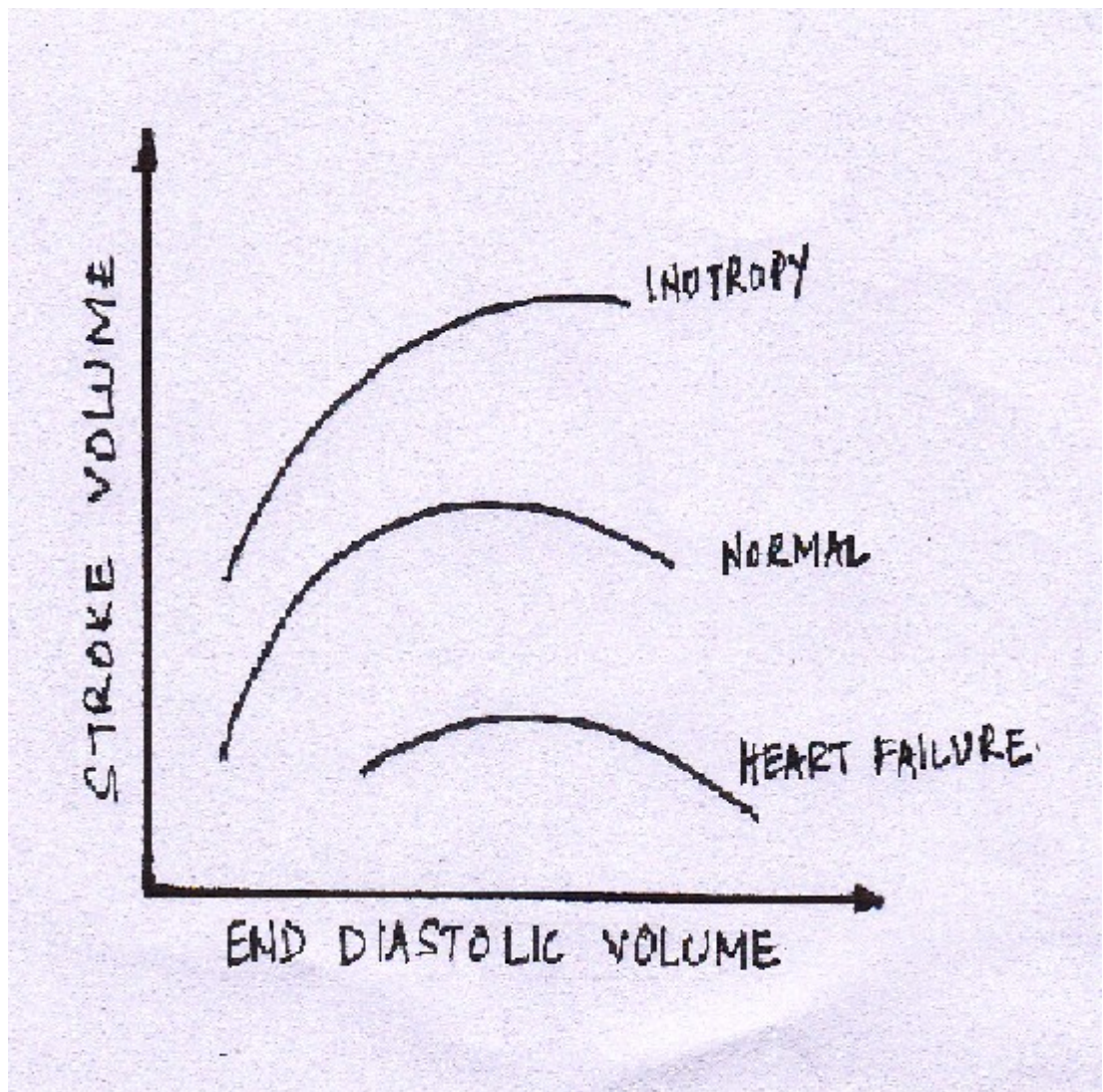
Figure 7: Frank-Starling Law.

MEASUREMENT OF CARDIAC OUTPUT

The ideal technology used to measure cardiac output should be accurate, non-invasive, continuous, reliable and compatible in the adult as well pediatric patient. Currently, no single technique incorporates all these facets. (25)

The methods available to calculate cardiac output may be classified as non-invasive methods, minimally invasive methods and invasive methods.(25)

INVASIVE METHODS:

THERMODILUTION TECHNIQUE

It is a variant of the indicator dye dilution method where indocyanine green dye is used. In the thermodilution technique, a thermistor which is attached to the distal end of the pulmonary artery catheter (PAC) is used to measure the change in temperature of the injectate which is introduced via the proximal lumen of the PAC located in the right atrium. Some fundamental methodological assumptions are made for valid measurement; the thermal indicator must be injected as a rapid bolus, there must be no intra-cardiac shunts and there must be complete mixing of the injectate with the blood in the right atrium. Physical basis for the thermodilution method is given by the Stewart-Hamilton equation. The average of three readings is taken.

FICK PRINCIPLE:(25)

The Fick principle is based on the law of conservation of mass and was postulated by Adolph Fick in 1870. It is considered the most accurate method of measuring cardiac output. This technique presumes a stable hemodynamic status that allows for diffusion of gas across the alveolar capillary membrane during the short transit time of the blood through the lungs. Is also assumes that all the oxygen is transferred to the blood in the lungs. The total oxygen consumption is the product of the arterio-venous oxygen content difference and the blood flow through the lungs (that is, the cardiac output)

$$VO_2 = CO \times (CaO_2 - CvO_2),$$

where, VO_2 is the oxygen consumption, CO is the cardiac output , CaO_2 is the arterial oxygen content of oxygen and CvO_2 the mixed venous oxygen content of oxygen. Cardiac output can be computed from the above equation.

MINIMALLY INVASIVE METHODS

DOPPLER ULTRASOUND(25)

Blood flow velocity is measured in the descending thoracic aorta using a transesophageal doppler probe. The flow rate of the blood passing through the aorta at a give instant is

expressed as the product of the cross-sectional area of the aorta at that time (either derived from a nomogram or measured using M-mode) and the average velocity of the blood over the area. This comprehensively and immediately reflects the function of the heart as a pulsatile organ modified by vascular tone. Stroke distance is the distance a column of blood travels during each systole and is the product of blood velocity and left ventricular ejection time.

Stroke distance = blood velocity x LV ejection time

Stroke Volume = stroke volume x cross-sectional area of aorta

Cardiac Output = stroke volume x heart rate

Analysis of the velocity-time waveforms provide information regarding preload, afterload and contractility.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Perrino et al demonstrated that multi-plane transesophageal echocardiography can be used to determine cardiac output. Aortic blood flow velocity was measured in the transverse plane mid-papillary transgastric short-axis view after rotating the imaging array to 120^0 and the aortic valve area was calculated using planimetry; the stroke volume was computed from these values.(26)

PARTIAL CARBON DIOXIDE REBREATHING

The basis of measuring cardiac output from partial carbon dioxide rebreathing is the Fick principle using carbon dioxide as the marker gas. As per Fick principle, all the oxygen taken up by the lungs is transferred to the blood. Cardiac output is measured as the ratio of consumption of oxygen to the difference in oxygen content between the arterial and venous blood. Carbon dioxide elimination is easier to measure than oxygen consumption.

TRANSPULMONARY THERMODILUTION

This technique utilizes the modified version of the Stewart-Hamilton equation. A cold indicator is injected into a central vein (PAC is not required) and the change in temperature is measured across the cardiopulmonary system at a centrally placed arterial site (for example, the femoral artery or axillary artery). The cardiac output is reflected by the change in temperature.

Although transpulmonary thermodilution has been shown to be comparable to thermodilution cardiac output determination using pulmonary artery catheter, it is non-continuous. Moreover, it is complex and labour intensive requiring frequent calibration. (27)

PULSE CONTOUR ANALYSIS

Analysis of the arterial pulse waveform is used to measure and monitor the stroke volume on a beat-to-beat and continuous basis. Aortic compliance is the change in aortic volume for unit change in aortic pressure (dv/dp); it exhibits a non-linear behaviour which makes it difficult to estimate the stroke volume. The stroke volume is estimated from the aortic waveform represented a peripheral pulse. Several knowledge models which represent the systemic circulation are used to compute the stroke volume from the arterial waveform. Some of the popular models include the modified three element windkessel model and the lumped windkessel model.

Pulse contour analysis allows for continuous monitoring of cardiac output and other hemodynamic variables on a beat-to-beat basis.

PiCCO SYSTEM

PiCCO is pulse-induced continuous cardiac output. When pulse contour analysis of the arterial waveform and continuous cardiac output monitoring by trans-pulmonary thermodilution are incorporated (as in PiCCO), a variety of hemodynamic variables besides cardiac output are obtained. These include stroke volume (SV), stroke volume variation (SVV), systemic vascular resistance (SVR) and intrathoracic blood volume. The basis for analysis is the pulse contour algorithm developed by Wesseling et al. The need for central venous and a central arterial access for injectate administration and calibration limit the use

of this device.(28)

LITHIUM INDICATOR DILUTION

The LiDCO system integrates a lithium indicator dilution cardiac output system with pulse contour analysis and requires administration of non-toxic doses of lithium via a centrally or peripherally placed venous access. A lithium-sensing electrode is attached to the arterial catheter which also has a device that draws blood at a constant rate. The cardiac output is calculated from the area under the concentration-time curve and has to be corrected for the PCV (packed cell volume) since distribution of lithium does not extend to the blood cell volume. The need for frequent calibration (every 8 hours) and concerns regarding use in patients on therapeutic lithium and on neuromuscular blocking agents limits the use of the LiDCO system. (25,28)

FLO TRAC/ VIGILEO

The PiCCO and the LiDCO systems require calibration. The Flo Trac/Vigileo™ system was developed by Edwards Life Sciences. It was released for clinical use in 2005. It computes cardiac output without external calibration.

The system consists of

- the Flo Trac sensor (Fig:8) - a specialised transducer which processes the arterial waveform

- the Vigileo monitor (Fig:9) – a stand-alone display unit. It applies the algorithm to calculate and display continuously the cardiac output and other hemodynamic

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variables.

The demographic data of the patient is fed into the monitor. The data entered is the following:

age

sex

height

weight.

The above have the ability to detect the changes in vascular compliance and peripheral vascular resistance of the patient through analysis of the arterial waveform morphology. Once the patient data is entered and the system is zeroed, hemodynamic variables are provided at intervals of 20 seconds.

The following formula is used to calculate the cardiac output

$$APCO = PR \cdot sd(AP). X,$$

where APCO is the arterial pressure cardiac output, PR is the pulse rate and $sd(AP).X$ represents the stroke volume.

$sd(AP)$ represents pulsatility using standard deviation of the pressure wave over an interval of 20 seconds. The frequency at which derived from the patient characteristics (i.e., age, sex, weight and height) and the morphology of the waveform. Langewouters et al quantified the compliance of the aorta in human cadavers(29); younger individuals who are male with a higher body surface area have more compliant aortas than those who are female, have a

lower body surface area or are older. Baseline determination of the patient's vascular tone is using the Langewouters' criteria. However, further analysis of the waveform for real-time effects of vascular tone are also incorporated into the system. Real-time effects of the vascular tone are described in terms of the following:

skewness - the slope exhibited on the rise of the arterial waveform

kurtosis – the degree of wideness or flatness.

An increase in vascular tone is determined as a decrease in the value of X; this will reduce the influence of the pulsatility index in determining the cardiac output. X is recalculated every minute.

Determining the real-time changes in the vascular tone allows reliable calculation of cardiac output without the need for calibration; hemodynamic variables are provided at intervals of 20 seconds.

Since its introduction in 2005, Flo Trac has undergone two major revisions. Whereas the first generation Flo Trac computed X at intervals of 10 minutes, this was improved to 1-minute intervals in the second generation. The third generation Flo Trac launched in 2009, has software which has improved accuracy for cardiac output measurement in patients in whom systemic vascular resistance is low. (28,30)

Figure 8: Flo Trac transducer

Figure 9: The Vigileo monitor displaying cardiac index (CI), stroke volume variation (SVV), cardiac output (CO) and stroke volume (SV)

NON-INVASIVE METHOD

ELECTRICAL IMPEDENCE CARDIOGRAPHY

Paired electrodes are placed at points that define the lower and upper limits of the thorax as well as the width (distance between the electrodes). A radiofrequency signal transmitted across the thorax from the outer section of the electrodes is sensed by the inner section of the electrodes. Changes in the blood volume of the thoracic aorta are correlated to the stroke volume. These pulsatile changes cause changes in the amplitude of the propagated electrical signal. Changes in intrathoracic volume also produce changes that are reflected as phase shifts between the applied and sensed signals. Non-invasive cardiac output monitors (NICOM) are less influenced by patient's movement, body shape or location of electrodes on the thorax.(25,30)

CARDIAC INDEX

Cardiac index(CI) is derived from the cardiac output. Since patients differ widely in body size and weight, cardiac output is frequently expressed in terms of cardiac index.

$$CI = CO / BSA$$

where, CI is the cardiac index, CO is the cardiac output and BSA is the body surface area. The unit is liters/minute/sq. meter. Normal range of CI is between 2.5-4.5l/min/sq.m. (14)

HEMODYNAMIC INDICES

DYNAMIC NON-INASIVE INDICES

INFERIOR VENA CAVA MEASUREMENTS

Measurement of central venous pressure is invasive requiring the presence of a central venous catheter. Inferior vena caval diameter(IVCD) measured by transthoracic echocardiography has been used as a non-invasive tool to measure the intravascular volume status.

The physiological basis behind measurement of IVC diameter is as follows. In an individual breathing spontaneously, during inspiration, there is a fall in the intrathoracic pressure causing an increase in the venous return; this leads to a decrease in the IVCD by about 50%. The reverse is observed during exhalation. In a patient being mechanically ventilated, the increase in pleural pressure caused by positive pressure ventilation leads to a fall in the venous return. The net result is the reverse of what is observed in a spontaneously breathing patient; that is, there is an increase in the IVCD during inspiration and a decease during expiration.

The subcostal approach is used, with the transducer being place 1-2cm to the right of the midline, just below the xiphisternum and the marker dot pointing cephalad towards the

sternal notch. A stable 2-D image (visualisation is not lost during movements of respiration) of the inferior vena cava entering the right atrium is obtained and the M-mode line is placed and M-mode tracing obtained. After freezing the M-mode image, the calipers are used to measure the maximum and the minimum diameter of the IVC tracing.

IVC DIAMETER

The IVC diameter indicates the volume status of the patient, but not the fluid responsiveness.

A low value less than 12mm is suggestive of a volume depleted status and is predictive of a low right atrial pressure.(31) Higher values may indicate either a normal right atrial pressure or a high pressure (high CVP). However, there are wide variations seen, and absolute values are not reliable in patients who are being mechanically ventilated, since IVC diameter varies with the end-expiratory pressure. IVC diameter increases as the end-expiratory pressure increases.

A 'virtual IVC' is when the IVC is so collapsed that it cannot be visualized. Such a condition indicates severe hypovolemia irrespective of whether the patient is spontaneously breathing or receiving positive pressure ventilation - the exception being the presence of raised intra-abdominal pressure so high as to cause compression of the IVC.

IVC COLLAPSABILITY INDEX

It is calculated as

$$(\text{IVC max} - \text{IVC min}) / \text{IVC max} \times 100.$$

In patients breathing spontaneously, a collapsability index of more than 50% has been found to be suggestive of low right atrial pressures (<10mm Hg). However, in mechanically ventilated patients, it has failed to reflect the CVP. (31)

IVC VARIABILITY INDEX (d IVC)

$$\text{dIVC} = (\text{IVC max} - \text{IVC min}) / \text{IVC mean}$$

In a mechanically ventilated patient, a variation of 12% or more indicates that the patient is likely to respond to fluids (>90% predictive value)(32)

IVC DISTENSIBILITY INDEX

It is calculated as

$$(\text{IVC max} - \text{IVC min}) / \text{IVC min} \times 100.$$

An 18% or more variation indicates responsiveness to fluids in mechanically ventilated patients.(specificity and sensitivity of 90%)(32)

Although the above measurements are non-invasive, they are not practical to apply in the operative room. They are also operator dependent.

PLETHYSMOGRAPHIC VARIABILITY INDEX (PVI)

The basis of this index is the respiratory variations in the pulse volume when preload is not adequate. Dynamic variations in the perfusion index over respiratory cycle are measured.

