JOURNAL of ANESTHESIA and PERIOPERATIVE MEDICINE

Original Article

Fluid Responsiveness Assessment Using Passive Leg Raising Test to Reduce Fluid Administration and Weight Gain in Patients with Septic Shock

Maria Cronhjort[1,2], Magnus Bergman[2], Eva Joelsson-Alm[1,2], Mona-Britt Divander[2], Emma Jerkegren[2], Anca Balintescu[2], Johan Mårtensson[3,4], and Christer Svensen[1,2,5]

ABSTRACT

Background: Several observational studies have demonstrated an association between fluid accumulation and mortality in sepsis. Our aim was to determine if assessment of fluid responsiveness by a passive leg raising (PLR) algorithm could reduce fluid accumulation after 3 days in the intensive care unit (ICU) in patients with septic shock.

Methods: This was an open-label single-centre randomised clinical trial performed in a surgical ICU in a tertiary centre in Stockholm, Sweden. We randomised adult (>18 years) patients with septic shock admitted to the ICU to a PLR group or a standard of care group. An increase in stroke volume index of at least 10% on the PLR test was required for the clinician to administer a fluid bolus to patients in the PLR group.

Results: We randomised 34 patients. The mean (SD) weight gain after three full ICU-days was 0.6 ± 3.2 kg in the PLR group and 1.3 ± 3.9 kg in the control group (P = 0.59). The median (IQR) amount of administered resuscitation fluid during the study period was 2103 (1283-2645) ml in the PLR group and 2408 (954-5045) ml in the control group (P = 0.38). We could implement a protocol that required a positive PLR-test before administration of resuscitation fluids, but recruitment rate was low. The trial was terminated early for futility.

Conclusion: The PLR protocol was not meaningful in our clinical setting, as weight gain was already low in the control group. To increase feasibility of a trial which implements a PLR-test we recommend using a non-invasive hemodynamic measurement, to include restriction of maintenance fluids in the protocol and to investigate the level of weight gain in the setting where the trial is to be performed before the start of the trial. (Funded by Stockholm County Council; ClinicalTrials.gov number, NCT02301585.)

From the [1]Department of Clinical Science and Education, Karolinska Institutet, Stockholm, Sweden; [2]Department of Anaesthesiology and Intensive Care, Södersjukhuset, Stockholm, Sweden; [3]Department of Physiology and Pharmacology, Section of Anaesthesia and Intensive Care Medicine, Karolinska Institutet, Stockholm, Sweden; [4]Department of Intensive Care, Austin Hospital, Melbourne, VIC, Australia; [5]The University of Texas Medical Branch UTMB Health, Department of Anesthesiology, John Sealy Hospital, Galveston, USA.

Correspondence to Dr. Maria Cronhjort at maria.cronhjort@sll.se.

Citation: Maria Cronhjort, Magnus Bergman, Eva Joelsson- Alm, Mona-Britt Divander, Emma Jerkegren, Anca Balintescu, et al. Fluid Responsiveness Assessment Using Passive Leg Raising Test to Reduce Fluid Administration and Weight Gain in Patients with Septic Shock. *J Anesth Perioper Med* 2017; 4 : x- xx. doi: 10.24015/JAPM.2016.0049

Optimal use of fluids in the management of septic shock is a major challenge. Unfortunately, commonly used parameters, such as clinical examination, blood pressure and central venous pressure (CVP) are unreliable predictors of fluid responsiveness (1-3). Accordingly, it has been suggested that static parameters should be replaced by dynamic parameters such as pulse pressure variation (PPV) and stroke volume variation (SVV) to assess hemodynamic status (4). These dynamic parameters require controlled mechanical ventilation with tidal volumes ⩾8 ml/kg and a regular heart rate. In a trial by Richard et al., these requirements were only fulfilled in 4% of test situations (5). In contrast to PPV and SVV, a passive leg raising (PLR) test can be used in patients with spontaneous breathing and irregular cardiac rhythm and may therefore be a more useful test of fluid responsiveness in critically ill patients (6). PLR is a simple test, but to be reliable it requires evaluation by cardiac output monitoring. The monitoring techniques validated for use in septic patients are invasive; pulmonary artery catheter (PAC) measurements, transpulmonary thermodilution (TPTD) assessments (7, 8) and lithium dilution techniques (9). New non-invasive techniques are promising but there are conflicting data regarding measurement performance (10).

Implementation of a PLR test in critically ill patients should make it possible to individualize fluid therapy, thus avoiding unnecessary fluid administration and reducing potentially harmful fluid accumulation (11). The PLR test has only been used in two clinical trials (5, 12). None of them measured the effect of the PLR test on fluid balance or weight gain as primary outcome. The trial by Richard et al. showed a significantly higher volume of median daily resuscitation fluid in the control group compared to the PLR group ($P = 0.04$) (5). It is, however, still unclear whether individualization of fluid therapy by means of a PLR test could reduce fluid overload and improve patient outcomes.

In this study, we aimed to reduce fluid administration and thus weight gain by restricting resuscitation fluids to patients who were considered fluid responsive by a PLR test. We hypothesized that implementation of a hemodynamic algorithm based on a PLR test for evaluation of fluid responsiveness would reduce weight gain on day 3 from 7% to 4% in patients with septic shock compared to standard care.

METHODS

This was an open-label single-centre randomized clinical trial performed in a surgical ICU in a tertiary centre in Stockholm.

