Predicting Fluid Responsiveness by Passive Leg Raising: A Systematic Review and Meta-Analysis of 23 Clinical Trials

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Objective: Passive leg raising creates a reversible increase in venous return allowing for the prediction of fluid responsiveness. However, the amount of venous return may vary in various clinical settings potentially affecting the diagnostic performance of passive leg raising. Therefore we performed a systematic meta-analysis determining the diagnostic performance of passive leg raising in different clinical settings with exploration of patient characteristics, measurement techniques, and outcome variables.

Data Sources: PubMed, EMBASE, the Cochrane Database of Systematic Reviews, and citation tracking of relevant articles.

Study Selection: Clinical trials were selected when passive leg raising was performed in combination with a fluid challenge as gold standard to define fluid responders and non-responders.

Data Extraction: Trials were included if data were reported allowing the extraction of sensitivity, specificity, and area under the receiver operating characteristic curve.

Data Synthesis: Twenty-three studies with a total of 1,013 patients and 1,034 fluid challenges were included. The analysis demonstrated a pooled sensitivity of 86% (95% CI, 79–92), pooled specificity of 92% (95% CI, 88–96), and a summary area under the receiver operating characteristic curve of 0.95 (95% CI, 0.92–0.98). Mode of ventilation, type of fluid used, passive leg raising starting position, and measurement technique did not affect the diagnostic performance of passive leg raising. The use of changes in pulse pressure on passive leg raising showed a lower diagnostic performance when compared with passive leg raising–induced changes in flow variables, such as cardiac output or its direct derivatives (sensitivity of 58% [95% CI, 44–70] and specificity of 83% [95% CI, 68–92] vs sensitivity of 85% [95% CI, 78–90] and specificity of 92% [95% CI, 87–94], respectively; $p < 0.001$).

Conclusions: Passive leg raising retains a high diagnostic performance in various clinical settings and patient groups. The predictive value of a change in pulse pressure on passive leg raising is inferior to a passive leg raising–induced change in a flow variable. (*Crit Care Med* 2016; XX:00–00)

Key Words: fluid challenge; fluid responsiveness; hemodynamic monitoring; meta-analysis; passive leg raising

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Unnecessary fluid administration in the treatment of shock can increase morbidity and mortality (1–3), whereas selective yet timely use of fluids has shown to be beneficial (4–7). The importance of adequate fluid therapy has received increasing attention in recent years to prevent both inadequate tissue blood flow and fluid overload. Nevertheless, accurate prediction when, to whom, and how much fluid to administer remains extremely challenging, as only half of critically ill patients respond to fluid loading with an increase in cardiac output called "fluid responsiveness" (8, 9). Clinical signs, as well as pressure and volumetric static variables, are unreliable predictors of fluid responsiveness preventing patient-tailored volume titration (10). Ventilator-induced dynamic variables, such as stroke volume variation and pulse pressure variation, have shown to be accurate in predicting fluid responsiveness (11–17), but several requirements limit their use in critically ill patients, such as a regular heart rhythm and controlled mechanical ventilation with tidal volumes greater than 8 mL/kg (9, 18–20).

To successfully predict fluid responsiveness, a change in preload needs to be created on one hand, as well as measuring the subsequent changes in a physiologic variable, such as cardiac output or a derivative-like pulse pressure on the other hand (21). Passive leg raising (PLR) induces a rapid yet reversible increase in biventricular preload through an increase in venous return mimicking fluid administration (22, 23). PLR has, therefore, been proposed as an attractive way to predict fluid responsiveness and showed good diagnostic accuracy in a prior meta-analysis of 9 studies with patients primarily suffering from circulatory failure caused by sepsis (24). However, the PLR-induced increase in venous return is dependent of the pressure gradient between the mean systemic filling pressure (MSFP) and right atrial pressure (RAP) limited by the venous resistance (R_v) according to the principle reported by Guyton (25). These variables may vary in different clinical settings, potentially limiting the predictive value of PLR. Furthermore, a fast response and direct measurement technique of the effect on cardiac output or its derivatives is needed. Although multiple measurement techniques and outcome variables on PLR are used in daily clinical practice, the diagnostic performance of each method remains unknown.

In this meta-analysis, we investigate the available literature on PLR and fluid responsiveness to provide the physician with an overview of the predictive value of PLR in various clinical settings and patient groups. In addition, we compared the diagnostic performance of different measurement techniques and outcome variables on PLR.