The PVI is calculated as the following

$$PVI = (PImax - PI\ min)/\ PI\ max\ X\ 100\%$$

Various studies have shown that PVI is a reliable index of fluid responsiveness.(33–35)

While it is a non-invasive method of assessing response to fluid challenge, its limitations include the fact that it is a peripheral measure and, as such, is subject to tissue perfusion and vasomotor tone. (36)

ECG VARIABILITY INDEX

Chnages in the morphology of the electrocardiogram has been suggested as being reflective of the change in volume status. The basis of this index is the 'Brody effect' - an increase in the preload of left ventricular increases the R wave amplitude. In a heart which is preload-dependent, changes in respiration during positive pressure ventilation will cause large changes in the cardiac volume. This will vary the resistance across cardiac tissue and is reflected as variation in the R wave amplitude.(36)

The variations in lead II of the electrocardiogram is studied. The amplitude of the QRS

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complex has been observed to increase with an increase in the preload. The maximum and minimum QRS amplitudes (ECG max and ECG min respectively) over a respiratory cycle are measured. The ECG variability is. calculated as

[(ECG max – ECG min) / (ECG max + ECG min)/2]

Studies have found that ECG variability correlates well with pulse pressure variation and stroke volume variation.(37–39)

DYNAMIC VARIABLES FROM ARTERIAL PRESSURE WAVEFORM ANALYSIS

Analysis of the arterial waveform provides dynamic indices other than cardiac output. These include the pulse pressure variation (PPV), systolic pressure variation (SPV) and the stroke volume variation(SVV).

HEART-LUNG INTERACTION

Changes in respiration cause variations in the systolic pressure as well as the pulse pressure. In an individual breathing spontaneously, a decrease in blood pressure is observed with inspiration. However, the maximum fall in systolic pressure that occurs does not exceed 5mmHg. Kussmaul described pulsus paradoxus, the exaggeration of this phenomenon, wherein the pulse disappears during inspiration and returns during expiration (seen in constrictive pericarditis).

During positive pressure ventilation, however, the reverse of this phenomenon is observed. During inspiration, there is an increase in arterial blood pressure and a fall in the blood pressure is observed during exhalation. This has been called reversed pulsus paradox, respirator paradox, systolic pressure variation, paradoxical pulsus paradox and pulse pressure variation at different times.

Changes in stroke volume during inspiration:(40,41)

1. There is a a decrease in the venous return or blood flow in the vena cava. This is attributed to the increase in pleural pressure caused by mechanical ventilation and rise in right atrial pressure. Fall in the venous return results in a decrease in the preload of the right ventricle, which in turn causes a low right ventricular output (Frank Starling law). A decrease in the right ventricular outflow translates to a fall in the pulmonary blood flow and subsequently to the left ventricular filling and output.

2. Alveolar pressure is the pressure surrounding the pulmonary capillaries. Pleural pressure is the pressure surrounding the pulmonary arterial bed. Transpulmonary pressure is the difference between the alveolar pressure and the pleural pressure. During inspiration, the rise in alveolar pressure is greater than that of the pleural pressure; as a result, transpulmonary pressure increases during this cycle of respiration. Increase in the transpulmonary pressure impedes right ventricular outflow by increasing the right ventricular afterload.

3. As the rise in alveolar pressure is greater than the rise in pleural pressure during inspiration, blood from the capillaries is squeezed towards the left side of the heart, resulting in an increase in the left ventricular preload.

4. During inspiration, left ventricular afterload is decreased. Positive pleural pressure decreases the systolic intracardiac pressure and increases the systolic extracardiac pressure because of a fall in the thoracic blood volume.

In short, during inspiration

–   right ventricular preload decreases and right ventricular afterload increases resulting in a decrease in the right ventricular stroke volume,

- left ventricular preload increases and left ventricular afterload decreases, resulting in an increase in the left ventricular stroke volume.

The transit time of blood in the pulmonary capillaries is approximately 2 seconds. Because of this transpulmonary delay, a fall in the right ventricular output during inspiration causes a fall in the left ventricular output only after a few heartbeats. This is usually manifested in the expiratory period.

Changes in pulse pressure with respiration(40)

The pulse pressure is directly proportional to the stroke volume and inversely proportional to the vessel (arterial) compliance. If the arterial compliance remains constant, the changes in stroke volume will vary only with changes in the pulse pressure with respiration. Unlike pulse pressure, systolic pressure is less closely related to ventricular stroke volume. This is because changes in systolic pressure depend on changes in the pleural pressure which may result in variance in systolic pressure even during a single mechanical breath.

SYSTOLIC PRESSURE VARAITION (SPV)

Systolic pressure variation determines the respiratory variation in systolic blood pressure by calculation the difference in the maximum systolic pressure and the minimum systolic pressure over a single mechanical breath. SPV is divided into 2 components δ up and δ down. **(Fig: 10)** The former is the difference between the maximal systolic pressure and the reference systolic pressure while the latter is the difference between the reference systolic pressure and the lowest systolic pressure, both over a single mechanical breath. The reference systolic pressure is the systolic pressure measured at end-expiration or during an apneic pause lasting 5-30seconds. The δup reflects the increase in systolic pressure during inspiration which may reflect the inspiratory increase in stroke volume of the left ventricle , the rise in pleural pressure or both. The δ down reflects the decrease in LV stroke volume during expiration as a consequence of the decrease in right ventricular stroke volume during inspiration.
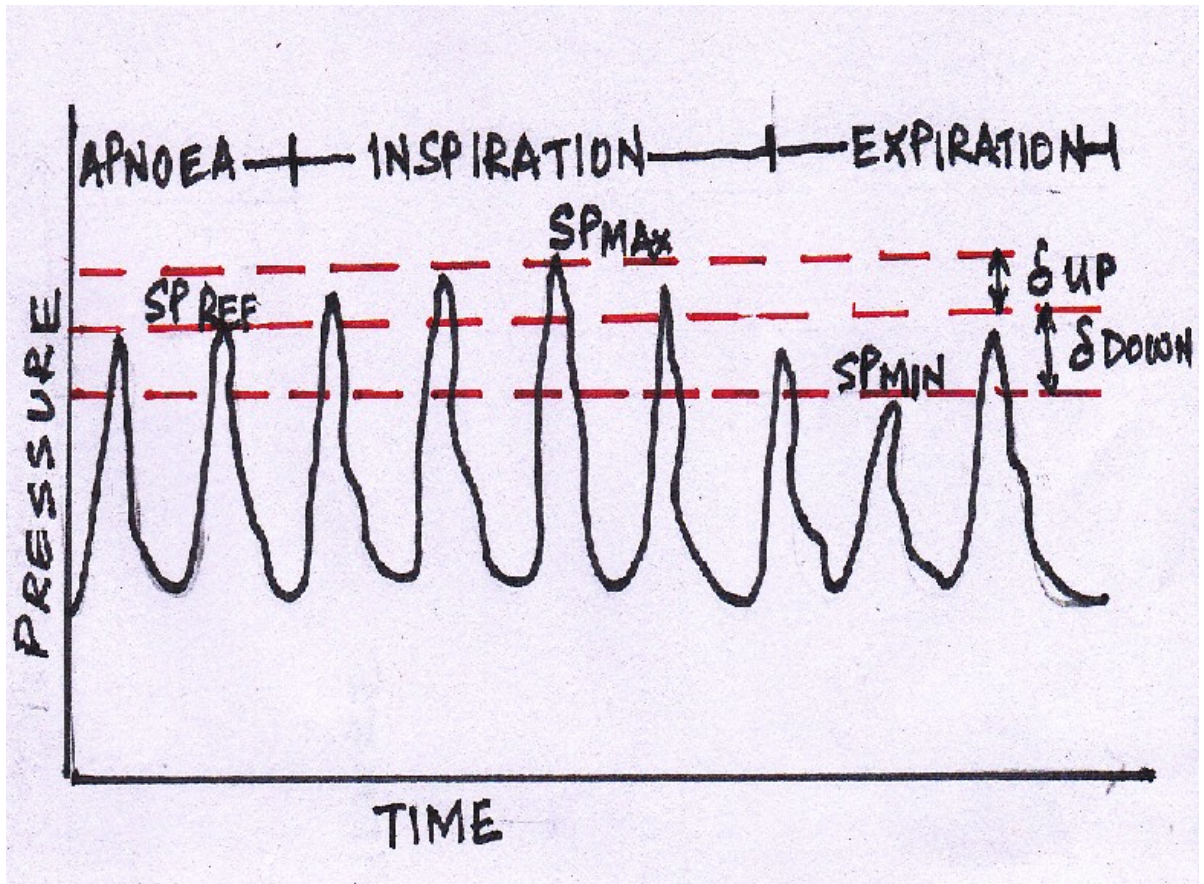
Figure 10: Systolic pressure variation.SP max- maximum systolic pressure during inspiration, SP min- minimum systolic pressure during expiration, SP ref – reference systolic pressure during apnoeic period. δ up = SP max – SP ref, δ down = SP ref – SP min

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PULSE PRESSURE VARIATION

Michard et al quantified variation in arterial pulse pressure with respiration using the following formula:

$$PPV = PPmax - PPmin / Ppmean,$$

where, PPmax is the maximum pulse pressure and PPmin is the minimum pulse pressure over a single mechanical breath and Ppmean is the mean of PPmax and PPmin. (42) **(Fig: 11)**
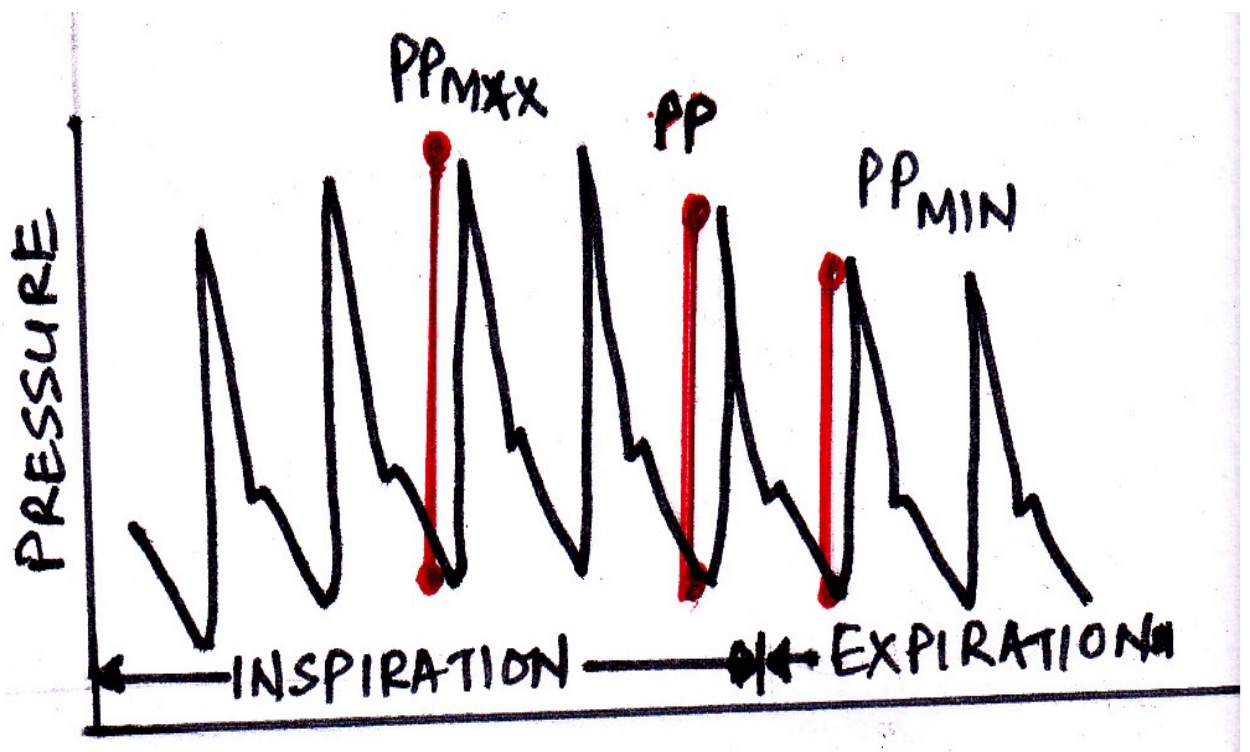
Figure 11: Pulse pressure variation.PP- pulse pressure , PP max – maximum pulse pressure during a single breath, PP min- minimum pulse pressure during a single breath.

STROKE VOLUME VARIATION

Pulse contour analysis computes the area under the systolic part of the pressure waveform based on the modified Wesseling algorithm. Variation of the stroke volume with respiration is calculated accurately when the time frame during which the calculations are made includes at least one complete respiratory cycle. (40)

SVV (%) = (SVmaximum -SVminimum) /SV mean

where, SV maximum and SVminimum are the maximum and minimum stroke volumes respectively and mean stroke volume of the values calculated over a particular time frame. **(Fig: 12)**
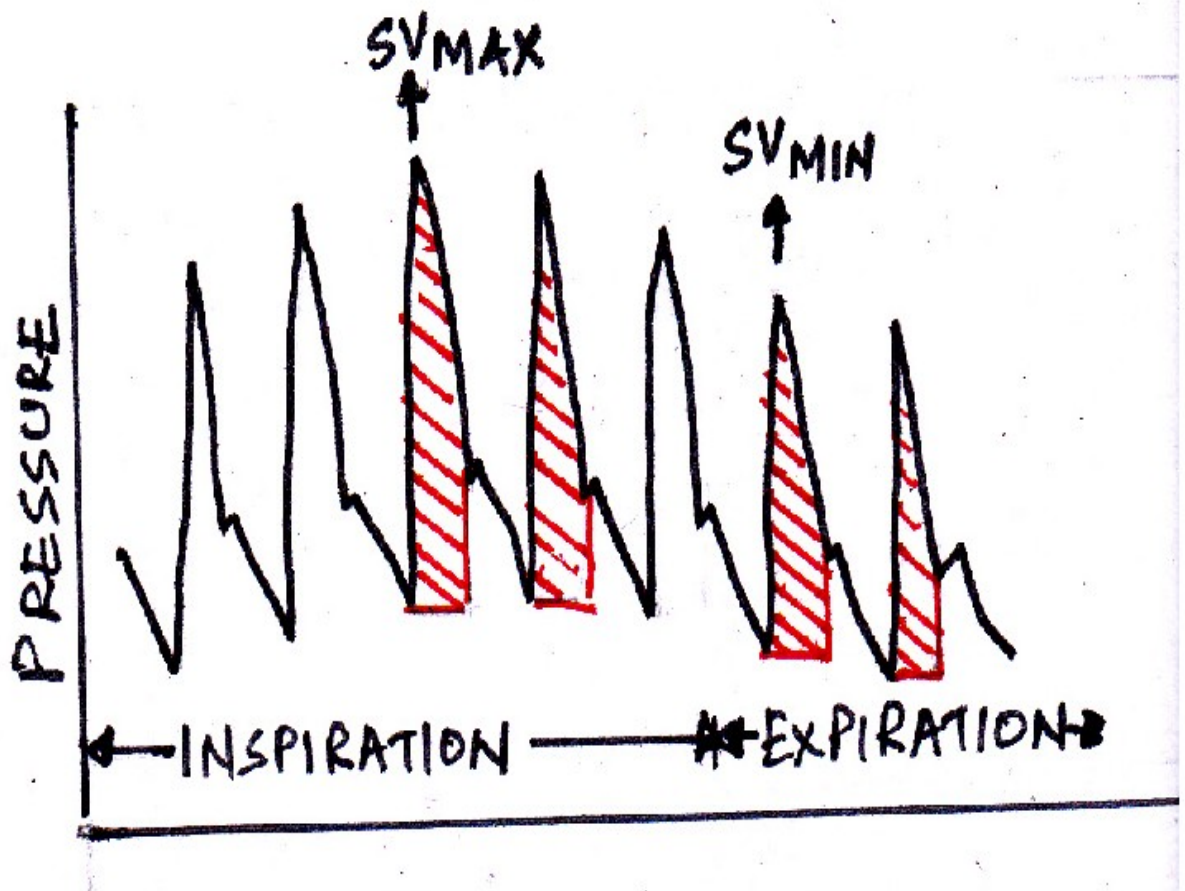
Figure 12: Stroke volume variation (SVV). SV max- maximum stroke volume during a mechanical breath, SV min – minimum stroke volume during a mechanical breath. Area under the systolic part of the arterial waveform represents the stroke work,

CLINICAL APPLICATION

The main applications of dynamic variables such as PPV and SVV are

- assessment of volume status and cardiac preload

- in predicting the hemodynamic response to intravascular volume expansion.

- In predicting hemodynamic response to positive end-expiratory pressure.

