Correlation between Pulse Pressure Variation (PPV) and adequacy of intra-vascular volume as reflected by time to urine output in renal transplant recipients: an observational study.

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE M.D. BRANCH X (ANAESTHESIOLOGY) EXAMINATION OF THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY, APRIL 2015
CERTIFICATE

This is to certify that the dissertation titled
Correlation between Pulse Pressure Variation (PPV) and adequacy of intra-vascular volume as reflected by time to urine output in renal transplant recipients is the bonafide work of

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in partial fulfilment of the rules and regulations for the M.D., Branch X, Anaesthesiology Examination of The Tamil Nadu Dr. M.G.R. University, to be held in 2015.

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AIM

To determine a correlation between pulse pressure variation (PPV) and intravascular volume as reflected by onset time of graft diuresis in renal transplant recipients.

OBJECTIVES

1. To determine a correlation between PPV at the time of graft revascularization and time to urine output.
2. To determine the best target PPV to achieve early post transplant diuresis.

HYPOTHESIS

Pulse pressure variation (PPV) is a useful measure of adequacy of the intravascular volume in patients undergoing renal transplant.
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ABSTRACT

Title: Correlation between Pulse Pressure Variation (PPV) and adequacy of intra-vascular volume as reflected by time to urine output in renal transplant recipients

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Objectives

1. To determine a correlation between PPV at the time of graft revascularization and Time to urine output
2. To determine the best target PPV to achieve early post transplant diuresis

Methods: 33 adult patients undergoing elective renal transplantation were studied. Intravascular volume was maintained with intravenous fluids, targeting a CVP of 10-15 mm of Hg. PPV was also monitored but not used to influence fluid management. Both CVP and PPV were monitored continuously and recorded every 15 minutes. The values measured at the time of release of the vascular cross clamps were assumed to indicate the situation at the time of graft reperfusion. The outcome measure used to assess intravascular volume was time to urine output following reperfusion in seconds (TUO). It was considered desirable for time to urine output to be \( \leq 120 \) seconds.

Results and Conclusions: It was found that PPV did not have a linear correlation with time to urine output. ROC analysis revealed that the most appropriate cut off to use was \(< 10\%\). In patients whose PPV value was \( > 10\% \), 83.33% had a time to urine output of over 120 seconds. Therefore it could be used as a parameter to monitor the state of intravascular volume and aid in intra-operative fluid management of patients undergoing renal transplantation.

Key words

Pulse Pressure Variation, Urine output, Renal transplantation
INTRODUCTION
Chronic kidney disease is a growing health problem worldwide and so too in India with the rising incidence of the following risk factors namely Diabetes Mellitus and Hypertension. A proportion of these patients will go on to develop end stage disease and will require dialysis and some will eventually require renal transplantation.

Long term graft survival depends on multiple factors. Early graft dysfunction and delayed graft dysfunction has been attributed to graft perfusion. While graft reperfusion is dependent on multiple contributors of the cardiovascular system, maintenance of the intravascular volume remains the key role of the anaesthetists.

Patients with end stage renal disease, awaiting renal transplant are usually on haemodialysis. Peri-operative dialysis has improved biochemical abnormalities and fluid overload status and hence improved postoperative outcomes.

However, in the peri-operative periods intravascular depletion occurs. Early correction and maintenance of this fluid depletion is important for adequate perfusion of
the organ both at the time of the revascularization and also for the long term function of the graft organ. Though a surrogate marker, an immediate indicator of adequate function of the renal graft is reflected as post operative urine output.

Often in the peri-operative period, intravascular volume is measured by assessing hemodynamic parameters such as central venous pressure (CVP). CVP is considered the gold standard measure in renal transplant recipients as it has been in use for many years. The targeted CVP for patients undergoing renal transplantation is 10-15 mm Hg (11).

Newer parameters, namely pulse pressure variation (PPV) and stroke volume variation (SVV) are dynamic parameters and therefore in theory superior to CVP in assessing intravascular volume. Though it has become possible to measure these parameters real time with new anaesthetic monitors, CVP remains the most widely used parameter as its value is proven and the accuracy of PPV has not been assessed adequately in various clinical scenarios.
This study examines the value of PPV in assessing intravascular volume as reflected by time to first urine output and total urine volume in the first 4 hours.
AIM AND OBJECTIVES
AIM

To determine a correlation between pulse pressure variation (PPV) and intravascular volume as reflected by onset time of graft diuresis in renal transplant recipients.

OBJECTIVES

1. To determine a correlation between PPV at the time of graft revascularization and Time to urine output
2. To determine the best target PPV to achieve early post transplant diuresis

HYPOTHESIS

Pulse pressure variation (PPV) is a useful measure of adequacy of the intravascular volume in patients undergoing renal transplant.
REVIEW OF LITERATURE
By definition, Chronic kidney disease (CKD) the presence of kidney damage or a decrease in renal function, for a duration of at least three.

There are five stages of chronic kidney disease as per the guidelines of the National Kidney Foundation, Kidney Disease Outcomes Quality Initiative depending on how severe the damage is to the kidneys, or the level of decrease in kidney function.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min/1.73m²)</th>
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<tr>
<td>1</td>
<td>Kidney damage with normal or ↑GFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild ↓GFR</td>
<td>60 - 89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓GFR</td>
<td>30 - 59</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓GFR</td>
<td>15 – 29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt; 15 (or dialysis)</td>
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The incidence of Chronic kidney disease (CKD) is on the increase worldwide. (2). The growing incidence of diabetes mellitus (3) and hypertension (4,5) could account for this. These trends are likely to be observed in India as well. It has been difficult to estimate the true numbers of patients with CKD and ESRD in India without a comprehensive national CKD registry. A voluntary online registry (www.ckdri.org) reflects only a small fraction of the total number of CKD patients in India. Workers in this field have reported that the incidence of ESRD in India is approximately 229 per million (6), and >100,000 new patients enter become dependent on dialysis every year (7). Reports from the SEEK (Screening and Early Evaluation of Kidney Disease) study showed that in their cohort of 5588 subjects the prevalence of CKD in India was 17.2% with approximately 1% of these having stage 5 disease (ESRD) (8).
APPREACH TO TREATMENT

The management of chronic kidney disease is basically to diagnose the disease early and evaluate for the underlying causes and treat it when possible. Appropriate preventive measures usually delay the progression and in some situations even halt disease. There are three components of treatment that should be instituted simultaneously.

These are

1. Measures to delay or halt progression.
2. Addressing the secondary manifestations
3. Planning of renal replacement therapy
Measures to delay or halt disease progression

- Evaluation and treatment of the underlying condition when possible
- Control of Hypertension
- Control of Diabetes target HbA1C< 7%
- Treatment of Hyperlipidemia
- Avoidance of nephrotoxins – drugs and IV contrast
- Blocking the renin-angiotensin axis blockers in patients with diabetic nephropathy

The secondary pathologic manifestations of CKD that need to be managed are:

- Anemia: erythropoiesis-stimulating agents
- Metabolic acidosis: Oral alkalinization
- Hyperphosphatemia: Dietary phosphate restriction, phosphate binders
- Hyperparathyroidism: Calcitriol, Vitamin D analogues
- Hypocalcemia: Calcium supplements
- Volume overload: Loop diuretics, Ultrafiltration
- Growth hormone for children with growth failure
Indications for renal replacement therapy in patients CKD

- Severe metabolic acidosis
- Hyperkalemia
- Intractable volume overload
- Pericarditis
- Encephalopathy
- Failure to thrive and malnutrition
- Peripheral neuropathy
RENAL REPLACEMENT THERAPY

Renal replacement therapy (RRT) is a broad term encompassing treatment modalities that replace the nonendocrine functions of the kidney. RRT is most often used in treatment of patients with end stage renal disease. It is occasionally used to treat patients with certain forms of poisoning (69). The following treatment modalities are used as RRT:

- Intermittent hemodialysis
- Continuous haemodialysis and haemofiltration
- Peritoneal dialysis.

Intermittent haemodialysis is the most commonly used modality and forms the backbone of treatment of patients with chronic kidney disease.
RENAL TRANSPLANTATION

Kidney transplantation is a surgical procedure that involves implanting normal kidneys from healthy donors to replace diseased ones. Renal transplantation usually becomes necessary when patients with chronic kidney disease progress to stage 5 CKD or ESRD when the kidneys are functioning at less than 15% of their normal capacity. Renal replacement therapy may be by either dialysis or by renal transplant.

In most health care systems and institutions, dialysis remains the mainstay of renal replacement therapy. Recently, significant improvement has been observed with graft survival and long term function and this has resulted in renal transplantation becoming more cost-effective in comparison with long term dialysis.
FACTORS AFFECTING GRAFT FUNCTION

There are a host of recipient factors that influence graft survival and function following renal transplantation as listed below (9).

- Age of the recipient
- Duration of dialysis pre-transplant
- Anti-HLA antibodies sensitization
- Delayed graft function
- Warm ischaemia
- Cold ischaemia
- Acute kidney injury (perfusion or reperfusion related)
- Surgical technique
- Acute rejection
- Nephrotoxicity due to Cyclosporine

The improvement in graft survival and function is as a result of these factors being understood and addressed by various members of the transplant team.
These factors could be broadly classified into two categories; immunological and technical. Adequate perfusion of the renal allograft is one of the many technical factors that are important in determining early graft survival and function. Adequate perfusion of the allograft is directly related to the intra-vascular volume status of the donor first and then the recipient and these particular factors to a great extent are under the control of the anaesthesiologist.
ANAESTHETIC MANAGEMENT

The anaesthesiologist’s role is just one step in the entire process of renal transplantation. However, the active role in maintaining adequate intravascular volume and intraoperative perfusion pressures would determine immediate graft function and delayed graft function (9).

Pre-operative considerations

The main technical factors that are important determinants of graft function are warm ischemia time (harvest and transplant time), cold ischemia time (storage time, transplanted graft perfusion and pre-donation graft state (9).

Graft perfusion is directly dependant on cardiac output which in turn is dependent on the intravascular volume state. When a recipient has been identified they need to be fasted and prepared for the transplant operation. This preparation often involves dialysis. Dialysis done before the operation can lead to fluid depletion, electrolyte disturbance and residual anticoagulation. Though living donor transplantation is a scheduled event and therefore allows optimal preparation of the donor and recipient,
Intra-operative considerations

Renal transplantation is most often performed under general anaesthesia although it can also be performed in certain extra-ordinary circumstances under neuraxial anaesthesia. General anaesthesia has the advantage of providing a haemodynamically stable patient with good muscle relaxation, and predictable depth of anaesthesia (10). Sometimes these techniques are combined to provide patients the benefits of both. There is no significant difference noted in the hemodynamic and renal function among these different techniques (10). Irrespective of the technique employed, adequate real time hemodynamic monitoring is essential in patients undergoing renal transplantation.