METHODS

Identification of Studies

A search of the PubMed database was performed for all full-text publications in English with no restriction on publication date using the following Medical Subject Headings and search terms: "passive leg raising" or "passive leg raise" or "passive leg elevation" or "passive leg movement" or "passive leg lifting" to identify all clinical trials performed in adults where PLR was used. Study selection was performed by two authors independently (T.G.V.C. and B.F.G.), with discrepancies resolved by a third party (A.H.). In addition, we searched EMBASE, the Cochrane Database of Systematic Reviews, and the references of all potentially eligible studies. We included all studies where 1) a fluid challenge was given as gold standard to delineate fluid responders from nonresponders, 2) PLR was performed, and 3) data were available to derive true positives/false positives/false negatives/true negatives to calculate sensitivity, specificity, and the area under the receiver operating characteristic curve (AUROC). Authors were contacted when data were not sufficient for analysis.

Data Extraction

For all included studies, the following study characteristics potentially influencing MSFP, RAP, and/or R_v and thus the diagnostic performance of PLR were collected: the use of vasoactive medication, sepsis, ventilation mode, PLR starting position, cardiac rhythm and function, type and amount of fluid administered, technique used to measure cardiac output or a derivative, and the outcome variable. When multiple techniques on PLR were used in one study, the method employed for defining fluid responders following the fluid challenge was regarded as the primary technique. The outcome variables were classified as "flow" variables, that is, cardiac output or its direct derivatives cardiac index, stroke volume (index), or aortic blood flow, or as "pressure" variables, such as pulse pressure. A change in stroke volume and/or pulse pressure induced by PLR may predict fluid responsiveness following a comparable mechanism as stroke volume variation and/or pulse pressure variation induced by mechanical ventilation in that regard that both methods provoke a preload change, although PLR causes an increase in preload, whereas mechanical ventilation generates a decrease in preload. Of all included studies, the patient characteristics, year of publication, study design and population, number of patients, used cutoff value, and percentage of fluid responders were recorded. The meta-analysis was reported in adherence with the guidelines provided by the Preferred Reporting Items for Systematic reviews and Meta-Analysis statement (26).

Statistical Analysis

A fluid challenge was employed as statistical unit as multiple fluid challenges were used in some patients. Analyses of patient characteristics were performed using SPSS Statistics version 22.0 (IBM, New York, NY) with values given as mean ± SD. For meta-analyses, we used the Hierarchical Summary Receiver Operating Characteristics (HSROC) model (27), a meta-regression method that incorporates both sensitivity and specificity while taking into account the possible correlation between the two. The model assumes that there is an underlying summary ROC curve to the study results. The HSROC model produces estimates for this curve: the accuracy (in terms of diagnostic odds ratio [DOR]), the threshold at which the tests are assumed to be working, and the shape of the curve. The shape of the curve provides information about how the accuracy (DOR) varies when the threshold varies. From these estimates, it is possible to derive an average sensitivity, specificity and AUROC with 95% CI using SAS version 9.3 (SAS Institute, Cary, NC), and for the ease of interpretation, we will present these. Heterogeneity was investigated by means of the I^2 with potential sources of heterogeneity assessed by adding them as covariates to the HSROC model. Covariates added to the HSROC model are assumed to explain variation in the actual accuracy (balance between sensitivity and specificity), in the threshold at which the tests operate, or on the shape of the curve. A p value of less than or equal to 0.05 between subgroups was considered statistically significant.

RESULTS

Study Selection

The process of the study selection is illustrated in **Figure 1**. Up to June 2015, we identified 274 articles with 51 full-text English publications describing PLR in the context of fluid