Ethical approval and registration of trial

Ethical approval was obtained from the Ethical Review Board of Stockholm (EPN 2013/1337-31/2) and the trial was registered at clinicaltrial.gov (NCT02301585). Informed consent was obtained from patients or next-of-kin before enrolment in the trial. The trial was performed in accordance with the 1964 Helsinki declaration and its later amendments.

Eligibility

The inclusion criteria were septic shock, defined as ⩾ 2/4 Systemic Inflammatory Response Syndrome (SIRS) criteria, a need for vasopressors despite fluid administration of ⩾30 ml/kg of crystalloid fluids, and a suspected or confirmed infection. The exclusion criteria were >12 hours since onset of septic shock, a contraindication to a femoral or axillary arterial line (severe atherosclerosis visible with ultrasound or previous surgery on the vessels), hip fracture or other pathology that would render the PLR-test painful, femoral amputation, the clinical suspicion of elevated intra-abdominal pressure, an elevated intracranial pressure or imminent death (within 24 hours). We used an electronic randomization process based on a randomization list uploaded to the electronic case report form (eCRF). As patients were eligible and an informed consent had been provided, patients were allocated 1:1 to the PLR group or the control group using permuted blocks of varied sizes (6-10 patients) by the researchers or the treating clinician. The study period was from the time of inclusion until the end of 3 full days. Data on patient characteristics, hemodynamic response and fluid therapy were collected for 3 full days or until ICU discharge. If the patient was discharged from the ICU before 3 full days, the patient was weighed on the ward by the researchers.

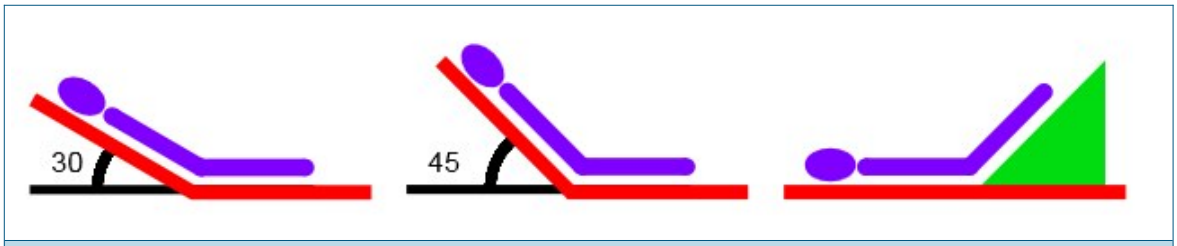


Figure 1. The Performance of The PLR Test.
We performed the PLR test as follows: hemodynamic measurements were done with the patient in a supine position with the Head-of-Bed (HOB) elevated to 30◦. We measured mean arterial pressure (MAP), pulse rate, cardiac index (CI) and stroke volume index (SVI). We then elevated the HOB to 45◦ for two minutes. We adjusted the bed to a flat position with HOB 0◦ and placed a triangular 45◦ pillow under the legs. After two minutes in the PLR-position we performed the same hemodynamic measurements.

Hemodynamic protocol

In the PLR group, the protocol was applied when the clinician considered it necessary to administer a fluid bolus. A PLR test was then performed to determine whether the patient was fluid responsive or not. Hence, the PLR tests were not scheduled on a regular time-basis. We performed the PLR test as follows: hemodynamic measurements were done with the patient in a supine position with the Head-of-Bed (HOB) elevated to 30°. We measured mean arterial pressure (MAP), pulse rate, cardiac index (CI) and stroke volume index (SVI). We then elevated the HOB to 45° for two minutes. We adjusted the bed to a flat position with HOB 0° and placed a triangular 45° pillow under the legs. After two minutes in the PLR-position we performed the same hemodynamic measurements. We then removed the pillow and repositioned the patient to the original position with a HOB elevation of 30° (Figure 1). The PLR test was performed from the 45° semi-recumbent position as this induces a larger increase in cardiac preload than a test from the supine position (13). An increase in stroke volume index (SVI) by 10% or more was regarded as a positive result allowing the clinician to administer intravenous fluid therapy. Choice of fluid type, fluid volume and rate of fluid administration was left to the discretion of the treating clinician (Figure 2). If the SVI increased less than 10% administration of fluid was not allowed. A subsequent PLR-test was required if the treating clinician deemed an additional fluid bolus necessary. The control group was treated at the clinicians' discretion. It was allowed to monitor the controls by TPTD, but not to perform any PLR tests in these patients.

Measurements of weight and stroke volume index

We measured weight in the ICU bed (TotalCare SpO2RT®, Hill-Rom Chicago, IL) according to a standardized ward protocol. According to the user manual, the accuracy of the scale was ±1% of patient weight and the precision was ± 0.3% within the range of 70.5-79.4 kg. The precision was ±0.1% within the range of 79.5-181.4 kg. Patients, who were discharged before the end of the study period of three full days, were weighed on the ward by the researchers using the same ICU-bed as was used during the ICU-stay. Measurements of cardiac index and SVI were performed with PiCCO® (Pulsion Medical Systems, Feldkirchen, Germany). Calibration with thermodilution was performed every 8 hours and in case of large fluctuations in norepinephrine dose. Primary outcome was weight difference from inclusion to day three. Planned secondary outcomes were 30-day mortality, ICU length of stay, cumulative fluid balance day three, number of days with mechanical ventilation, vasopressors/inotropic support and continuous renal replacement therapy, and ICU discharge status. However, since the trial was terminated early, only difference in weight, cumulative fluid balance, ICU length of stay and 30-day mortality are reported.