Rick and Burke, in 1978, were the first to establish a link between the variation in arterial pressure variation, then called the 'respirator paradox', and the volume status of critically ill patients.(43) Subsequently, many studies have shown that increasing the blood volume decreases the respiratory variation in the arterial pressure and vice versa. (44–46)

A fluid challenge should increase the cardiac preload and result in an increase the stroke volume and cardiac output (Frank-Starling mechanism). Predicting whether a patient is likely to respond to a fluid challenge would not only detect those who would benefit from fluid filling, but also avoid the hazards of unnecessary administration of intravascular fluids. Numerous studies have established the role of SPV, PPV and SVV in predicting responsiveness to fluid expansion.(44–48)

Application of positive end-expiratory pressure (PEEP) results in hemodynamic changes which may be deleterious. Increase in pleural pressure leads to a fall in the right ventricular filling; increase in the transpulmonary pressure causes a rise in the right ventricular

afterload. The above two changes are major determinants of respiratory variation of pulse pressure and stroke volume. When cardiac output falls with application of PEEP, pulse pressure variation increases with PEEP. If cardiac output is not affected by PEEP, PPV remains unaffected. (44,49)

Various factors affect the measurement of PPV and SVV. Technical factors such as clot formations, presence of air bubbles within the tubing, compliant tubing and excessive tube length can affect the dynamic response of the system.

THE PRONE POSITION

HEMODYANMIC CHANGES WITH CHANGE OF POSITION FROM SUPINE TO PRONE

The prone position was developed to enable surgical access for surgeries involving the back. However, the prone position is associated with a number of changes in the cardiovascular and respiratory physiology as well as complications as a result of the position, that need to be taken into account.

PHYSIOLOGICAL CHANGES

Backofen et al observed that when patients were moved from the supine to prone position, a decrease in cardiac index occurred. The main reason for the reduced cardiac output was a fall in the stroke volume; the heart rate remained more or less constant. A concomitant increase in the systemic vascular resistance maintained the mean arterial pressure. On the other hand, Yokoyama et al (50) observed that there were no significant hemodynamic changes on turning a patient to a flat prone position; however, on turning them onto a convex saddle frame, significant drop in cardiac output and stroke volume were observed. Other variables remained unchanged. It was suggested that the position of the heart at level that was higher that the limbs and head impeded venous return and caused a fall in the cardiac index. Various studies have confirmed the fall in cardiac output on turning prone. (51–53)

Pulmonary compliance is also decreased. The frame used to support the body or the surgical table applies pressure on the abdomen; this increased intra-abdominal pressure is referred to the diaphragm and the lungs resulting in a decrease in the pulmonary compliance. It manifests as a rise in peak airway pressures during mechanical ventilation.

The increased intrathoracic pressure has also been suggested as cause for the fall in cardiac output. A rise in the intrathoracic pressure causes a decrease in the arterial filling leading to a fall in the stroke volume. Baroreceptor inhibition as a result of the decreased arterial filling would cause an increase in the sympathetic activity. It is manifest as increased heart rate and total peripheral vascular resistance in prone patients. (54)

A decrease in the left ventricular compliance as a result of an increase in the intrathoracic pressure has also been suggested as a reason for fall in cardiac output.

Compression of the abdomen and viscera also results in compression of the blood vessels, mainly the inferior vena cava (IVC). This can result in decrease in venous return (preload) to the right heart and cause a fall in the stroke volume and cardiac output. Additionally, compression of the major intraabdominal vessels forces the blood to return via alternate pathways to the heart. One such alternate pathway is through the epidural plexus of vein, the engorgement of which during major spine surgery results in increased surgical blood loss.

The extent to which hemodynamic and pulmonary compliance changes occur vary with the type of frame used. In a study done on healthy volunteers, Waldsworth et al showed that

cardiac index significantly dropped in patients who were turned prone onto the Relton-Hall frame and knee-chest prone position (17% and 20% respectively) but not in those who were positioned on the evacuatable mattress and pillows(11% and 3%) respectively.(55)

PRONE POSITIONING FRAMES

THE ANDREW FRAME

It supports the patient in a kneeling position and does so by supporting the chest and allowing the abdomen to hang free. Patient is positioned in a modified knee-chest position with the help of a chest pad and a tibial support. The tibial support may be adjusted to obtain the required hip flexion. This support allows for better ventilation and prevents rise in intraabdominal pressure. Thigh support bolsters are essential to prevent the patient sliding off the table. The legs are at level below the heart and therefore there is risk of venous stasis.

THE RELTON-HALL FRAME

It consists of four individually adjustable supports which are placed in two V-shaped pairs, tilting inwards at and angle of 45 degree. (**Fig: 13**) It supports the antero-lateral pelvis and the lateral thoracic cage. The advantages of this support include that it reduces the intraabdominal pressure, tends to correct scoliosis, is adjustable for a variety of body habitus , is stable and can provide skeletal traction. However, it tends to increase lumbar lordosis which may make it unsuitable for lumbar disc surgeries. (56)
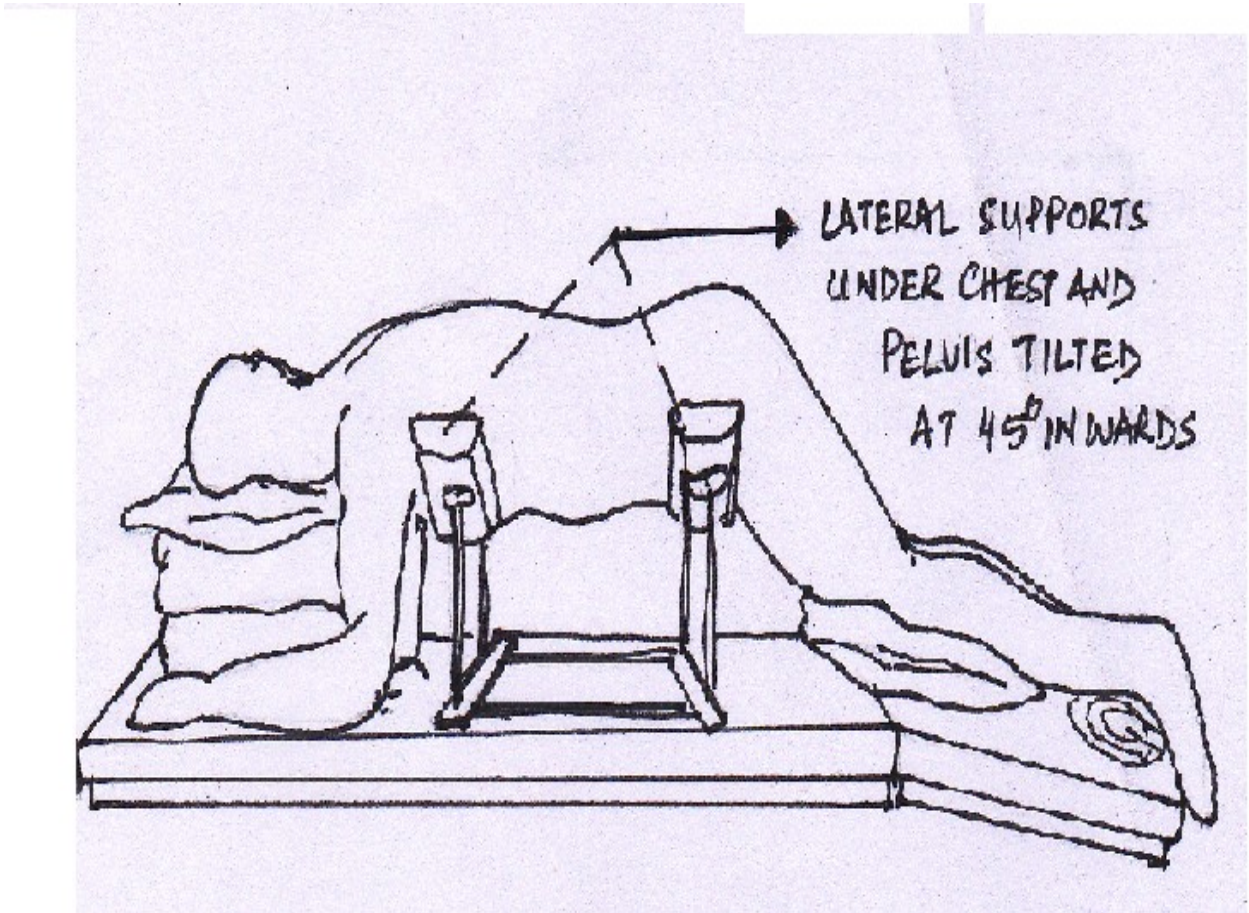
Figure 13: Patient positioned in the prone position on the Relton-Hall frame.

The Wilson frame is one of the simplest and most readily available frames. It consists of 2 curved full-length pads which provides support to the pelvis and chest. It can be adjusted laterally to relieve pressure on the abdomen. It provides good flexion of the lumbar spine and adequate decompression of the abdomen. The Wilson Plus frame which is a modification allows for complete radiolucency.(57) The Wilson frame has been associated with a higher incidence of post-operative vision loss as a result of ischemic optic neuropathy when compared to other frames. It was postulated that the reason for the same was the venous congestion that resulted from the position of the head below the heart. (58)

The choice of anesthetic used may influence the hemodynamic profile on turning prone. Sudheer et al(52) compared patients who received inhalational anesthetic with isoflurane to patients who receive total intravenous anesthesia(TIVA) with target controlled infusion of propofol. They found a significant drop in cardiac index in all patients on turning prone onto the Montreal mattress with a significantly greater fall in cardiac index in the patients who received TIVA.

All of the studies that have been done in patients undergoing surgery in the prone position have been on patients belonging to American Society of Anesthesiologist (ASA) Class I, II and III; majority belonging to the former two classes.(59–62)

Patients belonging to ASA Class II and Class III (for example, patients with controlled or uncontrolled diabetes mellitus and hypertension and ischemic heart disease) are often on

medications such as beta blockers, angiotensin receptor blockers, ACE inhibitors and nitrates. Additionally, autonomic dysfunction may be present in these patients.

PERIOPERATIVE AUTONOMIC DYSFUNCTION

The incidence of severe autonomic dysfunction is about 1 in 1000 individuals and is characterized by unpredictable responses to pharmacological and physiological stimuli. It may be primary or occur secondary to systemic illness such as diabetes mellitus. (63)

Autonomic dysfunction can occur as a result of dysfunction of the afferent limb , the autonomic center or the efferent limb. Supine hypertension results when dysfunction of the afferent limb is present, whereas dysfunction of the efferent limb or center results in orthostatic hypotension which may often be disabling.

In an individual with autonomic dysfunction, the couterregulatory effect of the barorecptor control is lost. Anesthetic agents further suppress the baroreceptor reflex and this patients are vulnerable to hypotension during to anesthesia. The loss of heart rate variability seen in many patients does not allow for appropriate cardiovascular response to acute changes in blood volume. Moreover, their response to vasopressors is unpredictable because of denervation hypersensitivity that exists.(63)

DIABETIC AUTONOMIC NEUROPATHY – CARDIOVASCULAR AUTONOMIC NEUROPATHY

Autonomic dysfunction is well documented in patients with diabetes mellitus. Although diabetic autonomic neuropathy can affect different organ systems, cardiovascular autonomic neuropathy (CAN) is the most important clinical form of diabetic autonomic neuropathy because of its life-threatening consequences.

CAN occurs because of damage to the autonomic nerves innervating the heart and blood vessels, resulting in abnormal control of heart rate and vasomotor responses.

A patient with CAN may present with one of the following : orthostatic hypotension, resting tachycardia, silent myocardial infarction, exercise intolerance.

Cardiovascular autonomic neuropathy is determined based on a battery of tests rather than a single test. Clinical tests available test both the parasympathetic and the sympathetic systems. (64)

Clinical tests of the parasympathetic nervous system:

Heart rate response to Valsalva maneuver: The Valsalva ratio is measured (ratio of longest to shortest R-R interval) in a seated subject who is made to blow in to a mouthpiece for 15 seconds while holding a pressure of 40 mm Hg. Normal value is >1.21

Heart rate response to standing: 30:15 ratio is measured as the patient stands from a supine position. A maximal tachycardia response seen around the 15th beat is normally followed by a bradycardia usually around the 30th beat. Ratio of the R-R interval at the30th (longest interval) to the 15th beat (shortest interval) is the 30:15 ratio. Normal value is >1.04

Heart rate response to deep breathing: The patient takes 6 deep breaths in a minute. Mean difference between the maximum and minimum heart rate during 3 breathing cycles is taken. Normal value is > 15 beats/minute.

Clinical tests of sympathetic nervous system:

Blood pressure response to standing: The difference between the standing systolic blood pressure and the resting supine systolic blood pressure is measured. Normal difference is < 10mm Hg.

Blood pressure response to sustained hand grip: Hand grip which is 30% of the maximum hand grip is maintained for 5 minutes. Normally, a difference of more than 16mmHg is observed between the initial diastolic blood pressure and the diastolic blood pressure just before release.

Involvement of the parasympathetic nervous system precedes the involvement of the sympathetic nervous system. Therefore, a positive test involving blood pressure changes

suggests severe autonomic dysfunction. Apart from the tests of autonomic dysfunction, diabetic autonomic dysfunction is characterised by resting tachycardia.

Perioperative management of patients with autonomic dysfunction should involve providing adequate hydration, maintaining euvolemic status and optimising pharmacological treatment. Hypotension is common during anesthesia and responds well to alpha 1 adrenoreceptor agonist such as phenylephrine. Indirect acting agents such as ephedrine may be less effective as they depend on the release of noradrenaline from postganglionic nerve fibers for their action; this may be lacking in this group of patients. (63)

Burgos et al in 1989 reported increased incidence of post-induction hypotension in diabetic patients with autonomic dysfunction.(65) Hemodynamic lability on induction of anesthesia in patients with autonomic dysfunction is well documented.(66,67).

Although autonomic dysfunction associated with diabetes has been well studied, autonomic nerve dysfunction also occurs in other conditions. Key among them are elderly patients, hypertensive patients, patients with coronary artery disease and patients on various medications such as calcium channel blockers, beta adrenergic blocking agents and angiotensin-converting enzyme inhibitors.

Hypotension following induction of anaethesia in patients on angiotensin receptor blockers (ARB) and angiotensin-converting enzyme inhibitors (ACEI)is a know complication. ACEI, because of its ability to inhibit angiotensin II mediated sympathetic response, may also reduce responsiveness to exogenous vasopressors used to treat the hypotension(68). Brabant

et al showed in their study that the incidence of hypotension was significant in patients on ARB than with other drugs, especially if these drugs were continued up to the day of surgery. The other group of drugs studied were ACEI, calcium channel blockers and beta blockers. Hypotension occurring in patients on ARB was more difficult to treat than that occurring in the other groups. (69) Rosenman et al found that patients receiving preoperative ARB /ACEI had higher incidence of intraoperative hypotension (RR 1.5, CI 1.15 – 1.96)(70)

The above mentioned studies have been performed on patients undergoing surgery in the supine position. Change of position from supine to prone will often cause an exaggerated hemodynamic response in patients with significant co morbid illnesses, more so in patients with autonomic dysfunction. (63)Presence of cervical spine pathology who have autonomic dysfunction also exhibit labile hemodynamic on turning to the prone position. (71)

This study observed the hemodynamic changes that occur in a specific group of patients belonging to either ASA Class II or III, on changing position from supine to prone. The Flo Trac/Vigileo™ system was used to measure the hemodynamic variables. It further observed the effect of fluid challenge of 10ml/kg of crystalloids administered to these patients before they were turned to the prone position.

MATERIALS AND METHODS

STUDY SETTING

This study was carried in the spine surgery(orthopedic) and the neurosurgery operating rooms. Subjects were selected the day before the surgery.

STUDY DESIGN

This study was designed to be an observational study.

CALCULATION OF SAMPLE SIZE

Biais et al , in their study *'Abilities of pulse pressure variations and stroke volume variations to predict fluid responsiveness in prone position during scoliosis surgery'* have reported that significant correlation between PPV and CO in prone position was 0.77. However, we expected a poor correlation in patients with co-morbid illnesses like diabetes mellitus, hypertension and ischemic heart disease. Therefore, we estimated the sample size with the correlation of around 0.4 to 0.5. Keeping Alpha and Beta errors at 5% and 20% respectively, we needed to study nearly 30 subjects.

