Comparison of Mean Systemic Pressure in Patients with Acute Circulatory Failure Receiving Passive Leg Raising vs. Pneumatic Leg Compression.

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Research

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Abstract

Background: Driving pressure of venous return (VR) is determined by mean systemic pressure (Pms) and central venous pressure (CVP). While passive leg raising (PLR) and pneumatic leg compression PC (PC) can increase VR, there is no study explore the effects of these two procedures on Pms and VR-related hemodynamic variables.

Methods: Forty patients with acute circulatory failure were included in this analysis. All patients were performed both PLR and PC, and were measured for Pms, CVP, mean arterial pressure (MAP), cardiac output (CO), VR resistance (RVR), and systemic vascular resistance (SVR) at baseline and immediately after procedures. To minimized carry-on effect, the patients were divided into 2 groups based on procedure sequence which were 1) the patients who received PLR first then PC (PLR-first), and 2) the patients who received PC first then PLR (PC-first). Both groups were waited for washing period before performed 2nd procedure. Primary outcome was difference in Pms between PLR and PC procedure. Secondary outcome were differences in CVP, MAP, CO, RVR, and SVR between PLR and PC procedure.

Results: There was no difference in baseline characteristics and no carry-on effect between 2 groups of patients. Compared to baseline, both PLR and PC significantly increased Pms, CVP, MAP, and CO. Compared to PC, PLR more increased Pms (9.0±2.3 vs 4.8±1.7 mmHg, p<0.001), CVP (4.5±1.2 vs. 1.6±0.7 mmHg, p<0.001), MAP (22.5±5.6 vs. 14.4±5.0 mmHg, p<0.001), and CO (1.5±0.5 vs. 0.5±0.2 L/min, p<0.001). PC, but not PLR also significantly increased RVR (16 ± 27.2 dyn.s/cm$^5$, p=0.001) and SVR (78.4 ± 7.2 dyn.s/cm$^5$, p<0.001).

Conclusion: In patients with acute circulatory failure, PLR more increased Pms, CVP, MAP, and CO than PC.

Background

According to the Guyton\textsuperscript{1} model of circulation, systemic venous return (VR) is determined by pressure gradient between mean systemic pressure (Pms) and right atrial pressure, as well as resistance to VR (RVR). Pms is defined as the pressure in the whole cardiovascular system when the heart is stopped and there is no fluid motion, it was first described by Bayliss and Starling in a dog model during cardiac arrest.\textsuperscript{2} Under steady conditions, the cardiac output (CO) and VR are equal, and any parameter determines VR will therefore also determine CO. Difference between Pms and RAP or central venous pressure (CVP) is the pressure gradient of VR (dVR). Under steady resistances, VR is approximately proportional to dVR. While classic study by Guyton noticed that an increase in blood volume increases Pms and decreases RVR because of vessels wall distension,\textsuperscript{2} recent studies found that vasopressor increase RVR and restore mean arterial pressure (MAP).\textsuperscript{3} Estimating Pms and RVR at the bedside has been proposed by Maas and co-workers, based on recording several pairs of CO and CVP measurements obtained by varying the intrathoracic pressure.\textsuperscript{4} Regards to the test to predict fluid responsiveness, passive leg raising (PLR) is supposed to transfer a significant volume of venous blood toward the intrathoracic compartment.\textsuperscript{5}
However, it has been suggested that it could have nonsignificant effects on cardiac preload, in particular case of intra-abdominal hypertension, result in a negative PLR test in spite of an actual fluid responsiveness. Nowadays, intermittent pneumatic compression (PC) is an alternative method to prevent venous thromboembolism (VTE) in the intensive care unit (ICU) patient by increasing flow of VR.\textsuperscript{6,7} While both PLR and PC can increase VR, there is no study explore effects of these two procedures on Pms and VR-related hemodynamic variables, this led us to conduct a study investigating effects of PC, compare to PLR, on Pms and VR-related hemodynamic variables.

**Methods**

We performed a prospective randomized cross-over study to compare changes in Pms and VR-related hemodynamic variables following PLR and PC in patients with shock. We used block of four method by randomize 1:1 ratio by variables block size and used computer-generated sequence and allocation, single blind by opaque envelopes (concealed with opaque envelopes), patients were classified into 2 groups which were PLR-first and PC-first as described in detail below.