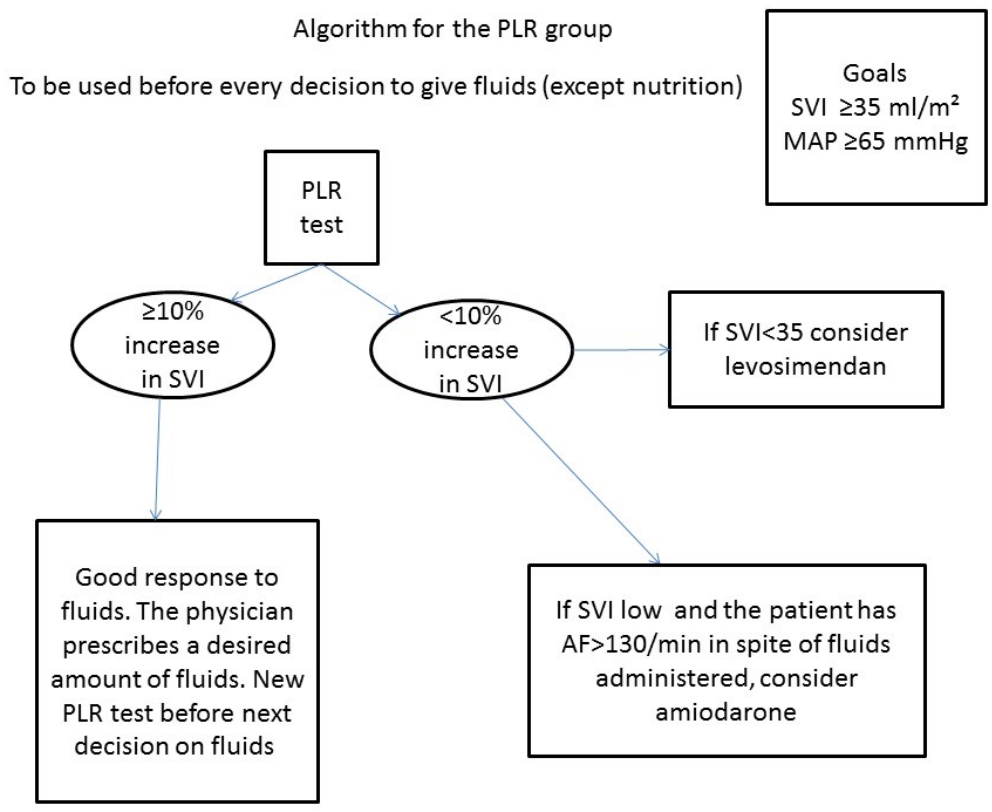


Figure 2. Hemodynamic Algorithm for The PLR Group.
PLR = Passive Leg Raising, SVI = Stroke Volume Index, MAP = Mean Arterial Pressure, AF = Atrial Fibrillation.

Statistical methods

We estimated that a sample size of 120 patients would be needed to detect a reduction in weight gain from 5 kg to 3kg in a 70 kg person (a reduction from 7% weight gain to 4% weight gain) with SD of 4 kg after three full fluid days with 80% power and $\alpha<0.05$. Thus, we planned to include 130 patients to compensate for potential drop-outs. We expected weight gain to be lower than in the Vasopressin in Septic Shock Trial (VASST) study, where mean cumulative fluid balance on day 4 was 11 ± 8.9 (11).

Descriptive statistics are means with standard deviation for continuous normally distributed data and medians with IQR for skewed data. We tested for normality by the Shapiro-Wilks test. For categorical data numbers and percentages are described. Continuous normally distributed data were analysed with independent samples t-test or ANOVA. Continuous data with skewed distribution were analysed with Mann-Whitney U-test. Categorical data were analysed by χ^2-test. In all tests, $P<0.05$ was regarded as statistically significant. We used IBM SPSS Statistics software version 22.0 (IBM Corp., Armonk, NY, USA) for statistical analyses.

RESULTS

We screened adult patients admitted to the ICU with suspected sepsis for inclusion between February 2014 and January 2016. We screened 79 patients for inclusion. The screening and randomization process is described in the CONSORT Flow diagram (Figure 3). Due to a low inclusion rate, we considered extending the study to other centres. Although not pre-planned, we performed an interim analysis to evaluate if it