Regression methods - Sample size for correlation coefficient analysis (testing against population value)			
Sample correlation coefficient	0.4	**0.5**	0.3
Population correlation coefficient	0	**0**	0
Power (1- beta) %	80	**80**	80
Alpha error (%)	5	**5**	5
1 or 2 Sided	2	**2**	2
Required sample size	47	**29**	85

SUBJECTS

Patients who belonged to ASA Class II or III with co-morbid illnesses such as diabetes mellitus, hypertension or ischemic heart disease and who were scheduled to undergo major instrumental spine surgery in the prone position were recruited after explaining the aims and objectives of the study and obtaining informed consent. The study was conducted over a period of 7 months. 31 patients were recruited; however 2 were excluded. One of the excluded patients had insufficient data and the other did not meet the inclusion criteria.

INCLUSION CRITERIA

- Age : 18-70 years

- ASA II or ASA III patient with co-morbid illnesses which included diabetes mellitus, hypertension and/or ishcemic heart disease.

- Undergoing elective major spine surgery in prone position.

EXCLUSION CRITERIA

- Age < 18 years, >65 years

- Left ventricular dysfunction or regional wall motion abnormality

- Emergency surgery

- ASA I/IV / V

- Valvular heart disease,

- Arrhythmia

- Pulmonary disease (COPD and asthma)

- Renal dysfunction

- BMI < 18kg/m^2 or > 40 kg/m^2

Data collection occurred within the confines of the operating theatre.

<u>METHODOLOGY</u>

After obtaining clearance from the Institutional Review Board (IRB), thirty-one patients belonging to American Society of Anesthesiologist (ASA) Class II and III undergoing elective major spine instrumentation surgery in the prone position were studied.

Major spine surgery was defined as

Posterior Lumbar Intervertebral Fixation (PLIF)

Transforaminal lumbar Intervertebral Fixation(TLIF)

Laminectomies in 3 or more levels with or without tumour excision.

Patients with valvular heart disease, chronic obstructive pulmonary disease, renal dysfunction , left ventricular dysfunction, valvular heart disease and arrhythmia were excluded from the study. Patients were recruited after obtaining informed consent on the day before the surgery.

In all patients, peripheral venous access was established using a large bore cannula. Percutaneous radial arterial cannulation was undertaken with a 20G cannula in an aseptic manner and after infiltration of local anesthetic (2% lignocaine). The standard technique or the transfixion technique was used. Needle-guidewire-catheter assemblies were used only in case of difficulty in cannulating the artery. The Flo Trac transducer was connected to the arterial line and zeroed after ensuring correct position at the mid-axillary level. The other monitors which included an electrocardiogram, pulse oximeter, end-tidal carbon dioxide, and temperature (post-induction) were connected and displayed using PHILIPS Intelli Vue MP50 monitor. A PHILIPS agent analyser was also used and the values displayed on the MP

50 monitor. Baseline values before induction (T0) were noted. Heart rate(HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) , mean arterial pressure (MAP) and pulse pressure variation (PPV) were displayed on the PHILIPS Intelli Vue MP50 or MP 40 monitor ,(**Fig:14**) whereas stroke volume variation(SVV), cardiac output (CO) and cardiac index (CI) were displayed on the Vigileo stand-alone monitor.

Following pre-oxygenation, induction of general anesthesia was carried out with fentanyl 2-4mcg/kg, propofol 2mg/kg and vecuronium 0.15mg/kg. After ventilating to ensure adequate time for the muscle relaxant to act, patients were intubated with appropriate endotracheal tube. Mechanical ventilation was established with intermittent positive pressure ventilation using volume controlled ventilation with tidal volumes of at least 8ml/kg. The ventilator used was DATEX-OHMEDA Aestiva /Aespire. Anesthesia was maintained with a mixture of air /oxygen and isoflurane titrated to an end-tidal value of 1.0(MAC value of 0.8).Following intubation, end-tidal carbon dioxide was maintained between 35 and 40mm Hg with inspired oxygen concentration of at least 0.40 (FiO_2). Muscle relaxation was maintained with boluses of vecuronium and analgesia was provided with intravenous morphine 0.1mg/kg and fentanyl as required. Before change of position all patients received crystalloids up to 10ml/kg. All variables were measured after establishing mechanical ventilation and before turning prone (T1)

Following preloading the patients with 10ml/kg of crystalloid, change in position from supine to prone was undertaken. This was done after ensuring complete muscle paralysis and an end-tidal isoflurane concentration of at-least 1.0(MAC of 0.8). Patients undergoing surgery under spine surgery were positioned on the Relton-Hall frame and patients

undergoing surgery under neurosurgery were positioned on 2foam bolsters, one under the chest and the other under the pelvis. Care was taken to ensure that the frames were positioned in such a manner so as to prevent abdominal compression. Ventilation was rechecked in the prone position. Head position was checked to ensure excessive neck flexion did not occur. Eyes were checked to ensure direct pressure on the eyeballs did not occur. Other position- related complications were looked for - excessive abduction at the shoulder was avoided, pressure over the axilla and the elbows was prevented with adequate padding, genitals in the male patients and breasts in the female patients were checked to ensure proper positioning and pressure points on the lower limbs were padded appropriately. All peripheral pulses were checked in the prone position.

The transducer of the Flo Trac was adjusted to the mid-axillary level and zeroed again. Five minutes after prone positioning, readings were noted for all variables(T2). Readings were noted every 5 minutes thereafter until skin incision.(T3 - Tn).

A fall in cardiac index by more than 25% from baseline (T1) warranted treatment with fluid bolus using crystalloids up to 10ml/kg and/or boluses of vasopressors such as ephedrine 6mg if heart rate was <80 beats per minute or phenylephrine 50-100mcg if heart rate was>80beats per minute. Failure to respond to fluid bolus up to 10ml/kg and repeated doses of vasopressors warranted institution of hemodynamic support with noradrenaline infusion.

Figure 14: PHILIPS Intelli Vue MP 40 monitor displaying ECG, HR (heart rate), ABP (arterial blood pressure) with waveform, SpO_2(saturation) with waveform, $etCO_2$ (end-tidal carbon dioxide) with waveform, PPV (pulse pressure variation), MAC (minimum alveolar concentration) of Isoflurane , Temp (nasopharyngeal temperature) , RR (respiratory rate), inO_2 and etO_2(inspired and expired oxygen concentrations) and inISO and etISO (inspired and expired isoflurane concentration)

STATISTICAL ANALYSIS

Since skin incision occurred in more that half the patients after 15 minutes of turning prone, analysis of the collected data was done only up to T4 (15 minutes after turning prone).

The data obtained was entered into an Excel spread sheet. Statistical analysis was performed using the SPSS software. All the hemodynamic variables were entered as continuous variables and the mean (+/-SD) of each variable at each time was computed.

A General Estimating Equations (GEE) analysis was performed to analyze the change in hemodynamic variables across the various time points. For this analysis, T1 (baseline, post-induction, supine) was taken as the reference. Variables at T2 (5 minutes after turning prone), T3 (10 minutes after turning prone) and T4 (15 minutes after turning prone) were compared to T1 and change in these variables along with the significance of change (p value) was computed.

A paired t-test analysis was additionally done between time points T1 and T4 . Mean values of the variables along with the mean change in the variables were calculated. This analysed whether the change in the variables was significant from T1 to T4.

Correlation between variables (PPV and CO, SVV and CO and PPV and SVV) were assessed in the prone position at two time points. Pearson correlation test was used for this purpose. The correlation coefficient (r) was calculated and correlation was described as positive, negative or inverse. The strength of correlation was also assessed was well as the

significance.

Levene's test for Equality of Variance was used to analyse the difference in variables among patients on differing prone supports and among diabetic versus non-diabetic patients. Mean values of the variables in each group was calculated and presence of any significant difference between values was examined.

PARTICIPANT FLOW CHART

31 patients recruited

2 excluded
- did not met criteria
-insufficient data

29 patients included
in study

SUPINE POSITION

Anesthesia induced
T1 reading of all
variables taken
10ml/kg crystalloid
administered

Patient turned
prone

PRONE POSITION

T2 to Tn readings taken
5 minutes apart.

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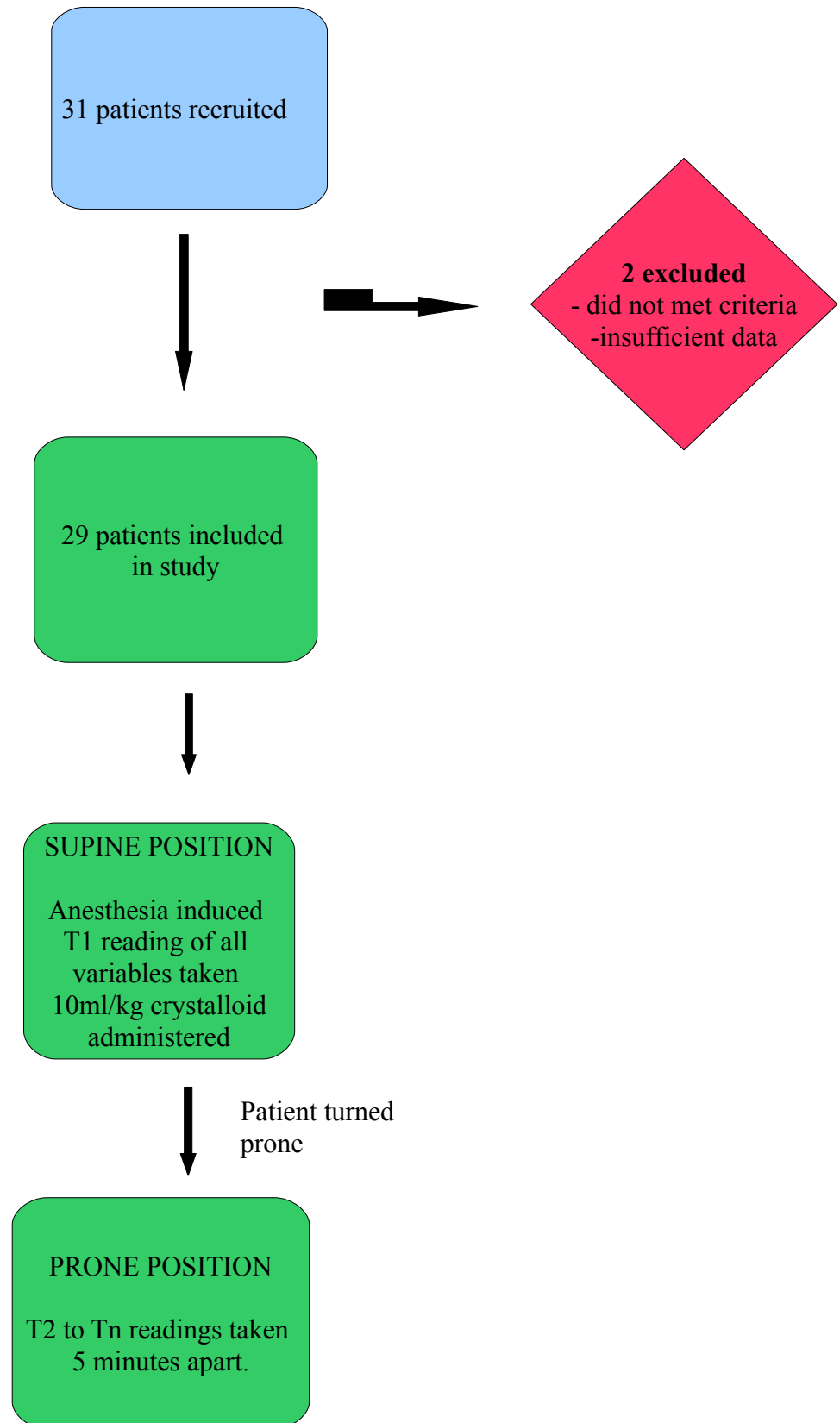
RESULTS

A total of thirty one patients were recruited for this observational study. Of the 31 patients, 1 did not meet the inclusion criteria and the other had missing data. Analysis was therefore done on data collected from twenty-nine patients. Heart rate (HR), Systolic Blood pressure (SBP), Diastolic Blood pressure (DBP), Mean Arterial Pressure (MAP) and Pulse Pressure Variation (PPV) were displayed on the PHILIPS Intelli Vue MP50 monitor and Stroke Volume Variation (SVV), Cardiac Output (CO) and Cardiac Index (CI) were displayed on the Flo Trac Vigileo monitor.

The age ranged from 41 to 70 years with a mean age of 56.4 years. Majority of the patients were female (62.1%). Approximately half the patients were in the normal range for body mass index (BMI) and the rest were overweight or belonged to grade I obesity category. Most of the patients belonged to ASA II (89.7%). The co-morbid illnesses seen in these patients were hypertension, diabetes mellitus and ishcemic heart disease in decreasing order of frequency. Most of the patients underwent orthopedic spine surgery and were positioned on the Relton-Hall frame (82.8%); the rest who underwent neurosurgical spine surgery procedures were positioned on foam bolsters positioned horizontally across the chest and pelvis **(Table 1)**.

Table 1: Demographic details of participants

Characteristics	
Age in years, Mean ± SD (range)	56.4 +/- 7.8 (41-70)
Gender	
Male, n (%)	11 (37.9)
Female, n (%)	18 (62.1)
Height in cm, Mean ± SD (range)	156.1 +/- 9.5 (140-174)
Weight in kg, Mean ± SD (range)	61.6+/- 11.2 (44 -90)
BMI in kg/m^2	
Normal (18.5 – 24.9), n (%)	16 (55.2)
Overweight (25- 29.9), n (%)	8 (27.6)
Obesity (30-34.9), n (%)	5 (17.2)
ASA Status	
ASA II, n (%)	26 (89.7)
ASA III, n (%)	3 (10.3)
Co-morbid illnesses	
Diabetes mellitus, n (%)	15 (51.7)
Hypertension, n (%)	24 (82.8)
IHD, n (%)	3 (10.3)
Type of support	
RH frame, n (%)	24 (82.8)
Bolsters, n (%)	5 (17.2)

Abbreviations: ASA – American Society of Anesthesiologists; BMI-Body Mass Index; IHD

– Ischemic Heart Disease; RH – Relton Hall; SD – Standard Deviation

Haemodynamic variables were assessed at various time points from baseline (T1 – values after induction in the supine position) to different time points five minutes apart after turning the patient prone. (T2, T3, T4 – 5, 10 and 15 minutes after turning prone respectively). The mean values of all the variables over these time periods are described in table 2.

<u>**Table 2**: Haemodynamic variables before and after turning prone</u>

Haemodynamic variables	Baseline (T1)	T2	T3	T4
HR (mean ± SD)	86.6 +/-16.08	85.03+/-16.12	81.55 +/-16.49	76.04+/- 16.31
SBP (mean ± SD)	125.16+/-23.67	111.69+/-27.38	116.45+/-25.76	102.8+/-17.97
DBP (mean ± SD)	67.16+/-10.7	63.28+/-17.34	62.72+/-17.45	61.52+/-14.27
MAP (mean ± SD)	88.16+/-16.54	80+/-20.71	83.24+/-18.01	76.04+/-16.26
SVV (mean ± SD)	11.29+/-4.85	14.86+/-5.36	14.5+/-4.73	14.79+/-3.78
PPV (mean ± SD)	11.04+/-4.51	14.67+/-5.24	13.84+/-4.72	14.67+/-5.05
CO (mean ± SD)	5.59+/-2.33	4.86+/-2.62	4.92+/-1.42	4.12+/-1.06
CI (mean ± SD)	3.46+/-1.72	2.90+/-1.47	3.02+/-0.75	2.52+/-0.57

Abbreviations: CI - cardiac index; CO - cardiac output; DBP – diastolic blood pressure; HR – heart rate; MAP – mean arterial pressure; PPV – pulse pressure variation; SBP – systolic blood pressure; SVV – stroke volume variation

A General Estimating Equations (GEE) analysis **(Table 3)**was performed to analyse the change in variables from baseline (T1 – values after induction in the supine position) through different time points five minutes apart after turning the patient prone. (T2, T3, T4 – 5, 10 and 15 minutes after turning prone respectively.)

