Changes in Cardiac Index Induced by Unilateral Passive Leg Raising: a Novel Way for Assessing Fluid Responsiveness

Zhiyong Zhao

Fudan University Shanghai Cancer Center

Zhongwei Zhang

Fudan University Shanghai Cancer Center

Qionghua Lin

Fudan University Shanghai Cancer Center

Lihua Shen

Fudan University Shanghai Cancer Center

Pengmei Wang

Fudan University Shanghai Cancer Center

Shan Zhang

Fudan University Shanghai Cancer Center

Zhili Xia

Fudan University Shanghai Cancer Center

Fangfang Li

Fudan University Shanghai Cancer Center

Qian Xing

Fudan University Shanghai Cancer Center

Biao Zhu (✉ zhubiaozs@126.com)

Fudan University Shanghai Cancer Center <https://orcid.org/0000-0002-5041-9630>

Research

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Abstract

Background: To evaluate the fluid responsiveness of patients, we examined the change in cardiac index (CI) during a unilateral passive leg raising (PLR) test using the ProAQT/Pulsioflex. In addition, we compared the change of CI triggered by bilateral PLR test and unilateral PLR test, and the ability to estimate volume responsiveness in patients.

Methods: This was a prospective, observational study, and we enrolled 40 individuals thought of volume expansion. The data of cardiac index, stroke variation in volume, stroke volume index, along with variation in pulse pressure were obtained with ProAQT/Pulsioflex at a semi-recumbent position, during unilateral PLR, bilateral PLR, as well as after expansion of volume (500 ml saline over 15 min). If CI improved more than 15% to the expansion of volume, patients were defined as responders.

Results: We excluded three patients. We found that a unilateral PLR-triggered CI increment $\geq 7.455\%$ forecasted a fluid-triggered CI increment $\geq 15\%$ with 77.27% sensitivity and 83.33% specificity. Meanwhile, bilateral PLR-triggered increases in CI $\geq 9.8\%$ forecasted a fluid-triggered CI increment $\geq 15\%$ with 95.45% sensitivity and 77.78% specificity. The area under the ROC curves constructed for unilateral and bilateral PLR-triggered changes in CI was not significantly different ($p=0.1544$).

Conclusions: The change of CI induced by unilateral PLR may estimate volume responsiveness in patients.

Trial registration: Unilateral passive leg raising test to assess patient volume responsiveness: Single-Center Observational Clinical Study, ChiCTR2100046762. Registered 28 May 2021, <https://www.chictr.org.cn/edit.aspx?pid=127104&htm=4>

Take-home Message

This was a prospective, observational study, and we enrolled 40 individuals thought of volume expansion. We performed unilateral passive leg raising (PLR) test and found that unilateral PLR may be able to predict fluid responsiveness.

Background

Circulatory failure is very common in intensive care unit (ICU) patients. In individuals with circulatory failure, fluid resuscitation is one of the most basic interventions for treatment. Nevertheless, only 50% of severely ill patients with acute circulatory failure benefit from an intravascular volume expansion[1, 2].

The expansion of volume harbors deleterious effects in the absence of preload dependence[3]. Treatment involving excessive intravenous fluid might result in pulmonary, as well as peripheral edema along with complication of the abdomen and other compartments and impair oxygen diffusion[4–6].

A patient who will have stroke volume (SV) increased after a fluid infusion, indicating that both ventricles in the ascending region of the Frank-Starling curve and characterize preload dependencies[7, 8].

Clinicians must accurately identify whether fluid resuscitation can increase the patient's cardiac output and avoid side effects from the unnecessary fluid infusion. It is of great significance to effectively evaluate the patient's capacity status in the clinic[9].

Passive leg raising (PLR) is a simple way to estimate volume responsiveness. Classic PLR test triggers a sudden increase in cardiac preload because of blood autotransfusion in the lower limbs and the vast splanchnic territory, resulting in cardiac output increase in patients dependent on preload. Under physiologic conditions, the volume of blood in the capacity veins in the lower limbs and the vast splanchnic territory, and returned during the classic PLR is estimated 300 ml[10].

However, in the PLR test for capacity assessment, some special situations are sometimes encountered, such as significant atrophy of the patient's unilateral lower extremity, deep vein thrombosis of lower extremities, and lower extremity amputation. When a patient cannot perform a bilateral passive leg lift test, then a unilateral PLR test can also evaluate the patient's capacity. This is a question worth discussing.