**Participants**

Forty patients who admitted to the ICU, Phramongkutklao hospital, Bangkok, Thailand from April 2020 to February 2021 with acute circulatory failure, were enrolled in this study. Inclusion criteria including age more than 18-year-old and acute circulatory failure (define as persistent MAP less than 65 mmHg at least 15 min despite adequate volume resuscitation or require vasopressor to maintain MAP more than 65 mmHg) and the exclusion criteria were patients who have contraindication for esophageal Doppler catheter placement, intolerate to esophageal Doppler probe insertion, coarctation of aorta, bleeding tendency, patients who have receive advance mechanical hemodynamic support, valvular heart disease, contraindication for fluid challenge, contraindication for PC (e.g. leg ulcer), limb amputation, bed ridden > 1 month before enrollment, deep vein thrombosis (DVT), peripheral arterial disease (ankle-brachial index < 0.9), pregnancy, intraabdominal pressure more than 16 mm Hg, acute respiratory distress syndrome, muscle atrophy of the leg, refractory shock (norepinephrine dose $\geq 0.5 \, \mu g/kg/min$), increased intracranial pressure, pneumothorax, cardiac arrhythmia. Withdrawal criteria were patients who have complication from esophageal Doppler insertion, hypoxemia (peripheral $O_2$ saturation ($SpO_2$) < 92%), increased vasopressor used, cardiac arrhythmia, pain when perform PLR and PC, and intraabdominal pressure more than 16 mm Hg during procedure. During 4-inspiratory hold maneuver to measure the Pms, if patients develop worsening hypotension or arrhythmia, the patients will be excluded from study.

**Interventions and hemodynamic monitoring**

All patients were mechanically ventilated using a volume-control ventilation with tidal volume 8 mL/kg of predicted body weight, respiratory rate was adjusted to maintain normocapnia, inspired oxygen fraction was adjusted to maintain $SpO_2$ above 94%, and inspiratory/expiratory ratio was 1:2. Sedative and paralysis agents were given to keep Richmond Agitation Sedation Scale less than −1. All patients were
measured for Pms, CVP, MAP, CO, RVR, and SVR at the baseline and immediately after each procedure. To minimized carry-on effect, the patients were divided into 2 groups based on procedure sequence which were 1) the patients who received PLR first then PC (PLR-first), and 2) the patients who received PC first then PLR (PC-first). Both groups were waited for washout period before performed 2nd procedure. In PLR-first patient group, sit patient at 45 degrees head up semi-recumbent position then lower patient’s upper body to horizontal and passively raise legs at 45 degrees up then keep maximal effect occurs at 30 seconds during 4-inspiratory hold maneuver method. In PC-first patient group, set the sleeves inflate pressure 40 mmHg for 2 minutes after immediately fully inflate at 2 minutes perform 4-inspiratory hold maneuver methods and then deflate.

All patients were monitored for MAP and CVP using radial arterial catheter and central venous catheter linked to a bedside monitor on one side and to a specific transducer (Philips Intellivue Philips MX600, USA). CO, SV, and SVR were monitored using esophageal Doppler catheter (CardioQ, Deltex medical, UK). Pms was measured using 4-inspiratory hold maneuver method suggested by Maas. Briefly, the patients received 4-inspiratory hold maneuver with PEEP of 5, 15, 25, 35 cmH₂O and record pairs of CO and CVP for generating a VR Guyton's curve (Fig. 1). The Pms was estimated as the pressure corresponding to the x-intercept of the regression line.

**Statistical analysis**

Primary outcome was difference in Pms between PLR and PC procedure and secondary outcome were differences in VR-related variables (including CVP, MAP, CO, RVR, and SVR) between PLR and PC procedure. In previous pilot study of PLR and volume expansion on Pms and VR, sample size estimation showed that at least 26 patients were required to evaluate ability and to compare difference in Pms between PLR and PC procedure. Results were expressed as mean ± SD if data were normally distributed or median and interquartile range (IQR) if not. Hemodynamic parameters were compared at baseline between PLR and PC procedure using the independent-t test, paired t-test, Fisher’s exact test, Pearson’s correlation, and repeated measure ANOVA test. The effects of volume expansion on hemodynamic parameters were analyzed using the Friedman nonparametric repeated measures comparisons. A p-value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS version 23.0.

