# The clinical value of passive leg raising plus ultrasound to predict fluid responsiveness in children after cardiac surgery

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**Research article**

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# Abstract

Background: There are few non-invasive monitoring methods that can reliably predict FR in children, this article aims to investigate the value of the doppler ultrasound evaluation of passive leg raising (PLR) induced changes in stroke volume (SV) and cardiac output(CO) in predicting the fluid responsiveness (FR) in children with mechanical ventilation after congenital cardiac surgery.

Methods: A total of 40 children with mechanical ventilation after congenital cardiac surgery who requiring volume expansion (VE) were eventually included in this observational study. Hemodynamic parameters such as heart rate (HR), blood pressure, SV, and central venous pressure (CVP) were monitored before and after PLR and VE respectively, and changes of SV and CO were assessed by bedside ultrasound as well. The patients showing an increase in SV >10% in response to VE were considered responders (26 patients), and the rest were defined as nonresponders (14 patients).

Results: The results showed that ΔSV-PLR and ΔCO- PLR were positively correlated with ΔSV-VE (r = 0.683, P<0.001 and r= 0.374, P = 0.017, respectively), and the area under the ROC curve (AUC) of ΔSV-PLR was 0.879 (95% CI [0.745 1.000], P < 0.001). The best cut-off value of ΔSV-PLR for predicting FR was 13%, with its sensitivity and specificity was 81.8% and 86.3%, respectively. ΔCVP, ΔHR, and ΔMAP were weak predictive FR in children patients.

Conclusion: Our study demonstrated that SV changes assessed by noninvasive ultrasound combined with PLR could be a feasible method for evaluating fluid responsiveness in children with congenital cardiac surgery and mechanical ventilation.


Keywords: congenital heart surgery; fluid responsiveness; passive leg raising; ultrasound.

# Introduction

Proper fluid loading is important to maintain hemodynamic stability in children after congenital cardiac surgery [1]. Nevertheless, classical fluid challenge method of evaluating the fluid responsiveness (FR) creates an extra fluid burden on patients with congenital heart disease and can cause a series of side effects, such as exacerbated tissue edema, organ failure, and increased mortality[2, 3]. Pulse index Continuous Cardiac Output (PiCCO), which integrates a wide array of both static and dynamic haemodynamic data including stroke volume (SV), is considered to be a “gold standard”, but it is expensive, invasive, and could cause catheter infection[4, 5]. Until now, there are few non-invasive monitoring methods that can reliably predict FR in children, except for respiratory changes in peak aortic flow velocity [6, 7]. Therefore, it is essential to explore a simple, effective, and non-invasive method to evaluate the FR and volume status in children.

Passive leg raising (PLR) is a repeatable self-replenishing fluid method by shifting venous blood from the lower limbs toward the intrathoracic compartment[8, 9].Transthoracic Doppler echocardiography ( TTE ) is a non-invasive method that allows for real-time monitoring of the descending aortic blood flow, and the estimation of SV[10, 11]. Therefore, using the bedside ultrasound to measure the variation of SV induced by PLR may be used to evaluate FR in these children patients.

The purpose of this study was to test whether PLR related change in stroke volume (SV) and cardiac output (CO) monitored by bedside echocardiography can accurately predict FR in children with mechanical ventilation after cardiac surgery.

# Materials And Methods

## Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Shangrao Fifth People's Hospital (No.2016-12-01). The informed consent was obtained from all patients prior to their enrollment in this study.

## General information

This prospective observational study was carried out at the Integrated Intensive Care Unit of the Fifth People's Hospital of Shangrao City (Shangrao, China) from December 2016 to July 2017. A total of 48 patients with mechanical ventilated after cardiac surgery were enrolled in the study, and the attending physician decided whether to perform a fluid challenge. This decision was based on at least one clinical sign of inadequate tissue perfusion and no contraindications for infusion. Clinical signs of inadequate tissue perfusion were defined as follows: clinical signs of acute circulatory failure (Mean arterial pressure [MAP] decreased by 30% from baseline value, or need vasopressor drugs maintaining normal systolic blood pressure; heart rate increased by 10% from baseline after excluding arrhythmia; urine output of < 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$ for at least 1 h; mottled skin, oliguria (diuresis below 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$), arterial blood lactic acid increases 1.5-fold from base value, acute kidney failure, and/or clinical and laboratory signs of extracellular dehydration[4,12]. Exclusion criteria included clinical signs of hemorrhage, failure to postpone fluid challenge for several minutes, arrhythmia, PLR contraindication, left ventricular ejection fraction less than 0.30, pulmonary artery systolic pressure greater than 40mmHg, or known allergic reaction to albumin.

