Title: **What is the normal haemodynamic response to passive leg raise? A study of healthy volunteers.**

Authors: Elwan MH[1,2], Roshdy A[3,4], Reynolds JA[2], Elsharkawy EM[5], Eltahan SM[5], Coats TJ[2]

1 Department of Emergency Medicine, Alexandria University, Alexandria, Egypt
2 Emergency Medicine Academic Group, Department of Cardiovascular Sciences, University of Leicester, Leicester, UK
3 Department of Critical Care Medicine, Alexandria University, Alexandria, Egypt
4 General Intensive Care Unit, Queen Elizabeth, Lewisham and Greenwich NHS Trust, UK
5 Department of Cardiology, Alexandria University, Alexandria, Egypt

Correspondence:

Dr Mohammed H Elwan, MBBCh, MSc, MRCEM

Address: Emergency Medicine Academic Group, Department of Cardiovascular Sciences, University of Leicester, Level G Jarvis Building RMO, Infirmary Square, Leicester, LE1 5WW, United Kingdom.

E-mail: mohammed.elwan@alexmed.edu.eg

Telephone: +44 (0) 116 2586388

Co-authors:

Dr Ashraf Roshdy, MBBCh, MSc, MD, FRCP (Edin)

Mr Joseph A Reynolds, Medical student

Dr Eman Elsharkawy, MBBCh, MSc, MD

Professor Salah Eltahan, MBBCh, MSc, MD

Professor Timothy Coats, BSc, MB BS, FRCS, FFAEM, MD

Keywords: Preload responsiveness, Fluid therapy, Haemodynamics, Emergency, Non-invasive monitoring, bioimpedance

Competing Interests

None declared.

Funding

MHE is funded by Newton-Mosharafa PhD Fund.

Word Count

3364

ABSTRACT

Objective

Passive leg raise (PLR) is used as self-fluid challenge to optimise fluid therapy by predicting preload responsiveness. However, there remains uncertainty around the normal haemodynamic response to PLR with resulting difficulties in application and interpretation in emergency care. We aim to define the haemodynamic responses to PLR in spontaneously breathing volunteers using a non-invasive cardiac output monitor, thoracic electrical bioimpedance, TEB (PLR-TEB).

Methods

We recruited healthy volunteers aged 18 or above. Subjects were monitored using TEB in a semi-recumbent position, followed by PLR for 3 minutes. The procedure was repeated after 6 minutes at the starting position. Correlation between the 2 PLRs was assessed using Spearman's r (r_s). Agreement between the 2 PLRs was evaluated using Cohen Kappa with responsiveness defined as ≥10% increase in stroke volume. Parametric and non-parametric tests were used as appropriate to evaluate statistical significance of baseline variables between responders and non-responders.

Results

We enrolled 50 volunteers, all haemodynamically stable at baseline, of whom 49 completed the study procedure. About half of our subjects were preload responsive. The ΔSV in the 2 PLRs was correlated (r_s = 0.68, 95% CI 0.49 to 0.8) with 85% positive concordance. Good agreement was observed with Cohen Kappa of 0.67 (95% CI, 0.45 to 0.88). Responders were older and had significantly lower baseline stroke volume and cardiac output.

Conclusion

Our results suggest that the PLR-TEB is a feasible method in spontaneously breathing volunteers with reasonable reproducibility. The age and baseline stroke volume effect suggests a more complex underlying physiology than commonly appreciated. The fact that half of the volunteers had a positive preload response, against the 10% threshold, leads to questions about how this measurement should be used in emergency care, and will help shape future patient studies.

KEY MESSAGES

What is already known on this subject?

- Too much or too little intravenous fluid for unstable patients is harmful.
- Passive leg raise test combined with cardiac output monitoring is used in critical care to stratify ventilated patients and optimise treatment.
- The utility of the passive leg raise test in spontaneously breathing patients has not been adequately tested.

What this study adds?