In addition to the basic vital parameters that are monitored during any surgical operation, monitoring of CVP and arterial blood pressure are considered mandatory given the wide variation in haemodynamic state often observed during these major operations. In the presence of co-existing heart disease resulting in cardiac dysfunction, patients are likely to benefit may also benefit from more advanced monitoring such as intraoperative transesophageal echocardiography (11).
Patients who have undergone recent dialysis are usually in a state of fluid depletion at the beginning of the operation and this is usually reflected as a low CVP. It has been shown that administering intravenous fluids to aim for a CVP of 10-15mmHg is desirable and results in good graft function (1). This is probably as a result of increased renal blood flow.

There is often a decrease in CVP observed in towards the end of the operation and immediately postoperative in spite of vigorous fluid resuscitation and positive balance. The reason for this is not clearly understood. It is believed to be due to two possible factors, namely fluid redistribution and change in the vascular tone (70).

The importance of fluid balance has been demonstrated beyond doubt in many studies. Graft acute tubular necrosis (acute graft injury) has been found to occur less often in patients who are vigorously hydrated (12-14). It was demonstrated by Ferris et al. that the fluid balance of recipients correlated strongly with immediate post-operative graft function (15).
In addition to intravenous fluids, pharmacological agents that improve renal blood flow such as dopamine and, dobutamine have been used to improve perfusion of the transplanted kidney. Diuretics such as Furosemide and Mannitol too have been used to improve function of the kidney after reperfusion. The incidence of acute tubular necrosis has been observed to be decreased by use of Mannitol (16). It is best to keep the patient normotensive or even a little hypertensive so as to assist graft perfusion and therefore function. However the use of alpha adrenergic agonists is not recommended as they produce vasoconstriction that decreases renal perfusion (16). The goal of the anaesthesiologist is to maintain adequate intravascular volume so that the transplanted kidney is adequately perfused.

Crystalloids are the intra-operative intravenous fluid of choice in renal transplant recipients. The fluid of choice is plasmalyte as the other commonly used crystalloids have the potential to cause disturbances in electrolyte and acid base balance. There is a risk of hyperkalaemia when Ringer’s lactate solution is used. Administration of large volumes of normal saline can result in hyperchloraemic metabolic acidosis. This can also lead to extracellular potassium shift, and hyperkalemia. Recent evidence suggests that plasmalyte more stably maintains acid-base and electrolyte balance compared with normal saline especially during the post reperfusion period. (17)
Colloids are not routinely used. They are useful in situations where the recipient is severely fluid depleted and requires large volume of fluid replacement. (18). Albumin is an endogenous colloid that is safe to use in such patients. Though various synthetic colloids are more commonly used that albumin in clinical practice, they do not seem to offer any significant advantages over albumin (18). The main disadvantage of colloids is that there are reports of bleeding complications and renal impairment as a result of them (19). Gelatins have a contain high levels of potassium and calcium content and are therefore inappropriate for use during renal transplantation (20). The disadvantage of Dextran solutions is that they have a tendency to produce severe hypersensitivity reactions and also induce a coagulopathy (21,22). Hydroxyethyl starch (HES) is a synthetic colloid with a very good safety profile and therefore preferred to the other colloids. It has the lowest in vivo molecular weight and is therefore easily eliminated from the system. It is also easily degradable. The most recently done meta-analysis showed no adverse renal effects with HES 130/0.4 although the conclusion of the study stated that the data was not convincing enough about its safety (23).

Of the living related renal transplants, about 90% have immediate urine output. Delayed graft diuresis is found to decrease 1-year survival rate from 75% to 49% (24).
Patients awaiting renal transplantation usually are on renal replacement programmes and undergoing haemodialysis that may result in intravascular volume depletion. Haemodialysis done even a few hours prior to surgery may result in weight loss of up to 2 Kg or more, indicative of severe dehydration. Among the various intraoperative measures taken to stimulate urine output, intravascular volume expansion is the most important one. Intravascular volume expansion has been associated with improved renal blood flow and better immediate graft function (16, 26). Aggressive intraoperative volume expansion (30ml.Kg-1.h-1) is warranted because a delayed return renal graft function causes a 20-40% decrease in transplant graft survival (24,26).

Hence an appropriate intraoperative monitor is necessary to access fluid responsiveness. Clinical signs such as skin turgor, pulse rate and urine output are easy to assess but remain crude and unreliable. Static hemodynamic variables central venous pressure (CVP) have remained the standard measuring index. Maintaining a CVP between 10 and 15 mm of Hg optimizes cardiac output and renal blood flow ensuring good immediate graft function (16,24).
ASSESSMENT OF INTRAVASCULAR VOLUME

Hypovolaemia if uncorrected results in end organ hypoperfusion and eventually failure which is of special significance to the renal graft. Patients with end stage renal disease (ESRD) awaiting renal transplant are usually on haemodialysis and therefore in a state of fluid depletion. This state requires to be rapidly corrected during the course of the operation so as to achieve a state of normovolaemia by the time circulation to the graft is established. This is achieved by intravenous fluid administration.

It must also be borne in mind that volume expansion when unregulated can be deleterious and therefore is best directed by certain established goals. The concept of goal directed volume expansion has been extensively studied in critically ill patients with sepsis in intensive care units and therefore, most of the evidence available is in this category of patients. These “goals” are essentially to achieve and maintain certain haemodynamic parameters that reflect the volume status of the patient within established target ranges. Various parameters are used to gauge the adequacy of intravascular volume and these are broadly classified as ‘static’ and ‘dynamic’ parameters depending on whether or not they are influenced by heart lung interactions.
CARDIAC PHYSIOLOGY

The heart is as a muscular pump that is responsible for receiving de-oxygenated blood returned from the various organs in the body and pumping oxygenated blood that is distributed via the circulatory system to the same organs to enable their vital functions. This is achieved by a series of regularly recurring contractions.

This pump has two circuits that are interconnected and interdependent. The first circuit is the pulmonary circuit (also referred to as the pulmonary circulation) comprising the right atrium that receives de-oxygenated blood from the various organs via the superior and inferior vena cava and the right ventricle that pumps this de-oxygenated blood to the lungs via the pulmonary arteries to the lungs where gas exchange occurs. The blood once oxygenated returns to the heart via the pulmonary veins and enters the second circuit, the systemic circuit. The systemic circuit (also referred to as the systemic circulation) comprises the left atrium that receives oxygenated blood from the lungs via the pulmonary veins and the left ventricle that pumps it distributes this oxygenated blood to all organs. Usually the left ventricle pumps out approximately 50-60% of the blood it receives from the left atrium into the systemic circulation.
The body has other regulatory mechanisms that regulate distribution depending on the state of body function at the same time maintaining necessary blood flow to vital organs such as kidney, liver, brain, intestines and lung. These synchronised functioning of these two circuits, that requires rhythmic and synchronised relaxation and contraction of the four chambers is controlled by the pacemakers and conduction fibres. The two circuits are significantly different in terms of the pressure range in which they function. The systemic circulation is a high pressure system, whereas the pulmonary circulation is working at low pressure.

The volume of blood that is pumped out by the ventricles of the heart with every contraction is referred to as the stroke volume (SV). The stroke volumes of right and left ventricle are approximately equal. The ventricular end diastolic volume (EDV) is the volume of blood in the heart when the ventricles have been filled with blood from the atria. The volume of blood being pumped out of the ventricle is dependent on the volume of blood that it receives from the atria i.e. the stroke volume is dependent on the ventricular end diastolic volume. This is dependent on the total intravascular volume. This is referred to as the Frank-Starling principle or the Frank-Starling law.
The Cardiac output (CO) refers to the total volume of blood that is pumped out of the ventricles every minute (mL blood/min). It is a function of the stroke volume and the heart rate and is calculated by the formula:

\[
\text{Cardiac Output} = \text{stroke volume (mL) } \times \text{ heart rate (beats/min)}
\]

The perfusion of various organs in the body is directly dependant on the heart providing and adequate output at the adequate pressure. Therefore organ perfusion is dependent on the left ventricular end diastolic volume which in a normally functioning heart is proportionate to the total intravascular volume.

It is easier to measure pressure in the vascular compartments and cardiac chambers than the volume and since there is a known relationship between volume and pressure in a closed chamber, CVP is accepted as an indicator of Right ventricular end diastolic volume and the Left ventricular end diastolic pressure (LVEDP) measured by Swan-Ganz catheter, an indicator of left ventricular end diastolic volume (LVEDV). Since it is also known that the systemic and pulmonary circulations are in equilibrium, the CVP has become over time the most widely used indicator of intravascular volume.
However it must be borne in mind that this works on three assumptions; firstly that there is a direct linear relationship between pressure and volume, secondly that the right and left ventricles are in equilibrium and thirdly that there LVEDV always reflects the stroke volume.
Frank Starling principle (law)

The Frank–Starling law of the heart states that the stroke volume of the heart increases with increase in the volume of blood filling the heart (the end diastolic volume) when all other factors remain constant.

Figure 1 – Frank Starling law
As preload increases, left ventricular stroke volume increases. This occurs until a situation when the stroke volume is optimum. This relationship is due intrinsic ability that heart possesses to adapt to increasing volumes of blood inflow. The curve depicted in Figure 1 illustrates this relationship. The steep segment of the curve depicts a low preload state. In this state, when the preload is increased by increasing intravascular volume there will be a corresponding and significant increase in stroke volume. Beyond a certain point, continuing to increase the preload does not produce a corresponding increase in stroke volume and it tends to remain more or less constant. A patient on the steep segment of the curve is considered a “responder”

If the preload is known, it will help in predicting the patients responsiveness to fluids. However, the shape of the Frank-Starling curve is affected by ventricular function. When there is impairment of ventricular function, the curve becomes flattened. That implies that there is a much shorter steep segment to the curve. In these situations it is not possible to predict the effects of increasing the preload on stroke volume. (27)
Heart-lung interactions

The cardiac pump does not function in isolation. It is present within the musculoskeletal structure of the thoracic cavity which by itself creates pressure changes and gradients during normal inspiration and expiration. These pressure variations which are transmitted to the alveoli of the lungs have a bearing on the functioning of the heart, particularly when the ventilation is taken over by a mechanical ventilator.