Table 3: Change in variables across time points T2 to T4 as compared to baseline T1

	T1 - baseline	T2 (p value)	T3 (p value)	T4 (p value)
HR	-	-1.59 (0.481)	**-5.06 (0.009)**	**-10.07 (<0.001)**
SBP	-	**-11.58 (0.025)**	-6.82 (0.286)	**-20.83 (<0.001)**
DBP	-	-2.58 (0.376)	-3.13 (0.355)	-4.93 (0.152)
MAP	-	-6.72 (0.078)	-3.48 (0.430)	**-11.2 (0.014)**
PPV	-	**2.9 (0.020)**	2.04 (0.122)	**3.10 (0.024)**
SVV	-	**3.31 (0.002)**	**2.9 (0.010)**	**3.33 (0.002)**
CO	-	-0.57 (0.185)	-0.54 (0.139)	**-1.34 (<0.001)**
CI	-	-0.55 (0.087)	-0.38 (0.192)	**-0.87 (0.003)**

Abbreviations: CI - cardiac index; CO - cardiac output; DBP – diastolic blood pressure; HR – heart rate; MAP – mean arterial pressure; PPV – pulse pressure variation; SBP – systolic blood pressure; SVV – stroke volume variation

HEART RATE:

Heart rate showed a downward trend (Fig:15) following turning prone with significant change noted 10 and 15 minutes after the position was assumed. (p<0.01)
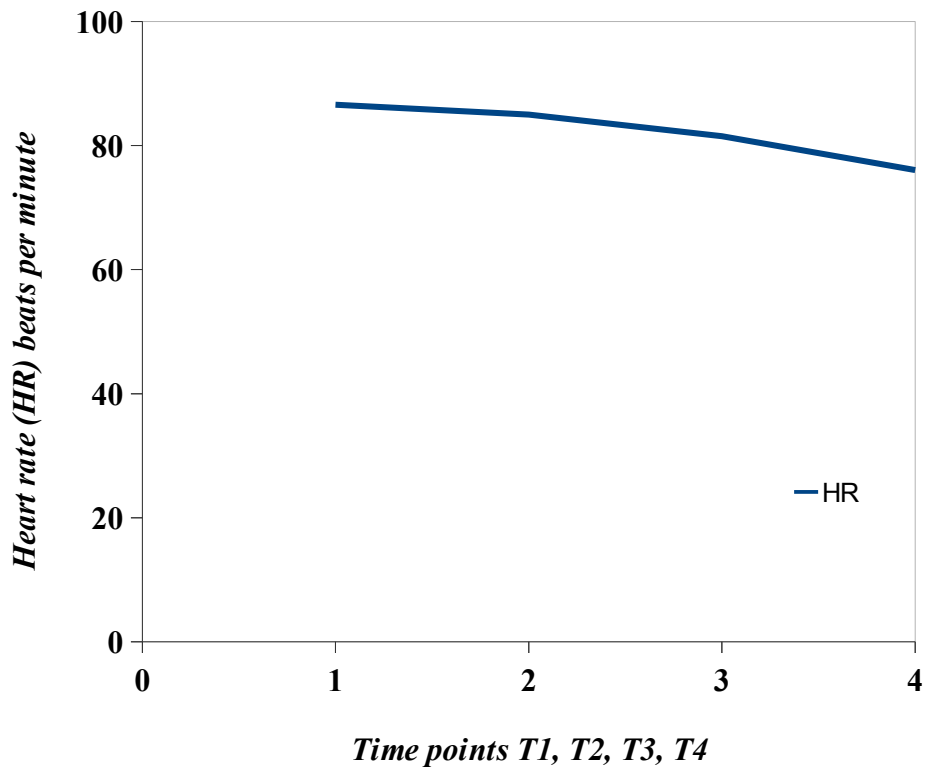
Figure 15 : Trend of heart rate from supine (T1) to prone (T2,T3,T4)

SYSTOLIC BLOOD PRESSURE

Significant fall in systolic blood pressure (p=0.025) was noted 5 minutes after turning prone and 15 minutes after turning prone (p<0.001). Although there was a fall in SBP as compared to baseline value 10 minutes after change of position, it was not significant.(**Fig:16**)
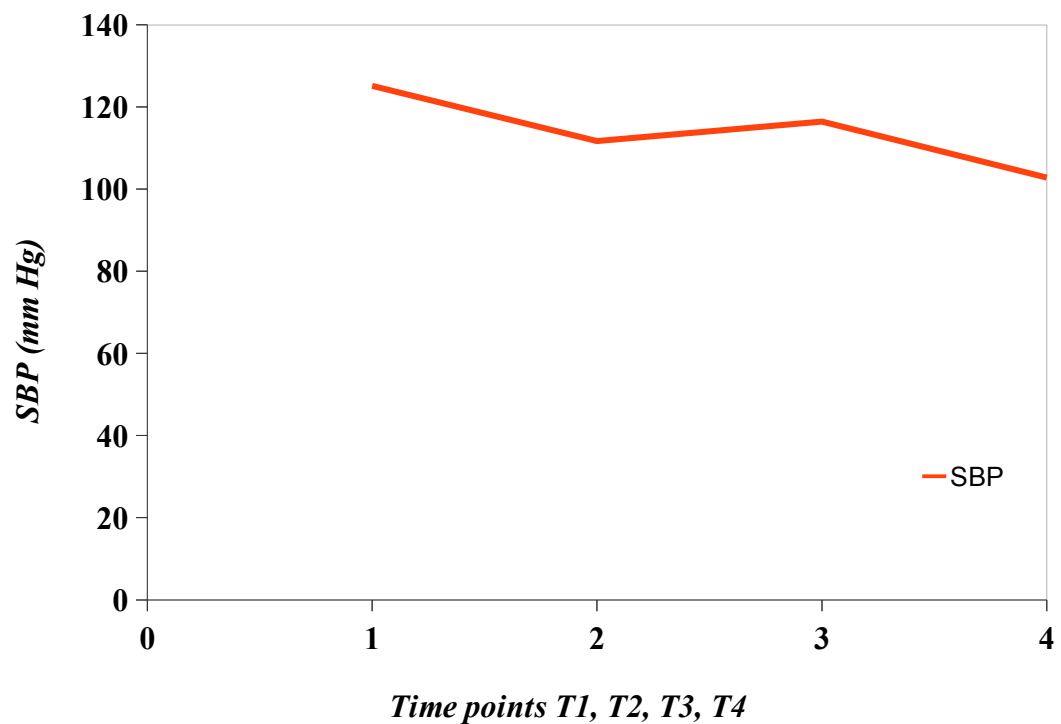
Figure 16: Trend of Systolic Blood Pressure (SBP) from supine T1 to prone (T2,T3, T4)

DIASTOLIC BLOOD PRESSURE

Although there was a decrease in the trend of diastolic blood pressure on turning prone, the change was not found to be significant at any time point.(Fig:17)
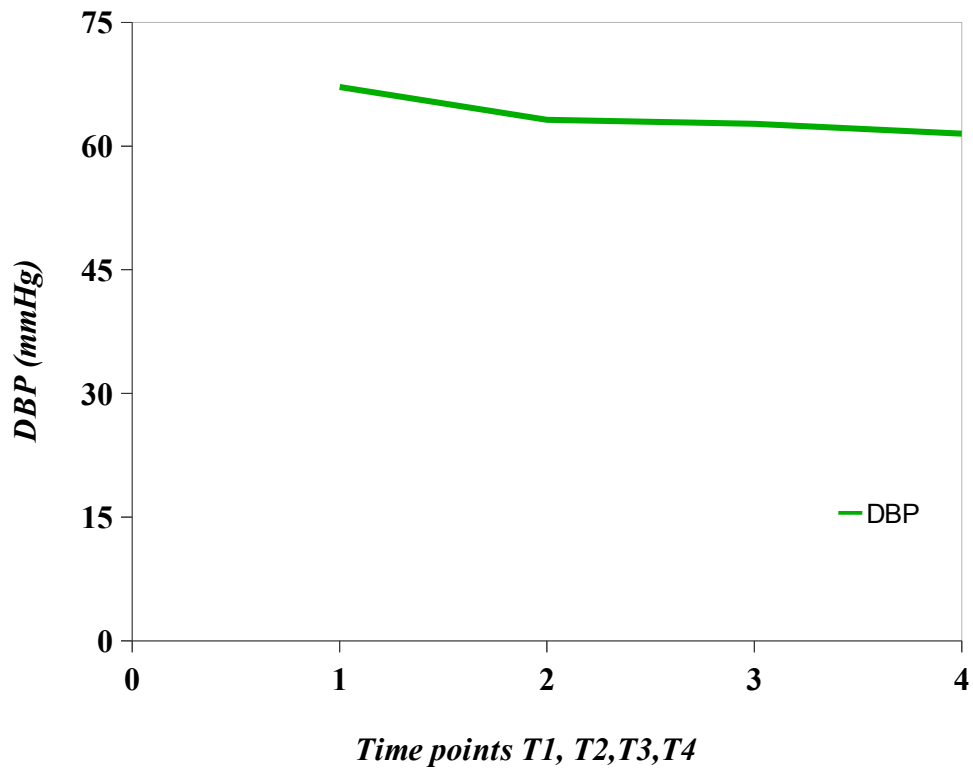
Figure 17 :Trend of Diastolic Blood Pressure (DBP) from supine T1 to prone (T2, T3,T4)

MEAN ARTERIAL PRESSURE

Fall in MAP was significant 15 minutes after changing to prone position. (p= 0.014)
(**Fig:18**)
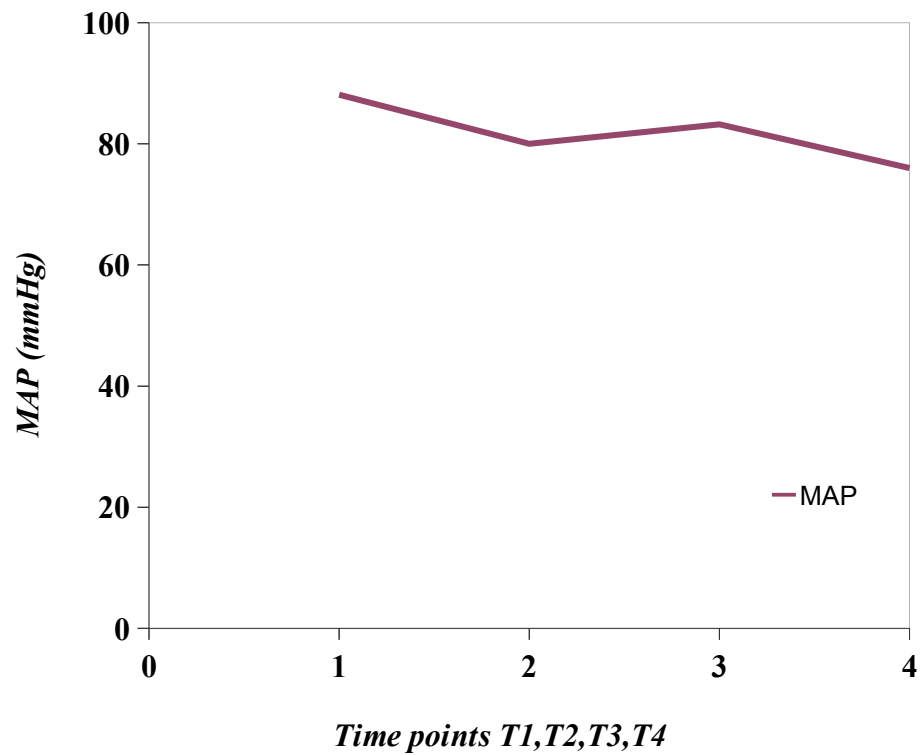
Figure 18: Trend of Mean Arterial Pressure (MAP) from supine T1 to prone (T2, T3,T4)

PULSE PRESSURE VARIATION

The rise in PPV with change in position **(Fig: 19)** to prone was significant at 5 minutes (p=0.020) and at 15 minutes (p=0.024)
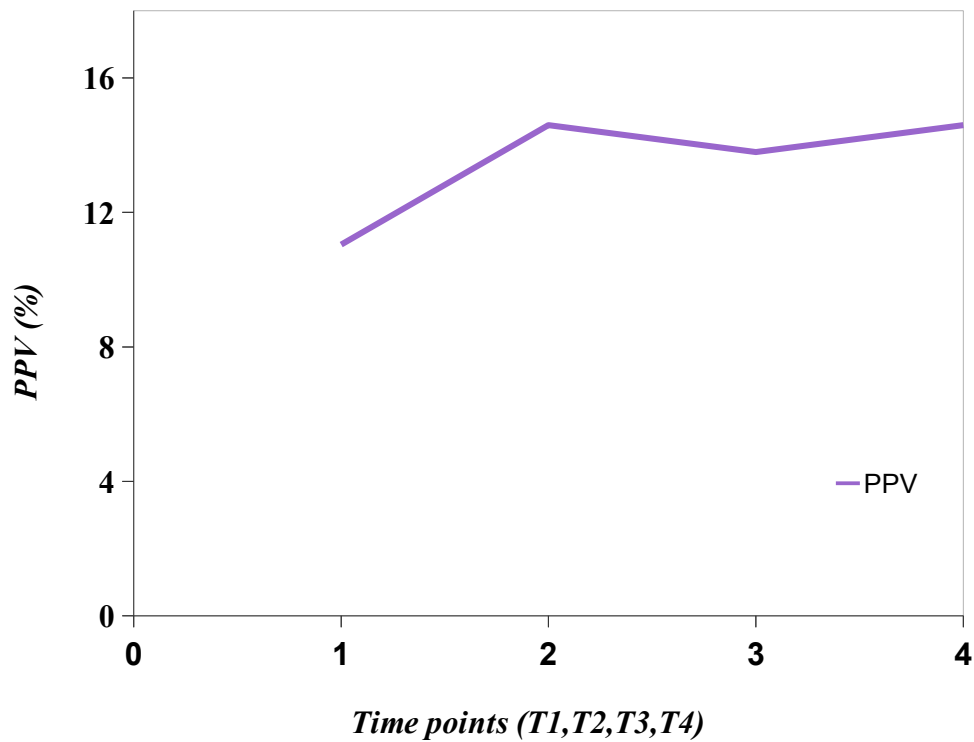
Figure 19 : Trend of Pulse Pressure Variation (PPV) from supine T1 to prone (T2,T3,T4)

STROKE VOLUME VARIATION

The increase in SVV **(Fig:20)** on turning prone was found to be significant at all time points (p = 0.002,0.010 and 0.002 at 5, 10 and 15 minutes respectively).
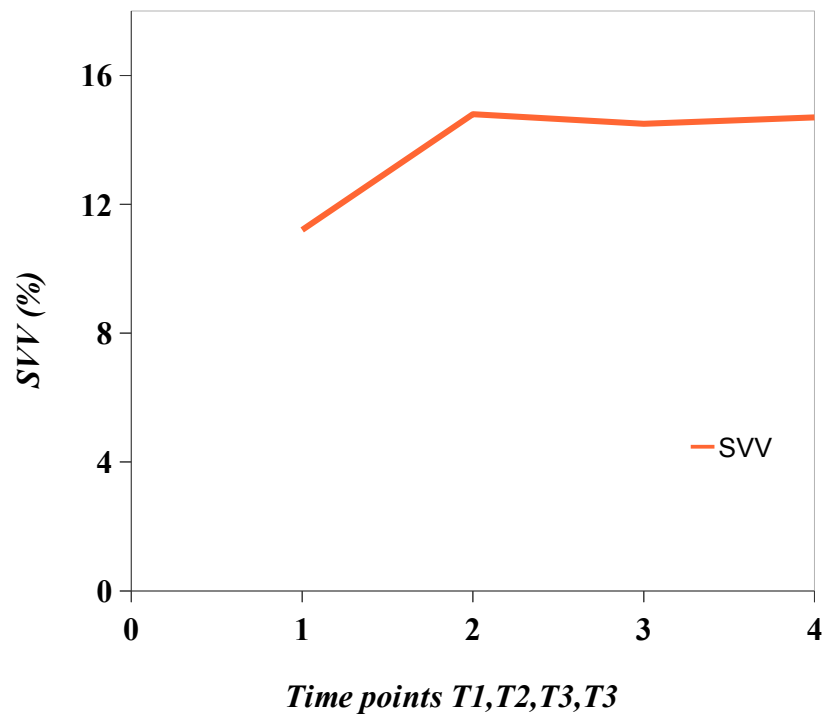
Figure 20 : Trend of SVV from supine T1 to prone (T2,T3,T4)

CARDIAC OUTPUT

Significant fall in cardiac output occurred at 15 minutes after tuning prone (p<0.001).