The blood volume recruited during a unilateral PLR test is less than 300ml, but similarly to the "min-fluid challenge", which may lead cardiac output response. This trial is based on the assumptions that a small quantity of fluid can remarkably raise cardiac preload and that this rise in preload is adequate to test the preload dependence of the two ventricles[11].

Herein, we purposed to explore (1) if cardiac index (CI) changes during a unilateral PLR could estimate fluid responsiveness. (2) To compare changes in CI triggered by classic bilateral PLR and unilateral PLR, and the ability to estimate volume responsiveness.

Patients And Methods

Patients

This single-center, prospective clinical study (ChiCTR2100046762) was conducted from June 1st, 2021 to July 15 at Fudan University Shanghai Cancer Center. The study was approved by the hospital's Ethical Committee (No. 2104233-4) and all patients enrolled were informed about the clinical trial and willing to participate.

40 patients were included. The inclusion criteria were: 1) Over 18 years old; 2) Tachycardia, mean arterial pressure of < 75 mmHg, stroke volume or variation in pulse pressure of > 12%, the pressure of central venous or right atrial pressure of < 5 mmHg, mixed venous oxygen saturation < 70%; 3) Based on the patient's gender, age, and body temperature, the actual cardiac output was lower than the expected output.

Patients were excluded if they have increased intra-abdominal pressure (IAP (intra-abdominal pressure) of > 12 mmHg)), arrhythmia, pulmonary hypertension, severe heart valve disease, severe thoracic aortic anatomy, external cardiac pacemaker, head trauma, severe heart failure patients, patients with thrombotic stockings, and uncooperative patients. Moreover, those who are not suitable for enrollment due to other reasons, such as patients with clear hemorrhage or active bleeding, and patients who need immediate rescue.

Study design and measurements

Figure 1. illustrates the protocol steps of current study. Hemodynamic variables, such as heart rate, pulse pressure variation (PPV), systolic blood pressure, central venous pressure (CVP), CI, stroke volume variation (SVV), mean arterial pressure, stroke volume index (SVI) along with diastolic blood pressure, were recorded.

Hemodynamic variables were measured during six sequential steps (Fig. 2.). The initial set of assessments was acquired at a semi-recumbent position (45°) (named as base 1), ensuring that the detected value is stable.

Then we performed a unilateral PLR test, the unilateral lower limbs were then raised at an 45° angle while the patients' trunk and other side of lower limbs were in supine posture. Therefore, the angle of the trunk with the lower limbs remained unaltered at 135° . A second assessment set (named unilateral PLR) was documented at the maximal effect of unilateral PLR on CI, which occurs within 1 minute.

The body position was then rendered to the base 1 posture and the CI return to its baseline value, then a third assessment set was documented (base 2).

To prevent possible pain from creating false positives, the automatic technique was used for bed elevation. The patients' lower limbs were lifted to a 45° angle from the horizontal position, whereas the trunk was lowered in a horizontal position, and the angle of the trunk and the leg is still 135° . The fourth set of values (termed bilateral PLR) were measured, when the CI reached its maximal value. Maximal impact on PLR on CI was detected within 1 min in all patients.

The position was sent back to base 1, then the fifth set of assessments was documented (base 3).

Finally, measurements were acquired after volume expansion (VE) (500 mL of saline more than 15 min) (designated post-VE).

The CVP was measured at each study step, evaluated the jugular venous pulse was to estimate CVP[12]. CVP was decided at end-expiration and demonstrated the averaged value from three sequential respiratory cycles.

Hemodynamic monitoring

The ProAQT/Pulsioflex (Pulsion Medical Systems, Munich, Germany, termed as 'Pulsioflex' hereafter) is a novel pulse contour assessment instrument that does not require external interference, calibration of pressure waveform assessment.

Monnet et al. investigate Pulsioflex's ability to monitor modifications in CI that were triggered by a rise expansion of volume or decrease in norepinephrine dosage in 60 study subjects at the department of intensive care. They discovered that the Pulsioflex was capable of keeping track of the changes in CI that were triggered by the expansion of volume (as illustrated by a concordance rate close of to 95%). For monitoring fluid-triggered alterations in CI, the Pulsioflex was trustworthy[13].