Intermittent positive pressure ventilation (IPPV) produces changes in the intrathoracic pressure that affect the venous return. This results in the preload and afterload of both ventricles to vary cyclically during the phases of ventilation. During insufflation of the lung there is a decrease in the right ventricular preload and increase in afterload. Increased intrathoracic that occurs when the lungs are insufflated results in decreased venous return. This causes the preload to decrease. During inspiration there is also an increased transpulmonary pressure. This results in an increased right ventricular afterload. The simultaneous decrease in preload and increase in afterload lead to a decrease in right ventricular stroke volume. This becomes apparent after two to three heart beats (28).
STATIC PARAMETERS

Central venous pressure

The measurement of central venous pressure (CVP) is very common in clinical practice. It is relatively easy to perform at the bedside and can be measured with a simple saline manometer or even by simply making a note of jugular venous distension on physical examination. However in the intra-operative setting it is usually measured continuously using pressure transducers and electronic monitors. The origins of CVP monitoring can be traced back to as early as 1959 when it was first described by Hughes and Macgovern (29).

The CVP has three positive waves and two negative waves that are easily to visualize. The positive waves are the ‘a,’ ‘c,’ and ‘v’ waves and the negative waves are the ‘x’ and ‘y’ descents. The ‘a’ wave occurs as a result of atrial contraction, the ‘c’ wave is produced by the bulging of the tricuspid valves into the right atrium at the onset of right ventricular contraction. The ‘x’ descent occurs due to a drop in right atrial pressure when the right atrium relaxes. The ‘v’ wave is due to increased atrial pressure as it fills
during diastole. The ‘y’ descent is due to the fall in atrial pressure when the atrioventricular valve opens and allows the atrium to empty into the ventricle.

Among other factors, the ‘y’ descent is affected by the compliance of the heart and intra-thoracic pressure (30). During inspiration the “y” descent is more marked and this is useful to mark inspiration on the hemodynamic recording of patients who are breathing spontaneously.

The best place to measure CVP is the edge of the ‘c’ wave, also called the ‘z’ point. This represents the pressure in the atrium and thus the ventricle at the end of diastole.

![Figure 2 – CVP trace](image)

‘a’ wave – atrial contraction
‘c’ wave – bulging of the tricuspid valve at the beginning of systole
‘x’ descent – atrial relaxation
‘v’ wave – atrial filling during diastole.
‘y’ descent – opening of atrioventricular valve to allow the atrium to empty into the ventricle
The CVP has been used for many years to guide fluid management in patients undergoing surgery and in the intensive care unit (ICU). A survey conducted in Canada on of practices of intensive care physicians revealed that almost 90% of them used the CVP as a guide for decisions on fluid management in patients with early septic shock (31).

Changes in intrathoracic pressures produced by positive pressure ventilation especially with positive end-expiratory pressure (PEEP) cause the relationship between CVP and right ventricular end-diastolic volume becomes less accurate. Though CVP is a marker of right ventricular preload, it is assumed that it reflects the left ventricular preload.

Marik et al reviewed 24 studies and published a systematic review. They showed that the relationship between CVP and intravascular fluid status was actually poor and that it was not possible to predict the hemodynamic response to a fluid challenge based on the CVP. (32)
However, CVP continues to be widely used as a marker of preload and is also one of the components of the Surviving Sepsis guidelines. According to these guidelines, once lactate is $>4$ mmol/L or the patient continues to be hypotensive after a fluid challenge, the patients should be given fluids so as to maintain a target CVP of $\geq 8$ mm Hg (12 mm Hg in mechanically ventilated patients). (33)

**Pulmonary artery occlusion pressure**

The pulmonary artery catheter, also called the Swan-Ganz catheter was invented in 1970. It measures the pulmonary artery occlusion pressure (PAOP) which for many years was thought to accurately reflect the left ventricular preload. Recent evidence however has emerged to suggest that this was not the case and that PAOP was in reality a poor reflection of left ventricular preload (34).

The Fluid and Catheter Treatment Trial (FACTT) from the Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network compared the outcomes of patients with acute lung injury managed using two fluid therapy protocols; one guided by CVP
and the other guided by PAOP. The clinical outcomes of these two groups of patients were no different (35).

The reason for this is that the PAOP value reflects left ventricular end-diastolic pressure and not left ventricular end-diastolic volume (preload). The relationship between ventricular end-diastolic pressure and end-diastolic volume is not a simple linear relationship, but curvilinear and unpredictable (36,37). Therefore PAOP is inaccurate in patients who are being mechanically ventilated. The nature of this relationship is also the reason why CVP likewise does not accurately reflect the right ventricular volume.

Though both the CVP and LVEDP have the limitation that pressure volume relationship is not linear, they are both accepted commonly and widely as a guide to volume management. It must be borne in mind that cardiac diseases and other conditions that may make this relationship unpredictable do not exist while managing volume based on these pressure measurements(71).
Left ventricular end-diastolic area

It had become obvious that pressure measurements were not an accurate method of estimating the ventricular volume. The next step was to measure the dimensions of the ventricle using echocardiography and use these measurements to estimate the volume.

Left ventricular end diastolic area (LVEDA) is the area mapped in two dimensions and measured by transoesophageal echocardiography (TOE/TEE). It has been used by both intensivists and anaesthetists and extrapolated to estimate the left ventricular end diastolic volume. It appears that there is a good correlation between LVEDA and LVEDV and therefore also with left ventricular preload. Development of single-use transoesophageal echocardiography probes that may remain in place for up to 72 hours has enabled continuous monitoring of left ventricular volumes and function over time. This also allows treating clinicians to assess the patient’s hemodynamic response to therapeutic interventions. Though it may be logical to conclude that LVEDA accurately assesses LV function, the evidence is equivocal and LVEDA has not been found to be consistently useful (38-41).
Inferior vena cava collapsibility

The diameter of the inferior vena cava (IVC) can be measured as it enters the right atrium by standard surface or transthoracic echocardiography (TTE). It has been demonstrated that the IVC diameter correlates well with central venous pressure and right atrial pressure (42). The limitation of the IVC diameter measurement is that it essentially reflects the CVP and therefore all the limitations of using CVP as a measure of preload are applicable to it as well.

More accurate than measuring the diameter of the IVC diameter is to measure the collapsibility of the IVC. The IVC collapsibility index is mathematically derived from the IVC diameter and is expressed as a percentage.

\[
\frac{(IVC\,\text{dia \, at \, end-inspiration} - \, IVC\,\text{dia \, at \, end-expiration})}{IVC\,\text{dia \, at \, end-expiration}} \times 100
\]

It was demonstrated by Barbier et al that in septic shock, IVC ‘collapsibility’ measured by TTE predicted fluid responsiveness accurately (43).
However these measurements too are inaccurate in patients who are undergoing positive pressure ventilation. Variations in airway pressure tend to have an effect on the dimensions of the IVC and hence the IVC collapsibility index.

Although this technique seems to provide a quick and non invasive assessment of intravascular volume, it is inaccurate in patients undergoing surgery under general anaesthesia by positive pressure ventilation (44).

**Intrathoracic blood volume and global end diastolic volume**

Intrathoracic blood volume (ITBV) and Global end-diastolic volume (GEDV) are both hypothetical volume measurements calculated by the technique of thermodilution.

Despite the usefulness of GEDV and ITBV for assessment of hemodynamic status, they have not been validated (45-47).
It is evident that the main limitation of these static parameters in assessing ventricular preload and therefore intravascular volume is that they cease to be accurate in patients who are undergoing positive pressure mechanical ventilation as the relationship between pressure and volume is altered. Therefore these parameters may be unreliable in assessing intravascular volume of patients during the operation.

DYNAMIC PARAMETERS OF INTRAVASCULAR VOLUME

Over the last decade there has been extensive study on heart-lung interactions during mechanical ventilation and this knowledge has been used to assess fluid responsiveness in patients. These parameters that take into consideration the effect of thoracic and pulmonary pressures on the measure intravascular volume are the “dynamic” parameters and provide an accurate measure of intravascular volume.
Classification of dynamic indices:

Dynamic indices can be classified according the methodology used to predict preload variation. The first group of indices are those which depend on cyclic variations of stroke volume or stroke volume related hemodynamic parameters like pulse pressure or aortic blood flow determined by mechanical ventilation induced variations in intrathoracic pressure. The second group of indices are those based on cyclic variation of non stroke volume related hemodynamic parameters like vena cava diameter determined by mechanical ventilation. The third group are those based on preload redistribution manoeuvres like passive leg raising.

Pulse pressure variation and Stroke volume variation

The pulse pressure (difference between systolic and diastolic pressure) is directly proportional to left ventricular stroke volume and inversely related to arterial compliance. The Pulse pressure variation (PPV) is the variation in this difference during the course of the respiratory cycle. Stroke volume variation is the variation that occurs in stroke
volume during the respiratory cycle. Both PPV and SVV can be measured continuously by most standard cardiac monitors.

Pulse Pressure Variation and Stroke Volume Variation predict an individual patient’s position on the Starling curve. This is independent of ventricular function and compliance as well as pulmonary pressures and mechanics.

Marik et al showed that PPV and SVV accurately predicted those patients who were likely to be responders to fluid challenge, even during volume-controlled mechanical ventilation (48). Lopes et al also demonstrated in another study that when fluid management was based on the PPV, the frequency of postoperative complications, duration of mechanical ventilation, ICU and hospital length of stay were all significantly reduced (49).

There are however certain situations such as cardiac arrhythmias and spontaneous breathing when PPV and SVV may not accurately reflect intravascular volume. Both these measurements are influenced by tidal volume and airway pressure. Therefore if tidal volume and airway pressure are controlled, PPV and SVV will accurately reflect intravascular volume. The effect of tidal volume on the ability of SVV
and PPV to predict intravascular volume has been studied and demonstrated. Reuter et al. demonstrated the effect of depth of tidal volume on SVV (51) and De Baker et al demonstrated that the tidal volume was to be set at least at 8 mL/kg for the PPV readings to be accurate (52).

**Pulse oximeter plethysmographic waveform**

Variations in the plethysmographic waveform amplitude during respiration have been correlated with respiratory variations in PPV and can predict fluid responsiveness in patients undergoing surgery (53). The pulsatile infrared signal is indexed against the nonpulsatile signal to derive the perfusion. This corresponds with the amplitude of the pulsoximeter wave.

