Evaluation of changes of Mean Arterial pressure measured by non invasive oscillometric readings (NIBP) with passive leg raise as an index of fluid responsiveness in patients with shock

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A dissertation submitted in partial fulfillment of M.D. General Medicine Branch I Examination of the Tamil Nadu Dr M.G.R. UNIVERSITY, CHENNAI to be held in 2016.

Certificate

This is to certify that the dissertation "**Evaluation of changes of Mean Arterial pressure measured by non invasive oscillometric readings (NIBP) with passive leg raise as an index of fluid responsiveness in patients with shock**" is a Bonafide work of Dr Aditya Vijayakrishnan Nair carried out under our guidance towards the M.D. Branch I (General Medicine) Examination of the Tamil Nadu Dr M.G.R. University, Chennai to be held in 2016

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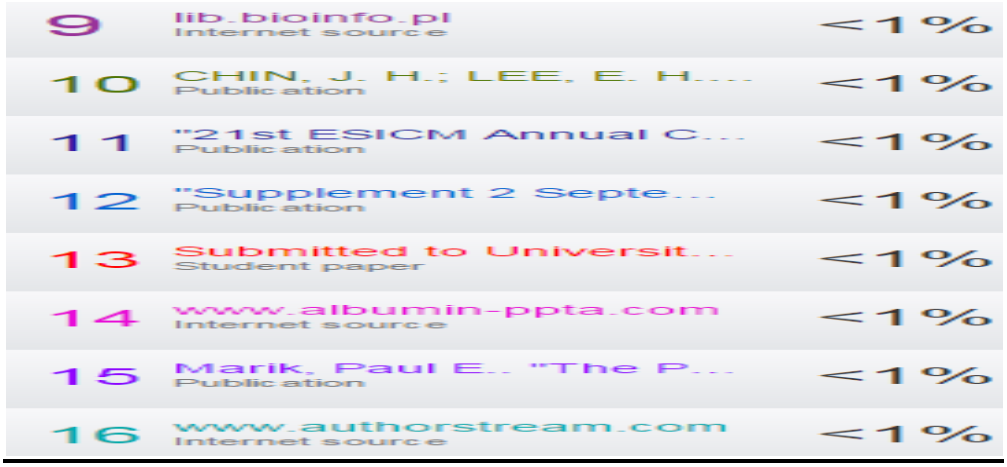
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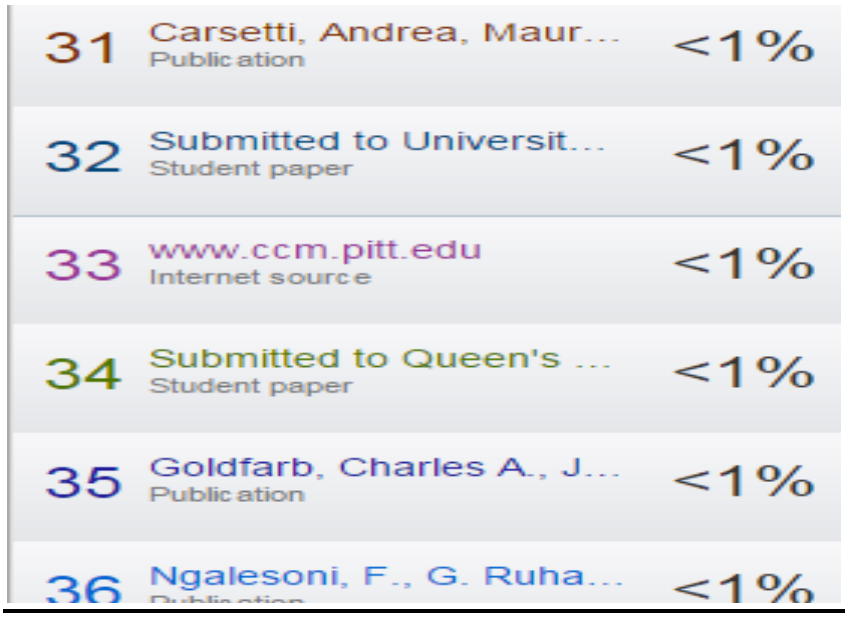

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Dr. Aditya Vijayakrishnan Nair
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Sub: **Fluid Research grant project:**
Evaluation of changes of Mean Arterial pressure measured by non invasive oscillometric readings (NIBP) with passive leg raise as an index of fluid responsiveness in patients with shock.
Dr. Aditya Vijayakrishnan Nair, Medicine, Dr. Kishore Pichamuthu, Division of Critical care, Dr. Anand Zachariah, Medicine 1, Dr. Thambu David, Medicine,
Dr. Soumya. S, Medicine, Dr. Samuel George, Medicine, Dr. Manjeera Jaganati, Medicine, Mrs. Tunny Sebastian, Biostatistician, CMC, Vellore.

Ref: IRB Min No. 8883 [DIAGNOSE] dated 07.04.2014

Dear Dr. Aditya Vijayakrishnan Nair,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Evaluation of changes of Mean Arterial pressure measured by non invasive oscillometric readings (NIBP) with passive leg raise as an index of fluid responsiveness in patients with shock." on April 7th 2014.

The Committees reviewed the following documents:

1. IRB Application format
2. Curriculum Vitae' of Drs. Aditya Vijayakrishnan Nair, Kishore Pichamuthu, Anand Zachariah, Thambu David, Soumya. S, Samuel George, Manjeera Jaganati, Mrs. Tunny Sebastian.
3. Case Report form
4. Informed Consent form (English, Tamil & Telugu)
5. Consent form (English, Tamil & Telugu)
6. No of documents 1-5

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on April 7th 2014 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. Paul Ravindran	PhD, Dip RP, FCCPM	Professor, Radiotherapy, CMC, Vellore	Internal, Clinician
Dr. J. Visalakshi	MPH, PhD	Lecturer, Dept. of Biostatistics, CMC.	Internal, Statistician
Dr. Inian Samarasam	MS, FRCS, FRACS	Professor, Surgery, CMC	Internal, Clinician
Dr. Anup Ramachandran	Ph. D	The Wellcome Trust Research Laboratory Gastrointestinal Sciences, CMC, Vellore	Internal, Basic Medical Scientist
Dr. Jacob John	MBBS, MD	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. Niranjan Thomas	DCH, MD, DNB (Paediatrics)	Professor, Neonatology, CMC, Vellore	Internal, Clinician
Dr. Vivek Mathew	MD (Gen. Med.) D.M (Neuro) Dip. NB (Neuro)	Professor, Neurology, CMC, Vellore	Internal, Clinician
Dr. Anand Zachariah	MBBS, PhD	Professor, Medicine, CMC, Vellore	Internal, Clinician
Dr. Chandra Singh	MS, MCH, DMB	Professor, Urology, CMC, Vellore	Internal, Clinician
Mrs. Pattabiraman	B. Sc, DSSA	Social Worker, Vellore	External, Lay person

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Dr. Nihal Thomas,	MD, MNAMS, DNB(Endo), FRACP(Endo) FRCP(Edin) FRCP (Glasg)	Professor & Head, Endocrinology. Additional Vice Principal (Research), Deputy Chairperson, IRB, Member Secretary (Ethics Committee), IRB, CMC, Vellore	Internal, Clinician

We approve the project to be conducted as presented.

IRB Min No: 8833 [DIAGNOSE] dated 07.04.2014

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

Fluid Grant Allocation:

A sum of 3,500/- INR (Rupees Three Thousand Five Hundred only) will be granted for 2 years.

Yours sincerely

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Cc: Dr. Kishore Pichamuthu, Division of Critical Care, CMC, Vellore.

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I am thankful to all my patients for their kind co-operation.

Evaluation of changes of Mean Arterial pressure measured by non invasive oscillometric readings (NIBP) with passive leg raise as an index of fluid responsiveness in patients with shock

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INTRODUCTION

Shock is defined as a state of cellular and tissue hypoxia due to reduced oxygen delivery and/or increased oxygen consumption or inadequate oxygen utilization[1]. Regardless of the cause hypoperfusion leads to deficient oxygen and substrate delivery leading to cellular dysfunction. This cellular dysfunction leads to production of "damage associated molecular patterns and inflammatory mediators which further decreases perfusion through structural and functional changes in microvasculature.[2] This vicious cycle is initially reversible, which become irreversible rapidly, resulting in multi-organ failure (MOF) and death.

Only rapid restoration of perfusion will prevent progression of shock

Clinical shock is often accompanied by hypotension(typically systolic pressure less than 90 mm Hg or Mean arterial pressure less than 70 mm Hg) and with evidence of tissue hypoperfusion in the form cold or clammy skin with or without cyanosis, oliguria(<0.5 ml/kg body weight).Biochemically its associated with hyperlactatemia (>1.5 mmol/liter) indicating abnormal tissue oxygen metabolism.[1]

Shock is mainly divided into 4 types

a)Hypovolemic b) Cardiogenic c) Distributive d) Obstructive

Strict adherence to this classification system is difficult from a clinical point of view because of the combination of two or more combinations of shock in any individual patient.

Septic shock which is a form of distributive shock is the most common subtype followed by Cardiogenic and hypovolemic ,Obstructive shock being the least common.[1]

The major physiological determinants of tissue perfusion (and blood pressure) are cardiac output (CO) and Systemic vascular resistance (SVR)

CO is product of heart rate (HR) and stroke volume (SV)

Stroke volume is governed by 3 factors

a) Preload b) myocardial contractility c) afterload

SVR is governed by a) vessel length b) viscosity c) vessel diameter

Changes in any of these will lead to shock. Most types of shock have diminished CO and/or SVR.

Fluid resuscitation which is the initial mode of resuscitation in patients with shock increases the preload and thus the cardiac output. Avoiding hypovolemia and fluid overload is of utmost importance in dealing with patients in shock.[3]Giving fluids to a non-responsive patient could potentially cause or contribute to problems such as pulmonary edema, raised intra-abdominal pressure and raised intracranial pressure. It is therefore very important to identify potential fluid responders prior to attempting volume expansion. Static indices such as CVP (central venous pressure) are no longer used. Dynamic indices based on passive leg raise and heart lung interactions are the current standard of care methods to identify fluid responsiveness. In "fluid depleted" patients PLR increases right and left ventricular preload and thereby left ventricular stroke volume.[4]Our study looked at use of non invasive oscillometric methods to monitor these dynamic indices during initial fluid resuscitation and whether they were comparable to existing invasive ones.

Aim

Evaluation of changes in Non invasive oscillometric blood pressure measurements with passive leg raise (PLR) as an index of fluid responsiveness in patients with shock.

Objectives

1 .a) To determine the sensitivity and specificity of non invasive Mean arterial pressure change (MAP) with passive leg raise (PLR) compared against a gold standard of more than or equal to 15 % increase in stroke volume.

b) To determine MAP change with best cut –off

2. a) To determine the sensitivity and specificity of non invasive Systolic blood pressure change (SBP) , Pulse pressure change (PP), heart rate change (HR) with passive leg raise compared against a a gold standard of more than or equal to 15 % increase in stroke volume.

b) To determine SBP change, PP change, HR change with best cut off

LITERATURE REVIEW

Shock is a common medical emergency which affects almost 33 % of patients being admitted in Medical ICU's[5].Among the various types of shock elucidated above , septic shock , a form of distributive shock remains to be the most common type. Vincent JL et al[6] in 2002 had done a multicentre prospective observational study evaluating the demographic data, co morbid diseases, and clinical and laboratory of patients admitted in 198 medical ICUS across Europe. He found that, of the 3147 patients admitted; 35 % of them had sepsis at admission.

Fluid management is paramount for good clinical outcomes. Too little worsens tissue perfusion while overzealous administration obstructs oxygen delivery. Uncorrected fluid deficit leads to inappropriate use of vasopressors which worsens tissue hypoperfusion.

There have been many observational and randomized trials showing effects of conservative fluid strategy in improving pulmonary function

Weidmann et al in a randomized trial consisting of 1000 patients compared liberal versus conservative fluid strategies in ARDS. The primary outcome was mortality rates at 60 days. They found that the rate of death at the end of designated period was 25.5% in conservative group and 28.4 % in liberal fluid group respectively. This difference was not statistically significant (p=0.3).The mean fluid balance in the conservative group was -136+/- 491 ml and the liberal fluid arm was 6992+/-502 ml. The researchers though noticed that oxygenation index and the lung injury score was clinically and statistically significant (14.6+/-0.5 vs. 12.1+/-0.5, P<0.001) .They also noticed that increased number of ventilator free days were also in the conservative fluid arm. [7]

Mitchel et al[8] in another randomized trial consisting of pulmonary edema patients wanted to evaluate the effect of fluid management on the pulmonary mechanics. They hypothesized that fluid management programme that emphasizes on fluid restriction and diuretics would lead to decreased Extravascular Lung Water (EVLW) and thereby decrease ventilator days .All patients required pulmonary artery catheter as they were critically ill. They found that the group assigned to the restricted fluid arm had significantly less EVLW and had increased ventilator free days

Martin and co-workers in a randomized trial comprising of 37 patients evaluated the deleterious effects of hypoproteinemia in patients with ARDS. They had randomized patients to a pre- specified regimen of furosemide and colloid replacement or placebo infusions. Diuresis and weight loss over the next 5 days (5.3 kg more in the treatment arm, $p<0.04$) was accompanied with improvements in the Pao2/Fio2 in the treatment group within 24 hours (171 to 236, $p <0.02$).though the study did not show any mortality benefit in using them.

The above examples have helped illustrate the relation between fluid balance and lung mechanics.

The only reason to give fluid is to increase the stroke volume. Fundamentally the point of fluid resuscitation is to rescue the patient from the steep phase of frank starling curve to the plateau phase. At the plateau phase further fluid loading does not improve stroke volume.[9]

This optimal preload physiologically indicates that actin and myosin fibrils of the cardiac myocardium have maximum overlap.

It’s important to note in the Frank Starling curve the actin and myosin filaments do

not disengage and hence there is no negative limb to the curve. In normal physiological conditions both the ventricles operate at the steep phase of the curve[9]

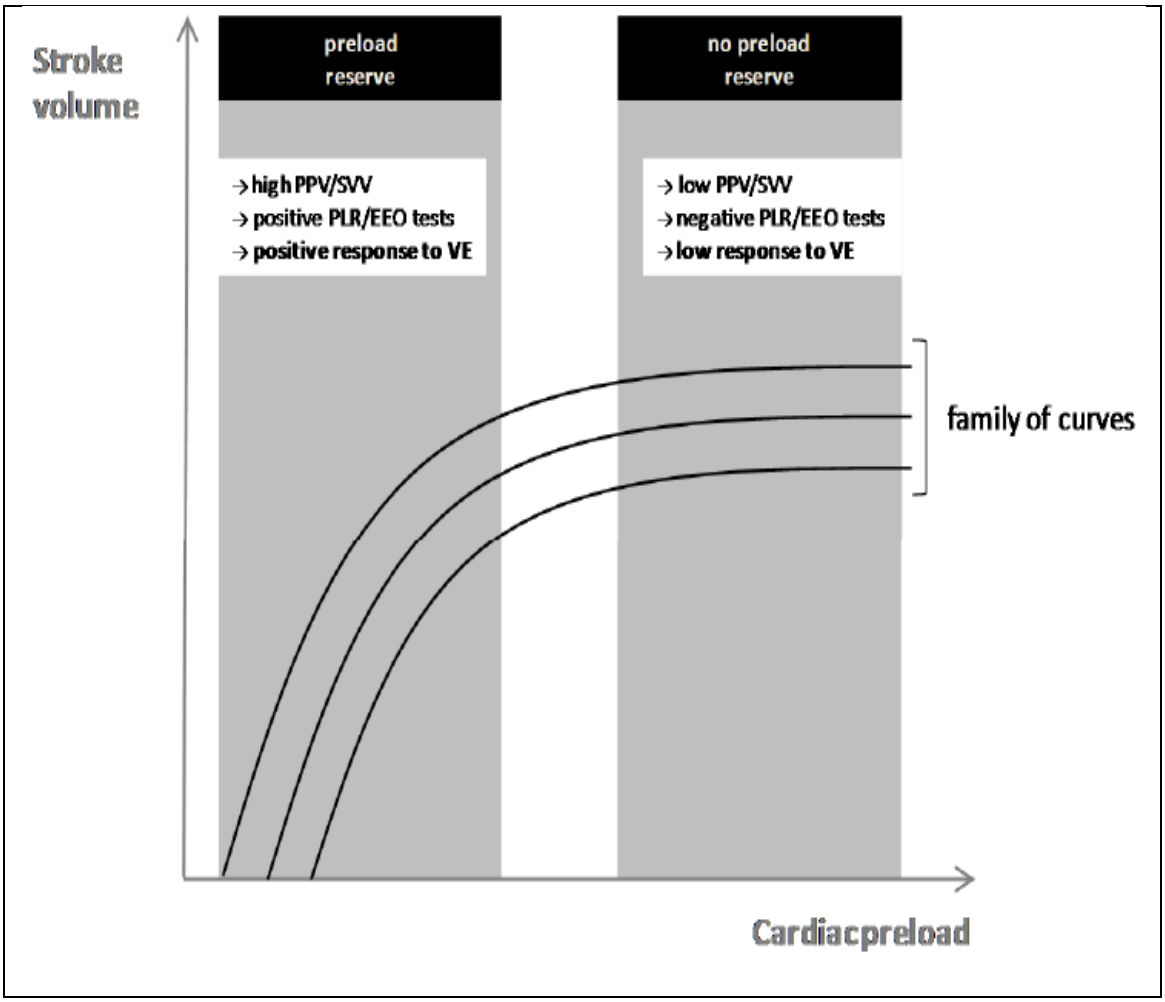


Figure 1 FRANK STARLING FAMILY OF CURVES

Greatest source of worry is the indiscriminate fluid boluses given in critical care setting when faced with sudden hypotension/oliguria/elevated lactate. Previously done Meta analysis have shown that mean responder rate in critical care units to be around 52.9%[10]. This means that approximately 47 % of patients are exposed to consequences of liberal fluid administration, and thereby its consequences.