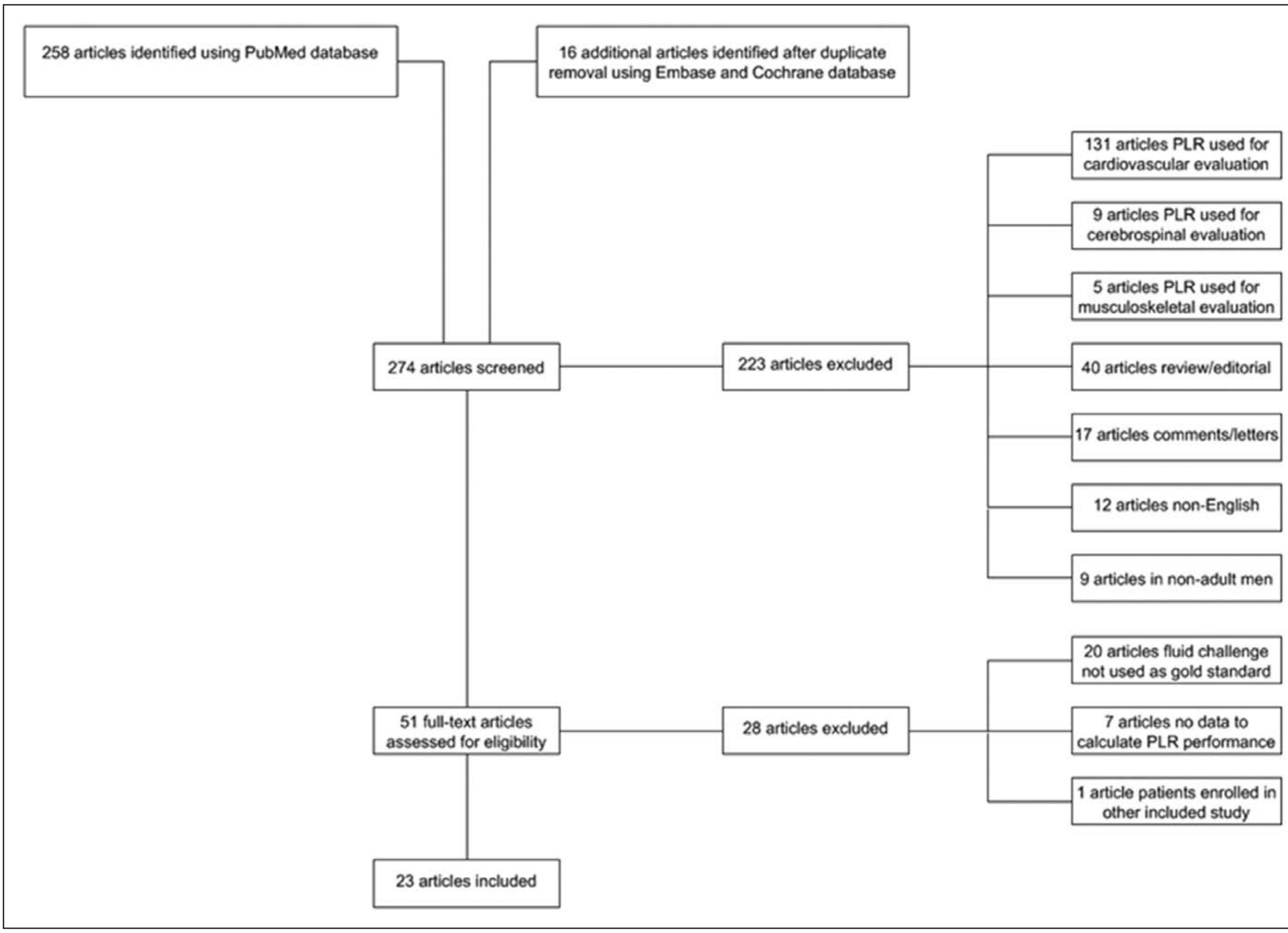

Figure 1. Flowchart of study selection and inclusion with no restriction on publication date. PLR = Passive leg raising.

responsiveness; of which, 28 studies were excluded because the diagnostic performance of PLR could either not be determined or was not investigated in combination with a fluid challenge as gold standard. All excluded articles are accessible and ordered by reason of rejection in the **Electronic Supplemental Files** (Supplemental Digital Content 1, http://links.lww.com/CCM/B579; Supplemental Digital Content 2, http://links.lww.com/CCM/B580; Supplemental Digital Content 3, http://links.lww.com/CCM/B581; Supplemental Digital Content 4, http://links.lww.com/CCM/B582; Supplemental Digital Content 5, http://links.lww.com/CCM/B583; Supplemental Digital Content 6, http://links.lww.com/CCM/B584; Supplemental Digital Content 7, http://links.lww.com/CCM/B585; Supplemental Digital Content 8, http://links.lww.com/CCM/B586; Supplemental Digital Content 9, http://links.lww.com/CCM/B587; Supplemental Digital Content 10, http://links.lww.com/CCM/B588; Supplemental Digital Content 11, http://links.lww.com/CCM/B589). Finally, a total of 23 studies were included in this meta-analysis (28–50).

Study Characteristics

The quality of the included studies were assessed by Quality Assessment of Diagnostic Accuracy Studies 2 available in the Electronic Supplemental File (Supplemental Digital Content 12, http://links.lww.com/CCM/B590) (51), whereas study characteristics are described in **Table 1**. In total, 1,034 fluid challenges were given with the most frequent indication being circulatory failure in the setting of sepsis, whereas two studies used multiple fluid challenges in some patients (33, 39). PLR was executed with the lower limbs lifted in a straight manner to an angle of 45°, mostly performed from the semirecumbent starting position. Different types of fluids were administered, namely saline, colloid, or gelatine, yet always 500 mL with time of infusion between 10 and 30 minutes. All studies were prospectively performed in the ICU except for one study executed in the Department of Anesthesiology and Obstetrics (48), one study in the Emergency Department (50), and one retrospective ICU study using an electronic chart review (45).

