

Volume responsive, but does the patient need volume?

Received: 26 November 2015 Accepted: 29 November 2015

© Springer-Verlag Berlin Heidelberg and ESICM 2016

J. Takala (🖂)

Department of Intensive Care Medicine, University Hospital Bern (Inselspital), 3010 Bern, Switzerland e-mail: jukka.takala@insel.ch Tel.: +41-31-632 4144

Rapid administration of intravenous fluid or a "fluid challenge" is one of the most common interventions in the intensive care patient with manifest or perceived hemodynamic problems. The concept of fluid administration to evaluate cardiovascular function in shock was probably first introduced by Max Harry Weil more than 50 years ago [1] and has been referred to as fluid challenge in textbooks and papers since the mid-1970s [2]. The fluid challenge was described as a concept to evaluate the ability of the heart to handle the fluid load in the presence of clinical signs and symptoms of insufficient circulation. A fundamental principle of fluid challenge was defined by Weil in 1965: "The effect of fluid replacement on the clinical status of the patient in shock is gauged by objective changes in circulation, such as blood pressure, mental alertness, urine flow, peripheral venous filling, and appearance and texture of the skin" [1]. Impaired tissue perfusion was already then recognized as a key defect in acute circulatory failure. Subsequently, administration of large volumes of fluids became popular in the management of the widest spectrum of disorders in intensive care patients. Much of this evolution can be traced back to misinterpretations and oversimplification

of basic physiology and pathophysiology—often accompanied by invasive hemodynamic monitoring with the pulmonary artery catheter.

CrossMark

Criticism against the apparently excessive and unnecessary volume loading started to evolve early: lung edema (including ARDS), edema in burns, surgical wounds, and gut were associated with excessive fluid loading [3–6], and positive fluid balance appeared as an independent predictor of mortality in various categories of critically ill patients [7].

The concept of predicting fluid responsiveness, an increase in cardiac output or its surrogates in response to fluid bolus, was introduced in clinical practice in the 1990s. Dynamic variations in systolic arterial pressure, arterial pulse pressure, or stroke volume induced by positive pressure ventilation have been used in attempts to guide volume administration. These approaches have several limitations, including highly variable predictive cutoff values, need for controlled mechanical ventilation without inspiratory efforts, and misleading results in the presence of right heart dysfunction. In order to avoid these problems, alternative approaches to predict fluid responsiveness have been developed. Perhaps the best documented is passive leg raising (PLR). The concept is simple: raising the patient's legs should enhance venous return by increasing the stressed volume. If this results in increased cardiac output, then the heart can handle a volume expansion. The advantage is that no volume needs to be given and the change in stressed volume should be reversible. The prerequisite for PLR is rapidly responsive, reproducible measurement of cardiac output or stroke volume.

In a recent article in *Intensive Care Medicine*, Monnet, Marik, and Teboul present a systematic review and metaanalysis of literature on the use of PLR to predict volume responsiveness [8]. They analyzed 21 studies including 991 patients and found in the pooled data that a PLRinduced increase of at least 10 % in cardiac output predicted an increase in cardiac output that was considered relevant in the original studies with a good pooled sensitivity and specificity. The increases in cardiac output considered relevant in the original studies ranged from more than 7 % to more than 15 %. Using surrogate markers resulted in poor sensitivity but good specificity.

The research group of Teboul et al. has had a leading role in testing and applying in clinical research the concept of predicting fluid responsiveness, with the laudable goal of avoiding unnecessary volume loading. It is not surprising that the bulk of the reviewed papers comes from their own work. Although evaluation of one's own work for quality and bias is itself susceptible to bias, publication bias of less well predictive results cannot be excluded, and the statistical approach can always be discussed, the physiologic and clinical message seems very clear: if cardiac output increases following PLR, it is also likely to do so following a fluid bolus. As pointed out by the authors, a standardized procedure including <u>starting</u> from a semirecumbent rather than horizontal supine position may augment the test effect.

The main issue concerning all attempts to predict fluid responsiveness is what to do with the results. Although the authors briefly discuss the crucial point that fluid responsiveness is not equal to need for fluid, this issue appears to have broad implications in clinical practice. As the recent European Society of Intensive Care Medicine supported **FENICE** survey shows, fluid challenges are repeated equally frequently regardless of whether the response to initial challenge was positive, uncertain, or negative [9]. Although the survey does not address specific techniques to evaluate the response to fluids. clinicians appear to be predisposed to give fluids even in patients considered to be non-responders according to the response criteria of their choice. The mere expression "fluid responsive" with its positive tone may predispose clinicians to give more fluids independent of whether the patient needs fluids. Indeed, being fluid responsive is

normal, whereas giving fluids until the patient is no longer fluid responsive equals creating a new pathologic state—a new iatrogenic problem.

Studies on fluid responsiveness indicate that around 50 % of the fluid challenges studied do not increase cardiac output, i.e., half of the patients are non-responders at the time of the fluid challenge—a surprisingly high proportion. Two very different mechanisms can explain the non-responsiveness. One is limitation of cardiac function; in this case giving more fluids is counterintuitive and may cause harm. The other one is failure to increase stressed volume; this may be due to too small a fluid bolus or slow infusion rate or, more importantly, ongoing vasodilation. Vasoconstriction is very common in hemodynamically unstable patients as a result of hypovolemia and administration of vasoconstricting drugs, and a relevant cause of tissue hypoperfusion. Vasodilatation is needed to restore the perfusion and more fluids will be necessary to maintain the stressed volume and avoid reduction of cardiac output. Importantly, cardiac function limitation and vasoconstriction do coexist; failure to provide fluids to enhance vasodilatation and restoration of tissue perfusion as a result of lack of concomitant increase in cardiac output is misguided. I therefore do disagree with the opening statement by Monnet et al.: "Fundamentally, the only reason to give a patient a fluid challenge is to increase cardiac output"; in my view, the only reason to give a patient a fluid challenge is to restore tissue perfusion. Giving volume to fluid responders as long as they respond should not become the iatrogenic syndrome of the decade: the same is true for failure to give volume to fluid non-responders, who need fluids to maintain their stressed volume while restoring perfusion of vasoconstricted vascular beds.

Compliance with ethical standards

Conflicts of interest None.

References

- Weil MH, Shubin H, Rosoff L (1965) Fluid repletion in circulatory shock: central venous pressure and other practical guides. JAMA 192:668–674
- Weil MH, Henning RJ (1979) New concepts in the diagnosis and fluid treatment of circulatory shock. Thirteenth annual Becton, Dickinson and Company Oscar Schwidetsky Memorial Lecture. Anesth Analg 58:124–132
- Eisenberg PR, Hansbrough JR, Anderson D, Schuster DP (1987) A prospective study of lung water measurements during patient management in an intensive care unit. Am Rev Respir Dis 136:662–868
- Roth E, Lax LC, Maloney JV Jr (1969) Ringer's lactate solution and extracellular fluid volume in the surgical patient: a critical analysis. Ann Surg 169:149–164
- 5. Cope O, Moore FD (1947) The
 - redistribution of body water and the fluid therapy of the burned patient. Ann Surg 136:1010–1045
- 6. Weinstein PD, Doerfler ME (1992) Systemic complications of fluid resuscitation. Crit Care Clin 8:439–448

- VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le Gall J-R, Payen D, on behalf of the Sepsis Occurrence in Acutely Ill Patients Investigators (2006) Sepsis in European intensive care units: results of the SOAP study. Crit Care Med 34:344-353
- 7. Vincent J-L, Sakr Y, Sprung CL, Ranieri 8. Monnet X, Marik P, Teboul J-L (2015) Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis. Intensive Care Med. doi: 10.1007/s00134-015-4134-1
- 9. Cecconi M, Hofer C, Teboul J-L, Pettila V, Wilkman E, Molnar Z, Della Rocca G, Aldecoa C, Artigas A, Sameer J, Sander M, Spies C, Lefrant J-Y, De Backer D, on behalf of the FENICE Investigators and the ESICM Trial Group (2015) Fluid challenges in intensive care: the FENICE study. A global inception cohort study. Intensive Care Med 41:1529-1537



Xavier Monnet Paul Marik Jean-Louis Teboul

Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis

Received: 19 June 2015 Accepted: 30 October 2015

 $\ensuremath{\mathbb{C}}$ Springer-Verlag Berlin Heidelberg and ESICM 2016

Take-home message: In this meta-analysis of 21 studies including 991 adult patients in whom 995 fluid challenges were performed, total, we found that the changes in cardiac output induced by a passive leg raising test are highly reliable in predicting fluid responsiveness. When its effects were assessed by changes in arterial pulse pressure, the specificity of passive leg raising remains good but its sensitivity is poor.