Thus it's vital to correctly identify patients with signs of systemic hypoperfusion who will improve after 500 ml fluid bolus.

This was previously judged by various static indices measuring preload such as Central venous pressure, pulmonary artery wedge pressure and end diastolic volumes. However recent studies have shown that this did not change patient outcomes. This proves that measurement of preload, does not predict preload responsiveness.[10]

Marik at al[11] had demonstrated in a systematic review of 24 studies comprising 803 patients showed that the pooled co relation coefficient between Central Venous Pressure and measured blood volume was only 0.16 (95% confidence interval [CI], 0.03 to 0.28) and pooled correlation between CVP and change in stroke index/cardiac index was 0.11 (95%

CI, 0.08 to 0.28) .This proved that Central venous pressure (CVP) poorly correlated with blood volume and that change in CVP % failed to predict fluid responsiveness.

Harvey et al in randomized trial of 1041 patients across 65 ICU's across UK evaluated the effectiveness in using pulmonary artery catheter in management of patients. Each arm had 520 patients and primary outcome measured was hospital mortality. The study did not report any statistically significant change in mortality to both patient arms. The groups recoded 68% [346 of 506] vs66% [333 of 507], p=0·39; adjusted hazard ratio 1·09, 95% CI 0·94–1·27) [8.]

Bigatello [12]et al had raised the question of uncertainty in accurately deriving volumetric hemodynamic indices from the Transthoracic Thermo dilution curve and its physiological application.

Dieben et al[13] had studied the use of measuring RV end diastolic volume(RVEDI) as a surrogate marker to assess fluid status. He had compared it to the Pulmonary artery wedge pressure (WP). Regression analysis of 131 hemodynamic studies showed that Cardiac index co related better with RVEDI ($r^2$0.61) than WP (($r^2$0.42).But the sensitivity and specificity was not compelling enough for clinical use.

Current research has been involved in discerning of those indices that predict a response to a fluid bolus .These indices termed "dynamic indices" provoke a cardiac reaction which is brought about without the need for a fluid bolus .Instead it utilizes the interaction between the cardiopulmonary changes during mechanical ventilation or changes in posture of the patient which mimics the effect of a fluid bolus .These interaction would tell us how the fluid bolus would change the stroke volume.

They have been divided into

1) Stroke volume changes during mechanical ventilation

2) Pulse pressure changes

3) Oximetric waveform changes

All of them are based on the cyclical changes in cardiac output mentioned below.

Mechanically ventilated patients who are completely sedated do not have spontaneous respiratory effort; demonstrate a cyclical change in left and right heart pressure secondary to change in intrathoracic pressure during ventilation. During inspiration phase of mechanical ventilation, due to positive pressure nature of ventilation, will lead to increase in intrapleural pressure. This pressure leads to compression of pulmonary vasculature and venous inflow and also compression of the heart itself.

Consequently this decreases the right ventricular preload and left ventricular afterload. All these changes reverse during the expiratory phase of ventilation.

Hence these cyclical changes in intrapleural pressure leads to cyclical changes in cardiac output.

In those patients who are concurrently hypovolemic , these changes appear to be accentuated.[14]

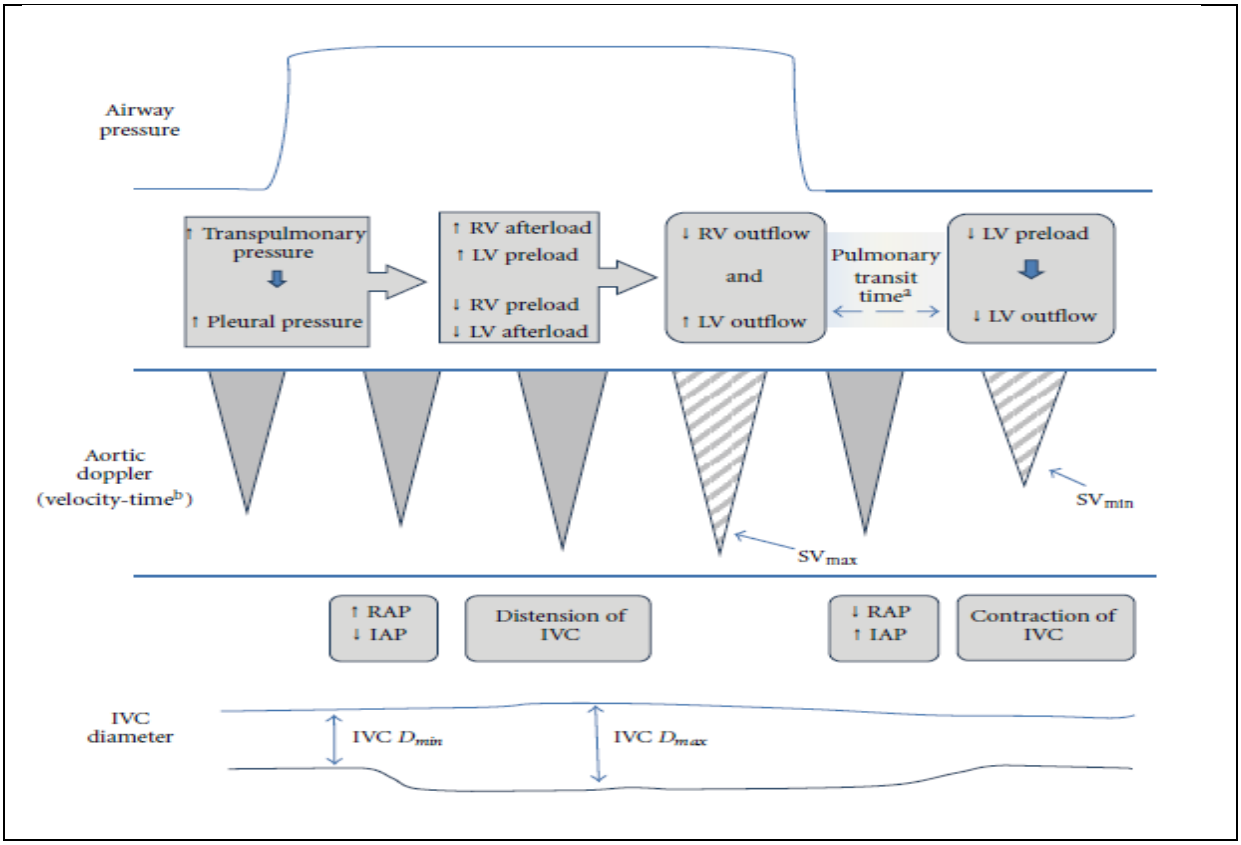


Figure 2 CARDIOPULMONARY CHANGES IN MECHANICAL VENTILATION

Pulse pressure variation was from analysis of the arterial waveform (PPV), the pulse contour analysis gave the stroke volume variation (SVV), and the amplitude variation was of the pulse oximeter was derived from the plethysmograph.

The possibility of using stroke volume variation in assessing fluid responsiveness came about when Michard et a[15] in 2000 evaluated 40 patients in septic shock who were mechanically ventilated. They noticed that in those patients who were volume responsive (responders), Pulse pressure variation (Pp) during the respiratory cycle was >13 % and in those patients cardiac output increased by >15% after fluid bolus. Since pulse pressure was a surrogate marker for stroke volume, they found that stroke volume variation could be used for evaluating fluid responsiveness. VE-induced changes in CI closely correlated with Pp before volume expansion ($r^2 = 0.85$, $p < 0.001$).

Since then a number of studies have evaluated their effectiveness in clinical scenario. Marik et al in met analysis looked at various studies which looked at PPV from arterial waveform analysis, SVV from pulse contour analysis. They foretold with high degree of accuracy , the intravascular volume state and amount of change in cardiac output post volume expansion(VE).All studies were very consistent and reported a threshold between 11-13%.[16]

Method	Technology	AUC*
Pulse pressure variation (PPV)	Arterial waveform	0.94 (0.93-0.95)
Systolic pressure variation (SPV)	Arterial waveform	0.86 (0.82-0.90)
Stroke volume variation (SW)	Pulse contour analysis	0.84 (0.78-0.88)
Left ventricular end-diastolic area (LVEDA)	Echocardiography	0.64 (0.53-0.74)
Global end-diastolic volume (GEDV)	Transpulmonary thermodilution	0.56 (0.37-0.67)
Central venous pressure (CVP)	Central venous catheter	0.55 (0.48-0.62)

*AUC = area under the curve with 95% confidence intervals.

Table 1FOREST PLOT OF DYNAMIC INDICES IN COMPLETE MECHANICAL VENTILATION

All of the above given methods required using an arterial line in situ .Hence focus was on techniques for non invasively measuring such changes. Dynamic changes in the plethysmographic waveform have shown a significant co relation with PPV and accurately predict fluid responsiveness.

Feissel et al[17] in 23 patients in sepsis who were mechanically ventilated demonstrated that change in PPV versus change in peak and amplitude of Plethysmograph(PLETH) before VE ,were 12 and 14 % which allowed discrimination between responders and non-responders with sensitivity of 100% and 94% and specificity of 70% and 80% respectively.

Cannesson et al[18] studied in 22 mechanically ventilated patients compared PPV to PLETH, among whom 14 of them were in shock. They noticed that ΔPLETH values above 15% was associated with ΔPPV value of above 13% (positive predictive value 100%).Similarly ΔPLETH values less than 15 was associated with ΔPPV value of above 13% with NPV of 94%.

But there were limitations in using the above given indices .It was to be noted that arrhythmias and spontaneous breathing activity would lead to misinterpretation of values of SVV and PPV. They also noted that at any particular preload, the PPV and SVV will vary according to the Tidal volume.

Reuter et al[19] had demonstrated this in a study of 20 patients post cardiac surgery .10 of them were fluid responsive and they monitored the change in SVV at different Tidal volumes. They found that SVV was different when Tidal volumes (TV) were altered and showed a linear relationship.

Similarly Backer et al [20] they evaluated ΔPPV at different TV in 30 patients who were Mechanically ventilated. But they noticed that sensitivity of ΔPPV was different at different TV and they got the best results at TV of 8 ml/kg.

They also noted that such values required the use of an invasive arterial catheter for their measurement. The other difficulty was that most of the patients required a fluid bolus at the start of admission, where one would usually not have an arterial line due to time constraints in resuscitating the patient. The other complications of arterial lines in the form of ischemia and blood stream infections were well known.

Scheer et al [21] in a meta analysis had looked at 19,000 radial cannulation, 3000 femoral cannulation and 2000 axillary artery cannulation from 1978 to 2001.Common complication was temporary occlusion of the cannula in 19.7 %.This has lead to serious ischemic risk leading to gangrene /amputation only in 0.09 % of cases. The major complications were pseudoaneurysm and sepsis which were reported to be 0.09 and 0.13% respectively.

Hence the need of the hour was to get other dynamic indices to look for respiratory variation in stroke volume. Research was focussed on evaluating stroke volume variation at the aortic annulus using Doppler echocardiography. The aortic annulus diameter was assumed to be constant during the cardiac cycle, and that changes in aortic blood velocity would reflect stroke volume variation.

Feissel et al [22]had studies the use of transesophageal echocardiogram (TEE) for the measuring beat to beat variability in 1 respiratory cycle and its correlation with fluid responsiveness. They demonstrated that change in Velocity (Vpeak) had a sensitivity of 100 % and specificity of 89 %.This closely correlated with volume expansion induced changes ($r2 = 0.83$; $p < 0.001$).

Similarly Monnet et al[23] evaluated the use of oesophageal Doppler in predicting fluid responsiveness in mechanically ventilated patients in sinus rhythm. Respiratory variation in Doppler > 19 % was associated with a sensitivity of 90% and specificity of 94%.

In view of difficulty in inserting a transesophageal echocardiogram and technical expertise to measure abdominal aortic Doppler, researchers turned to evaluation of Superior and inferior Vena caval measurement during mechanical ventilation.

Barbier and colleagues [24]demonstrated that IVC distended during positive pressure ventilation due to the elevated intrathoracic pressure .They demonstrated that change in IVC diameter during inspiration co related well with intravascular volume.

They had studied 23 patients in septic shock who were mechanically ventilated .They had measured the IVC diameter at end of expiration and inspiration and calculated the distensibility index(dIVC) which was expressed as percentage .dIVC of 18 % was

taken as the cut off and it discriminated responders from non responder with 90% sensitivity and specificity.

Similarly Veillard-baron[25] had demonstrated the efficacy of collapsibility of the Superior vena cava. In a study of 66 mechanically ventilated patients who were in septic shock, Veillard measured the collapsibility index of superior vena cava using TEE. At a threshold of 36 % collapsibility, the test discriminated between responders and non responders with 90 % sensitivity and 94 % specificity.

It was now common knowledge that inspiratory phase of mechanical ventilation would lead to decrease in preload due to raise intra thoracic pressure. Thus if the mechanical insufflations could be stopped at end expiration; there would be an increase in preload and cardiac output. This increase in cardiac output could be measured with an arterial line. Hence Monnet et al[26] evaluated the efficacy in 34 mechanically ventilated patients . They also included in this study, patients who had cardiac arrhythmia. This test predicted fluid responsiveness when arterial pressure increased by 5 % with a sensitivity of 87 % and specificity of 100 %.

This test unlike other tests could be easily used in clinical practice as all it required was an arterial line for measuring the cardiac output .The other advantage was that this test could be used in patients with cardiac arrhythmia and patients with low tidal volume , both of which makes Pulse pressure variation and stroke volume variation unreliable.

The major flaws of all these dynamic indices were that none of them could be used during initial resuscitation of the patient as they required completely sedating the

patient or invasive arterial lines. These are usually not available during the first hour of resuscitation. Also these methods could not be used when intensivists are weaning a patient as sedative requirements will come down and patient will start spontaneously breathing. Hence hemodynamic changes during mechanical ventilation were not a good enough option.

Therefore researches continued to look for other non invasive methods to change cardiac output.

