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REVIEW

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Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies

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Abstract *Purpose:* To systematically review the published evidence on the ability of passive leg raising-induced changes in cardiac output (PLR-cCO) and in arterial pulse pressure (PLR-cPP) to predict fluid responsiveness. *Methods:* MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews were screened. Clinical trials on human adults published as full-text articles in indexed journals were included. Two authors independently used a standardized form to extract data about study characteristics and results. Study quality was assessed by using the QUADAS scale. *Results:* Nine articles including a total of 353 patients were included in the final analysis. Data are reported as point estimate (95% confidence intervals). The pooled sensitivity and specificity of PLR-cCO were 89.4% (84.1–93.4%) and 91.4% (85.9–95.2%) respectively. Diagnostic odds ratio was 89.0 (40.2–197.3). The pooled area under the receiver operating characteristics curve (AUC) was 0.95 (0.92–0.97). The pooled correlation coefficient r between baseline value of PLR-cCO and CO increase after fluid load was 0.81 (0.75–0.86). The pooled difference in mean PLR-cCO values between responders and non-responders was 17.7% (13.6–21.8%). No significant differences were identified between patients adapted to ventilator versus those with inspiratory efforts nor between patients in sinus rhythm versus those with arrhythmias. The pooled AUC for PLR-cPP was 0.76 (0.67–0.86) and was significantly lower than the AUC for PLR-cCO ($p < 0.001$). The pooled difference in mean PLR-cPP values between responders and non-responders was 10.3% (6.5–14.1%). *Conclusions:* Passive leg raising-induced changes in cardiac output can reliably predict fluid responsiveness regardless of ventilation mode and cardiac rhythm. PLR-cCO has a significantly higher predictive value than PLR-cPP.

Keywords Hemodynamics · Shock · Cardiac output · Blood volume · Blood pressure · Fluid therapy

Introduction

To stabilize hemodynamics and optimize preload of patients in shock, physicians should assess the *fluid responsiveness*, that is the ability of cardiac output to increase in response to a fluid infusion.

Static measures of preload—filling pressures and volumes—are poor predictors of fluid responsiveness [1]. Therefore dynamic indices, which measure the hemodynamic response of the cardiovascular system to a controlled variation in preload [2], have been introduced in clinical practice. The most investigated dynamic indices (e.g. the pulse pressure variation, PPV) measure the response to preload variations induced by mechanical ventilation. They are good predictors of fluid responsiveness [3], but they lose [4–7] their value in patients with spontaneous breathing activity and arrhythmias.

To overcome this limitation, the *passive leg raising* (PLR) has been proposed as an alternative preload-modifying manoeuvre: when inferior limbs are raised, an amount of blood is "auto-transfused" into the central circulation [8]. The increase in cardiac output and/or arterial pressure after PLR could predict the corresponding response after a fluid infusion.

Evidence supporting the use of PLR is still limited and it has not yet been systematically evaluated. The aim of this systematic review is to assess the predictive value of the hemodynamic response after PLR as a dynamic index of fluid responsiveness.

Materials and methods

Study selection and inclusion criteria

All clinical trials investigating the ability of hemodynamic response after PLR (the *index*) in human adults to predict the increase in cardiac output after a subsequent fluid infusion (the *outcome*) were considered for inclusion.

Only studies published or accepted for publication as full-text articles in indexed journals were included. Reviews, case reports and studies published in abstract form were excluded. No language restriction was imposed.

We included only studies in which the predictive value of the index had been assessed by calculating at least one of the following variables: (1) sensitivity and specificity of the index in identifying those patients who subsequently responded to fluids (*responders*); (2) the difference between the mean value of the index in responders versus non-responders; (3) the correlation coefficient between the hemodynamic response after PLR and the increase in cardiac output after fluid load.

Search strategy

Two authors independently performed a search in MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews with the following keywords: "fluid OR preload OR volume responsiveness", "cardiovascular monitoring", "fluid challenge", "functional hemodynamic monitoring", "dynamic indices OR indexes", "passive leg raising", in order to identify all published studies which met the inclusion criteria. The automatic alert system of MEDLINE was used to identify studies published during the process of data extraction and analysis. References of included papers were examined to identify other studies of interest.