Electronic supplementary material The online version of this article (doi: 10.1007/s00134-015-4134-1) contains supplementary material, which is available to authorized users.

X. Monnet () J.-L. Teboul
Service de Réanimation Médicale, Hôpital
de Bicêtre, Hôpitaux Universitaires ParisSud, 78, Rue du Général Leclerc, 94270 Le
Kremlin-Bicêtre, France
e-mail: xavier.monnet@bct.aphp.fr
Tel.: + 33 1 45 21 35 39

X. Monnet · J.-L. Teboul Faculté de Médecine Paris-Sud, Inserm UMR S_999, Univ Paris-Sud, Le Kremlin-Bicêtre, France

Introduction

P. Marik

Division of Pulmonary and Critical Care Medicine, Department of Medicine, Eastern Virginia Medical School, Norfolk, VA, USA

Abstract Purpose: We performed a systematic review and meta-analysis of studies investigating the passive leg raising (PLR)-induced changes in cardiac output (CO) and in arterial pulse pressure (PP) as predictors of fluid responsiveness in adults. Methods: MEDLINE, EMBASE and Cochrane Database were screened for relevant original and review articles. The meta-analysis determined the pooled area under the ROC curve, the sensitivity, specificity and threshold for the PLR test when assessed with CO and PP. Results: Twenty-one studies (991 adult patients, 995 fluid challenges) were included. CO was measured by echocardiography in six studies, calibrated pulse contour analysis in six studies, bioreactance in four studies, oesophageal Doppler in three studies, transpulmonary thermodilution or pulmonary artery catheter in one study and suprasternal Doppler in one study. The pooled

correlation between the PLR-induced and the fluid-induced changes in CO was 0.76 (0.73–0.80). For the PLRinduced changes in CO, the pooled sensitivity was 0.85 (0.81-0.88) and the pooled specificity was 0.91 (0.88–0.93). The area under the ROC curve was 0.95 ± 0.01 . The best threshold was a PLR-induced increase in CO $\geq 10 \pm 2$ %. For the PLR-induced changes in PP (8 studies, 432 fluid challenges), the pooled sensitivity was 0.56 (0.49-0.53), the pooled specificity was 0.83 (0.77-0.88) and the pooled area under the ROC curve was 0.77 ± 0.05 . Sensitivity and subgroup analysis were consistent with the primary analysis. Conclusions: PLR-induced changes in CO very reliably predict the response of CO to volume expansion in adults with acute circulatory failure. When PLR effects are assessed by changes in PP, the specificity of the PLR test remains acceptable but its sensitivity is poor.

Keywords Passive leg raising · Meta-analysis · Fluid responsiveness · Volume expansion

Fundamentally, the only reason to give a patient a fluid predicting we challenge is to increase cardiac output (CO) [1]. induce a si patients who increase their CO following a fluid challenge are known as fluid responders. Studies in diverse guidelines guidelines patient populations have demonstrated that only about research [2].

50 % of haemodynamically unstable patients are fluid responders [2]. In patients with acute circulatory failure, predicting whether volume expansion will actually induce a significant increase in CO has become a common practice, is recommended by International guidelines [3, 4] and has generated considerable research [2]. Among the tests and indices that have been developed to predict fluid responsiveness, the passive leg raising (PLR) test has gained considerable attention [4, 5]. The PLR is performed by raising the legs of the patient to 45° [6]. This results in a hydrostatic increase in the mean systemic pressure, thus mimicking the effects of volume expansion. In case of preload dependence of both ventricles, the resultant increase in central venous return will result in an increase in CO and venous return.

The substantial increase in cardiac preload induced by PLR [7] challenges preload dependence of both ventricles. One of the advantages of the PLR test is that it can be used in instances in which the fluid responsiveness indices that are based on the respiratory variation of stroke volume are not reliable, such as spontaneous breathing, cardiac arrhythmias, low lung compliance and low tidal volume [8]. Furthermore, no fluid is actually administered and the PLR can thereby be considered a reversible or "virtual" fluid challenge.

Following the first study demonstrating the accuracy of the PLR test [9], this test has been the subject of a number of publications. In 2010, a meta-analysis pooling the nine studies that had been published at that time confirmed its accuracy [10]. Since this meta-analysis, some original articles dealing with the PLR test have been published [11–23], some of them casting doubt on its reliability.

We conducted a systematic review of all these studies and performed a meta-analysis in order to assess the ability of PLR to predict fluid responsiveness, to determine the pooled threshold of the PLR-induced increase in CO (or surrogates) that should be considered as significant, and to compare the diagnostic accuracy of PLR when assessed by changes in CO (or surrogates) or by changes in arterial pulse pressure (PP). Our hypothesis was that the diagnostic ability of the PLR test is good when its effects are assessed on CO and less when its effects are assessed on PP.

Methods

Clinical research question

The clinical research question was: What is the sensitivity and specificity of the passive leg raising test to predict fluid responsiveness when assessing its effects on cardiac output and arterial pressure?

PICO statement

The PICO statement was the following:

P-patient, problem or population: Patients with acute circulatory failure in whom the effect of volume expansion on cardiac output is unknown and needs to be predicted.

I-intervention: Passive leg raising (PLR), induced by moving the patient from the semi-recumbent or horizontal position

C-comparison, control or comparator: Fluid responsiveness was defined as a significant increase of cardiac output during a volume expansion.

O-outcomes: Ability of the PLR test to predict fluid responsiveness.

Identification of records

Our aim was to identify all studies evaluating the ability of the PLR test to predict a significant increase in CO, cardiac index, stroke volume or a surrogate (aortic flow velocity, aortic velocity time integral) compared to that induced by a subsequent fluid infusion. We only included studies that provided the sensitivity and specificity of the PLR test. Furthermore, only studies that were published in full text or accepted for publication in indexed journals were included in this analysis. We excluded studies in which fluid was not administered to test fluid responsiveness. We included only studies performed in adult patients. Figure 1 illustrates the search strategy.

We searched the US National Library of Medicine's MEDLINE database, the EMBASE database and the Cochrane Database of Systematic Reviews for relevant studies published in English from 1966 to April 2015. We used the following medical subjects headings and key-



Fig. 1 Flowchart of study selection

words: "passive leg raising or raise", "fluid or preload or Assessment of risk of bias in included studies volume responsiveness", "fluid or preload challenge", "preload dependence or independence or dependency or independency", "functional haemodynamic monitoring" and "fluid therapy or management". We also looked for relevant articles cited in review articles, commentaries and editorials. The search was performed iteratively until no new records could be found. The quality of the included studies was evaluated by using the QUADAS-2 scale [24]. The meta-analysis was performed according to the PRISMA statement (http://www.prisma-statement. org).

Data extraction

Using a standardised data form, we extracted several data elements from the included studies including characteristics of the investigated population, the methods used to perform the PLR test and to assess its haemodynamic effects, the modalities of fluid administration and definition of fluid responsiveness, the correlation observed between the changes in CO or surrogates induced by volume expansion and by PLR, the number of true positives, true negatives, false positives and false negatives, the area under the receiver operation characteristics (ROC) curve and the best threshold of PLR-induced increase in CO or surrogates that was found to predict fluid responsiveness. If the ability of the PLR-induced changes in arterial PP to predict fluid responsiveness were also investigated, these results were also extracted. For studies in which more than one technique was used to estimate CO, we only included the technique which is considered to be the most reliable. When both calibrated pulse contour analysis and end-tidal carbon dioxide or bioreactance were used to estimate CO, only the results provided by the calibrated pulse contour analysis were evaluated. Indeed, end-tidal carbon dioxide has been suggested to reflect cardiac output changes in very few studies [25, 26] and the reliability of bioreactance has been questioned by some studies [13, 27, 28]. When the effects of PLR were assessed by echocardiography and by uncalibrated pulse contour analysis or end-tidal carbon dioxide or Doppler femoral peak velocity, only the results provided by echocardiography were included in the analysis. The reliability of uncalibrated pulse contour analysis in patients receiving vasopressors has been questioned [4, 29] and the reliability of Doppler femoral peak velocity to estimate CO changes has not been evaluated. When the effects of PLR were assessed by bioreactance and carotid Doppler, only the results provided by bioreactance were included in the analysis. No other publications support the use of carotid Doppler as a reflection of change in CO.

