The Passive Leg Raising Maneuver and Prediction of Fluid Responsiveness: Noninvasive Monitoring of Pulse Pressure and Systolic Blood Pressure

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A dissertation

submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

University of Washington

2015

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Nursing

DEDICATION

This dissertation is dedicated to my parents and my family

Gloria DeLucia

Vincent DeLucia

and

Dennis Pickett

and

Derek, Jenessa, and Bradley

for their unconditional support and love

ACKNOWLEDGEMENTS

The author would like to express sincere appreciation to Dr. Elizabeth Bridges, committee chair, for her continued guidance, expertise, encouragement, and unwavering support during the preparation and writing of this dissertation. The author also acknowledges the invaluable contributions of committee members Dr. Patricia Kritek, Dr. Joann Whitney, and Dr. Jack Hildebrandt.

Introduction

Fluid resuscitation with a goal of hemodynamic optimization is important in the management of patient in shock with signs of hypoperfusion.[1] However, only approximately 50% of patients respond to a fluid bolus with a clinically significant (10 - 15% increase), in stroke volume (SV) or SVI.[3] The continued administration of intravenous fluids to patients who do not increase their SV in response to a fluid bolus may cause fluid overload, which can exacerbate pulmonary edema, precipitate respiratory failure, and prolong mechanical ventilation.[4] Alternately, undertreated hypovolemia leading to inappropriate use of vasopressors may increase organ hypoperfusion and ischemia.[3] To avoid the potential deleterious effects associated with fluid overload, it is important to predict which patients with indications of hypoperfusion will increase their SV in response to a fluid bolus.[3,4]

The response to the passive leg raising maneuver (PLRM) has been found to be an accurate predictor of fluid responsiveness in the critically ill patient. The PLRM is a combination of lifting the legs to a 45^0 angle, while at the same time lowering the head and upper trunk from a 45^0 semirecumbent position to the supine (flat) position. The PLRM causes a transient reversible autotransfusion, which temporarily increases preload; thus mimicking a fluid bolus. If the patient responds to the PLRM with a clinically significant increase in SV, or its surrogates (e.g., aortic blood flow or pulse pressure), the patient would likely respond to a fluid bolus.

The first paper in this document, "The Passive Leg Raising Maneuver and Prediction of Fluid Responsiveness" synthesizes the evidence on the accuracy of the PLRM to predict fluid responsiveness in critically ill patients. Additional topics discussed in the paper include the physiologic effects of the PLRM, factors affecting the response to the PLRM, safety, and implications for practice and future research. Studies suggest PLRM-induced changes in SVI, and its surrogates, such as radial artery pulse pressure (PP) predict fluid responsiveness

regardless of type of ventilation and cardiac rhythm. Research in less invasive methods to measure the response to the PLRM is needed. Early intervention in patients with signs of hypoperfusion has been shown to improve outcomes. Rapid fluid administration is recommended during the first few hours of onset of symptoms, making this an optimal time to use the PLRM to predict fluid responsiveness and guide therapy. Invasive arterial blood pressure monitoring used to evaluate the response to the PLRM may not be readily available and may delay care. Less invasive methods of monitoring the response to the PLRM, such as oscillometric non-invasive blood pressure monitoring (NIBP), which is readily available at the bedside, may be valuable in predicting a patient's fluid responsiveness.

The second paper reflects a research study, "Passive Leg Raising Maneuver and Prediction of Fluid Responsiveness: Noninvasive Monitoring of Pulse Pressure and Systolic Blood Pressure." The purpose of the study was to determine if PLRM-induced changes in PP and SBP, measured by oscillometric NIBP, are sensitive and specific indicators of a clinically significant increase in SV (≥ 10 - 15%) in healthy volunteers. Hemodynamic measurements (i.e., heart rate, systolic, diastolic and mean blood pressure, stroke volume index and cardiac index) were taken before and after performing the PLRM to determine the accuracy of oscillometric NIBP measurements to predict the response to PLRM. The study found that NIBP measurements of PP and SBP were not sensitive or specific predictors of fluid responsiveness in the healthy volunteer, and were not recommended.

Future research considerations include studies using oscillometric NIBP monitoring of the response to the PLRM in the critically ill. Studies of the critically ill have shown accuracy in the use of NIBP monitoring if there was a concurrent increase in central venous pressure of ≥ 2 mm Hg. Further study may help to identify other critically ill patient populations where the use

of NIBP monitoring is accurate. Use of a 60^0 leg elevation has been primarily studied in the healthy volunteer, using this degree of leg elevation in the critically ill may help to increase accuracy in patients with certain conditions (e.g., hypovolemia).

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The Passive Leg Raising Maneuver and Prediction of Fluid Responsiveness

Review of the Literature

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Abstract

Fluid boluses are often administered with the aim of improving tissue hypoperfusion in shock. However, only approximately 50% of patients respond to fluid administration with a clinically significant increase in stroke volume. Fluid overload can exacerbate pulmonary edema, precipitate respiratory failure, and prolong mechanical ventilation. Therefore, it is important to predict which hemodynamically unstable patients will increase their stroke volume in response to fluid administration, thereby avoiding deleterious effects. The passive leg raising maneuver (lowering the head and upper torso from a 45^0 angle of elevation while simultaneously raising the legs to a 45^0 angle) is a transient reversible autotransfusion simulating a fluid bolus, which is performed to predict a response to fluid administration. The purpose of this article is to review the accuracy, physiologic effects, and factors affecting the response to the passive leg raising maneuver to predict fluid responsiveness in critically ill patients.

Fluid resuscitation with a goal of hemodynamic optimization is important in the clinical management of patients in shock.[1] However, only approximately 50% of patients respond to fluid administration with a clinically significant ($\geq$ 10 - 15%) increase in stroke volume (SV).[2,3] The administration of fluids to patients who do not improve their SV in response to fluid administration may cause fluid overload, which can exacerbate pulmonary edema, precipitate respiratory failure, and prolong mechanical ventilation (MV).[3,4,5] Alternately, undertreated hypovolemia may lead to inappropriate use of vasopressors and may increase organ hypoperfusion and ischemia.[3] In patients with septic shock, a more positive fluid balance at twelve hours (positive fluid balance of 4.2 liters or greater) and on day four (positive fluid balance of 11 liters or greater) from initial treatment was associated with increased mortality,[6] and negative fluid balance (fluid balance of $\leq$ -500 mL) in one of the first 3 days of treatment was associated with improved survival.[7] Similarly, in patients with acute lung injury a negative cumulative fluid balance was associated with a lower mortality.[8,9] To avoid the deleterious effects associated with fluid overload and undertreated hypovolemia, it is important to predict which patients in shock with signs of hypoperfusion will increase their SV in response to fluid administration.[3,10]

Recently, the response to the passive leg raising maneuver (PLRM) has been found to be an accurate predictor of fluid responsiveness in the critically ill patient. [5,11-19] The PLRM is a combination of lifting the legs to a 45^0 angle, while at the same time lowering the head and upper trunk from a 45^0 semirecumbent positon to the supine (flat) position. The PLRM causes a transient reversible autotransfusion which temporarily increases preload; thus mimicking a fluid bolus. If the patient responds to the PLRM with a clinically significant increase in SV, or its

surrogates (e.g., aortic blood flow or pulse pressure), the patient would likely respond to a fluid bolus.

This article synthesizes the evidence on the accuracy of the PLRM to predict fluid responsiveness in the critically ill patient. Additional topics include physiologic effects of the PLRM, factors affecting the response to the PLRM, safety, and implications for practice and future research.

Search Strategies

A literature search was conducted including the following databases: PubMed (MEDLINE), CINAHL Plus, COCHRANE library, EMBASE and Clinical Trials.gov. The search terms consisted of: (Medline associated results): "passive leg raising" (142 articles), "fluid responsiveness" and "passive leg raising and fluid responsiveness" (48 articles), "passive leg raising and device" (13 articles). Studies evaluated included 1) prospective design 2) use of a "gold standard" instrument to measure the response to the PLRM 3) use of a predefined cutoff point used to stratify patients as responders versus nonresponders in response to a fluid bolus and 4) studies measuring the response to the PLRM at baseline, and after performing the PLRM to predict an increase in SV or cardiac output (CO). Fifteen studies were reviewed from the year 2002 through 2014.

Fluid Responsiveness and the Frank-Starling Law of the Heart: Responder versus Nonresponder

The purpose of administering a fluid bolus to a patient in shock is to increase the SV. Therefore, resuscitation of patients in shock requires an assessment of the probability that the patient will respond (increase SV) to a fluid bolus (fluid responsiveness).[3,20] Fluid

responsiveness is generally defined as ≥ 10 -15% increases in SV or CO in response to a 500 mL crystalloid fluid bolus.[11,12,21,22]

The Frank-Starling Law of the Heart explains the relationship between preload, cardiac function, and SV. When both the right and the left ventricles are operating on the ascending portion of the Frank-Starling curve, an increase in preload (amount of myocardial fiber stretch at end-diastole) will induce a similar, but not necessarily proportional, increase in SV (Figure 1). The relationship between preload and SV is not linear but rather it is curvilinear (as one goes up the other does not necessarily go up in the same proportion). Thus, an increase in preload will induce a significant increase in SV only if both ventricles are operating on the ascending portion of the curve. In contrast, if the ventricle operates on the flat portion of the curve (e.g., patients with heart failure) a similar increase in preload will not induce a significant increase in SV. Therefore, a patient is a "responder" to volume expansion only if both ventricles are operating on the ascending portion of the curve. If one of the ventricles or both ventricles operate on the flat portion of the curve, then the patient is a "nonresponder" (i.e., SV will not increase significantly in response to a fluid bolus).

Static versus Dynamic Hemodynamic Monitoring Parameters

Traditionally, static hemodynamic indicators, such as CVP and pulmonary artery occlusion pressure (PAOP), have been used to guide fluid administration. However, these indicators do not predict the response to a fluid bolus.[23-26] Dynamic or functional hemodynamic parameters, such as arterial pulse pressure variation (PPV) and stroke volume variation (SVV), have been shown to predict the response to a fluid bolus.[3,22] These indices reflect ventilator-induced cyclic changes in cardiac preload.[27] Therefore, these indices are of value only in patients receiving total mechanical ventilation with adequate tidal volumes,[28] and they cannot be used in

the spontaneously breathing patient. Additionally, these indicators cannot be used in patients with cardiac arrhythmias.[2,3]

The Passive Leg Raising Maneuver

Lifting the legs is a rescue maneuver that has been used for years in providing immediate first aid to patients with circulatory shock. The PLRM is a transient reversible autotransfusion, which temporarily increases preload, thus mimicking a fluid bolus. The PLRM recruits the unstressed venous volume of blood from the legs and splanchnic compartment and shunts it towards the central circulation, causing a transient increase in systemic venous return and increasing cardiac preload. [29-31] As described above, if both the right and left ventricles are operating on the ascending portion of the Frank-Starling curve the PLRM induced increase in preload will cause a clinically significant increase in SV.

The PLRM can be performed using two slightly different methods: 1) Supine method: lifting the legs passively from the horizontal position to a 30^0 to 45^0 elevation while the head-of-bed is flat, or 2) Semirecumbent method: moving the patient from a semirecumbent head-of-bed elevation 45^0 position to a supine (flat) position, while concurrently elevating the legs to a 45^0 angle[31] (Figure 2). A study[31] comparing the two different methods of PLRM found that the 45^0 semirecumbent position induced additional venous blood recruitment from the splanchnic reservoir.[31] Studies using the supine PLRM[32,33] demonstrated that this maneuver mimics a 300 mL fluid bolus; whereas the semirecumbent PLRM[17,31,34] mimics a 400- 450 mL fluid bolus.[34] Therefore, if possible, the semirecumbent PLRM method is recommended.[31]

Studies conducted in various hemodynamic conditions have demonstrated a PLRM induced increase in CVP[11,12] and PAOP,[29,30,32,35] providing evidence that the volume of blood transferred to the heart in response to the PLRM is sufficient to increase the right and left

ventricular preload, and thus to challenge the Frank-Starling curve.[32] The peak effects of the PLRM occur between 60 seconds[29] (measured by aortic blood flow using an esophageal Doppler) and 90 seconds[15,17] (measured by transthoracic echocardiology), suggesting measurements of the response to the PLRM need to be conducted rapidly after the onset of the PLRM test. The effects of PLRM are rapidly reversed when the legs are retuned to a horizontal position; therefore the PLRM constitutes a transient reversible "self-volume" challenge.[5,29,32,36]

The hemodynamic effects of the PLRM persist over several respiratory and cardiac cycles; thus, in addition to their accuracy in patients receiving MV, the PLRM can be used to predict fluid responsiveness in spontaneously breathing patients and patients with cardiac arrhythmias.[5,12,13,15,16,31,34,37,38]

Measurement of the Response to the PLRM: Stroke Volume and Pulse Pressure

To evaluate the effect of the PLRM, hemodynamic measurements (e.g., SV, PP) are obtained with the patient in the semirecumbent position (head-of-bed elevation 45^0), and then within 60 - 90 seconds after the maneuver (patient is moved to a supine flat position, while concurrently elevating the legs to a 45^0 angle) is completed. The preponderance of studies evaluated measured the response to the PLRM using the change in SV. Stroke volume can be measured using various surrogate methods. Pulse pressure, which is a surrogate of SV [3,20] has also been utilized to measure the response to the PLRM. Pulse pressure is calculated as the systolic blood pressure (SBP) minus the diastolic blood pressure (DBP). The PLRM-induced change in PP is reported as a percent change. The change in PP, indirectly reflects the change in SV, but may also be affected by arterial compliance and arterial resistance.[39]

Clinical Studies Evaluating the Passive Leg Raising Maneuver

Studies have been conducted to assess the accuracy of PLRM-induced changes in SV or a surrogate to accurately predict fluid responsiveness. Measurement of the response to the PLRM as a predictor of fluid responsiveness has been studied in patients receiving total mechanical ventilation (MV), MV with assist, spontaneously breathing patients, patients with cardiac arrhythmias and those receiving vasoactive medications. Table 1 and Table 2 summarize the characteristics of the PLRM studies that evaluated the accuracy of the PLRM. Table 3 describes key statistical terms used in the review of the literature.