Passive leg raise (PLR) was thought to be an attractive alternative option .Monnet et al[4] had theorized that passively raising the legs up to 45 degree from horizontal position , leads to transfer of blood from lower limbs to intrathoracic compartment by gravity, which would lead to increase in venous return and thereby stroke volume. This was physiogically demonstrated by Rutlen et al[27] in 1981 where there showed by radio tagging erythrocytes, a volume of 150 ml of blood was transferred from the calves to the right ventricle. This causes an increase in cardiac preload due to increase in mean circulatory pressure.

The next question was that, if this volume was sufficient to cause a change in cardiac preload, enough to cause change in stroke volume and shift the Frank Starling curve to the left.

Numerous clinical studies have demonstrated that this venous return is sufficient enough to change cardiac preload significantly.

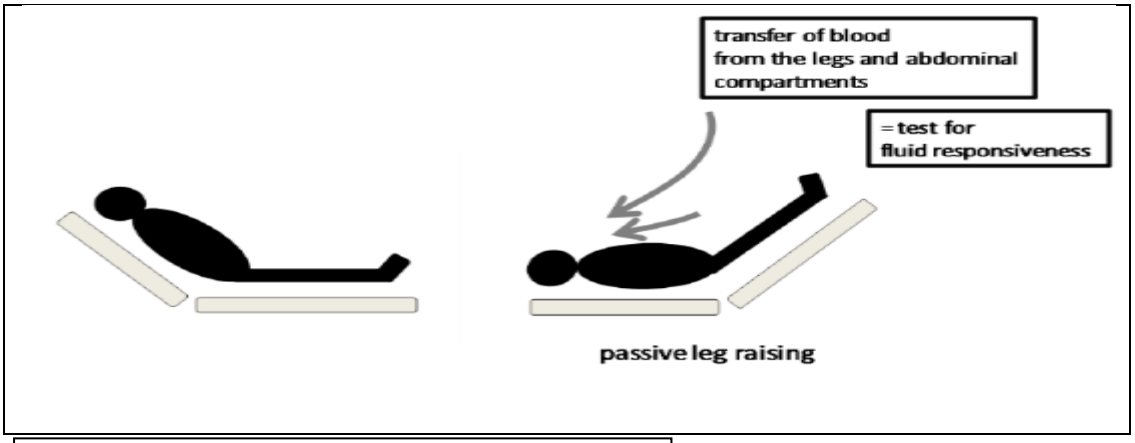


Figure 3 PASSIVE LEG RAISE MODEL

Pozzoli M et al had studies mitral flow velocity pattern in 173 chronic heart failure patients and he noted that LV end diastolic volume and Pulmonary artery occlusion pressure and E wave of the mitral inflow velocity waveform increased after PLR.

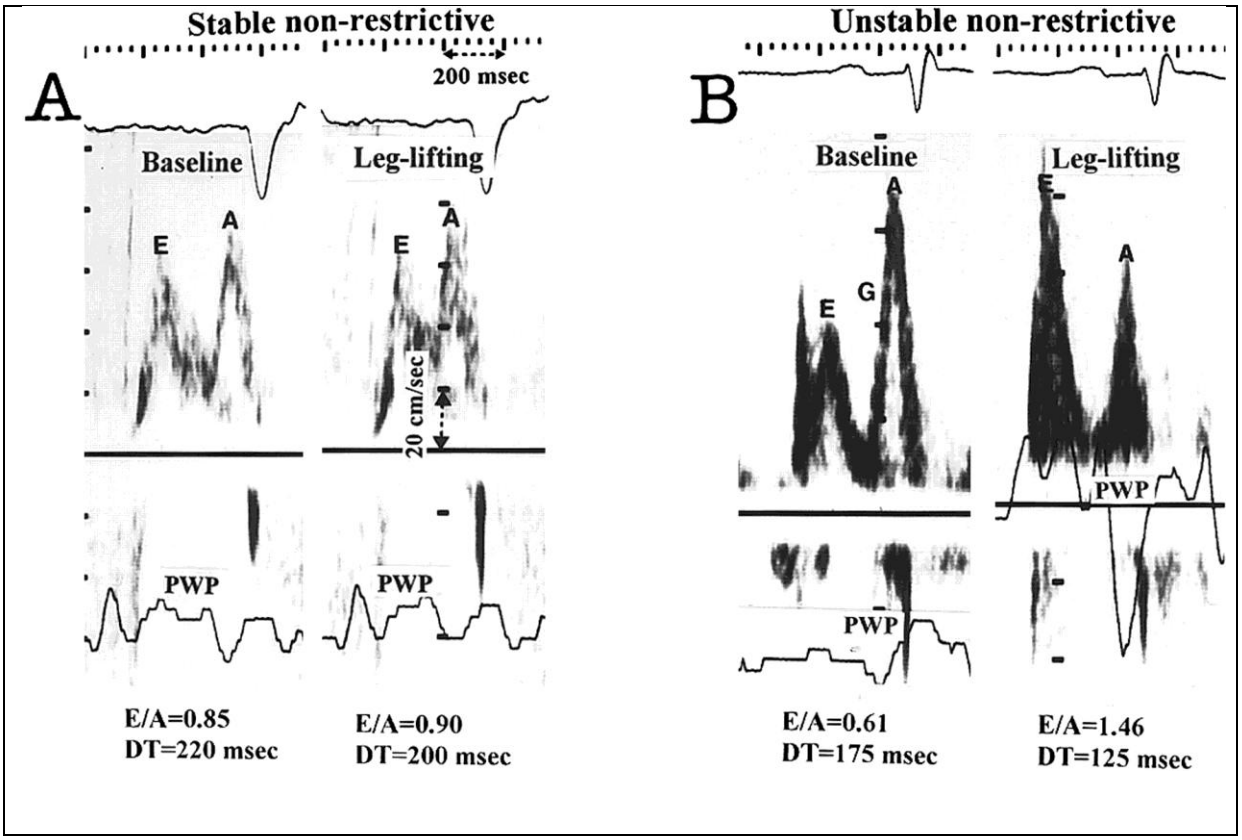


Figure 4MITRAL FLOW WAVE VELOCITY IN PLR

Boulain et al[28] in the following diagram demonstrated the increase in the Pulmonary artery occlusion pressure(PAOP), Stroke volume(SV) and radial pressure

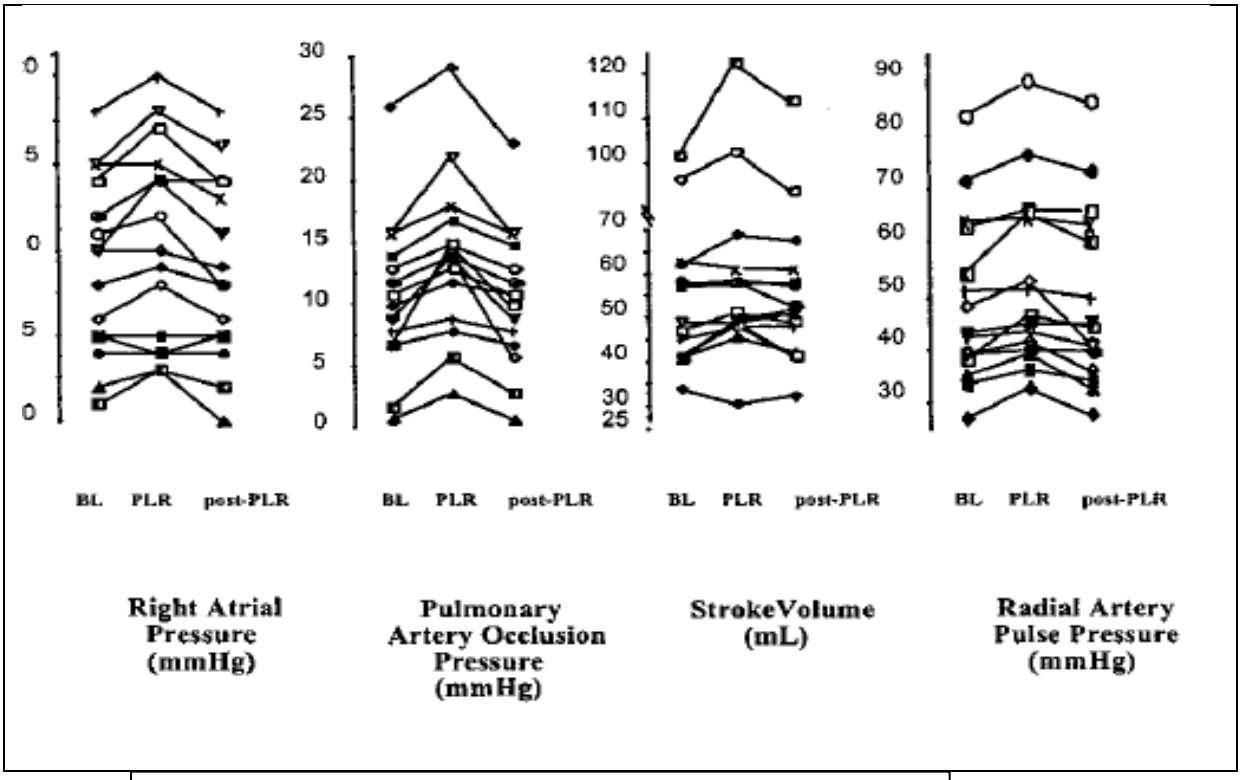


Figure 5 **CARDIOVASCULAR CHANGES IN PLR**

Another important point to be noted was that the PLR induced change in stroke volume was reversible. In other words when the lower limbs were brought back to horizontal position all the changes made to cardiac preload were nullified. These studies have also been confirmed by radionuclide tagging of erythrocytes by Rutlen et al[27] and in studies done by Boulain et al[28].

Therefore PLR was an attractive option to give a reversible "auto- transfusion and decreases chances of excess fluid load for the patient.

The other fact about PLR was that the changes which occurred to PAOP, SV and arterial pressure were all transient. Monnet et al[23] in 2005 had looked at changes in descending aortic flow with esophageal Doppler during PLR in 71 patients admitted in ICU with various condition 37 of whom were fluid responsive. He found that PLR induced changes in the various dynamic indices like aortic blood flow; arterial pressure increased within the first 30 seconds and peaked at 1 minute for all the responders. All the patients had basic systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR) measured in baseline which was 45 degree head up. They underwent PLR and all indices were measured after 1 minute. The patient was put back to baseline position and all variable were measured again. All the responders had a fluid bolus given and then the changes in the variable were again monitored after 1 minute.

In the same study by Monnet et al[23], out of 71 patients 11 patients had arrhythmia and PLR was accurately able to predict fluid responsiveness even in those individuals. Similarly efficacy of PLR in those with spontaneous inspiratory effort on mechanical ventilation was also studied and this too showed good co- relation.

A meta-analysis in 2010 by Cavallaro et al[10] had looked at 9 articles , which included 353 patients. The sensitivity and specificity of PLR induced change in cardiac output was 89.4% (84.1–93.4%) and 91.4% (85.9–95.2%) respectively. The Area under Curve (AUC) for the same was 0.95 (0.92–0.97).

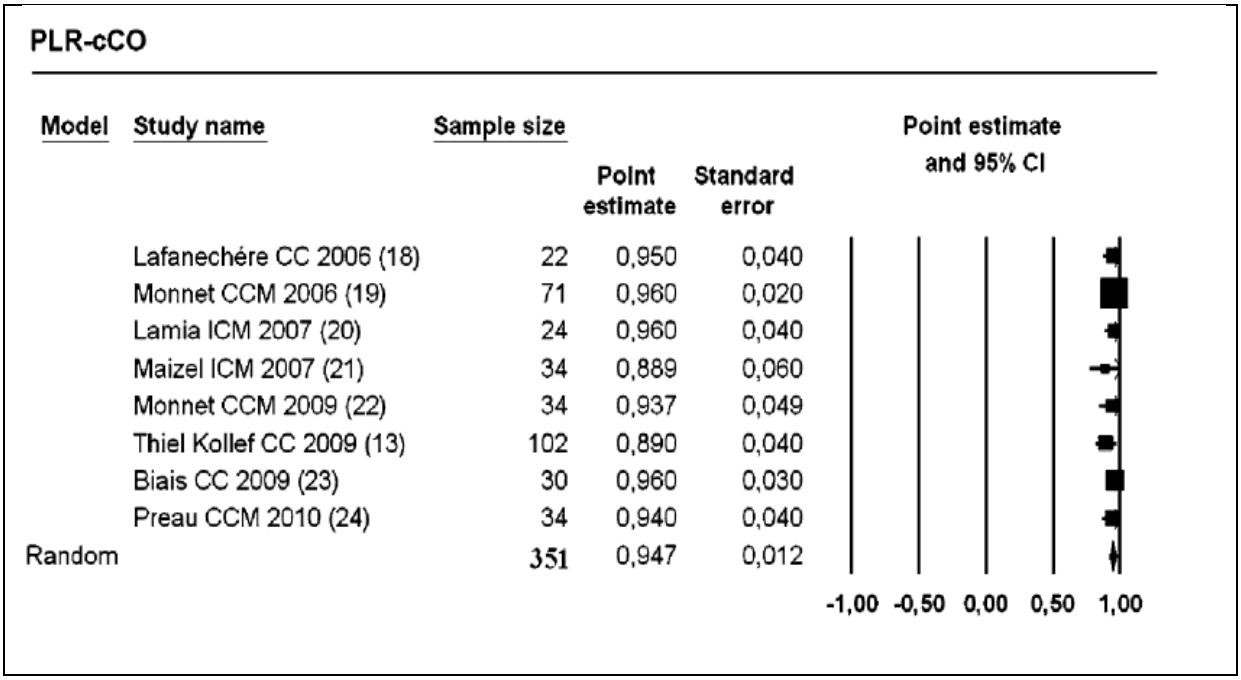


Table 2 FOREST PLOT OF PLR INDUCED CHANGES IN CARDIAC OUTPUT

Thus it was comprehensively demonstrated that PLR induced changes in cardiac output are very sensitive and specific index for fluid responsiveness for all varieties of patients.

The next problem that arose was to look for the ideal method to demonstrate the change in cardiac output. Some argued that since Pulse pressure is a surrogate marker for cardiac output, Pulse pressure variation could also be used to demonstrate increase in cardiac output.

In the same Meta analysis by Cavallaro et al, it was demonstrated that pulse pressure variation induced by PLR was a very poor index.

Reference	Index	No. of pts/boluses	% Resp.	Mean (SD) resp.	Mean (SD) non-resp.	*r*	AUC (SE)	Best threshold	Sens.	Spec.	DOR
Boulain et al. [17]	cPP	39/39				0.74					
Monnet et al. [19]	cPP%	71/71	52	19.3 (18.8)	4.9 (14.6)		0.75 (0.060)	12.0	60	85	9
Monnet et al. [22]	cPP%	34/34	68	15.5 (19.9)	6.4 (6.2)		0.68 (0.085)	11.0	48	91	9
Préau et al. [24]	cPP%	34/34	41	12.0 (8.0)	3.0 (6.0)		0.86 (0.080)	9.0	79	85	11
Overall (95% CIs)		178/178	53.7	Pooled difference in means 10.3% (6.5–14.1%)			0.76 (0.67–0.86)		59.5 (47.4–70.7)	86.2 (75.3–93.5)	10.8 (4.4–26.1

AUC area under the receiver operating characteristics curve, *cPP* PLR-induced changes in pulse pressure, *DOR* diagnostic odds ratio, *pts* patients *r* correlation coefficient, *resp.* responders, *SD* standard deviation, *SE* standard error, *Sens* sensitivity, *Spec* specificity

Table 3 PLR INDUCED CHANGES IN PULSE PRESSURE

As we can clearly see, the sensitivity and specificity decreased when pulse pressure was used to monitor changes in cardiac output. The reason hypothesized was change in arterial compliance and that pulse pressure was not directly derived from stroke volume. All the above studies that were done were using Transesophageal echocardiogram or esophageal Doppler, both which is cumbersome to use at bedside and require technical expertise. With the advent of portable sonography machines, bedside transthoracic echocardiogram (TTE) was common equipment used by medical personnel. Hence researchers looked at the sensitivity and specificity of using TTE for measuring fluid responsiveness.