## Echocardiography and Hemodynamic Data collection

Before operation, a 4-5.5fr central venous catheter was inserted into the right internal jugular vein or the right/left subclavian vein to monitor CVP, while a 7cm 3fr arterial catheter was inserted into the right or left femoral artery to monitor blood pressure dynamically. The standard transthoracic probe (3SP-D) of GE VIVIVIXE9 Doppler echocardiography was used to measure SV. On the five chambers apical view, the aortic blood flow was recorded using pulsed Doppler, with the sample volume placed on the annulus aorta. A velocity-time integral of the aortic blood flow was also measured. The aortic valve area was calculated from the diameter of the aortic orifice, measured at the insertion of the aortic cusps, as aortic area = $(\text{aortic diameter}/2)^2$. SV and CO were measured with the equations SV = velocity-time integral (VTI) × aortic area, and CO = SV × heart rate. The aortic area was considered stable during the trial and was measured only once in the beginning. Every VTI measurement was taken based on approximately two to three measurements during one breathing cycle. All of the measurements were conducted by a cardiologist.

## Study Design

The patient was in a supine position, with the upper body parts being 45° higher (Base 1) and four hemodynamic parameters (heart rate, blood pressure, SV, and CVP) were measured: The upper parts of the body were then lowered to achieve a horizontal position with the lower extremities being raised 45° using a specially formed angled board, and within 30 seconds to 1 minutes, the four hemodynamic parameters were measured again (Base 2). The patient was then placed back in the initial position (the upper parts being 45° higher) for 10 mins and the hemodynamic parameters were remeasured (Base 3). Subsequently, a bolus of the intravenous fluid challenge was given to the patient using 10 ml/kg of 5% albumin in 15 mins and the four hemodynamic parameters were measured immediately following the challenge. The patients showing an increase in SV >10% in response to volume expansion (VE) were considered responders, and the rest were defined as nonresponders. During the above-mentioned procedure, patients were kept fully sedated, and the parameters of vasoactive drugs, sedatives and mechanical ventilation remained unchanged.

## Statistical methods

Continuous variables were presented as the mean ± standard deviation if normally distributed or median (range) if the distribution was not normal. Student's unpaired t-test or the Mann–Whitney U-test was used to evaluate group differences. To assess the correlation between ΔSV-VE and PLR related ΔSV, ΔMAP, ΔHR, ΔCVP, and ΔCO, linear regression analysis was performed. Linear correlations were tested using the Pearson test and linear regression method. To determine the ability of all variables to predict fluid responsiveness, receiver operating characteristic (ROC) curves were generated, and the area under the ROC curve was calculated. The ROC curves were compared using the Hanley–McNeil test [13]. Youden's index which was calculated as follows: Youden's index = sensitivity + specificity – 1[14]. Cut-off values for ΔSV, ΔCO, ΔCVP, ΔMAP, and ΔHR were chosen to correspond to the best respective. Threshold indicator values such as sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated for each hemodynamic indicator testing. A value of $P < 0.05$ was taken to indicate statistical significance. All statistical analysis was performed with IBM SPSS 23.0 for Windows (SPSS, Inc, Armonk, NY).

# Results

### Patient Characteristics

A total of 48 mechanical ventilation patients with presumed hypovolemia and considered for VE were included in the study from December 2016 to December 2017. Among these eligible patients, 8 were excluded because of poor transthoracic insonation. Therefore, 40 patients (18 females and 22 males) with mean age of 5.41 ± 3.25 years were included in the study. Among them,ventricular septum defect (VSD) (n = 18, 45%), tetralogy of fallot (TOF) (n = 4, 10%), atrial septal defect (ASD) (n = 11, 27.5%), or ASD + VSD (n = 7, 17.5%). There was no significant difference in age, gender, vasoactive drug score, ventilator parameters, and indication for ICU stay ($P > 0.05$). The clinical characteristics of the two groups were shown in Table 1.