Patient Characteristics

The characteristics of the patients are given in **Table 2**. Altogether, 1,013 patients with a mean age of 59 ± 9 years were included who were mostly in sinus rhythm with an average cardiac output of 5.5 ± 1.2 L/min. Most patients were considered to suffer from inadequate tissue perfusion based on hemodynamic variables, such as systolic blood pressure below

TABLE 1. Main Characteristics of Included Studies

Author	Year	No. of Fluid Challenges in Combination With Passive Leg Raise	Patient Population	Ventilation Mode	Starting Position	Fluid Type	Time of Fluid Infusion, min
Monnet (28)	2006	71	Circulatory failure (mostly sepsis)	Mixed	Semirecumbent	Saline	10
Lafanechère (29)	2006	22	Circulatory failure (mostly sepsis)	Controlled MV	Supine	Saline	–
Lamia (30)	2007	24	Circulatory failure (mostly sepsis)	Spontaneous	Semirecumbent	Saline	15
Maizel (31)	2007	34	Circulatory failure	Spontaneous	Supine	Saline	15
Monnet (32)	2009	34	Circulatory failure (mostly sepsis)	Mixed	Semirecumbent	Saline	10
Thiel (33)	2009	102	Circulatory failure (mostly sepsis)	Mixed	Semirecumbent	Any	–
Biais (34)	2009	30	General ICU patient	Spontaneous	Semirecumbent	Saline	15
Préau (35)	2010	34	Circulatory failure (mostly sepsis)	Spontaneous	Semirecumbent	Colloid	30
Lakhal (36)	2010	102	Circulatory failure (mostly sepsis)	Controlled MV	Supine	Gelatine	30
Benomar (37)	2010	75	Post–cardiac surgery	Mixed	Semirecumbent	Colloid	15
Monnet (38)	2011	25	Septic shock	Mixed	Semirecumbent	Saline	10
Guinot (39)	2011	25	Venovenous extracorporeal membrane oxygenation	Controlled MV	Semirecumbent	Saline	15
Monnet (40)	2012	54	Circulatory failure (mostly sepsis)	Controlled MV	Semirecumbent	Saline	20
Dong (41)	2012	32	Severe sepsis	Mixed	Semirecumbent	Colloid	30
Monge García (42)	2012	37	Circulatory failure (mostly sepsis)	Controlled MV	Semirecumbent	Colloid	30
Monnet (43)	2012	39	Circulatory failure (mostly sepsis)	Controlled MV	Semirecumbent	Saline	30
Fellahi (44)	2012	25	Post–cardiac surgery	Controlled MV	Semirecumbent	Colloid	15
Marik (45)	2013	34	Circulatory failure (mostly sepsis)	Mixed	Semirecumbent	Saline	10
Monnet (46)	2013	40	Circulatory failure (mostly sepsis)	Controlled MV	Semirecumbent	Saline	30
Saugel (47)	2013	24	General ICU patient	Spontaneous	Semirecumbent	Saline	30
Brun (48)	2013	23	Severe preeclampsia with oliguria	Spontaneous	Semirecumbent	Saline	15
Kupersztych (49)	2013	48	Circulatory failure (mostly sepsis)	Mixed	Semirecumbent	Saline	10
Duus (50)	2014	100	At discretion of physician	Spontaneous	Semirecumbent	Saline	–

MV = mechanical ventilation.