Six studies,[11-13,16,32,33] including 404 patients, examined the effects of PLRM in patients requiring complete MV. Five studies,[5,14,15,17,29] consisting of 252 patients, evaluated the effect of the response to the PLRM in patients receiving MV with varying amounts of ventilator assisted breathing and arrhythmias. Two studies,[31,40] with a total of 64 spontaneously breathing patients in sinus rhythm, were evaluated. Inclusion criteria focused on the healthcare provider ordering a fluid bolus based on their clinical assessment of inadequate tissue perfusion (e.g., hypotension, oliguria, altered mental status). Primary exclusion criteria were related to contraindications for a fluid challenge (e.g., pulmonary edema). Other exclusion criteria included hemorrhage, head trauma,[13] leg amputation, intra-abdominal balloon pump support, limb and pelvic fractures,[38] and increased abdominal pressure.[15] Exclusion criteria specific to the hemodynamic measurement method (e.g., patients with suspected esophageal malformations when esophageal Doppler[33] was utilized) were also included. In some studies the use of a lower extremity compression device was considered an exclusion criteria,[13] while in other studies the compression device was removed prior to the initiation of the study.[5]

In all of the studies patients were stratified into “responder” or “nonresponders,” based on predetermined cutoff points used to define the changes in the SV or a surrogate (e.g., PP or aortic

blood flow), in response to a fluid bolus. The amount of fluid administered in the bolus varied between studies; however, in general 500 mL was delivered. In one study[33] it was noted that if the bolus volume was not sufficient, the patient may have been classified as "nonresponsive" simply because the patient did not receive enough volume to affect preload. Future studies need to examine the effect of different volumes of fluid administration (e.g., 500 mL vs. 1000 mL) on fluid responsiveness.

Studies Using Changes in Stroke Volume to Measure the Response to the PLRM

In a study[32] of 15 patients with sepsis or post cardiac surgery, the PLRM-induced increase in SV was significantly related to the fluid-bolus induced increase ($r = 0.89$, $p < 0.001$), as measured with a pulmonary artery catheter. The PLRM-induced changes in radial-artery PP was significantly correlated with the PLRM-induced changes in SV ($r = 0.77$, $p < .001$), and with fluid bolus induced changes in SV ($r = 0.84$, $p < .001$). In the same study, in a second group of 24 critically ill patients, the PLRM-induced changes in radial-artery PP were also significantly related to the fluid bolus- induced changes in SV ($r = 0.73$, $p < .001$). In a study of 34 patients receiving MV with various amounts of assisted ventilations and arrhythmias, changes in SV were measured using transthoracic echocardiography and a minimally invasive radial artery device (FloTrac™, Edwards Lifesciences, Inc., Irvine)[15] in response to the PLRM and after a subsequent fluid bolus. A PLRM-induced increase in SV ≥ 13%, measured via transthoracic echocardiography, was predictive of a response to a fluid bolus (sensitivity 100%, specificity 80%), while a PLRM-induced increase in SV ≥ 16% (FloTrac), was predictive of a response to a fluid bolus (sensitivity 85%, specificity 90%). This study demonstrates that the description of the PLRM response may vary depending on how the SV was measured. In another study[5] of 89 critically ill patients receiving MV with varying amounts of ventilator assisted breathing and

arrhythmias, a PLRM-induced increase in SV ≥ 15% predicted the response to a subsequent fluid bolus, with a specificity of 93%, and a sensitivity of 81%. The lower sensitivity was attributed to the inclusion of patients who had conditions that might lessen the effect of the PLRM (e.g., abdominal ascites, lower extremity contracture and amputations, leg deep venous thrombosis).

Stroke volume was also used to measure the response to the PLRM in non-intubated spontaneously breathing patients. In a study[34] of 34 patients with severe sepsis or acute pancreatitis, a PLRM-induced increase in SV of ≥ 10% predicted fluid responsiveness (sensitivity 86%, sensitivity 90%), measured with transthoracic echocardiography. In another study[40] of spontaneously breathing patients, the PLRM-induced increase in SV of ≥ 12%, measured with transthoracic echocardiography, predicted a response to a fluid bolus (sensitivity 69%, specificity 89%), and an area under the curve of 0.9 ± 0.06 (95% CI 0.74 - 0.97).

A systematic review and meta-analysis published in 2010[38] evaluated nine studies, including 353 critically ill patients, on the ability of PLRM-induced changes in CO to predict fluid responsiveness. A PLRM-induced increase in CO or other similar physiologic variables (e.g., SV, cardiac index, or aortic blood blow) discriminated between fluid responders and nonresponders, when compared with fluid bolus induced increases in cardiac output. The pooled sensitivity and specificity were 89.4% (95% CI 84.1% - 93.4%) and 91.4% (95% CI 85.9% - 95.2%) respectively. The pooled AUC was 0.95 (95% CI 0.92 - 0.97). No significant differences were noted between patients receiving total MV versus those with inspiratory efforts or between patients in sinus rhythm versus those with an arrhythmia. These studies suggest that the measurement of the response to the PLRM using SV accurately predicts fluid responsiveness in various patient populations (total MV, MV with assist ventilation, and spontaneously breathing).

Studies Using Changes in Pulse Pressure to Measure the Response to the PLRM

Pulse pressure, a surrogate hemodynamic parameter related to SV, has also been utilized to measure the response to the PLRM. In a study[33] of 22 patients with sepsis receiving total MV, the PLRM-induced increase in PP of $\geq$ 12%, measured by radial-artery monitoring, predicted fluid responsiveness (sensitivity 70%, specificity 92%). In a study[29] of 71 general medical-surgical critically ill patients and patients with sepsis, sedated and receiving MV with spontaneous respirations and cardiac arrhythmias, a PLRM induced increase in radial artery PP of $\geq$ 12% predicted a response to a subsequent fluid bolus (sensitivity 60%, specificity 85%). The researchers[29] noted that although PP had lower sensitivity compared to aortic blood flow, the less invasive monitoring of radial-artery PP during PLRM provided a fair prediction of volume responsiveness even in MV patients with inspiratory efforts and arrhythmias. There were no differences noted in patients receiving total ventilatory support versus patients who were assisting the ventilator. In a previously mentioned study[34] of 34 spontaneously breathing patients with severe sepsis or pancreatitis, a $\geq$ 9% PLRM-induced increase in radial-artery PP predicted a response to a fluid bolus (sensitivity 79%, specificity 85%). These studies suggest that measuring the change in radial-artery PP in response to the PLRM predicts fluid responsiveness to a subsequent fluid bolus in patients receiving MV with or without spontaneous breathing.

In the previously mentioned meta-analysis,[38] PLRM-induced changes in PP were also analyzed. Pooled data from four studies noted that a PLRM-induced increase in radial-artery PP predicted a response to a fluid bolus with sensitivity 60% (95% CI: 47%-71%) and specificity of 86% (95% CI: 75% - 94%). The threshold for a PLRM-induced increase in radial-artery PP varied between 9% and 12%. These results indicate an increased incidence of false negatives (i.e., patient is thought to be a fluid nonresponder but is a fluid responder), but a low incidence of false positives (patient is thought to be a responder based on PLRM-induced PP change, but is

actually a fluid nonresponder). Table 2 summarizes the characteristics of the studies included in the meta-analysis.

Methods to Measure the Response to the PLRM

The response to the PLRM can be measured using various hemodynamic monitoring devices. Use of a fast-response device is essential as the hemodynamic changes caused by the PLRM are transient.[15] Transesophageal Doppler,[29,33] transthoracic echocardiography,[15,17,34,40] and transthoracic Doppler ultrasound[5] have been used to measure the response to the PLRM. While these methods can be used to measure the response to the PLRM, they require significant training and skill, and may not be readily available at the bedside. Other studies utilized less-invasive monitoring methods including transpulmonary thermodilution,[11-14,16,31] pulse contour analysis,[15] and arterial pressure monitoring.[12,29,14,32,33,34] However, these methods limit the use of the PLRM to a small proportion of the critically ill, especially in the early phase of shock states when invasive monitoring may not have been initiated. A summary of various methods[41] used to measure the response to the PLRM in the studies evaluated are presented in Table 4.

Recently, non-invasive methods have been used to measure the response to the PLRM. Oscillometric non-invasive blood pressure monitoring (NIBP) was utilized in a study[11] of patients receiving total MV with cardiac arrhythmias to measure the response to the PLRM. A PLRM-induced increase in SBP of $\geq$ 9% concurrent with an increase in the CVP of $\geq$ 2 mmHg (suggesting that the PLRM altered cardiac preload) predicted fluid responsiveness (AUC 0.94; 95% CI 0.85-0.98). However, there is limited research on the use of NIBP to measure the response to PLRM, such that it cannot currently be recommended.

Safety

Patient safety is a key consideration in applying evidence to practice. In the studies presented regarding PLRM there were no reports of patients dropping out of the study due to the maneuver. Study drop-out rates[5,29] were due to the inability to obtain a correct outcome measurement reading (e.g., quality of Doppler signal). Pain induced during the PLRM may alter the response to the PRLM.[11] Pain induced by the PLRM may cause vasoconstriction and increase the volume of unstressed blood that is transferred to the central circulation from the legs and splanchnic compartment.[42] The PP may be affected by changes in the arterial compliance. If the arterial compliance decreases (e.g., vasoconstriction) the PP will increase relative to the SV, in contrast, if the arterial compliance increases (e.g., vasodilation) the PP will decrease relative to the SV. Changes in arterial compliance may cause PP to inaccurately reflect the patients SV.

In a study[43] of 20 patients undergoing coronary artery bypass surgery, performing the PLRM in patients with depressed right ventricular function (RV ejection fraction < 40%) versus patients with preserved function, the response to the PLRM in patients with depressed right ventricular function produced a decrease in cardiac index instead of an increase. To prevent cardiac overload, the PLRM should be used with caution in patients with depressed right ventricular function.[39,43]

Implications for Practice

The classic fluid challenge, consisting of administering a fluid bolus with invasive measurement of cardiac filling pressures (e.g., CVP), remains a widely used treatment to detect fluid responsiveness.[5] However, CVP is a poor predictor of fluid responsiveness.[26] Evaluation of the response to the PLRM, a transient reversible autotransfusion, which increases preload and simulates a fluid bolus, is an accurate test to determine if a patient will increase their SV or CO in response to a fluid bolus (fluid responsiveness). It is important to note that fluid resuscitation

is indicated in patients with evidence of inadequate tissue perfusion (e.g. mean arterial pressure ≤ 65 mm Hg, oliguria, altered mental status[22,26,44]). Administering fluid boluses to increase CO in patient with adequate organ perfusion is not recommended and may be harmful.[3,20]

Overall, the evidence supports the use of the PLRM in predicting the response to a subsequent fluid bolus in various populations of patients (total MV, MV with assist, spontaneously breathing, and patients with arrhythmias). In general, a PLRM-induced increase in SV or CO ≥ 10 - 15% or an increase in invasive radial-artery PP ≥ 9 - 12% is an accurate predictor of the response to a fluid bolus. Further research is needed regarding NIBP measurements.

Factors that may affect the results of the PLRM include vasoactive medications and patients with an intra-abdominal pressure ≥ 16 mmHg. Table 5 summarizes the potential factors affecting the response to the PLRM. Generalization of the evidence using different modifications to the PLRM (e.g., recumbent versus semirecumbent methods) is not recommended as the differences in body position may transfer a different volume of blood to the central circulation potentially altering differences in preload and therefore the response to the PLRM. Table 6 is a scenario that depicts how the PRLM can be applied to practice. Table 7 is a summary of considerations for future research.

Conclusions

Studies suggest PLRM-induced changes in SV and its surrogates are reliable predictors of fluid responsiveness regardless of type of ventilation and cardiac rhythm. Additionally, the PLRM-induced change in PP is a weaker, but significant predictor of fluid responsiveness. Further research is needed to validate these results with larger sample sizes to identify whether results can be repeated using the same methods with comparable patients. Potential confounding

variables include vasoactive medications and intra-abdominal hypertension. Table 8 is a summary of key points highlighted from the review of the literature.

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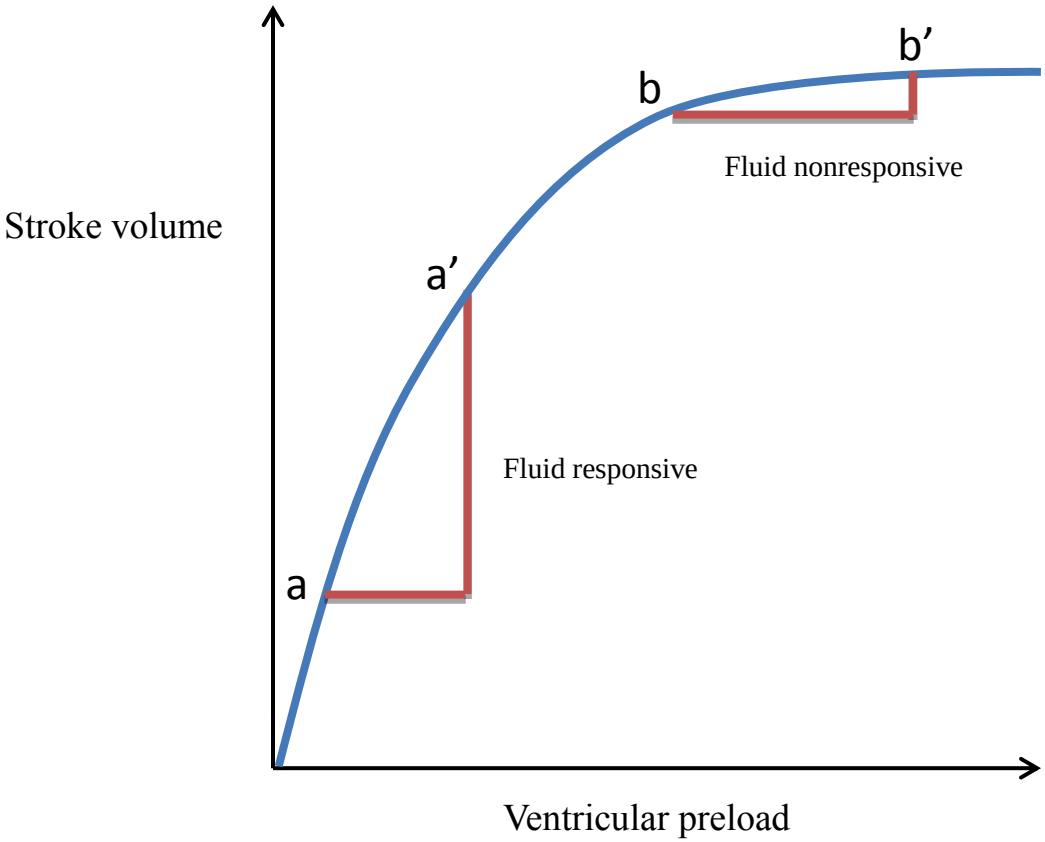
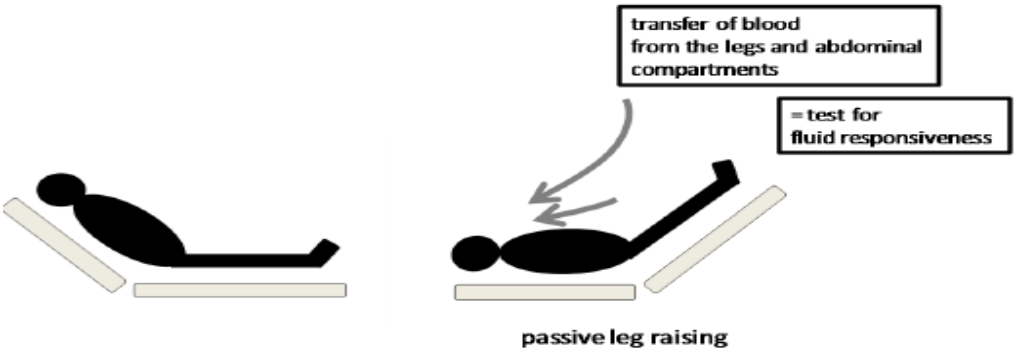
Figures and Tables

Figure 1. Frank-Starling Law of the Heart (Curve)



Frank-Starling relationship between ventricular preload and stroke volume. When the ventricle is operating on the ascending portion of the curve an increase in preload (e.g., fluid bolus, passive leg raising maneuver) induces an increase in stroke volume (**a-a'**). Alternately, when the ventricle is operating on the flat portion of the curve an increase in preload does not induce an increase in stroke volume (**b-b'**).