(Fig:21)
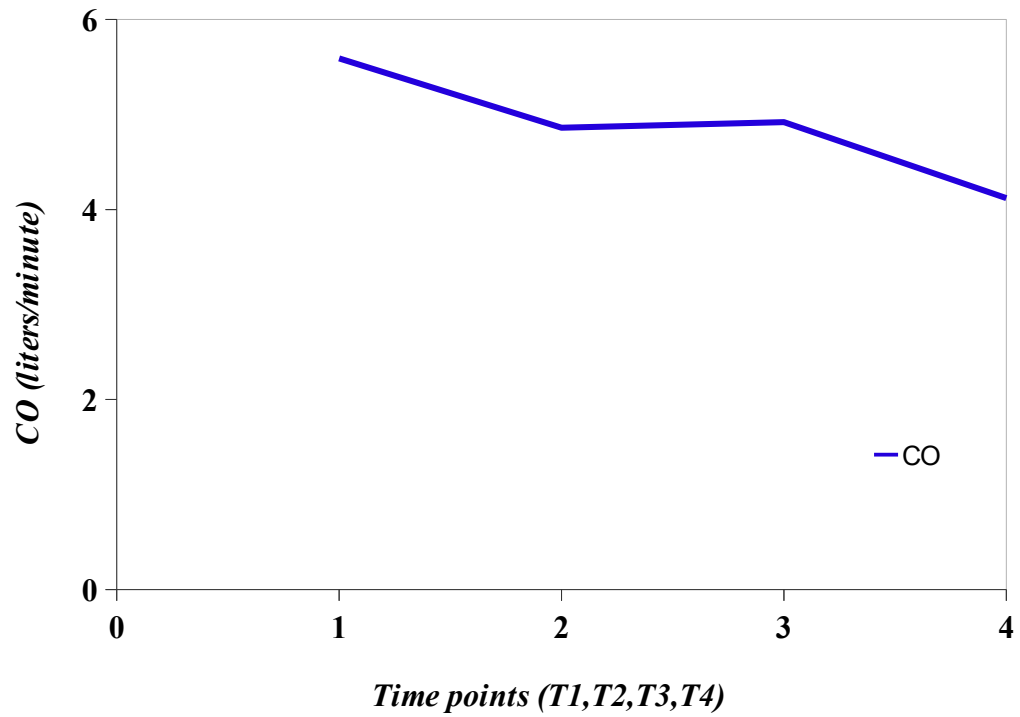
Figure 21 : Trend of Cardic output from supine T1 to prone (T2,T3,T4)

CARDIAC INDEX

Fall in cardiac index **(Fig:22)** was significant at 15 minutes after change in position to prone (p=0.003).
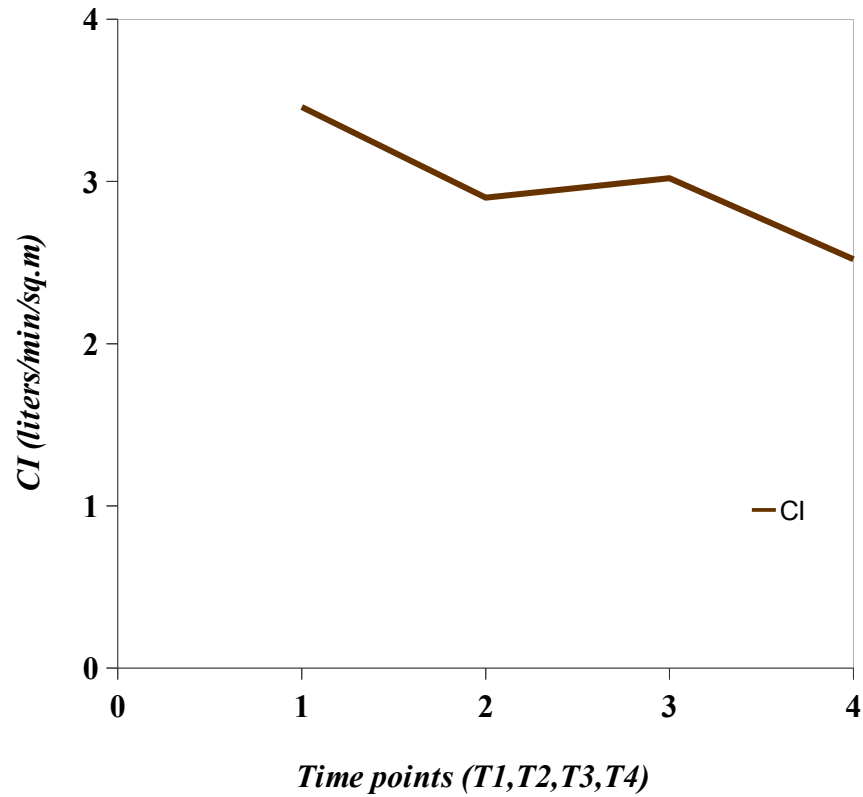
Figure 22:Trend of Cardiac Index from supine T1 to prone (T2,T3,T4)

Comparison between T1 and T4 using paired t-test revealed statistically significant changes in the various haemodynamic parameters (Table 4). Except DBP, all other variables showed a significant change at time T4.

Table 4: Change in variables from T1 to T4 (paired t-test)

Haemodynamic variables	Baseline (T1)	T4	Difference	95% CI	p-value
HR (mean ± SD)	86.6 +/-16.08	76.04+/-16.31	10.56+/-11.96	5.61-15.5	<0.001
SBP (mean ± SD)	125.16+/-23.67	102.8+/-17.97	22.36+/-30.68	9.69-35.02	0.00 1
DBP (mean ± SD)	67.16+/-10.7	61.52+/-14.27	5.64+/-18.07	-1.820-13.1	0.13
MAP(mean ± SD)	88.16+/-16.54	76.04+/-16.26	12.12+/-24.48	2.01-22.22	0.02
SVV (mean ± SD)	11.29+/-4.85	14.79+/-3.78	-3.5+/-5.16	-5.68 - -1.31	0.03
PPV (mean ± SD)	11.04+/-4.51	14.67+/-5.05	-3.63+/-6.87	-6.52- -0.72	0.02
CO (mean ± SD)	5.59+/-2.33	4.12+/-1.06	1.46+/-2.05	0.61 – 2.31	0.0 2
CI (mean ± SD)	3.46+/-1.72	2.52+/-0.57	0.95 +/-1.67	0.24 – 1.65	0.01

Abbreviations: CI - cardiac index; CO - cardiac output; DBP – diastolic blood pressure; HR – heart rate; MAP – mean arterial pressure; PPV – pulse pressure variation; SBP – systolic blood pressure; SVV – stroke volume variation

CORRELATION STUDIES

Correlations were assessed for PPV and CO, SVV and CO and PPV and SVV using Pearson Correlation.(Table 5)

Table 5 : Correlations between SVV and PPV with CO at T2 an T4

Correlations	Pearson's correlation coefficient	
	T2	T4
PPV and CO	-0.15	-0.16
SVV and CO	-0.37	-0.06
PPV and SVV	**0.83 ***	**0.75 ***

*p<0.001

<u>PPV and CO:</u>

A weak inverse correlation was found at T2 (r= -0.15; p= 0.452) and T4 (r = -0.16; p=0.434).

SVV and CO:

A weak inverse correlation was found to exist between SVV and CO at T2 (r= -0.374; p=0.046) and T4 (r=-0.061; p=0.777)

PPV and SVV

A strong positive correlation was found to exist between SVV and PPV at T2 (r=0.835; p=<0.001) and T4 (r=0.75; p<0.001).

COMPARISON OF HEMODYNAMIC VARIABLES BETWEEN DIFFERENT PRONE SUPPORTS

Hemodynamic variables of the patients who were positioned on the Relton-Hall frame were compared to those of the patients placed on foam bolsters. Statistical analysis was carried out using Levene's test for Equality of Variances . (Table 6)

Heart rate and cardiac index were the two variables which showed significant change over the time period based on the type of support used. ($p=0.02$ for HR and $p=0.03$ for CI). None of the other variables changed significantly as a result of the difference in prone support used. (Table 6)

Table 6: Comparison of hemodynamic variables on Relton-Hall frame versus foam bolsters.

	Relton-Hall frame	Foam bolsters	95% CI (confidence interval)	p value
HR(mean+/-SD)	84.2+/-16.7	74.7+/-15.5	1.47-17.6	**0.02**
SBP(mean+/-SD)	115+/-25.3	108.8+/-24.1	-6.11-18.5	0.32
DBP(mean+/-SD)	63.5+/-15.4	62.8+/-15.6	-6.81 – 8.29	0.85
MAP(mean+/-SD)	82.2+/-18.45	79.4+/-18.7	-6.25-11.83	0.54
SVV(mean+/-SD)	13.9+/-5.17	13.55+/-5.88	-2.19-3.0	0.76
PPV(mean+/-SD)	14.1+/-5.37	11.7+/-4.54	-0.35-5.03	0.08
CO(mean+/-SD)	4.96+/-2.13	4.30+/-0.99	-0.3-1.63	0.18
CI(mean+/-SD)	3.11+/-1.33	2.45+/-0.6	0.05-1.23	**0.03**

Abbreviations: CI - cardiac index; CO - cardiac output; DBP – diastolic blood pressure; HR – heart rate; MAP – mean arterial pressure; PPV – pulse pressure variation; SBP – systolic blood pressure; SVV – stroke volume variation

COMPARISON OF HEMODYNAMIC VARIABLES BETWEEN DIABETIC AND NON-DIABETICS

Hemodynamic variables of the patients who were diabetic were compared to those of the patients who were not. Statistical analysis was carried out using Levene's test for Equality of Variances . **(Table 7)**

No statistical significance was found in any of the hemodynamic variables between diabetic and non-diabetic patients**(Table 7)**

Table 7: Comparison of hemodynamic variables between diabetic and non-diabetic

patients

	Diabetics	Non-diabetics	95% confidence interval	p value
HR (mean+/-SD)	83.1+/-14.7	81.9+/-18.8	-5.09-7.56	0.7
SBP(mean+/-SD)	115+/-26.4	112.8+/-24	-7.26-11.66	0.65
DBP(mean+/-SD)	62.6+/-16.7	64.2+/-13.6	-7.33-4.22	0.6
MAP(mean+/-SD)	81.7+/-19.1	81.6+/-17.8	-6.89-6.98	0.99
SVV(mean+/-SD)	13.4+/-5.3	14.2+/-5.2	-2.81-1.18	0.42
PPV(mean+/-SD)	13.2+/-4.8	14.1+/-5.6	-2.93-1.17	0.4
CO(mean+/-SD)	5.1+/-2	4.5+/-1.8	-0.17-1.31	0.13
CI(mean+/-SD)	3.1+/-1.2	2.8+/-1.3	-0.18-0.76	0.23

Abbreviations: CI - cardiac index; CO - cardiac output; DBP – diastolic blood pressure; HR – heart rate; MAP – mean arterial pressure; PPV – pulse pressure variation; SBP – systolic blood pressure; SVV – stroke volume variation

<u>DISCUSSION</u>

In this study, I found that although cardiac output and cardiac index did not immediately decrease in the prone position, there was a significant decrease these variables at a later time point. SVV and PPV showed significant change immediately following position change (5 minutes) and at a later time point (15 minutes).

Surgery of the spine performed in the prone position is associated with multiple hazards, of which those relating to hemodynamic changes are most acute and may be life-threatening. Change of position to prone in associated with a decrease in the cardiac output. Yokoyama et al found a significant fall in cardiac index and stroke volume when positioning patients on a convex saddle as opposed to a flat surface(50)

The data from this study shows that there was a significant increase in PPV and SVV within 5 minutes of turning prone. Biais et al reported an increase in SVV and PPV on turning prone in their study (59)This phenomenon may be explained by different mechanisms.

Positioning the patient in the prone position causes the heart to be at a higher hydrostatic level as compared to the lower limbs. Such a position would impede the venous return. This results in a fall the preload to the right side of the heart. Decrease in the right ventricular preload causes more pronounced cyclic variations produced by mechanical ventilation and is manifest as an increase in the PPV and SVV.

A decrease in the chest compliance is often recognised during change in position from supine to prone. This is often the result of abdominal compression due to improper

positioning on the prone frame. A fall in the compliance of the chest could impede venous return and subsequently cause an increase in the SVV. Although care was taken to ensure that the abdomen hung free, change in the compliance of the respiratory system was not monitored in this study. Moreover, intra-abdominal pressure monitoring was not undertaken. Hence it is difficult to ascertain whether rise in abdominal pressure caused a rise in PPV and SVV.

Although there was a change in the cardiac output and cardiac index after 5 minutes of prone position, it was not a significant change (p=0.185 p= 0.087 respectively). All patients received 10ml/kg of crystalloids before they were turned to the prone position. This suggests that the preload that was administered may have prevented a fall in the cardiac output and cardiac index. However, it is not possible with this study to determine that preload prevented a fall in the cardiac output; a randomized control study with patients who received preload and who did not receive preload would be needed to determine the same.

There was a significant fall in the systolic blood pressure 5 minutes after turning prone (p=0.025). Blood pressure is the product of cardiac output and systemic vascular resistance(SVR).

Blood pressure = cardiac output X systemic vascular resistance.

Significant change in mean arterial pressure (MAP) did not occur. Fall in cardiac output did occur, although it was statistically insignificant. It can be postulated that there was probably an increase in the SVR which maintained the MAP even with fall in the cardiac

output/index. This this has been explained to occur in earlier studies with ASA I and ASA II patients, In the absence of a central venous catheter, is is not possible to measure SVR using Flo Trac. Pump et al postulated that a decrease in the arterial pressure causes baroreceptor inhibition which leads to sympathetic stimulation and an increase in the systemic vascular resistance.(54)

Ten minutes following prone position, a significant fall was noted in the heart rate (p=0.009) and in the SVV (p=0.010). Change in the other variables (SBP, DBP, MAP, PPV, CO and CI) were not found to be significant. A lack of surgical stimulus while patient was being prepared for surgery would explain the fall in heart rate.

Fifteen minutes after assuming the prone position, significant fall was noted in HR, SBP, MAP, CO and CI (p<0.001, p<0.001, p=0.014, p<0.001 and p=0.003 respectively) and significant rise in SVV and PPV were noted (p=0.002 and p=0.024 respectively). Poon et al, in their study , found significant change in heart rate, stroke volume, cardiac index and blood pressure 10 minutes after change of position to prone.(53)Anesthetic agents cause fall peripheral vasodilation and myocardial depression. Peripheral vasodilation causes a fall in the systemic vascular resistance. Myocardial depression causes a fall in the stroke volume and cardiac output. Combination of the above mentioned factors along with a lack of surgical stimulus could explain the fall in the HR, SBP, MAP, CO and CI. In a vasodilated patient, the variations of pulse pressure and stroke volume with respiration would be more prominent and result in higher SVV and PPV values.

Additionally, administration of analgesic agents such as morphine could have further caused

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fall in peripheral venous tone and vascular resistance. Morphine has been shown to have parasympathomimetic and sympatholytic effects as well as effects on the baroreceptor reflex.(72,73) Since there is no data available on the time of administration of morphine, it is not possible to ascertain whether this caused significant changes or not.

The pulse pressure is directly proportional to the stroke volume and inversely proportional to the vessel (arterial) compliance. If the arterial compliance remains constant, the changes in stroke volume will vary only with changes in the pulse pressure with respiration.(40) In the Pearson Correlation done for SVV and PPV, a similar result was obtained. In the prone position, SVV was found to have a strong significant positive correlation with PPV($p<0.001$). Biais et al also found similar correlation between SVV and PPV in prone position in their study ($r=0.77$; $p<0.0001$)(59)

However, a weak correlation was found to exist between SVV and CO ($r= -0.374$, $p=0.046$ at T2 and $r=0.061$, $p=0.777$ at T4) and PPV and CO ($r= -0.15$, $p=0.452$ at T2 and $r= -0.16$; $p=0.434$ at T4).The relationship was also inverse; that is, as SVV and PPV increased, CO was found to decrease. This is observed clinically. When volume expansion is administered, and increase in the preload results in an increase in the stroke volume; which subsequently leads to an increase in the cardiac output. As the patient is filled, the variation in stroke volume and pulse volume with respiration decreases. The lack of strength of correlation between SVV and CO,and PPV and CO suggests that changes in pulse pressure and stroke volume cannot be used as a surrogate or indicator for changes in the cardiac output. Monnet et al, in their study on ICU patients, found that systolic pressure and pulse pressure could be used to detect changes in cardiac output.($r= .56$, $p < .0001$for pulse pressure and $r = .55$, p

< .0001for systolic pressure).(74) However, this study was done in patients who were in the supine position. Moreover the sample size for the above mentioned study was much larger.

Hemodynamics in the prone position are affected by a number of variables; one of the main factors which affect it is the type of support that is used. Numerous studies have shown fall in cardiac index based on the type of support that was used. Various explanations have been put forward for the observed fall in cardiac index. Depending on the type of support that is used, the heart may be positioned at a hydrostatically higher level that the lower limbs. This impedes venous return to the heart, resulting in a decrease in the preload and thus the cardiac output. Compression of the abdomen has been implicated in causing fall in the cardiac output. Abdominal compression results in decreased pulmonary compliance which in turn causes decreased cardiac filling due to a fall in the compliance of the left ventricle. This results in a fall in the stroke volume and cardiac output. Compression of the abdomen may also cause direct compression of the inferior vena cava which would result in a decrease in the venous return.