The ‘pleth variability index’ (PVI) is an automated measure of the dynamic change in the perfusion index (PI) that occurs during a respiratory cycle. Zimmerman et al showed that PVI was as accurate as SVV in predicting fluid responsiveness (53). Though this technique seems an excellent and at the same time simple and non-
invasive method of monitoring of fluid responsiveness it may be erroneous in patients who are on inotropes as they will not have good waves on pulse oximetry.

**Dynamic changes in aortic flow velocity**

Transoesophageal echocardiography is used to measure changes in aortic blood flow velocity at the aortic annulus. Aortic blood flow volume changes should reflect changes in LV stroke volume assuming that the diameter of the aorta is constant.

**Superior vena cava collapsibility index**

Fluid responsiveness is predicted by the changes in superior vena cava (SVC) diameter that occur in a cyclical manner. It is measured using transoesophageal echocardiography.
Off all the dynamic parameters described above, the one that is simplest to measure and therefore the focus of further discussion is the PPV. The most commonly used static parameter is CVP and is often used as the standard against which PPV and other newer parameters are compared.
The pulse pressure is defined as the difference between the systolic and the diastolic pressure. It is directly proportional to LV stroke volume. The pulse pressure is not directly influenced by the variations in intrathoracic pressure produced by mechanical ventilation. This is because mechanical ventilation affects both diastolic and systolic pressures and this effect gets cancelled out as this is a mathematical difference. Changes in peripheral pulse pressure during the respiratory cycle therefore reflect the LV stroke volume (54). There has been a lot of interest recently in studying the use of pulse pressure (PPV) to assess fluid responsiveness and fluid status.

It was possible to discriminate between responders (defined as patients who experienced an increase in cardiac index of 15% in response to volume expansion) and non-responders using PPV. A cut off value of 13% had sensitivity and a specificity of 94 and 96%, respectively.

PPV was a more reliable indicator of fluid responsiveness than the respiratory changes in systolic pressure (55). The increase in cardiac index as a result of volume expansion correlated well with a decrease in PPV, such that changes in PPV could be
used to assess the hemodynamic changes that occurred as a result of volume expansion. Various studies have been done using these dynamic indices as markers of volume in patients (55).

Figure 3 – Impact of mechanical ventilation on the stroke volume
Until recently, it was not possible to obtain a realtime PPV value as it had to be calculated offline. Of late most standard bed side monitors have software built in to automatically calculate and display the PPV as a continuous realtime reading. This has made it extremely simple to measure this parameter without any additional procedures or the use of special monitoring devices.
ADVANTAGES OF PPV OVER CVP

Of all the parameters listed above the simplest to estimate are the central venous pressure (CVP) and the pulse pressure variation (PPV).

Central venous pressure is considered equivalent to right atrial pressure, which, in the absence of tricuspid valve disease, is equal to right ventricular end diastolic pressure. Central venous pressure in addition to tricuspid valve abnormality is influenced by intravascular volume and right ventricular function. It therefore can be considered to be an accurate indicator of right ventricular preload in the absence of any right heart disease.

It however must be remembered that measuring the CVP alone cannot provide an assessment of volume status and assessment of the preload of the heart. This is because CVP and cardiac output are determined by the interaction of two function curves: the cardiac function curve and the venous return curves (56). Therefore to interpret CVP one has to have a fairly good idea of the cardiac output. This does not
have to be an actual measurement of cardiac output and could even be a clinical assessment (57).

Figure 4 – interaction of cardiac function and venous return curves
Dynamic measures such as the systolic pressure variation (SPV), pulse pressure variation (PPV) and the stroke volume variation (SVV) are derived from the analysis of the arterial pressure waveform.

Dynamic variables based on the respiratory induced arterial pressure variations (RIAPV) appear as cyclical peaks and troughs on the arterial pressure waveform. Intermittent positive-pressure ventilation results in the occurrence of cyclic changes in the preload and after load of both the ventricles. Mechanical insufflation decreases right ventricular preload and increases its afterload. The reduced RV preload and increased RV afterload leads to a decrease in RV stroke volume. This reduction in RV ejection during inspiration leads to a decreased return to the left atrium and therefore a reduction in left ventricle (LV) filling after a phase lag of two or three heartbeats because of the time it takes for blood to go through the pulmonary circulation. This is referred to as the pulmonary transit time. The resulting LV preload reduction causes a subsequent decreased LV stroke volume. There is therefore a cyclic variation that occurs in the stroke volumes of both the left and right ventricles as a result of positive pressure ventilation. These changes are more pronounced when the ventricles operate on the steep rather than the flat portion of the Frank-Starling curve. Therefore, the magnitude
of the respiratory change in LV stroke volume is an indicator of biventricular preload
dependence predictive factors of volume expansion efficacy to select patients who
could benefit from volume expansion and avoid ineffective fluid therapy in
“nonresponders” in whom inotropic and/or vasopressor support should preferentially be
used (48).

PPV is derived from the arterial catheter placed to measure ABP by means of
commonly available transducers and modules. The airway pressure too is monitored to
estimate the commencement and completion of the respiratory cycle. Pulse pressure
(PP) is calculated as the difference between systolic and diastolic arterial pressure.
Maximal PP (PPmax) and minimal PP (PPmin) are calculated over a single respiratory
cycle, which is determined from the airway pressure signal. PPVs are calculated in
terms of PPmax and PPmin and expressed as a percentage.

The PPV is calculated using the following formula:-

\[
PPV = \frac{(\text{PP max} - \text{PP min})}{\frac{1}{2} \times (\text{PP max} + \text{PP min})} \times 100
\]

Recently monitoring software has been developed that enables the automated
estimation and display of PPV (58).
Though commonly used, the standard preload indices such as Central Venous Pressure (CVP) have been shown to be inferior to Pulse Pressure Variation (PPV) and Stroke Volume Variation (SVV) in predicting cardiac function (58-60). Measurement of PPV has the advantage of being able to predict an increase in cardiac output induced by volume expansion even before fluids are administered (61). PPV being a dynamic parameter is in theory, a more accurate reflection of the intravascular fluid volume than CVP which is a static parameter (48, 61-63). In spite of this recent knowledge CVP enjoys more favour as a measure of intra-vascular volume mainly because PPV has not been studied in many situations, one of them being in patients undergoing renal transplantation.
Auler et al studied if fluid responsiveness could be predicted by PPV in patients who were being mechanically ventilated. This was a prospective observational study. 59 patients who were mechanically ventilated in the postoperative period following cardiac surgery were studied. None of the patients were at high risk for fluid overload as a result of fluid administration (pulmonary artery occlusion pressure < 20 mm Hg, left ventricular ejection fraction ≥ 40%). A peripheral arterial cannula and a pulmonary artery catheter were inserted in all patients. Cardiac filling pressures and cardiac output were measured before and after intravascular fluid administration and pulse pressure variation was automatically calculated and continuously monitored. In 39 of the 59 patients (approximately 66%) there was an increase cardiac output by at least 15% with administration of intravenous fluids. These patients were considered responders and the others, non responders. Both responders and nonresponders had comparable right atrial and pulmonary artery occlusion pressures prior to fluid administration. However, there was a significantly greater variation in pulse pressure in responders than in nonresponders. A cut-off value of 12% allowed identification of responders with a sensitivity of 97% and a specificity of 95%. They concluded that pulse pressure variation was a reliable method to predict fluid responsiveness after cardiac surgery (64)
Kramer et al studied ability of PPV to predict fluid responsiveness in patients who had undergone coronary artery bypass grafting. The study was done to determine whether fluid responsiveness as evidenced by an increase in cardiac output could be predicted by the degree of pulse pressure variation (PPV) and systolic pressure variation (SPV) in postoperative patients following CABG, and to determine whether PPV was superior to SPV in this setting. Twenty-one patients who had undergone CABG were studied immediately after arrival in the ICU following the operation. Hemodynamic parameters such as central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), Cardiac output, SPV and PPV were measured when the patient was brought into the ICU. All the patients received a rapid infusion fo 500mL of intravenous fluid after which all the parameters were measured again. They were classified into two groups based on whether or not the carciac output had increased by ≥ 12%. Those whose cardiac output increased were considered to be fluid responders and the others, non responders. The ability of the various haemodynamic parameters to distinguish between responders and nonresponders was compared.

In response to the fluid infusion, 6 patients were responders and 15 were nonresponders. It was found that there was no difference in the change in CVP and PAOP between these two groups. However, the SPV and the PPV were significantly
higher in responders than in nonresponders. ROC curve analysis suggested that the PPV was the best predictor of fluid responsiveness. The ideal PPV threshold for distinguishing responders from nonresponders was found to be 11. A PPV value of >11% predicted an increase in CO with 100% sensitivity and 93% specificity. It was also shown that PPV was superior to SPV at predicting fluid responsiveness. Both of these measures were far superior to both CVP and PAOP (65).

Benes et al studied the use of stroke volume variation in patients coming for high risk major abdominal surgery. The study aimed at evaluating whether fluid management and optimization based on stroke volume variation (SVV) made a difference to the postoperative vital organ function and morbidity. This study was done on high risk patients undergoing major abdominal surgery. Fluid fluid optimization guided by SVV was found to be associated with better a significantly lower incidence of postoperative complication (66).

Lopes et al studied goal-directed fluid management based on achieving a target value of pulse pressure variation during high-risk surgery. This was a prospective, randomized, single-centre study. The primary end point was the length of postoperative stay in hospital. Pulse pressure variation was monitored during the surgery and fluid management was carried out keeping the PPV targeted to less than 10%. They found
that the group that received IV fluids based on PPV had less complications in the post operative period and had shorter post operative stay in hospital (67).

Mayer et al performed a randomised controlled trial to aimed to study the advantage of goal-directed intraoperative fluid therapy that was based on cardiac index over intra-operative fluid therapy based on standard protocol in patients undergoing abdominal surgery and to evaluate possible improvements in patient outcome as determined by the duration of hospital stay and the incidence of complications compared to a standard fluid management protocol. Cardiac index was estimated using a minimally invasive, easy to use, commercially available device (FloTrac/Vigileo), 60 high-risk patients scheduled for major abdominal surgery were included and randomised into one of two arms of 30 each. Patients in the study arm were monitored using a FloTrac/Vigileo device and had fluid management using a cardiac index based intraoperative optimization protocol. Patients in the control group were managed using traditional monitoring and a fluid management protocol. It was found that patients in the study group in whom intraoperative goal-directed hemodynamic optimization protocol using the FloTrac/Vigileo device was carried out, had a shorter duration of hospital admission and fewer complications compared to those in the control arm (68).
This study aims to assess how accurately PPV reflects adequacy of intravascular volume in patients who are undergoing renal transplantation by checking its correlation with time to graft diuresis onset.