Figure 2. Passive Leg Raising Maneuver



The passive leg raising maneuver is performed by raising the legs to a 45^0 angle while simultaneously lowering the head and upper torso from a semi-recumbent (head-of-bed elevation 45^0) to a supine (flat) position.

Adapted: Marik PE, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. *Annals of Inten Care*, 2011, 1:1, 1-9.

Table 1. Characteristics of the Passive Leg Raising Maneuver Studies

Study	Population (n)	Rhythm	Initial HOB^0 ↑Leg^0	Bolus mL Mins	Vaso Meds (n)	R/NR (n)	Fluid Response %	PLRM Response %	Sens %	Spec %	AUC 95% CI	PPV/ NPV %	Device
Mechanical Ventilation													
Lakhal 2012[11]	112 Sepsis Card Surg	Arrhy	Supine Legs 45	500 30	NE 97 Epi 44 Dob 53	R 44 (39%) NR 68 (60%)	CO > 10	#SAP > 9	94	83	.94 (.85-.98)	*	TPTD Oscillo NIBP
Monnet 2012[13]	54 ARDS/ Non Sepsis	Sinus	Semi-recum NR	500 20	NE 23	R 30 (55%) NR 24 44%	CI ≥ 15	CI ≥ 10	†Crs ≤ 30 94 †Crs ≥ 30 93	†Crs ≤ 30 100 †Crs ≥ 30 91	.94 (.84-1.0) .91(.79-1.0)	*	TPTD Echo
Lakhal 2010[12]	102 Sepsis Card	Sinus	Supine Legs 45	500 < 15	*	R 43 (42%) NR 59 (58%)	CO ≥ 10	#CO ≥ 7 #PP ≥ 8	*	*	.98 (.89-1.0) .91 (.79-.97)	*	TPTD A-line
Benomar 2010[16]	75 Card Surg	*	*	500	NE 3 Epi 6 Dob 18	R 64 (85%) NR 11 (15%)	CO ≥ 9	CO > 9	68	95	.84	*	Bio-reactance
Lafan-echere 2006[33]	22 Sepsis	Sinus	Supine Legs 45	500	NE 10 Epi 11	R 10 (45%) NR 12 (55%)	ABF ≥ 15	ABF > 8 PP ≥ 12	90 70	83 92	*	82/91 87/78	EDoppler A-line

Study	Population (n)	Rhythm	Initial HOB^0 ↑Leg^0	Bolus mL/ Min	Vaso Meds (n)	R/ NR (n)	Fluid Response %	PLRM Response %	Sens %	Spec %	AUC 95% CI	PPV/ NPV %	Device
Mechanical Ventilation with Assist													
Biais 2009[15]	34 Gen Surg	*	Semi-recum	500	0	R 20 (67%) NR 10 (33%)	SV ≥ 15	SV_{TTE} ≥ 13 SVFloTrac ≥ 16	100 85	80 90	.96 (.90-1.0) .92 (.82-1.0)	*	TTE Pulse contour
Thiel 2009[5]	89 Sepsis Gen Med	Arrhy	Semi-recum 45	500	59	R 47 (46%) NR 55 (54%)	SV > 15	SV ≥ 15	81	93	.89 (.81-.97)	91/85	Trans-thoracic Doppler Ultrasound
Lamia 2007[17]	24 Resp Sepsis	Arrhy	Semi recum 45	500/15	NE 11 Dobut 1	R 13 (54%) NR 11 (46%)	SVi ≥ 15	SVi ≥ 12.5	77	100	*	*	TTE
Monnet 2006[29]	71 Sepsis Gen Med	Arrhy	Semi-recum 45	500 10	NE 29 Dopa 5 Dobut 2	R 37 (52%) NR 34 (48%)	ABF ≥ 15	ABF ≥ 10 PP ≥ 12	97 60	94 85	.96 (.92-.99) .75 (.63-.87)	*	EDoppler A-line
Spontaneously Breathing													
Preau 2010[34]	34 Sepsis Pancreas	Sinus	Semi 30-45	500/ 30	6	R 14 (41%) NR 20 (59%)	SV ≥ 15	SV ≥ 10 PP ≥ 9 VF ≥ 8	86 79 86	90 85 80	.94 (.86-1.0) .86 (.60-1.0) .93 (.85-1.0)	*	TTE A-line
Maizel 2007[40]	34 Cardiac GenMed	Sinus	Supine 30	500/15 15	0	R 17 (50%) NR 17 (50%)	CO ≥ 12	CO ≥ 12 SV ≥ 12	63 69	89 89	* *	83/73 85/76	TTE

ABF- aortic blood flow, A-line- arterial pressure line, Arrhy- arrhythmia, ARDS- acute respiratory distress syndrome, AUC- area under curve, Card – cardiac, CI- cardiac index, CO- cardiac output, CVP- central venous pressure, Dob- dobutamine, Echo- echocardiography, EDoppler- esophageal Doppler, Epi- epinephrine, GenMed- general medical, GenSurg- general surgery, N- nonresponder, NE- norepinephrine, Oscillo NIBP-oscillometric non-invasive blood pressure, PAC- pulmonary artery catheter, PLR semi- semirecumbent, PLR-supine (flat), PLRM- passive leg raising maneuver, PP- pulse pressure, PPV- positive predictive value, NPV- negative predictive value, R- responder, SAP- systolic arterial pressure-noninvasive, SE- standard error, Sens- sensitivity, Spec-

specificity, Supine- head of bed flat, SV-stroke volume, SVi- stroke volume index; TPTD- transpulmonary thermodilution, TTE- transthoracic echocardiography, VF- femoral artery velocity flow, *Not recorded, #Concomitant increase in CVP ≥ 2 mmHg , †Compliance respiratory system- cm H_20 pressure, ^Fluid challenges

Table 2. -Pulse Pressure Studies

Study	Pop (n)	Rhythm	Initial HOB^0 ↑Leg^0	Bolus mL Mins	Vaso Meds (n)	Resp/ NResp (n)	Fluid Response %	PLRM Response %	Sens %	Spec %	AUC 95% CI	Device
Preau 2010[34]	34 Sepsis Pancreatitis	Sinus	Semi-recum 30-45	500 30	6	R 14 (41%) NR 20 (59%)	SV ≥ 15	SV ≥ 10 PP ≥ 9 VF ≥ 8	86 79 86	90 85 80	.94 (.86-1.0) .86 (.60-1.0) .93 (.85-1.0)	TTE A-line
Monnet 2009[14]	34 Sepsis ARDS	Arrhy	Semi-recum 45	500 10	NE 23	R 23 (68%) NR 11 (32%)	CI ≥ 15	CI ≥ 10 PP ≥ 11	91 48	100 91	.94 (.80-.99) .68 (.50-.83)	TPTD A-line
Monnet 2006[29]	71 Sepsis GenMed	Arrhy	Semi-recum 45	500 10	NE 29 Dopa 5 Dobut 2	R 37 (52%) NR 34 (45%)	ABF ≥ 15	ABF ≥ 10 PP ≥ 12	97 60	94 85	.96 (.92-.99) .75 (.63-.87)	EDoppler A-line

ABF- aortic blood flow, A-line- arterial pressure line, Cardio-medical cardiac, CI- cardiac index, Dobut- dobutamine, Echo- echocardiography, EDoppler- esophageal, Doppler, Epi- epinephrine, GenMed-general medical, NE- norepinephrine, PLR semi- semirecumbent, PLR-supine (flat), PLRM- passive leg raising maneuver, PP- pulse pressure, Supine - head of bed flat, SV-stroke volume, TPTD- transpulmonary thermodilution, TTE- transthoracic echocardiography, VF- femoral artery flow, *Not recorded

Table. 3 Data

Understanding Statistics and Interpreting the Data

Test validity- is the extent a test measures what it is supposed to measure, also known as, the accuracy of a test. The accuracy of a test depends on how well a test separates the individuals being tested into those with and without the condition. Measures of a test's accuracy include sensitivity, specificity, area under the ROC curve (AUC), positive predictive value (PPV^+), and negative predictive value (PPV^-).

Test thresholds or cutpoint values- are established for tests to identify the true positive test results from the true negative test results. For example, when using changes in SV to identify fluid responders from fluid nonresponders, a cutoff point of ≥ 15 percent increase as compared to baseline, has been studied and accurately predicts fluid responders from fluid nonresponders.

Sensitivity- is the ability of a test to identify the proportion of people who have a condition, also known as, the true positives. Sensitivity of the PLRM indicates the proportion of fluid responders who are correctly identified by a given cutoff point. For example, an increase in SV of ≥ 15 percent.

Specificity- is the ability of a test to identify the proportion of people who do not have a condition, also known as, the true negatives. Specificity of the PLRM indicates the proportion of fluid nonresponders who are correctly identified by a given cutoff point. For example, a change in SV of < 15 percent.

Area under the curve (AUC) - measures how well a test discriminates between those with a condition (true positives) and without a condition (false positives) for different cutoff points. The true positive rate (sensitivity) is plotted against the false positive rate (1- specificity). Each plot on the curve measures a sensitivity/specificity pair corresponding to a particular cutoff point. The test classifies or 'tests' the two conditions in the pair. An AUC of 1.0 represents a perfect test, while an AUC of 0.5 or less represents a very poor test. For example, an AUC of 0.60 indicates the test is unable to identify the patients who are fluid responders from those who are nonresponders for a given cutoff point.

Example:
In a study[11] by Lakhal and colleagues, a PLRM-induced increase in SBP of ≥ 9% (in subjects who also had a 2 mmHg or greater increase in CVP) identified fluid responsiveness with a sensitivity of 94% and a specificity of 83%. This means that a SBP cutoff of ≥ 9%, accurately predicted fluid responsiveness 94% of the time (few false negatives), and accurately predicted fluid nonresponsiveness 83% of the time (moderate false positives). The AUC was 0.94 indicating that the test was able to discriminate between those that were responders (true positives) and nonresponders (false positives)..

PPV$^+$ - answers the question what is the chance a person with a positive test result truly has the condition? PPV is the proportion of people with positive test results that actually have the condition. If the number is close to 100 it suggests that the new test is doing as well as the "gold standard" test.

NPV$^-$ – answers the question what is the chance a person with a negative test truly does not have the condition? NPV is the proportion of people with negative test results who actually do not have the condition. If the number is close to 100 it suggests that the new test is doing as well as the "gold standard" test.

Example:
In a study[33] by Lafanechere and colleagues, a PLRM-induced increase in ABF > 8, measured by esophageal Doppler, predicted fluid responsiveness with a PPV of 82% and a NPV of 91%. This means if the patient has a positive test result (a PLRM-induced increase indicating the patient was a fluid responder) the patient was actually responsive to a fluid bolus responder 82% of the time. If the patient has a negative test result (a fluid nonresponder) the patient failed to respond to a fluid bolus 91% of the time.

Table 4. Methods to Measure the Response to the PLRM (SV/CO or surrogate)

Invasive

- Transesophageal Doppler

*Less- invasive**

- Arterial-line pressure monitoring
- Pulse contour analysis using transpulmonary thermodilution (e.g., lithium)
- Pulse contour analysis using demographic data and physical characteristics

Non-invasive

- Bioreactance
- Echocardiography
- Oscillometric NIBP
- Transthoracic Doppler Ultrasound

CO- cardiac output, NIBP- non-invasive blood pressure, PLRM- passive leg raising maneuver, SV-stroke volume

Table 5. Potential Factors Affecting the Response to the Passive Leg Raising Maneuver

Factor	Mechanism	Evidence	Conclusion
Cardiac arrhythmias	Irregular heart rhythms can cause alterations (e.g., decrease in stroke volume).	Meta-analysis[18] of critically ill patients demonstrated the PLRM similarly predicted the response to fluid bolus in patients with sinus rhythm (AUC 0.96; 95% CI 0.92 - 0.99), versus those with arrhythmias (AUC 0.96; 95% CI 0.89-1.03).	The accuracy of the PLRM is not affected by cardiac arrhythmias.
Norepinephrine	Catecholamines, due to their vasoconstrictor effects, may alter the response to the PLRM.	Multiple studies[12,16,17,29,32] maintained a constant rate of infusion while performing the PLRM. In a study[45] of the effects of norepinephrine on cardiac preload, after an increase in the dose of norepinephrine, a second PLRM test in comparison to the baseline PLRM was able to predict fluid responsiveness with a sensitivity of 95%, (95% CI 76-99%), specificity of 100% (95% CI 30 - 100%).	Maintain a constant infusion rate while performing the PLRM.
Intra-abdominal hypertension	Causes a decrease in cardiac output by decreasing venous return.	In a study[46] of 41 patients with a baseline PPV > than 12% (i.e., fluid responders), and if the intra-abdominal pressure cutoff value was less than 16 mmHg fluid responsiveness was predicted with sensitivity 100% (95% CI 78% - 100%), specificity 87.5% (95% CI 62% - 98%).	An intra-abdominal pressure of $\geq$ 16 mmHg may affect the accuracy of the PLRM to predict fluid responsiveness.
Adult respiratory distress syndrome (ARDS)	Lung compliance may affect the accuracy of the PLRM.	In a comparison study[13] of PPV and the PLRM in 27 patients with shock and ARDS, if respiratory system compliance was $\leq$ 30 mL/cm H_2O, then PLRM (AUC 0.94, 95% CI 0.84 - 1.0) performed better than PPV (AUC 0.69, 95% CI 0.49 - 0.87).	PLRM was noted to be more accurate than PPV in patients with respiratory system compliance $\leq$ 30 mL/cm H_2O.