TABLE 2. Main Baseline Patient Characteristics

Author	No. of Patients Undergoing Passive Leg Raising and a Fluid Challenge	Age	Men (%)	Sepsis (%)	Vasopressor Use (%)	Sinus Rhythm (%)	Heart Rate (Beats/min)	Mean Arterial Pressure (mm Hg)	Cardiac Output (L/min)	Systemic Vascular Resistance (dyn·s·cm^{-5})
Monnet (28)	71	58 ± 16	44 (62)	46 (65)	36 (51)	60 (85)	103 ± 23	74 ± 18	3.3	1,552
Lafanechère (29)	22	69	13 (59)	13 (59)	21 (95)	22 (100)	101	71	3.4	1,435
Lamia (30)	24	65 ± 15	13 (54)	18 (75)	12 (50)	18 (75)	95 ± 26	67 ± 9	6.0 ± 1.7	760
Maizel (31)	34	61 ± 17	19 (56)	–	–	34 (100)	90 ± 21	75 ± 20	5.0 ± 1.4	1,040
Monnet (32)	34	–	–	32 (94)	23 (68)	23 (68)	107 ± 27	68	4.9	955
Thiel (33)	89	59 ± 15	51 (57)	54 (61)	52 (58)	73 (82)	96 ± 20	71 ± 13	7.4 ± 2.8	681
Biais (34)	30	55 ± 17	21 (70)	7 (23)	0 (0)	–	78	82	6.0	933
Préau (35)	34	53 ± 19	19 (56)	28 (82)	5 (15)	34 (100)	101 ± 21	77 ± 14	5.0	1,063
Lakhal (36)	102	59 ± 16	72 (71)	52 (51)	94 (92)	102 (100)	97 ± 23	71 ± 13	6.0 ± 2.3	800
Benomar (37)	75	66 ± 11	52 (72)	0 (0)	27 (36)	–	88 ± 18	–	4.2 ± 1.0	–
Monnet (38)	25	62 ± 13	13 (52)	25 (100)	25 (100)	–	103 ± 19	71 ± 7	5.4	1,722
Guinot (39)	17	–	11 (65)	–	4 (24)	–	95	76	5.7	940
Monnet (40)	54	63 ± 12	33 (61)	44 (81)	41 (76)	54 (100)	87 ± 18	73 ± 21	6.3	800
Dong (41)	32	59 ± 14	21 (66)	32 (100)	–	32 (100)	96 ± 22	73 ± 13	5.8	967
Monge García (42)	37	64 ± 13	16 (43)	26 (70)	28 (76)	37 (100)	98 ± 23	77 ± 13	5.9 ± 2.3	1,203 ± 482
Monnet (43)	39	–	–	28 (72)	25 (64)	39 (100)	93 ± 24	73 ± 18	6.1	826
Fellahi (44)	25	64 ± 13	17 (68)	0 (0)	8 (32)	25 (100)	71 ± 15	63 ± 9	3.6	1,289
Marik (45)	34	64 ± 10	18 (53)	22 (65)	21 (62)	34 (100)	–	–	–	–
Monnet (46)	40	60 ± 14	37 (57)	59 (91)	63 (97)	33 (83)	96 ± 19	69 ± 14	5.2	904
Saugel (47)	24	60	17 (71)	2 (8)	9 (38)	24 (100)	102	81	7.6	738
Brun (48)	23	28	0 (0)	0 (0)	17 (74)	–	87	101	6.4	1,138
Kupersztych (49)	48	–	28 (58)	40 (83)	32 (67)	46 (96)	92 ± 21	80 ± 13	6.7	841
Duus (50)	100	49 ± 18	31 (31)	0 (0)	0 (0)	–	80 ± 15	90	–	–

Mean arterial pressure, when not reported derived from systolic pressure + (2 × diastolic pressure)/3; cardiac output (CO), when not reported derived from stroke volume × heart rate or from body surface area × cardiac index, systemic vascular resistance, when not reported derived from MAP – 10/CO). Date are presented as number of patients with percentage in parenthesis or as means ± SD. When not reported or in case of a derived hemodynamic variable, no SD is given.

90 mm Hg in combination with several clinical features, such as decreased urine production, cold extremities, and skin mottling. More than half (56%) of patients required vasopressors, in line with the high fraction of patients suffering from sepsis (57%).

Measurement Techniques and Outcome Variables

An overview of measurement techniques and outcome variables is depicted in **Table 3**. Four methods were used as a primary measurement technique for the fluid challenge as gold standard in combination with PLR: esophageal Doppler, transthoracic echocardiography, calibrated pulse contour analysis, and bioreactance. All primary methods measured a flow variable as outcome, that is, cardiac output or its direct derivatives cardiac index, stroke volume (index), or aortic blood flow. As cutoff value to discriminate fluid responders from nonresponders, generally an increase of 15% was chosen, resulting in 53% ± 12% of patients responding to a fluid challenge. In multiple studies, a secondary and sometimes third, although mostly experimental, measurement technique and outcome variable were used, but only one method was applied more than once, namely, the arterial blood pressure transducer measuring pulse pressure as outcome.

TABLE 3. Overview of Measurement Techniques and Outcome Variables

Author	Method 1	Outcome 1	Cutoff (%)	% Fluid Responders	Method 2	Outcome 2	Method 3	Outcome 3
Monnet (28)	Esophageal Doppler	ABF	15	52	ABP transducer	PP		
Lafanechère (29)	Esophageal Doppler	ABF	15	45				
Lamia (30)	Echocardiography	SVI	15	54				
Maizel (31)	Echocardiography	CO	12	50	Echocardiography	SV		
Monnet (32)	Pulse contour	CI	15	68	ABP transducer	PP		
Thiel (33)	Echocardiography	SV	15	46				
Biais (34)	Echocardiography	SV	15	67	Pulse contour[a]	SV		
Préau (35)	Echocardiography	SV	15	41	ABP transducer	PP	Femoral Doppler	Femoral blood flow
Lakhal (36)	Pulse contour	CO	10	42	ABP transducer	PP		
Benomar (37)	Bioreactance	CO	9	49				
Monnet (38)	Pulse contour	CI	15	88				
Guinot (39)	Echocardiography	SV	15	52	Echocardiography	CO		
Monnet (40)	Pulse contour	CI	15	56				
Dong (41)	Pulse contour	SVI	15	69	Central venous catheter	Central venous pressure		
Monge García (42)	Esophageal Doppler	CO	15	57	ABP transducer	PP	Gas analyzer tube	Partial end-tidal carbon dioxide
Monnet (43)	Pulse contour	CI	15	44				
Fellahi (44)	Pulse contour	CI	15	56	Endotracheal bioimpedance	CI		
Marik (45)	Bioreactance	SVI	10	53	Carotid Doppler	Carotid blood flow		
Monnet (46)	Pulse contour	CI	15	53	ABP transducer	PP	Capnography	End-tidal carbon dioxide
Saugel (47)	Pulse contour	CI	15	29	ABP transducer	Mean arterial pressure	Pulse contour	Cardiac power index
Brun (48)	Echocardiography	SVI	15	52	Brachial cuff	PP		
Kupersztych (49)	Pulse contour	CI	15	40	Bioreactance	CI		
Duus (50)	Bioreactance	SV	10	64				