A meta analysis by Mandeville and Coleburn[14] demonstrated the effectiveness of TTE to pick up changes in cardiac output due to PLR. Also the study performed well even in cases when patient had an arrhythmia. Also the bedside echo also gives us other valuable volumetric indices which are crucial for the treating intensivist. It had looked at 6 studies in mixed ICU's and 3 from pure surgical ICU's. All studies had taken a threshold of 15 % increase in cardiac output as the discriminatory index.

All studies showed good sensitivity (77%-100 %) and specificity (88%-99%).Hence TTE was an excellent method to monitor changes in cardiac output at the bedside. The limitations were that, it was not a continuous measurement and that all echo required technical expertise to operate.

Researcher looked for alternative methods to measure changes in cardiac output.

The past 10 years has brought on newer methods to measure cardiac output on continuous basis like pulse contour analysis and biorectance.

Transpulmonary thermo dilution using the PICCO^{TM} Pulsion device (Munich, Germany) has been used for continuous non invasive measurement of Cardiac output. But it required pulse contour analysis and calibration for the correct assessment of cardiac output.

Flotrac vigelo (Edward Lifescience, Irvine, CA) measures it uncalibrated.

The Flotrac vigelo is transducer which is attached to the radial artery line which gives the intensivist beat to beat cardiac output.

Bias M[29] had compared the use of Flotrac versus TTE in 34 patients who were on

intubated and ventilated medical ICU's. The investigators found that > 16 % change in cardiac output measured by Flotrac during PLR had a sensitivity of 85 % and specificity of 90 %.

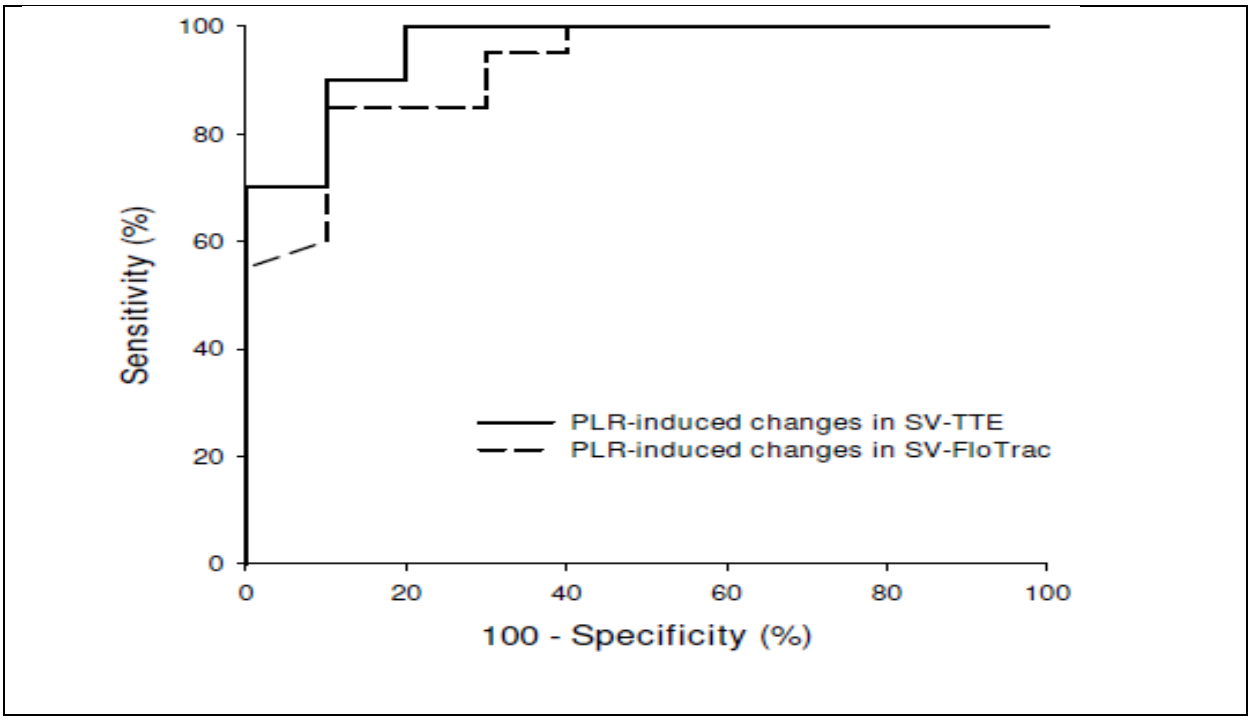


Figure 6 ROC CURVE COMPARING FLO TRAC VERSUS TRANS THORACIC ECHO DURING PLR

But there have been studies which have shown that Flotrac device underestimates cardiac output.[30]

The other problems with transpulmonary thermodilution and and Flotrac devices were that they were still invasive and could not be used to measure fluid responsiveness as they were still invasive methods.

Researcher realized that if a high frequency current of a particular amplitude is applied across the thorax we would able to calculate the resistance from the ratio of

voltage to current amplitude, which is called thoracic impedance. This thoracic impedance is a direct reflection of the instantaneous aortic blood flow from which stroke volume could be calculated. This technique failed in critical care set up due to significant electrical noise and body shifts.[31]

Keren et a[32]l in 2007 had proposed a new method to measure cardiac output which was based on the Principle of Biorectance. She found out that changes in intrathoracic blood volume also changes the electrical capacitance of the afferent signal received, which produces a phase shift .She hypothesized that analysis of the phase shifts would lead to better accuracy and this was less susceptible to electrical noise and body motion.

All this requires special high frequency generator with dual electro codes to establish body contact.

The mean change cardiac output measured by the biorectance and PAC were highly correlating with an r value of 0.84 total cardiac output measured was also co relating.

Benomar et al[33] had demonstrated the efficacy of using NICOM ™ device in predicting fluid responsiveness by changes induced by PLR.They had 75 post cardiac surgery patients in ICU where NICOM ™ device was used to measure CO at baseline, during PLR and after fluid bolus .They found that with threshold of 10 % change in CO, the NICOM ™ had sensitivity of 88 % and specificity of 100 % with correlation coefficient of 0.91.

RATIONALE FOR CURRENT STUDY

With respect to our study, very few ICU's in India use the biorectance system for monitoring changes in cardiac output. Therefore the need of the hour; as far as our country is concerned are non invasive relatively inexpensive easily available methods to monitor changes in cardiac output bright about by PLR.

Hence we decided to evaluate the effectiveness of NIBP (non invasive blood pressure) cuff which is relatively ubiquitous in all ICU's across the country to track changes in mean arterial pressure (MAP) which is a surrogate marker of cardiac output and thereby predict fluid responsiveness.

NIBP cuff measures blood pressure by oscillometric methods. The pulsatile blood flow produces oscillations which are superposed on the pressure which is brought about bu the cuff. When the cuff is deflated the oscillations amplitude will increase and then mean arterial pressure is reached at a certain point. The minimum cuff pressure at which maximum amplitude oscillations are produced is taken as the MAP. From this the systolic and diastolic blood pressure cuff which is microprocessor controlled[34]. But these reading were always different from the arterial ones and so inferior .Hence researchers decided to study the changes in MAP, SBP and PP instead of absolute values to predict fluid responsiveness .To date only 1 study has been done by Lakhal et al[35] looking at above mentioned changes in variables. Here he included 112 patients (19% with arrhythmia) and observed the changes in NIBP measured SBP, PP, MAP before and after PLR, and its co relation to fluid responsiveness by measuring cardiac output using transpulmonary thermo dilution.

He found that with a cutoff of 17 % increase in SBP, the sensitivity and specificity of NIBP measured indices were 39 % and 99% respectively. Change in MAP of 12 % displayed a sensitivity of 48 % and specificity of 76 %; PP with a threshold of 7 % demonstrated a sensitivity of 77 % and specificity of 66 %.

The above given study had various limitations in the form of:

1) It included patients who were deeply sedated and did not include spontaneously breathing patients

2) Only in 66 % of patients were they able to get data in the first 24 hours of resuscitation. Since most of fluid requirement occurs within the first 24 hours these cohort of patients were missed.

3) They used invasive methods for measuring cardiac ouput (PAC) which is not as sensitive or specific as other methods like transthoracic echocardiogram

4) The number of patients enrolled could have been too less to demonstrate a significant enough change hence leading to low sensitivity and specificity.

5) No Indian data available on these proposed lines and hence requiring further validation.

Due to above mentioned reasons; it was decided to evaluate the changes of Mean Arterial pressure measured by non invasive oscillometric readings (NIBP) with passive leg raise as an index of fluid responsiveness in patients with shock in a tertiary care hospital in South India.

PATIENTS AND METHODS

Study type: Prospective observational study

Study design: Cohort

Setting: This study was conducted in the Medical intensive care unit of the Department of Medicine, Christian Medical College, Vellore**.**

Duration of study: The recruitment phase spanned a 14 month period (March 2014 to May 2015).

Study population: Patients admitted to the medical intensive care unit during the period of recruitment

Inclusion criteria

1. Patients with evidence of hypoperfusion (hypotension, elevated lactate, decreased urine output, cold extremities)

2. These patients should be deemed by the treating intensivist to require a fluid challenge. The doctor is free to base this decision on hemodynamic patterns, tests of volume responsiveness or clinical judgement.

3. Patients should be more than 18 years of age

**** Patients were eligible to enter the study multiple times. For the sake of data analysis each volume challenge was taken as an independent observation regardless of whether it was part of multiple studies performed on the same patient**

Exclusion Criteria

1. Patients unwilling to participate
2. Raised intra-abdominal pressure (>15mmHg)
3. Pregnancy
4. Arrhythmias except for occasional ventricular ectopics
5. Contraindications to a passive leg raise such as spinal, lower limb and pelvis surgeries or fractures of lower limb.
6. Prior below or above knee amputations
7. Inability to interrogate the left ventricular outflow tract because of a poor thoracic echo window
8. Mid upper arm circumference more than 35 cm or less than 27 cm

Withdrawal criteria

1. Patient unwilling to continue participation in the study

Sources of information:

1. Laboratory records
2. Study participants/relatives
3. Hospital records

Outcome measures

The following parameters were planned and specifically assessed in this study

PRIMARY OUTCOME:

1 .a) To determine the sensitivity and specificity of non invasive Mean arterial pressure change (MAP) with passive leg raise (PLR) compared against a gold standard of more than or equal to 15 % increase in stroke volume.

b) To determine MAP change with best cut –off

2. a) To determine the sensitivity and specificity of non invasive Systolic blood pressure change (SBP) , Pulse pressure change (PP), heart rate change (HR) with passive leg raise compared against a a gold standard of more than or equal to 15 % increase in stroke volume.

b) To determine SBP change, PP change, HR change with best cut off.

Statistical methods

Data entry was done using the Epidata software version 3.1. Descriptive statistics were calculated using SPSS software (version 14). Sample size was calculated based on the study done by Lakhal et al[35].

Based on the thorough review of the ROC analyses by Lakhal et al, we had decided to calculate the sample size with reasonable Sensitivity (70 to 80%) rather than 48% sensitivity with 91% specificity as done in the previous paper. In order to get a range of sensitivity from 70 to 80%, with the precision of 10% and 95% CI, the calculated

sample size was 70 observations in the responder group and 70 observations in the non responder group.

Single Proportion - Absolute Precision		
Expected Proportion (Sensitivity)	0.7	0.8
Precision (%)	10	10
Desired confidence level (1- alpha) %	95	95
Required sample size	81	61

Methodology

Step 1: Recruitment

Since this was a prospective observational study, all patients were recruited after an explanation of the study and the protocol. In the event that the patient was sedated or in an altered state of consciousness, consent was obtained from the nearest relative or guardian accompanying the patient (Annexure I).

Step 2: Data collection

All consecutive patients admitted to the medical ICU/HDU and fulfilling the inclusion criteria and exclusion criteria who required a fluid bolus when the Principal investigator was present in the MHDU/MICU were recruited.. Data was collected in data abstraction forms (Annexure II). The following data were collected specifically:

1. Baseline demographics – age, sex, hospital number, height, weight, BMI, Mid upper arm circumference (MUAC)

2. Admission source(casualty/ward),Date of admission to hospital, ICU and date of discharge and date of examination

3. Provisional diagnosis at admission

4. Number of observational attempts done on the particular patient.

5. History of co morbidities.

6. Date of cardiac arrest if any in patient

7. Indication of fluid challenge

8. Type of shock

9. Ventilator parameters

10. Variables necessary for computing the SAPS II score at admission

11. Inotropes if any and dose of each inotrope

12. Changes in variable like Heart rate, SBP, DBP, PP, MAP before and after PLR

13. Variables in echo to calculate stroke volume ,cardiac output and cardiac index

14. Duration of ICU stay

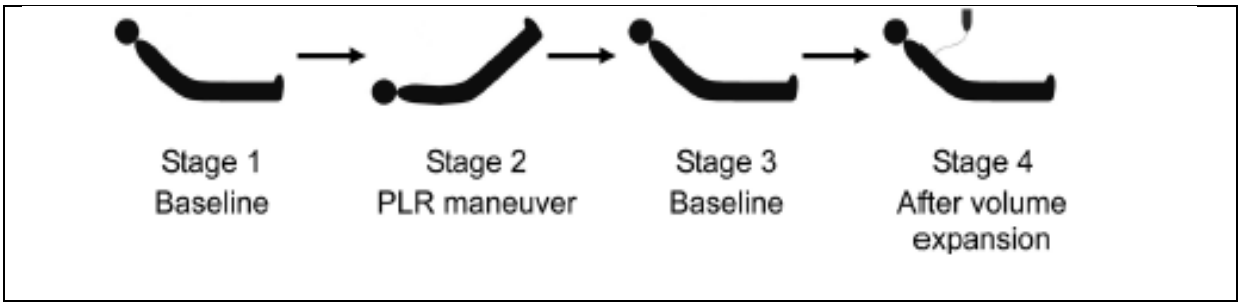
15. Duration of hospital stay

16. Blood pressure measured in which arm

17. ICU and hospital outcome in terms of mortality

Algorithm of the study:

Figure 7 STUDY ALGORITHM



STAGES	STAGE 1	STAGE 2	STAGE 3	STAGE 4
MESUREMENTS	HR,SBP,PP	HR,SBP,PP	HR, SBP,PP	HR,SBP,PP
	MAP	MAP	MAP,SV	MAP,SV

LEGEND

HR- HEART RATE
SBP- SYSTOLIC BLOOD PRESSURE
PP- PULSE PRESSURE
MAP-MEAN ARTERIAL PRESSURE
SV- STROKE VOLUME MEASUREMENT

STUDY PROTOCOL:

All consenting patients who were admitted with shock in MICU and MHDU fulfilling the inclusion and exclusion criteria were included. It was also necessary that the Principal investigator himself was present at the time of study for carrying out the measurements.

The Principal investigator (PI) obtained non invasive oscillometric blood pressure measurements (NIBP) as outlined in the diagram above.

An improvement in stroke volume by 15% after the IV fluid bolus indicated that the patient was fluid responsive. [10]

We compared the change in blood pressure measurements and heart rate (MAP/SBP/PP) during passive leg raise to the gold standard of a 15% increase in stroke volume after the IV fluid bolus

Technique of MAP measurement by NIBP cuff

The blood pressure was measured, using the Phillips intelliVue MP5 monitor. This was the standard monitor used for all the patients in the medical ICU. The upper-arm circumference was measured according to the present recommendations at the midpoint between the tip of the acromion and Olecranon. A standard Adult size cuff of the dimensions 30 X 16 cm, (which is the standard adult cuff size for measuring a mid upper arm circumference between 27-35 cm) was placed over the brachial artery of the arm.

As mentioned before, NIBP cuff measures blood pressure by oscillometric methods. The pulsatile blood flow produces oscillations which are superposed on the pressure which is brought about by the cuff. When the cuff is deflated the amplitude of oscillations will increase and then mean arterial pressure will be reached at a certain point. The minimum cuff pressure at which maximum amplitude oscillations are produced is taken as the MAP. From this the systolic and diastolic blood pressure cuff is derived which is microprocessor controlled[34].