- Passive leg raise test combined with non-invasive cardiac output monitoring is feasible in spontaneously breathing volunteers.
- Half of the volunteers had a positive preload response.
- As with many other measures of physiology, a simple normal / abnormal dichotomy is unlikely to be useful in emergency care.

INTRODUCTION

Despite decades of research, fluid therapy optimisation remains a challenge. This is particularly important in Emergency Department (ED) where prompt resuscitation to prevent grave outcomes has to be weighed against the adverse effects of overzealous treatment. Fixed goal resuscitation strategies have been popular, but are recently challenged and more individualised paradigms are being sought.[1]

Treatment of shocked patients in ED is currently guided by clinical signs and basic monitoring parameters (e.g. blood pressure and heart rate), which are not good proxies of volume status or cardiac function.[2] When immediate resuscitation is required, there is often uncertainty about the benefit of fluid therapy, the volume required or alternative interventions to support the circulation (e.g. vasopressors or inotropes). Many EDs have introduced ultrasound and echocardiography to support decisions in these situations, but the data provided is complex, operator dependent, and only give snap-shots of haemodynamics.

Only 50% of haemodynamically unstable patients increase their cardiac output (CO) in response to volume loading.[3] Therefore, 'preload responsiveness' (the ability of the heart to respond to an increase in preload) has been suggested to stratify patients into those who may benefit and those who may be harmed by fluid administration. This concept rests on the assumption that fluid therapy should only be useful if it results in a 10-15% increase in stroke volume (SV) or CO – otherwise the balance will be more towards the inherited harms of fluid administration (e.g. pulmonary oedema, prolonging mechanical ventilation, abdominal hypertension, etc).[4]

To evaluate preload responsiveness a preload challenge is used (e.g. fluid challenge or passive leg raise, PLR) while monitoring the subsequent changes in SV, CO or one of their surrogates. PLR acts as a reversible self-fluid challenge and has been suggested as a replacement of a classic fluid challenge, in order to avoid adverse effects.[5] The PLR test requires a rapidly responsive, direct CO monitor to evaluate the effect (basic monitoring parameters are not sufficient).[6]

Several non-invasive CO monitors have been developed, making this concept more feasible in emergency care.[7] Thoracic Electrical Bioimpedance (TEB) monitors apply a small electric current across the chest using four pairs of electrodes, continuously measure impedance and calculate CO from impedance changes. TEB has been used to evaluate preload responsiveness in a number of studies with reasonable accuracy and trending ability.[8 9] It should be noted that TEB has a number of limitations including excessive thoracic fluid, low baseline impedance, motion artefact and tachyarrhythmia.[10]

Estimating preload responsiveness is a common intervention in ICU and peri-operatively and has been recently recommended by the international guidelines [11] – although the evidence quality is low. Most of this evidence comes from sedated, mechanically ventilated patients who have altered cardiovascular reflexes due to anaesthesia, and it is difficult to extrapolate these data to a spontaneously breathing patient group in ED.

In spontaneously breathing subjects preload responsiveness is often assumed to be a normal cardiovascular phenomenon [4] - according to Frank-Starling experiment. However previous studies examining the effects of postural change on CO in human volunteers have used heterogeneous methods and given inconsistent results. The rate of preload responsiveness to PLR in spontaneously breathing, healthy volunteers ranged from 18.5% to 90% with a mean change in SV or CO of 2.4-23.6%.[12-17] In this context, little focus was paid to TEB which we considered to be the most practical method in ED.

This leave us uncertain of the effect of a PLR test in normal subjects. As the definition of 'normal' is required before 'abnormal' can be studied, we chose a non-invasive CO based method (PLR-TEB) in order to define the haemodynamic response to PLR in spontaneously breathing volunteers.

METHODS

An experimental study was carried out, after obtaining the relevant ethical committee approval, on a convenience sample of volunteers in Leicester Royal Infirmary, UK between April and September 2016. A written informed consent was obtained from all participants. We included healthy subjects aged 18 years or above, and collected demographic data (age, sex and race), height and weight. Subjects were asked to sit semi-recumbent on a trolley with the backrest raised to give approximately 45° flexion at the hips. Baseline non-invasive blood pressure was recorded then a TEB monitor (Niccomo, Medis, Germany) was attached according to the manufacturer's recommendation: 2 electrodes to each side of the neck and 2 electrodes to each side of the lower chest (at the level of xiphysternum) in addition to 3 ECG electrodes.