Quality assessment

The QUADAS scale [9] is a tool developed to assess quality of studies on diagnostic accuracy to be included in systematic reviews, and is based on a 14-item evaluation sheet. Accordingly each included study was scored from 0 to 14. Since overall quality was satisfactory (see "Results") sensitivity analysis was not needed [10].

Data extraction

Two authors independently extracted the following information from included articles by using a standardized form: study setting, patient population, use of inotropes/vasopressors, ejection fraction, ventilation mode, cardiac rhythm (sinus vs. arrhythmias), type and amount of fluid infused, definition of responders, instrument(s) used for measuring index and cardiac output, number of patients included, number of fluid boluses administered, number and percentage of responders, mean value (with standard deviation) of the index in responders and in non-responders, correlation coefficient (Spearman or Pearson), sensitivity, specificity, best threshold and area under the ROC curve (AUC). When reported data were not sufficient to perform the planned statistic analysis, whenever possible the first authors were contacted in order to obtain additional information.

Data analysis

Using Comprehensive Meta-Analysis® version 2.2 (Biostat Inc, Englewood, NJ, USA http://www.meta-analysis.com), we performed a meta-analysis to calculate: (1) the pooled AUC for PLR as a predictor of fluid responsiveness; (2) the pooled correlation coefficient between the hemodynamic response induced by PLR and that induced by the fluid load; (3) the pooled difference in means between the values of the index in responders and non-responders. All values are reported as point estimate with 95% confidence intervals (95% CI) in parentheses. When needed, standard error was calculated from reported 95% CIs to obtain the variance and the relative weight of each study for AUC meta-analysis. Funnel plots were drawn to assess the possibility of publication bias.

Using MetaDiSC®, version 1.4 (http://www.hrc.es/investigacion/metadisc.html), we calculated pooled values of sensitivity, specificity and diagnostic odds ratio (DOR). A summary ROC (SROC) curve was drawn according to the regression model proposed by Moses et al. [11].

Heterogeneity was evaluated with Q and I^2 tests and it was regarded as significant when $p < 0.1$ and $I^2 > 50\%$. According to heterogeneity, a random effect model was used to perform meta-analysis. For sensitivity and specificity, the Spearman correlation coefficient between those two parameters was calculated to evaluate a threshold effect determining heterogeneity [12].

Subgroup analysis was performed to compare the predictive value of PLR in patients with sinus rhythm versus those with arrhythmias and in patients adapted to ventilator versus those with inspiratory efforts. Moreover a comparison was made between studies in which PLR was performed starting from a semirecumbent versus supine position. The differences between subgroups were examined by using a test of interaction and regarded as significant with $p < 0.05$. A further comparison was performed between the predictive value of PLR-induced changes in cardiac output (PLR-cCO) and the predictive value of PLR-induced changes in arterial pulse pressure (PLR-cPP).

Since in one study [13] multiple fluid boluses per patient were administered and results are reported by using bolus—and not patient—as a statistical unit, we did the same in meta-analysis. Predictive value of the index was thus investigated in all subsequent loading steps.

Data reporting conformed to quality of reporting of meta-analyses (QUOROM) [14] and preferred reporting items for systematic reviews and meta-analyses (PRISMA) [15] statements.

Results

Process of study selection

The process of study selection and inclusion is summarized in Fig. 1 and detailed in the "Electronic