AUC- area under the curve, CI- confidence interval, PLRM- passive leg raising maneuver, PPV- pulse pressure variation

Table 6. Scenario

Scenario: Application of the PLRM

Mr. A.T. was admitted to the intensive care unit from the floor. After receiving 20 ml/kg of crystalloid the patient remained hypotensive. A PLRM maneuver was performed using the radial-arterial PP to evaluate the response to the PLRM. Ninety seconds after performing the PLRM, the PP increased only 6%. In this case, the patient would be considered a fluid nonresponder (i.e., the patient would not be expected to increase their SV in response to a fluid bolus). Initiation of a vasopressor would be appropriate for Mr. A. T. however; the continued administration of fluids may place the patient at an increased risk of fluid overload.

Table 7. Considerations for Future Research

Review of the Literature	Future Research	Benefit
Lack of studies using non-invasive measurement of the response to the PLRM.	Non-invasive blood pressure is often used as an initial assessment of the response to treatment. Focus on non-invasive measurement of the response to the PLRM that can be used during early resuscitation.	Arterial-based hemodynamic indicators require that an arterial line be inserted potentially excluding the use of these hemodynamic monitoring parameters in the early phase of fluid resuscitation. Noninvasive monitoring of the response to the passive leg raising maneuver may facilitate earlier determination of fluid responsiveness.
Variability in study designs made comparisons between studies difficult.	Increase consistency between interventions, standardize the time to measurement of the response to the PLRM	Standardizing these variables improves the ability to analyze outcomes across studies, increase generalizability, and applicability to clinical practice.
Lack of studies comparing patients with differences in cardiac function.	Studies comparing patients with preserved function versus poor (e.g., ejection fraction < 40%) cardiac function to determine if a different threshold might be more accurate in this population of patients.	It is more difficult to predict the response to fluid in patients with a low ejection fraction. Increased research in this population of patients may improve outcomes specific to patients with poor cardiac function.
Lower extremity compression devices.	Lower extremity compression device were considered exclusion criteria,[13] while in other studies the compression device was removed prior to initial readings.[5]	Patients often have lower extremity compression devices. There is a need to study the effect of compression devices on the e accuracy of the PLRM

PLRM- passive leg raising maneuver, SV- stroke volume, PP- pulse pressure ABF- aortic blood flow

Table 8. Summary Key Points

Key Points

1. The passive leg raising maneuver can accurately predict fluid responsiveness in various populations of critically ill patients, including patients with spontaneous breathing and arrhythmias.
2. The preferred passive leg raising maneuver is the semirecumbent method, in order to maximize the volume of blood transferred to the central circulation. The semirecumbent maneuver is a combination of leg raising to a 45^0 angle, while simultaneously lowering the head and upper trunk from a 45^0 angle to the supine (flat) position.
3. Vasoconstrictor medications, such as norepinephrine, may alter the response to the PLRM. Maintain a constant rate of administration of vasoactive medications while performing the passive leg raising maneuver.
4. The effects of the PLRM are rapid and transient, therefore, measurement of the response to the PLRM within 60 to 90 seconds is recommended.

The Passive Leg Raising Maneuver and Prediction of Fluid Responsiveness: Noninvasive Monitoring of Pulse Pressure and Systolic Blood Pressure

Research Study

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Abstract

Background: Fluid boluses are administered to improve tissue hypoperfusion in shock. However, only approximately 50% of patients respond to a fluid bolus with a clinically significant increase in stroke volume index (SVI). Measurement of the response to the passive leg raising maneuver (PLRM) is an accurate method to predict fluid responsiveness using invasive and minimally invasive methods. A PLRM-induced increase in direct arterial pulse pressure (PP) ≥ 9% and systolic blood pressure (SBP) increase ≥ 9% accurately predict fluid responsiveness. Limited research has been done to evaluate non-invasive blood pressure (NIBP) response to the PLRM.

Objectives: Determine if a PLRM-induced increase in PP or SBP, using oscillometric NIBP, are sensitive and specific predictors of a clinically significant increase in SVI in healthy volunteers.

Methods: A repeated measures design with a convenience sample of thirty healthy volunteers was used. Hemodynamic measurements were taken pre/post PLRM, with the procedure completed twice. Bioreactance was used to measure the SVI.

Results: A PLRM-induced increase in SVI of ≥ 15% classified 20 subjects (69%) as responders and 9 (31%) as nonresponders. In a repeat test, 15 subjects (50%) were responders, and 15 subjects (50%) were nonresponders. A PLRM-induced increase in PP ≥ 9% predicted fluid responsiveness with a sensitivity of 50%, specificity of 44%, similar results in the repeat test. There was no association between the PLRM-induced change in SBP and fluid responsiveness.

Conclusion: The PLRM-induced change in SVI allowed for delineation of fluid responders and non-responders. However, NIBP PP and SBP were not sensitive or specific predictors of fluid responsiveness in the healthy volunteer.

Key words: passive leg raising, fluid responsiveness, pulse pressure, blood pressure

Administration of fluid boluses is often one of the first interventions considered for patients in shock with signs of hypoperfusion.[1,2] However, only approximately 50% of patients respond to fluid administration with a clinically significant, 10 - 15% increase, in stroke volume (SV) or SVI.[3-12] The administration of fluid to patients who do not improve their SV in response to fluid administration may cause fluid overload, which can exacerbate pulmonary edema, precipitate respiratory failure, and prolong mechanical ventilation.[11,13,14] Alternately, undertreated hypovolemia leading to inappropriate use of vasopressors may increase organ hypoperfusion and ischemia.[12] In patients with septic shock, a positive cumulative fluid balance was associated with increased mortality,[15] and negative fluid balance was associated with improved survival.[16] To avoid the deleterious effects associated with fluid overload and undertreated hypovolemia, it is important to predict which patients in shock with signs of hypoperfusion will increase their SV in response to fluid administration.[12,17]

Traditionally, static parameters, such as central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP), have been used to guide fluid administration; however, these parameters do not predict fluid responsiveness.[12,17-19] Dynamic or functional hemodynamic parameters, such as PP variation and SV variation, measured from an invasive arterial line, are highly predictive of the response to a fluid bolus.[12,20,21] These dynamic indices reflect mechanical ventilator-induced cyclic changes in cardiac preload, which causes variation in SV.[22] However, these indices can be used only in patients who are ventilated with adequate tidal volumes, and are fully supported by the ventilator, without spontaneous breathing.[21] These functional indicators cannot be used in the spontaneously breathing patient or in patients with cardiac arrhythmias.[20,23] An alternate method to predict fluid responsiveness is the PLRM. The PLRM is a combination of lifting the legs to a 45^0 angle, while at the same time lowering the head and

upper trunk from a 45^0 semirecumbent position to the supine (flat) position.[23] The PLRM causes a transient reversible autotransfusion temporarily increasing preload; thus, mimicking a fluid bolus.[11,24-26] If the patient responds to the PLRM with an increase in SV, or its surrogates, such as aortic blood flow or PP, the patient would likely respond to a fluid bolus.

The PLRM recruits the unstressed venous volume of blood from the legs and the splanchnic compartment and shunts approximately 400-500 mL of blood towards the central circulation, causing an increase in systemic venous return and increasing cardiac preload.[4] The effects of the PLRM are rapidly reversed when the legs are returned to a horizontal position.[11,24,26] The effects of the PLRM persist over several respiratory and cardiac cycles; thus, the PLRM is a suitable test to predict fluid responsiveness in various patient populations, including spontaneously breathing patients and patients with cardiac arrhythmias.

Studies evaluating the effect of the PLRM have demonstrated an increase in CVP [6,7] and PAOP,[24-26] providing evidence that the volume of blood transferred to the heart in response to the PLRM is sufficient to increase the right and left ventricular preload, and thus challenge the Frank-Starling curve.[25] The PLRM-induced increase in preload will induce a clinically significant increase in SV if both the right and left ventricles are functioning on the ascending portion of the Frank-Starling curve.[12]

Early volume resuscitation improves outcomes in patients with severe sepsis and septic shock.[1,27,28] As a part of early goal-directed therapy, rapid fluid administration is recommended during the first few hours of onset of symptoms. PLRM-induced changes in SV, PP, and SBP using direct arterial monitoring are sensitive and specific indicators of fluid responsiveness in mechanically ventilated and spontaneous breathing patients.[3-6,8-10] However, previous research of these parameters requires invasive monitoring methods. [4,24,29,30] NIBP monitoring, readily

available at the bedside, is often the initial method used to evaluate a patient's response to fluid administration. Only one study[7] has evaluated the PLRM-induced changes in PP and SBP, measured by NIBP. The PLRM-supine (lifting the legs passively from the horizontal position to a 30^0 to 45^0 elevation while the head and upper torso remain flat) was used, however, this method has been shown to recruit less unstressed venous blood volume, in comparison to the PLRM-semirecumbent (moving the patient from a semirecumbent head and upper torso 45^0 elevation to a supine position, while concurrently elevating the legs to 45^0), used in the current study. The purpose of this study is to determine if PLRM-induced changes in PP and SBP, measured by oscillometric NIBP, are sensitive and specific indicators of a clinically significant increase in SV in healthy volunteers.

Methods

Design

The study was a single group repeated measures design. The PLRM procedure was repeated after a five minute washout period (change to the standing position). The following parameters were measured pre/post PLRM: non-invasive SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), SVI, and cardiac index (CI).

Sample and setting

A convenience sample of 30 volunteers with self-report of no major health problems was recruited. A Health History Questionnaire was completed by the potential subjects for determination of the inclusion and exclusion criteria. Inclusion criteria consisted of the following: subjects 18 years of age or older, pulse rhythm regular, pulse rate 60 - 120 beats/minute, SBP $\geq$ 90 mm Hg and $\leq$ 160 mm Hg. Exclusion criteria included a self-report history of the following: pulmonary edema, mitral or aortic stenosis, cardiac dysrhythmias,

peripheral vascular disease, musculoskeletal deformities (e.g., limb amputations), implanted devices (e.g., pacemakers), pregnancy, or inability to lie flat with legs elevated.

A systematic review of the literature of the PLRM identified a meta-analysis[31] of the PLRM-induced changes in radial artery PP to predict fluid responsiveness. An increase in radial artery PP in response to the PLRM, threshold of 8 -15%, indicated sensitivity was 60% and specificity 86%. Alpha (α) was set at .05 and Beta (β) .80. Based on the literature review of the precision of the sensitivity and specificity of the PLRM, a sample size of 30 subjects was used to provide the precision of the measurement of the response to the PLRM ± 15%.

Variables and Measurement Instruments

Passive Leg Raising Maneuver. A triangular 45^0 angle wedge pillow was used to perform the PLRM. Baseline measurements were obtained with the wedge behind the upper torso to ensure a semirecumbent 45^0 angle. In a study[23] comparing the PLRM-supine to the PLRM-semirecumbent the PLRM-semirecumbent method induced additional venous blood recruitment from the splanchnic reservoir and had a greater increase in CO (PLRM-semirecumbent 22% [17-28%], PLRM-supine 9% [5-15%]; thus, the PLRM-semirecumbent method was used in the current study. The PLRM-semirecumbent was performed by lowering the head and upper torso, by removing the wedge pillow, from the semirecumbent 45^0 angle to a supine position. The legs were simultaneously elevated, with the use of the wedge pillow, to a 45^0 angle. Figure 1 illustrates the different PLRM positions and the sequence of the study.

Blood Pressure Measurements. The variables of interest in this study were PP and SBP. SBP, DBP, MAP, and HR were measured from the brachial artery using oscillometric NIBP monitoring (Critikon Dinamap, GE Medical Systems, Tampa Fla.). Oscillometric NIBP measurement is based on the principle that pulsatile blood flow produces oscillations in the

arterial wall. Oscillometric NIBP devices directly measure the MAP and extrapolate the SBP and DBP. Oscillometric NIBP has been shown to be accurate in a wide variety of clinical situations, such as cardiac ectopy, respiration-induced variations in BP, and vasoconstriction.[32]

Stroke Volume Index. SVI was measured using the NICOM® CO monitor as the "gold standard" comparison. The NICOM (Cheetah Medical, Inc., Indianapolis) is a noninvasive continuous cardiac output (CO) monitoring system, which uses bioreactance technology.[3] Four electrodes are placed on the anterior chest. A small alternating electric current is passed between the two outer pair of electrodes, and the resulting voltage signal is sensed by the inner pair of electrodes. Comparison of phase shifts between the current and the voltage signal provide an instantaneous recording that is proportional to aortic flow. The frequency shift is used to determine the SVI. The NICOM signal is averaged every 10 seconds and recorded as a digital display.[3]

Bioreactance Accuracy and Precision in the Measurement of Fluid Responsiveness. The NICOM CO monitor has demonstrated accuracy in various patient populations and with changes in clinical condition. According to Critchley and Critchley,[33] acceptance of a new technique should have agreement between the two devices within ± 30% error. In a study of 110 critically ill patients,[34] which compared the NICOM to the thermodilution continuous cardiac output pulmonary artery catheter (PAC-CCO), bias was 0.16 ± 0.52 L/min (95% LOA -0.82 to 1.18 L/min). The percent error was 9% to 20% (stable CO versus increasing CO). Positive and negative challenges were performed to determine responsiveness to changes. During positive challenges (e.g., seven rapid fluid challenges, six dobutamine challenges, four adrenaline infusions, and six high PEEP stops) both NICOM and PAC-CCO increased in all 23 challenges (1.5 ± 0.09 L/min vs.1.7 ± 1.3 L/min, p = .07), respectively. During negative challenges (e.g., 14

PEEP changes, and three stops in dobutamine infusions), NICOM and PAC-CCO had similar results (-1.7 ± 1.0 L/min vs. -1.7 ± 1.2 L/min, p = .25), respectively.