Subjects were monitored in the semi-recumbent position for at least 2 minutes. PLR1 was performed by tilting the whole trolley to bring the trunk as close as possible to supine position with the legs elevated up to 45° for 3 minutes. Subjects were then returned to semi-recumbent position for 6 minutes. The procedure was then repeated to give PLR2.

TEB data were transferred to Microsoft Excel (Microsoft Corporation, United States) and data on CO, SV and HR were extracted. A minute by minute average was calculated for each parameter across the whole time series. To evaluate the overall trend, each parameter was averaged across the study cohort. To estimate preload responsiveness we considered the haemodynamic variables at 5 time periods: Baseline1, the minute immediately before leg raise; PLR1, the middle 1-minute of PLR1; Baseline2, the minute immediately before PLR2; PLR2 the middle 1-minute of the second test and Baseline3, 2 minutes after PLR2.

Descriptive data were presented as means with 95% confidence interval (CI), medians with interquartile ranges (IQR) and proportions as appropriate. Data analysis was performed using Graphpad Prism 7 (California, United States). Correlation between the 2 PLRs was assessed using Spearman's r (r_s). Categorical agreement between PLR1 and PLR2 was evaluated using Cohen Kappa with preload responsiveness defined as ≥10% increase of SV. Parametric and non-parametric tests were used as appropriate to evaluate statistical significance of baseline variables between responders and non-responders. A two-sided p value of less than 0.05 was considered to indicate statistical significance with no correction for multiple comparisons.

RESULTS

We enrolled 50 volunteers, all haemodynamically stable at baseline, of whom 49 completed the study procedure (one procedure aborted due to nausea in a subject with pre-existing vertigo). One dataset was excluded due to accidental deletion during data transfer. We found that the method was feasible, as adequate signal quality was obtained in the remaining 48 patients throughout the monitoring sessions (Table 1).

Table 1 Baseline characteristics of responders and non-responders

	All subjects n=48	Responders n=22	Non-responders n=26	p Value
Age	35 (26-50)	47 (30-54)	32 (23-37)	0.0076**
Female gender, n (%)	30 (63)	16 (76)	14 (52)	0.1331
Ethnicity Caucasian Other	 35 (73) 13 (27)	 17 (81) 4 (19)	 18 (67) 9 (33)	0.3377
BMI	25 ± 4.1	25 ± 4.5	25±4	0.7722
SBP (mmHg)	123 ± 14	125 ± 15	120 ± 13	0.2542

DBP (mmHg)	70 ± 10	73 ± 11	67 ± 8	0.0273**
MAP (mmHg)	87 ± 10	91 ± 12	85 ± 9	0.0591
Heart rate (bpm)	66 ± 9	67 ± 10	65 ± 7	0.3274
Stroke volume (mL/min)	94 ± 21	81 ± 14	104 ± 20	0.0001**
Cardiac output (L/min)	6.1 ± 1.4	5.4 ± 1.2	6.7 ± 1.3	0.0013**
Impedance* (Ohm)	33 (30-38)	33 (31-38)	32 (29-37)	0.2146
ICG quality indicator (%)*	94 (86-98)	87 (80-96)	95 (91-98)	0.0772
Data presented as median (interquartile range), mean ± standard deviation or proportions as appropriate *TEB signal quality indicators throughout the whole monitoring session ** Statistically significant, $p < 0.05$				

Haemodynamic changes during PLR

- Between subjects variability (overall effect of PLR)

A stable SV and CO measurement was seen during Baseline1 followed by an immediate increase after PLR1 and then a gradual fall within 2-3 minutes during baseline2. A similar pattern was observed in PLR2. The HR did not show any specific pattern related to PLR (Figure 1).