Comparison of effects of four different types of prone-positioning frames on hemodynamics was performed by Waldsworth et al in their study which revealed that cardiac index significantly dropped in patients who were turned prone onto the Relton-Hall frame and knee-chest prone position (17% and 20% respectively) but not in those who were positioned on the evacuatable mattress and pillows(11% and 3%) respectively. (55)

In this study, a significant change in cardiac index was detected (p=0.03) between the patients positioned on Relton-Hall frame and bolsters. There was no significant change in

cardiac output statistically. This discrepancy can be explained by the missing data in cardiac output at time T4 which could have affected the results. Because of this, the effect of the type of support on cardiac output and cardiac index cannot be commented upon. There was a significant change in heart rate between the two groups; none of the other variables showed significant difference between the groups.

It is also important to note that the distribution of patients between the two groups was unequal . (n=24 for Relton-Hall and n=5 for bolsters). If the number of patients was comparable, it is conceivable that the results may have been different.

Autonomic dysfunction among patients with diabetes mellitus has been well researched. Perioperative management of patients with autonomic dysfunction should involve providing adequate hydration, maintaining euvolemic status and optimising pharmacological treatment. Hypotension is common during anesthesia and responds well to alpha 1 adrenoreceptor agonist such as phenylephrine. Indirect acting agents such as ephedrine may be less effective as they depend on the release of noradrenaline from postganglionic nerve fibers for their action; this may be lacking in this group of patients. (63)

Burgos et al reported increased incidence of post-induction hypotension in diabetic patients with autonomic dysfunction.(65) Hemodynamic lability on induction of anesthesia in patients with autonomic dysfunction is well documented.(66,67). Change in position from supine to prone may compound and worsen hypotension in these group of patients. Effect of change in position on hemodynamics in anesthetised patients with diabetic autonomic dysfunction has not been well studied. Approximately half the patients in this study were

diabetics (n=15). Hemodynamic variables were compared between diabetic and non-diabetics on turning prone and did not show any significant difference between the groups. However, tests of autonomic dysfunction were not performed on these group of patients preoperatively; therefore,with this study, it is not possible to state that diabetic patients with autonomic dysfunction are more at risk of developing hemodynamic instability on turning prone. Moreover, autonomic dysfunction is not isolated to diabetic patients; it can occur in other clinical conditions such as elderly patients, hypertensive patients, patients with coronary artery disease and patients on various medications such as calcium channel blockers, beta adrenergic blocking agents and angiotensin-converting enzyme inhibitors.

CONCLUSION

This observational study on the hemodynamic changes in ASA II and III patients undergoing major spine surgery in the prone position using Flo Trac sensor showed that -

- There was no statistically significant fall in cardiac output or cardiac index immediately after change of position (5 minutes) to prone. Significant change in pulse pressure variation and stroke volume variation was observed during this time.

- There was a statistically significant change in all hemodynamic variables except diastolic blood pressure 15 minutes after turning prone.

- A strong correlation was found to exist between SVV and PPV in the prone position. However, CO correlated weakly with SVV and PPV.

- Type of support (Relton-Hall vs. bolsters) did not significantly affect PPV and SVV.

- Hemodynamic variables did not vary significantly between diabetic and non-diabetic patients.

LIMITATIONS

This study had the following limitations:

The time of administration of intravenous drugs which may have had effects on hemodynamics is not known.

The presence or absence of autonomic dysfunction is not known; therefore the impact it may have had on hemodynamics on turning to the prone position cannot to ruled out.

The distribution of patients on the different supports was unequal. If the number were more equal, the results may have been different.

There was missing data in some of the variables, which may have affected results.

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ANNEXURE

ANNEXURE 1 – PATIENT INFORMATION SHEET

A observational study to define hemodynamic changes from supine to prone position in ASA 2 and 3 patients undergoing major spine surgery in prone position using FloTrac sensor.

You are requested to participate in a study that measures the use of a new test called "cardiac output monitoring" during the operation.

What will be done during this study?
Normally, Blood Pressure (BP) during major surgeries such as yours is measured using a cannula inserted into an artery in your hand. This allows continuous measurement parameters such as BP. You will be turned on your stomach (called 'prone position') after general anesthesia is administered for the purpose of the surgery. Prone position is associated with rapid changes in BP and heart rate. The cannula in your hand attached to the monitors will help in early detection of these changes and help in deciding when to administer fluids and how much of it to administer at such crucial stages of the procedure. If you agree to participate in this study, the arterial cannula will be connected to a special equipment, which is not routinely used. This special equipment measures other parameters (called '**cardiac output**', '**PPV**' and '**SVV**') which helps making better decision regarding fluid administration.

Will the participation cost me any money?
Agreeing to participate in this test will not cost you any money. The charge for the additional equipment will be paid from the research fund.

Will I be given any remuneration for participating in the study?
Participation in the study is voluntary and there is no remuneration or incentive for participation.

What if I do not agree to participate in the study?
You will continue to get the usual care whether you participate in the study or not.

What if I decide to change my mind after initially agreeing to participate?
You may withdraw your permission at any time and this will not affect your treatment in any way.

How will I benefit from the study?
If you have to undergo future spine operations, the findings in this study may help in decision making regarding fluid administration. In addition, the findings of this test may help other patients who undergo similar spine operations after you, in future.

Who will have access to the information in the study?
Only the researchers will have access to information related to the study. All the information will be kept confidential.

Who should I contact if I have additional questions?
You may contact Dr.Nisha Sara M. Jacob, anytime, at 9500574751, if you have any further doubts.

CONSENT FORM

Study Title: *Hemodynamic changes from supine to prone position in ASA 2 and 3 patients undergoing major spine surgery in prone position using FloTrac sensor.*

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

I_____

_____, son/daughter of _____

declare that I have read the information sheet provided to me regarding this study and have clarified any doubts that I had.

I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights

I also understand that although I have to pay for the anesthetic drugs and equipment for the surgery, the special sensor used for the purpose of the study will be provided free of cost.

I understand that no study related injury or adverse event is expected since there is no intervention instituted and therefore any injury or adverse event encountered is considered that of routine anesthesia and that I will not receive compensation for such injury.

I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access.

I understand that my identity will not be revealed in any information released to third parties or published.

I voluntarily agree to take part in this study.

Name of participant (or thumb impression):
Signature:
Date:

Name of witness:
Signature of witness:
Relation to participant:
Date:

Name of investigator:
Signature of investigator
Date:

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DATA SHEET

NAME

HOSPITAL NO:

S. NO:

AGE (yrs) :

Date of surgery

SEX : MALE   FEMALE

WEIGHT (kg)

HEIGHT(cm)

BMI(kg/m2)

BSA (m2)

TYPE OF PRONE SUPPORT :

CO-MORBID ILLNESS AND DURATION

ASA STATUS

MEDICATIONS

SURGERY:

DIAGNOSIS

NO: OF LEVELS:

HEMODYNAMIC VARIABLES

	T0 (preinduction)	T1(post-induction, supine)	T2(5 min post prone)	T3 (10 min after prone position)	T4- Tn (readings every 5 minutes until skin incision)
HR(bpm)					
SBP (mmHg)					
DBP(mmHg)					
MAP(mmHg)					
PPV(%)					
SVV(%)					
CO(l/min)					
CI(l/min/sq.m)					
MAC					
IV fluids					
Vasopressors					
Vt (ml)					
PEEP					
Peak pressure					

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ANNEXURE 4 – DATA SPREADSHEET

DATA SPREADSHEET

S. NO	HOSP NO	age (years)	gender 1=M, 2=F	height (cm)	weight (kg)	BMI (kg/m2)	ASA 1=II, 2=III	comorbid illness
1	6487962	55	2	154	68	28.7	1	D,H
2	6903962	54	2	166	65	23.5	1	D,H
3	7835212	42	2	154	79	33.3	1	H
4	7196082	58	1	164	57	21.1	1	H
5	7864552	56	2	140	54	27.6	1	H
6	7704512	62	1	164	61	22.6	1	H
7	1640192	48	2	151	44	19.3	1	H,D
8	7015952	57	2	150	50	22.2	1	H
9	6715312	49	2	151	57	24.9	1	D
10	4021062	60	2	143	45	22	1	D
11	7122512	67	1	165	68	24.9	1	D
12	6991632	57	2	156	73	30	1	H
13	8141142	70	1	160	65	25.3	1	D
14	16542IB	59	1	170	55	19	2	IHD,H,D
15	7049772	51	1	165	55	20.2	2	IHD,H,D
16	949502C	55	1	165	90	33	2	H, D, IHD
17	19072	70	2	146	59	27.6	1	H
18	8414262	52	2	158	83	33.2	1	H,D
19	7800352	50	1	174	69	22.7	1	D
20	8594162	53	1	165	70	25.7	1	D,H
21	5888062	69	2	145	51	24.2	1	H
22	448674A	47	2	151	70	30.7	1	H
23	7855412	52	2	149	64	28.8	1	D,H
24	8483992	69	2	152	61	26.4	1	H
25	8830752	55	1	172	65	21.9	1	H
26	8599662	64	2	146	56	26.3	1	H,D
27	8452832	41	2	140	45	23	1	H
28	8940522	58	2	154	48	20.2	1	H
29	016741G	56	1	157	61	24.7	1	H

DATA SPREADSHEET

D 1=YES, 2=NO	D DURATION	H 1=YES, 2=NO	H DURATION	IHD 1=YES, 2=NO	IHD DURATION	level of surgery
1	10	1	12	2	0	2
1	10	1	12	2	0	2
2	0	1	2	2	0	2
2	0	1	0.5	2	0	2
2	0	1	4	2	0	2
2	0	1	5	2	0	2
1	10	1	2	2	0	2
2	0	1	10	2	0	2
1	5	2	0	2	0	2
1	10	2	0	2	0	3
1	5	2	0	2	0	4
2	20	1	10	2	0	2
1	20	2	0	2	0	2
1	20	1	20	1	20	4
1	15	1	2	1	2	4
1	3	1	3	1	4	2
2	0	1	20	2	0	2
1	3	1	3	2	0	2
1	4	2	0	2	0	4
1	5	1	5	2	0	2
2	0	1	20	2	0	2
2	0	1	0.5	2	0	2
1	10	1	10	2	0	2
2	0	1	5	2	0	2
2	0	1	20	2	0	3
1	2	1	0.5	2	0	2
2	0	1	2	2	0	2
2	0	1	2	2	0	2
2	0	1	3	2	0	5

DATA SPREADSHEET

type of support	T0 HR	T0 SBP	T0 DBP	T0 MAP	T0 PPV	T0 SVV	T0 CO	T0 CI	T0 FLUIDS	T1 HR
RH	100	176	86	117	19	14	6.2	3.7	0	88
RH	114	160	70	102	6	8	7.4	4.4	700	99
RH	99	137	88	103	12	16	6.7	3.8	700	113
RH	134	152	87	111	10	7	7.5	4.7	0	115
RH	67	155	82	111	12	11	5	3.6	600	62
RH	66	147	68	93	7	11	5	3	500	86
RH	80	173	69	101	2	7	6.5	4.8	0	72
RH	90	154	76	104	13	11	5.9	4.1	500	100
RH	78	177	80	114	10	7	7.8	5.1	0	85
RH	99	140	59	95	10	16	3	2.3	0	77
RH	61	149	72	96	7	11	5.3	3	0	78
RH	76	154	68	99	8	10	6.9	4	0	72
RH	125	166	72	102		17	6.9	4	0	99
RH	72	136	61	86	8	11	8.2	5	0	73
RH	95	151	77	106	9	14	8.7	5.1	0	110
BOLTSER	73	92	53	68	6	18	4.6	2.2	500	79
BOLTSER	56	153	73	104	9	10	3.8	2.5	500	61
RH	103	140	76	100	12	12	5.4	2.9	300	80
RH	85	150	73	106	15	19	8.7	4.7	0	85
BOLTSER	75	157	72	107	11	10	8.3	4.7	0	76
RH	112	160	90		12	12	5.2	3.7	0	81
BOLTSER	98	169	80	105	10	10	6.7	4.1	0	98
RH	100	150	81	103	4	7	4.8	3	0	91
RH	52	215	74	106					0	58
BOLTSER	91	182	94	125	13	13	7.2	4.3	500	93
RH	105	146	77	103	22	24	3.6	2.5	0	85
RH	98	141	65	99	5	14	7.5	3.7	0	121
RH	85	199	109	141	16	26	4.8	3.4	0	77
RH	94	165	76	111		10	8.4	5.2	0	98

DATA SPREADSHEET

T1 SBP	T1 DBP	T1 MAP	T1 PPV	T1 SVV	T1 CO	T1 CI	T1 FLUIDS	T1 VASOPR	T1 et ISO	T1 VT
158	84	112	20	21	4.6	2.8	0	0	0.4	434
94	51	66	15	16	5.2	3.2	300	PNP 50	0.7	450
140	84	105	15	13	8.4	4.7	0	0		500
107	65	77	17	16	3.9	2.4	600	0	0.8	380
93	55	71	11	10	3.4	2.4	0	0		400
138	76	101	11	10	6.2	3.8	100	0	1	420
124	54	75	1	5	4.3	3.2	700	0	0.7	360
126	71	93	10	7	5.2	3.7	0	0	0.5	420
120	65	86	13	7	4.7	3.1	300	0	1	370
90	39	58	14	5	3.7	2.8	750	0		350
168	83	118	16	10	8.1	4.6	500	0	0.7	440
98	51	69	4	4	3.9	2.2	0	0	0.6	376
84	56	62		16	4.5	2.5		0		400
123	64	78	9	5	9.7	5.9	500	0		381
100	57	72	29	29	5.5	3.4	500	PNP80	0.3	370
127	76	98	8	6	5.4	2.7	0	NORAD	0.6	400
155	74	107	6	6	4.1	2.7	0	0	0.8	360
89	60	70	16	17	5.6	3.1	200	0		360
123	60	83	8	14	6.7	3.7	500	0	0.9	400
107	54	74	7	6	5.1	2.9	500	0	0.7	480
118	62	82	17	10	4	3.5	300	0	0.7	412
144	67	92	9	8	5.7	3.4	500	0	0.8	450
117	62	81	6	6	4.9	3.1	650	0	0.6	450
144	57	79	16	14	4.2	2.6	650	0	0.8	301
121	73	91	11	14	5.2	2.9	0	PNP 150	0.6	525
147	87	110	13	25	3.5	2.4	400	0	0.7	475
182	87	128	4	8	13.6	10.8	150	0	0.8	362
115	65	83	9	12	2.3	1.6	250	0	1.1	364
123	71	94	17	15	5.9	4.2	100	0	0.7	424

DATA SPREADSHEET

T1 PEEP	T1 PEAK PR	T1 MEAN PR	T2 HR	T2 SBP	T2 DBP	T2 MAP	T2 PPV	T2 SVV	T2 CO	T2 CI
5	22	11	92	149	82	105	20	22	5.3	3.2
4	21	8	115	172	95	122	16	13	10	5.4
4	20	9	103	140	92	110	13	16	5.1	2.9
4	15	8	105	100	60	74	15	20	6.5	4
4	16	7	64	76	48	58	13	10	2.3	1.6
	14	9	76	90	52	65	5	10	3.2	1.9
	13	6	70	117	56	76	12	10	4.3	3.2
	17	7	102	131	94	109	23	20	3.7	2.2
	20	9	71	96	52	68	14	14	3.6	2.4
	21	8	105	92	44	62	12	9	3.5	2.7
	12	6	69	117	67	84	11	11	3.7	2.2
	19	8	77	126	67	85	15	18	4	2.3
	17	8	103	89	55	68		13	5.1	3.1
	12		73	158	93	110	10	5	15.1	9.2
4	16	7	91	72	35	49	20	21	4.4	2.8
4	16	8	86	136	86	107	14	13	5	2.5
	19	6	61	100	51	69	8	11	3	2
	16	6	89	110	55	66	12	12	5.4	2.9
	18	8	81	116	67	84	17	17	5	2.7
	21	8	61	66	34	44	11	14	2.5	1.4
	19	8	79	103	49	64	12	11	3.2	2.5
	20	10	93	128	65	86	14	15	5.7	3.4
	25	12	91	90	50	68	14	14	4.7	3
	19	8	54	118	60	83	15	14	3.7	2.3
4	23	7	90	98	67	77		25	3.6	2.1
	19	8	90	109	75	87	21	23	2.9	2
	18	8	81	161	77	111	8	9	7.2	3.4
	20	8	81	74	48	52	30	28	1.7	1.2
	19	7	113	105	59	77	21	13	7.6	3.8