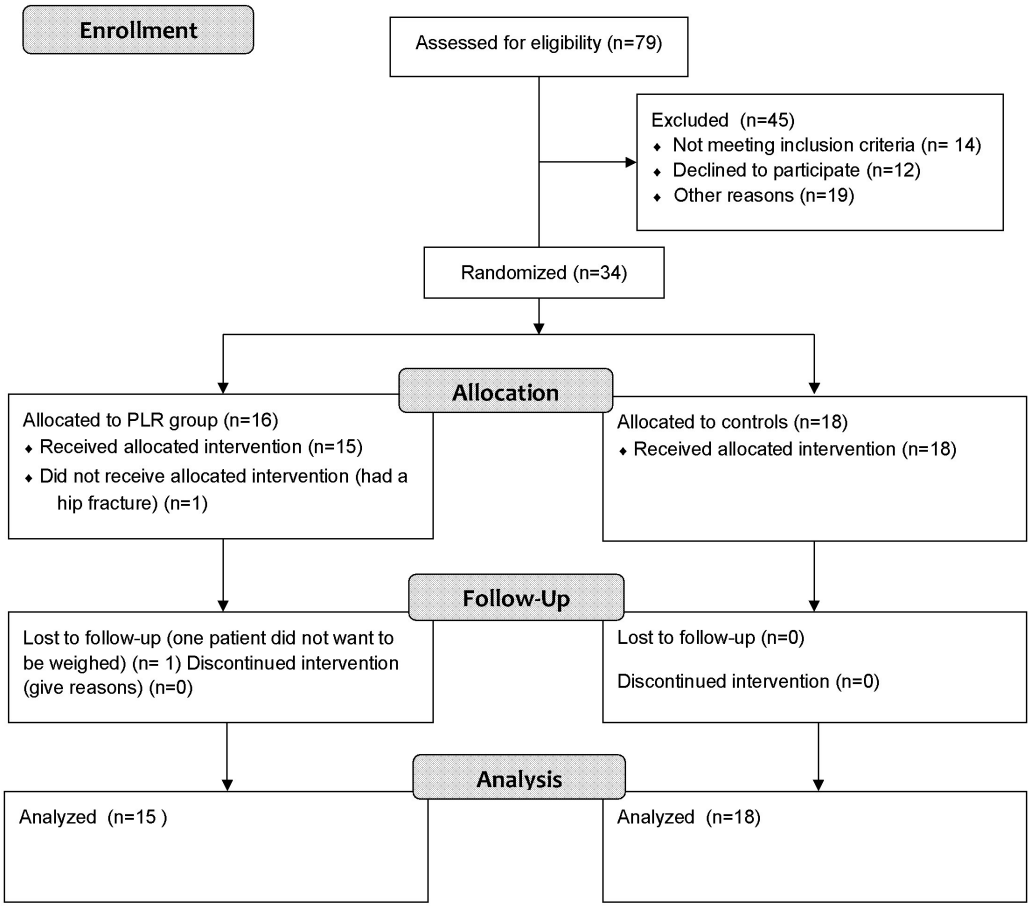


Figure 3. Flow Diagram for The PLR Trial.
The screening and randomization process is described in the CONSORT Flow diagram.

would be worthwhile to continue in other centres. We judged the difference in weight gain between the groups to be of minimal clinical importance. We thus decided to end the study instead of expanding to other centres. We randomised 34 patients; 16 patients to the PLR-group and 18 to the control group. One patient in the PLR group had a hip fracture and no PLR test could be performed. This patient was analysed according to an intention to treat approach. One patient in the PLR group refused to be weighed, and was thus included in the hemodynamic analyses but not in the analysis of primary outcome. The PLR group was slightly older, had fewer female patients and had lower creatinine at ICU-admission and a lower SOFA-score compared with the standard care group. None of these differences were statistically significant. The mean SAPS-3 score was similar, as was the primary source of sepsis (abdomen) (Table 1). The median (IQR) study time was 86.5 (81-92) hours in the PLR group and 86.5 (82-90) hours in the control group. In the PLR-group 31% were discharged from the ICU before the final weight measurement vs. 39% in the control group.

Complications

We experienced initial problems of bleeding following the removal of the femoral catheter in one patient. This led us to protocolize the use of a pressure application by compression equip-

Table 1. Patient Characteristics in The PLR Group and The Control Group.

	PLR (n = 16)	Controls (n = 18)	P- value
Age (years)	71 ± 11	66 ± 15	0.25
Weight (kg)	74 (62-79)	75 (56-93)	0.62
Female Sex	5 (31.3%)	10 (55.6%)	0.19
SAPS 3 score	64 ± 12	64 ± 10	0.85
Co-morbidities			
NYHA IV	0	0	
Liver cirrhosis	0	1(5.6%)	N/A
Disseminated cancer	2 (12.5%)	4 (22.2%)	N/A
Hematologic malignancy	0	0	
SOFA score at admission	5.9 ± 3.3	7.2 ± 2.2	0.25
Lactate at ICU admission mmol/l	2.2 (1.4-4.1)	2.5 (2.0-4.3)	0.48
Creatinine at ICU admission µmol/l	110 (54-194)	93 (64-220)	0.81
Surgery before admission	10 (62.5%)	9 (50%)	0.43
Time from ICU admission to randomization (hours)	5.0 (1.3-14)	5.0 (1.5-9.3)	0.65
Positive blood culture	7 (43.7%)	10 (55.6%)	0.87
Primary source of infection			
Lungs	4 (25.0%)	4 (22.2%)	N/A
Abdomen	9 (56.3%)	7 (38.9%)	0.49
Urinary tract	2 (12.5%)	1 (5.6%)	N/A
Soft tissue	1 (6.3%)	3 (16.7%)	N/A
CNS	0	0	
Unclear source	0	2 (11.1%)	N/A

Central measurements are means with standard deviation for continuous normally distributed data and medians with IQR for skewed data. For categorical data numbers and percentages are described.

ment (Femostop®, St. Jude Medical Systems AB, Uppsala, Sweden) for 60 minutes following the removal of the catheter. We also had one case of a femoral thrombosis following arterial cannulation that required surgical trombectomy. Thus, we had a rate of serious complications of 12.5% from the use of the PiCCO.

