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Review Article

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Physiological controversies and methods used to determine fluid responsiveness: a qualitative systematic review

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Summary

Accurate assessment of intravascular fluid status and measurement of fluid responsiveness have become increasingly important in peri-operative medicine and critical care. The objectives of this systematic review and narrative synthesis were to discuss current controversies surrounding fluid responsiveness and describe the merits and limitations of the major cardiac output monitors in clinical use today in terms of usefulness in measuring fluid responsiveness. We searched the MEDLINE and EMBASE databases (2002–2015); inclusion criteria included comparison with an established reference standard such as pulmonary artery catheter, transthoracic echocardiography and transoesophageal echocardiography. Examples of clinical measures include static (such as central venous pressure) and dynamic (such as stroke volume variation and pulse pressure variation) parameters. The static parameters measured were described as having little value; however, the dynamic parameters were shown to be good physiological determinants of fluid responsiveness. Due to heterogeneity of the methods and patient characteristics, we did not perform a meta-analysis. In most studies, precision and limits of agreement (bias ±1.96SD) between determinants of fluid responsiveness measured by different devices were not evaluated, and the definition of fluid responsiveness varied across studies. Future research should focus on the physiological principles that underlie the measurement of fluid responsiveness and the effect of different volume expansion strategies on outcomes.

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Introduction

Fluid responsiveness is a topic that has provoked much discussion both at the bedside and in the literature in recent years. It is now widely recognised that both inadequate and excessive fluid replacement are deleterious to health, and both can affect recovery in the peri-operative period and during critical illness. The definition of fluid responsiveness varies in both clinical and research settings. A recently proposed definition is 'an increase in a physiologic parameter, preferably cardiac output, within 15 min, superseding twice the error of the measuring technique after a 15-min administration of 6 ml.kg^{-1} of crystalloids' [1]. In the operating theatre, emergency department and critical care settings, only 50% of haemodynamically unstable patients are 'fluid-responders' when the fluid bolus is given on 'clinical grounds' [2, 3]. This emphasises that fluid loading is not always the correct therapy for a clinically hypoperfused patient and that 'non-responders' are exposed to the risks of volume overload, systemic and pulmonary oedema and tissue hypoxia [4]. In other words, fluid responsiveness is a measure of 'preload dependence' or 'preload reserve' but not all 'fluid-responders' necessarily need volume loading [1–6].

One of the major issues with the concept of fluid responsiveness is what values to measure and how, and many devices have been developed and tested over the last 10 years or so in an attempt to find the ideal. In addition, complications associated with the use of the pulmonary artery catheter have led to a drive to develop less invasive measurement devices. This makes deciding which device to use and how, a major challenge, especially as different parameters are measured by different means by different devices. We performed a systematic review of fluid responsiveness and how to measure it and sought the evidence for the different monitors currently marketed to assess it.

Methods

A systematic search was performed using the MEDLINE and EMBASE bibliographic databases for articles published since 2002. We searched using the following terms (in the title or abstract): fluid responsiveness; volume responsiveness; preload responsiveness; pulmonary artery catheter; transoesophageal echocardiography; transthoracic echocardiography; oesophageal Doppler monitoring; and cardiac output. A mixture of keyword (free text) and subject headings mapped to the Thesaurus were used to ensure a thorough search of the selected databases. Separate searches were carried out for each individual concept and then combined using AND/OR at a later stage. References and/or subject headings cited in the results were checked where relevant. The 'Explode' tool on databases was used where appropriate to include narrower subject headings, and truncations for keyword searches were used where applicable. Restrictions on databases were avoided in the first instance; once relevant papers had been identified, the following filters were applied: studies involving adult subjects conducted in the last eleven years and published in English; human studies; papers in English language only. The last search was performed on July 16th 2015. The results were de-duplicated using the HDAS tool and scanned to abstract level to ensure relevance. Any remaining duplicates were removed manually in addition to irrelevant results. Two authors (BA and VZ) performed data extraction independently using predefined data fields, including study quality indicators. Figure 1 shows the process of filtering the studies selected for the review. The Standards for Reporting of Diagnostic Accuracy (STARD) initiative developed a guide for assessing the quality of reporting of studies of diagnostic accuracy [7, 8]. A 19-point score was devised by Mandeville et al. [8], using 19 of the 25 STARD criteria. In this review, we adopted the modified 19-point STARD score to judge the quality of the investigation in the selected studies (Table 1). Each criterion was assigned one point and the overall score divided into categories: poor (score 0–10), adequate (11–15) and good (16–19). The results of the selected studies were not meta-analysed due to the heterogeneity in methodologies, patient populations, modes of mechanical ventilation, definitions of fluid responsiveness and volume of fluid challenges given. Predefined eligibility criteria were used: a study was included if (i) a prospective cohort study design had been used; (ii) fluid responsiveness had been evaluated by measurement of a change in cardiac output, stroke volume or cardiac index; and (iii) the predictive method had been compared with pulmonary artery catheter, transthoracic echocardiography or transoesophageal echocardiography. All papers investigating solely static parameters as predictors were excluded.