Two authors (X.M. and P.E.M.) assessed the risk of bias of the included studies by following the criteria specified in the QUADAS-2 scale [24]. For the "patient selection" domain, they examined whether patients were consecutively included and whether inappropriate exclusions were avoided. For the "index test" domain, they examined whether the threshold used to define volume responsiveness was pre-specified. For the "reference standard" domain, they examined whether the result of volume expansion on CO was assessed without knowledge of the PLR test result and whether the reliability of the device used to estimate changes in CO induced by PLR is widely validated. Finally, for the "flow and timing" domain, the authors examined whether there was an appropriate interval between PLR and volume expansion, whether patients received the same volume expansion and whether all patients were included in the analysis. For each criterion, the risk was judged as high, low or unclear.

Statistical analysis

We performed a meta-analysis in order to determine the pooled area under the ROC curve, the pooled sensitivity and specificity and pooled threshold for PLR as a predictor of fluid responsiveness when its effects are assessed on CO (or surrogate) and when they are assessed on PP. The pooled correlation between the PLR-induced and the fluidinduced changes in CO (or surrogate) was also determined.

Homogeneity between studies was tested by the Chisquared test (likelihood ratios test for sensitivity and specificity and Cochran's Q test based upon inverse variance weights for likelihood ratios and diagnostic odds ratios) and by the I^2 index. To investigate a threshold effect, we also calculated the Spearman correlation coefficient between sensitivity and specificity. According to heterogeneity, a random effect model was used to perform meta-analysis.

In addition, in order to investigate the influence of study heterogeneity, we conducted subgroup analyses. We compared studies with ICU setting versus non-ICU setting, making the hypothesis that the PLR test could be more reliable in ICU patients. We compared studies with pulse contour analysis or echocardiography versus studies with other methods for measuring CO, making the hypothesis that the reliability of the PLR test is better when assessed by pulse contour analysis-derived cardiac output or by echocardiography than by other techniques. We compared studies with suprasternal Doppler or bioreactance versus studies with other methods for measuring CO, making the hypothesis that the reliability of the PLR test is poorer when assessed by suprasternal Doppler or bioreactance than by other devices. We compared studies where fluid responsiveness was defined by an increase in CO or surrogate >15 % versus studies with other definitions of fluid responsiveness, testing the hypothesis that the reliability of the PLR test is better when fluid responsiveness is defined by a larger increase in cardiac output. We compared studies where volume expansion was performed with crystalloids versus studies where it was performed by colloids, testing the hypothesis that the reliability of the PLR test is better when volume expansion is performed with colloids. Finally, we compared studies with the lowest risk of bias versus highest risk of bias, testing the hypothesis that the reliability of the PLR test is the best in studies with a highest risk of bias. To distinguish studies with the lowest and highest risks of bias, we attributed points to the risk of bias for each item of the QUADAS evaluation (one point for low risk, three points for high risk, two points for unclear risk). For each study, we calculated the sum of these points, which was used as an estimate of the global risk of bias. If the sum was below the median of the sums of all studies, the study was classified in the lowest risk of bias group, and the opposite if the sum was higher than the median. A subgroup analysis was also performed with the method of PLR (starting with the trunk at 0° or at 30° – 45°) as moderating variables. The hypothesis was that the PLR test was more reliable to detect fluid responsiveness when started from the 45° semi-recumbent position than from the horizontal position. Causes of heterogeneity were also investigated by meta-regression based on the Littenberg and Moses linear model and including the same criteria as the subgroup analyses.

Results are expressed as mean (95 % confidence interval) or as mean \pm standard deviation. The metaanalysis was performed with Meta-Disc v.1.4 (Universidad Complutense, Madrid, Spain) [30]. The additional statistical analysis was performed with MedCalc 15.2.2 (MedCalc Software, Mariakerke, Belgium).

Results

Characteristics of included studies

A flow diagram describing the study selection is provided in Fig. 1. We identified 21 studies (991 adult patients, 995 fluid challenges) that reported the ability of the PLR to predict fluid responsiveness [9, 11–23, 31–37]. The characteristics of the included studies are presented in Table 1. Thirteen studies [11–23] had not been included in the meta-analysis of Cavallaro et al. [10]. The vast majority of the studies were conducted in patients with acute circulatory failure. The absence of intra-abdominal hypertension was mentioned in four studies [14, 17, 18, 35]. The PLR was started from the supine position at 0° in four studies [21, 23, 31, 37] and from the semi-recumbent position in the remaining studies (Table 1).

Fluid responsiveness was defined by an increase in CO (or surrogate) by more than 15 % in 16 studies [9, 11–19, 31–36], 10 % in 2 studies [20, 21], 12 % in 1 study [37], 9 % in 1 study [22] and 7 % in 1 study [23] (Table 1).

CO was measured by echocardiography in 6 studies [16, 19, 32, 35–37], calibrated pulse contour analysis in 6 studies [12–14, 17, 18, 34], bioreactance in 4 studies [11, 20, 22, 23], oesophageal Doppler in 3 studies [9, 15, 31], either transpulmonary thermodilution or pulmonary artery catheter in 1 study [21] and suprasternal Doppler in 1 study [33] (Table 1). For the 2 studies in which the effects of PLR were assessed by echocardiography using both cardiac output and aortic velocity time integral [32, 37], we included only the cardiac output data.

For 2 studies in which the effects of PLR were assessed by calibrated pulse contour analysis and by end-tidal carbon dioxide [17] or bioreactance [13], only the results provided by the calibrated pulse contour analysis were evaluated. For the 3 studies in which the effects of PLR were assessed by echocardiography and by uncalibrated pulse contour analysis [35] or end-tidal carbon dioxide [15] or Doppler femoral peak velocity [36], only the results provided by echocardiography were included in the analysis. For the study in which the effects of PLR were assessed by bioreactance and carotid Doppler [20], we included only the results provided by bioreactance. The diagnostic accuracy of the PLR-induced changes in PP was investigated in 8 studies (392 fluid challenges) [9, 14, 15, 17, 18, 21, 34, 36].

The results of the QUADAS-2 evaluation are provided in Table 2 and Fig. 2. Among the sources of potential biases, 19 studies did not include consecutive patients (or no information was provided on this item).

Correlation between the PLR-induced and the fluidinduced changes in CO

The correlation between the changes in CO (or surrogate) induced by the PLR and volume expansion was reported in 14 studies (541 fluid challenges) [9, 13–19, 22, 31, 32, 34, 36, 37]. The pooled correlation coefficient was 0.76 (0.73–0.80) (p < 0.001) (Fig. 3).

Prediction of fluid responsiveness by the PLR-induced changes in CO

Among the 995 fluid challenges, 54 ± 9 % led to a positive response. All studies but four [11, 19, 21, 22] reported the value of percent changes in CO (or surrogate) induced by PLR in case of response to volume expansion. On average, the increase in CO in such cases was 20 ± 9 %.