Table 1
Patient characteristics. Values are expressed in frequencies (%), median (with IQR) or mean (± SD).

| Characteristics | Responders (n = 26) | Nonresponders (n = 14) | P value |
|---|---|---|---|
| Age(years) | 3.76 ± 1.57 | 3.65 ± 1.54 | 0.36 |
| Weight(kg) | 8.50 ± 6.47 | 8.30 ± 7.50 | 0.91 |
| Sex ratio n (%) | | | |
| Male | 12(45.0) | 6(45.0) | 0.82 |
| Female | 14(45.0) | 8(45.0) | |
| Sedation and analgesics use/not use | 26/3 | 14/2 | 0.80 |
| Ventilation | | | |
| Tidal volume (mL/kg) | 7.50 ± 0.51 | 7.64 ± 0.63 | 0.44 |
| PEEP(cm$H_2O$) | 5.19 ± 2.02 | 4.64 ± 1.21 | 0.55 |
| Plateau pressure (cm$H_2O$) | 20.1 ± 2.0 | 20.3 ± 3.3 | 0.84 |
| VIS | 5.69 ± 2.42 | 4.07 ± 2.67 | 0.06 |
| Cardiac function(GEF, %) | 34 ± 4.5 | 32 ± 6.0 | 0.24 |
| Indication for ICU stay n (%) | | | |
| VSD | 12(46.2) | 6(42.9) | 0.84 |
| ASD | 8(30.8) | 3(21.4) | 0.53 |
| VSD + ASD | 3(11.5) | 4(28.6) | 0.18 |
| TOF | 3(11.5) | 1(7.1) | 0.66 |

VSD: Ventricular septum defect, ASD: atrial septal defect, TOF: Tetralogy of Fallot, VIS: vasoactive-inotropic score; PEEP: positive end expiratory pressure; GEF: Global ejection fraction.

### Hemodynamic changes to PLR and VE

The hemodynamic parameters before and after PLR and VE were listed in Table 2 and Fig 1. ΔSV in 26 children (responders) increased by more than 10% from the base 3 value after VE, while ΔSV in 14 patients (nonresponders) increased by less than 10%. There were no significant changes in all hemodynamic changes ($p > 0.05$) between Base 3 and Base 1.

Table 2
Hemodynamic parameters in responders and nonresponders.

| | Base 1 | Base 2 | $^{a}$P | Base 3 | $^{b}$P | Base 4 | $^{c}$P |
|---|---|---|---|---|---|---|---|
| Reponders | | | | | | | |
| HR,Beats/min | 133.1±11.3 | 128.5±12.2 | 0.16 | 132.2±10.8 | 0.77 | 128.3±11.2 | 0.21 |
| MAP, mmHg | 58.3±3.6 | 60.4±3.2 | 0.03 | 59.0±3.9 | 0.13 | 62.5±2.8 | 0.01 |
| CVP, mmHg | 9.3±0.7 | 10.7±1.3 | 0.00 | 9.6 ± 0.8 | 0.08 | 10.8 ± 1.2 | 0.00 |
| CO, L/min | 2.8±0.2 | 3.1±0.5 | 0.01 | 2.8 ± 0.3 | 1.00 | 3.2 ± 0.5 | 0.00 |
| SV, mL | 19.7±3.3 | 24.1±5.0 | 0.00 | 20.2±4.0 | 0.63 | 24.5±4.6 | 0.00 |
| ΔSV (%) | | 20.1±7.0 | | | | 22.1±7.0 | |
| Nonresponders | | | | | | | |
| HR,Beats/min | 129.0±11.0 | 127.2±7.2 | 0.61 | 129.8±11.6 | 0.85 | 127.4±10.5 | 0.57 |
| MAP, mmHg | 61.3±3.6 | 65.6±4.9 | 0.49 | 61.7±3.8 | 0.78 | 66.0±4.2 | 0.01 |
| CVP, mmHg | 9.4±0.9 | 10.8±0.9 | 0.00 | 9.5 ± 1.4 | 0.82 | 10.4 ± 1.4 | 0.10 |
| CO, L/min | 2.8±0.3 | 3.0±0.6 | 0.27 | 2.8 ± 0.3 | 1.00 | 3.0 ± 0.4 | 0.15 |
| SV, mL | 22.1±3.8 | 23.6±3.6 | 0.29 | 22.8±4.7 | 0.67 | 24.1±5.0 | 0.48 |
| ΔSV (%) | | 8.7±6.5 | | | | 5.8±2.8 | |

HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; SV, stroke volume; CO, Cardiac Output. $^{a}$p = Base 2 vs. Base 1; $^{b}$p = Base 3 vs. Base 1, $^{c}$p = Base 4 vs. Base 3 Values given as mean ± SD.

### Correlations and receiver operating characteristic curves

The correlation between Δ-PLR and ΔSV-VE was shown in Table 3 and Fig 2. ΔSV-PLR and ΔCO- PLR were positively correlated with ΔSV-VE (Pearson's r = 0.683, P<0.001 and r= 0.374, P = 0.017, respectively). The highest area under the ROC curve (AUC) for ΔSV-PLR predicted FR in children was 0.879 ± 0.069 (95% CI [0.745 1.000], P < 0.001).

Table 3
Diagnostic accuracy of index changes induced by PLR for predicting fluid responsiveness.

| Items | r | P | AUC | P | Threshold(%) | Sensitivity(%) | Specificity(%) | PPV(%) | NPV(%) |
|---|---|---|---|---|---|---|---|---|---|
| Δ SV | 0.683 | 0.000 | 0.879 | 0.000 | 13 | 81 | 86 | 85 | 82 |
| Δ CO | 0.374 | 0.017 | 0.753 | 0.009 | 8 | 81 | 71 | 79 | 81 |
| Δ HR | 0.101 | 0.263 | 0.585 | 0.379 | -5 | 46 | 78 | 68 | 59 |
| ΔMAP | 0.178 | 0.273 | 0.640 | 0.148 | 5 | 50 | 71 | 63 | 59 |
| ΔCVP | 0.253 | 0.116 | 0.530 | 0.755 | 18 | 39 | 71 | 57 | 54 |

PLR: Passive leg raising; ΔSV: PLRinduced change in stroke volume; ΔCO: PLRinduced change in cardiac output; ΔHR: PLRinduced change in heart rate; ΔMAP: PLRinduced change in mean arterial pressure; ΔCO: PLRinduced change in pulse pressure; PPV: Positive predictive value; NPV: Negative predictive value; r: Correlation coeffcient between Δ-PLRand ΔSV-VE; AUC: Area under the receiver operation characteristics curve.

### Diagnostic performance of fluid responsiveness

The optimal threshold values and associated sensitivities and specificities were presented in Table 3 and Fig 3. The thresholds of ΔSV-PLR for predicting FR was 13%, and its sensitivity and specificity were 81.8% and 86.3%, respectively. The positive predictive value was 85.0%, while the negative predictive value was 82.0%.

## Discussion

The prediction of FR is critical for fluid therapy in children after cardiac surgery, because significant changes in ventricular systolic and diastolic functions after cardiac surgery often lead to difficulties in predicting FR [15,16]. The main findings of this study were that PLR related SV changes (ΔSV-PLR) monitored by bedside ultrasound can be effectively used to predict FR in intubated children undergoing congenital heart surgery procedure, and the optimal threshold was 13%.

PLR is a simple, noninvasive and repeatable method to change the cardiac preload [8,9,17]. Studies have shown that hemodynamic changes such as SV and aortic blood flow can be observed from 30 seconds after the lower limbs elevation [18]. Our results showed that PLR can cause significant changes in hemodynamic parameters such as MAP, CVP, CO and SV (from base 1 to base 2), and all these parameters can also be restored to baseline level when the body position was returned to the Base 1 position (base 3 vs base 1), which indicated that PLR can be used as a reversible fluid challenge.