We have assumed that time to graft diuresis is a good indicator of the intravascular volume status,
MATERIALS AND METHODS
STUDY DESIGN:
Observational study – Cohort design

INCLUSION CRITERIA:
All patients with ESRD undergoing renal transplantation

DURATION OF STUDY:
January 2014 to August 2014

EXCLUSION CRITERIA:
Age < 18 yrs.
Ejection fraction < 40%
Cardiomyopathy
Arrhythmias
Emergency transplants.
PROCEDURE

- Clearance was obtained from the institutional review board to perform the study in its present format.
- All adult patients undergoing elective renal transplantation who did not have significant cardiac dysfunction were included after obtaining written consent.
- In all patients peripheral venous access was first established and basic monitoring (ECG and Pulse-oximeter) was commenced. End tidal CO2 monitoring was commenced after induction.
- Anaesthesia was induced with Fentanyl 2mcg/Kg, Propofol 2mg/Kg and Rocuronium 0.1mg/Kg.
- Patients were intubated using an appropriate sized endotracheal tube and intermittent positive pressure ventilation established using a mechanical ventilator (Datex Ohmeda Aestiva / Aespire) with volume control ventilation and tidal volume set at 8ml/Kg.
- All patients had a triple lumen 8F catheter inserted into the internal jugular under aseptic precautions to measure CVP and a 20G cannula into the radial artery to monitor arterial blood pressure (ABP) as was standard practice.
- All hemodynamic parameters including the CVP and ABP were measured continuously throughout the procedure using pressure.
- PPV is mathematically derived from the ABP using the following formula:

\[
PPV = \frac{1}{2} \times \frac{(PP_{max} - PP_{min})}{\frac{1}{2} \times (PP_{max} + PP_{min})} \times 100
\]
• This calculation was performed automatically by the anaesthetic monitor (Philips Intelli Vue MP50) and displayed as a continuous real-time value.

• All variables as mentioned in the proforma (attached) were recorded every 15 minutes.

• Intra-operative fluid management was planned to target a CVP of 15mm of Hg.

• It was planned that hypotension would be treated by either fluid boluses or vasopressors such as ephedrine depending on the CVP.

• The PPV value was recorded but not used to make decisions in fluid management.

• The time to urine output (in seconds) following revascularization of the renal graft (release of vascular clamps) was recorded and this was used as an indirect indicator of adequacy of intravascular volume.

• The total estimated blood loss was noted down at the end of surgery.

• Reversal of neuromuscular blockade was done with neostigmine and glycopyrolate.

• Patients were extubated when fully awake.

• Post operatively patients were shifted to the recovery area within the operating theatre complex where they continued to be monitored.

• Urine output in the first 4 hours was measured and recorded.
OUTCOMES

Primary - Time to urine output (sec)

Secondary - Urine output (mL)

As all hemodynamic measurements were recorded directly from a monitor there was no room for bias or subjective error.
Figure 5 – Screen shot from Philips Intelli-Vue MP50 monitor
## SAMPLE SIZE CALCULATION

Regression methods - Sample size for correlation coefficient analysis (testing against population value)

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In order to get a correlation of -0.8 (correlation between PPV and time to urine production), and show that it is significantly different from null hypothesis correlation of -0.5, instead of 0, keeping alpha and beta errors at 5% and 20% respectively we need to study 29 subjects. However this size is 43, when we test the correlation of -0.7 with -0.4 with the same errors levels. Therefore, we planned to study 40 subjects.
The PPV and time to urine were considered as continuous variables to study the correlation between the two variables and construct the scatter plot. However, for the ROC analysis to the time to urine was categorized as <120 seconds and $\geq 120$ seconds.

Data was entered in EPIDATA software and was cleaned using Box-Cox plots, histogram and scatter plots. The histograms were used as a guide to identify the distribution such as normal or non-normal etc. It was planned to derive the Person Correlation coefficient if the distribution is nearly normal and to use a nonparametric method if the distribution was not normal. Time to urine was categorized as <120 sec and $\geq 120$ sec for the purpose of the ROC curve analysis and the best cut off was identified. After finding the best cut off value validity and predictive values such as Sensitivity, Specificity, Positive and Negative Predictive values will be estimated and presented with 95% CI.
RESULTS
All patients undergoing elective renal transplantation

37

Cohort of patients included in the study

33

Measurement of CVP
Measurement of Arterial BP, PPV

Assessment of correlation of PPV with time to urine output

Exclusion Criteria
Consent denied - 2
Age < 18 yrs - 1
EF < 40% - 1
Cardiomyopathy - 0
Arrhythmias - 0
**CONSOLIDATED DATA OF ALL SUBJECTS RECRUITED**

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<td>8</td>
<td>14</td>
<td>3</td>
<td>7</td>
<td>62</td>
<td>700</td>
</tr>
<tr>
<td>27</td>
<td>23</td>
<td>M</td>
<td>22</td>
<td>10</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>45</td>
<td>2100</td>
</tr>
<tr>
<td>28</td>
<td>19</td>
<td>F</td>
<td>18</td>
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<td>15</td>
<td>12</td>
<td>6</td>
<td>3</td>
<td>7</td>
<td>660</td>
<td>2000</td>
</tr>
<tr>
<td>29</td>
<td>43</td>
<td>M</td>
<td>ND</td>
<td>12</td>
<td>12</td>
<td>11</td>
<td>12</td>
<td>21</td>
<td>20</td>
<td>10</td>
<td>1500</td>
</tr>
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<td>24</td>
<td>F</td>
<td>46</td>
<td>7</td>
<td>14</td>
<td>7</td>
<td>13</td>
<td>4</td>
<td>6</td>
<td>203</td>
<td>2400</td>
</tr>
<tr>
<td>31</td>
<td>57</td>
<td>M</td>
<td>17</td>
<td>13</td>
<td>16</td>
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<td>7</td>
<td>3</td>
<td>3</td>
<td>88</td>
<td>3200</td>
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<tr>
<td>32</td>
<td>21</td>
<td>M</td>
<td>21</td>
<td>0</td>
<td>14</td>
<td>20</td>
<td>13</td>
<td>6</td>
<td>4</td>
<td>70</td>
<td>3800</td>
</tr>
<tr>
<td>33</td>
<td>20</td>
<td>M</td>
<td>20</td>
<td>11</td>
<td>15</td>
<td>17</td>
<td>16</td>
<td>14</td>
<td>20</td>
<td>300</td>
<td>2500</td>
</tr>
</tbody>
</table>

**Mean 32.18 19 8.818182 13.18182 13.8182 8.39394 7.72727 6.90909**

**TOD** – Time from last haemodialysis  
**CVP CCR** – CVP at cross clamp release  
**PPV start** – PPV at start of operation  
**PPV UO** – PPV when urine output started  
**UO 4 hrs** – Urine output in first 4 hours
DEMOGRAPHICS

Of the 37 elective renal transplants that happened during the study period, 33 patients were included in the study. Two patients did not consent to participate, one was less than 18 years of age and one had severe cardiac disease with an ejection fraction of 40%.

There were 22 males and 11 females and the mean age of the study group was 32.2 years.

Figure 6 - Sex distribution

- Male: 67%
- Female: 33%
Most patients (22 of 33) were hypertensive. This was probably a consequence of the renal failure rather than its cause.

Of the 33, 29 were on maintenance haemodialysis and one was on continuous ambulatory peritoneal dialysis. Three were not on any form of renal replacement prior to transplant. The average duration between last haemodialysis and transplant for the 29 patients that were on haemodialysis was 19 hours.
CVP MEASUREMENT

At the start of the operation only 16 of the 33 patients had CVP that was within the desired range of 10-15 mm of Hg. 17 of the 33 patients had a CVP below the desired range of 10-15 mm Hg.

At the time of cross clamp release, 22 of the 33 patients had a CVP within the desired range of 10-15 mm Hg and 6 patients had CVP over 15 mm Hg. Only 5 patients had CVP still less than 10 mm Hg.

<table>
<thead>
<tr>
<th></th>
<th>Start of operation</th>
<th>Reperfusion of graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVP &lt; 10 mm Hg</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>CVP 10 -15 mm Hg</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>CVP &gt; 15 mm Hg</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>
This shows that a significant number of the patients were in a fluid depleted at the start of the operation, but with intra-operative fluid management this state was corrected in most of them.

**PRIMARY OUTCOME MEASURE – TIME TO URINE OUTPUT**

When grouped according to time to urine output it was observed that most 24 of the 33 patients (72.7%) had a urine output within 120 seconds of revascularization of the graft as illustrated in figure 5.

![Figure 7 – Distribution of patients according to time to urine output](image-url)
DESCRIPTIVE STATISTICS OF PULSE PRESSURE VARIATION AT CROSS CLAMP RELEASE (PPV-CCR) AND TIME TO URINE OUTPUT (TUO):

All baseline variables were summarized using descriptive statistical methods (Mean, Standard deviation, Frequencies and Percentages).

The mean and the median values of the PPV and the two outcome variables, Time to urine output (TUO) and Urine output in the first 4 hours (4 hr UO) are as follows:-

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean(SD)</th>
<th>Median (IQR)</th>
<th>Min</th>
<th>max</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVP (in mm Hg)</td>
<td>13.18 (4.29)</td>
<td>14.00 (5.00)</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>PPV CCR (%)</td>
<td>7.73 (4.30)</td>
<td>7.00 (6.00)</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>TUO (in sec)</td>
<td>133.15 (140.37)</td>
<td>88.00 (77.00)</td>
<td>3</td>
<td>660</td>
</tr>
<tr>
<td>4 hr UO (in ml)</td>
<td>1954.24 (830.10)</td>
<td>2000.00 (900.00)</td>
<td>100</td>
<td>3800</td>
</tr>
</tbody>
</table>
It is evident from the above table that both Pulse Pressure Variation measurements at the time of cross clamp release (PPV-CCR) and Time to Urine Output (TUO) were not normally distributed. This was confirmed by the Shapiro Wilk test that is a statistical test for normality (p value=0.003 for PPV CCR & p value=0.000 for TUO). The time to urine output varied from as low as 3 seconds to as 660 seconds.