For the PLR-induced changes in CO (or surrogate), the pooled sensitivity was 0.85 (0.81–0.88) and the pooled specificity was 0.91 (0.88–0.93) (Table 3). All studies but

Setting used to estimate used to estimate setting used to estimate setting cardiac outputSetting used to estimate for volu cardiac outputMonnet et al. [13] Nonnet et al. [12]ICU Calibrated PCAACF ACF ACFMonnet et al. [13] Sitva et al. [14] Nonnet et al. [17] Nonnet et al. [17] Sitva et al. [17] Nonnet et al. [17] Nonnet et al. [17] Nonnet et al. [17] CU Calibrated PCAACF ACF ACF ACF ACF Calibrated PCAMonnet et al. [17] Sitva et al. [17] Naizel et al. [37] Biais et al. [36] Brun et al. [19] Nonnet et al. [10] Brun et al. [19] Nonnet et al. [20] Brun et al. [15] Nonnet et al. [20] Brun et al. [21] CU BioreactanceMCF (all Sophageal Doppler ACF (all Bioreactance ACF Bioreactance ACF Dus et al. [21] Thiel et al. [23]Patients VolumeVolume Type of fluid Type of fluid to to to to to to to to	S					
Monnet et al. [34]ICUCalibrated PCAACFMonnet et al. [18]ICUCalibrated PCAACFDong et al. [12]ICUCalibrated PCAACFSilva et al. [14]ICUCalibrated PCAACFSilva et al. [17]ICUCalibrated PCAACFMonnet et al. [17]ICUCalibrated PCAACFMonnet et al. [17]ICUCalibrated PCAACFMonnet et al. [37]ICUCalibrated PCAACFMaizel et al. [37]ICUEchocardiographyACFMaizel et al. [36]ICUEchocardiographyACFMaizel et al. [37]ICUEchocardiographyACFBiais et al. [36]ICUEchocardiographyACFMonnet et al. [19]ICUEchocardiographyACFBrun et al. [19]ICUEchocardiographyACFMonnet et al. [23]ICUEchocardiographyACFMonnet et al. [23]ICUEsophageal DopplerACFMonge-Garcia et al. [15]ICUBioreactanceACFMonge-Garcia et al. [15]ICUBioreactanceACFMonge-Garcia et al. [23]ICUBioreactanceACFMonse et al. [23]ICUEsophageal DopplerACFMonse et al. [23]ICUBioreactanceACFMonse et al. [23]ICUBioreactanceACFMonse et al. [23]ICUBioreactanceACFMarik et al. [23]ICUBioreactanceACFDuus et al. [23] <td< td=""><td>device Indicat to estimate for vol ac output expans</td><td>ion ume ion</td><td>No. of N included fl patients cl</td><td>lo. of Type uid patien hallenges</td><td>of Spontaneous ts breathing</td><td>Cardiac rhythm</td></td<>	device Indicat to estimate for vol ac output expans	ion ume ion	No. of N included fl patients cl	lo. of Type uid patien hallenges	of Spontaneous ts breathing	Cardiac rhythm
Kupërsztych-Hagège et al. [13]ICUCalibrated PCAACFSilva et al. [17]ICUCalibrated PCAACFMonnet et al. [17]ICUCalibrated PCAACFMaizel et al. [37]ICUEchocardiographyACFMaizel et al. [37]ICUEchocardiographyACFMaizel et al. [37]ICUEchocardiographyACFMaizel et al. [36]ICUEchocardiographyACFBiais et al. [36]ICUEchocardiographyACFGuinot et al. [19]ICUEchocardiographyACFBrun et al. [19]ICUEchocardiographyACFMonnet et al. [19]ICUEchocardiographyACFMonnet et al. [19]ICUEchocardiographyACFMonnet et al. [23]ICUEchocardiographyACFMonnet et al. [23]ICUEsophageal DopplerACFMonge-Garcia et al. [15]ICUBioreactanceACFMonse dati [23]ICUBioreactanceACFMonse dati [23]ICUBioreactanceACFMarik et al. [20]EDBioreactanceACFDuras et al. [13]ICUSuprasternal DopplerACFThiel et al. [33]ICUSuprasternal DopplerACFThiel et al. [33]PatientsVolumeType of fluidVolumeThiel et al. [33]PatientsVolumeType of fluidVolume	rated PCA ACF rated PCA ACF rated PCA Severe	sepsis and septic shock	32 4 4 32 4 4 32 5 3	4 Adult 4 Adult 2 Adult	s SB and non-SB s Non-SB s Non-SB	Sinus and arrhythmias Sinus Sinus
Monnet et al. [17]ICUCalibrated PCAACFLamia et al. [32]ICUEchocardiographyACFMaizel et al. [37]ICUEchocardiographyACFBiais et al. [35]ICUEchocardiographyACFPréau et al. [36]ICUEchocardiographyACFPréau et al. [36]ICUEchocardiographyACFPréau et al. [19]ICUEchocardiographyACFRun et al. [19]ICUEchocardiographyACFMonnet et al. [19]ICUEchocardiographyACFMonnet et al. [15]ICUEsophageal DopplerACFMonge-Garcia et al. [15]ICUBioreactanceACFMonge-Garcia et al. [23]ICUBioreactanceACFMarik et al. [23]ICUBioreactanceACFDuus et al. [23]ICUBioreactanceACFThiel et al. [33]ICUBioreactanceACFThiel et al. [33]PatientsVolumeType of fluidVolumeType of fluidVolumeType of fluid	rated PCA ACF rated PCA ACF		48 20 4 2	8 Adult 0 Adult	s SB and non-SB SB and non-SB	Sinus and arrhythmias Sinus and arrhythmias
Maizel et al. [37]ICUEchocardiographyACFBiais et al. [35]ICUEchocardiographyACF (schocardiography)Préau et al. [36]ICUEchocardiographyACF (schocardiography)Guinot et al. [19]ICUEchocardiographyACF (schocardiography)Brun et al. [19]ICUEchocardiographyACF (schocardiography)Monnet et al. [9]ICUEchocardiographyPre-eclaMonnet et al. [9]ICUEsophageal DopplerACFMonge-Garcia et al. [15]ICUEsophageal DopplerACFMonge al. [23]ICUBioreactanceACFMarik et al. [20]BioreactanceACFACFDuus et al. [13]ICUBioreactanceACFThiel et al. [33]ICUBioreactanceACFThiel et al. [33]PatientsVolumeType of fluidVolumeType of fluidVV	rated PCA ACF cardiography ACF		40 40	0 Adult 4 Adult	s Non-SB	Sinus/arrhythmias Sinus and arrhythmias
Préau et al. [36]ICUEchocardiographyACF (stBrun et al. [16]ICUEchocardiographyACF (uBrun et al. [19]ICUEchocardiographyACF (uBrun et al. [19]ICUEchocardiographyACF (uMonnet et al. [9]ICUEchocardiographyACF (uMonnet et al. [9]ICUEchocardiographyACF (uMonnet et al. [13]ICUEchocardiographyACF (aMonge-Garcia et al. [15]ICUEsophageal DopplerACF (a)Monge-Garcia et al. [15]ICUBioreactanceACF (a)Marik et al. [23]ICUBioreactanceACF (a)Duus et al. [11]EDBioreactanceACFDuus et al. [21]ICUBioreactanceACFThiel et al. [33]PatientsVolumeType of fluidVreceivingof fluidVVreceivingre	cardiography ACF			4 Adult 0 Adult	SB	Sinus only No mention
Brun et al. [19] ICU Echocardiography Pre-ecla Monnet et al. [9] ICU Esophageal Doppler ACF Lafanechère et al. [31] ICU Esophageal Doppler ACF Monge-Garcia et al. [15] ICU Esophageal Doppler ACF Monge-Garcia et al. [15] ICU Esophageal Doppler ACF Kang et al. [23] ICU Bioreactance ACF (at all all all all all all all all all a	cardiography ACF (s cardiography ACF (s	sepsis or pancreatitis) ander ECMO)	25 20 26 20 26 20	5 Adult	SB Non-SB	Sinus No mention
Lafanechère et al. [31]ICUEsophageal DopplerACFMonge-Garcia et al. [15]ICUEsophageal DopplerACFKang et al. [23]ICUBioreactanceACF (atBenomar et al. [22]ICUBioreactanceACF (atMarik et al. [20]EDBioreactanceACFDuus et al. [21]ICUBioreactanceACFDuus et al. [11]EDBioreactanceACFDuus et al. [11]ICUBioreactanceACFThiel et al. [23]ICUSuprasternal DopplerACFPatientsVolumeType of fluidVreceivingof fluidtoto	cardiography Pre-ecl nageal Doppler ACF	ampsia	23 71 7	3 Adult 1 Adult	s SB s SB and non-SB	Sinus Sinus and arrhythmias
Kang et al. [23]ICUBioreactanceACF (alBenomar et al. [22]ICUBioreactanceACF (alMarik et al. [20]ICUBioreactanceACFDuus et al. [11]EDBioreactanceACFLakkhal et al. [21]ICUPAC + TPTDACFThiel et al. [33]ICUSuprasternal DopplerACFPatientsVolumeType of fluidVreceivingof fluidtoto	ageal Doppler ACF ageal Doppler ACF		322	2 Adult 7 Adult	Non-SB Non-SB	Sinus only Sinus
Benomar et al. [22] ICU Bioreactance ACF (a) Marik et al. [20] ICU Bioreactance ACF Duus et al. [11] ED Bioreactance ACF Lakkhal et al. [21] ICU PAC + TPTD ACF Thiel et al. [33] ICU Suprasternal Doppler ACF Patients Volume Type of fluid Vo receiving of fluid V	actance ACF (a	after cardiac surgery)	5	4 Adult	Non-SB	Sinus
Durase at al. [11] ED Bioreccance ACF Durast at al. [21] EU PAC + TPTD ACF Thiel et al. [33] ICU PAC + TPTD ACF Thiel et al. [33] ICU Suprasternal Doppler ACF Patients Volume Type of fluid to<	actance ACF (a	after cardiac surgery)	75 72	5 Adult 4 Adult	S No mention SR and non-SR	No mention Sinus only
Lakkhal et al. [21] ICU PAC + TPTD ACF Thiel et al. [33] ICU Suprasternal Doppler ACF Patients Volume Type of fluid V receiving of fluid V to	actance ACF		109	00 Adult	SB	No mention
Patients Volume Type of fluid V receiving of fluid to inotropes infused re	+ TPTD ACF tsternal Doppler ACF		102 89	02 Adult 02 Adult	Non-SB SB and non-SB	Sinus Sinus and arrhythmias
	ume Type of fluid	Variable used Percen to define volume increas	tage se used	Method used to	Time frame for PLR assessment	Analysis of PLR effects on
	I I I I I I I I I I I I I I I I I I I	responsiveness to testion	siveness (%) PLR		anenai pressure
Monnet et al. [34] 0 500 mL Crystalloids C	mL Crystalloids (CI 15		45°–45°	Max within 5 min	Yes
Monnet et al. [18] 0 500 mL Crystalloids C	mL Crystalloids	CI 15		45°-45°	Max within 5 min	Yes
Dong et al. [12] No menuon 200 mL Contoucs 3 Kupersztych-Hagège 4 500 mL Crystalloids C	mL Colloids of mL Crystalloids 0			45°-45°	At 2 min Max within 5 min	No
et al. [13] Silva et al. [14] 0 500 mL Crystalloids C	mL Crystalloids	CI 15		45°–45°	Max within 5 min	Yes
Monnet et al. [17] 0 500 mL Crystalloids C	mL Crystalloids	CI 15 SV 15		45°-45° 15° 15°	Max within 5 min	Yes
Maizel et al. [37] No mention ^a 500 mL Crystalloids C	mL Crystalloids	CI 12		$0^{\circ}-30^{\circ}$ at	aT 2 min	
Biais et al. [35]0500 mLCrystalloidsSPréau et al. [36]No mention500 mLColloidsS	mL Crystalloids and Colloids	SV 15 SV 15		45°-45° 30°-45° to 30°-45° to	Max within 90 sec Within 5 min	No Yes
Guinot et al. [16] 44 500 mL Crystalloids S	mL Crystalloids	SV 15		45°-45°	Max within 1 min	No
Brun et al. [19] 0 500 mL Crystauoues 5 Monnet et al. [9] 4 500 mL Crystalloids C	mL Crystalloids 0	CI 15		45°-45°	Max Max within 5 min	Yes
Lafanechère et al. [31]50500 mLCrystalloidsCMonge-Garcia et al. [15]5500 mLColloidsC	mL Crystalloids	CI 15 CO 15		0°-45° 45°-45°	Each min during 4 Max within 5 min	min No Yes