Outcome

The mean (SD) weight gain after three full days was 0.6 ± 3.2 kg in the PLR group and 1.3 ± 3.9 kg in the control group (P = 0.59). The median (IQR) amount of administered resuscitation fluid during the study period was 2103 (1283-2645) ml in the PLR group and 2408 (954-5045) ml in the control group (P = 0.38). The corresponding mean (SD) cumulated fluid balance was 1566 ± 3725 ml in the PLR-group and 2669 ± 2675 ml in the control group (P = 0.33) (Table 2). Thirty-day mortality was 12.5% in the PLR group and 11.1% in the control group (P = 1.00). Median (IQR) ICU length of stay was 141 (66-278) hours in the PLR group and 139 (43-251) hours in the control group (P = 0.73).

Hemodynamics

Mean SVI changed from 30.4 ± 8.4 ml/m2 to 33.1 ± 7.8 ml/m2 during the first PLR (P = 0.026), whereas CI, MAP and heart rate did not change significantly (Figure 4). The results of PLR occasion 2 and 3 are available in Appendix 1. We performed the PLR test 46 times, and it was positive 32 times (69%). The mean number of PLR-test per patient was 2.9 and the majority of the PLR tests were performed during the first day. Most patients had both positive and negative PLR tests during the study period. One patient was fluid unresponsive in all PLR tests. Compliance to give fluids following the protocol when the PLR test was positive was 100%. There were six protocol violations when fluid was administered without a prior PLR-test. The total amount of norepinephrine in the groups was nearly the same (Table 2).

DISCUSSION

This is the first clinical trial exploring the possibility of reducing weight gain in patients with septic shock by evaluation of fluid responsive-

Table 2. Hemodynamic Management in The PLR-Group and the Control-Group During The Study Period.

	PLR-group	Control-group	P-value
Total resuscitation fluid (ml)	2103 (1283-2645)	2408 (954-5045)	0.38
Total input (ml)	10646 (7851-12092)	10526 (6158-12902)	0.67
Total output (ml)	7960 ± 4028	7257 ± 3854	0.61
Cumulative fluid balance (ml)	1566 ± 3725	2669 ± 2675	0.33
Urinary output (ml)	6522 ± 4005	5474 ± 3888	0.45
Total dose Norepinephrine (mg/kg)	0.36 (0.15-0.59)	0.35 (0.14-0.69)	0.67
Number of patients with inotropy (n)	3 (18.8%)	4 (22.2%)	N/A

Cumulated values are up to day 3 or truncated at discharge from the ICU or death. Central measurements are means with standard deviation for continuous normally distributed data and medians with IQR for skewed data. For categorical data numbers and percentages are described.