This is also evident from the histograms and Box Cox plots of these two variables. These plots indicate that both the variables were not normally distributed and with presence of outliers.
Figure 8 – Histogram of Pulse pressure variation at cross clamp release (PPV CCR):
Figure 9 – Box Cox Plot of PPV CCR:

There was one patient with a PPV of 21% at the time of cross clamp release and this was clearly an outlier. This patient had a CVP of 11 mm of Hg at the time of cross clamp release, which was within the normal range of 10-155 mm of Hg, and the time to urine output was 10 seconds, which too was well within the desired time limit.
Figure 10 – Histogram of Time to Urine Output (TUO) (in sec)
Though this distribution was closer to normal than the distribution of PPV, there were four outliers with very delayed urine outputs.
There was no obvious linear correlation between the CVP and TUO when plotted together as illustrated in figure 10. The CVP measurements are arranged in ascending order and there is no corresponding inverse linear pattern as would be expected.
CORRELATION BETWEEN PULSE PRESSURE VARIATION (PPV) AND TIME TO URINE OUTPUT

PPV was measured automatically by the monitor but these values did not influence decisions on fluid management. There was no obvious linear correlation between the PPV and TUO when plotted together as illustrated in figure 11. The PPV measurements are arranged in ascending order and there is no corresponding linear pattern.

Figure 13 – Distribution of TUO measurements after arranging PPV in order
Scatter Plot of Pulse pressure variation at cross clamp release (PPV-CCR) and time to urine output (TUO)

Figure 14 – Scatter plot of PPV-CCR and TUO
Correlation between PPV CCR and TUO (Non parametric Spearman)

<table>
<thead>
<tr>
<th>Correlations</th>
<th>PPV CCR (%)</th>
<th>TUO (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spearman's rho Correlation Coefficient</td>
<td>1.000</td>
<td>.002</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.</td>
<td>.990</td>
</tr>
<tr>
<td>N</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>TUO (sec) Correlation Coefficient</td>
<td>.002</td>
<td>1.000</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.990</td>
<td>.</td>
</tr>
<tr>
<td>N</td>
<td>33</td>
<td>33</td>
</tr>
</tbody>
</table>

There was no correlation between pulse pressure variation at cross clamp release (PPV CCR) and Time to Urine Output (TUO).
Based on the scatter plot, the outliers were removed (considered only TUO less than or equal to 250) i.e., 4 observations were removed.

**Scatter Plot of PPV CCR and TUO after deleting the outliers:**

![Scatter plot of PPV-CCR and TUO after deleting outliers](image)

*Figure 15 – Scatter plot of PPV-CCR and TUO after deleting outliers*
Correlation between PPV CCR and TUO (Non parametric Spearman) after removing the outliers:

<table>
<thead>
<tr>
<th></th>
<th>PPV CCR (%)</th>
<th>TUO (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spearman's rho PPV CCR</td>
<td>1.000</td>
<td>.038</td>
</tr>
<tr>
<td>Correlation Coefficient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.</td>
<td>.843</td>
</tr>
<tr>
<td>N</td>
<td>29</td>
<td>29</td>
</tr>
</tbody>
</table>

There was no correlation between pulse pressure variation at cross clamp release (PPV CCR) and Time to Urine Output (TUO) even after removing the outliers.
ROC analysis using 60 seconds as the cut off value for time to urine output

ROC curve

Sensitivity %

100% - Specificity %
Area under the ROC Curve:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Area</td>
<td>0.5000</td>
</tr>
<tr>
<td>Std. Error</td>
<td>0.1134</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.2777 to 0.7223</td>
</tr>
<tr>
<td>P value</td>
<td>1.000</td>
</tr>
</tbody>
</table>

From the graph of ROC curve, the best cut off may be taken as “≥8” which gives the Sensitivity of 50% and Specificity of 71.43%. The Likelihood Ratio suggests the same best cut off value.

The sensitivity of 50% and specificity of 71.43% indicate that this PPV is highly specific but not very sensitive.
ROC analysis using 120 seconds as the cut off for time to urine output

**ROC curve**

![ROC curve diagram]

- Sensitivity %
- 100% - Specificity %
- Time intervals: $\geq 4$, $\geq 5$, $\geq 6$, $\geq 7$, $\geq 8$, $\geq 9$, $\geq 10$, $\geq 12$, $\geq 13$, $\geq 15$
Area under the ROC Curve:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Area</td>
<td>0.5694</td>
</tr>
<tr>
<td>Standard Error</td>
<td>0.1334</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.3079 to 0.8310</td>
</tr>
<tr>
<td>P value</td>
<td>0.5443</td>
</tr>
</tbody>
</table>

From the graph of ROC curve, the best cut off was taken as “≥10” which gives the Sensitivity of 55.56% and Specificity of 83.33%. The Likelihood Ratio suggests the same best cut off value.

The sensitivity of 55.56% and specificity of 83.33% indicate that PPV is highly specific but not very sensitive.
It was considered more appropriate to use 120 as the cut off as most patients would fall within the desired range and therefore the results would be clinically more relevant.

The sensitivities and specificities from the ROC curve are in the tables that follow.
<table>
<thead>
<tr>
<th>Cutoff</th>
<th>Sensitivity%</th>
<th>95% CI</th>
<th>Specificity%</th>
<th>95% CI</th>
<th>Likelihood ratio</th>
<th>PPV%</th>
<th>95% CI of PPV</th>
<th>NPV%</th>
<th>95% CI of NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;= 4</td>
<td>88.89</td>
<td>51.75% to 99.72%</td>
<td>12.5</td>
<td>2.656% to 32.36%</td>
<td>1.016</td>
<td>27.59</td>
<td>11.32</td>
<td>43.85</td>
<td>75.00</td>
</tr>
<tr>
<td>&gt;= 5</td>
<td>55.56</td>
<td>21.20% to 86.30%</td>
<td>25</td>
<td>9.773% to 46.71%</td>
<td>0.7407</td>
<td>21.74</td>
<td>4.88</td>
<td>38.60</td>
<td>60.00</td>
</tr>
<tr>
<td>&gt;= 6</td>
<td>55.56</td>
<td>21.20% to 86.30%</td>
<td>37.5</td>
<td>18.80% to 59.41%</td>
<td>0.8889</td>
<td>25.00</td>
<td>6.02</td>
<td>43.98</td>
<td>69.23</td>
</tr>
<tr>
<td>&gt;= 7</td>
<td>55.56</td>
<td>21.20% to 86.30%</td>
<td>45.83</td>
<td>25.55% to 67.18%</td>
<td>1.026</td>
<td>27.78</td>
<td>7.09</td>
<td>48.47</td>
<td>73.33</td>
</tr>
<tr>
<td>&gt;= 8</td>
<td>55.56</td>
<td>21.20% to 86.30%</td>
<td>58.33</td>
<td>36.64% to 77.89%</td>
<td>1.333</td>
<td>33.33</td>
<td>9.48</td>
<td>57.19</td>
<td>77.78</td>
</tr>
<tr>
<td>&gt;= 9</td>
<td>55.56</td>
<td>21.20% to 86.30%</td>
<td>75</td>
<td>53.29% to 90.23%</td>
<td>2.222</td>
<td>45.45</td>
<td>16.03</td>
<td>74.88</td>
<td>81.82</td>
</tr>
<tr>
<td>&gt;= 10</td>
<td>55.56</td>
<td>21.20% to 86.30%</td>
<td>83.33</td>
<td>62.62% to 95.26%</td>
<td>3.333</td>
<td>55.56</td>
<td>23.09</td>
<td>88.02</td>
<td>83.33</td>
</tr>
<tr>
<td>&gt;= 11</td>
<td>44.44</td>
<td>13.70% to 78.80%</td>
<td>83.33</td>
<td>62.62% to 95.26%</td>
<td>2.667</td>
<td>50.00</td>
<td>15.35</td>
<td>84.65</td>
<td>80.00</td>
</tr>
<tr>
<td>&gt;= 12</td>
<td>44.44</td>
<td>13.70% to 78.80%</td>
<td>91.67</td>
<td>73.00% to 98.97%</td>
<td>5.333</td>
<td>66.67</td>
<td>28.95</td>
<td>100.00</td>
<td>81.48</td>
</tr>
<tr>
<td>&gt;= 13</td>
<td>22.22</td>
<td>2.815% to 60.01%</td>
<td>91.67</td>
<td>73.00% to 98.97%</td>
<td>2.667</td>
<td>50.00</td>
<td>1.00</td>
<td>99.00</td>
<td>75.86</td>
</tr>
<tr>
<td>&gt;= 15</td>
<td>0</td>
<td>0.0% to 33.63%</td>
<td>91.67</td>
<td>73.00% to 98.97%</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>70.97</td>
</tr>
<tr>
<td>&gt;= 18</td>
<td>0</td>
<td>0.0% to 33.63%</td>
<td>95.83</td>
<td>78.88% to 99.89%</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>71.88</td>
</tr>
</tbody>
</table>

**SENSITIVITY AND SPECIFICITY VALUES USING DIFFERENT CUTOFFS OF PPV (TAKING 120 SECONDS TO BE DESIRED TIME TO URINE OUTPUT)**