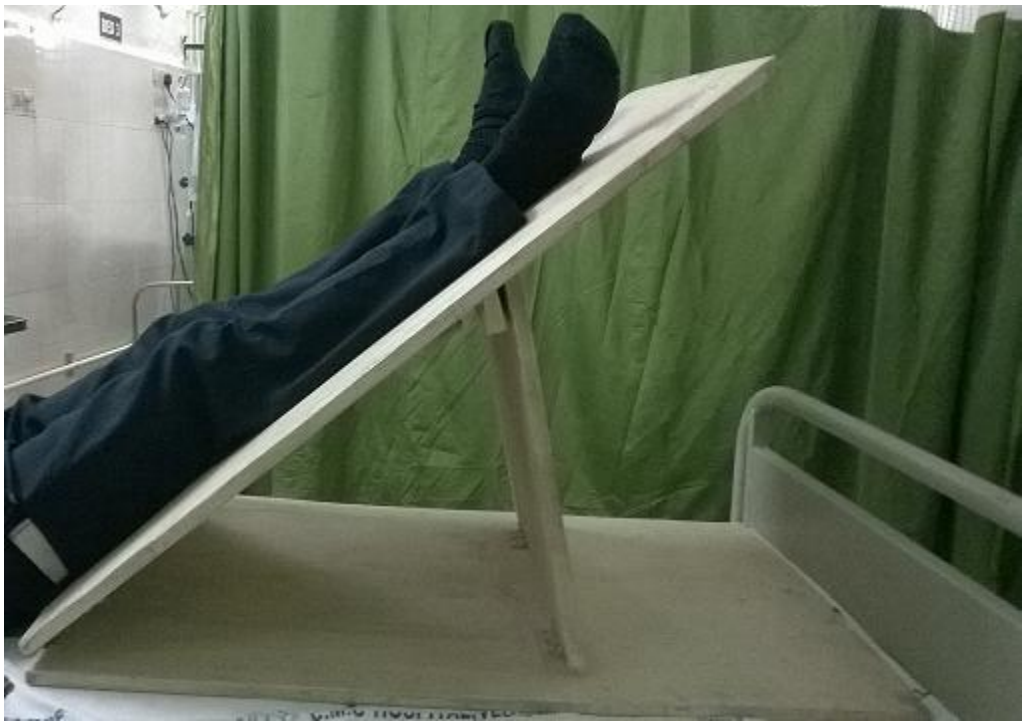
Technique of PLR

The patient was kept in the 45 degree semi recumbent position; the angle being confirmed by angle markers at the head end; following which the patient undergoes a passive leg raise. We had to improvise our technique of PLR as we did not have automatic leg raise option in our beds in ICU. We had constructed a specially

designed 45 degree angled slope from plywood of dimension 45 X 25 cm which is depicted below. This was kept covered with a sterile cover to prevent hospital acquired infections. The slope had a wedge attached to maintain the leg elevation at 45 degree

Figure 8 PLR – HORIZONTAL POSITION

Figure 9 PLR – 45 DEGREE LEG UP POSITION



The PLR was initiated by lowering the head end to make the bed flat. The lower limbs were placed on the slope following it was elevated .The wedge maintained the 45 degree elevation.

We took special precautions of not disturbing the femoral catheters or induce pain during movement which might cause sympathetic stimulation and alter hemodynamic variables

.

Technique of stroke volume measurement:

The stroke volume was measured with the help of velocity time integral and left ventricular outflow tract diameter. For calculating the flow the apical 5 chamber view is visualized using the Sonosite Micromaxx cardiac phased array probe. Following this we obtained that spectral waveform at the outflow tract using the Doppler mode at the level of the aortic valve. The velocity time integral of the Doppler waveform is calculated using the calculations menu on the portable echocardiogram.

The LVOT diameter was measured after freezing the parasternal long axis view in mid systole. Stroke volume was determined using the formula: Stroke volume = π x (LVOT radius) ^{2} x velocity time integral. Cardiac output = Stroke volume x heart rate

.

The Stroke volume was measured both pre and post fluid bolus, i.e stage 3 and 4 described in the above algorithm. A 15 % variation in stroke volume predicts fluid responsiveness[10]

Time interval between the index and reference standard was 4 minutes .The patient's health condition did not change in this time frame.

.

Step 3: Statistical Analysis:

All study variables were presented using descriptive statistical methods. Continuous variables which were normally distributed were summarized using mean and standard deviations. Non normally distributed continuous variables were summarized using median. ROC curve was utilized in demonstrating the clinical utility of the new test as compared to the standard.

Multiple ROC curves were simultaneously utilized to compare and contrast different variables. Tests were analyzed using the SPSS software (version14)

Funding

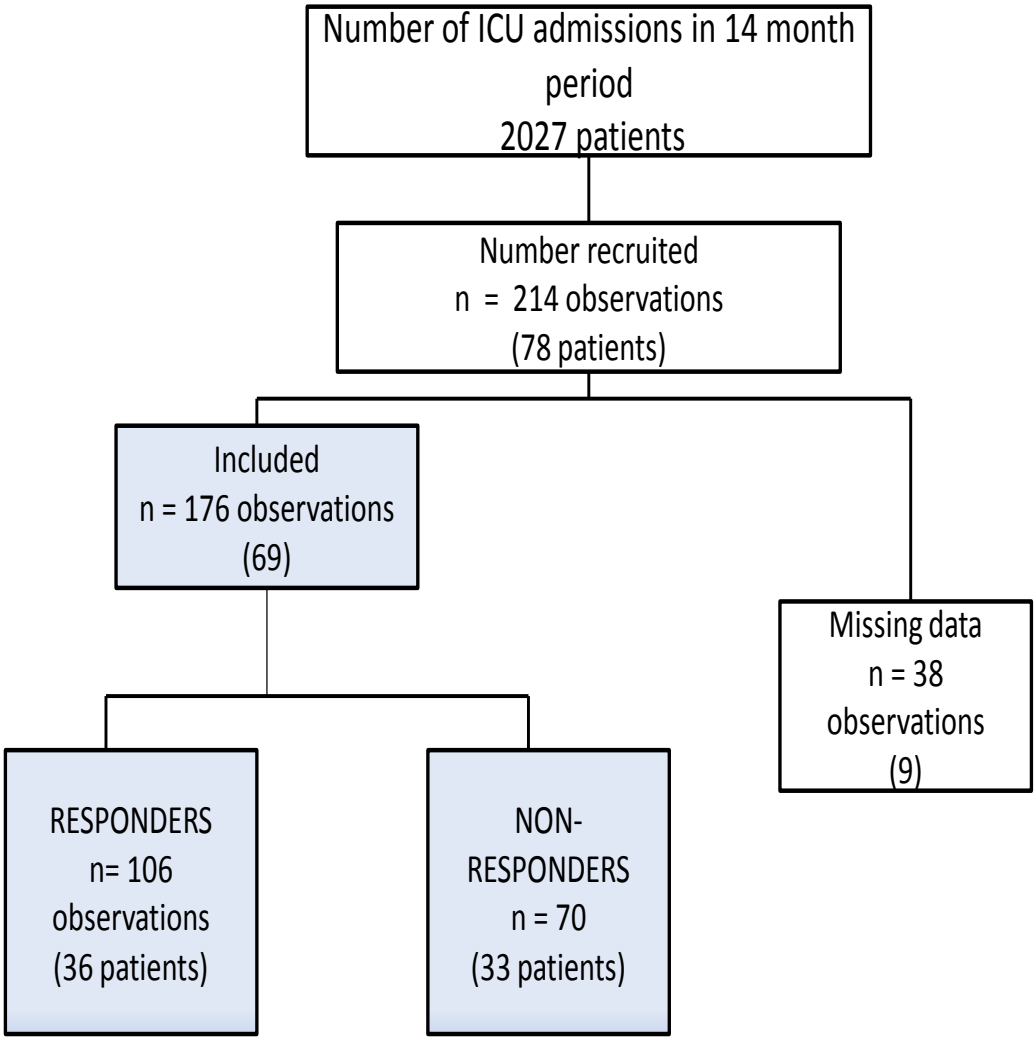
The cost of the wedge utilized for PLR was borne by the institution, through a fund allocated by the institutional review board for thesis purpose.

Institutional Research Board Approval and Ethical considerations

Since this was a purely observational study, there were no ethical issues. Consent was obtained at admission in ICU/HDU from the relatives before the test was done. Institutional research board approval (IRB) was obtained prior to the study.

RESULTS

Figure 10 STROBE DIAGRAM



A total of 2027 patients were admitted in the medical intensive care unit during the course of this study. Totally 214 observations (78 patients) were included out of which only 176 observations (69 patients) were taken for final analysis. 38 of the observations (9 patients) of them were excluded due to missing data.

PATIENT DEMOGRAPHICS

Table 4 DEMOGRAPHICS TABLE

Age (Mean ± SD) (years)	46±16
Male/Female (n)	33/36
Male : Female ratio	0.9:1
BMI (Mean ± SD) kg/m2	24.75±3.74
MUAC (Mean ± SD)(cm)	28.6±2.25
Arterial lactate concentration (Mean ± SD) (mmol/L) Concentration> 2.5 mmol/L(n)	3.46±2.17 119/176 observations (67.6%)
Ventilation(n) - Mechanical ventilation - Non invasive ventilation	 58/69 (84.1%) 11/69 (15.9 %)
MODE of mechanical ventilation(n=58) -SIMV - SPONT	 53/58 (91.6%) 5/58(8.4%)
SAPS II score (Mean ± SD)	65±19
Admission source(n) - Casualty - Ward	 43/69(62.3%) 26/69(37.7%)

Inter-hospital transfer(n) -Yes - No	54/69(78.3%) 15/69(21.7%)
Indication for fluid challenge (n) - Low BP - Oliguria - High lactate(>2.5 mmol/l)	 13/69(18.8%) 34/69(49.3%) 22/69(31.9%)
Type of shock at admission (n) - Septic - Cardiogenic - Hypovolemic - Anaphylatic - Obstructive	 59/69 (85.5%) 2/69 (2.9%) 4/69 (5.8%) 3/69 (4.3%) 1/69 (1.4%)
Inotrope requirements (n) - No inotrope - Single inotrope - Double inotrope - Three inotropes	 23/69 (33.3%) 26/69 (37.7%) 16/69 (23.2%) 4/69 (5.8%)
Cardiac arrest (n) - Yes - No	 7/69 (10.1%) 62/69 (89.9%)

Co-morbidities (n)	
- Nil illness	11/69 (15.9%)
- OAD	2/69 (2.9%)
- CAD	1/69 (1.4 %)
- DM	16/69 (23.1%)
- HTN	10/69 (14.4 %)
- CCF	2/69 (2.8%)
- CKD	1/69 (1.4%)
- HIV	2/69 (2.8%)
- CLD	4/69 (5.7%)
- Malignancy current	8/69 (11.5%)
- Immunosuppresants	12/69 (17.3%)

In our study, the **mean age** of our population studies was 46 years, which was rather young when compared to usual demographic profile of patients being admitted in ICU. In Lakhal's [35]study , the average age was 61 years.

In the break up of the study patients there were an equal number of male and female patients and the **ratio of male to female** was 0.9:1.In Lakhals[35] study, the male :female ratio was almost 3:1,indicating an overwhelming majority were males.

The average **Body Mass Index** of the study population was 24.75 kg/m^2 .This indicates that the most of the patients were in the normal BMI category.

The average **Mid upper arm circumference** was 28.6 cm.

The **mean arterial lactate concentration** was 3.46 mmol/L; consistent with patients in shock. Almost 66 % of patients had an elevated arterial lactate concentration at baseline. This is far higher as compared to Lakhals[35] study where only 39 % of the population studied showed elevated lactate concentrations

The average **SAPS II score at admission** was 65 which corresponded to a mortality of around 78 %.This was also higher as compared to previous study done by Lakhal[35], indicating this particular subset were more morbid as compared to Lakhal's study

Majority of patients required Invasive ventilation (84%) for various causes, indicating severe cardiopulmonary distress .Of the patients who were mechanically ventilated, 91% of them were on SIMV mode of ventilation. Hence this was the ideal subgroup of patients where such a study could be done and required validation.

More than half of the patients (62 %) were admitted from casualty .It was also noticed that majority of the patients (78%) were referred from other hospitals rather than primarily coming to out institution

.The most **common indication for fluid bolus** was oliguria (49.3%) followed by elevated lactate concentration (31.9%) and lastly hypotension which comprised of 18.8 %

Septic shock comprised the majority (85%) of patients who were admitted with hemodynamic instability in the ICU. This was higher as compared to Lakhal[35] study, where septic shock comprised only 48 % of the study population. In our study the other forms of shock in order of magnitude were hypovolemic > anaphylactic> Cardiogenic.

There was only 1 case of acute pulmonary embolism which was classified under obstructive shock.

Around a third of patients did not require inotropes at baseline. Of the 2/3rd that required Inotropes, 6 % of them required more than 3 inotropes for maintaining blood pressure.

Around 37 % of patients were on single inotrope and 23 % of them were on 2 inotropes.

There were 7 cardiac arrests at baseline during admission in the study population.

Around 16 % of patients did not have any co morbidities at admission. In the 84 % of the rest, Diabetes Mellitus was the most common risk factor identified which accounted for 23.8%.Hypertension was the second most common co morbidity identified which was around 14.4 %.Surprisingly the 3rd most common risk factor was immunosuppressive drug use which was around 17 % and presence of current malignancy, accounting for 11.5 %.Chronic liver disease was the most common chronic organ damage identified in this study.

Below we have looked at the ventilator parameters of patients who were on non invasive and mechanical ventilation respectively

NIV patients (n=11/69)

Table 5 NIV VENTILATION PARAMETERS

variable	FiO2 (%)	P/F ratio	Tidal Volume(ml)	PEEP(cm of H_2O)	Pressure support(PS)
MEDIAN	28	265	320	8	8
MINIMUM	24	220	300	6	8
MAXIMUM	60	320	400	10	15

As one can interpret from the above table, among the 11 patients who were given non invasive ventilation (NIV), the average FiO2 was 28 % with a P/F ratio of 265.

The average Peak end inspiratory pressure utilized was 8 cm of H2O and average pressure support applied was 8.

Mechanical ventilation patients (n=58/69)

Table 6 MECHANICAL VENTILATION PARAMETERS

Variable	FiO2(%)	P/F ratio	Tidal Volume (ml)	PEEP (cm of H_2O)	PS
MEDIAN	60	259	300	10	15
MINIMUM	30	146	300	5	8
MAXIMUM	90	389	480	15	20

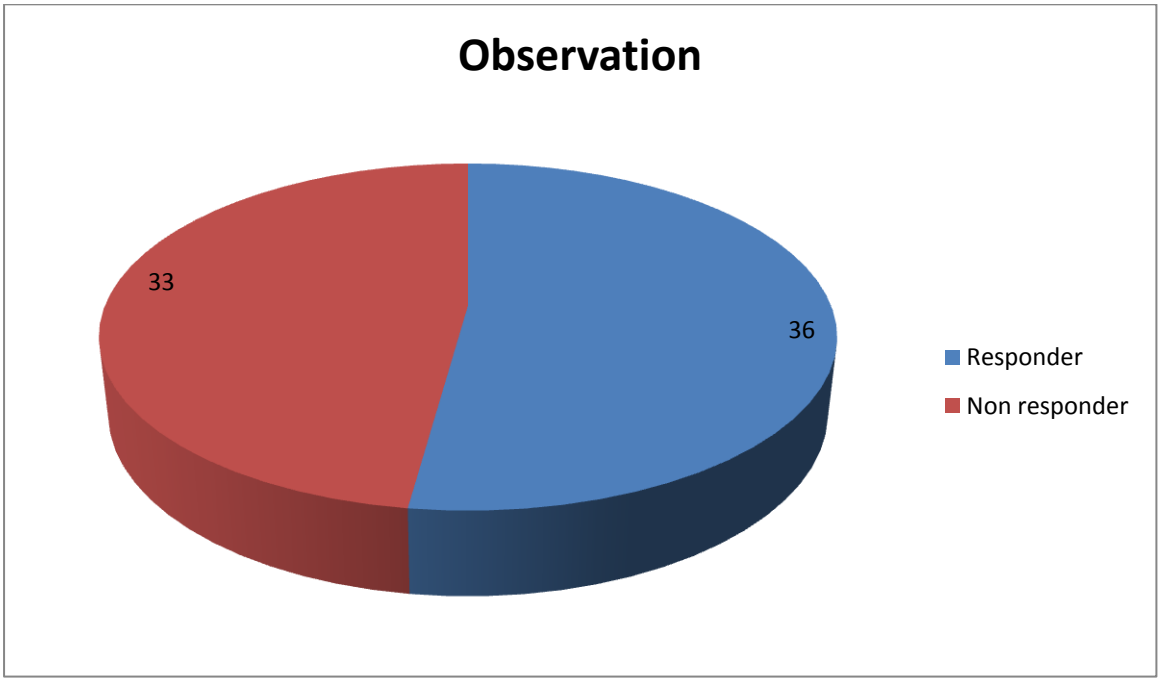
Its clear from above that most of the patients required mechanical ventilation. The average tidal volume mentioned was 300 ml corresponding to approximately 6 ml/kg.