A radial arterial catheter was connected to Pulsioflex to observe SVI, SVV, and PPV. Cardiac output's initial value was assessed with a proprietary algorithm conducting an "auto-calibration". The stroke volume at that point was calculated using pulse contour assessment. PPV along with SVV was continuously shown on the Pulsioflex screen. SVI, SVV, CI, as well as PPV estimations utilizing Pulsioflex are a mean over the last 12 s and are modernized every second. SVI, CI, PPV, and SVV are shown beat-to-beat in the form of a "sliding average" of 12 s. When extracting information through a USB harbor to an Excel file, values were shown every 12 s.

Statistical analysis

After completing of the study protocol, patients were divided into two groups: responders and non-responders to fluid loading.

Patients with CI increase more than 15% by volume expansion from base 3 were classified as responders, otherwise, as non-responders.

The data distribution normality was screened with the Kolmogorov-Smirnov examination. Data are presented as mean [standard deviation (SD)], median (interquartile range), or number (frequency in %).

The comparison of patient's characteristics, medical history, and cause of circulatory failure between responders and non-responders was performed using a nonparametric Mann–Whitney U test for continuous variables and a chi-square test for categorical variables.

Comparison of hemodynamic variables between time points of the study was performed by paired Student's t-test or Wilcoxon test, based on the data distribution. Comparison between volume responders and non-responders was performed using the two-sample Student's t-test or the Mann-Whitney U-test, as appropriate.

Receiving operating characteristic (ROC) curves were produced for unilateral PLR-induced changes in continuous variables (CI, PPV, SVI and SVV). The area under the ROC curves for unilateral PLR-triggered changes of CI and bilateral PLR-triggered changes of CI were compared in all patients using a Hanley-McNeil test[14].

A two-tailed p -value < 0.05 showed statistical significance. Statistical analysis was implemented in the MedCalc Statistical Software version 19.0.4 (MedCalc Software bvba, Ostend, Belgium; <https://www.medcalc.org>; 2019).

Results

Forty-three patients were enrolled (Fig. 1). Two patients were not included because to uncooperative of the test. One patient was not included because of pain, when performing a unilateral PLR test. No patient was excluded based on other reasons. Finally, 40 patients were enrolled and analyzed, which are enlisted in Table 1.

No patients received β -blockers. Eight patients (20%) were intubated and ventilated, and pressure support was the ventilation mode (fraction of inspired oxygen = $35 \pm 5\%$, inspiratory pressure = 10 ± 4 cmH₂O, and positive end-expiratory pressure = 5 cmH₂O). Thirty-two patients were not intubated.

Twenty-two patients were responders to the expansion of volume, and eighteen were non-responders. The impacts of unilateral PLR, bilateral PLR, along with the expansion of volume on hemodynamic variables in responders and non-responders are shown in Table 2.

In all patients, changes in CI triggered by unilateral were significantly higher in responders and non-responders ($p = 0.0005$; Fig. 3). In responders, CI increased by 10.1528 (8.4275 to 11.8782) % from baseline to unilateral PLR. In non-responders, CI increased by 6.2691 (5.2223 to 7.3158) % from baseline to unilateral PLR.

In all patients, changes in CI triggered by bilateral were significantly higher in responders and non-responders ($p < 0.0001$; Fig. 3). In responders, CI increased by 16.9080 (14.6406 to 19.1753) % from baseline to bilateral PLR. In non-responders, CI increased by 9.0929 (7.5387 to 10.6472) % from baseline to bilateral PLR.

As shown in Fig. 4 and Table 3, the area under the ROC curves established for the unilateral PLR-triggered change in PPV, SVI, and SVV was significantly lower compared to the unilateral PLR-triggered changes in CI.

The result showed that a unilateral PLR-triggered CI increment of $\geq 7.455\%$ forecasted a fluid-triggered CI increment of $\geq 15\%$ with 77.27% sensitivity and 83.33% specificity (Table 4; Fig. 5). Meanwhile, bilateral PLR-triggered increases in CI $\geq 9.8\%$ forecasted a fluid-triggered CI increment of $\geq 15\%$ with 95.45% sensitivity and 77.78% specificity (Table 4; Fig. 5). The area under the ROC curves constructed for unilateral and bilateral PLR-triggered alterations in CI was not statistically different ($p = 0.1544$). (Table 4; Fig. 5).