Two other validation studies[35] compared thermodilution PAC-CCO to the NICOM in the critically ill (bias -0.9 L/min, 95% LOA -2.5 to 2.31 L/min) and catheterization laboratory patients (bias -0.18 L/min, 95% LOA -2.21 to 1.87 L/min). Overall, these results indicate that the NICOM CO in comparison to the PAC-CCO is within the proposed ± 30% limits of agreement recommendations.[33,36] One validation study[37] compared the change in CI before and after a 500 mL saline bolus using transpulmonary thermodilution ($PICCO_2$™) and the NICOM. The bias was 0.9 L/min/m^2 (95% LOA - 2.2 to 4.1 L/min/m^2), and 82% error. One explanation for the differences in results is that thermodilution CO was the average of three boluses compared to one instantaneous value of bioreactance CO.

Procedure

Approval was obtained from the Human Subjects Division and study notification flyers were posted. The potential subjects called the researcher and an appointment was made to provide an overview of the study and obtain consent. The subject completed a Health History Questionnaire to identify the inclusion and exclusion criteria.

Before each test the NICOM monitor underwent internal calibration. The skin on the anterior chest and abdomen were prepped according to the manufacturer's instructions. Four electrodes were placed on the thorax (two on the shoulders, two on the abdomen) and connected to the NICOM monitor.

The NIBP blood pressure (BP) was measured in each arm and the reading from the arm with the highest SBP was used for the study.[38] The BP cuff was placed on the upper two thirds of the arm, 2-3 cm above the antecubital fossa.[38,39] Positioning of the arm, with the assistance of

pillows, was such that the upper arm was at the level of the right atrium (e.g., phlebostatic axis: 4th intercostal space, halfway between the anterior and posterior diameter of the chest[39]). The BP cuff was sized for each subject. Adult (arm circumference 27 - 34 cm) and extra-large (arm circumference greater than 45 cm) sized BP cuffs were used.

The procedure began after a 10 minute stabilization period in the baseline position. The baseline position consisted of the subject in the supine, 45° backrest elevation position, legs horizontal on the bed. The subject was then quickly moved into the PLRM position, by removing the wedge pillow from behind the upper torso and lowering the head/torso to the flat position while the legs were simultaneously elevated to a 45^0 angle using the wedge pillow. Activation of the NIBP BP readings occurred immediately after placing the patient in this position. After completion of the three-minute PLRM procedure, the subject was returned to the baseline position. The subject stood up and was instructed to move their legs for a washout period of five minutes. After the washout period the procedure was repeated.

Hemodynamic measurements (e.g., HR, SBP, DBP, MAP, CI, and SVI) were obtained at baseline; immediately after the subject assumed the PLRM position; and post-PLRM. Three measurements were taken during each phase at approximately 1 min, 1 min 40 secs, and 2 mins 20 secs.

Statistical Analysis

Descriptive statistics were used to summarize the sample demographics. Continuous data were expressed as mean value ± standard deviation (SD). Based on a review of the literature subjects were classified *a priori* as a fluid "responder" if SVI increased by ≥ 15%, [3,22,31,40] in response to the PLRM. If the PLRM-induced change in SVI was < 15% the subject was classified as a fluid "nonresponder." The PLRM-induced increase in SVI was calculated from the

NICOM PLRM-Protocol. NICOM calculates the percent change in SVI (Δ SVI) as follows: 1) the average SVI at baseline is calculated 2) the maximum SVI in response to the PLRM is calculated and 3) the percent change in SVI (Δ SVI) is calculated using the percent difference between the maximum SVI in the maneuver stage and the average SVI during the baseline stage. Relative changes in hemodynamic indices induced by the PLRM are expressed in percentages as follows: Percent change (Δ %) = (PLRM value - baseline value)/(baseline value) x 100. Height and weight were measured and entered into the NICOM data monitor to calculate the SVI.

The PP was calculated as follows: SBP-DBP for each set of measurements and then the mean ± SD of the three repeated measures. SBP was calculated using the mean ± SD of the three repeated measures. The mean PP and SBP were used for comparison analysis. Paired T-tests were used to compare the pre-post hemodynamic measurements. The independent (Student's t-test) was used for comparisons between the responders and nonresponders. Classification of the subjects as responders or nonresponders for the variables, SVI, PP, and SBP were compared using chi-square statistics.

The sensitivity and specificity of PLRM-induced changes in oscillometric NIBP PP and SBP were analyzed using cut-off values based on *a priori* studies of fluid responsiveness, PP change $\geq 9\%$[31] and SBP change $\geq 9\%$.[7] Post-hoc, cut-off values were evaluated using the Youden's index[40] (sensitivity + specificity – 1). Threshold indicator values for sensitivity, specificity, positive predictive (PPV) and negative predictive (NPV) values, and positive likelihood (LR^+) and negative likelihood (LR^-) ratios were calculated for the PP and SBP in response to the PLRM. The area under the receiver operating characteristic curve (AUC) was calculated for PP and SBP.

Data were analyzed with SPSS version 19 statistical software (SPSS, Chicago, IL). All tests of significance were 2-tailed and the level of significance was set at .05.

Results

Sample and setting

Thirty volunteers with self-report of no health problems were enrolled. All subjects who enrolled into the study met the inclusion criteria and completed the study without complication. Figure 2 outlines study enrollment and subjects. One potential subject was excluded from the study due to an implanted device that may have contained metal. In Test A, one subject's NICOM sensor detached and the response to the PLRM could not be measured. The NIBP monitor was able to measure blood pressure (BP) in all subjects. The data were collected over a 2 month period.

There were 11 males (37%) and 19 (63%) females enrolled in the study. The mean age of the sample was 37 ± 14 years, height 68 ± 4 inches, weight 181 ± 46 pounds, and a body surface area (BSA) of 1.94 ± .23. No significant demographic differences were noted in the baseline characteristics in responders versus nonresponders (Table 1).

PLRM-induced Changes in Stroke Volume Index

A PLRM-induced increase in SVI of ≥ 15% was used to classify responders from nonresponders. In Test A, there were 20 responders (69%) and 9 nonresponders (31%). Test B was a repeat of the procedure in Test A, using the same subjects, after a 5 minute washout period. In Test B there were 15 responders (50%) and 15 nonresponders (50%). In Test A, the PLRM-induced percent change in SVI was significantly greater in responders (26% ± 10%) versus nonresponders (7% ± 6%, $p < .001$). Test B had similar results. In Test B, the PLRM-induced percent change in SVI was significantly greater in responders (31% ± 12%) versus

nonresponders (5% ± 6%, $p < .001$). Table 2 and Table 3 compare the hemodynamic variables at baseline, PLRM-induced, percent change (% Δ) from baseline, and post-PLRM in Test A and Test B.

Prediction of Fluid Responsiveness: Pulse Pressure

In Test A, the PLRM-induced percent change in PP was 9% ± 11% in responders and 8% ± 11% in nonresponders, $p = .90$. In responders, the PLRM-induced absolute increase in PP was significantly different compared to baseline (baseline 47 ± 11 mm Hg vs. PLRM 51 ± 13 mm Hg, $p < .001$), but it was not significantly different in the nonresponders (baseline 44 ± 12 mm Hg vs. PLRM 47 ± 11 mm Hg, $p = .11$). Figure 3 is a comparison of the relationship between the PLRM-induced percent change in SVI and the PLRM-induced percent change in PP, for Test A. As the scatter plot depicts all subjects had an increase in SVI except for 1 subject. In all but 5 subjects (responders 3, nonresponders 2) there was a concurrent increase in the PLRM-induced percent change PP. However, the associated change in PP was not related to the change in SVI ($r = .03$, $p = .88$). Twenty subjects had a clinically significant increase in SVI (≥ 15% percent).

The *a priori* threshold of a PLRM-induced increase in PP was ≥ 9% as a predictor of a 15% PLRM-induced increase in SVI. In Test A, the sensitivity of a ≥ 9% increase in PP was 50% (95% CI 27%, 73%), and specificity 44% (95% CI 14%, 79%). In Test A, the AUC for a ≥ 9% PLRM-induced increase in PP was 0.49 ($p = .96$; 95% CI 0.25, 0.74). Analysis using the Youden's statistic to identify the value providing the optimum sensitivity and specificity indicated that a cutoff value of a PLRM-induced increased in PP of 6% had a sensitivity of 70% and a specificity of 44%. Table 4 summarizes the positive likelihood ratio (LR^+), negative

likelihood ration (LR^-), positive predictive value (PV^+), and negative predictive value (PV^-) for Test A and Test B.

In Test B, the PLRM-induced percent change in PP was 7% ± 10% in responders and 3% ± 9% in nonresponders (p = .23). In responders, the PLRM-induced absolute increase in PP was significantly different compared to baseline (baseline 44 ± 10 mm Hg vs. PLRM 47 ± 10 mm Hg, p = .02), but it was not significantly different in the nonresponders (baseline 53 ± 13 mm Hg vs. PLRM 53 ± 11 mm Hg, p = .47). Figure 4 is a comparison of the relationship between the PLRM-induced percent change in SVI and the PLRM-induced percent change in PP, for Test B. As the scatter plot depicts all subjects had an increase in SVI except for two subjects and 19 subjects had a clinically significant (≥ 15 %) increase in SVI. Ten subjects had a decrease in PP (5 responders, 5 nonresponders). There was no relationship between the PLRM-induced increase in SVI and the PLRM-induced change in PP (r = .10, p = .61).

In Test B, a PLRM-induced increase in PP of ≥ 9% predicted fluid responsiveness with a sensitivity of 47% (95% CI 21, 73) and specificity 67% (95% CI 38, 88), with an e AUC for a ≥ 9% PLRM-induced increase in PP of 0.61 (p = .31; 95% CI 0.40, 0.81). Using the Youden's index, a cutoff of a 2% PLRM-induced increase in PP had a sensitivity of 67% and a specificity of 47%. These data indicate that the PP as measured by NIBP was a poor predictor of fluid responsiveness.

Prediction of Fluid Responsiveness: Systolic Blood Pressure

The SBP decreased in both Test A and Test B compared to baseline. In Test A, the PLRM-induced percent change in SBP decreased in both responders -4% ± 4% and nonresponders -4% ± 6% (p = .99). In Test A, for all subjects, the PLRM-induced absolute change (decrease) in SBP was significantly different compared to baseline (baseline 115 ± 16

mm Hg vs. PLRM 110 ± 17 mm Hg, p = .03). In responders, the PLRM-induced absolute change (decrease) in SBP was significantly different compared to baseline (baseline 114 ± 16 mm Hg vs. PLRM 109 ± 17 mm Hg, p = .001); however, in nonresponders, it was not significantly different compared to baseline (baseline 115 ± 16 mm Hg vs. 109 ± 15 mm Hg, p = .06).

Figure 5 is a comparison of the relationship between the PLRM-induced percent change in SVI and the PLRM-induced percent change in SBP, for Test A. As the scatter plot depicts 5 subjects increased their SBP in response to the PLRM (responders 3, nonresponders 2), all the other subjects had a decrease in SBP. There was no association (r = 0.12, p = .53) between the PLRM-induced increase in SVI and the PLRM-induced change in SBP.

In Test B, the PLRM-induced percent change in SBP was a decrease in responders -4% ± 4, and a decrease in nonresponders -6% ± 4, (p = .12). In Test B, for all subjects, the PLRM-induced absolute change (decrease) in SBP was significantly different compared to baseline (baseline 116 ± 16 mm Hg vs. PLRM 109 ± 14 mm Hg, p < .001). The PLRM-induced absolute change (decrease) in SBP was significantly different compared to baseline for both responders (baseline 109 ± 12 mm Hg vs. PLRM 105 ± 12 mm Hg, p < .001) and nonresponders (122 ± 17 mm Hg vs. 114 ± 15 mm Hg, p = .000).

Figure 6 is a comparison of the relationship between the PLRM-induced percent change in SVI and the PLRM-induced percent change in SBP, for Test B. The results of Test B are similar to the results of Test A. As the scatter plot depicts 4 subjects (responders 3, nonresponder 1) had an increase in SBP in response to the PLRM. Two subjects had a PLRM- induced decrease in SVI. There were 15 responders and 15 non-responders. In Test B, there is no association (r = .02, p =.17) between the PLRM-induced increase in SVI and the PLRM-induced decrease in SBP.

The *a priori* threshold of a PLRM-induced increase in SBP was ≥ 9% as a predictor of a PLRM-induced increase in SVI ≥ 15%. In Test A and Test B, the PLRM-induced change in SBP did not predict fluid responsiveness. Figure 7 demonstrates the PLRM-induced changes in SBP for individual subjects, compared to baseline, for Test A and Test B. Overall, there were no relationships shown between the PLRM-induced change in SVI and SBP in Test A ($r = 0.12$, $p = .53$) and Test B ($r = 0.23$, $p = .17$). Of the 30 subjects, there were five subjects whose SBP increased in Test A (0.6% to 6% mm Hg) and in Test B there were four subjects whose SBP increased (1% to 4% mm Hg) in response to the PLRM. The remaining 25 subjects had a PLRM-induced decrease in SBP in Test A (- 0.6% to -17% mm Hg) and Test B (-1% to -12% mm Hg). In Test A, in the 19 responders the SBP increased (2% to 6% mm Hg) in only three subjects. In Test B, in the 15 responders the SBP increased (1% to 2%) in only three subjects. In general there was a decrease in SBP from baseline to maneuver, which is contrary to what was expected to occur in response to the PLRM.

Similar results were noted for the PP. Overall, there were no relationships between the PLRM-induced changes in SVI and PP in Test A, ($r = 0.03$, $p = .88$) and Test B ($r = 0.10$, $p = .61$). Of the 30 subjects, there were 24 subjects whose PP increased in Test A (2% to 38% mm Hg), and in Test B, 20 subjects had an increase in PP (0.5% to 25% mm Hg), in response to the PLRM. In Test A, five subjects had a PLRM-induced decrease in PP (-2% to -11% mm Hg) and in Test B, nine subjects had a PLRM-induced decrease in PP (-0.8% to -12% mm Hg). In Test A and Test B, one subject per test, had no change in PP in response to the PLRM. In Test A, the PP increased in 17 of 19 responders (2% - 38% mm Hg), with 10 responders increasing greater than 9%. In Test B, the PP increased in 10 of 15 responders (2% - 25% mm Hg), with 7 responders increasing greater than 9%.

PLRM-induced Changes in the Other Measured Hemodynamic Variables

The PLRM-induced changes in the other measured hemodynamic variables are reported in Tables 2 and 3. The HR was relatively unchanged. In Test A, the PLRM-induced percent change in HR decreased -1% ± 7% in responders and nonresponders ($p = .91$), compared to baseline, with similar results in Test B (-0.15% ± 4%, $p = .82$), compared to baseline. The CI increased significantly compared to baseline. In Test A, compared to baseline the PLRM-induced percent increase in CI in responders was 26% ± 12%, versus an increase of 7% ± 6% in nonresponders ($p < .001$). In Test B, compared to baseline the PLRM-induced percent increase in CI in responders was 25% ± 12% versus an increase of 5% ± 6% in nonresponders ($p < .001$).