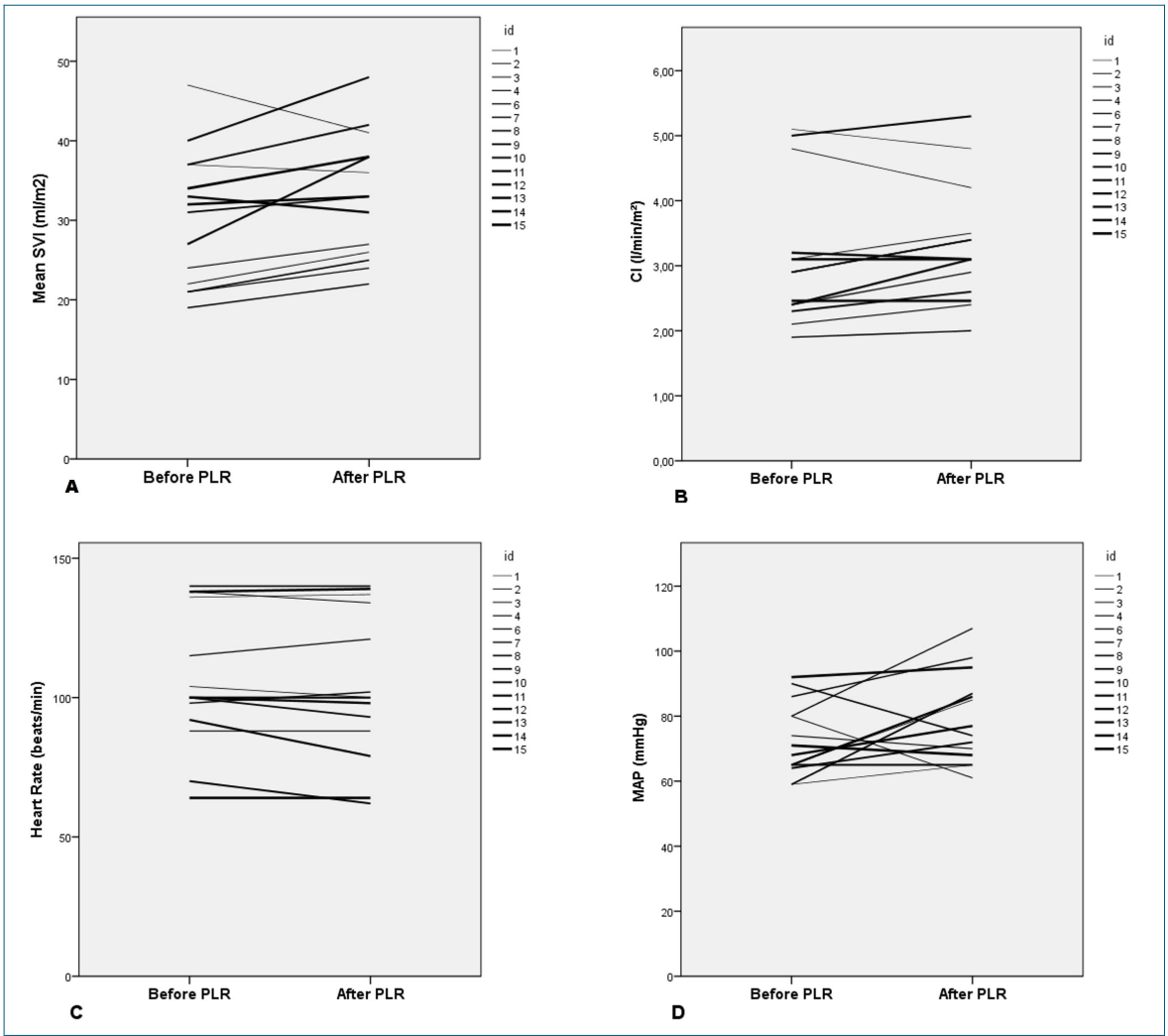


Figure 4. Hemodynamic Response to The First PLR Test in 14 Patients in The PLR Group. A. SVI before and after the first PLR test; B. CI before and after the first PLR test; C. Heart Rate before and after the first PLR test; D. MAP before and after the first PLR test.

ness by a PLR test. However, the magnitude of weight gain in the control group was too low for such an intervention to be meaningful. A possible explanation for the low weight gain in our control group is that the clinicians were influenced by the PLR protocol in their management of the controls (contamination bias). The contemporary scientific discussion on fluid management following studies that have shown an association between fluid balance and mortality (11, 14, 15) and recent multicenter trials that questioned the importance of early goal directed fluid therapy (16-18) might also have led the clinicians to a more restrictive fluid administration regimen in the controls (19).

We experienced a low inclusion rate. We screened nearly all patients with septic shock coming to our institution. However, some of them were recognized after more than 12 hours from the onset of septic shock (11 patients). This could partly be explained by lack of time to include patients during the night shift. The major time-consuming events were to find relatives to get informed consent prior to inclusion, and to insert the arterial line for the PiCCO® monitoring. If a patient was not included during the night, it was often too late to do it in the morning. Another PLR trial also experienced a low recruitment rate. Richard et al. included 60 patients in septic shock over six years (5). The introduction of a non-invasive cardiac output device that could replace the TPTD technique would minimize the effort demanded from the clinician to include patients.

Kuan et al. performed a PLR trial with higher recruitment rate (12). It was a clinical trial of a PLR test in patients with sepsis and elevated lactate levels in the emergency room. They used bioreactance, a non-invasive cardiac output monitoring technique, and performed PLR tests at regular intervals to ensure that patients who were fluid responsive received more fluids.

In this study, the PLR test was performed approximately 3 times per patient, and it was positive in 69% of the occasions. The PLR test was only performed when the clinicians wanted to administer fluids. Since the test was applied so few times, it is not astonishing that the difference in weight gain between the groups was small. It is possible that the protocol would have been more efficient in reducing weight gain if it could have been implemented already in the emergency room, where more patients might still have been in the resuscitation phase.

It is interesting that the difference in cumulative fluid balance was greater than the difference in the actual amount of resuscitation fluid. The amount of fluids administered for maintenance and drug administration during 3 days was 4 times higher than the amount of resuscitation fluid. To reduce weight gain during an ICU stay it might be important to also target fluid restriction as proposed by Chen et al. (20). They performed a feasibility trial where both a PLR test and fluid restriction were performed.

Hemodynamic monitoring was achieved with transesophageal Doppler in intubated patients and with continuous transthoracic Doppler in nonintubated patients. They found that the protocol was feasible and the median cumulative fluid balance day three was 3124 (IQR, 767-10103) ml in the controls and 1952 (IQR, 48-5003) ml in the PLR group. However, the important question is, if reducing fluid overload and thus weight gain improves patient outcome. A pilot trial of restrictive fluid management without advanced hemodynamic monitoring has been performed in patients with septic shock (21), where the restrictive protocol was safe regarding mortality, kidney injury and ischemic events. The impact of a restrictive protocol for resuscitation of septic patients' needs evaluation in large RCTs.

The poor precision of the bed scale (± 0.24 kg for a 79 kg person) might have attenuated our ability to detect a real difference in weight gain between the groups. Since the weight gain was lower than we expected, the potential influence of this was greater than we had expected. A problem with the accuracy of weighing in the bed is that it is easy to forget a pillow, blanket or other extra items in the bed. This could possibly have a greater impact on the results than the precision of the bed scale.

We used a 10% increase in SVI as a cut-off in the PLR-test, which corresponds to the recommended cut off ⩾10 ± 2% increase in CO. Other studies have chosen different cut-offs to define fluid responsiveness, ranging from 7%-15% increase in CI (22). A higher cut-off means a risk of classifying potentially fluid responsive patients as non-responsive. We chose 10% cut off, as it is easy to cal-

culate if the test is positive, and as a lower margin decreases the risk of withholding fluids from patients who might benefit from a fluid bolus.