We have divided the patient categories into 2:

Responders – i.e those observations in whom the change in stroke volume variation was more than or equal to 15 %.

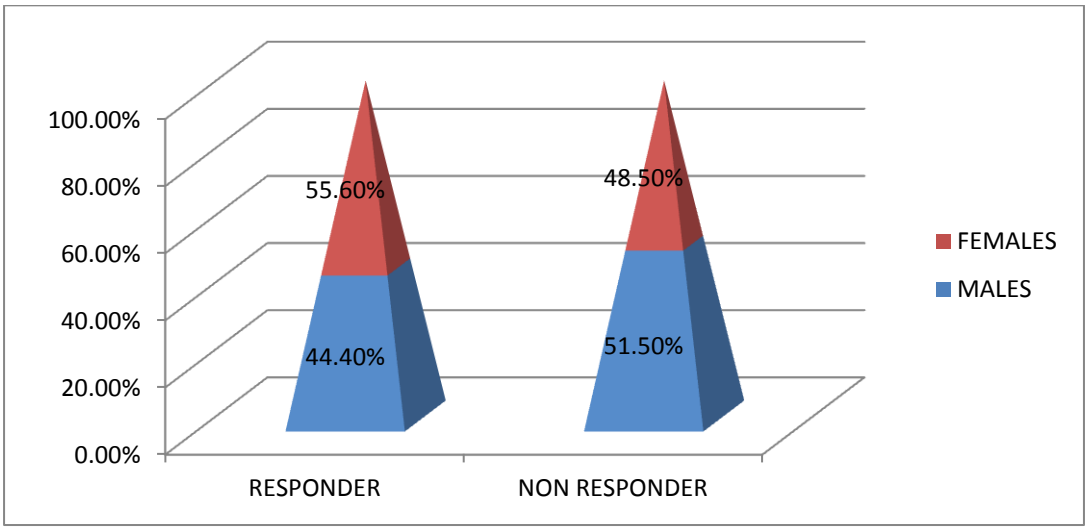
Non responders- those observations in whom, the change in stroke volume was less than 15 %

As once can notice from the above strobe diagram, 106 responder variations corresponded to 36 patients (n) and the 76 non responder variations which corresponded to 33 patients (n)



We have relooked at certain demographic characteristic which might have influenced the final outcome.

Table 7 Sex distribution among the responder and non responder

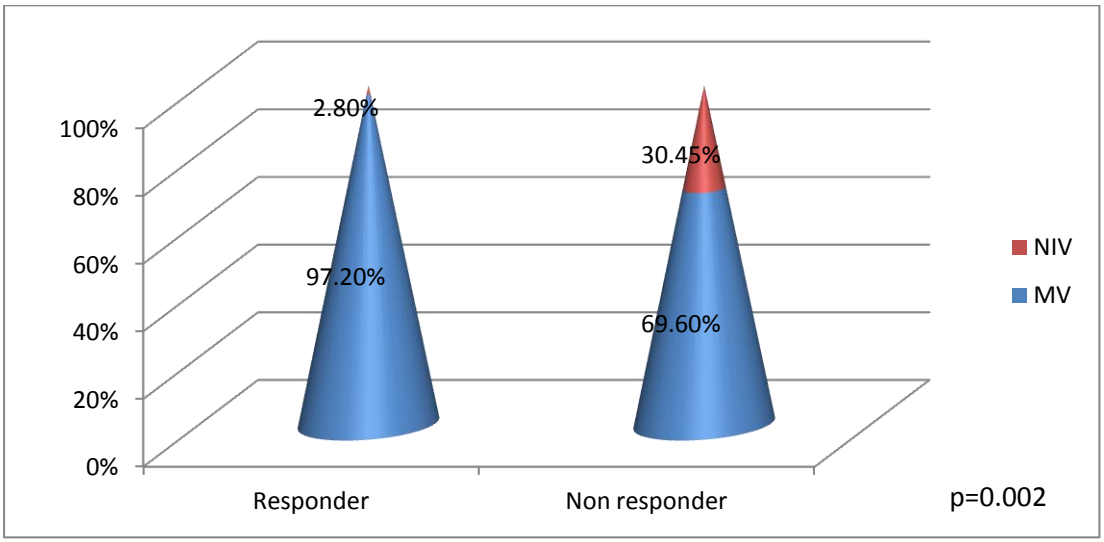


The above graph indicates fairly equal distribution of males and females among the responder and non responder group. The p value for the difference among them was calculated by the chi square test and was found to be 0.557

	RESPONDER	NON RESPONDER
AGE DISTRIBUTION Age (Mean ± SD) (years)	45.33 ±15.2	47.82±17.4

Independent t test analysis between the 2 groups showed an insignifanct difference (p =0.53) There was no significant difference in the mean age of the 2 groups.

Table 8 VENTILATION TYPE IN THE TWO GROUPS



The overwhelming majority of patients in the responder arm where mechanically ventilated (MV) (35/36 patients).Chi square analysis indicated a significant difference between the 2 groups with p value of <0.002.

Mechanical ventilation would lead to decrease in venous return due to positive pressure ventilation, thereby increasing the number of responder observations.

Table 9 INOTROPE REQUIREMENT IN RESPONDER AND NON RESPONDER

RESPONDER STATUS	N	MEDIAN
YES	36	1
NO	33	1

As once can see in the above table, there was no significant difference in the use of inotropes among the 2 groups .p value was calculated using the Mann Whitney test to be 0.262 which was insignificant.

Table 10 MID UPPER ARM CIRCUMFERENCE IN RESPONDER and NON RESPONDER ARM

	RESPONDER	NON RESPONDER
MID UPPER ARM CIRCUMFERENCE (Mean ± SD) (CM)	28.47±2.28	28.76 ±2.23

Independent t test analysis between the 2 groups showed an insignifanct difference (p =0.603).

Table 11 ARTERIAL LACTATE CONCENTRATION IN RESPONDER AND NON RESPONDER ARM

	RESPONDER	NON RESPONDER
ARTERIAL LACTATE CONCENTRATION (Mean ± SD) (mmol/L)	3.9±1.9	2.9±2.3

Independent t test analysis between the 2 groups showed an insignifanct difference (p =0.077) between the 2 groups.

Table 12 CARDIAC ARREST AT ADMISSION ION IN RESPONDER AND NON RESPONDER ARM

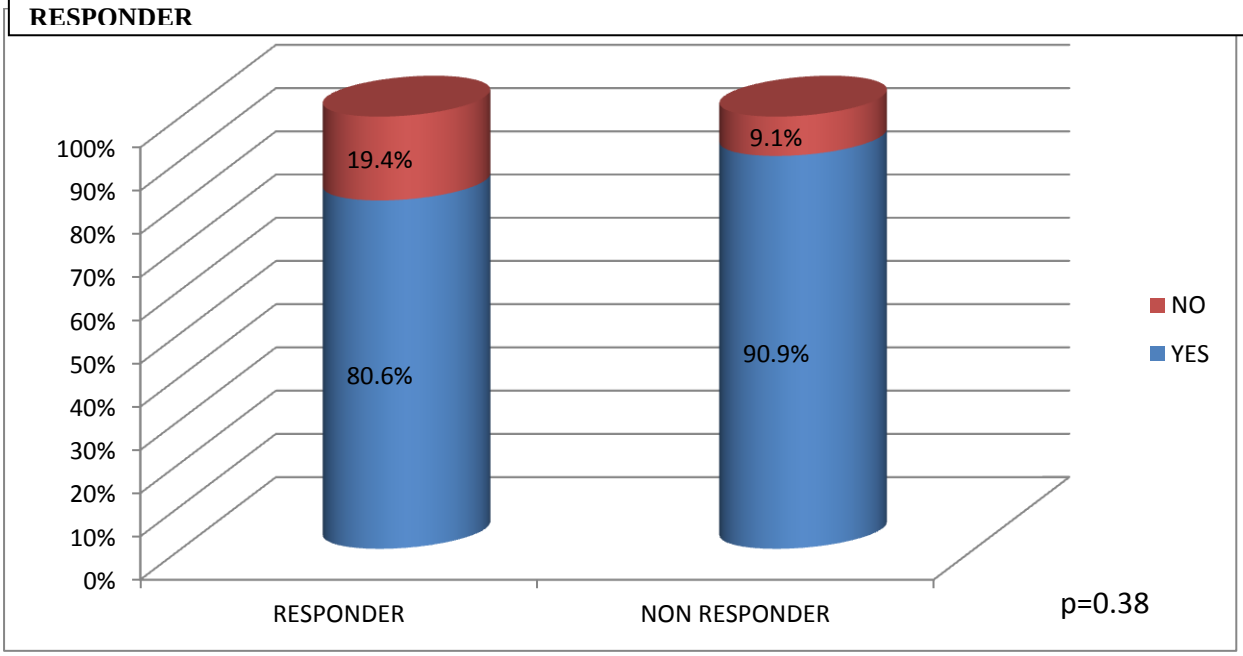
	RESPONDER	NON RESPONDER	TOTAL
NUMBER OF CARDIAC ARREST (n)	3	4	7

No significant differences were found in the 2 groups in the number of cardiac arrest

TYPE OF SHOCK

SEPTIC SHOCK

Table 13 BREAKUP OF PATIENTS WITH SEPTIC SHOCK IN RESPONDER AND NON RESPONDER

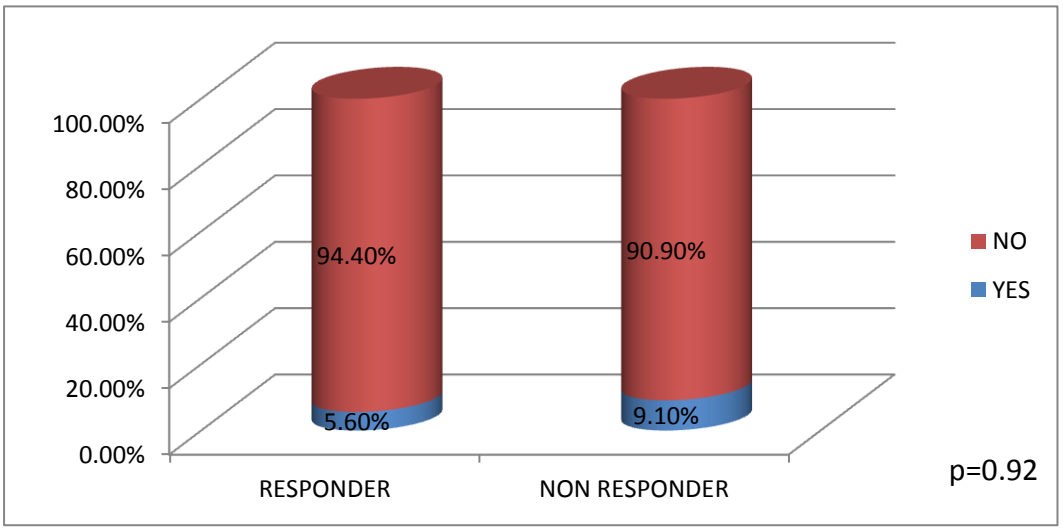


SEPTIC SHOCK(n)	YES	RESPONDER	NON RESPONDER
		29(80.6%)	30(90.9%)
	NO	7(19.4%)	3(9.1%)

P value calculated by chi square was 0.380, insignificant

CARDIOGENIC SHOCK

Table 14 BREAKUP OF PATIENTS WITH CARDIOGENIC SHOCK IN RESPONDER AND NON RESPONDER



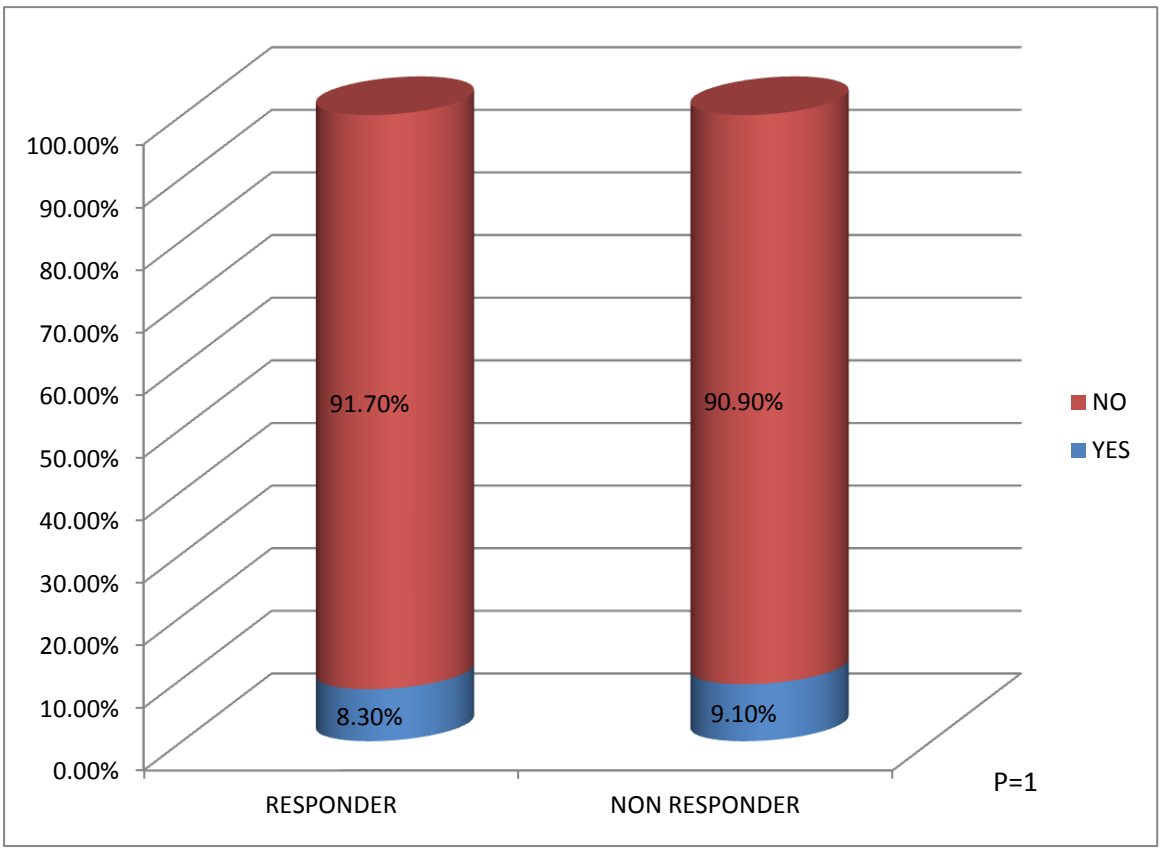
CARDIOGENIC SHOCK (n)	YES	RESPONDER	NON RESPONDER
		2(5.6%)	3(9.1%)
	NO	34(94.4%)	30(90.9%)