Discussion

In this prospective, observational study, we found that CI, which induced by unilateral PLR detected by Pulsioflex, could predict the fluid responsiveness in spontaneous breathing patients without using vasoactive drugs. To the best of our knowledge, this is the first clinical trial to evaluate this problem.

Unilateral PLR test can only induce small increase in cardiac preload, so the technique used to measure changes in cardiac output must be very precise. Pulsioflex is a new pulse contour assessment device; its accuracy has been tested previously[15]. Bioreactance[16], transthoracic echocardiography[17], and capnography[18], which are used in classic PLR tests, and showed good accuracy in detecting changes in cardiac output, need further test verification when used in unilateral PLR test.

ROC operating characteristic curves were employed to explore the diagnostic efficacy, and the area under the ROC curves (AUC) was compared between unilateral and bilateral PLR-induced changes of CI, the *p-value* was 0.1544. Although there are no significant differences between the two groups, the sensitivity and specificity are not as good as classic bilateral PLR. Because of its advantages, classic bilateral PLR can't be replaced by unilateral PLR test.

The unilateral PLR test could also be a promising maneuver for evaluation of volume responsiveness. More research should be conducted to compare the accuracy of unilateral PLR relative to boluses as assessed by other noninvasive tools other than the Pulsioflex. To evaluate clinical application, larger sample randomized controlled trials of the prospective impact of unilateral PLR response-directed fluid resuscitation on morbidity, as well as mortality for patients should be conducted for more in-depth exploration.

There are some limitations to this study. First, the sample size was not large. Second, when the unilateral PLR test was performed, we lift manually one of the lower limbs holding the heels of the patients. However, we performed gently and maximize to prevent possible pain from lifting a leg. Moreover, one patient was excluded because of pain. Third, only seven patients with septic shock, and none were put under vasoactive support. The findings cannot be extrapolated for patients with septic shock and receiving vasopressive support. Finally, this study was conducted using pro-AQT's algorithms, and our results cannot be extrapolated to other algorithms. The hemodynamic parameters are an average during the last 12 s, at any time, and the value of outcomes from both the former auto-calibration the pulse contour assessment that run afterward. Data lag is inevitable.

Conclusions

The changes of CI induced by unilateral PLR may be able to predict fluid responsiveness, in patients with spontaneously breathing patients while not vasoactive support. In addition, the significance meaning of this study may not lie in how much value of CI changes of unilateral PLR can determine whether the volume response is positive, but a new method that can be used to predict fluid responsiveness. Especially for those patients who cannot perform bilateral PLR, but unilateral PLR.

Abbreviations

ICU: intensive care unit

SV: stroke volume

PLR: Passive leg raising

CI: cardiac index

IAP: intra-abdominal pressure

PPV: pulse pressure variation

CVP: central venous pressure

SVV: stroke volume variation

SVI: stroke volume index

VE: volume expansion

SD: standard deviation

ROC: receiving operating characteristic

AUC: area under the ROC curves

Declarations

Ethics approval:

This study was approved by the ethics committees of Shanghai cancer center, Fudan University, China, and the registration number is ChiCTR2100046762.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

Funding:

No funding was received.

Authors' contributions:

ZzZ, ZwZ, QL and BZ conceived and designed the study. LS, PW and SZ performed data acquisition. ZX, QX and FL participated in the data analysis and interpretation of the results. ZzZ and BZ were involved in the statistical analysis and wrote the paper. All authors read and approved the final manuscript.

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Tables

Due to technical limitations, table 1 to 4 PDFs are only available as a download in the Supplemental Files section.

Figures

Figure 1

Flow of patients through the study

Figure 2

Study protocol.

Figure 3

Representation of the changes of CI in responders and non-responders. CI: cardiac index; PLR: passive leg raising.

Figure 4

ROC curves comparing changes in CI, PPV, SVI, and SVV to discriminate responders and non-responders. CI: cardiac index; PPV: pulse pressure variation; SVI: stroke volume index; SVV: stroke volume variation; ROC: Receiving operating characteristic.

Figure 5

ROC curves showing the ability of changes in CI induced by unilateral PLR and bilateral PLR to predict an increase in cardiac index $\geq 15\%$ during the volume expansion. ROC: Receiving operating characteristic; CI: cardiac index; PLR: passive leg raising.

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