Our study has several strengths. First, it applies the PLR test which has been held up as the best way to determine fluid responsiveness in critically ill patients (23). Another advantage is that fluids were not administered only because of fluid responsiveness, but rather the PLR test was used to restrict the fluid administration in patients where the clinician wanted to administer fluids. Thus, we reduced the problem that all patients who are fluid responsive do not necessarily require fluids. We used the PiCCO® monitoring device which correlates well with PAC thermodilution (24). We compared the effect of a PLR-based protocol to usual care. We evaluated the outcome by weight in ICU beds which is more robust than calculation of fluid balance (25).

The main weakness is that we terminated the study early. However, this attempt to find a way to guide clinical decision making on fluid administration might guide others who are planning to perform similar studies. It was a single-centre trial, with mainly surgical patients, which limits the generalizability. We experienced more complications than previously described from the PiCCO® monitoring. We therefore started to use a Femostop® device at removal of the catheter, which is not a requirement from the manufacturer of the PiCCO®.

CONCLUSION

We implemented a protocol that required a positive PLR-test before administration of resuscitation fluids, but recruitment rate was low. The trial was terminated early because of futility since weight gain in the control group was insignificant. To increase feasibility of a trial which implements a PLR-test we recommend using a non-invasive hemodynamic measurement, to include restriction of maintenance fluids in the protocol and to investigate the level of weight gain in the setting where the trial is to be performed before the start of the trial.

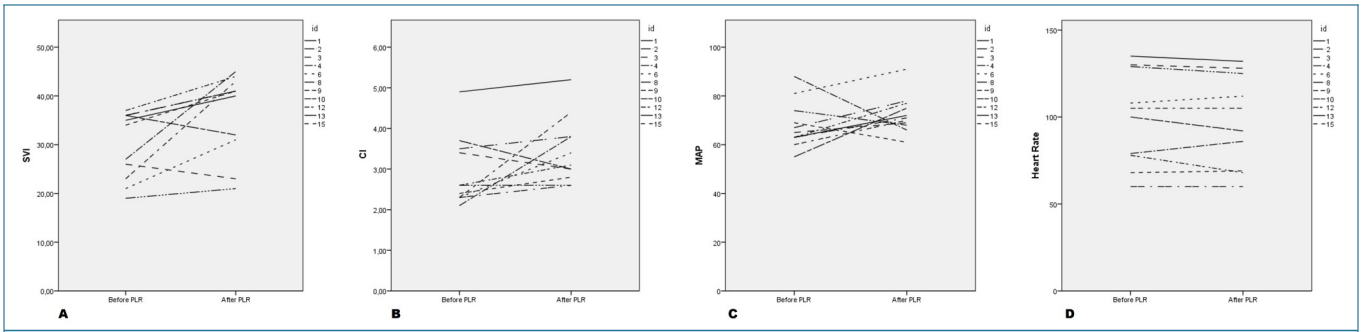
This study was supported by a research grant from the Stockholm County Council (Grant Number: 20130312). The authors have no other potential conflicts of interest for this work. The authors thank the clinical staff at the ICU of Södersjukhuset who made this trial possible by their willingness to adopt new ideas.