P value calculated by chi square was 0.92 which was insignificant

HYPOVOLEMIC SHOCK

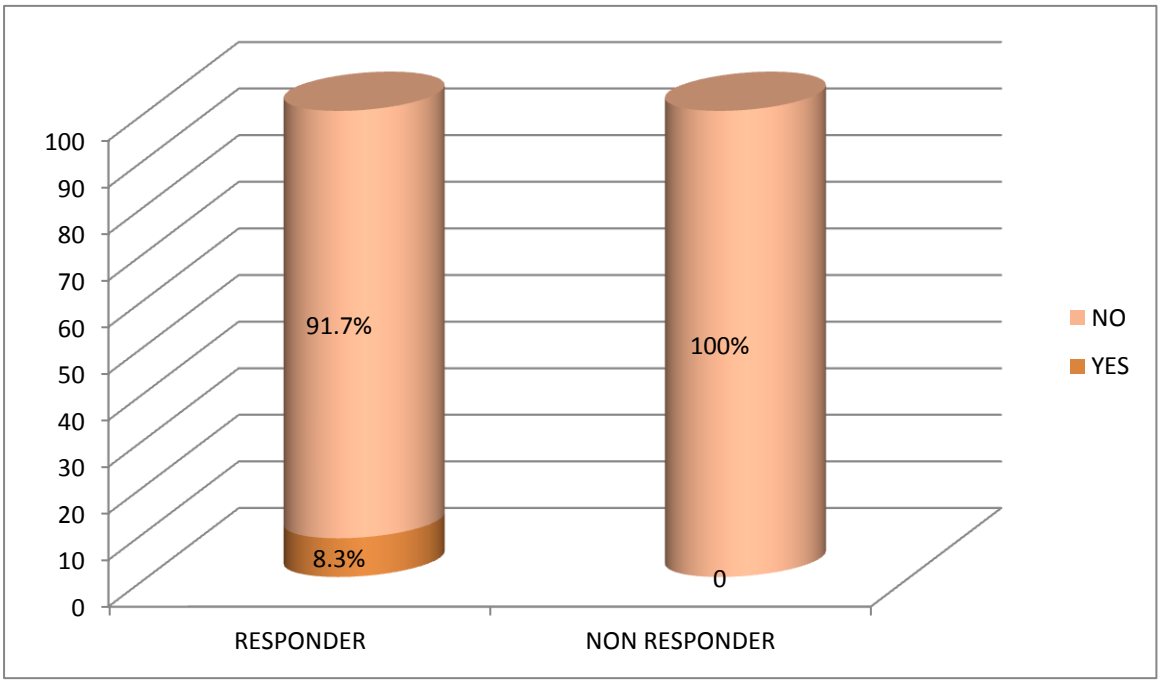
		RESPONDER	NON RESPONDER
HYPOVOLEMIC SHOCK (n)	YES	3(8.3%)	3(9.1%)
	NO	33(91.7%)	30(90.9%)

Table 15 BREAKUP OF PATIENTS WITH HYPOVOLEMIC SHOCK IN RESPONDER AND NON RESPONDER



P value calculated by chi square was 0.92 which was insignificant

Anaphylactic shock



p value was 0.266 which was insignificant

OBSTRUCTIVE SHOCK

There was only 1 case of obstructive Shock (pulmonary embolism) in the whole study which was in the responder group. p value was not significant.

PRIMARY OUTCOME

The primary outcome we looked at was the sensitivity and specificity of change in Mean arterial pressure which co related with a 15 % increase in stroke volume on fluid loading as measured by an echocardiogram

We also looked at changes in SBP, PP and HR which co related with a 15 % increase in stroke volume on fluid loading as measured by an echocardiogram

For this we have constructed a table which shows the baseline hemodynamic parameters of variables used in the study

Table 16 HEMODYNAMIC PARAMETERS OF THE STUDY POPULATION

RESPONDER					**NON RESPONDER**			
VARIABLES	***BASE***	***POST PLR***	**PRE BOLUS**	**POST BOLUS**	**BASE**	**POST PLR**	**PRE BOLUS**	**POST BOLUS**
HR (beats/ min)	***116±23.5***	***112±22.6(a)***	**116±22.9**	**118±68**	**109±22.9**	**109±23.1**	**108±21.69**	**107±21.74**
SBP mm hg	***105±16.4***	***109±18.3(a)***	**106±16.3**	**113±17.9**	**109±14.8**	**109±16.07**	**109±13.1**	**110±14.01**
MAP mm hg	***77±9***	***79±10.8***	**77±8.6**	**83±9.4**	**76±10.7**	**77±9.9**	**77±7.9**	**79±8.7**
PP mm Hg	***38±14.2***	***41±15.4 (a)***	**38±14.8**	**42±16.1**	**41±12.03**	**42±14.3**	**42±13.75**	**42±14.2**

ALL VALUES EXPRESSED AS MEAN ± SD

HR-heart rate

SBP-systolic blood pressure

MAP-Men arterial pressure

PP-pulse pressure

a- P < 0.05 compared to baseline.

The above hemodynamic parameter gives us the entire gamut of the observations recorded during the study. It's clear from the data above that significant differences were present only in heart rate, Pulse pressure and systolic blood pressure after PLR was instituted.

.ROC CURVES OF NIBP PARAMETERS

We have calculated the ROC curves for the following variables:

1) MEAN ARTERIAL PRESSURE CHANGE

2) SYSTOLIC BLOOD PRESSURE CHANGE

3) PULSE PRESSURE CHANGE

4) HEART RATE CHANGE

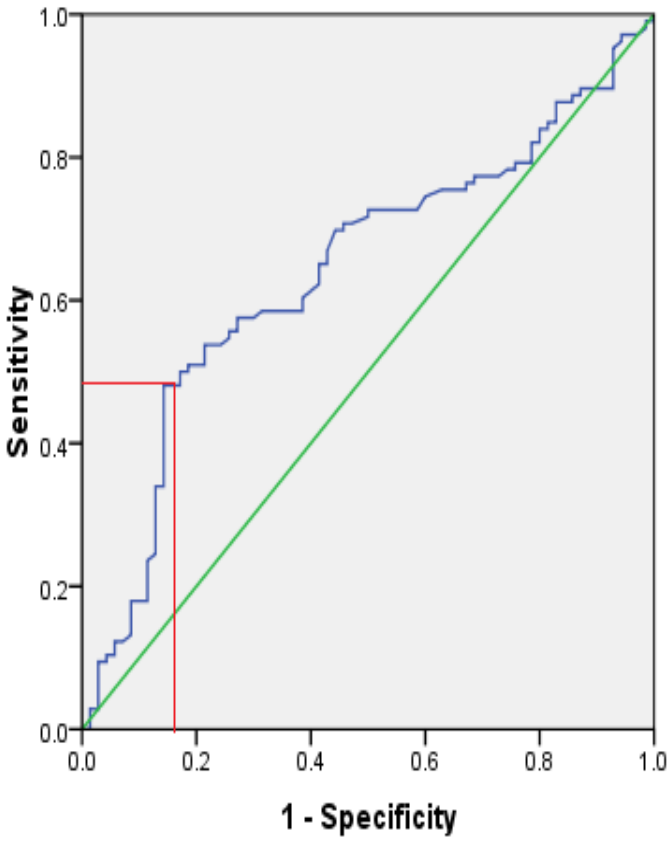
ROC CURVE FOR MEAN ARTERIAL PRESSURE

We have constructed the ROC curve by comparing the **change in mean arterial pressure** in **percentage to gold standard**, **which is increase in stroke volume of >= 15 %**on fluid loading. On evaluation of the ROC curve for mean arterial pressure, the area under the curve obtained was 0.64 with a standard error of 0.042.

We found that, **with a MAP change of 3.0 % corresponded to a sensitivity of 50 % and specificity of 82.9 %.**

Figure 11 ROC CURVE MAP

AREA UNDER THE CURVE WAS 0.640



Diagonal segments are produced by ties.

Table 17 **MAP 2X2 TABLE**

	RESPONDER	**NON RESPONDER**	TOTAL
MAP CHANGE >= 3%	53	12	65
MAP CHANGE <3%	53	58	111
TOTAL	106	70	176

We have included a lower sensitivity in our readings so as to maintain a higher specificity for our test and to have a meaningful change in the mean arterial pressure percentage which can be used at the bedside.

We were unable to select a cut off with higher sensitivity due to intersection of the ROC curve with null hypothesis at higher sensitivities.

ROC CURVE FOR SYSTOLIC BLOOD PRESSURE CHANGE

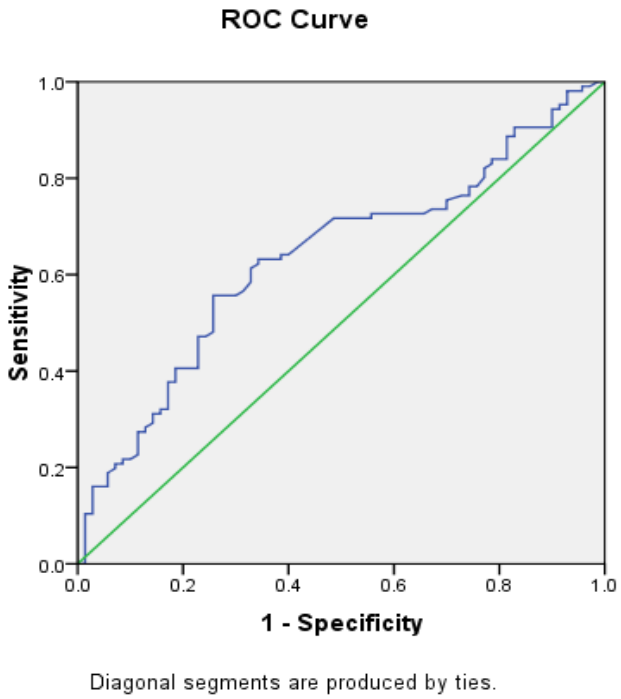


Figure 12 ROC CURVE SBP

AREA UNDER THE CURVE- 0.636

The area under the curve of the above given ROC was 0.636, marginally poorer than Mean arterial ROC tracing.

	RESPONDER	**NON RESPONDER**	TOTAL
SBP CHANGE >= 2%	51	17	68
SBP CHANGE <2%	55	53	108
TOTAL	106	70	176

Table 18 SBP CHANGE 2X2 TABLE

Systolic blood pressure also did not give us a very good sensitivity or specificity. On ROC curve evaluation, an **increase in SBP by 2 % on PLR, would give a 48 % sensitivity and 75 % specificity in predicting fluid responsiveness.**

As mentioned previously, we are forced to choose lower sensitivity values in view of the ROC curve deviating towards the right of the graph at higher values

ROC CURVE FOR PULSE PRESSURE CHANGE

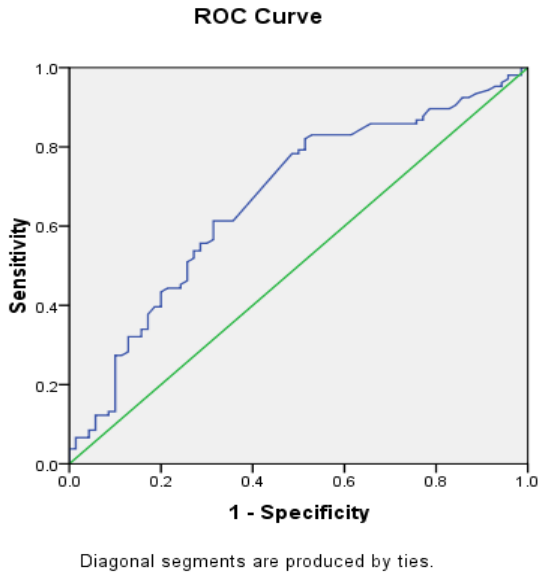


Figure 13 ROC CURVE PULSE PRESSURE

AREA UNDER THE CURVE =0.668

Table 19PULSE PRESSURE 2X2 TABLE

	RESPONDER	**NON RESPONDER**	TOTAL
PP CHANGE >= 5%	51	17	68
PP CHANGE <5%	55	53	108
TOTAL	106	70	176

Pulse pressure ROC tracing had a higher Area under the curve as compared to MAP (0.668 vs. 0.640).

Evaluation of ROC curve shows that a Pulse pressure cut off of 5 % would give us a sensitivity of 48 % and specificity of 75 % in predicting fluid responsiveness.

ROC CURVE FOR HEART RATE CHANGE

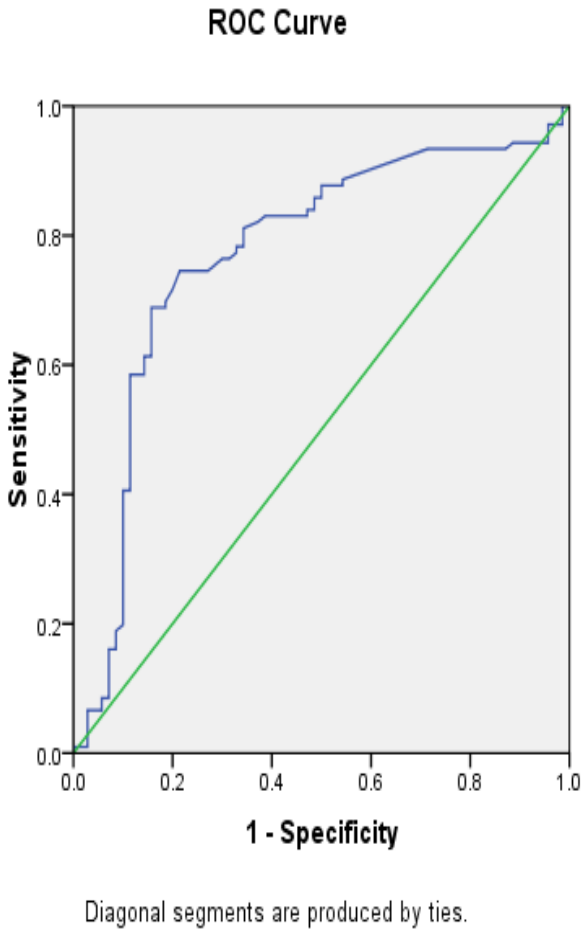


Figure 14 ROC CURVE HEART RATE CHANGE

AREA UNDER THE CURVE=0.771

Table 20 HEART RATE CHANGE 2X2 TABLE

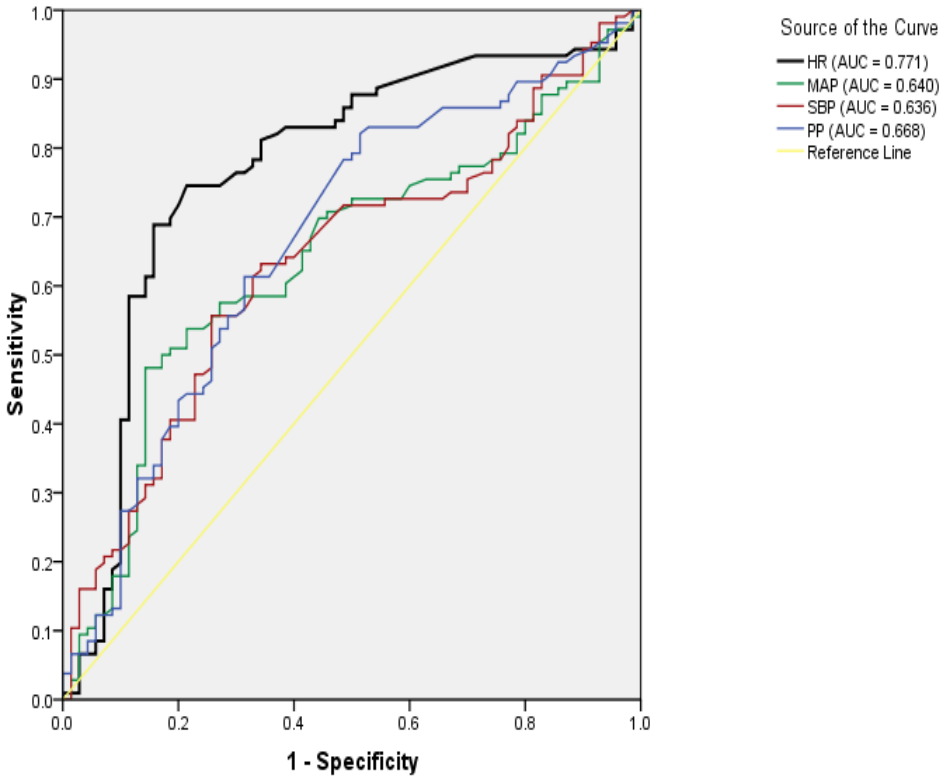
	RESPONDER	**NON RESPONDER**	TOTAL
HR CHANGE <= 5%	103	68	171
HR CHANGE >5%	3	2	5
TOTAL	106	70	176

Heart rate change had the maximum area under the curve with value of 0.771.**Evaluation shows that *a decrease in heart rate* by 5 % gave a sensitivity of 97 % and specificity of 3 %.**

Here we have selected a Heart rate cut off which favours a higher sensitivity than specificity.