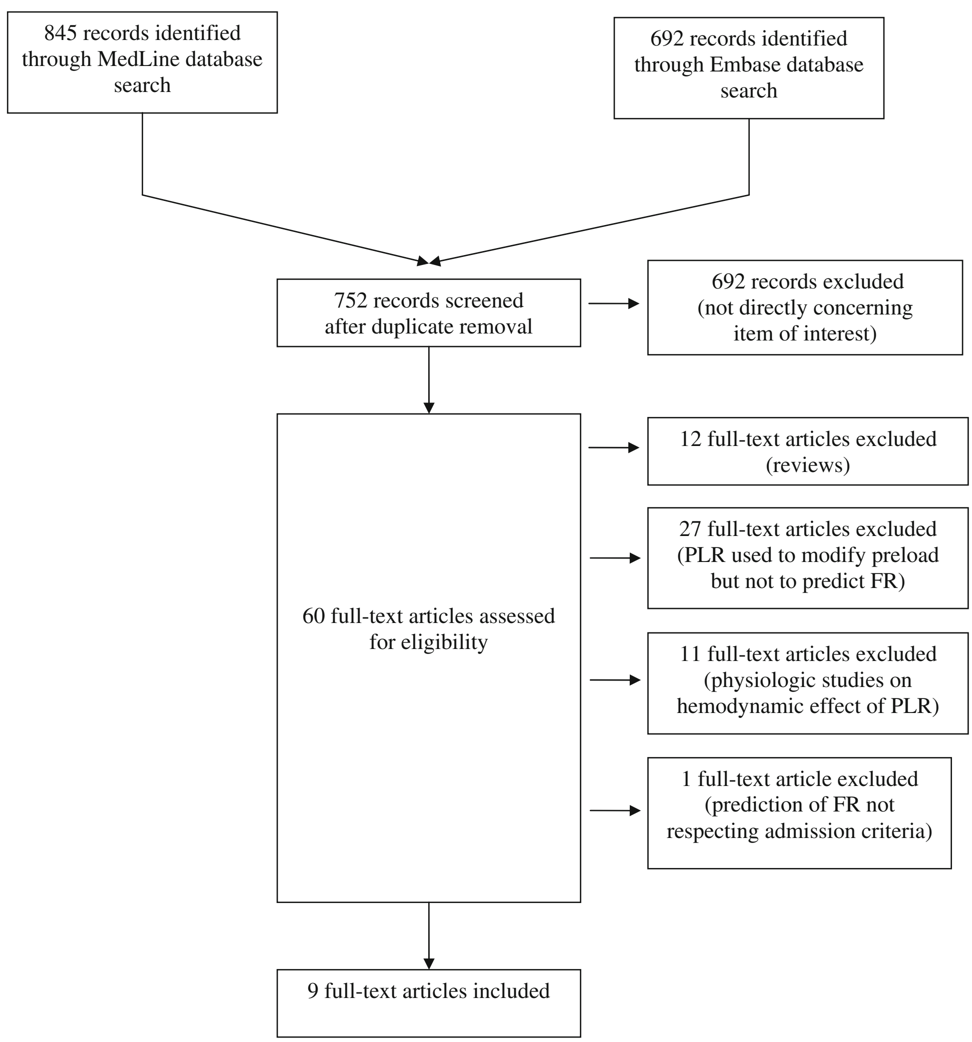

Fig. 1 Flow chart of study selection and inclusion

supplementary material" (ESM) 1. After an initial dataset of 845 records, we identified 60 full-text articles regarding PLR. Among them, 27 were excluded because the predictive value for fluid responsiveness was not investigated, 11 because they were physiologic studies on hemodynamic effects of PLR, 1 [16] because only responders were enrolled, 12 were reviews. Nine articles [13, 17–24] were included for final analysis.

Characteristics of the included studies

Characteristics of the nine included papers are summarized in Table 1 and main results are reported in Tables 2 and 3. The median quality (QUADAS) score was 13 (range 12–14).

A total of 353 patients were enrolled (range 15–89 for single paper), to whom a total of 366 fluid boluses were administered. The mean responder rate was 52.9%.

All studies were conducted in intensive care units (ICU) on patients in shock due to various etiologies. Two studies [17, 18] enrolled only patients adapted to ventilator and in sinus rhythm, the others [13, 19–24] also enrolled patients with spontaneous respiratory efforts and/or arrhythmias. The threshold increase in CO (or its surrogates) after fluid bolus for definition of responders ranged between 12 and 15%. PLR was executed starting from a supine position in three studies [17, 18, 21], and from semirecumbent position in six studies [13, 19, 20, 22–24]. The interval between PLR execution and index measurement was 60 s [19], 90 s [20, 23], 120 s [13, 21] 4 min [17, 18], 5 min [24], not reported [22].