The areas under the receiving operating characteristic curve (AUROC) and their 95% confidence intervals (CI) were the primary measures for comparison. Any variable with an area under the ROC curve that was significantly above 0.5 (i.e. the lower limit of the 95% CI was above 0.5) was considered predictive. Any variable with a 95% CI overlapping 0.5 was agreed to be no better than chance and was considered not predictive [9]. Correlation index, sensitivity and specificity were extracted in cases where AUROC curves were not used.

Results

In all, 34 clinical studies involving 957 patients and 828 fluid boluses were analysed. Most studies were performed during elective cardiac surgery or in the intensive care unit (ICU). Most studies were prospective observational studies (Table 2) [10–43]. All studies used similar exclusion criteria in patient selection, for example, cardiac arrhythmias, intracardiac shunt and left ventricular dysfunction. The STARD quality scores ranged between 12 and 16, suggesting an 'adequate' standard (Table 2).

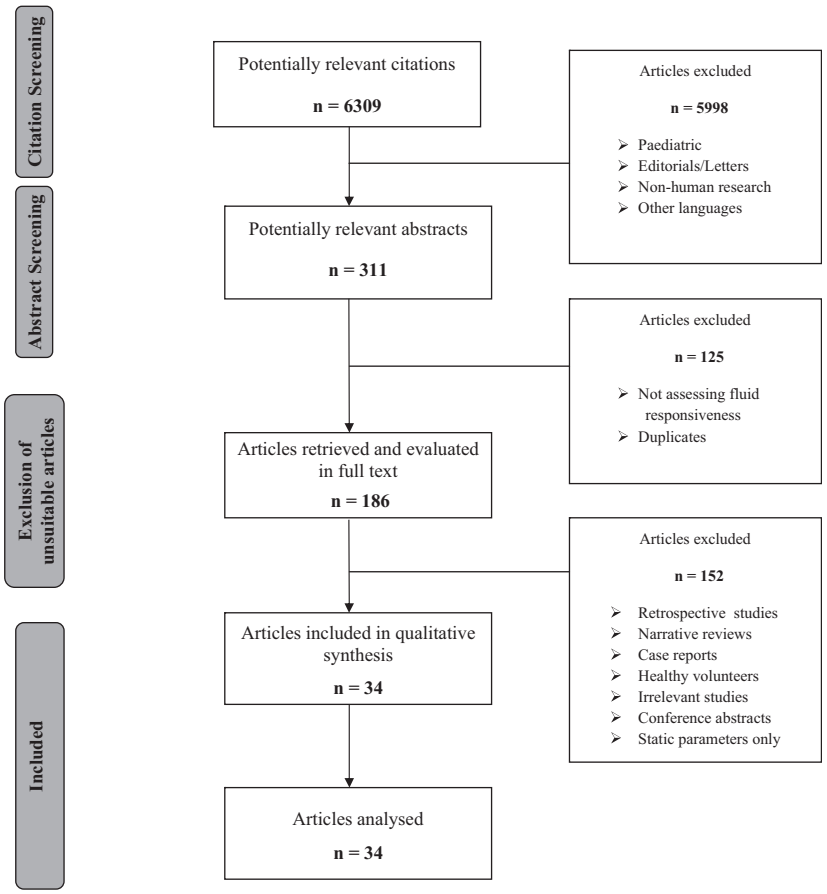

Figure 1 Citation filtering strategy.