At Baseline1 subjects had a median SV of 88 (IQR, 78-110) compared to 101 (IQR, 91-120) during PLR1, with a similar change during PLR2. CO followed a similar pattern, but HR did change significantly with either PLR (Table 2).

Table 2 Haemodynamic changes during passive leg raise

	Baseline 1	PLR 1	Baseline 2	PLR 2	Baseline 3
SV (mL)	88 (78-110)	101 (91-120)*	90 (80-106)*	101 (88-115)*	86 (74-102)*
CO (L/min)	6.2 (5-7.3)	7 (5.8-7.7)*	6.2 (4.9-7.2)*	6.8 (5.3-7.7)*	5.6 (4.7-7)*
HR (bpm)	65 (60-71)	65 (59-74)	65 (58-72)	64 (58-71)	65 (57-71)

Data presented as median (interquartile range)
* statistically significant change (P < 0.05)

- Within subject variability (individual preload responsiveness)

The median SV response (∆SV) was 8% (IQR, 4-20%) in PLR1 and 8% (IQR, 3-14%) in PLR2. CO response (∆CO) was 12% (IQR, 4-18%) and 8% (IQR, 2-14%) in PLR1 and PLR2 respectively. Heart rate changed more during PLR1 compared to PLR2 with a ∆HR of 1.5% (IQR, -2-3.5%) and -0.6% (IQR, -3-2.6%) respectively. Negative, but non-significant correlation was found between ∆HR and ∆SV in both PLR1 and PLR2 – r_s = -0.14 (95% CI -0.41 to 0.16) and -0.17 (95% CI -0.44 to 0.13) respectively.

Using a change of ≥10% to define a positive response, 48% of subjects had a positive SV response in PLR1 compared to 44% in PLR2. The distribution of ∆SV compared to baseline SV is shown in (Figure 2).

Reproducibility of PLR

- Correlation and concordance

The ∆SV in the 2 PLRs was correlated (r_s = 0.68, 95% CI 0.49 to 0.8) with 85% positive concordance. Similar correlation observed for ∆CO (r_s = 0.62, 95% CI 0.4 to 0.77) with 77% positive concordance (Figure 3).

- Agreement

Good categorical agreement was observed for a ≥10% response, with Cohen Kappa of 0.67 (95% CI, 0.45 to 0.88) for ∆SV compared to moderate agreement for ∆CO (0.5; 95% CI, 0.26 to 0.74), Table 3.

Table 3 Agreement of stroke volume and cardiac output responsiveness

		PLR 1	
		SV Responsive	SV Unresponsive
PLR 2	SV Responsive	18	3
	SV Unresponsive	5	22

Good agreement: Kappa = 0.67, 95% confidence interval, 0.45 to 0.88

		PLR 1	
		CO Responsive	CO Unresponsive
PLR 2	CO Responsive	19	4
	CO Unresponsive	8	17

Moderate agreement: Kappa= 0.5, 95% confidence interval, 0.26 to 0.74

Responders vs non-responders

Preload responders (≥10% increase in SV) had median ΔSV of 21% (IQR, 13-32) and median ΔCO of 19% (IQR, 15-32) compare to 4% (IQR, 2-6) and 5% (IQR, 1-9) in non-responders. ΔHR was similar in both groups: 1% (IQR, -2-3) and 2% (IQR, -2-5) in responders and non-responders respectively.

When divided by preload response the responders had significantly lower baseline SV and CO (81 ± 14 and 5.4 ± 1.2 vs 104 ± 20 and 6.7 ± 1.3 in non-responders). Age was significantly higher in responders, 43±13 vs 33± 12 in non-responders (Table 1).

LIMITATIONS

This is one of the largest studies of preload responsiveness in healthy volunteers, however, it has a number of limitations: There is lack of older subjects, which may affect the generalisability of our results to this group of patients. We have recruited a convenience sample which may be subject to selection bias. The procedure was carried out by a single operator (MHE) so we cannot present any data on inter-rater reliability. However, some variability of PLR technique has been reported in the literature – but with no reported impact on results [18]. We did not mandate a regime of diet or adequate hydration before the test, so there may have been variation in the volunteer's volume status, which might have affected the results. However, all subjects should still have been within the physiological range and we wanted to capture normal variation.