Meta-analysis of PLR-induced changes in cardiac output (PLR-cCO) or its surrogates

We meta-analysed as a single group all nine papers which investigated the predictive value of PLR-induced changes in CO or in other hemodynamic parameters having the same physiological meaning, such as cardiac index (CI), stroke volume (SV), aortic blood flow (ABF), aortic velocity–time integral (VTIAo). Results are reported in Table 2. When a study reported analysis for two indices of the same category [20, 21, 23] only one was included in the meta-analysis in order to avoid duplication of sample size.

Eight out of 9 papers (351 boluses) reported sensitivity and specificity of the index. Pooled values for sensitivity and specificity were 89.4% (84.1–93.4%) and 91.4% (85.9–95.2%), respectively. DOR was 89.0 (40.2–197.3) (in "ESM 2" the complete pooling analysis generated by MetaDiSC software is provided). The pooled AUC was 0.95 (0.92–0.97) (Fig. 2). Heterogeneity was non-significant. The threshold for prediction of fluid responsiveness varied between 8 and 15%.

After having excluded a threshold effect by using the Moses–Shapiro–Littenberg method [11], a symmetrical summary ROC curve (SROC) was fitted (Fig. 3). Area under the SROC was 0.96 (0.94–0.98).

Five out of 9 papers (166 boluses) reported the *r* correlation coefficient between PLR-cCO and the corresponding increase in CO after a subsequent fluid infusion. The pooled *r* was 0.81 (0.75–0.86), which was highly significant ($p < 0.0001$). Heterogeneity was non-significant for all calculations (Forrest plot in "ESM 3").

Six out of 9 papers (299 boluses) reported the difference between the mean value of index in responders and in non-responders. The pooled difference in mean was 17.7% (13.6–21.8%), which was highly significant ($p < 0.0001$). Heterogeneity was significant ($Q = 15.025$, $I^2 = 67.22\%$, $p = 0.009$) (Forrest plot in "ESM 3").

Subgroup meta-analysis between studies including patients in sinus rhythm versus patients with arrhythmias and patients adapted to ventilator versus spontaneously breathing did not find any significant difference. Similarly no significant differences were found between studies in which PLR was performed starting from supine versus semirecumbent position (see Table 4). Forrest plots for subgroup analysis are in "ESM 4".

Meta-analysis of PLR-induced changes in pulse pressure (PLR-cPP)

Four out of 9 studies (178 patients and 178 fluid boluses) investigated the predictive value of PLR-induced changes in pulse pressure. The pooled value of sensitivity and specificity (3/4 papers, 139 boluses) were 59.5% (47.4–70.7%) and 86.2% (75.3–93.5%) respectively. DOR was 10.8 (4.4–26.1) (in "ESM 2" the complete pooling analysis generated by MetaDiSC software is provided). Pooled AUC for PLR-cPP was significantly lower than the pooled AUC for PLR-cCO (0.76 [0.67–0.86] vs. 0.95 [0.92–0.97], $p < 0.001$) (Fig. 2). The threshold for prediction of fluid responsiveness varied between 9 and 12%.

The pooled mean difference of the index between responders and non-responders (3/4 papers, 139 boluses) was 10.3% (6.5–14.1%, $p < 0.0001$) (Forrest plot in "ESM 3"). The *r* coefficient was not pooled because it was reported only in one study. Heterogeneity was not significant for all calculations.