Method 1 = primary measurement technique for fluid challenge as gold standard in combination with passive leg raising, outcome 1 = primary outcome variable, cutoff = set percentage of increase in outcome variable following the fluid challenge to define fluid responders, method 2 = secondary measurement technique on passive leg raising, outcome 2 = outcome variable of secondary measurement technique, method 3= third measurement technique on passive leg raising, outcome 3 = outcome variable of third measurement technique, ABF = aortic blood flow, ABP = arterial blood pressure, PP = pulse pressure, echocardiography = transthoracic echocardiography, SVI = stroke volume index, CO = cardiac output, SV = stroke volume, pulse contour = calibrated pulse contour analysis, CI = cardiac index.

[a]Uncalibrated.

Global Diagnostic Performance of PLR

The pooled sensitivity and specificity from all 23 studies using the primary measurement techniques were 86% (95% CI, 79–92) and 92% (95% CI, 88–96) respectively, with a summary AUROC of 0.95 (95% CI, 0.92–0.98) displayed in **Figure 2**. Seventeen studies (74%) took place in France, and no difference was seen in diagnostic performance of PLR compared with the other six studies (p = 0.10). When studies were

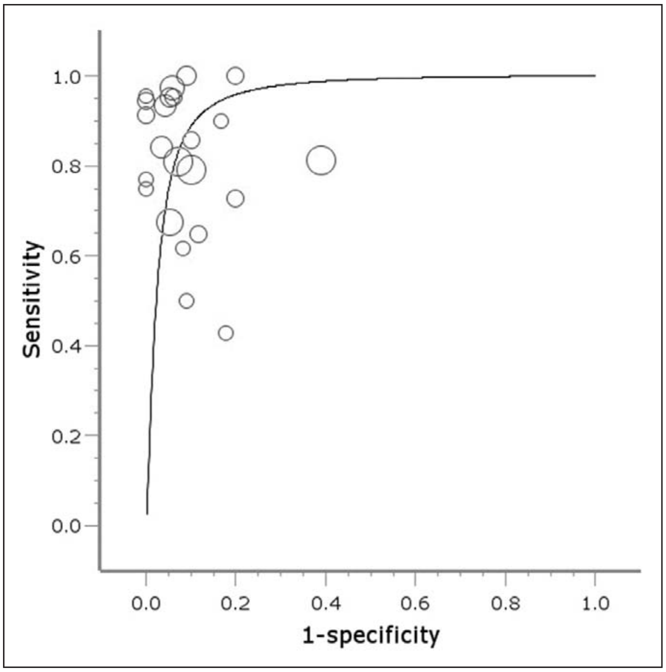

Figure 2. All 23 studies plotted in a summary receiver operating characteristic curve with the circle size representing the number of patients in each study. All studies used a flow variable as primary outcome, that is, cardiac output or its direct derivatives cardiac index, stroke volume (index), or aortic blood flow. The pooled sensitivity is 86% (95% CI, 79–92), pooled specificity is 92% (95% CI, 88–96), with a summary area under the receiver operating characteristic curve of 0.95 (95% CI, 0.92–0.98).

divided in older (till 2010) versus newer (from 2011) studies, no difference was seen in diagnostic performance either (p = 0.73). The I^2 amounted to 50.9% for sensitivity and 35.3% for specificity.

Subgroup Comparisons

The diagnostic performance of PLR was similar in spontaneously breathing patients versus controlled mechanically ventilated patients (p = 0.10). Furthermore, no difference was observed when PLR was performed from the supine starting position versus the semirecumbent position (p = 0.33). When saline fluid challenges were used compared with other fluid types, no effect on diagnostic performance of PLR was seen (p = 0.36). No comparison between regular heart rhythm versus arrhythmia could be made as the vast majority of patients in the included studies were in sinus rhythm.

The primary measurement techniques obtaining a flow variable as outcome showed no difference in diagnostic performance (**Table 4**). PLR-induced changes in flow variables showed a sensitivity of 85% (95% CI, 78–90) and a specificity of 92% (95% CI, 87–94). The use of changes in pulse pressure on PLR showed a sensitivity of 58% (95% CI, 44–71) and a specificity of 83% (95% CI, 68–92). Changes in pulse pressure on PLR exhibited a lower diagnostic performance compared with PLR-induced changes in flow variables (p < 0.001).