**Results**

**Patient characteristics**

All 40 patients were successfully measured for Pms, CVP, MAP, CO, RVR, and SVR at baseline and immediately after procedures. Most of the patients were female (52%) with average ages of 68 years old. The most frequent coexisting disease was hypertension and the most frequent etiology of acute circulatory failure was septic shock (Table 1). Average of baseline norepinephrine dosage was 0.35 ± 0.06
µg/kg/min and baseline pulse pressure variation of 15.35 ± 0.92%. There was no difference in baseline characteristics between two groups of patients (Table 2).

### Table 1
Demographic data of 40 patients with acute circulatory failure.

| Variables                          | N = 40                  |
|------------------------------------|-------------------------|
| Male, n (%)                        | 19 (47.5)               |
| Age (yrs)                          | 68.25 ± 17.23           |
| Weight (kg)                        | 58.25 ± 5.38            |
| **Co-morbidity, n (%)**            |                         |
| Hypertension                       | 29 (72.5)               |
| Dyslipidemia                       | 18 (45)                 |
| Diabetes mellitus                  | 18 (45)                 |
| Chronic kidney disease             | 10 (25)                 |
| Chronic liver disease              | 9 (22.5)                |
| Coronary artery disease            | 4 (10)                  |
| Other diseases                     | 21 (52.5)               |
| IV fluid (mL)                      | 1725 ± 521              |
| **Type of shock, n (%)**           |                         |
| Septic                             | 33 (82.5)               |
| Cardiogenic                        | 4 (10)                  |
| Hypovolemic                        | 3 (7.5)                 |
| Norepinephrine dosage (µg/kg/min)  | 0.35 ± 0.06             |
| APACHE II score                    | 12.68 ± 2.07            |
| MAP at enrollment (mmHg)           | 80.25 ± 7.39            |
| Blood lactate at enrollment (mmo/L)| 9.23 ± 5.8              |
| Pulse pressure variation at enrollment (%)| 15.35 ± 0.92 |
Table 2
Baseline characteristics comparison between two patient groups.

| Variables                        | PLR → PC (n = 20) | PC → PLR (n = 20) | p-value |
|----------------------------------|-------------------|-------------------|---------|
| Male, n (%)                      | 9 (45)            | 10 (50)           | 1.0     |
| Age (yr)                         | 66.1 ± 18.5       | 70.4 ± 16.04      | 0.437   |
| Body weight (kg)                 | 58.5 ± 5.4        | 58 ± 5.48         | 0.773   |
| Coexisting diseases, n (%)       | 16 (80)           | 13 (65)           | 0.480   |
| Hypertension                     |                   |                   |         |
| Dyslipidemia                     | 10 (50)           | 8 (40)            | 0.751   |
| Diabetes                         | 10 (50)           | 8 (40)            | 0.751   |
| Chronic kidney disease           | 8 (40)            | 2 (10)            | 0.065   |
| Chronic liver disease            | 4 (20)            | 5 (25)            | 1.0     |
| Coronary artery disease          | 4 (20)            | 0 (0)             | 0.106   |
| APACHE II score                  | 12.7 ± 1.95       | 12.65 ± 2.23      | 0.940   |
| IV fluid received (mL)           | 1651.5 ± 470.15   | 1798 ± 570.53     | 0.381   |
| Type of Shock                    |                   |                   |         |
| Septic                           | 17 (85)           | 16 (80)           | 1.0     |
| Cardiogenic                      | 2 (10)            | 2 (10)            | 0.605   |
| Hypovolemic                      | 2 (10)            | 1 (5)             | 0.231   |
| NE dosage (µg/kg/min)            | 0.34 ± 0.07       | 0.35 ± 0.06       | 0.486   |

Value presented as mean ± SD. or n (%). P-value corresponds to Independent-t test and Fisher’s exact test.