Discussion

Our meta-analysis shows that the changes in CO, CI, SV or aortic blood flow induced by PLR are well correlated with the increase in CO induced by a fluid infusion and can discriminate well between fluid responders and non-responders. The positive results of 9 relatively small

Table 1 Main characteristics of included studies

Reference	Setting/ patients	Ventilation	Rhythm	Fluid challenge	Definition of responders	Index	Device	QUADAS score
Boulain et al. [17]	ICU/shock	MV adapted		Colloids 300 ml		cPPrad cSV	Arterial BP transducer PAC	12
Lafanechère et al. [18]	ICU/shock	MV adapted	Sinus	Crystalloids 500 ml	ΔABF > 15%	cABF%	Esophageal Doppler	13
Monnet et al. [19]	ICU/shock	MV adapted/trigger	Sinus/arrhythmias	Crystalloids 500 ml	ΔABF > 15%	cPP% cABF%	Arterial BP transducer Esophageal Doppler	13
Lamia et al. [20]	ICU/shock	MV trigger/SB	Sinus/AF	Crystalloids 500 ml	ΔSVI > 15%	cVTIAo cCO	TTE TTE	13
Maizel et al. [21]	ICU/shock	SB	Sinus	crystalloids 500 ml	ΔCO > 12%	cSV% cCO%	TTE TTE	13
Thiel et al. [13]	ICU/shock	MV adapted/trigger/SB	Sinus/arrhythmias	Crystalloids or colloids 500 ml	ΔSV > 15%	cSV%	Transthoracic Doppler USCOM®	12
Monnet et al. [22]	ICU/shock	MV adapted/trigger	Sinus/arrhythmias	Crystalloids 500 ml	ΔCI > 15%	cCI% cPP%	PiCCO® Arterial BP transducer	13
Biais et al. [23]	ICU/shock	MV trigger/SB	Sinus	Crystalloids 500 ml	ΔSV > 15%	cSV% cSV %	TTE Vigileo/FloTrac®	14
Préau et al. [24]	ICU/shock	SB	Sinus	Colloids 500 ml	ΔSV > 15%	cSV% cPP% cVF	TTE Arterial BP transducer Doppler	13

AF atrial fibrillation, *BP* blood pressure, *ICU* intensive care unit, *MV* mechanical ventilation, *PAC* pulmonary artery catheter, *SB* spontaneous breathing, *TTE* transthoracic echocardiography, Δ variation; *c* PLR-induced changes in…, *ABF* aortic blood flow, *CI* cardiac index, *CO* cardiac output, *PP* pulse pressure, *PPrad* radial pulse pressure, *SV* stroke volume, *SVI* stroke volume index, *VF* peak velocity in femoral artery, *VTIAo* aortic velocity–time integral

Table 2 Main results of studies on passive leg raising-induced changes in cardiac output and its surrogates

Reference	Index	No. of pts/boluses	% Resp.	Mean (SD) resp.	Mean (SD) non-resp.	*r*	AUC (SE)	Best threshold	Sens.	Spec.	DOR
Boulain et al. [17]	cSV	15/15				0.89					
Lafanechère et al. [18]	cABF%	22/22	45			0.71	0.95 (0.040)	8.0	90	83	45
Monnet et al. [19]	cABF%	71/71	52	28.4 (20.6)	1.2 (6.1)	0.83	0.96 (0.020)	10.0	97	94	576
Lamia et al. [20]	cVTIAo	24/24	54	24.5 (9.7)	5.0 (5.5)	0.83	0.96 (0.040)	12.5	77	100	69
	cCO	24/24	54			0.79					
Maizel et al. [21]	cSV%	34/34	50	14.8 (8.8)	1.3 (8.6)	0.56	0.89 (0.059)	8.0	88	83	
	cCO%	34/34	50	12.0 (4.2)	−0.5 (10.0)	0.75	0.89 (0.060)	5.0	94	83	75
Thiel et al. [13]	cSV%	89/102	46	21.0 (12.5)	3.2 (10.4)		0.89 (0.040)	15.0	81	93	66
Monnet et al. [22]	cCI%	34/34	68	21.9 (17.9)	1.3 (0.7)		0.94 (0.050)	10.0	91	100	198
Biais et al. [23]	cSV% (TTE)	30/30	67				0.96 (0.030)	13.0	100	80	139
	cSV% (Vigileo®)	30/30	67				0.92 (0.050)	16.0	85	90	
Préau et al. [24]	cSV%	34/34	41	17.0 (7.0)	4.0 (5.0)		0.94 (0.040)	10.0	86	90	54
Overall (95% CIs)		353/366	52.9	Pooled difference in means 17.7% (13.6–21.8%)		0.81 (0.75–0.86)	0.95 (0.92–0.97)		89.4 (84.1–93.4)	91.4 (85.9–95.2)	89.0 (40.2–197.3)