Pulmonary artery catheter

We identified 30 potentially relevant publications involving the use of the pulmonary artery catheter. Of these, the following were excluded: one retrospective study; eight reviews, surveys and consensus statements; three animal studies; four that examined static parameters only; and one study where fluid responsiveness was not measured. Of the remaining 14 studies, only one was randomised but non-blinded; the remainder were prospective, observational, non-randomised and unblinded studies (Tables 2 and 3). All studies were conducted in mechanically ventilated patients; ten were peri-operative and five were in the ICU. Fluid responsiveness was defined as a change in cardiac output, cardiac index, stroke volume or stroke volume index of ≥ 10–20%, as measured with the bolus thermodilution technique. Pulmonary artery catheter-derived indices were compared with indices measured by LiDCO™plus (LiDCO Ltd, London, UK) [19], automated pulse pressure variation (Intellivue MP70; Philips Medical Systems, Suresnes, France) [20]; PiCCOPlus [22,25]; transoesophageal echocardiography [26]; Phillips Intellivue (Intellivue MP70, Philips Medical Systems) [24, 28, 37] infrared photoplethysmography using the Finapres™ (Ohmeda Monitoring Systems, Englewood, CO, USA) [15]; and the Flotrac/Vigileo™ (Edwards Lifesciences, Irvine, CA, USA) [28,29] (Table 3).

Dynamic parameters of fluid responsiveness assessed across studies included: systolic pressure variation; pulse pressure variation; stroke volume variation; respiratory variability of peak aortic blood flow velocity; and arterial pulse pressure variation. In general, most studies demonstrated that dynamic indices of fluid responsiveness have much better AUROC than static parameters measured by pulmonary artery catheter (Table 3).

Table 1 Modified STARD criteria assessment [8].

Criteria	Specific question
1.	Was the study population described (inclusion and exclusion criteria included)?
2.	Is there a description of the sampling (e.g. consecutive patients, if not why not?)?
3.	Is it clear whether the tests were done prospectively or retrospectively?
4.	Is there a description of the response test (including fluid bolus)?
5.	Is there a detailed description of the equipment and techniques used in the tests?
6.	Is the rationale for cut-offs and ranges given?
7.	Is there detail of the operators in terms of number and training?
8.	Is there detail of what information was available to the readers of the response ?
9.	Were the statistical methods for comparing diagnostic accuracy detailed?
10.	Are there details of tests of reproducibility?
11.	Are the patients' characteristics and co-morbidities shown?
12.	Is there detail of those meeting inclusion criteria but not undergoing either test?
13.	Was there detail of the interval between predictive and response tests?
14.	Is there a report cross-tabulating predictive and response test results?
15.	Is diagnostic accuracy described, including likelihood ratios or data to calculate them?
16.	Is there mention of how missing values were dealt with (i.e. unobtainable values)?
17.	Are the estimates of accuracy variability between operators/readers included?
18.	Are there estimates of reproducibility?
19.	Is the clinical applicability of the study findings discussed?

Transthoracic echocardiography

We identified 30 potentially relevant publications involving the use of transthoracic echocardiography (Table 4). Two duplicate papers, four review articles and three studies conducted in children were excluded. Four papers were excluded as fluid responsiveness was not being tested. Of the remaining 17 studies, only one was a randomised blinded study; the others were prospective observational studies (Tables 2 and 4). Eight studies used primarily transthoracic echocardiography-derived data as markers of fluid responsiveness (stroke volume, cardiac output, cardiac index, plethysmographic variability index, aortic velocity–time integral, variability of peak aortic blood flow velocity, subaortic velocity–time index, left ventricular end-diastolic area, ratio of mitral inflow E-wave velocity to early diastolic mitral annulus velocity and variation of pulse oximetric plethysmographic waveform amplitude). Eleven studies were conducted in patients whose lungs were mechanically ventilated and six in spontaneously breathing subjects. The majority of studies were performed in an ICU setting; one was done in the emergency department [29] and in three healthy volunteers, rather than patients, participated [28, 32, 37].