DISCUSSION

This is the first series of TEB-PLR testing in healthy subjects, and demonstrates that the PLR-TEB test was feasible, reasonably reproducible and positive in about half of our healthy subjects, at a 10% change threshold. This evidence is the first step to evaluating whether the widespread ICU use of this technique can be translated into emergency care.

The feasibility of monitoring in non-ventilated subjects was shown by adequate TEB signals throughout the monitoring sessions with a clear overall pattern (Figure 1). The one subject

who was unable to complete the protocol had a pre-existing medical condition (vertigo) that may have contributed to the feeling of nausea. This suggests that TEB can probably be used to assess short-lived CO changes in awake, spontaneously breathing patients in ED. However, there is likely to be more signal variation ('noise') in the less controlled environment of the sick patient in the ED, so feasibility in the real life situation also needs to be established.

The test had a reasonable reproducibility, and the overall pattern of increased SV and CO, but little change in HR was seen across all subjects (Figure 1). A similar pattern was seen in previous volunteer studies.[16 17] However, in Godfrey et al. study, cardiac index (CI) changes to PLR had a greater contribution from HR than SV.[15] This may be related to their use of maximum HR change during the whole PLR duration, which may not be matched in time to maximum SV and CI values. In our study, we calculated the mean value for each parameter at a fixed time period during PLR to avoid this (Table 2).

Heart rate changed more during PLR1 giving rise to more prominent CO changes compared to SV. This may be due to less pronounced neurologic reflexes during PLR2 (habituation). While ΔCO is the outcome of changes in SV and HR, it is difficult to ascertain whether heart rate change is part of the response or merely a sympathetic reflex. Monnet and colleagues suggested that *"A misleading sympathetic stimulation can be suspected if PLR is accompanied by a significant increase in heart rate, which normally should not occur*".[6] There is probably a complex interplay between the three variables.

Better correlation, concordance and agreement between PLR1 and PLR2 were observed for SV changes than CO changes. While both indices had been previously used interchangeably in the literature,[19] they have not been previously well compared and our results suggest that SV may be a better measure in spontaneously breathing patients due to less variability.

There is some variation in the current literature about the length of time to keep the legs raised in a PLR test and the time frame for assessing the effects of PLR. We undertook a 3 minute test, however Figure 1 shows that the change happens within one minute as the PLR induced a fast SV response that was sustained during the leg raise and completely reversible afterwards (within around 2 minutes). This finding raises the potential for using a 1 minute PLR test in the ED, as this might be more acceptable to acutely unwell patients and busy staff. A sustained PLR effect up to 10 minutes was observed in previous studies[20] and these effects have been shown to fade out quickly after the test in ICU studies.[5] It has been suggested that a sustained response after return to baseline position may be inherently related to disease and not the cardiac preload changes.[6] However, the basis for this postulation is unclear.

We have shown that about half of our subjects had a positive response (using the conventional ≥ 10% increase in SV) with PLR. Previous work on normal volunteers, using different cardiac monitoring methods, has shown a similar rate of responsiveness to PLR at a 10-15% threshold.[15-17] A systematic review by the authors showed a responsiveness rate of 31% to 79% in 8 heterogeneous studies of ED patients.[21] A meta-analysis of studies evaluating PLR (most in ventilated ICU patients) found 54 ± 9% positive response rate to the reference fluid challenge.[18] The positive responders among these sick patients had a mean CO increase of 20 ± 9% with PLR, which is similar to our findings in healthy non-ventilated responders.

Baseline SV and CO in our study were significantly lower in responders (Figure 2), which may imply that responders had a higher available physiologic reserve as they were operating on the lower bounds of SV/CO. However, responders also had a significantly higher age, so an alternative interpretation is that the positive PLR test in older volunteers may be due to a less compliant circulation. DBP was higher in responders, which may be due to higher vascular resistance (less compliance) in this group of patients leading to more preload responsiveness. It may be that our younger subjects were compensating for the effects of the PLR with vaso-motor changes – physiological effects that are more like those seen in children, who have a relatively fixed SV.