AUC area under the receiver operating characteristics curve, *95% CIs* 95% confidence intervals, *DOR* diagnostic odds ratio, *pts* patients, *r* correlation coefficient, *resp.* responders, *SD* standard deviation, *SE* standard error, *Sens* sensitivity, *Spec* specificity; *c* PLR-induced changes in…, *ABF* aortic blood flow, *CI* cardiac index, *CO* cardiac output, *SV* stroke volume, *VF* peak velocity in femoral artery, *VTIAo* aortic velocity–time integral

studies are therefore confirmed in a larger sample of 353 patients. Moreover, the good predictive value was confirmed in mixed populations including patients with arrhythmias and/or spontaneous respiratory efforts.

Jabot et al. [16] found significant differences in hemodynamic response to PLR performed by starting from supine versus semirecumbent position but in our analysis the reliability of PLR-cCO was proven to be independent from how the PLR manoeuvre was performed. It was also independent from the device used to measure CO: PiCCO®, Vigileo/FloTrac®, esophageal Doppler, echocardiography.

Dynamic indices based on the oscillations in preload induced by mechanical ventilation [2, 25, 26], such as SPV, PPV and SVV, are not predictive in patients with arrhythmias and spontaneous respiratory efforts [4–7]: to measure a regular "variation" in CO it is necessary that intrathoracic pressure oscillates with a regular rhythm, which is not the case if the patient has spontaneous inspiratory efforts; moreover, cardiac arrhythmias induce an irregular SV variability.

During PLR an amount of blood is transferred from lower limbs and abdominal compartment to the central circulation [8, 27, 28], determining an increase in preload which, if the heart is preload-responsive, in turn increases CO. The hemodynamic effect of PLR is similar to the intravenous infusion of fluids [27] and should not be affected by the presence of spontaneous breathing. Moreover, since mean change in CO after PLR is measured over several heartbeats, it should not be affected by cardiac arrhythmias.

A recent meta-analysis by Marik et al. [3] evaluated the predictive value of PPV, SVV and SPV on 685 patients (29 studies), all adapted to ventilator and in sinus rhythm. Results showed that PPV was the best-performing index, having a pooled correlation coefficient of 0.78 (0.74–0.82) and a pooled AUC of 0.94 (0.93–0.95). Predictive value for SVV and SPV was slightly lower. Results of our study showed that PLR-cCO was at least as accurate as PPV and performed better that SVV and SPV. Moreover this index is suitable to a much wider range of patients, except those in which the manoeuvre cannot be performed, as in the case of limb and pelvic fractures or during some surgical procedures.

The pooled AUC for PLR-cPP was significantly lower than the AUC for PLR-cCO. This is probably because PP is not a direct measure of SV and also depends on arterial compliance. Both these parameters can vary with patient's hemodynamic conditions and can be directly altered by PLR [22]. This is consistent with results from Monnet et al. [22], who found that PLR-induced changes in PP was a worse predictor than PLR-induced changes in CI, while changes in PP and CI after an expiratory pause, a preload-increasing manoeuvre that does not alter the arterial tone, had the same predictive value.