Test A to Test B: Conversion of Responders and Nonresponders

Ten subjects (34%) changed their PLRM-response status from Test A to Test B. Eight subjects (28%) changed from responders to nonresponders and two subjects (7%) changed from nonresponders to responders. In Test A, at baseline, there were no significant differences in the hemodynamic parameters between responders and nonresponders. However, in Test B at baseline there were significant difference in SVI (responders 47 ± 9 mL/beat/m^2 vs. nonresponders 59 ± 11 mL/beat/m^2, $p = .004$), MAP (responders 81 ± 8 mm Hg versus nonresponders 88 ± 10 mm Hg, $p = .004$), and SBP (responders 109 ± 12 mm Hg versus nonresponders 122 ± 17 mm Hg, $p = .03$).

Two subjects changed from nonresponders to responders from Test A to Test B. The first subject, in Test A, had a 13% increase in SVI (nonresponder), the PP increased 13%, and the SBP decreased 9% from an absolute baseline value of 118 mm Hg to 107 mm Hg, during PLRM. In Test B, the subject's SVI increased 35% (responder), with a PP increase of 10%, and a SBP decrease of 7.5% (from 110 mm Hg to 107 mm Hg). The second subject, in Test A, had a 3%

increase in SVI (nonresponder), an 18% increase in PP, and the SBP decreased 2% from an absolute baseline value of 107 mm Hg to 108 mm Hg, during PLRM. In Test B, the subjects SVI increased 33% (responder) with a PP increase of 7%, and a SBP decrease of -1.0% (from 101 mm Hg to 100 mm Hg).

Discussion

The results of this study are in contrast to a meta-analysis[31] of the PLRM. Pooled data from four studies noted that a PLRM-induced increase in direct radial artery PP (threshold 9% - 12%) predicted a response to a fluid bolus with sensitivity 60% (95% CI 47%, 71%) and specificity of 86% (95% CI 75%, 94%), in patients with indications of hypoperfusion thought to require a fluid bolus. The subjects were critically ill receiving titrating doses of vasopressors and PP was measured using direct arterial monitoring. In another study[7] in patients with septic and cardiogenic shock (n = 112), using oscillometric NIBP to measure the response to the PLRM, an increase in SBP of ≥ 9% predicted fluid responsiveness with AUC 0.75 (95% CI 0.66, 0.83). In comparison, the current study was conducted in healthy volunteers.

The PLRM-induced decrease in SBP, DBP, and MAP in the current study is congruent with the results of other studies[41-44] in healthy volunteers. Kamran et al.,[41] in a study of the effects of the PLRM on central hemodynamics in 50 healthy volunteers, the central aortic (CA) and brachial artery (BA) SBP, DBP, MAP, and PP decreased in response to the PLRM. In this study the brachial artery pressures were measured using NIBP obtained one minute after 60° PLRM. Brachial artery pressures decreased significantly from baseline in response to PLRM (BA- SBP 123 ± 14 mm Hg, to 116 ± 14 mm Hg, p <.001; BA-DBP 75 ± 10 mm Hg, to 72 ± 10 mm Hg, p = .001;, BA-PP 48 ± 9 mm Hg to 44 ± 8 mm Hg, p <.001; and BA-MAP 91 ± 10 mm Hg to 87 ± 11 mm Hg, p <.001). Likewise, central aortic pressures as measured by applanation tonometry

also decreased (CA-SBP 109 ± 13 mm Hg to 103 ± 14 mm Hg, p <.001), CA-DBP (76 ± 10 mm Hg, PLRM-induced 73 ± 12 mm Hg, p = .001), CA-PP (baseline 33 ±7 mm Hg, PLRM-induced 31 ± 7 mm Hg, p <.001), and CA-MAP (87 ±10 mm Hg, PLRM-induced 83 ± 12 mm Hg, p <.001). The mechanism of BA dilation is not well understood, and several mechanisms may simultaneously occur which contribute to the cardiovascular changes.[45] Kamran et al., and other researchers,[46-48] conclude that the decrease in BP is likely due to activation of low-pressure baroreceptors due to the PLRM-induced transfer of blood from the legs and splanchnic compartment to the central circulation, which decreases sympathetic activity and increases parasympathetic activity. Other researchers state that the response to the PLRM induces cardiopulmonary changes, such as a decrease in vascular tone, leading to a decrease in BP, as a result of intra-thoracic pooling and low and high pressure baroreceptor activation.[46,49,50]

Delerme et al.,[43,44] showed similar decreases in SBP, DBP, and MAP. In a study[44] conducted to evaluate variations in pulse oximetry plethysmographic (ΔPOP) induced by the PLRM, ΔPOP was measured before and after performing the PLRM. Using a PLRM 30^0 SBP (baseline 119 ±10 mm Hg, PLRM-induced 115 ±12 mm Hg), DBP (72 ± 10 mm Hg baseline, PLRM-induced 67 ± 11mm Hg), and MAP (baseline 90 ± 9 mm Hg, PLRM-induced 86 ±10 mm Hg) all decreased from baseline in response to the PLRM. PP increased slightly (baseline 47 ± 6 mm Hg, PLRM-induced to 48 ± 10 mm Hg). CI increased, measured by transthoracic echocardiography, from 1.94 ± 0.30 L/min/m^2 to 2.26 ± 0.41 L/min/m^2, in response to the PLRM. Delerme concluded, in healthy volunteers the decrease in sympathetic tone (vasodilation) produced by the PLRM, is demonstrated by the variation in capillary perfusion displayed in the ΔPOP waveform.

Boulain et al.,[25] studied 39 critically ill patients, with sepsis and post-thoracic and cardiac surgery, and in acute circulatory failure, receiving mechanical ventilation and vasopressors, invasive radial artery monitoring was used to measure the response to the PLRM. Boulain et al., and other researchers[6,25,32] concluded that the arteries of the upper limbs dilate in response to the PLRM, mechanical ventilation (due to increases in positive intrathoracic pressure), reduces the stretch of the baroreceptors in the pulmonary vessels, thus attenuating baroreceptor stimulation and the subsequent arterial dilation. Geerts et al.,[51] suggest that using a PLRM-supine (lifting the legs passively from the horizontal position to a 30^0 to 45^0 elevation while the head and upper torso remain flat), maintains the heart and baroreceptors level and thus may limit baroreceptor activation. In the current study, as the subjects were spontaneously breathing and not receiving mechanical ventilation, there may have been a relatively greater increase in vasodilation, in comparison to the mechanically ventilated patient, which resulted in a decrease in BP.

Another explanation for the differences in results may be due to the limitations of NIBP monitoring. NIBP measurements can be obtained only after the BP cuff is inflated to approximately 160 - 200 mm Hg. Maximal inflation was variable depending on the subject, as the NIBP algorithm determined the maximal inflation based on initial SBP reading. This constraint may have created a lag time and variability between the peak effect of the PLRM maneuver and the measurements obtained. Therefore, causing a false negative response. Additionally, NIBP monitoring directly measures the MAP and then extrapolates SBP and DBP. PP is determined by both SBP and DBP, both of which are extrapolated measurements, therefore increasing the potential for measurement error in the variable PP.

One potential cause of false negative results (i.e., subject was a fluid responder but was classified as a nonresponder) may be due to an insufficient amount of venous unstressed blood shifted to the central circulation by the PLRM to alter cardiac preload. In a study[7] of 112 critically ill patients in shock, a PLRM-induced increase in SBP was a good diagnostic test to predict fluid responsiveness provided that PLRM additionally increased the CVP by 2 mm Hg or more (indicating an increase in cardiac preload and thus a challenge for the subject's Frank-Starling curve). In all subjects, SBP had an AUC = 0.75 (0.66 – 0.83) versus 60 subjects with a PLRM-induced increase in CVP of at least 2 mm Hg AUC = 0.94 (0.85 - 0.98). In the present study it is possible that the volume of blood translocated by the PLRM may not have been sufficient to alter cardiac preload, thus, insufficient to increase PP and SBP significantly, resulting in false negative results and decreasing the accuracy of the NIBP to detect fluid responsiveness. The present study used a 45° PLRM leg elevation, while other studies[41,52] of the PLRM in healthy subjects, used a 60° leg elevation. A 60° leg elevation may cause a greater amount of unstressed venous volume of blood transfer to the central circulation to increase cardiac preload, in comparison to the 45^{0} leg elevation.

The PLRM recruits unstressed blood from the venous reservoir. Boulain[25] suggests that patients in shock receiving catecholamines with α-adrenergic properties causing venous vasoconstriction may shift venous blood from an unstressed to a stressed volume, and thus amplify the preload augmentation of PLRM in patients in shock. Monnet[53] proposes a difference in response to the PLRM dependent upon the ability of the reservoir to be recruited. In hypovolemic shock the venous reservoir is likely reduced and the volume recruited by the PLRM would be expected to be less. In contrast, a patient with a vasodilatory state such as septic shock, a higher unstressed volume may be recruited. Based on this hypothesis, PLRM should

theoretically increase right ventricular preload less in patients with hypovolemia than in those with septic shock. Monnet further points out that his theory of hypovolemic shock causing a reduction in the volume of blood available to be recruited by the PLRM conflicts with the findings of Wong and researchers.[54] In a study of healthy volunteers hypovolemia (removal of 500 mL blood) caused a significant increase in the CI response to the PLRM as compared to their normovolemic baseline. Wong[54] et al., reported that the increase in CI induced by a 45° leg lift in healthy subjects was of larger magnitude after withdrawal of 500 mL of blood. PLRM increased CI 6.8% (0.3 ± 0.1 L/min/m^2, p = .001), before blood withdrawal and after blood withdrawal PLRM increased the CI 11 % (0.4 ± 0.1 L/min/m^2, p = .001). The results of the current study in the healthy volunteer are in contrast to Monnet's theory, that the PLRM-induced response is enhanced in the critically ill patient in vasodilatory shock. In the present study, the PLRM likely induced a vasodilatory response leading to a subsequent decrease in MAP, SBP and DBP rather than an increase. Further research is needed to confirm the differences in these findings. Differences in healthy volunteers as compared to patients in vasodilatory shock or receiving catecholamines may be factors in the differences noted in the present study.[7,31]

Eight (28%) subjects converted from responders to nonresponders from Test A to Test B. In Test A, subjects had no significant differences in any of the baseline hemodynamic indices (i.e., HR, SBP, DBP, MAP, PP, CI, and SVI) between responders and nonresponders. In contrast, at baseline, Test B subjects had significant differences, comparing responders to nonresponders, in SVI (responders 47 ± 9 mL/beat/m^2 vs. nonresponders 59 ± 11 mL/beat/m^2, p = .004), MAP (responders 81 ± 8 mm Hg vs. nonresponders 88 ± 10 mm Hg, p, = .004) , and SBP (responders 109 ± 12 mm Hg vs. nonresponders 122 ± 17 mm Hg , p = .03). A possible explanation for the significant differences in Test B at baseline compared to Test A, may be that

as subjects completed Test A the stressed volume of blood remained in the central circulation, despite a five minute washout period. Thus, the PLRM may have had insufficient unstressed blood volume to increase cardiac preload in Test B to test the subject's Frank Starling curve (false negative). Researchers[43,55] report that the effects of the PLRM are not sustained for longer than 5-10 minutes. Future studies are needed to consider the optimal time, for example a 15 minute stabilization period, in-between PLRMs to allow the return of blood to the venous reservoir (e.g., splanchnic vascular compartment). Due to differences in the critically ill (e.g., hemorrhage, vasopressor medications, mechanical ventilation) differences in optimal time for stabilization between PLRMs may be different between the healthy volunteer and the critically ill.

Two subjects changed classification from nonresponder to responder from Test A to Test B. At baseline in Test B, the two subjects who converted from nonresponder to responder classification had a lower baseline SVI in Test B than they did in Test A. In Test A, the first subject had a 13% increase in SVI and in Test B a 35% increase in SVI in response to the PLRM. The second subject, in Test A, had a 13% increase in SVI and in Test B a 33% increase in SVI in response to the PLRM. HR remained relatively unchanged in Test A and Test B for both subjects. In Test A and Test B, the first subject's mean HR decreased in response to the PLRM from a baseline of 67 beats/min to 62 beats/min. In Test B, the HR decreased from 70 beats/min to 62 beats/min after the PLRM. The second subject's mean HR, decreased in Test A and remained relatively unchanged in Test B (baseline 52 beats/min, PLRM-induced 45 beats/min) and (baseline 45 beats/min, PLRM-induced 46 beats/min), respectively. After further analysis it is difficult to make deductions with the available data and the results of the two

subjects that changed classification from nonresponder to responder in Test B, results of these two subjects are inconclusive.

Study Limitations and Future Research

This study has several limitations. The relatively small subgroup (i.e., responder, nonresponder) sizes may have precluded the discrimination needed to accurately predict the response to the PLRM. The studies inclusion criteria of a healthy volunteer were based on the subject's self-report health history. However, subjects self-report of health may not accurately reflect underlying conditions. In this study of healthy volunteers, the PLRM-induced changes in SVI, PP, SBP and other hemodynamic measurements were not confirmed with comparison to fluid bolus-induced changes, as they are in studies of the critically ill. Other stressors, such as pain, anxiety, or being cold or warm, which may change the cardiopulmonary response to the PLRM, were not measured in this study. Measuring these variables may have helped to distinguish causes of the change in hemodynamic variables in the healthy volunteer, in addition to the PLRM-induced changes.

Considerations for future research include continued study of the use of NIBP measurement of the response to the PLRM in the critically ill. In comparison to studies in the healthy volunteer, researchers[7] measuring the response to the PLRM using NIBP monitoring in the critically ill have shown a sensitivity of 94% and a specificity of 83%, if the subject had a concurrent 2 mm Hg or greater increase in CVP. Studies comparing subjects with different types of shock, for example, septic versus hemorrhagic shock may identify specific differences between groups, or a specific within group pattern. There are few studies in the critically ill using a 60^0 leg elevation. Use of the 60^0 leg elevation may increase accuracy in patients with certain conditions (e.g., hypovolemia). It is unknown whether the volume status of a patient will change

the volume of autotransfusion by the PLRM.[51] Studies comparing normovolemic to hypovolemic patients may increase the understanding of potential difference between them. Finally, there are limited studies using the PLRM for the prediction of fluid responsiveness in the emergency department, or the general post-operative surgical patient. Research in these patient populations may help to broaden the use of the PLRM. Future studies are needed to confirm the results of this study using larger sample sizes. Healthy volunteers have different hemodynamic responses than the critically ill patient, thus, results cannot be generalized to the critically ill.