In recent years, bedside ultrasonography has been considered as a noninvasive, real-time, convenient, low-cost, and repeatable means of hemodynamic monitoring [10,11,19-21]. Previous studies have confirmed that echocardiography was highly correlated with PICCO in CO and SV, and PLR combined with non-invasive ultrasound has significant advantages in evaluating FR, which can be determined by monitoring SV and aortic blood flow [22-24]. ΔSV-PLR can be used to predict FR is based on the beneficial effects of cardiac preload on left ventricle function [25], which is not affected by changes in intrathoracic pressure, myocardial compliance, mechanical ventilation, and drug use. The best cut-off value of ΔSV for predicting FR fluctuates from 7% to 20%, indicating a large variation among different studies [22-24]. Our study demonstrated that an increase of more than 13% in the ΔSV-PLR can predict the FR in children after cardiac surgery, with a sensitivity of 81%, a specificity of 86%, and the area under the ROC curve of 0.879.

CVP, MAP, and HR were relatively easy to monitor, however, we have not observed any correlation between these parameters with ΔSV-VE. Our results showed that ΔCO-PLR seems to be able to predict FR, with an optimal threshold of 8%, sensitivity of 81% and specificity of 71%. But the correlation between ΔCO-PLR and ΔSV-VE was not as good as that of the ΔSV-PLR, which may be due to the influence of heart rate on CO measurement. Our study found that ΔSV-PLR can better predict FR compared with other PLR-Δ, which is in consistengt with previous studies [26].

There are some limitations in this study. First, echocardiographic measurement errors may have occurred, even though the same expert obtained all of the echocardiographic data. Second, because of the different types of congenital heart disease, great changes have taken place in cardiac structure after operation, so our results cannot be extrapolated to other types of congenital heart disease and to children of all ages, because leg elevation in newborns or infants obviously does not have the same volume effect as leg elevation in older children. Third, we defined a 10% increase in SV with rapid fluid loading as FR-positive, which was selected according to previous studies, whether it is appropriate threshold needs further research. Another limitation is that it is also a small sample, non-blinded study, and the results may not be applicable to other centers. Finally, someone is a fluid "responder" does not mean that they need a fluid bolus. If a healthy normally hydrated person is given a fluid bolus, their stroke volume will also increase, however, that

does not mean that they need fluid. This is probably why the increases in MAP overall are very modest in our study even in responders. Therefore, further investigations of high-quality are needed to assess the FR in children.

# Conclusion

In conclusion, our study demonstrated that SV changes assessed by noninvasive ultrasound combined with PLR could be a feasible method for evaluating fluid responsiveness in children with congenital cardiac surgery and mechanical ventilation.

# Abbreviations

ASD: atrial septal defect; AUC: area under the ROC curve; CVP: central venous pressure; CO: cardiac output; FR: fluid responsiveness; HR: heart rate; MAP: Mean arterial pressure; PiCCO: Pulse index Continuous Cardiac Output; PLR: passive leg raising; ROC: receiver operating characteristic; SV: stroke volume; TTE: Transthoracic Doppler echocardiography; TOF: tetralogy of fallot; VTI: velocity-time integral; VE: volume expansion; VSD: ventricular septum defect.

# Declarations

## Ethical approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and a written approval letter was obtained from the Ethics Committee of Shangrao Fifth People's Hospital (No.2016-12-01). The written informed consent was obtained from the parent or guardian of all participants.

## Consent for publication

Not applicable.

## Availability of data and material

We declare that all relevant data and materials are available from the corresponding author on reasonable request.

## Competing interests

The authors have declared that there is no conflict of interests.

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## Author’s contributions

All authors have made significant contributions to the whole process including research design, data acquisition and analysis, and article drafting or revision.