Table 1 continued								
	Patients receiving inotropes	Volume of fluid infused	Type of fluid	Variable used to define volume responsiveness	Percentage increase used to define volume responsiveness (%)	Method used to perform PLR	Time frame for PLR assessment	Analysis of PLR effects on arterial pressure
Kang et al. [23] Benomar et al. [22] Marik et al. [20] Duus et al. [11] Lakkhal et al. [21] Thiel et al. [33]	No mention 32 0 No mention 41 0	250 mL 500 mL 500 mL 5 mL/kg 500 mL 500 mL	Colloids Colloids Crystalloids Crystalloids Colloids Crystalloids or colloids	SCI SSCI O	7 9 10 10 15	0°-45° 45°-45° 45°-45° 45°-45° 0°-30° 45°-45°	Max within 5 min Every minute within 10 min Max within 3 min Within 3 minutes At one min Not specified	No No Yes No
ACF acute circulator raising, SAP systolic	y failure, <i>CI</i> c arterial pressu	cardiac inde tre, SB spor	x, ED emergency departme ntaneous breathing, SV strol	nt, <i>ICU</i> intensive te volume, <i>TPTD</i>	care unit, OR operation transpulmonary therm	ng room, <i>H</i> odilution	AC pulmonary artery catheter,	PLR passive leg

of patients were under "vasoactive treatment"

^a 9 % (

two [11, 20] reported the area under the corresponding ROC curve. The pooled AUC was 0.95 ± 0.01 (Table 3; Fig. 4). All the studies but one [23] reported the best threshold of the PLR-induced increase in CO (or surrogate) that predicted fluid responsiveness; this averaged 10 ± 2 %, ranging from 7 % [21] to 15 % [33] (Table 3).

When including only studies in which PLR was started from the semi-recumbent position (n = 17, 783 fluid challenges), the pooled sensitivity for the PLR-induced changes in CO (or surrogate) was 0.85 (0.81–0.88) and the pooled specificity was 0.91 (0.88–0.94).

Prediction of fluid responsiveness by the PLR-induced changes in arterial PP

For the PLR-induced changes in PP (8 studies, 432 fluid challenges), the pooled sensitivity was 0.56 (0.49–0.53) and the pooled specificity was 0.83 (0.77–0.88). The pooled area under the ROC curve was 0.77 \pm 0.05 (Fig. ESM2). The best threshold of PLR-induced increase in PP that predicted fluid responsiveness was 12 \pm 4 % on average, ranging from 6 [17] to 18 % [14] (Table 3).

Investigation of heterogeneity and of causes of heterogeneity

The Spearman correlation coefficient between sensitivity and specificity was -0.178 (p = 0.441), indicating no threshold effect. The heterogeneity Chi-squared was 58 % for sensitivity and 47 % for specificity. The I^2 statistics was 67 % for sensitivity, 58 % for specificity, 34 % for the pooled ROC curve analysis and 10 % for the coefficient of correlation analysis.

Subgroup analyses are presented in Fig. ESM1. None of the covariates included in the meta-regression were found to be the significant source of heterogeneity (Table ESM1). In particular, the comparison between studies with pulse contour analysis or echocardiography versus studies with other devices, and between studies with bioreactance or suprasternal Doppler versus other devices had no influence on sensitivity and specificity. In studies with pulse contour analysis or echocardiography, the average threshold indicating a positive PLR was 10 ± 2 %. In the studies with bioreactance or suprasternal Doppler, it was 11 ± 3 %. Sensitivity and subgroup analyses were consistent with the primary analysis

Discussion

This meta-analysis which summarised the results of 21 studies conducted in 991 adult patients and including 995