DISCUSSION

We found 23 studies with a combined total of 1,013 patients in a wide diversity of clinical settings. The global predictive value of PLR was strong with a pooled sensitivity of 86%, specificity of 92%, and a summary AUROC of 0.95. The diagnostic performance of PLR was unaffected by ventilation mode, type of fluid used, PLR starting position, or technique measuring the change in flow induced by PLR. However, changes in pulse pressure on PLR were inferior in predicting fluid responsiveness compared with changes in flow variables. Our meta-analysis shows that PLR is a reliable predictor of fluid responsiveness and can be used in a variety of clinical settings as long as the PLR effects are assessed by a direct measure of cardiac output.

The passive 45° raising of straightened legs was originally used by clinicians to assess lumbar nerve root compression and hamstring muscle length. Already in 1965, Thomas and Shillingford (52) demonstrated the effect of PLR on cardiac output. Since 1982, PLR has been described as a method to induce a reversible "autotransfusion" (53) but has later been removed from cardiopulmonary resuscitation guidelines. Boulain et al(22) was the first to document the usefulness of PLR to predict fluid responsiveness, generating growing interest in PLR as only half of critically ill patients turn out to be fluid responders (8, 9), in correspondence with the observed prevalence of 53% in this meta-analysis.

Although PLR offers a reversible and thus attractive tool to augment cardiac preload within a minute (54), the exact

TABLE 4. Comparison of the Primary Measurement Techniques Measuring Flow Variables

Technique	No. of Studies	No. of Fluid Challenges in Combination With Passive Leg Raise	Sensitivity	Specificity	Area Under the Receiver Operating Characteristic Curve
Esophageal Doppler	3	130	96 (84–99)	92 (77–97)	0.96
Transthoracic echocardiography	7	272	79 (68–87)	91 (86–95)	0.88
Pulse contour analysis	10	423	84 (77–89)	92 (87–95)	0.92
Bioreactance	3	209	84 (67–93)	86 (68–94)	0.89

The 95% CI is given in parentheses. When calibrated pulse contour analysis was used as reference, applied in 10 studies and consequently the most frequent applied measurement technique, no significant differences were found compared with esophageal Doppler (p = 0.43), transthoracic echocardiography (p = 0.69), and bioreactance (p = 0.37).

amount of increase in venous return is unpredictable. The reported amount of volume "autotransfused" by PLR ranges from 250 to 350 mL (29, 55, 56). When using the semirecumbent starting position, PLR induces the transfer of a larger blood volume compared with the supine starting position (57) because venous blood not only from the legs but also from the large splanchnic compartment is mobilized. However, we did not find a difference in diagnostic performance of PLR between the semirecumbent and supine positions nor did an earlier smaller meta-analysis (24). It is important to consider that the effect of PLR is not only dependent on the amount of recruited volume but on other factors as well, as demonstrated by the wide variety of stroke volume responses on PLR in healthy volunteers (58). Central volume status, norepinephrine, and propofol have demonstrated to influence the degree of preload dependency and subsequently the effect of PLR (38, 59, 60). In the case of intra-abdominal hypertension, possibly provoking increased resistance to venous return (61), PLR seems inaccurate in predicting fluid responsiveness (62). Although in this meta-analysis, a good performance of PLR was seen in a study with pregnant women (48), another study with a high percentage of patients with decompensated liver cirrhosis and ascites with a subsequent greater likelihood of increased intra-abdominal pressures found a poor performance of PLR (47).

No difference in diagnostic performance of PLR was seen in spontaneously breathing patients compared with controlled mechanically ventilated patients. Mechanical ventilator–induced dynamic variables, such as pulse pressure variation and stroke volume variation, have shown to be unreliable predictors of fluid responsiveness in the setting of spontaneous breathing (8), so PLR-induced changes in cardiac output or stroke volume can be used instead in this patient population. One would expect that arrhythmia has no effect on the diagnostic performance of PLR either because the effect of PLR is measured over multiple heartbeats and multiple breaths probably nullifying potential distorting effects of arrhythmia and spontaneous breathing, respectively. However, in contrast to an earlier report (24), no conclusions can be drawn from this meta-analysis as only a small portion of patients experienced arrhythmia in the 23 included studies.

Although Trof et al(63) showed that fluid loading using colloids results in a greater cardiac response after 90 minutes, the type of fluids used for the volume challenge did not affect the diagnostic performance of PLR. As the time of infusion was between 10 and 30 minutes after which the effect on the outcome variable was measured, no large differences were to be expected between saline and other fluid types. Interestingly, mostly colloids were used in the meta-analyses reviewing fluid responsiveness prediction by central venous pressure, stroke volume variation, pulse pressure variation and systolic pressure variation, in contrast to this meta-analysis on PLR (8, 64). In light of the recent literature on the association between adverse effects and colloids (65), crystalloids are preferred when assessing the diagnostic performance of PLR.