Differences in Pms and VR-related variables compared between PLR and PC

There was no carry-on effect between two patient groups and for crossover study, period effect analysis and sequence effect analysis were shown in Table 3. Compared to baseline, both PLR and PC significantly increased Pms, CVP, MAP, and CO (Table 3). Both PC and PLR significantly increased Pms (Fig. 2). Compared to PC, PLR more increased Pms (9.0 ± 2.3 vs 4.8 ± 1.7 mmHg, p < 0.001) (Fig. 3A), MAP (22.5 ± 5.6 vs. 14.4 ± 5.0 mmHg, p < 0.001) (Fig. 3B), CO (1.5 ± 0.5 vs. 0.5 ± 0.2 L/min, p < 0.001) (Fig. 3C), CVP (4.5 ± 1.2 vs. 1.6 ± 0.7 mmHg, p < 0.001) (Fig. 3D), and dVR (4.4 ± 2.6 vs. 3.2 ± 1.7, p < 0.001) (Fig. 4A). PC, but not PLR, also significantly increased RVR (16 ± 27.2 dyn.s/cm⁵, p = 0.001) (Fig. 4B) and
SVR (78.4 ± 7.2 dyn.s/cm$^5$, p < 0.001) (Fig. 4C). We additionally explored effects of NE on Pms and RVR, we found a fair correlation between NE dosage and RVR following PLR procedure (r = 0.35, p = 0.027) but not PC procedure.
Table 3
Changes in hemodynamic variables from baseline, compared between PLR and PC maneuvers.

| Variables       | Baseline       | PLR            | PC             | Difference between PLR vs. PC |
|-----------------|----------------|----------------|----------------|------------------------------|
| MAP (mmHg)      | 74.95 ± 4.68   | 97.43 ± 7.78   | 89.3 ± 6.5     | 8.13 ± 3.47                 |
| Mean change from baseline | 22.48 ± 5.6     | 14.35 ± 5      | < 0.001*       | < 0.001*#                   |
| Pms (mmHg)      | 25.73 ± 7.05   | 34.65 ± 7.45   | 30.5 ± 6.94    | 4.15 ± 1.08                 |
| Mean change from baseline | 8.93 ± 2.34     | 4.78 ± 1.72    | < 0.001*       | < 0.001#                    |
| CO (L/min)      | 6.49 ± 1.27    | 7.97 ± 1.14    | 7.01 ± 1.28    | 0.97 ± 0.38                 |
| Mean change from baseline | 1.48 ± 0.47     | 0.52 ± 0.17    | < 0.001*       | < 0.001#                    |
| CVP (mmHg)      | 7.68 ± 1.49    | 12.2 ± 1.18    | 9.28 ± 1.13    | 2.93 ± 1.05                 |
| Mean change from baseline | 4.53 ± 1.22     | 1.6 ± 0.71     | < 0.001*       | < 0.001#                    |
| RVR (dyn.s/cm$^5$, Wood units) | 245.6 ± 144.8 | 236 ± 107.2   | 261.6 ± 130.4  | -25.6 ± 34.4                |
| Mean change from baseline | -9.6 ± 54.4    | 16 ± 27.2      | 0.001*         | < 0.001#                    |
| Pms-CVP (mmHg) | 18.05 ± 7.61   | 22.45 ± 7.99   | 21.23 ± 7.38   | 1.23 ± 1.59                 |
| Mean change from baseline | 4.4 ± 2.61     | 3.18 ± 1.72    | < 0.001*       | < 0.001#                    |

Value presented as mean ± SD, and mean change. * depicts p < 0.05 and compared between baseline vs. each intervention, # depicts p < 0.05 and compared between two interventions. P-value analyzed using the paired t-test.
| Variables    | Baseline | PLR       | PC         | Difference between PLR vs. PC |
|--------------|----------|-----------|------------|------------------------------|
| SVR (dyn.s/cm\(^5\), Wood units) | 877.6 ± 264 | 876.8 ± 176.8 | 956 ± 252.8 | -80 ± 91.2 |
| Mean change from baseline | -0.8 ± 124 | 78.4 ± 7.2 | < 0.001* | < 0.001# |
| p            | 0.959    |           |            |                              |

Value presented as mean ± SD, and mean change. * depicts p < 0.05 and compared between baseline vs. each intervention, # depicts p < 0.05 and compared between two interventions. P-value analyzed using the paired t-test.