Table 2 QUADAS-2 results

	Patient sel	ection	Index test		Reference	standard	Flow and
	Risk of bias	Applicability judgements	Risk of bias	Applicability judgements	Risk of bias	Applicability judgements	timing
Monnet et al. [9]	Unclear	Low	High	Low	Low	Low	Low
Lafanechère et al. [31]	Unclear	Unclear	High	Low	High	Low	Low
Lamia et al. [32]	Unclear	Low	High	Low	Low	Low	Low
Maizel et al. [37]	Unclear	Unclear	High	Low	High	Low	Low
Thiel et al. [33]	Low	Low	High	Low	Low	Low	Low
Monnet et al. [34]	Unclear	Low	High	Low	Low	Low	Low
Biais et al. [35]	Unclear	Low	High	Low	Low	Low	Low
Préau et al. [36]	Unclear	Unclear	High	Low	Low	Low	Low
Benomar et al. [22]	Low	Low	High	Low	High	Low	Low
Lakkhal et al. [21]	Unclear	Unclear	High	Low	High	Low	Low
Guinot et al. [16]	Unclear	Low	High	Low	Low	Low	Low
Monnet et al. [18]	Unclear	Low	High	Low	Low	Low	Low
Brun et al. [19]	Low	High	High	Low	Low	Low	Low
Kang et al. [23]	Unclear	Unclear	High	Low	High	Low	Low
Dong et al. [12]	Low	Unclear	High	Low	Low	Low	Low
Monge-Garcia et al. [15]	Unclear	Unclear	High	Low	Low	Low	Low
Kupersztych-Hagège et al. [13]	Unclear	Low	High	Low	Low	Low	Low
Silva et al. [14]	Unclear	Low	High	Low	Low	Low	Low
Monnet et al. [17]	Unclear	Unclear	High	Low	Low	Low	Low
Marik et al. [20]	Unclear	Low	High	Low	High	Low	Low
Duus et al. [11]	Unclear	Low	High	Low	High	Low	Low



fluid challenges demonstrated that the changes in CO (or surrogate) during a PLR test predicted fluid responsiveness with excellent pooled sensitivity and specificity. The pooled area under the <u>ROC curve was 0.95</u> \pm 0.01. The mean of the best threshold was a PLR-induced increase in CO of more than 10 \pm 2 %. The PLR test less accurately predicted fluid responsiveness when its effects were assessed by the arterial PP.

The PLR test has been developed to predict whether volume expansion will increase CO during the resuscitation of patients with acute circulatory failure. Moving the patient to a position in which the trunk is horizontal and the lower limbs are lifted at 45° increases the stressed

blood volume due to the gravitational transfer of some venous blood from the lower limbs and the abdomen toward the cardiac cavities. PLR significantly increases the mean systemic pressure [38], what promotes venous return. It increases the right and left cardiac preload to an extent that is sufficient to challenge preload responsiveness of both ventricles [7], although this has been challenged [21, 39]. The PLR is now accepted as a test for predicting fluid responsiveness in clinical practice. It is recommended by a recent consensus conference of the European Society of Intensive Care Medicine [4] and has been implemented in the bundles of the surviving sepsis campaign [5].

Fig. 3 Forest plot for the correlation coefficients (with 95 % confidence intervals) between the changes in cardiac output or surrogates induced by passive leg raising and those induced by volume expansion



Correlation coefficient

In 2010, Cavallaro and co-workers performed a systematic review and meta-analysis that included nine studies evaluating the diagnostic accuracy of the PLR test in predicting fluid responsiveness [10]. These authors concluded that the PLR-induced changes in CO reliably predicted fluid responsiveness regardless of ventilation mode, underlying cardiac rhythm and technique of CO measurement. Since this meta-analysis, additional studies have been published, some of them reporting less positive results [21, 22]. In addition, some studies and one editorial [40] have suggested that the PLR would not be reliable under specific conditions, such as insufficient increase in central venous pressure [21] or intra-abdominal hypertension [39]. Furthermore, recent publications have offered the opportunity to better establish the threshold of PLR-induced increase in CO that must be considered to detect volume responsiveness. Finally, the meta-analysis of Cavallaro et al. included only three studies investigating the prediction of fluid responsiveness provided by PLR when assessed by changes in PP [10]. All these arguments justified an updated meta-analysis.

Our meta-analysis confirms the meta-analysis performed by Cavallaro et al. [10] and reinforces the message that the PLR test is valid to test fluid responsiveness. Based on the results obtained in a large number of patients, we found that the area under the pooled ROC curve was large and close to one. In addition, the studies reported threshold values of PLR-induced increases in CO that were close to each other, which further reinforce the consistency of our positive conclusion.

Some authors have claimed that, in order to be a valid test of preload responsiveness, the PLR should increase the central venous pressure by more than 2 mmHg, reflecting an adequate increase in cardiac preload [21]. The present meta-analysis does not support this concept, as we demonstrated that the PLR was highly predictive of fluid responsiveness without taking into account how the PLR changed the central venous pressure. It has already been suggested that the results obtained by Lakhal et al. were explained by the fact that PLR was started from the supine position and not from the semi-recumbent position [41]. This may have resulted in a lesser increase in the mean systemic pressure, which is the upstream pressure of venous return, and thus of central venous pressure.

Mahjoub et al. have suggested that the PLR test produces false negative results in patients with intraabdominal pressure [40]. The results of this study were not included in the present meta-analysis as it only included patients who were fluid responsive. This study has a number of limitations, including the fact that the investigators did not measure the intra-abdominal pressure during the test [40]. We postulate that the PLR may decrease intra-abdominal pressure by reducing the weight of the diaphragm and thorax on the abdominal cavity.

	Percentage	Correlation	PLR-induced chan	ges in cardiac outp	ut		PLR-induced char	iges in arterial pulse	e pressure	
	CO (or surrgoate) induced by volume expansion in fluid (%)	coefficient	Sensitivity	Specificity	Area under the ROC curve	Best threshold ^b (%)	Sensitivity	Specificity	Area under the ROC curve	Best hreshold ^b
Monnet et al. [9]	24	0.83	0.97	0.94	0.96	10	60	85	1	12
Lafanechère et al. [31]	17	0.71	0.90	0.83	0.95	8	NA	NA	NA	AA
Lamia et al. [32]	19	0.79	0.77	1.00	0.96	13	NA	NA	NA	NA
Maizel et al. [37]	17	0.75	0.63	0.89	0.89	12	NA	NA	NA	NA
Thiel et al. [33]	18	NA	0.81	0.93	0.89	15	NA	NA	NA	NA
Monnet et al. [34]	23	0.6	0.91	1.00	0.94	10	43	91	0.68	11
Biais et al. [35]	20	NA	1.00	0.80	0.96	13	NA	NA	NA	NA
Préau et al. [36]	16	0.86	0.86	0.90	0.94	10	62	85	0.86	•
Benomar et al. [22]	NA	0.77	0.68	0.95	0.84	9	NA	NA	NA	NA
Lakkhal et al. [21]	NA	NA	0.79	0.90	0.89	7	99	80	0.76	•
Guinot et al. [16]	2	0.85	0.62	0.92	0.88	10	NA	NA	0.62	NA
Monnet et al. [18]	26	0.7	0.93	0.96	0.93	10	25	94	0.56	18
Brun et al. [19]	NA	0.64	0.75	1.00	0.93	12	NA	NA	0.58	NA
Kang et al. [23]	6	NA	1.00	1.00	1.00	NA	NA	NA	NA	NA
Dong et al. [12]	14	NA	0.73	0.80	0.88	6	NA	NA	NA	NA
Monge-Garcia et al. [15]	21	0.84	0.95	0.94	0.97	12	67	81	NA	11
Kupersztych-Hagège et al. [13]	14	0.74	0.84	0.97	0.87	9	NA	NA	NA	NA
Silva et al. [14]	38	0.65	1.00	1.00	0.93	10	46	100	0.66	18
Monnet et al. [17]	33	0.79	0.95	0.95	0.98	10	68	59	0.67	2
Marik et al. [20]	34	NA	0.94	1.00	NA	10	NA	NA	NA	NA
Duus et al. [11]	NA	NA	0.80	0.61	NA	NA	NA	NA	NA	NA
Pooled value/mean	20 ± 9	0.76 (0.73-0.80)	$0.85 \ (0.81 - 0.88)$	0.91 (0.88 - 0.94)	0.95 ± 0.01	10 ± 2	0.56(0.49-0.53)	0.83 (0.77–0.88)	0.77 ± 0.05	$12 \pm 4\%$
	C.									

Table 3 Main results of included studies with pooled and mean values

Results are reported as values, mean \pm SD or mean (95% confidence interval) NA not available ^a Between PLR-induced and volume expansion-induced changes in cardiac output or surrogates ^b For the PLR-induced increase in CO or surrogate

Fig. 4 Receiver operating characteristics curve (with 95 % confidence interval) for the prediction of fluid responsiveness by the effects of passive leg raising on cardiac output or surrogates. *Circles* represent each study included in the meta-analysis. The *size of each solid circle* indicates the size of each study



Nevertheless, since the intra-abdominal pressure was not assessed in the studies included in the present metaanalysis, the question remains unresolved as to whether intra-abdominal hypertension reduces the diagnostic accuracy of the PLR test in predicting fluid responsiveness.