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## Figures

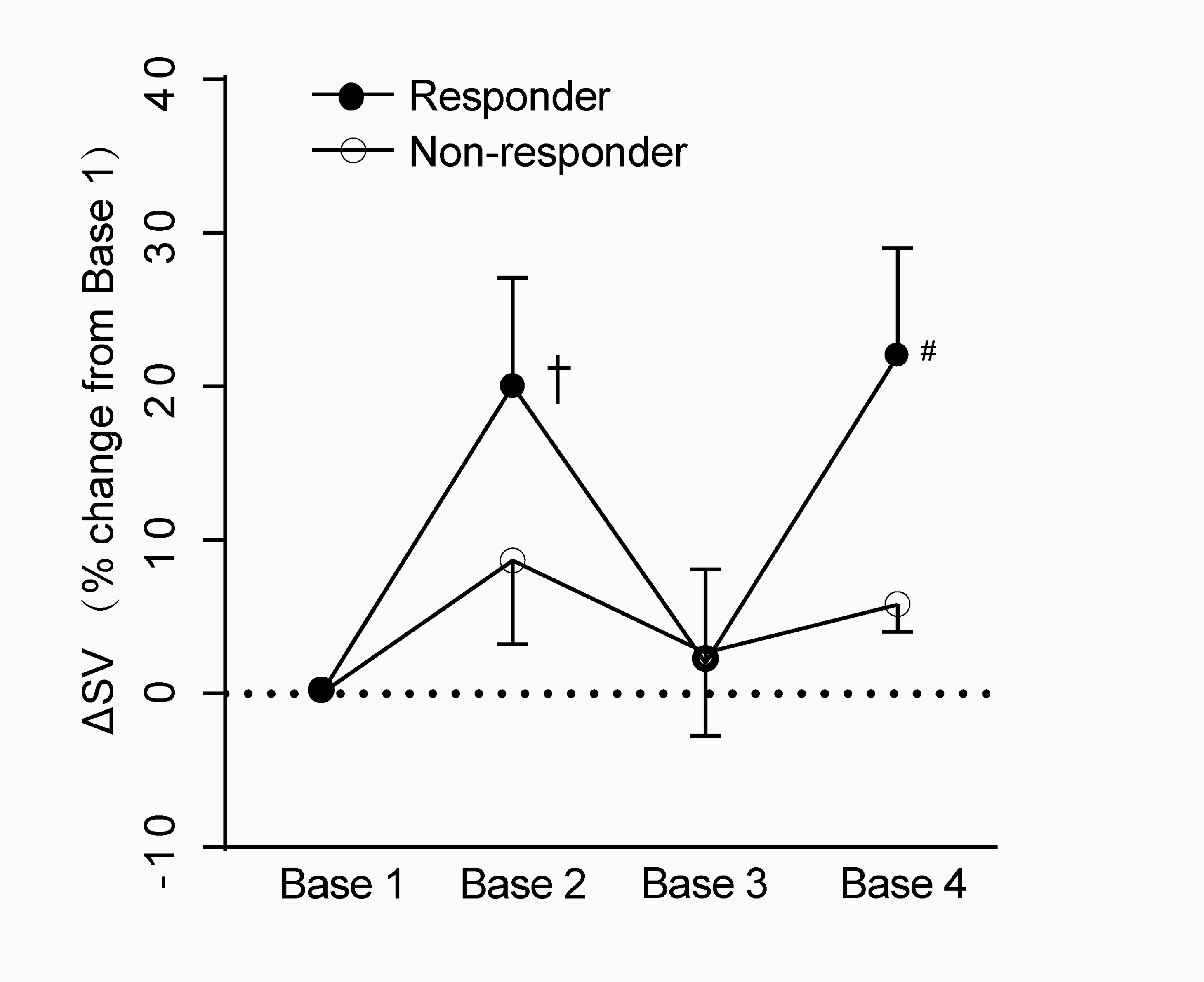
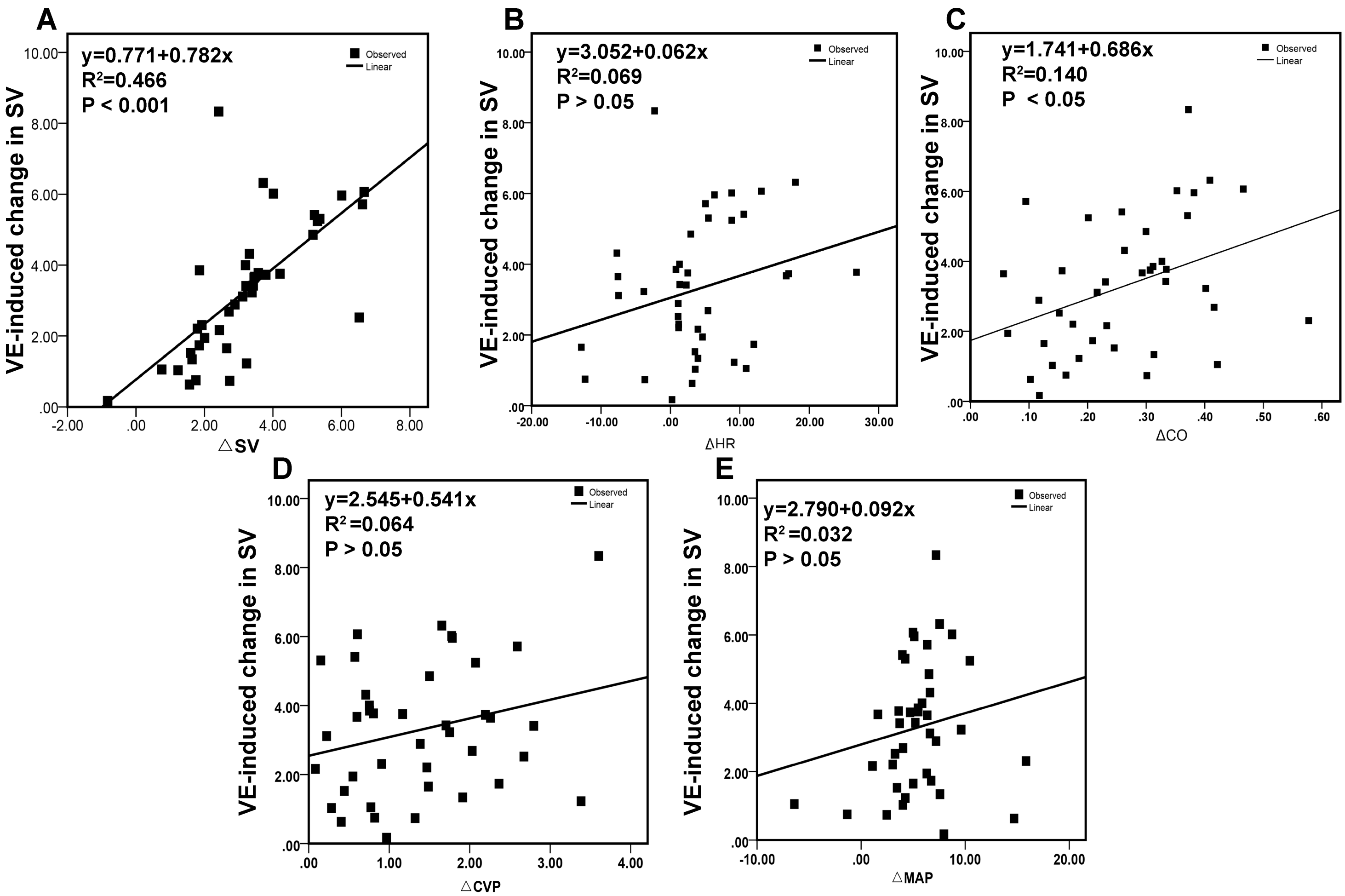