Table 3 Main results of studies on passive leg raising-induced changes in pulse pressure

Reference	Index	No. of pts/boluses	% Resp.	Mean (SD) resp.	Mean (SD) non-resp.	*r*	AUC (SE)	Best threshold	Sens.	Spec.	DOR
Boulain et al. [17]	cPP	39/39				0.74					
Monnet et al. [19]	cPP%	71/71	52	19.3 (18.8)	4.9 (14.6)		0.75 (0.060)	12.0	60	85	9
Monnet et al. [22]	cPP%	34/34	68	15.5 (19.9)	6.4 (6.2)		0.68 (0.085)	11.0	48	91	9
Préau et al. [24]	cPP%	34/34	41	12.0 (8.0)	3.0 (6.0)		0.86 (0.080)	9.0	79	85	11
Overall (95% CIs)		178/178	53.7	Pooled difference in means 10.3% (6.5–14.1%)			0.76 (0.67–0.86)		59.5 (47.4–70.7)	86.2 (75.3–93.5)	10.8 (4.4–26.1)

AUC area under the receiver operating characteristics curve, *cPP* PLR-induced changes in pulse pressure, *DOR* diagnostic odds ratio, *pts* patients, *r* correlation coefficient, *resp.* responders, *SD* standard deviation, *SE* standard error, *Sens* sensitivity, *Spec* specificity

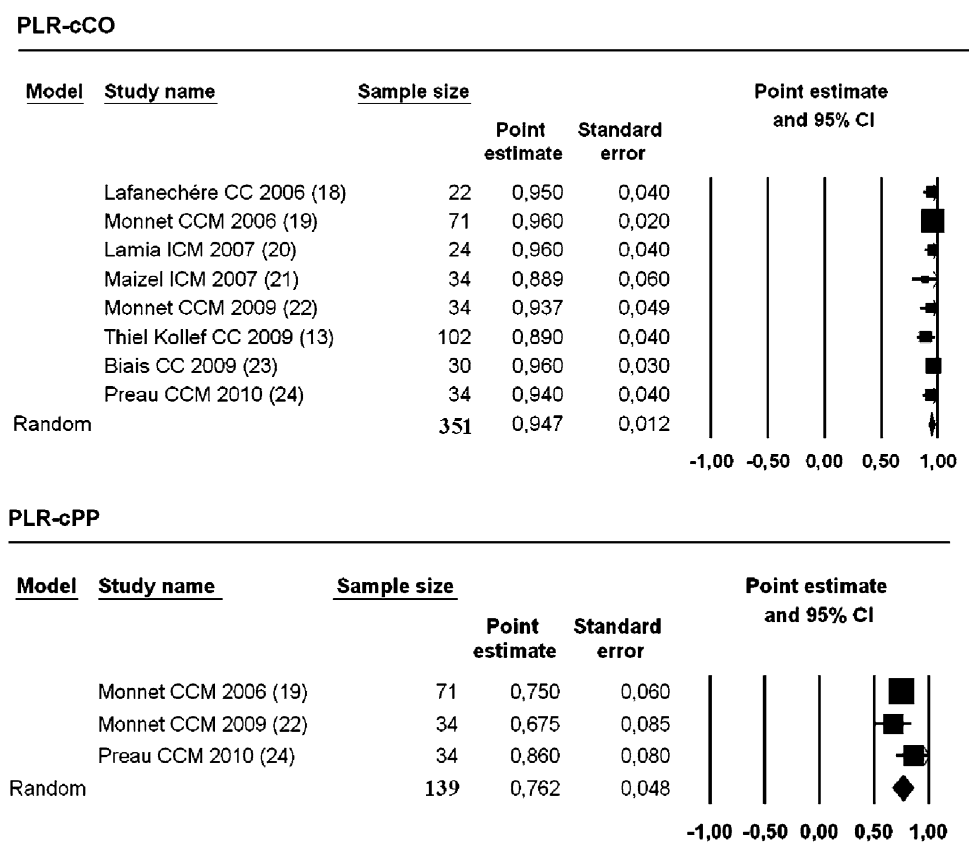

Fig. 2 Forest plot for pooled value of area under the receiver operating characteristics curve in studies on passive leg raising-induced changes in cardiac output and pulse pressure [software Comprehensive Meta-Analysis® version 2.2 (Biostat Inc, Englewood, NJ, USA, http://www.meta-analysis.com)]

Limitations

We pooled studies in which the hemodynamic response to PLR was measured by using different parameters, such as CO, CI, ABF, SV and VTIAo. This could be viewed as a source of heterogeneity. However, all these parameters derive from CO and have the same physiological meaning. The consistency of our results is confirmed by the very low value of heterogeneity.