The diagnostic accuracy of the PLR test was poorer when its haemodynamic effects were assessed on the arterial PP than on CO, confirming what had been already observed by Cavallaro et al. [10]. This is likely due to the fact that changes in <u>PP and CO are not well correlated and that changes in PP are a poor indicator of the changes in CO [43, 44]. When assessed through changes in PP, the specificity of the PLR test was 0.83. The sensitivity was much poorer. This suggests that, when assessed by changes in PP, the PLR should be taken into account only if it increases PP, and that even in such a case, this should be done cautiously. This finding illustrates an important shortcoming of the PLR test, that <u>only the CO (or surrogate) should be used when performing the PLR test</u>.</u>

The importance of correct positioning of the patient when performing the PLR test has been previously emphasised [45]. Compared to starting the test from the horizontal lying position, starting it from the semi-recumbent position augments the effects of the test on cardiac preload [45], likely by mobilising the venous blood from the abdominal compartment in addition to that of the lower limbs [6]. This meta-analysis could not confirm this finding. However, this result should be interpreted with caution since PLR was started from the horizontal position in only four studies.

An important point to keep in mind is that a positive PLR test should not systematically lead to administering fluid. It is only in cases of circulatory failure, as assessed by low arterial pressure and/or signs of poor tissue perfusion, when the need for increasing CO is required, that fluid administration should be considered. In addition, the beneficial increase of CO induced by volume expansion in patients who are fluid responsive must always be balanced with the risk of excessive fluid administration, which may be harmful, especially in patients with septic shock [46], acute renal failure [47] and acute respiratory distress syndrome [48]. Of note, using the PLR test has never been demonstrated to improve survival. Fluid responsiveness is not associated with improved outcome. This is not surprising since it is a diagnostic tool. Nevertheless, as many diagnosis tools, the test is not required to change outcome to be useful.

Various methods of measuring CO were used in the studies included in this meta-analysis. This must be regarded as a limitation, since the reliability of the PLR test likely depends on the accuracy of the device used to measure CO [49]. In particular, the threshold used to define fluid responsiveness should be higher than the least significant change of the CO measurement method. While this least significant change has been reported to be lower than 5 % for echocardiography [50], pulse contour analysis [34, 51] or oesophageal Doppler [15], it has been reported to be higher for bioreactance [22, 52, 53], while, as far as we know, it has not been investigated for suprasternal Doppler. Subgroup analysis does not support that the reliability of the PLR test was influenced by the

type of cardiac output monitoring device, including bioreactance and suprasternal Doppler. Nevertheless, some of the subgroups were small. Thus, it is reasonable to consider that the reliability of the PLR test may be less solid if assessed with less reliable measures of cardiac output.

The heterogeneity of the included studies represents a limitation of the meta-analysis. Nevertheless, no threshold effect was detected. Furthermore, both the subgroup analyses and the meta-regression argued against the influence of heterogeneity on the results. A further limitation of this study is that the included studies were mainly conducted in the ICU, the sample size was generally small and that several different methods of measuring of CO were used. Therefore, this systematic review is only applicable to the specific patient populations studied and the devices used to measure CO. In addition, this systematic review was not prospectively registered in Prospero, an international database of prospectively registered systematic reviews in health and social care, what may have increased the risk of reporting bias. Additional limitations include the fact that we did not include studies not reporting sensitivity/specificity, non-full-text studies, studies not in English, and

unpublished studies. This may have also increased the risk of reporting bias. Since the reliability of the PLR test in cases of intra-abdominal hypertension and in cases of insufficient increase in central venous pressure was investigated in one study for each condition, the meta-analysis does not definitely come to a conclusion about this reliability of PLR in these circumstances. Finally, two of the authors (X.M. and J.L.T.) were the authors of a large number of the studies included in the meta-analysis. Nevertheless, this was not the case for the third author (P.E.M.), so that the risk of bias was minimized.

In conclusion, this meta-analysis shows that the PLR test is accurate to predict fluid responsiveness in the intensive care unit. Its accuracy is better when its haemodynamic effects are assessed by a direct measurement of CO than by the arterial PP.

Compliance with ethical standards

Conflicts of interest Jean-Louis Teboul and Xavier Monnet are members of the Medical Advisory Board of Maquet. They are the authors of the majority of the studies included in this meta-analysis. Paul E Marik has no conflicts to disclose.

References

- 1. Lira A, Pinsky MR (2014) Choices in fluid type and volume during resuscitation: impact on patient outcomes. Ann Intensive Care 4:38
- Marik PE, Monnet X, Teboul JL (2011) Hemodynamic parameters to guide fluid therapy. Ann Intensive Care 1:1
- Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 39(2):165–228
- 4. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, Jaeschke R, Mebazaa A, Pinsky MR, Teboul JL, Vincent JL, Rhodes A (2014) Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med 40:1795–1815
- 5. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R (2015) Updated bundles in response to new evidence. In: Surviving sepsis campaign. http://www.survivingsepsis. org/sitecollectiondocuments/ ssc. bundle.pdf (in press)
- ssc_bundle.pdf (in press)
 6. Monnet X, Teboul JL (2015) Passive leg raising: five rules, not a drop of fluid! Crit Care 19:18
- Boulain T, Achard JM, Teboul JL, Richard C, Perrotin D, Ginies G (2002) Changes in BP induced by passive leg raising predict response to fluid loading in critically ill patients. Chest 121:1245–1252
- 8. Monnet X, Teboul JL (2013) Assessment of volume responsiveness during mechanical ventilation: recent advances. Crit Care 17:217
- Monnet X, Rienzo M, Osman D, Anguel N, Richard C, Pinsky MR, Teboul JL (2006) Passive leg raising predicts fluid responsiveness in the critically ill. Crit Care Med 34:1402–1407

- Cavallaro F, Sandroni C, Marano C, La Torre G, Mannocci A, De Waure C, Bello G, Maviglia R, Antonelli M (2010) Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies. Intensive Care Med 36:1475–1483
- Duus N, Shogilev DJ, Skibsted S, Zijlstra HW, Fish E, Oren-Grinberg A, Lior Y, Novack V, Talmor D, Kirkegaard H, Shapiro NI (2015) The reliability and validity of passive leg raise and fluid bolus to assess fluid responsiveness in spontaneously breathing emergency department patients. J Crit Care 30(217):e211–e215
- Dong ZZ, Fang Q, Zheng X, Shi H (2012) Passive leg raising as an indicator of fluid responsiveness in patients with severe sepsis. World J Emerg Med 3:191–196
- Kupersztych-Hagege E, Teboul JL, Artigas A, Talbot A, Sabatier C, Richard C, Monnet X (2013) Bioreactance is not reliable for estimating cardiac output and the effects of passive leg raising in critically ill patients. Br J Anaesth 111:961–966