The best cut off value was ≥10%. Therefore the targeted PPV should be <10% to predict post transplant diuresis in under 120 seconds.
<table>
<thead>
<tr>
<th>Cutoff</th>
<th>Sensitivity%</th>
<th>95% CI of Sensitivity</th>
<th>Specificity%</th>
<th>95% CI of Specificity</th>
<th>Likelihood ratio</th>
<th>PPV%</th>
<th>95% CI of PPV</th>
<th>NPV%</th>
<th>95% CI of NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;=4</td>
<td>84.62</td>
<td>65.13% to 95.64%</td>
<td>0</td>
<td>0.0% to 40.96%</td>
<td>0.85</td>
<td>75.86</td>
<td>60.29 to 91.44</td>
<td>0.00</td>
<td>0.00 to 0.00</td>
</tr>
<tr>
<td>&gt;=5</td>
<td>65.38</td>
<td>44.33% to 82.79%</td>
<td>14.29</td>
<td>0.3610% to 57.87%</td>
<td>0.76</td>
<td>73.91</td>
<td>55.97 to 91.86</td>
<td>10.00</td>
<td>0.00 to 28.59</td>
</tr>
<tr>
<td>&gt;=6</td>
<td>61.54</td>
<td>40.57% to 79.77%</td>
<td>42.86</td>
<td>9.899% to 81.59%</td>
<td>1.08</td>
<td>80.00</td>
<td>62.47 to 97.53</td>
<td>23.08</td>
<td>0.17 to 45.98</td>
</tr>
<tr>
<td>&gt;=7</td>
<td>53.85</td>
<td>33.37% to 73.41%</td>
<td>42.86</td>
<td>9.899% to 81.59%</td>
<td>0.94</td>
<td>77.78</td>
<td>58.57 to 96.98</td>
<td>20.00</td>
<td>0.00 to 40.24</td>
</tr>
<tr>
<td>&gt;=8</td>
<td>50</td>
<td>29.93% to 70.07%</td>
<td>71.43</td>
<td>29.04% to 96.33%</td>
<td>1.75</td>
<td>86.67</td>
<td>69.46 to 100.00</td>
<td>27.78</td>
<td>7.09 to 48.47</td>
</tr>
<tr>
<td>&gt;=9</td>
<td>38.46</td>
<td>20.23% to 59.43%</td>
<td>85.71</td>
<td>42.13% to 99.64%</td>
<td>2.69</td>
<td>90.91</td>
<td>73.92 to 100.00</td>
<td>27.27</td>
<td>8.66 to 45.88</td>
</tr>
<tr>
<td>&gt;=10</td>
<td>30.77</td>
<td>14.33% to 51.79%</td>
<td>85.71</td>
<td>42.13% to 99.64%</td>
<td>2.15</td>
<td>88.89</td>
<td>68.36 to 100.00</td>
<td>25.00</td>
<td>7.68 to 42.32</td>
</tr>
<tr>
<td>&gt;=11</td>
<td>26.92</td>
<td>11.57% to 47.79%</td>
<td>85.71</td>
<td>42.13% to 99.64%</td>
<td>1.89</td>
<td>87.50</td>
<td>64.58 to 100.00</td>
<td>24.00</td>
<td>7.26 to 40.74</td>
</tr>
<tr>
<td>&gt;=13</td>
<td>11.54</td>
<td>2.446% to 30.15%</td>
<td>85.71</td>
<td>42.13% to 99.64%</td>
<td>0.81</td>
<td>75.00</td>
<td>32.57 to 100.00</td>
<td>20.69</td>
<td>5.95 to 35.43</td>
</tr>
<tr>
<td>&gt;=15</td>
<td>3.846</td>
<td>0.09733% to 19.64%</td>
<td>85.71</td>
<td>42.13% to 99.64%</td>
<td>0.27</td>
<td>50.00</td>
<td>0.00 to 100.00</td>
<td>19.35</td>
<td>5.45 to 33.26</td>
</tr>
<tr>
<td>&gt;=18</td>
<td>0</td>
<td>0.0% to 13.23%</td>
<td>85.71</td>
<td>42.13% to 99.64%</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00 to 0.00</td>
<td>18.75</td>
<td>5.23 to 32.27</td>
</tr>
</tbody>
</table>

SENSITIVITY AND SPECIFICITY VALUES USING DIFFERENT CUTOFFS OF PPV (TAKING 60 SECONDS TO BE DESIRED TIME TO URINE OUTPUT)

The best cut off value was ≥8%. Therefore the targeted PPV should be <8% to predict post transplant diuresis in under 60 seconds.
DISCUSSION
Outcome following renal transplantation is dependent on many factors some of these are immunological and therefore not under the control of the surgical procedure. Also donor kidney related factors have a role to play in graft function and outcomes. There are technical or mechanical factors often directly related to the actual surgical procedure which have over the years been standardized. Of the technical factors, the one factor that is directly under the control of the anaesthesiologist is the intravascular volume status of the recipient. This in turn has a bearing on the cardiac output and therefore perfusion of the graft. The intravascular volume status is controlled effectively by fluid management.

Fluid management in renal transplant can be specially challenging to the anaesthesiologist as most patients are in a state of fluid depletion as a result of haemodialysis while waiting for a transplant. There is a need to rapidly correct this intravascular depletion before the time of perfusion of the renal graft that occurs with vascular cross clamps on the vascular pedicle of the graft being released. To ensure appropriate fluid management, various hemodynamic parameters are measured during the course of the operation. The most widely used parameter to assess intravascular volume is central venous pressure (CVP). Though this has been used for many years and is widely accepted by most anaesthesiologists and intensivists as a good indicator of intravascular volume, it has its limitations. Primarily it is based on certain
assumptions about the relationship between the pulmonary and systemic circulations and that pressure in the cardiac chambers reflects volume. This may not always be the case, particularly in patients undergoing intermittent positive pressure ventilation with positive end expiratory pressure. Renal transplants are invariably done under general anaesthesia and patients are on IPPV with PEEP. Secondly the use of central venous pressure may not be reliable when the patient’s position is changed during the operation. This too happens frequently during the course of the operation to facilitate better vision during the vascular anastomosis.

Direct arterial pressure monitoring is routinely done during renal transplant surgery and with newer anaesthetic monitors with the facility to measure PPV; this parameter may be easily monitored in all patients. The primary advantage of PPV is that being a dynamic parameter it is unaffected by variations of intrathoracic pressure and patient position. It is recorded from a peripheral arterial canula and therefore does not require central venous access that may be associated with line sepsis considering the renal graft recipient is under immunosuppression.

The aim of this study was to ascertain if there was a correlation between PPV and intravascular volume as measured indirectly by the time between reperfusion of the graft and onset of post transplant diuresis. Fluid balance was achieved and maintained by achieving and maintaining a target CVP of 10-15 mm of Hg. The PPV too was
monitored but there was no target value set and there was no intervention initiated based on the PPV value.

It was found that neither CVP nor PPV had a correlation with time to urine output at the time of reperfusion of the renal graft. This could be due to various reasons. Firstly intravascular volume is only one factor that affects graft function. There are many other factors such as the surgical technique, the cold and warm ischaemia times and even the donor characteristics that were not considered in the analysis. Secondly time to urine output was used as a surrogate marker of adequacy of intravascular. Though it is known that the earlier post transplant diuresis begins, the better the outcome, it may not be an accurate marker of intravascular volume and cardiac output.

Though the two values did not correlate, the ROC curve analysis revealed that if a certain target PPV could be achieved at the time of reperfusion of the renal graft, this was a reasonably good predictor of time to urine output as the specificity was as high as 85% though the sensitivity was not higher than 50%. If a PPV of <10% could be achieved, there was a high likelihood of the time to urine output being less than 120 seconds. Though it was also noted that a target PPV of < 8% there was a high likelihood of urine output in less than 60 seconds, this was disregarded as the number of patients falling into this category of urine output in less than 60 seconds was very
small (7 out of 33). Therefore it was inferred that the most suitable cut off was ≥10% which meant the target PPV to achieve would be <10%.
CONCLUSIONS
1. Though there is no apparent linear correlation between PPV and TUO, it could be used as a tool to predict the likelihood of time to urine output.

2. The best cut off value for PPV to achieve a urine output within 120 seconds was <10%.

   In other words patients in whom a target PPV of <10% is achieved at the time of revascularization of the graft are likely to start producing urine in <120 seconds.
LIMITATIONS
• The sample size was small – only 33 patients. The planned sample size of 40 could not be achieved.

• The variables (CVP, PPV and Time to urine output) were not normally distributed. This could be due to the small sample size.

• The primary outcome variable that was used was “Time to urine output”. This is not solely dependent on intravascular volume and there could have been other factors such as surgical technique and ischemia time that could affect this measurement.

• Donor factors were not taken into account

• This study did not look at early and delayed indicators of renal dysfunction which would be indicated by biochemical tests and glomerular filtration rates.
BIBLIOGRAPHY


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ANNEXURES

Consent forms

Proforma

Anaesthesia protocol

IRB minute
CONSENT FORM

Study Title: Correlation between Pulse Pressure Variation (PPV) and adequacy of intravascular volume as reflected by time to urine output in renal transplant recipients

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.

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:
உயிர்நிலை விளக்கம்

அம்மனே குருவும்: குறிப்பிட்டால் சித்திரம் முற்பு குருவான்களுக்கு வரும் அச்சுத்தையிலும், குறிப்பிட்டால் விளக்கும் சித்திரங்கள் தொடர்பில் அழகும் ஐதான் அம்மன்.

அம்மன் சந்தர்:

பந்துடங்காமுணி குரும்:

புத்தக தொன்று, மூலம் (அம்மன் குருவின்):


class="kfs"

மற்றும் / மற்றும்

தங்க அம்மன் பொறியிய தரும்: பாரல்லாய்ம முன்னணி அவியல் குரு குரு முற்பு அச்சுத்தையிலும் கொள்ளையிய சித்திரங்கள் தொடர்பில் அழகும் ஐதான் அம்மன் நிலையானவை என்று அம்மன் என்றும்.

உயிர்நிலை சித்திரங்கள் விளக்கம் மாகாணத்தின் பெரும் பார்வை பாருளும் கற்கற்றங்களும் பெரும் குழுமத் டச்சில்லியம் என்று அம்மன் என்றும்.

தங்க அம்மன் சந்தர் பொறியிய தரும்: குருவான்களுக்கு வரும் அச்சுத்தையிலும் கொள்ளையிய சித்திரங்கள் தொடர்பில் அழகும் ஐதான் அம்மன் நிலையானவை என்று அம்மன் என்றும்.

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நற்று என்ற அம்மன் பொறியிய தரும்: குருவான்களுக்கு வரும் அச்சுத்தையிலும் கொள்ளையிய சித்திரங்கள் தொடர்பில் அழகும் ஐதான் அம்மன் நிலையானவை என்று அம்மன் என்றும்.