On combining all the ROC's for all variables together, we find that heart rate has the maximum area under the curve as compared to previous other variables which is depicted graphically below.

Figure 15 COMBINED ROC CURVE FOR ALL VARIABLES



Diagonal segments are produced by ties.

SUBGROUP ANALYSIS OF RESPONDER OBSERVATIONS AND MEAN ARTERIAL PRESSURE CHANGE

ΔMAP change did not predict fluid responsiveness as well as we had hoped..In view of this we had looked at potential confounding factors that might have lead to this poor reading.

We had divided the entire 106 responder observations into 2 groups. **Group 1** in which the ΔMAP predicted fluid responsiveness and **Group 2** where the ΔMAP did not predict fluid responsiveness.

Since the sensitivity of the ΔMAP was 50 % there were 53 observations in **group 1** and 53 observations in **group 2**.

We have divided the analysis based on below given variables:

1) *Type of shock*

SEPTIC SHOCK

Table 21 SEPTIC SHOCK BREAKUP IN RESPONDERS

TEST	SEPTIC SHOCK (RESPONDER OBSERVATIONS)
MAP+	36 /53
MAP -	47 / 53

MAP + →mean arterial pressure change > 3 %
MAP - → mean arterial pressure change < 3 %

The p value calculated by Chi square test was 0.01 which was significant.

This means that the number of patients in the MAP negative group were significantly more .This could be because the vasodilatory state in septic shock patients reduced NIBP accuracy.

CARDIOGENIC SHOCK

Table 22 CARDIOGENIC SHOCK BREAKUP IN RESPONDER

TEST	CARDIOGENIC SHOCK (RESPONDER OBSERVATIONS)
MAP+	6 / 53
MAP -	2 / 53

The p value calculated by Fishers exact test was 0.27 and was not significant.

Here the number of patients in the MPA negative group was insignificantly less. This could mean that NBP measurements were better in a vasoconstricted state

HYPOVOLEMIC SHOCK

Table 23 HYPOVOLEMIC SHOCK BREAKUP IN TEST AND GOLD STANDARD

TEST	HYPOVOLEMIC SHOCK (RESPONDER OBSERVATIONS)
MAP+	16 / 53
MAP -	6 / 53

P value calculated by Chi square test was 0.017, indicating that the number of observations in the MAP + group was significantly more than the other. This could mean that NIBP measurements performed better in vasoconstricted state.

ANAPHYLACTIC SHOCK

Table 24 ANAPHYLACTIC SHOCK BREAKUP IN RESPONDER

TEST	ANAPHYLACTIC SHOCK(RESPONDER OBSERVATIONS)
MAP+	6 / 53
MAP -	1 / 53

P value by Fisher's exact test was found to be 0.11, and indicated that the number of patients in the MAP + group was insignificantly more.

2) VENTILATION TYPE AND MODES

Table 25 VENTILATION TYPE AND MODE BREAKUP IN TEST AND GOLD STANDARD

TEST	VENTILATION(N)				TOTAL
	NIV	SPONT	SIMV	PSIMV	
MAP+	2	5	42	4	53
MAP-	4	5	44	0	53

P value between the 2 groups by chi square test was 0.19 and was not found to be significant. We could infer that ventilation modes did not affect NIBP accuracy.

3) INOTROPE USE

Table 26 INOTROPE USE BREAKUP IN RESPONDER

TEST	INOTROPE (N)				TOTAL
	0	1	2	3	
MAP+	12	23	13	5	53
MAP-	19	22	11	1	53

P value calculated by chi square test was 0.25 and was insignificant among the groups.

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4) ARTERIAL LACTATE CONCENTRATION

Table 27 LACTATE CONCENTRATION IN RESPONDER STANDARD

TEST	LACTATE CONC >2.5
MAP+	41/53
MAP-	39/53

P value was calculated between the 2 groups was >0.05 and insignificant among the 2 groups.

DISCUSSION

Pulse pressure change with PLR using invasive blood pressure monitoring has already been established as standard of care for patients in ICU for assessing fluid responsiveness .This was able to track the changes produced and accurately identify responders and non responders.

We had expected the same for Non invasive blood pressure monitoring. During the first hour of resuscitation, one has access usually only to non invasive blood pressure measurements, hence its utility cannot be over emphasized. This would have also been invaluable in resource limited settings where arterial transducer or portable echocardiograms are not available at the bedside.

The study presented was adequately powered to determine if NIBP measurements could replace invasive arterial measurements during PLR for volume responsiveness. We had attained the target sample size that was envisioned at the onset of the study. The population studied was also an adequate representation of the kind of patients that medical ICU's in India face on a day to day basis.

On analysis of the data that was collected, we found that:

1) ΔMean arterial pressure (MAP percentage change), of 3 % had a very poor predictive value, as evidenced by a sensitivity of 50 % and specificity of 83 %. The area under the curve was calculated to be 0.640. We also noticed that Passive leg raise failed to produce a significant difference in the MAP in the responder group from baseline.
2) We also looked at other variables, in the form of Systolic blood pressure change, Pulse pressure change and heart rate change

ΔSystolic blood pressure (SBP change) of 2 % had a sensitivity and specificity of 48 % and 75 % respectively. Area under the curve was 0.636 which was inadequate.

ΔPulse pressure (pulse pressure change) of 5 % had a sensitivity and specificity of 48 % and 75 % respectively, with an Area under the curve of 0.668 which was adequate.

ΔHeart rate (heart rate change) of 5 % had a sensitivity and specificity of 97 % and specificity of 3 %. This had the maximum area under the curve of 0.771, which was adequate

Hence of the parameters studied, Δheart rate and ΔPulse pressure looked promising.

We had also pondered on the reasons for NIBP to fare so poorly in our study. Previous studies indicated that location of cuff, arterial elasticity, change in vasomotor tone, pressure exerted on artery on surrounding structures, arm circumference, arrhythmia were the major reasons why non invasive blood pressure readings deviate from invasive ones. Algorithms used to calculate the blood pressure is also different for different manufacturers.

We had tried to correct some of the above mentioned problems by keeping the cuff site constant (arm), excluding patients beyond the cuff limits mentioned by the manufacturer and excluding patients with arrhythmia. We had also used the same Phillips MP50 machine for all our patients in Medical ICU, so that we eliminate the bias produced by algorithm.

The areas which we did not account for are the vasomotor tone and the pressure exerted on the arteries by surrounding structures.

Most of our patients (67 %) required high inotropic support during their stay, which leads to severe peripheral vasoconstriction, causing problems in calculating readings. Also the surrounding subcutaneous edema also increases as the patients remain in ICU for prolonged duration, which causes compression of arteries and interferes with reading.

We had done a subgroup analysis among responders, comparing the prevalence of confounding variables between those ΔMAP successfully predicted fluid responsiveness and those in whom it did not.

- ΔMAP was less likely to successfully predict fluid responsiveness in those with septic shock
- ΔMAP was more likely to predict fluid responsiveness for patients in hypovolemic shock
- There was no correlation between inotrope use and ability of ΔMAP to predict fluid responsiveness.

This showed comprehensively that NIBP readings could not be used in a critical care setting for predicting fluid responsiveness.

LIMITATIONS

Some of the limitations of this study were:

1) Arterial line blood pressure readings were not incorporated in the study. This would have greatly helped us in proving if the ΔMAP failed because of inaccuracy of the NIBP or inadequacy of fluid shift during PLR.
2) We also think that the passive leg raise itself might have been insufficient in a certain number of patients to elicit a change in blood pressure, as measured by the NIBP cuff. Lakhal had circumvented this in his study by looking at change in central venous pressure in IJV and if that was >= 2 cm of H20, then adequate fluid shift had occurred. Since we had envisioned our study to be completely non invasive, we could not assess this particular problem.
3) We had not looked at the site of the central venous catheters (CVC) which were inserted. During the study we had noticed that, MAP actually fell in a certain proportion of patients while undergoing PLR, even when they were responders. We hypothesized that, this phenomenon occurs especially in patients with Femoral CVC, which gets kinked during the PLR. This was another major limitation of our study

CONCLUSIONS

1. A) The sensitivity and specificity of non invasive Mean arterial pressure change (MAP) with passive leg raise (PLR) was calculated to be 50 % and 82.9 % respectively.

   B) The above given sensitivity and specificity co related with a MAP cut off of 3 %

2. A) The sensitivity and specificity of non invasive Systolic blood pressure change (SBP) with passive leg raise was 48 % and 75 % respectively.This co related with SBP cut off of 2 %

   B) The sensitivity and specificity of non invasive Pulse pressure change (PP) with passive leg raise was 48 % and 75 % respectively. This co related with PP cut off of 5 %

   C) The sensitivity and specificity of Heart rate change (HR) with passive leg raise was 97 % and 3 % respectively. This co related with HR change cut off of 5 %.

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APPENDIX

List of annexures included:

Annexure I - Patient information and consent sheet

Annexure II - Data abstraction form

Annexure III – Data entry

ANNEXURE I-
INFORMATION SHEET

Evaluation of changes of blood pressure measured by non-invasive automated arm cuff with passive leg raise as an index of fluid responsiveness in patients with shock

You or your relative admitted to the MICU or MHDU with shock are/is being requested to participate in a study to see if measurement of changes of blood pressure by automated BP cuff in the arm will help us find out which patients will benefit from rushing in IV fluids?

What is the purpose of this study?

Many sick patients in the ICU have low blood pressure and this is called shock. One of the best treatments for this is to give IV fluids fast through an IV line. However only half of such patients will respond well to this treatment and some may be harmed by it. So, it is very important to find out which patients will respond to the IV fluids before we give it to them.

One of the best ways of doing this is to raise up the patients legs for one minute and measure changes in the blood pressure or heart function using cardiac ultrasound. This is routinely done for patients with low blood pressure in the medical ICU and HDU.

Some doctors in the United States of America have suggested that we could also easily simple NIBP blood pressure machines to measure changes in blood pressure in the arm when the legs are raised to find which patients will benefit from rushing in IV fluids.

In this study, we will use this blood pressure measurement in addition to the usual heart function assessment for patients with shock who may require IV fluids to see if it is a good and useful test. We hope to make 140 observations from the Medical ICU and HDU for this study

What will you/your relative have to do in this study?

If you agree to participate in this study, whenever the ICU doctor treating you/your relative feels the patient in shock may need IV fluids rushed, a BP cuff will be placed on the arm and blood pressure measured. Heart function assessment with cardiac ultrasound will be done as usual. The patients' legs will then be raised for one minute and these measurements repeated. The patient will be then given one bottle of IV fluid and these measurements repeated. You/your relative will continue to get the standard treatment required by his / her disease state and there will be no change to this because of the study

What will you benefit from this study?

The patient may or may not benefit from this study. Your treating doctor will be aware of the results of the ultrasound test and can use it to decide on the best treatment for the patient ,however your participation is likely to help us find the answer to this important question which will benefit many sick patients in the future.

Can you withdraw from this study after it starts?

Your/your relative's participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

What will happen if you develop any study related injury?

Blood pressure measurement with a cuff is extremely safe and painless and so we do not expect any injury to happen to you/your relative.

Will you have to pay for these ultrasound scans?

No, both the blood pressure measurements and the cardiac ultrasound to predict response to IV fluids will be done free of charge.

Any other treatment that you usually take will continue but the usual arrangements that you have with the hospital will decide how much you pay for this.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

Whom to contact?

If you have any questions you may ask them now or later.
This proposal has been reviewed and approved by the Institutional Review Board, CMC Hospital, Vellore, whose task is to make sure that research participants are protected from harm.
If you have any questions or if any clarifications are needed, you may contact me

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Dr. Aditya Vijayakrishnan Nair,
PG registrar,
Department of General Medicine
Mo. No 9496372762
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You can contact the Institutional Review Board at

Research Office,
Second floor,
Carman block,
Christian Medical College,
Bagayam, Vellore 632002.
Email:research@cmcvellore.ac.in
telephone: 04162284294

INFORMED CONSENT FORM

Informed Consent form to participate in study to evaluate changes of blood pressure measured by non-invasive automated arm cuff with passive leg raise as an index of fluid responsiveness in patients with shock

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

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

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

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

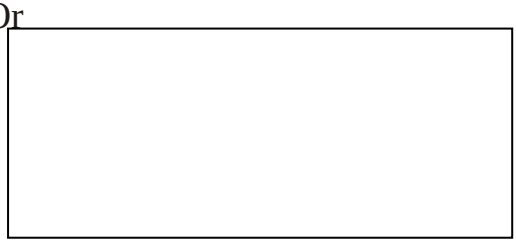
(v) I agree to take part in the above study.

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

Date: _____/_____/_____

Signatory's Name: _____ Signature:

Or



Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature (or) thumb impression of the Witness: _____

Date: _____/_____/_____

Name and Address of the Witness: _____

_____

ANNEXURE II
CASE REPORT FORM-BEFORE TRIAL

Name: **Hospital Number:**
Age: **Sex:**
Height: **Weight:** **BSA:**
MUAC:

Admission source: Casualty / Ward **Interhospital transfer**: Y / N
Date of hospital admission: **Date of discharge:**
Date of ICU admission: **Date of examination:**
observation attempt:
Co-morbidities at admission:

Obstructive airway disease	Valvular heart disease	CAD
Diabetes	Hypertension	Chronic heart failure
Chronic smoker	Chronic renal failure	HIV infection
Chronic liver disease	Current malignancy	Immunosuppressants
Cardiac arrest (date)		Others

Diagnosis:

Indication for fluid challenge: Low blood pressure / low urine output / high lactate / other

Type of shock: Septic / Cardiogenic / hypovolemic / distributive / obstructive

Fluid administred since onset of circulatory insufficiency (litres):

Ventilation: NIV/Spontaneous/SIMV/PSIMV/ASV/APRV
FiO2: P/F RATIO: TIDAL VOLUME: PEEP: PS:

ARTERIAL LACTATE CONCENTRATION:
SAPS II SCORE :

Inotrope / Vasopressor requirement:

Inotrope	Dose
Adrenaline	ug/min
Noradrenaline	ug/min

Dopamine	ug/kg/min
Vasopressin	IU/min
Dobutamine	ug/kg/min

Measurement	Pre-PLR	Post-PLR	% change	Pre-volume exp.	Post-volume exp.	VTI % change
HEART RATE						
SYSTOLIC BP						
DIASTOLIC BLP						
PP						
MAP						
LVOT VTI						
CARDIAC INDEX						

LVOT diameter: **Blood pressure measured from arm**: Right / Left

Adverse events during PLR:

Duration of ICU stay (days): **Duration of hospital stay (days):ICU**

outcome: Dead / Alive / DAMA **Hospital outcome**: Dead / Alive / DAMA

ANNEXURE III

DATA ENTRY ATTACHED