Conclusion

PLRM-induced changes in oscillometric NIBP measurements of PP and SBP were not sensitive or specific predictors of fluid responsiveness, and are not recommended. Further study is needed to determine if these results would be similar in patients in shock with signs of hypoperfusion.

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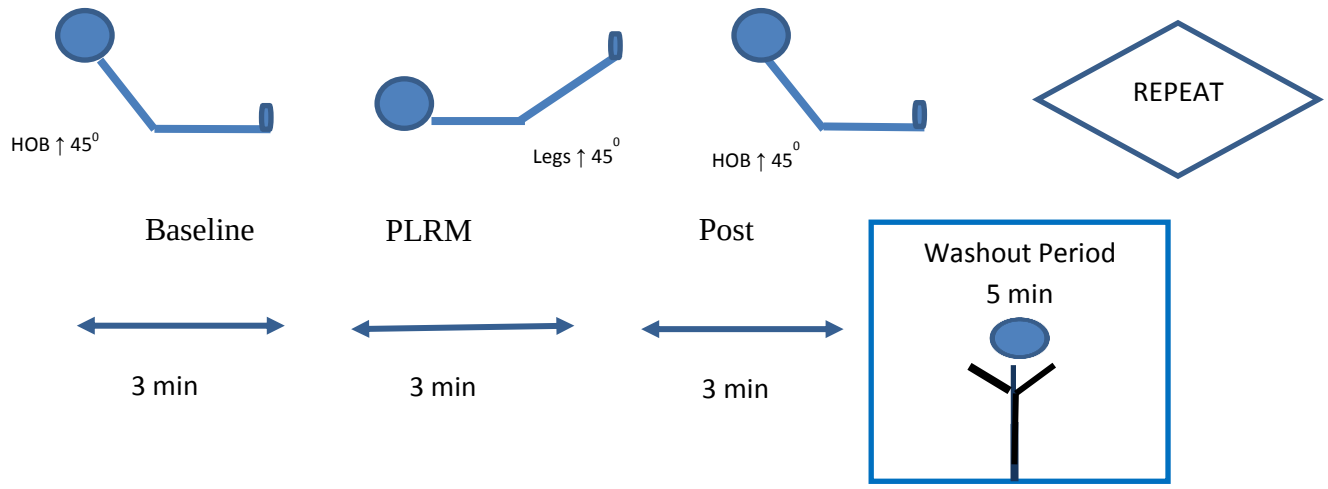
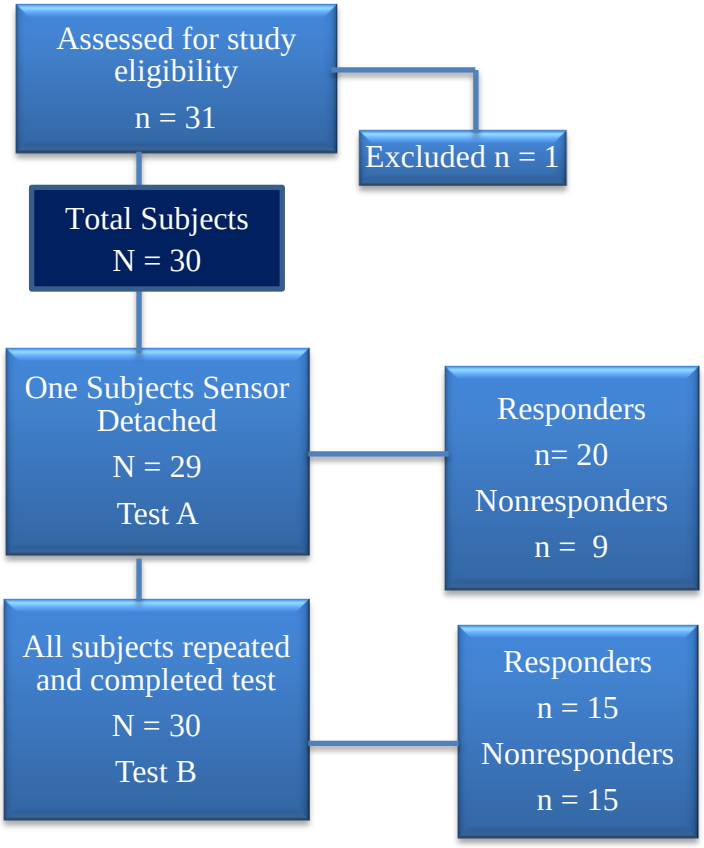
Figures and Tables

Figure 1. Passive Leg Raising Maneuver Procedure



HOB- head of bed, PLRM- passive leg raising maneuver

Figure 2. CONSORT diagram



CONSORT diagram representing the study enrollment and description of subjects.

Table 1. Demographic and subject characteristics of the total sample and by responders and nonresponders for Test A and Test B

Variable	Test A	p-value^	Test B	p-value^
Age (yrs.)				
Responders	38 ± 14	.99	40 ± 14	.38
Nonresponders	38 ± 15		35 ± 13	
Gender, No. (%)				
Male				
11/ (38)		.24*		.06*
Responders	9 (82)		3 (27)	
Nonresponders	2 (18)		8 (73)	
Female				
19/ (63)				
Responders	11 (61)		12 (63)	
Nonresponders	7 (39)		7 (37)	
Height (in.)				
Responders	68 ± 3	.99	67 ± 4	.11
Nonresponders	68 ± 4		69 ± 3	
Weight (lbs.)				
Responders	185 ± 42	.21	178 ±51	.73
Nonresponders	163 ± 45		184 ± 42	
BSA				
Responders	1.96 ± 0.19	.28	1.90 ± 0.24	.34
Nonresponders	1.86 ± 0.29		1.98 ± 0.22	

BSA- body surface area, ^p-value- between responders and nonresponders,* No significant differences between males and females

Table 2. Test A Hemodynamic Variables

Test A Hemodynamic variables at baseline, response to the PLRM, percent change (% Δ) from baseline, and post-PLRM

N = 29 Responder (n = 20) Nonresponder (n =9)	Baseline	PLRM	p-value compared baseline	% Δ	p-value	Post PLRM
HR (beats/min)						
Responder	69 ± 9	68 ± 10	.47	-1 ± 7	.91	69 ± 10
Nonresponder	64 ± 11	63 ±12	.53	-1 ± 7		64 ± 11
SBP (mm Hg)						
Responder	114 ± 16	109 ± 17	.001	-4 ± 4	.99	113 ± 18[a]
Nonresponder	115 ±16	109 ± 15	.06	-4 ± 6		111 ± 15
DBP (mm Hg)						
Responder	68 ± 8	58 ± 6	.001	-12 ± 6	.78	66 ± 7[a]
Nonresponder	71 ± 9	62 ±11	.001	-13 ± 6		69 ± 8[a]
MAP (mm Hg)						
Responder	84 ± 10	74 ± 10	.001	-12 ± 6	.76	84 ± 10[a]
Nonresponder	87 ± 10	77 ± 13	.001	-11 ± 6		84 ± 12[a]
PP (mm Hg)						
Responder	47 ± 11	51 ± 13	.001	9 ±11	.90	47 ± 13[a]
Nonresponder	44 ± 12	47 ± 11	.11	8 ± 11		43 ± 11[a]
CI (L/min/m^2)						
Responder	3.4 ± 0.60	4.3 ± 0.64	.001	26 ± 12	.001	3.8 ± 0.64

Nonresponder	3.6 ± 0.38	3.9 ± 0.47	.01	7 ± 6		5.0 ± 4.0
SVI (mL/beat/m^2)						
Responder	51 ± 8	63 ± 10	.001	26 ± 10	.001	55 ± 9
Nonresponder	57 ±11	62 ± 14	.01	7 ± 6		59 ± 12

CI- cardiac index, DBP- diastolic blood pressure, HR- heart rate, MAP- mean arterial pressure, SBP- systolic blood pressure, PLRM- passive leg raising maneuver, PP- pulse pressure, SVI- stroke volume index; mean ± SD

[a]$p \leq 0.05$ compared to maneuver

Table 3. Test B Hemodynamic Variables

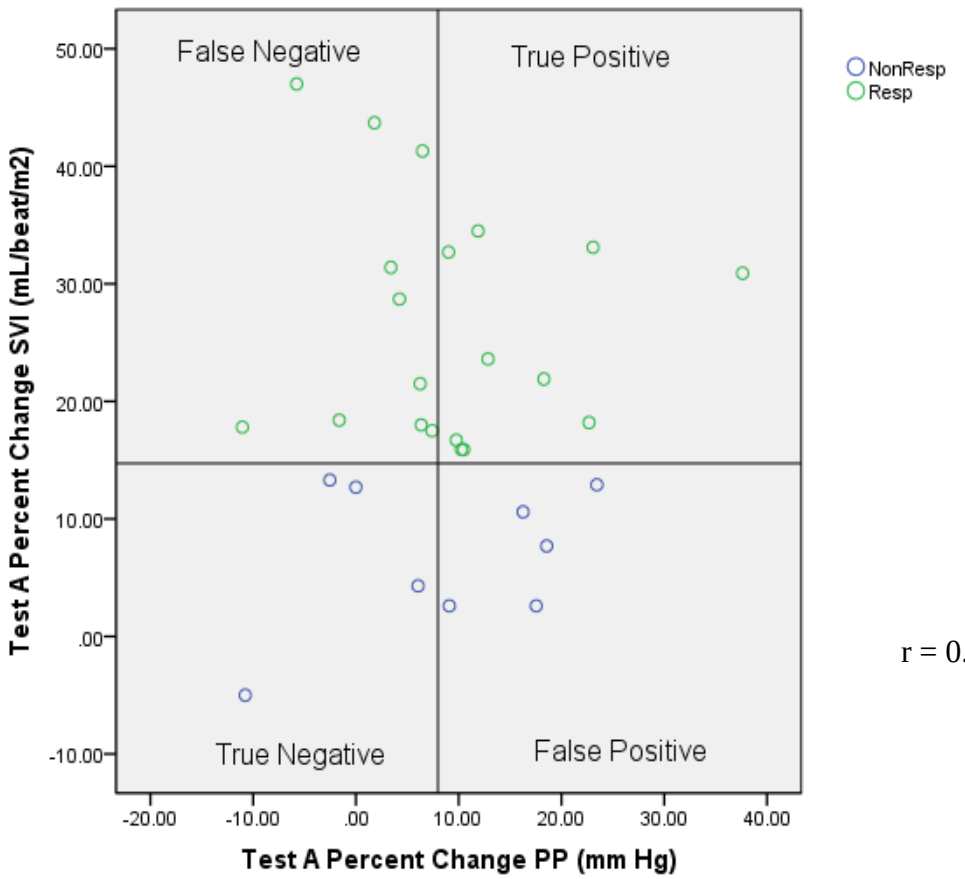
Test B Hemodynamic variables at baseline, response to the PLRM, percent change (% Δ) from baseline, and post-PLRM

N = 30 Responder (n=15) Nonresponder (n=15)	Baseline	PLRM	p-value compared baseline	% Δ	p-value	Post PLRM
HR (beats/min)						
Responder	69 ± 13	68 ± 11	.51	-0.59 ± 6	.82	71 ± 13[a]
Nonresponder	64 ± 9	64 ± 9	.81	-0.15 ± 4		66 ± 10
SBP (mm Hg)						
Responder	109 ± 12[^]	105 ± 12	.001	-4 ± 4	.12	109 ± 12[a^]
Nonresponder	122 ± 17	114 ± 15	.001	-6 ± 4		121 ± 17[a]
DBP (mm Hg)						
Responder	65 ± 7	58 ± 5	.001	-11 ± 6	.40	65 ± 6[a]
Nonresponder	69 ± 7	60 ± 9	.001	-13 ± 9		70 ± 8[a]
MAP (mm Hg)						
Responder	81 ± 8[^]	73 ± 6	.001	-10 ± 6	.52	81 ± 9[a]
Nonresponder	88 ± 10	78 ± 11	.001	-11 ± 7		88 ± 11[a]
PP (mm Hg)						
Responder	44 ± 10	47 ± 10	.02	7 ± 10	.23	44 ± 10[a]
Nonresponder	53 ± 13	53 ± 11	.47	3 ± 9		52 ± 14

CI (L/min/m^2)						
Responder	3.3 ± 0.80	4.1 ± 0.82	.001	25 ± 12	.000	3.6 ± 0.81
Nonresponder	3.9 ± 0.46	4.0 ± 0.43	.16	3 ± 7		3.8 ± 0.47
SVI (mL/beat/m^2)						
Responder	47 ± 9^	61 ± 12	.001	31 ± 12	.000	52 ± 11
Nonresponder	59 ± 11	63 ± 11	.003	5 ± 6		58 ± 11

CI- cardiac index, DBP- diastolic blood pressure, SBP- systolic blood pressure, HR- heart rate, MAP- mean arterial pressure, PLRM- passive leg raising maneuver, PP- pulse pressure, SVI- stroke volume index; mean ± SD

[a]$p \leq 0.05$ compared to maneuver; ^$p \leq 0.05$ between responders and nonresponders



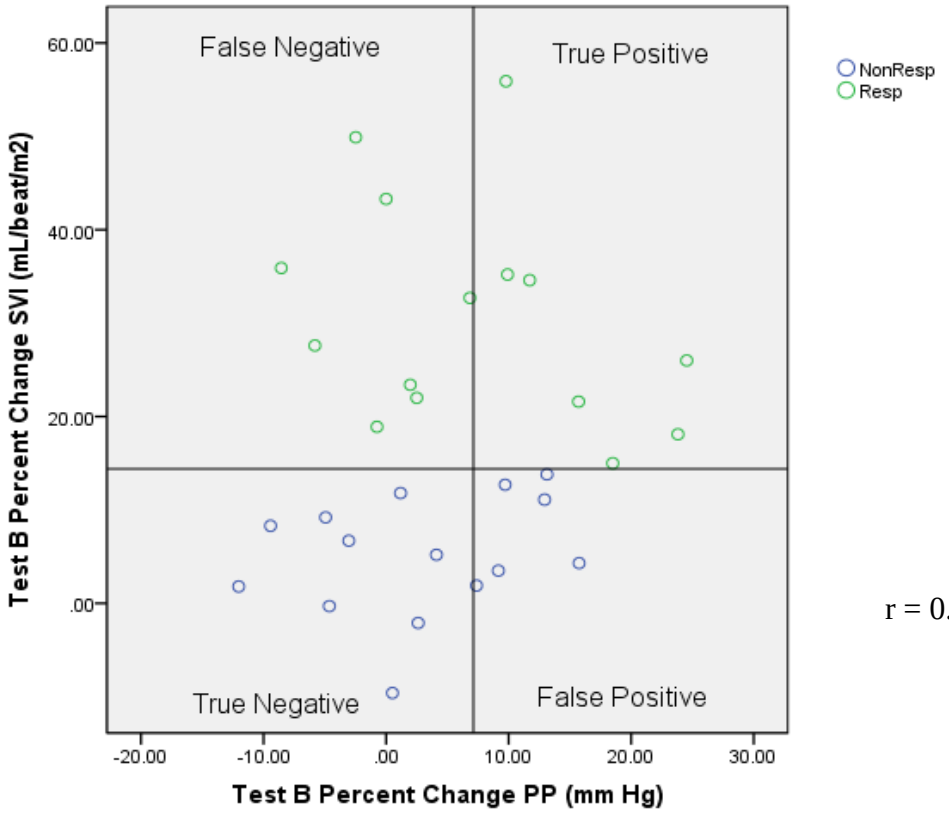
r = 0.03, p = .88

Figure 3. Test A, Relationship between PLRM-induced Percent Change in SVI and PLRM-induced Percent Change in Pulse Pressure
PLRM- passive leg raising maneuver, PP- pulse pressure, SVI- stroke volume. The horizontal line lies at the *a priori* threshold of a PLRM-induced increase in SVI of ≥ 15% classified as the responders (green circles), and a SVI of < 15% classified as the nonresponders (blue circles). The vertical line lies at the *a priori* 9% threshold value.