**Figure 1**

Evalution of ΔSV at the four steps of the study expressed as percent change from Base 1. †p < 0.05 vs.Base 1; #p < 0.05 vs. Base 3.




## Figure 2

Linear correlation (A) between ΔSV-PLR and ΔSV-VE. (B) between ΔHR-PLR and ΔSV-VE. (C) between ΔCO-PLR and ΔSV-VE. (D) between ΔCVP-PLR and ΔSV-VE. (E) between ΔMAP-PLR and ΔSV-VE. PLR: Passive leg raising; VE: Volume expansion.

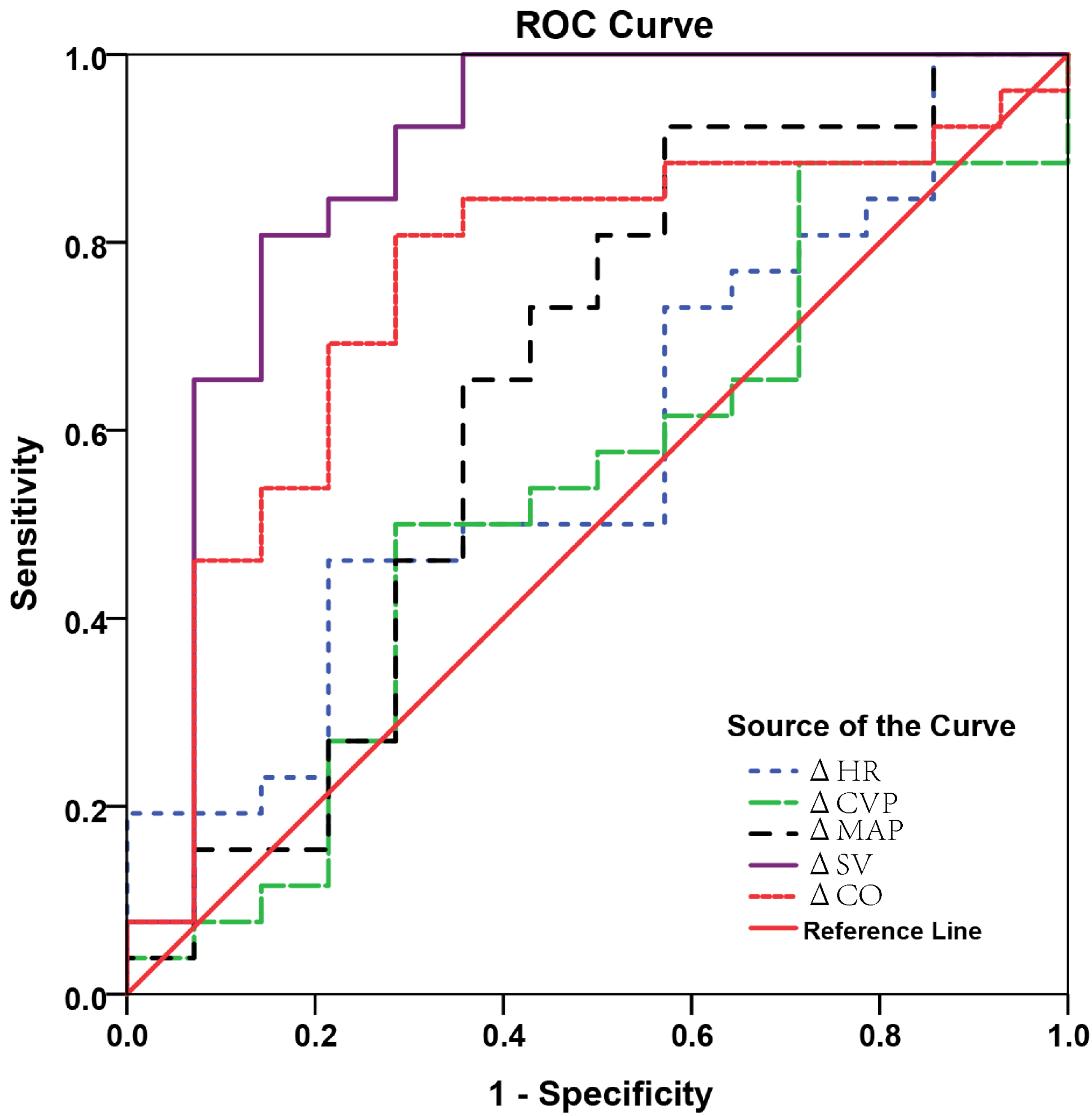



**Figure 3**

ROC curves comparing the ability of PLR induced changes to discriminate responders from nonresponders regarding volume expansion. PLR: Passive leg raising; ROC: Receiver operating characteristic.

## Supplementary Files

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