- 14. Silva S, Jozwiak M, Teboul JL, Persichini R, Richard C, Monnet X (2013) End-expiratory occlusion test predicts preload responsiveness independently of positive endexpiratory pressure during acute respiratory distress syndrome. Crit Care Med 41:1692–1701
- 15. Monge Garcia MI, Gil Cano A, Gracia Romero M, Monterroso Pintado R, Perez Madueno V, Diaz Monrove JC (2012) Non-invasive assessment of fluid responsiveness by changes in partial end-tidal CO₂ pressure during a passive leg-raising maneuver. Ann Intensive Care 2:9
- 16. Guinot PG, Zogheib E, Detave M, Moubarak M, Hubert V, Badoux L, Bernard E, Besserve P, Caus T, Dupont H (2011) Passive leg raising can predict fluid responsiveness in patients placed on veno-venous extracorporeal membrane oxygenation. Crit Care 15:R216
- 17. Monnet X, Bataille A, Magalhaes E, Barrois J, Le Corre M, Gosset C, Guerin L, Richard C, Teboul JL (2013) Endtidal carbon dioxide is better than arterial pressure for predicting volume responsiveness by the passive leg raising test. Intensive Care Med 39:93–100
- Monnet X, Bleibtreu A, Ferré A, Dres M, Gharbi R, Richard C, Teboul JL (2012) Passive leg raising and endexpiratory occlusion tests perform better than pulse pressure variation in patients with low respiratory system compliance. Crit Care Med 40:152–157
- Brun C, Zieleskiewicz L, Textoris J, Muller L, Bellefleur JP, Antonini F, Tourret M, Ortega D, Vellin A, Lefrant JY, Boubli L, Bretelle F, Martin C, Leone M (2013) Prediction of fluid responsiveness in severe preeclamptic patients with oliguria. Intensive Care Med 39:593–600
- 20. Marik PE, Levitov A, Young A, Andrews L (2013) The use of bioreactance and carotid Doppler to determine volume responsiveness and blood flow redistribution following passive leg raising in hemodynamically unstable patients. Chest 143:364–370
- 21. Lakhal K, Ehrmann S, Runge I, Benzekri-Lefevre D, Legras A, Dequin PF, Mercier E, Wolff M, Regnier B, Boulain T (2010) Central venous pressure measurements improve the accuracy of leg raising-induced change in pulse pressure to predict fluid responsiveness. Intensive Care Med 36:940–948

- 22. Benomar B, Ouattara A, Estagnasie P, Brusset A, Squara P (2010) Fluid responsiveness predicted by noninvasive bioreactance-based passive leg raise test. Intensive Care Med 36:1875–1881
- 23. Kang WS, Kim SH, Kim SY, Oh CS, Lee SA, Kim JS (2014) The influence of positive end-expiratory pressure on stroke volume variation in patients undergoing cardiac surgery: an observational study. J Thorac Cardiovasc Surg 148:3139–3145
- 24. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM, Group Q (2011) QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 155:529–536
- Tautz TJ, Urwyler A, Antognini JF, Riou B (2010) Case scenario: increased end-tidal carbon dioxide: a diagnostic dilemma. Anesthesiology 112:440–446
- Weil MH, Bisera J, Trevino RP, Rackow EC (1985) Cardiac output and end-tidal carbon dioxide. Crit Care Med 13:907–909
- 27. Conway DH, Hussain OA, Gall I (2013) A comparison of noninvasive bioreactance with oesophageal Doppler estimation of stroke volume during open abdominal surgery: an observational study. Eur J Anaesthesiol 30(8):501–508
- Fagnoul D, Vincent JL, Backer DD (2012) Cardiac output measurements using the bioreactance technique in critically ill patients. Crit Care 16:460
- Monnet X, Teboul JL (2015) Minimally invasive monitoring. Crit Care Clin 31:25–42
- 30. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A (2006) Meta-DiSc: a software for meta-analysis of test accuracy data. BMC Med Res Methodol 6:31
- 31. Lafanechère A, Pène F, Goulenok C, Delahaye A, Mallet V, Choukroun G, Chiche JD, Mira JP, Cariou A (2006) Changes in aortic blood flow induced by passive leg raising predict fluid responsiveness in critically ill patients. Crit Care 10(5):R132
- 32. Lamia B, Ochagavia A, Monnet X, Chemla D, Richard C, Teboul JL (2007) Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneously breathing activity. Intensive Care Med 33:1125–1132
- 33. Thiel SW, Kollef MH, Isakow W (2009) Non-invasive stroke volume measurement and passive leg raising predict volume responsiveness in medical ICU patients: an observational cohort study. Crit Care 13:R111

- 34. Monnet X, Osman D, Ridel C, Lamia B, Richard C, Teboul JL (2009) Predicting volume responsiveness by using the end-expiratory occlusion in mechanically ventilated intensive care unit patients. Crit Care Med 37:951–956
- 35. Biais M, Vidil L, Sarrabay P, Cottenceau V, Revel P, Sztark F (2009) Changes in stroke volume induced by passive leg raising in spontaneously breathing patients: comparison between echocardiography and Vigileo/FloTrac device. Crit Care 13:R195
- 36. Preau S, Saulnier F, Dewavrin F, Durocher A, Chagnon JL (2010) Passive leg raising is predictive of fluid responsiveness in spontaneously breathing patients with severe sepsis or acute pancreatitis. Crit Care Med 38:989–990
- 37. Maizel J, Airapetian N, Lorne E, Tribouilloy C, Massy Z, Slama M (2007) Diagnosis of central hypovolemia by using passive leg raising. Intensive Care Med 33:1133–1138
- Guérin L, Teboul JL, Persichini R, Dres M, Richard C, Monnet X (2015) Effects of passive leg raising and volume expansion on mean systemic pressure and venous return in shock in humans. Crit Care 19:411. doi: 10.1186/s13054-015-1115-2
- Mahjoub Y, Pila C, Friggeri A, Zogheib E, Lobjoie E, Tinturier F, Galy C, Slama M, Dupont H (2009) Assessing fluid responsiveness in critically ill patients: false-positive pulse pressure variation is detected by Doppler echocardiographic evaluation of the right ventricle. Crit Care Med 37:2570–2575
- 40. Malbrain ML, Reuter DA (2010) Assessing fluid responsiveness with the passive leg raising maneuver in patients with increased intra-abdominal pressure: be aware that not all blood returns! Crit Care Med 38:1912–1915
- Monnet X, Teboul JL (2010) Passive leg raising: keep it easy! Intensive Care Med 36:1445–1446
- 42. Mahjoub Y, Touzeau J, Airapetian N, Lorne E, Hijazi M, Zogheib E, Tinturier F, Slama M, Dupont H (2010) The passive leg-raising maneuver cannot accurately predict fluid responsiveness in patients with intra-abdominal hypertension. Crit Care Med 38:1824–1829
- 43. Monnet X, Letierce A, Hamzaoui O, Chemla D, Anguel N, Osman D, Richard C, Teboul JL (2011) Arterial pressure allows monitoring the changes in cardiac output induced by volume expansion but not by norepinephrine*. Crit Care Med 39:1394–1399

- 44. Pierrakos C, Velissaris D, Scolletta S, Heenen S, De Backer D, Vincent JL (2012) Can changes in arterial pressure be used to detect changes in cardiac index during fluid challenge in patients with septic shock? Intensive Care Med 38:422–428
- 45. Jabot J, Teboul JL, Richard C, Monnet X (2009) Passive leg raising for predicting fluid responsiveness: importance of the postural change. Intensive Care Med 35:85–90
- Marik PE (2014) Early management of severe sepsis: concepts and controversies. Chest 145:1407–1418
- Prowle JR, Kirwan CJ, Bellomo R (2014) Fluid management for the prevention and attenuation of acute kidney injury. Nat Rev Nephrol 10:37–47
- 48. Jozwiak M, Silva S, Persichini R, Anguel N, Osman D, Richard C, Teboul JL, Monnet X (2013) Extravascular lung water is an independent prognostic factor in patients with acute respiratory distress syndrome. Crit Care Med 41:472–480
- 49. Marik PE (2013) Noninvasive cardiac output monitors: a state-of the-art review. J Cardiothorac Vasc Anesth 27:121–134
- 50. Muller L, Toumi M, Bousquet PJ, Riu-Poulenc B, Louart G, Candela D, Zoric L, Suehs C, de La Coussaye JE, Molinari N, Lefrant JY (2011) An increase in aortic blood flow after an infusion of 100 ml colloid over 1 minute can predict fluid responsiveness: the mini-fluid challenge study. Anesthesiology 115:541–547
- 51. Hamzaoui O, Monnet X, Richard C, Osman D, Chemla D, Teboul JL (2008) Effects of changes in vascular tone on the agreement between pulse contour and transpulmonary thermodilution cardiac output measurements within an up to 6-hour calibration-free period. Crit Care Med 36:434–440
- 52. Squara P, Denjean D, Estagnasie P, Brusset A, Dib JC, Dubois C (2007) Noninvasive cardiac output monitoring (NICOM): a clinical validation. Intensive Care Med 33:1191–1194
- 53. Marque S, Cariou A, Chiche JD, Squara P (2009) Comparison between Flotrac– Vigileo and bioreactance, a totally noninvasive method for cardiac output monitoring. Crit Care 13:R73