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பார்வைக்குழியின் விளக்க (பயிற்சியின் ஆராய்ச்சியால்):

குறிப்பிட்டுள்ளாமாறு:

குறிப்பிட்டுள்ளாமாறு:

குறிப்பிட்டுள்ளாமாறு:

குறிப்பிட்டுள்ளாமாறு:

குறிப்பிட்டுள்ளாமாறு:
கிளெத்தராய நபர்கள் தன்னாளிடம், முற்பக்க புரத்தியாளர் பி.ஜே.எம். ஜெ.ஆர் புரத்தியாளர்

ஓப்பாலையூர் நகர் குன்று

அப்படி குறிப்பிட்டு: கிளெத்தராய புரத்தியாளர் தன்னாளிடம் தன்னாளிடம் குறிப்பிட்டு, கிளெத்தராய புரத்தியாளர் புரத்தியாளர் தன்னாளிடம் தன்னாளிடம் வேறுபாடு. ஆனால்

மன்னன் ரைல்பயின் கிளெத்தராய புரத்தியாளர் தன்னாளிடம் தன்னாளிடம் வேறுபாடு. ஆனால்

இதே அப்படி இனத்து வழங்க செய்யலாம்? மட்டுமே ஜெ.ஆர் புரத்தியாளர் புரத்தியாளர் புரத்தியாளர் வேறுபாடு. ஆனால்

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இதே பருவத்தாக்குதல் செய்யலாம் வேறுபாடு? மட்டுமே ஜெ.ஆர் புரத்தியாளர் புரத்தியாளர் புரத்தியாளர் வேறுபாடு. ஆனால்

இதே அப்படி பருவத்தாக்குதல் செய்யலாம் வேறுபாடு? மட்டுமே ஜெ.ஆர் புரத்தியாளர் புரத்தியாளர் புரத்தியாளர் வேறுபாடு. ஆனால்

மன்னன் இந்த அப்படி பருவத்தாக்குதல் செய்யலாம் வேறுபாடு? மட்டுமே ஜெ.ஆர் புரத்தியாளர் / பிரான்கள் புரத்தியாளர் மட்டுமே அப்படி பருவத்தாக்குதல் செய்யலாம் வேறுபாடு.
தந்தைவு கருவறிக்கை வைத்துக்குத் தடை விளக்க மிக்கம், கல்வியாளர் பார்வைய பயிற்சியும், தமிழ்கிழக்கு பெரும் பயிற்சியும்?

தந்தைவு நூற்றண்டுகளின் முன் ஆற்றிய டீகராக விளக்கும் விளக்கம் மிக்கம் மறுமழையை குறித்து பார்வையும் தமிழ்கிழக்கு பெரும் பயிற்சியும் இருக்கின்றது.

நேரடி அமைப்பில் வளர்க்க வேண்டும் படையும்?

நேரடி அமைப்பில் வளர்க்க வேண்டும் படையும் அறியப்பட்டுள்ளது. இது ஆற்றிய ஆற்றியாக கல்வியாளர்களுக்கு பயிற்சியும் மறுமழை அமைந்து குறித்து பார்வையும் தமிழ்கிழக்கு பெரும் பயிற்சியும் இருக்கின்றது.

நேரடி அமைப்பில் வந்து கொண்டு அழுகுவேண்டும்?

நேரடி அமைப்பில் வந்து கொண்டு அழுகுவேண்டும் அப்படி விளக்கத்தை தோற்றுவிக்கைக்கூட வெளியிட்டும்.

தந்தைவு கருவறிக்கை வைத்துக்குத் தடை விளக்கம் மிக்கம் வழி வழி விளக்க மிக்கம் வழி வழி விளக்க மிக்கம்?

தந்தைவு கருவறிக்கை வைத்துக்குத் தடை விளக்கம் மிக்கம் வழி வழி விளக்க மிக்கம் வழியில் வழி வழி விளக்கம் வழியில் வழி வழி விளக்கம் வழியில் வழி வழி விளக்கம் வழியில் வழி வழி விளக்கம் வழியில் 

Dr. Y. பார்வையும் தமிழ்கிழக்கு பெரும் பயிற்சியும், 9486843882 எண்ணவை அணிக்கவை.
### DEMOGRAPHIC

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### Co Morbid Diseases

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### Transplant Recipient characteristics and lab values

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<td>Duration of CKD (years)</td>
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<td>HD</td>
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<tr>
<td>Peritoneal dialysis</td>
<td>Y/N</td>
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<tr>
<td>Duration of HD (months)</td>
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<td>Last HD/PD (hours)</td>
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<td>Pre HD/PD weight (Kg)</td>
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<tr>
<td>Post HD/PD weight (Kg)</td>
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<td>Total weight loss/gain</td>
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<th>Calcium</th>
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| Pre Op Hb    |   |
| Pre Op Creatinine |   |

### Study Protocol

Activate PPV in OR 4 monitor, Set to Screen D
Induction:
- Propofol 2mg/Kg
- Fentanyl 2 mcg/Kg
- Rocuronium 0.1mg/Kg
Arterial Line under sterile condition
Triple lumen IJV with ultrasound
Collect data q15mins- set to ALL
Clamp release to first urine:- time in seconds
Total urine output till recovery room
### Hemodynamic Monitoring

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<th>SBP</th>
<th>DBP</th>
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<td>Just Prior to Venous clamp release</td>
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<td>At first Urine Output</td>
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<td>Clamp release to onset of urine formation in Recipient</td>
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</table>

**Turgidity score:** I (soft graft), II (moderately turgid graft), and III (highly turgid and firm graft)
### Kidney Donor Characteristics

<table>
<thead>
<tr>
<th>Age of Donor</th>
<th>cm</th>
<th>Height of Donor</th>
<th>cm</th>
<th>Weight of Donor</th>
<th>Kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co morbidity</td>
<td>Y / N</td>
<td>Hypertension</td>
<td>Y / N</td>
<td>DM</td>
<td>Y / N</td>
</tr>
<tr>
<td>Open Donor Nephrectomy</td>
<td>Y / N</td>
<td>Laparoscopic Donor Nephrectomy</td>
<td>Y / N</td>
<td></td>
<td></td>
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<tr>
<td>Warm Ischemia Time</td>
<td>min:sec</td>
<td>Cold Ischemia Time</td>
<td>min:sec</td>
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<tr>
<td>Total fluids to donor</td>
<td>ml</td>
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### Intake Output measure

<table>
<thead>
<tr>
<th>Fluid Balance</th>
<th>Fluid Balance</th>
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</thead>
<tbody>
<tr>
<td>Intake</td>
<td>Crystalloids</td>
</tr>
<tr>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>RL</td>
<td>RL</td>
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<tr>
<td>Blood transfused</td>
<td>Blood transfused</td>
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<tr>
<td>Output</td>
<td>Total urine till recovery room</td>
</tr>
<tr>
<td>Blood Loss</td>
<td>Blood Loss</td>
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</table>

### Intake Output measure

<table>
<thead>
<tr>
<th>Intake Output measure</th>
<th>post induct</th>
<th>pre re perfusion</th>
<th>post re perfusion</th>
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</thead>
<tbody>
<tr>
<td>ABG</td>
<td>VBG</td>
<td>ABG</td>
<td>VBG</td>
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<td>pH</td>
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<td>CO2</td>
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<td>HCO3</td>
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<td>Hb</td>
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<td>SpO2</td>
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### Intra Operative Vasoactive Drugs

<table>
<thead>
<tr>
<th>Intra Operative Vasoactive Drugs</th>
<th>Total</th>
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<tbody>
<tr>
<td>Ephedrine</td>
<td>mg</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>mcg</td>
</tr>
<tr>
<td>Dopamine</td>
<td>mcg</td>
</tr>
<tr>
<td>Nor Adrenaline</td>
<td>mcg</td>
</tr>
<tr>
<td>Furosemide</td>
<td>mg</td>
</tr>
<tr>
<td>Mannitol</td>
<td>g</td>
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</table>
ANAESTHESIA PROTOCOL FOR RENAL TRANSPLANTATION  
FOR STUDY COMPARING CVP AND PPV

Pre-induction Checklist
Creatinine and Electrolytes (Na,K,HCO3) after last dialysis  
Weight loss after last dialysis

Monitors – ECG, SaO2, NIBP, ABP, EtCO2, Temperature, CVP, MAC, PPV

Warming devices
Level 2 fluid warmer
Bair hugger

Induction
Fentanyl 2mcg/Kg IV  
Propofol 2mg/Kg IV  
Rocuronium 1mg/Kg IV  
Intubation using appropriate sized tube  
Antibiotics as per surgeons’ preference

Insert and secure ABP cannula (radial artery on the hand without the AV fistula)  
Insert CVP cannula under ultrasound guidance. Scan both IJV before selectving one. After guide wire insertion, please correct location using ultrasound.

Maintenance
O2+Air+Isoflurane  
Morphine 0.15mg / Kg just prior to incision  
Methylprednisolone 1g IV  
IV fluids – Ringer Lactate 15-30 ml/Kg/hr

Haemodynamic monitoring and management
Target CVP > 12-15 mm Hg  
Maintain MAP ≥ 90 mm Hg  
Maintain SBP ≥ 120 mm Hg  
Mannitol 0.5 mg/Kg IV over 30 mins, when the donor kidney is brought into the OR  
ABG at the end of venous anastomosis  
Furosemide 1mg/kg, IV during second half of arterial anastomosis  
Ephedrine 5-10 mg at the end of arterial anastomosis  
Adrenaline 5-10 mcg just prior to release of Satinsky clamp from the External Iliac vein

Reversal
Neostigmine and Glycopyrolate given at the time of closure of muscle layer.  
Change to PSVPPro at pressure support of 10 cm  
Titrate Morphine to maintain respiratory rate of > 15-20/min

Urine
Record the urine produced till recovery
February 24th 2014

Dr. Bernice Theodore
PG Registrar
Department of Anaesthesiology
Christian Medical College
Vellore 632 004

Sub: Fluid Research grant project : ( RESUBMISSION)
Correlation between Pulse Pressure Variation (PPV) and adequacy of intra-vascular volume as reflected by time to urine output in renal transplant recipients.
Dr. Bernice Theodore, PG Registrar, Anaesthesiology, Dr. Tony Thomson Chandy, Anaesthesiology, Dr. Aparna Williams, Anaesthesiology.

Ref: IRB Min No. 8660 dated 19.02.2014

Dear Dr. Bernice Theodore,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled “Correlation between Pulse Pressure Variation (PPV) and adequacy of intra-vascular volume as reflected by time to urine output in renal transplant recipients.” on February 19th 2014. I am quoting below the minutes of the meeting.

The Committee raised the following queries:

a) Which aspect of the PPVs is going to used for the ROC curve.

Dr. Bernice Theodore and Dr. Tony Thomson Chandy were present during the presentation of the proposal and satisfactorily responded to the queries raised by the Members. After discussion, it was resolved to ACCEPT the proposal AFTER receiving the suggested modifications and answers to the queries.
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 responses.

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. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Cc: Dr. Tony Thomson Chandy, Anaesthesiology, CMC