References

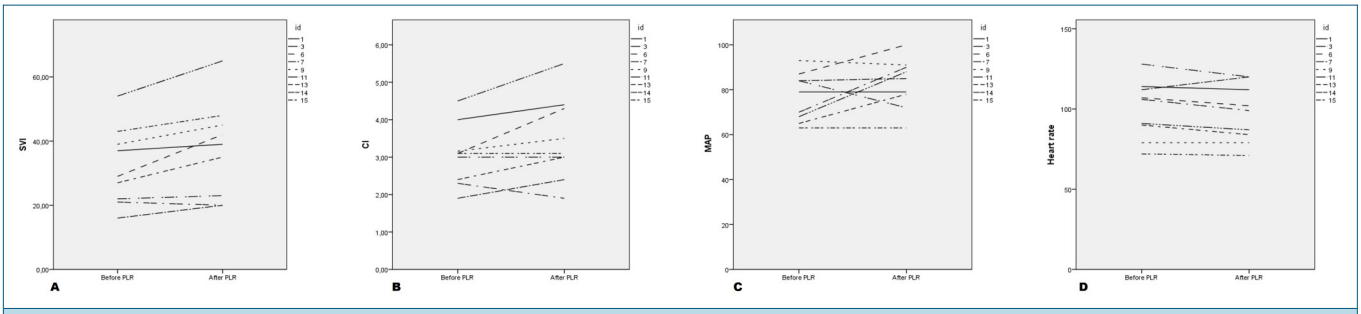
1. McGee S, Abernethy WB 3rd, Simel DL. The rational clinical examination. Is this patient hypovolemic? *JAMA* 1999;281(11):1022-9.
2. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest* 2008;134(1):172-8.
3. Pierrakos C, Velissaris D, Scolletta S, Heenen S, De Backer D, Vincent JL. Can changes in arterial pressure be used to detect changes in cardiac index during fluid challenge in patients with septic shock? *Intensive Care Med* 2012;38(3):422-8.
4. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med* 2014;40(12):1795-815.
5. Richard JC, Bayle F, Bourdin G, Leray V, Debord S, Delannoy B, et al. Preload dependence indices to titrate volume expansion during septic shock: a randomized controlled trial. *Crit Care* 2015;19:5.
6. Cavallaro F, Sandroni C, Marano C, La Torre G, Mannocci A, De Waure C, et al. Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta- analysis of clinical studies. *Intensive Care Med* 2010;36(9):1475-83.
7. Goedje O, Hoeke K, Lichtwarck- Aschoff M, Faltchauser A, Lamm P, Reichart B. Continuous cardiac output by femoral arterial thermodilution calibrated pulse contour analysis: comparison with pulmonary arterial thermodilution. *Crit Care Med* 1999;27 (11):2407-12.
8. Zollner C, Haller M, Weis M, Morstedt K, Lamm P, Kilger E, et al. Beat-to-beat measurement of cardiac output by intravascular pulse contour analysis: a prospective criterion standard study in patients after cardiac surgery. *J Cardiothorac Vasc Anesth* 2000;14 (2):125-9.
9. Linton RA, Band DM, Haire KM. A new method of measuring cardiac output in man using lithium dilution. *Br J Anaesth* 1993;71(2):262-6.
10. Saugel B, Cecconi M, Wagner JY, Reuter DA. Noninvasive continuous cardiac output monitoring in perioperative and intensive care medicine. *Br J Anaesth* 2015;114(4):562-75.
11. Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011;39(2):259-65.
12. Kuan WS, Ibrahim I, Leong BS, Jain S, Lu Q, Cheung YB, et al. Emergency Department Management of Sepsis Patients: A Randomized, Goal-Oriented, Noninvasive Sepsis Trial. *Ann Emerg Med* 2016; 67(3):367-78 e3.
13. Jabot J, Teboul JL, Richard C, Monnet X. Passive leg raising for predicting fluid responsiveness: importance of the postural change. *Intensive Care Med* 2009;35(1):85-90.
14. Micek ST, McEvoy C, McKenzie M, Hampton N, Doherty JA, Kollef MH. Fluid balance and cardiac function in septic shock as predictors of hospital mortality. *Crit Care* 2013;17(5):R246.
15. Sadaka F, Juarez M, Naydenov S, O'Brien J. Fluid resuscitation in septic shock: the effect of increasing fluid balance on mortality. *J Intensive Care Med* 2014; 29(4):213-7.
16. Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014;370(18):1683-93.
17. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015;372(14):1301-11.
18. Peake SL, Delaney A, Bailey M, Bellomo R, Cameron PA, Cooper DJ, et al. Goal- directed resuscitation for patients with early septic shock. *N Engl J Med* 2014;371(16):1496-506.
19. Marik P, Bellomo R. A rational approach to fluid therapy in sepsis. *Br J Anaesth* 2016;116(3):339-49.
20. Chen C, Kollef MH. Targeted Fluid Minimization Following Initial Resuscitation in Septic Shock: A Pilot Study. *Chest* 2015;148(6):1462-9.
21. Hjortrup PB, Haase N, Bundgaard H, Thomsen SL, Winding R, Pettila V, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. *Intensive Care Med* 2016;42(11):1695-705.
22. Monnet X, Marik P, Teboul JL. Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis. *Intensive Care Med* 2016;42 (12):1935-47.
23. Marik PE, Lemson J. Fluid responsiveness: an evolution of our understanding. *Br J Anaesth* 2014; 112(4):617-20.
24. Vincent JL, Rhodes A, Perel A, Martin GS, Della Rocca G, Vallet B, et al. Clinical review: Update on hemodynamic monitoring-- a consensus of 16. *Crit Care* 2011;15(4):229.
25. Perren A, Markmann M, Merlani G, Marone C, Merlani P. Fluid balance in critically ill patients. Should we really rely on it? *Minerva Anestesiol* 2011; 77(8):802-11.

Appendix

The following is the supplementary appendix to the article: Fluid Responsiveness Assessment Using Passive Leg Raising Test to Reduce Fluid Administration and Weight Gain in Patients with Septic Shock. *J Anesth Perioper Med* 2017; 4 : x- x. doi: 10.24015/ JAPM.2016.0049



Appendix Figure 1. Hemodynamic Response to The Second PLR Test in 11 Patients in the PLR Group.
A. SVI Before and after the second PLR test. The mean increase in SVI was 6.7 ± 7.8 ml/m2 (P = 0.015); B. CI before and after the second PLR test. The mean increase in CI was 0.51 ± 0.84 l/min/ m2 (P = 0.071); C. MAP before and after the second PLR test. The mean increase in MAP was 4.5 ± 12 mm Hg (P = 0.24); D. Heart rate before and after the second PLR test. The mean decrease in heart rate was 1.5 ± 5.1 beats/min (P = 0.38).



Appendix Figure 2. Hemodynamic Response to The Third PLR Test in 9 Patients in The PLR Group.
A. SVI Before and after the third PLR test. The mean increase in SVI was 5.4 ± 4.6 ml/m2 (P = 0.008); B. CI before and after the third PLR test. The mean increase in CI was 0.40 ± 0.50 l/min/ m2 (P = 0.042); C. MAP before and after the third PLR test. The mean increase in MAP was 5.9 ± 11 mm Hg (P = 0.15); D. Heart rate before and after the third PLR test. The mean decrease in heart rate was 2.8 ± 4.9 beats/min (P = 0.13).