In general, good measures of fluid responsiveness, as assessed by transthoracic echocardiography and determined by AUC > 0.86, were changes in cardiac output, stroke volume and velocity–time integral. Poor predictors included the ratio of early to late ventricular filling velocities (E/Ea ratio), left ventricular end-diastolic area index and variation in the maximum flow velocity of aortic systolic blood flow.

Transoesophageal echocardiography

We identified 14 potentially relevant publications involving the use of transoesophageal echocardiography. Five papers were excluded, as PiCCO was the only device used to measure cardiac output, cardiac index or stroke volume. One paper was excluded as its primary focus was echocardiographic signs in sepsis rather than fluid responsiveness. A seventh study was excluded as no intervention (fluid bolus or passive leg raise) was performed to assess fluid responsiveness. The remaining eight were prospective observational studies (Table 5). Three studies were common to our previous searches for other devices [15, 19, 26]. Four studies were conducted in patients undergoing elective cardiac bypass graft surgery, and the others in cardiac surgery without bypass, hepatic surgery and robotic-assisted laparoscopic prostatectomy. All studies were conducted in patients whose lungs were mechanically ventilated.

Transoesophageal echocardiography-derived parameters were compared with parameters measured with a 7.5 Fr right-heart ejection fraction pulmonary artery catheter (CCOmboV 774HF75; Edwards Lifesciences) [9]; LiDCO™plus (LiDCO Ltd) [19]; PiCCOPlus [12]; infrared photoplethysmography using the Finapres™ (Ohmeda Monitoring Systems) [15]; and the Flotrac/Vigileo™ (Edwards Lifesciences) [40] (Table 5).

Table 2 Evidence grading of studies included in the review.

Study	Type of evidence	Level of evidence*	STARD SCORE
Lattik et al. 2002 [10]	Prospective observational study	2b	13
Wiesenack et al. 2005 [11]	Prospective observational study	2b	14
Wiesenack et al. 2005 [12]	Prospective observational study	2b	13
Feissel et al. 2005 [13]	Prospective observational study	2b	15
Natalini st al 2006 [14]	Prospective observational study	2b	16
Solus-Biguenet et al. 2006 [15]	Prospective observational study	2b	15
Cannesson et al. 2006 [16]	Prospective observational study	2b	15
Lamia et al. 2007 [17]	Prospective observational study	2b	14
Soubrier et al. 2007 [18]	Prospective observational study	2b	15
Belloni et al. 2008 [19]	Prospective observational study	2b	16
Cannesson et al. 2008 [20]	Prospective observational study	2b	15
Auler et al. 2008 [21]	Prospective observational study	2b	14
Huang et al. 2008 [22]	Prospective observational study	2b	13
Biais et al. 2008 [23]	Prospective observational study	2b	13
Keller et al. 2008 [24]	Prospective observational study	2b	12
Mutoh et al. 2009 [25]	Randomised non-blinded study	2b	13
Ranucci et al. 2009 [26]	Prospective observational study	2b	15
Gouvea et al. 2009 [27]	Prospective observational study	2b	15
Cannesson et al. 2009 [28]	Prospective observational study	2b	15
Biais et al. 2009 [29]	Prospective observational study	2b	15
Skulec et al. 2009 [30]	Randomised blinded study	2b	16
Preau et al. 2010 [31]	Prospective observational study	2b	15
Delerme et al. 2010 [32]	Prospective observational study	2b	15
Desgranges et al. 2011 [33]	Prospective observational study	2b	14
Guinot et al. 2011 [34]	Prospective observational study	2b	15
Muller et al. 2011 [35]	Prospective observational study	2b	14
Muller et al. 2012 [36]	Prospective observational study	2b	15
de Oliveira-Costa et al. 2012 [37]	Cross-sectional observational study	2b	14
Feissel et al. 2013 [38]	Prospective observational study	2b	14
Brun et al. 2013 [39]	Prospective observational study	2b	15
Chin et al. 2013 [40]	Prospective observational study	2b	15
Wu et al. 2014 [41]	Prospective observational study	2b	16
Fischer et al. 2014 [42]	Prospective observational study	2b	14
Cinotti et al. 2014 [43]	Prospective observational study	2b	15

*Evidence rating scale adopted from: Centre for evidence based medicine, Oxford www.cebm.net/?o=1025.
STARD, standards for reporting of diagnostic accuracy score.