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T2 FLUIDS	T2 VASOPR	T2 et ISO	T2 VT	T2 PEEP	T2 PEAK PR	T2 MEAN PR	T3 HR	T3 SBP	T3 DBP	T3 MAP
0	0	0.4	440	5	22	11	90	163	85	115
200	0	0.6	430	4	22	11	104	176	90	123
500	0	0.7	500	4	19	8	100	128	87	102
360	0	0.9	360	4	15	8	107	122	67	87
0	EPHED 6	1	380	4	18	8	51	106	67	83
100	PNP 100	1	420		14	9	64	83	47	61
200	0	1	330		14	7	67	118	55	75
0	0	0.8	400		17	9	90	115	72	89
200	0	1	400		19	8	70	108	63	80
900	PNP 100		256		16	8	78	120	54	79
250	0	0.8	430		13	6	65	109	67	82
700	0	0.6	400		18	8	77	117	65	82
500	0		355		18	9	105	121	7	92
0					14		102	148	79	96
500	PNP40, NORAD	0.6	297	4	17	8	98	77	36	51
0	NORAD	0.6	443	4	16	8	84	135	90	108
100	0	0.8	400		19	6	55	106	52	70
200	EPHED 6		404		15	6	81	165	85	110
0	0	0.9	420		18	8	75	101	57	71
500	EPHED6	0.7	450		16	8	62	96	53	68
200	0	0.8	390		17	6	70	91	57	61
200	0	1	475		18	9	86	88	55	67
0	EHPED 5	0.6	370		19	9	92	99	56	69
0	0	0.8	296		19	8	61	134	72	98
300	PNP 100	0.8	523		24	7	84	103	72	82
100	0	0.9	475	4	22	8	88	98	60	72
50	0	0.8	342		18	9	111	157	63	105
250	EHPED 10	1	370		21	9	75	108	60	75
200	0	0.8	413		20	8	73	85	46	61

DATA SPREADSHEET

T3 PPV	T3 SVV	T3 CO	T3 CI	T3 FLUIDS	T3 VASOPR	T3 et ISO	T3 VT	T3 PEEP	T3 PEAK PR
17	17	6	3.6			0.7	435	5	22
9	13	9.2	5.5	200	0	0.7	430	4	23
17	12	4.8	2.7	0	0	0.7	500	4	20
12	14	5.6	3.5	0		0.9	360	4	15
10	14	3.2	2.3	100	PNP 100	0.8	380	4	18
7	11	3.9	2.3	100	0	1	420		14
11	11	5.2	3.8	100	0	1	330		14
19	16	4	2.8	0	0	0.8	400		17
9	12	4.3	2.8	0	0	1	400		19
8	8	3.7	2.8	1000	PNP 200		340		17
7	9	4.3	2.5	100	0	0.9	430		13
16	18	4.3	2.5	0	0		400		18
	16	4.8	3	0	0		360		17
14	13	6.1		500					
19	18	7.4	4.6	0	NORAD	0.6	287		17
11	13	5.3	2.7	0	NORAD	0.7	400	4	16
8	10	4.3	2.8	100	0	0.8	400		19
			3.4	0	0	0.7	279		14
10	11	4.8	2.6	0	0	0.9	430		18
14	12	4.6	2.6	0	0	0.7	450		16
15	12	3.2	2.7	0	EHPED 6	0.8	397		17
17	16	4.3	2.8	100	0	1	475		18
16	15	4.8	3	0	0	0.6	367		19
15	17	4	2.5	0	0	0.8	267		19
	29	3.1	1.7	0	PNP 100	0.9	475		23
20	20	3.6	2.4	0	0	0.8	425	4	21
15	7	8	3.9	20	0	0.9	340		18
26	24	4.5	3.1	0		1.1	354		20
18	18	5.2	3.2	200	PNP100	0.8	424		20

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DATA SPREADSHEET

T3 MEAN PR	T4 HR	T4 SBP	T4 DBP	T4 MAP	T4 PPV	T4 SVV	T4 CO	T4 CI	T4 FLUIDS
11									
11	108	140	78	100	15	16	6.6	4	100
8	96	112	74	88	14	13	4.9	2.7	300
8	104	95	57	69	17	13	4.2	2.6	100
8	49	90	51	67	10	11	3	2.2	100
6	60	87	50	63	8	12	3.8	2.3	100
7	69	98	47	64	17	12	4	2.9	0
8	90	101	68	78	23	19	3.4	2.4	0
8	60	100	58	74	11	15	3.7	2.5	0
9									
6	62	107	65	80	7	11	3.6	2.2	0
8									
8	93	124	73	98		19	3.1	2.3	500
	90	96	69	74	15		3.8		500
10									
8	48	108	70	86	10	13	4	2	0
6	51	68	33	44	16	16	2.5	1.1	
5	86	102	60	73	9	7	4.4	2.4	0
8	61	120	65	82	11	14	6.8	3.7	0
8	61	79	44	57	13	13	3.7	2.1	0
6	67	91	50	66	15	11	3.6	2.5	0
9	81	97	63	76	10	11	4.5	2.7	100
9	91	97	52	67	17	13	4.4	2.8	0
8	57	152	104	124	16	17	3	1.8	0
8	84	115	77	85	25	20	4.5	2.5	100
8	85	91	55	69	21	21	3.1	2.2	0
8	96	112	67	89	10	18	5.9	2.9	20
9	76	96	60	70	24	22	3.6	2.6	0
8	76	92	48	58	18	18	5	3	0

DATA SPREADSHEET

T4 VASOPR	T4 et ISO	T4 VT	T4 PEEP	T4 PEAK PR	T4 MEAN PR
PNP 50	0.8	450	4	22	11
0	0.7	500	4	20	8
0	1	350	4	15	8
EHED 6	0.9	370	4	17	7
0	1	420		14	7
0	1	330		14	6
0	0.9	420		16	8
0	0.9	350		17	7
0	0.9	460		14	6
0		415		18	8
NORAD					
NORAD	0.7	400	4	16	8
PNP50, EPHED5	0.8	400		18	6
0	0.7	465		18	6
0	0.9	430		18	8
EPHED 6	0.7	420		16	8
0	0.8	396		18	6
0	0.9	475		18	9
0	0.6	290		17	8
0	0.8	273		19	8
PNP100	0.9	475		23	7
0	0.8	425	4	20	8
0	0.9	338		18	9
0	1.1	372		20	8
0	0.8	428		20	8

LIST OF ABBREVIATIONS USED IN DATA SPREADSHEET

ABBREVIATION	EXPANSION
M	Male
F	Female
BMI	Body Mass Index
ASA	American Society Anesthesiology
D	Diabetes mellitus
H	Hypertension
IHD	Ischemic heart disease
RH	Relton-Hall
HR	Heart rate
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
MAP	Mean Arterial Pressure
PPV	Pulse Pressure Variation
SVV	Stroke Volume Variation
CO	Cardiac output
CI	Cardiac Index
VASOPR	Vasopressors
PR	Pressure
VT	Tidal volume
PEEP	Positive end-expiratory pressure
Et ISO	End-tidal Isoflurane

ANNEXURE 5 – INSTITUITIONAL REVIEW BOARD (IRB) PAPERS

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Glas) (EDIN)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

November 16, 2013

Dr. Nisha Sara M Jacob
Department of Anaesthesiology
Christian Medical College
Vellore 632 004

Sub: **Fluid Research grant project:**
Hemodynamic changes from supine to prone position in ASA 2 and 3
patients undergoing major spine surgery in prone position using FloTrac
sensor.
Dr. Nisha Sara M Jacob, Anaesthesia, Dr. Sajan P. George, Anaesthesia,
Dr. Georgene Singh, Dr. P. Kalyana Chakravarthy, Anaesthesia.

Ref: IRB Min. No B563 dated 12.11.2013

Dear Dr. Nisha Sara M Jacob,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian
Medical College, Vellore, reviewed and discussed your project titled "" on November 12,
2013. I am quoting below the minutes of the meeting.

1. The consent forms and information sheets need modifications.
2. Dr. Jeyaseelan's and Chakravorthy's signatures are missing.

Dr. Nisha Sara M Jacob and Dr. P. Kalyana Chakravarthy were present during the
presentation of the proposal and satisfactorily responded to the queries raised by the
Members. After discussion, it was resolved to be **ACCEPT the proposal AFTER receiving
the suggested modifications and answers to the queries.**

1 of 2

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202   Fax : 0416 - 2262788, 2284481   E-mail : research@cmcvellore.ac.in

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Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Glas) (EDIN)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Note:
1. Kindly **HIGHLIGHT** the modifications in the revised proposal.
2. Keep a **covering letter and point out the answer to the queries**.
3. Reply to the queries should be submitted within **3 months** duration from the time of the thesis/ protocol presentation, if not the thesis/protocol have to be resubmitted to the IRB.
4. The **checklist** has to be sent along with the answers to queries.

Email the details to research@cmcvellore.ac.in and send a hard copy through internal dispatch to Dr. Nihal Thomas, Addl. Vice-Principal (Research), Principal's Office, CMC.

Yours sincerely,

Dr. Alfred Job Daniel
Chairperson (Research Committee)
Institutional Review Board

Chairperson (Research Committee) &
Principal
Christian Medical College
Vellore - 632 002, Tamil Nadu, India

2 of 2

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202   Fax : 0416 - 2262788, 2284481   E-mail : research@cmcvellore.ac.in

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Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Glas) (EDIN)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

January 14, 2014

Dr. Nisha Sara M Jacob
PG Registrar
Department of Anaesthesiology
Christian Medical College
Vellore 632 002

Sub: **Fluid Research grant project:**
Hemodynamic changes from supine to prone position in ASA 2 and 3
patients undergoing major spine surgery in prone position using FloTrac
sensor.
Dr. Nisha Sara M Jacob, PG Registrar, Anaesthesia, Dr. Sajan P., Anaesthesia,
Dr. Georgene Singh, Dr. P. Kalyana Chakravarthy, Anaesthesia.

Ref: IRB Min. No. 8563 [OBSERVE] dated 12.11.2013

Dear Dr. Nisha Sara M Jacob,

I enclose the following documents:

1.   Institutional Review Board approval   2.   Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal
(Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD,MNAMS,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

CC: Dr. Sajan P., Anaesthesiology, CMC.

1 of 5

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202   Fax : 0416 - 2262788, 2284481   E-mail : research@cmcvellore.ac.in

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OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

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Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

January 14, 2014

Dr. Nisha Sara M Jacob
PG Registrar
Department of Anaesthesiology
Christian Medical College
Vellore 632 002

Sub: **Fluid Research grant project:**
Hemodynamic changes from supine to prone position in ASA 2 and 3 patients undergoing major spine surgery in prone position using FloTrac sensor.
Dr. Nisha Sara M Jacob, PG Registrar, Anaesthesia, Dr. Sajan P., Anaesthesia, Dr. Georgene Singh, Dr. P. Kalyana Chakravarthy, Anaesthesia.

Ref: IRB Min. No. 8565 [OBSERVE] dated 12.11.2013

Dear Dr. Nisha Sara M Jacob,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Hemodynamic changes from supine to prone position in ASA 2 and 3 patients undergoing major spine surgery in prone position using FloTrac sensor." on November 12th 2013.

The Committees reviewed the following documents:

1. IRB application format
2. Curriculum Vitae' of Dr. Nisha Sara M Jacob, Dr. Sajan P. George, Dr. Georgene Singh, Dr. P. Kalyana Chakravarthy
3. Consent form (English, Hindi Tamil & Telugu)
4. Information sheet (English, Hindi Tamil & Telugu)
5. No of documents 1-4

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on November 12th 2013 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.   2 of 5

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202   Fax : 0416 - 2262788, 2284481   E-mail : research@cmcvellore.ac.in

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Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Glas) (EDIN)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Name	Qualification	Designation	Other Affiliations
Dr. Simon Rajaratnam	MBBS, MD, DNB (Endo), MNAMS (Endo), PhD (Endo), FRACP	Professor, Endocrinology, CMCH.	Internal, Clinician
Dr. T. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMCH.	Internal, Clinician
Dr. Chandra Singh	MS, MCH, DMB	Professor, Urology, CMCH.	Internal, Clinician
Dr. Visalakshi	MPH, PhD	Lecturer, Dept. of Biostatistics, CMC.	Internal, Statistician
Dr. Benjamin Perakath	MBBS, MS, FRCS	Professor, Colorectal Surgery, CMCH.	Internal, Clinician
Dr. Anup Ramachandran	Ph. D	The Wellcome Trust Research Laboratory Gastrointestinal Sciences, CMCH.	Internal, Basic Medical Scientist
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMCH.	Internal, Clinician
Dr. Rajesh Kannangai	MD, Ph D	Professor & In-charge Retrovirus Laboratory (NRL under NACO), Department of Clinical Virology, CMCH.	Internal, Clinician
Mrs. Pattabiraman	B. Sc, DSSA	Social Worker, Vellore	External, Lay person
Mr. C. Sampath	B. Sc, BL	Legal Expert, Vellore	External, Legal Expert
Rev. Joseph Devaraj	B. Sc, BD	Chaplaincy Department, CMCH.	Internal, Social Scientist

IRB Min. No. 8563 [OBSERVE] dated 12.11.2013   3 of 5

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202   Fax : 0416 - 2262788, 2284481   E-mail : research@cmcvellore.ac.in

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Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Glas) (EDIN)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Dr. Vathsala Sadan	M.Sc, PhD	Professor, Community Health Nursing, CMCH.	Internal, Nurse
Dr. Ebenezer Ellen Benjamin	M.Sc, PhD	Professor, Maternity Nursing, CMCH.	Internal, Nurse
Dr. B. J. Prashantham	MA(Counseling Psychology), MA(Theology), Dr. Min (Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
Dr. Anuradha Rose	MBBS, MD	Assistant Professor, Community Health, CMCH	Internal, Clinician
Dr. Jayaprakash Muliyil	B. Sc, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, Vellore	External, Scientist & Epidemiologist
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL	Sr. Legal Officer, CMCH.	Internal, Legal Expert
Dr. Nihal Thomas,	MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin), FRCP (Glasg)	Professor & Head, Endocrinology. Additional Vice Principal (Research), CMCH. Deputy Chairperson, IRB, Member Secretary (Ethics Committee), IRB	Internal, Clinician

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Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Glas) (EDIN)
Deputy Chairperson
Secretary, Ethics Committee, IRB
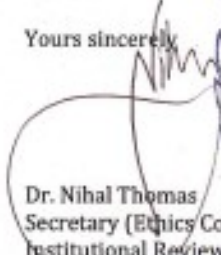Additional Vice Principal (Research)

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/index.html.

Fluid Grant Allocation:

A sum of 77,500 INR (Rupees Seventy Seven Thousand Five Hundred only) will be granted for 2 years.

Yours sincerely,

Dr. Nihal Thomas
Secretary [Ethics Committee]
Institutional Review Board

Dr. NIHAL THOMAS
MD, MNAMS, DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glas)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

CC: Dr. Sajan P., Anaesthesiology, CMC.

IRB Min. No. 8563 [OBSERVE] dated 12.11.2013

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OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD
CHRISTIAN MEDICAL COLLEGE,
BAGAYAM, VELLORE 632002, TAMIL NADU, INDIA

Ref: FG/8563/11/2013

January 17, 2014

[Stamp: OFFICE OF THE TREASURER — 18 JAN 2014 — CMC, VELLORE - 632 004]

The Treasurer
Christian Medical College,
Vellore.

Dear Mr. Denzil,

Sub: **Fluid Research grant project:**
Hemodynamic changes from supine to prone position in ASA 2 and 3 patients undergoing major spine surgery in prone position using FloTrac sensor. Dr. Nisha Sara M Jacob, PG Registrar, Anaesthesia, Dr. Sajan Philip George, Anaesthesia, Dr. Georgene Singh, Dr. P. Kalyana Chakravarthy, Anaesthesia.

Ref: IRB Min. No. 8563 dated 12.11.2013

The Institutional Review Board at its meeting held on November 12th 2013 vide IRB Min. No. 8563 accepted the project *for a total sum of 77,500 INR (Rupees Seventy Seven Thousand Five Hundred only) will be granted for 2 years. If overspent the excess should be debited form the respective departmental or Special funds.* Kindly arrange to transfer the sanctioned amount to a separate account to be operated by Dr. Nisha Sara M Jacob and Dr. Sajan P.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD MAMS, DNB (Endo) FRACP (Endo), FRCP (Edin,) FRCP (Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

CC: Dr. Nisha Sara M Jacob, Anaesthesiology, CMC.
Dr. Sajan Philip George, Anaesthesiology, CMC
File

22Y245.RF. Dr. Nisha .sara M Jacob - Anaesthesiology (8563)

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