**Discussion**

In this study, we evaluated the effects of PC and PLR on Pms and VR-related parameters in patients with acute circulatory failure. We found that both PLR and PC significantly increased Pms, CVP, MAP, and CO from baseline. We also found that, compared to PC, PLR increased more Pms, CVP, MAP, and CO. Regards to venous and arterial systems, PC, but not PLR, significantly increased RVR and SVR respectively. According to Pms, it can be interfered by exogenous fluid loading. Hence, in this study, we did not give fluid bolus to our patients to avoid confounding factor from volume expansion.

To date, PC is recommended by Surviving Sepsis Campaign guideline and European Society of Intensive Care Medicine for DVT prophylaxis in critically-ill patients who is at risk of DVT with contraindication to anticoagulant medication.\(^{10}\) Interestingly, the application of PC is already used for augment VR purpose at least a decade ago in the military way, known as military anti-shock trousers.\(^{11}\) Basically, it improves hemodynamic by increased Pms, then augment VR. Hence, MAP is increased. Our findings were aligned to previous studies,\(^9\) which evaluated effects of PC and found that the PC significantly augmented flow velocity and volume flow in patients with varicose vein. In addition, previous study in healthy volunteers found that there was increasing of venous volume by using thigh cuff pressure.\(^9\) In this study, we not only demonstrated that PC can increased VR by increased Pms but we also demonstrated that PC increased MAP in patients with acute circulatory failure.
Contrast to PLR, we found that PC significantly increased RVR and SVR, and these findings may be because of vasoconstriction effect from direct compression of the PC on both arterial and venous vessels in both thighs. Compared to PC, we also found that PLR increased more Pms, CVP, MAP, and CO.

However, this study has some limitations. Firstly, measurement of CO in our study was monitored by esophageal Doppler and this technology is operator-dependent as well as angle of probe must be steady. Secondly, this prospective cross-over trial was conducted in patients who were received mechanical ventilation, so our findings cannot be extrapolated in patients with spontaneous breathing. Thirdly, PC may stimulate sympathetic tone and interfere hemodynamic interpretation in our study. However, using the changes of heart rate as a surrogate of sympathetic stimulation, we found that there was no difference in heart rate at any timepoint. Therefore, we speculated that effect of sympathetic stimulation during interventions maybe minimal. Finally, our study was conducted in single center and confined in patients with acute circulatory failure, many exclusion criteria were used, our findings may not generalizable in overall critically-ill patients.

Conclusions

In patients with acute circulatory failure, both PLR and PC increased Pms, CVP, MAP, and CO. Compared to PC, these parameters was increased more with PLR. PC, but not PLR, increased RVR and SVR. Our findings supported Guyton’s theory regards to venous return physiology.

Declarations

Ethics approval and consent to participate:

Institutional Review Board Royal Thai Army Medical Department Ethics Committee approved this study on March 4, 2020. Research no. R177h/62 followed Council for International Organization of Medical Science (CIOMS) Guidelines 2012 and Good Clinical Practice of International Conference on Harmonization statement no.IRBRTA 292/2563.Ethics Committee included Suthee Panichkul, MD (chair), Thawee songpatanasilp, MD (vice chair), and Sahaphol Anannamcharoen, MD (vice chair).

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 in this section.

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Authors' contributions:

PB, PW, and PF participated in the study concept and design. PB and PW carried out the acquisition of data. PB and PW participated in the statistical analysis and interpretation of data. PB and PW carried out the drafting of the manuscript. PB, PW, and PF carried out the critical revision of the manuscript for important intellectual content. PB, PW, and PF participated in the administrative, technical, or material support. All authors read and approved the final manuscript.

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Figures

Figure 1

Venous return Guyton's curve generating from 4-inspiratory hold maneuver method.
Figure 2

Guyton's VR curves and Pms in patients received PC and PLR.
Figure 3

Figure 3A Comparison Pms between PLR-first and PC-First Figure 3B Comparison MAP between PLR-first and PC-First Figure 3C Comparison CO between PLR-first and PC-First Figure 3D Comparison CVP between PLR-first and PC-First
Figure 4

Figure 4A Comparison Pms-CVP between PLR-first and PC-First

Figure 4B Comparison RVR between PLR-first and PC-First

Figure 4C Comparison SVR between PLR-first and PC-First