The age effect is an indication of the complexity of the multiple factors which are involved in the response to any preload responsiveness test. It may be that a negative response can be explained by being on the flat part of the Frank-Starling curve (unlikely to benefit from fluid therapy). However, there are many other ways in which the circulation may respond to a preload challenge that do not involve a change in SV/CO.[22] For example, if there is central venodilation as an autonomic response to the PLR test there will be no actual 'preload challenge' to the heart and so no change in SV/CO. All of these physiological responses will be more complex in spontaneously breathing patients as they have a more intact autonomic system. This implies that the existing literature on PLR in ICU may not be applicable to the ED setting, and that the test may be more complex to interpret.

We found that most normal volunteers responded in a positive direction to PLR. When compared to the previously defined 10% 'clinically significant change' threshold, about half were positive. The 10% threshold seems to have become 'standard' in the ICU literature derived from the estimated precision of thermodilution.[23] We forward the interested reader to the work of Critchley in the analysis of precision limits in cardiac output monitoring.[24 25]

Our results coupled with the variation seen in the existing literature lead us to challenge the current assumption (based on the Staling Curve) that a positive response to preload challenge is normal. Many 'normal' subjects do not have a positive response and there seem to be more complex response patterns that occur in different groups of patients. Understanding this variation is an important area for future investigation. It is unlikely that the same threshold is optimal for every method and situation (patient group and underlying disease). Therefore, it is difficult to see how a test (PLR with a 10% threshold) in which 50% of normal volunteers are 'positive' could be useful in emergency care.

It could be that we do not need a single diagnostic threshold. The term 'testing preload responsiveness' may be causing to incorrectly think that we are discussing a diagnostic test, and it may be better to use the term 'monitoring preload responsiveness'. Many of the haemodynamic parameters that are well-established in daily use (e.g. blood pressure and heart rate) have the sort of complex physiology and inter-subject variation that we have seen in our human volunteer study. Just because a cardiovascular measurement has a complex underlying physiology does not mean that it is not potentially useful. The utility of these parameters does not depend on their ability to precisely separate heath and disease, but on giving the clinician an insight into the cardiovascular response to both the disease and the treatment. Thinking of preload responsiveness as an additional cardiovascular parameter to

be monitored, rather than a dichotomous diagnostic test, may resolve some of the current difficulties in its interpretation.

CONCLUSION

Our results suggest that the PLR-TEB test is feasible in spontaneously breathing volunteers with reasonable test / retest reproducibility. The age and baseline stroke volume effect suggest a more complex underlying physiology than commonly appreciated. The fact that half of the volunteers had a positive preload response, against the conventional 10% threshold, leads to questions about how this measurement should be used in emergency care, and will help shape future patient studies.

COMPETING INTERESTS

None declared.

ACKNOWLEDGEMENTS

The authors would like to thank the staff and students at the University of Leicester, UK who volunteered to this study. MHE would like to thank the Ministry of Higher Education – Missions Sector, Egypt and the British Council for their support through Newton-Mosharafa Fund.