Table 4. Noninvasive Blood Pressure Measurement of the Response to the PLRM: Accuracy of Pulse Pressure and Systolic Blood Pressure

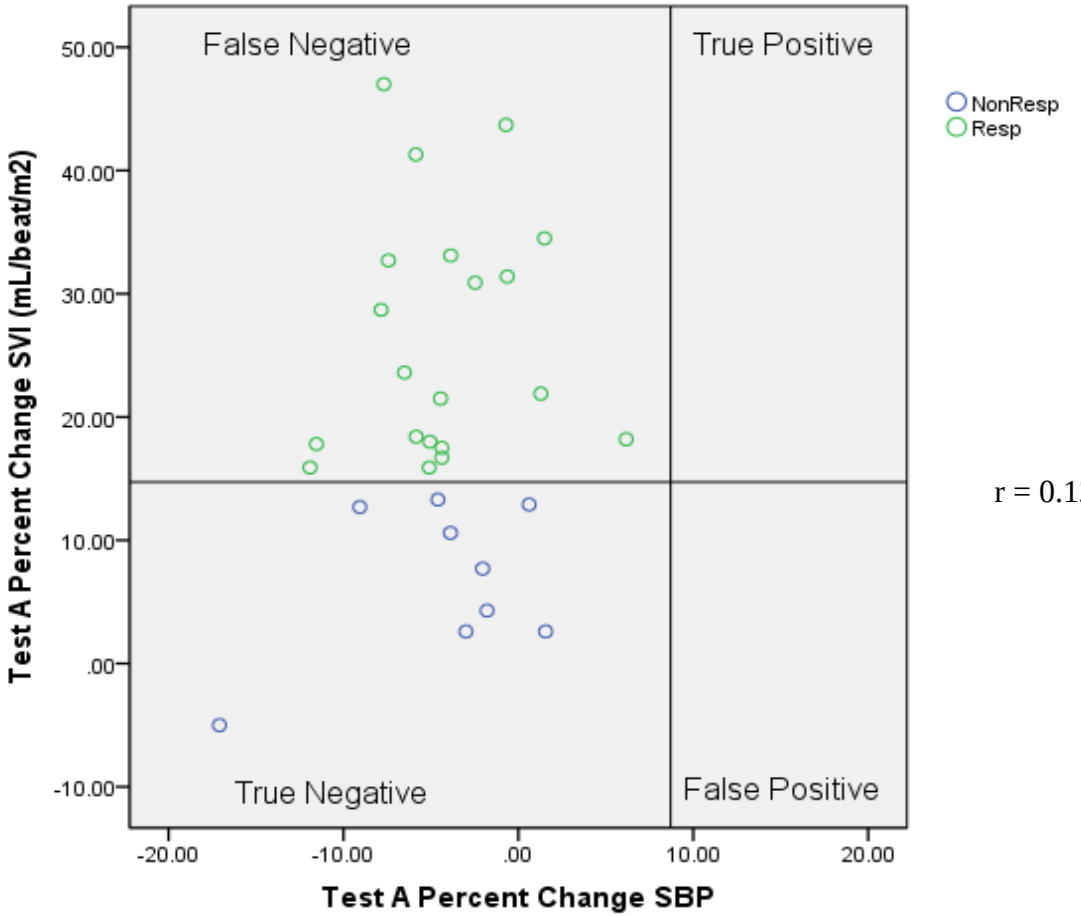
	AUC	Cutoff	Sensitivity	Specificity	LR^+	LR^-	PV^+	PV^-
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Test A % ΔPP	0.49	9	50	44	0.90	1.12	67	29
Test B % ΔPP	0.61	9	47	67	1.40	0.80	58	56
Test A % Δ SBP*	0.42	-2	25	56				
Test B % Δ SBP*	0.73	-6	80	67				

AUC- area under curve, LR^+- positive likelihood ratio, LR^- - negative likelihood ratio, PP-pulse pressure, PV^+- positive predictive value, PV^- negative predictive value, *The PLRM-induced change in SBP did not discriminate responders versus nonresponders.



r = 0.10, p =.61

Figure 4. Test B, Relationship between PLRM-induced percent change in SVI and PLRM-induced percent change in pulse pressure. PLRM- passive leg raising maneuver, PP- pulse pressure, SVI- stroke volume index. The horizontal line lies at the *a priori* threshold of a PLRM-induced increase in SVI of ≥ 15% classified as the responders (green circles), and a SVI of < 15% classified as the nonresponders (blue circles). The vertical line lies at the *a priori* 9% threshold value.



r = 0.12, p =.53

Figure 5. Test A, Relationship between PLRM-induced percent change in SVI and PLRM-induced percent change in SBP. PLRM- passive leg raising maneuver, SBP- systolic blood pressure, SVI- stroke volume index. The horizontal line lies at the *a priori* threshold of a PLRM-induced increase in SVI of ≥ 15% classified as the responders (green circles), and a SVI of < 15% classified as the nonresponders (blue circles). The vertical line lies at the *a priori* 9% threshold value.

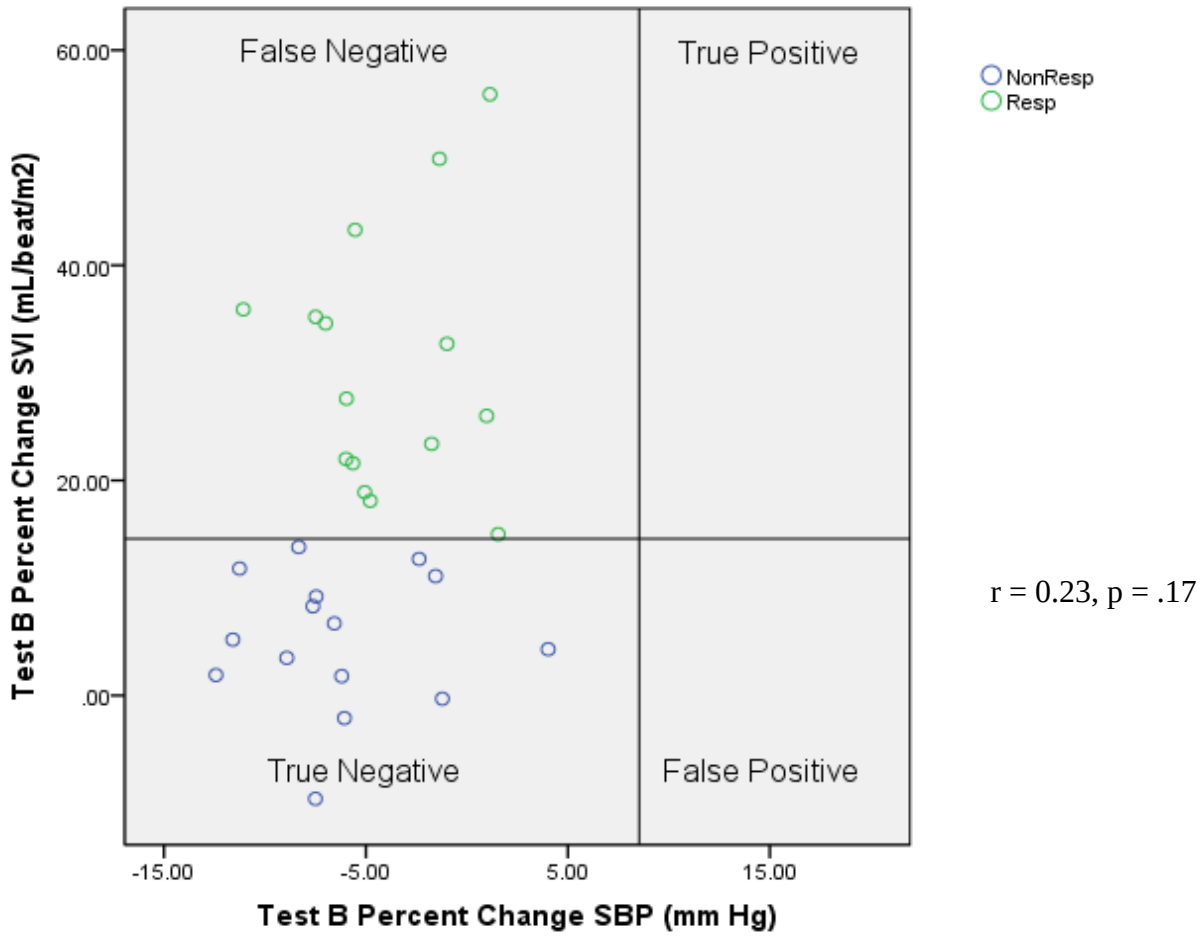


Figure 6. Test B, Relationship between PLRM-induced percent change in SVI and PLRM-induced percent change in SBP. PLRM- passive leg raising maneuver, SBP- systolic blood pressure, SVI- stroke volume index. The horizontal line lies at the *a priori* threshold of a PLRM-induced increase in SVI of ≥ 15% classified as the responders (green circles), and a SVI of < 15% classified as the nonresponders (blue circles). The vertical line lies at the *a priori* 9% threshold value.

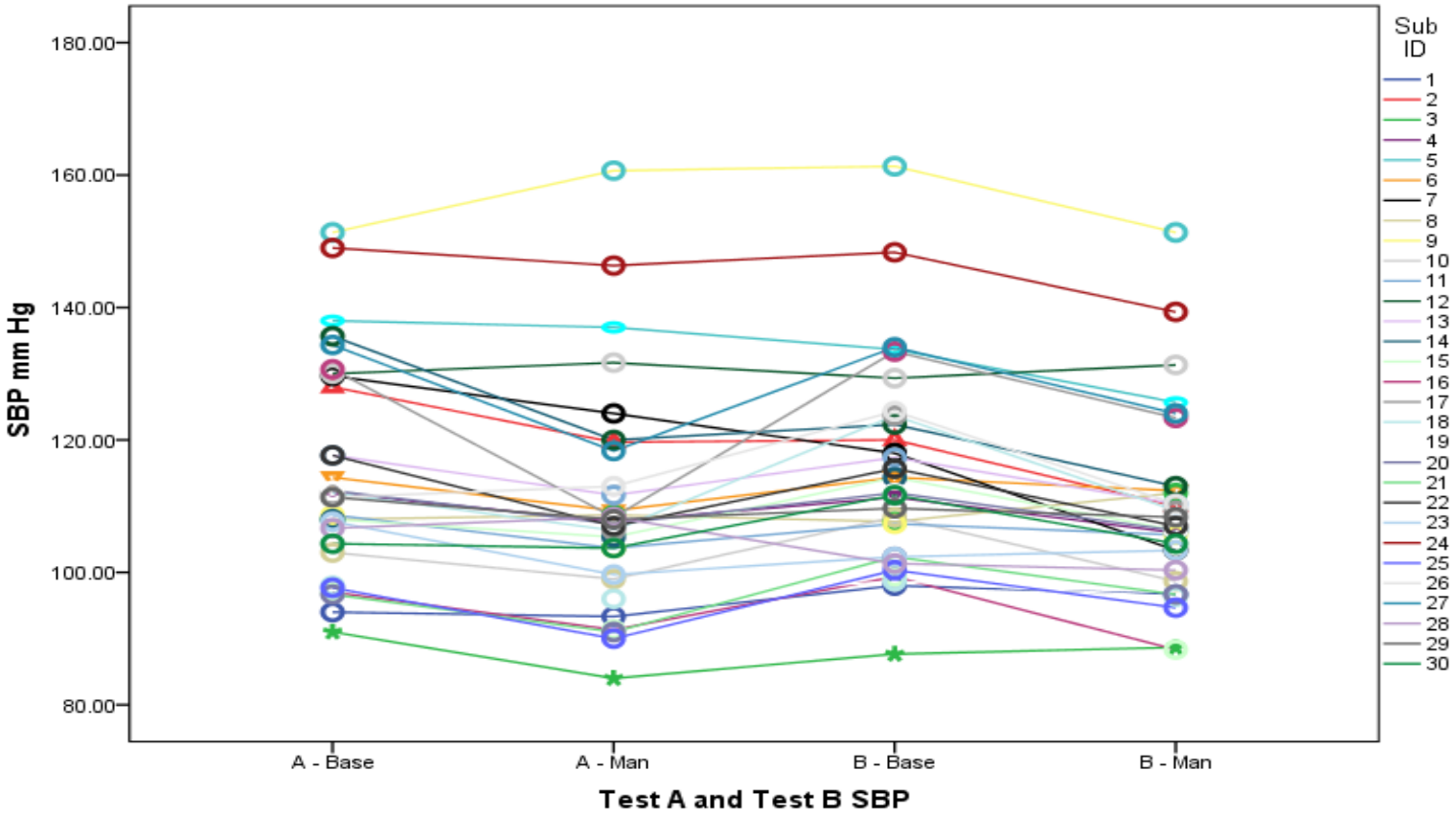


Figure 7. Changes in Systolic Blood Pressure: Test A, Baseline to PLRM-induced Change and Test B, Baseline to PLRM-induced Change. SBP- systolic blood pressure.