Subgroup analysis could have been suboptimal since in the original studies the subpopulations of patients with arrhythmias or inspiratory efforts actually also included some patients in sinus rhythm or adapted to ventilator. However, mixed groups are more representative of actual ICU population and predictive ability in these patients is confirmed.

No stratification was possible for ejection fraction (EF), which was reported only in two studies [22, 24]. Assessing the reliability of indices in the case of reduced EF deserves further investigation.

Funnel plot analysis, whose value is limited by the small number of studies, showed a slight asymmetry that could be due to publication bias (funnel plots are provided in "ESM 5"). This means that smaller studies showing

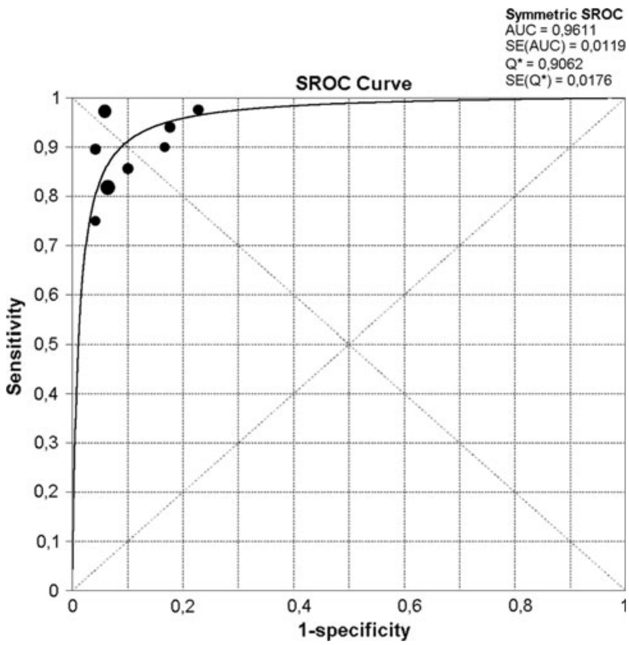

Fig. 3 Summary receiver operating characteristics curve for the ability of passive leg raising-induced changes in cardiac output to discriminate between responders and non-responders (software MetaDiSC®, version 1.4 (http://www.hrc.es/investigacion/metadisc.html))

poor prediction or smaller associations could have not been published. Moreover, only three studies [13, 17, 24] enrolled consecutive patients; in others convenience samples were chosen. These factors could have led to some effect overestimation.

Table 4 Results of subgroup analysis: pooled values (95% confidence intervals) of correlation coefficient and area under the receiver operating characteristics curve (AUC) in subgroups: controlled ventilation versus spontaneous inspiratory efforts, sinus rhythm versus arrhythmias, supine versus semirecumbent starting position

Subgroup	Correlation *r*	*p**	AUC	*p**
Ventilation				
Adapted	0.81 (0.53–0.93)	0.97	0.94 (0.87–1.00)	0.74
Inspiratory efforts	0.81 (0.74–0.87)		0.95 (0.91–0.99)	
Cardiac rhythm				
Sinus rhythm	0.73 (0.58–0.84)	0.15	0.96 (0.92–0.99)	0.94
Arrhythmias	0.83 (0.75–0.89)		0.96 (0.89–1.03)	
Starting position				
Supine	0.78 (0.64–0.87)	0.39	0.93 (0.87–1.00)	0.62
Semirecumbent	0.83 (0.75–0.89)		0.95 (0.92–0.97)	

* Test for interaction

Conclusions

Passive leg raising-induced changes in cardiac output reliably predict fluid responsiveness regardless of ventilation mode, underlying cardiac rhythm and technique of measurement and can be recommended for routine assessment of fluid responsiveness in the majority of ICU population. PLR-induced changes in pulse pressure can be a viable alternative with lower predictive ability.

Conflict of interest statement The authors disclose that no financial or ethical conflict of interest exists regarding the content of the submission. All the authors take the responsibility for content of submission.

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