REFERENCES

1. Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis. New England Journal of Medicine 2017;**376**(23):2223-34.
2. Maurer C, Wagner JY, Schmid RM, et al. Assessment of volume status and fluid responsiveness in the emergency department: a systematic approach. Medizinische Klinik - Intensivmedizin und Notfallmedizin 2015:1-8.
3. Michard F, Teboul J-L. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. CHEST Journal 2002;**121**(6):2000-08.
4. Marik P, Lemson J. Fluid responsiveness: an evolution of our understanding. British journal of anaesthesia 2014:aet590.
5. Cherpanath TG, Hirsch A, Geerts BF, et al. Predicting Fluid Responsiveness by Passive Leg Raising: A Systematic Review and Meta-Analysis of 23 Clinical Trials. Crit Care Med 2016;**44**(5):981-91.
6. Monnet X, Teboul J-L. Passive leg raising: five rules, not a drop of fluid! Critical Care 2015;**19**(1):18.
7. Elwan MH, Hue J, Green SJ, et al. Thoracic electrical bioimpedance versus suprasternal Doppler in emergency care. Emergency Medicine Australasia 2017.
8. Guinot PG, Bernard E, Defrancq F, et al. Mini-fluid challenge predicts fluid responsiveness during spontaneous breathing under spinal anaesthesia: An observational study. Eur J Anaesthesiol 2015;**32**(9):645-9.
9. Lorne E, Mahjoub Y, Diouf M, et al. Accuracy of impedance cardiography for evaluating trends in cardiac output: a comparison with oesophageal Doppler. British journal of anaesthesia 2014:aeu136.

10. Summers RL, Shoemaker WC, Peacock WF, et al. Bench to bedside: electrophysiologic and clinical principles of noninvasive hemodynamic monitoring using impedance cardiography. Academic Emergency Medicine 2003;**10**(6):669-80.
11. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Critical Care Medicine 2017;**45**(3):486-552.
12. Peachey T, Tang A, Baker EC, et al. The assessment of circulating volume using inferior vena cava collapse index and carotid Doppler velocity time integral in healthy volunteers: a pilot study. Scand J Trauma Resusc Emerg Med 2016;**24**(1):108.
13. Miller J, Ho CX, Tang J, et al. Assessing Fluid Responsiveness in Spontaneously Breathing Patients. Academic Emergency Medicine 2016.
14. Vårtun Å, Flo K, Acharya G. Effect of passive leg raising on systemic hemodynamics of pregnant women: a dynamic assessment of maternal cardiovascular function at 22–24 weeks of gestation. PloS one 2014;**9**(4):e94629.
15. Godfrey G, Dubrey S, Handy J. A prospective observational study of stroke volume responsiveness to a passive leg raise manoeuvre in healthy non-starved volunteers as assessed by transthoracic echocardiography. Anaesthesia 2014;**69**(4):306-13.
16. Delerme S, Castro S, Freund Y, et al. Relation between pulse oximetry plethysmographic waveform amplitude induced by passive leg raising and cardiac index in spontaneously breathing subjects. The American journal of emergency medicine 2010;**28**(4):505-10.
17. Keller G, Cassar E, Desebbe O, et al. Ability of pleth variability index to detect hemodynamic changes induced by passive leg raising in spontaneously breathing volunteers. Critical Care 2008;**12**(2):1-7.
18. Monnet X, Teboul J. Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis. Intensive Care Medicine Experimental 2015;**3**(Suppl 1):A587.
19. Toscani L, Aya HD, Antonakaki D, et al. What is the impact of the fluid challenge technique on diagnosis of fluid responsiveness? A systematic review and meta-analysis. Critical Care 2017;**21**:207.
20. Geerts BF, van den Bergh L, Stijnen T, et al. Comprehensive review: is it better to use the Trendelenburg position or passive leg raising for the initial treatment of hypovolemia? Journal of clinical anesthesia 2012;**24**(8):668-74.
21. Elwan MH, Roshdy A, Elsharkawy EM, et al. The haemodynamic dilemma in emergency care: Is fluid responsiveness the answer? A systematic review. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine 2017;**25**(1):25.
22. Oscier C, Cecconi M. Goal-directed therapy to maintain haemostasis. Best Practice & Research Clinical Anaesthesiology 2016;**30**(2):217-28.
23. Stetz CW, Miller RG, Kelly GE, et al. Reliability of the Thermodilution Method in the Determination of Cardiac Output in Clinical Practice 1, 2. American Review of Respiratory Disease 1982;**126**(6):1001-04.
24. Critchley LA, Lee A, Ho AM-H. A critical review of the ability of continuous cardiac output monitors to measure trends in cardiac output. Anesthesia & Analgesia 2010;**111**(5):1180-92.
25. Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. Journal of clinical monitoring and computing 1999;**15**(2):85-91.