A fast response and direct measurement technique of cardiac output or its derivatives is necessary to assess the effect of PLR. Although PLR induces an increase in cardiac preload with its maximum effect at approximately 1 minute, the effect is not sustained and vanishes completely when the legs are returned to the horizontal position (66). Thus, the hemodynamic effects of PLR must be assessed during a time frame of 30–90 seconds with a fast responding method. All 23 studies used fast responding techniques as primary method, and we did not found a difference between the four measurement techniques. The use of transthoracic echocardiography can be limited by varying acoustic windows and its noncontinuous nature. Especially, obtaining apical views for stroke volume determination may prove an ordeal in ICU patients, with reported problematic views up to 40% suggesting carotid Doppler as an alternative (67). Indeed, the two studies in this meta-analysis examining carotid Doppler and femoral Doppler showed a good diagnostic performance of PLR (35, 45). The three studies using esophageal Doppler showed comparable results (28, 29, 42), with this technique being user dependent as well, whereas probe repositioning may be necessary (68). Bioreactance was used in four studies in this meta-analysis with three studies demonstrating good diagnostic performance of PLR (37, 45, 50) and one study reporting an AUROC not significantly different from 0.5 (49). Unfortunately, the latter study could not be included in our evaluation on the performance of bioreactance as the published data were not sufficient for analysis and additional data were not provided on request. These missing data could have influenced the diagnostic performance of bioreactance. Pulse contour analysis, preceded by calibration using thermodilution, was the most frequent applied measurement technique, demonstrating good results in a variety of clinical settings.

Pulse pressure changes on PLR had a lower diagnostic performance than changes in cardiac output and its direct derivatives, which is in accordance with the literature (24). This can be explained by the fact that PLR normally exhibits no effect on blood pressure and heart rate through the counterbalancing increase in cardiac preload and dilatation of peripheral arteries (69). However, when arterial baroreceptors are stimulated, for example, through pain, arterial compliance can change causing pulse pressure to inaccurately reflect stroke volume (70). It is, therefore, important to avoid any pain-induced sympathetic stimulation that can result in erroneous interpretation of the hemodynamic effects of PLR. Furthermore, pulse pressure has shown to poorly reflect stroke volume during sepsis because of an increase in total arterial compliance (71, 72). As PLR usually does not affect heart rate, the change in stroke volume or aortic blood flow can be attained as suitable alternative to cardiac output. Interestingly, promising results have been achieved using changes in (partial) end-tidal carbon dioxide demonstrating good diagnostic performance predicting fluid responsiveness on PLR as well (42, 46).

PLR cannot be implemented in every clinical setting, and specific rules should be followed when performing PLR (73). Evidently, in patients after amputations, hip or extensive lower leg surgery and some gynecologic and urologic operations, PLR is not either possible or painful. Furthermore, PLR can be cumbersome to perform during surgery as it may interfere with the ongoing procedure. Furthermore, PLR should be avoided in patients with head trauma since it can increase intracranial pressure. In addition, keeping the thorax in the horizontal position, and not lower, may reduce the risk of gastric inhalation. Care should be taken to maintain the pressure transducers, when used, at heart level during the PLR maneuver. Finally, PLR may interfere with the measurement technique used, mostly echocardiography or esophageal Doppler.

Limitations

No definition on fluid responsiveness was available until recently (10). The use of different cutoff values, as well as different measurement techniques and outcome variables, to determine fluid responsiveness created heterogeneity in the combined included studies. We have not formally investigated the presence of publication bias as the necessary tests are not valid for meta-analyses of diagnostic accuracy studies, whereas the existence of publication bias has not yet been shown for systematic reviews covering diagnostic test accuracy (74, 75). Furthermore, the number of 23 included studies sometimes led to small subgroups prohibiting further analysis. Therefore, specific trials are needed if the predictive value of PLR is to be demonstrated in certain patient populations. Because we only included studies performed in adults, no statement can be made about the predictive value of PLR in children using this meta-analysis. However, recent literature suggests that PLR may be a useful predictor of fluid responsiveness in children as well (76). Finally, studies on outcome using PLR to guide fluid administration in the ICU are of the utmost importance but are regrettably still lacking.

CONCLUSIONS

This systematic review and meta-analysis provides a large dataset on PLR and its predictive value on fluid responsiveness. Our results show that PLR is a reliable tool to predict fluid responsiveness in various clinical settings, provided that the PLR effects are determined by a fast and direct measurement technique of cardiac output or its derivatives. PLR can be considered as a substitute of the classic fluid challenge without the risk of fluid overload.

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