Dynamic parameters measured included: respiratory variations in left ventricular stroke area; ratio of velocity of the E-wave to velocity of the A-wave in $cm.s^{-1}$ recorded by pulse Doppler in the apical four-chamber view at the distal extremity of the mitral leaflets; and stroke volume variation. The best AUROC was found for respiratory variation in left ventricular stroke area measured using transoesophageal echocardiography (0.958), which was demonstrated to be as reliable as pulse pressure variation in one paper (AUROC 0.910) [16]. The AUC for other preload indices ranged from 0.70 to 0.81 (Table 5).

Discussion

The results of this qualitative systematic review confirm the shortcomings of static measurements (such as central venous pressure and pulmonary artery occlusion pressure) and affirm the potential for dynamic measurements (such as stroke volume variation and pulse pressure variation) as determinants of fluid responsiveness, provided patients were receiving mechanical ventilation of the lungs with a tidal volume of $> 8\ ml.kg^{-1}$, in sinus rhythm and their chest was closed (i.e. not during sternotomy). Dynamic indices had better AUROC and correlation than static measures across studies. Furthermore, in addition to

Table 3 Studies evaluating the pulmonary artery catheter.

Study	Setting	Patients (n)	Device	Fluid bolus	Response	Potential predictor	Level of evidence	ROC	Sensitivity (%)	Specificity (%)
Natalini et al. 2006 [14]	ICU	22	Direct arterial trace vs photoplethysmogram	500 ml	ΔCI > 15%	PVap, PVplt, SVap, SVplt	2b	0.74, 0.72, 0.64, 0.72	N/A	N/A
Solus-Biguenet et al. 2006 [15]	liver	8	Finapres	250 ml	ΔSVI ≥ 10%	PPVfina	2b	0.81 (0.70–0.93)	N/A	N/A
Biais et al. 2008 [23]	liver	40	Flotrac/Vigileo	20 × BMI	ΔCO > 15%	SVV	2b	0.95 (0.81–0.99)	94	94
Huang et al. 2008 [22]	ICU	22	PICCO	500 ml	ΔCI ≥ 15%	PPV	2b	0.77	68	100
Belloni et al. 2008 [19]	cardiac	19	LidcoPlus	7 $ml.kg^{-1}$	ΔCI > 15%	SPV	2b	Not stated in paper	Not stated in paper	Not stated in paper
Cannesson et al. 2008 [20]	cardiac	25	PPV index	500 ml	ΔCI > 15%	ΔPP(auto)	2b	0.90	88	100
Auler et al. 2008 [21]	cardiac	59	ΔPP(auto)	20 $ml.kg^{-1}$	ΔCO > 15%	ΔPP(auto)	2b	0.98	97	95
Mutoh et al. 2009 [25]	neuro	16	PICCO	500 ml	ΔSVI > 10%	GEDI	2b	0.73	70	70
Ranucci et al. 2009 [26]	cardiac	65	TOE	7 $ml.kg^{-1}$	SV> 20%	ΔVAo	2b	0.71 (0.56–0.87)	70	72
Gouvea et al. 2009 [27]	liver	15	Datex-Ohmeda AS/5	350 ml	ΔSVI > 10%	PPV	2b	N/A	N/A	N/A
Cannesson et al. 2009 [28]	cardiac	25	Flotrac/Vigileo	500 ml	ΔCI > 15%	SVV	2b	0.87 (0.79–0.96)	82	88
Desgranges et al. 2011 [29]	general	28	PVI	500 ml	ΔCI > 15%	PVI	2b	0.91	89	78
de Oliveira-Costa et al. 2012 [37]	ICU	37	Philips IntelliVue	1000 or 500 ml	ΔCI > 15%	ΔrespPP	2b	0.74 (0.56–0.90)	53	95

ICU, intensive care unit; Lidco, lithium dilution cardiac output; PiCCO, pulse contour continuous cardiac output; FloTrac/Vigileo, FloTrac™/Vigileo™ system (Edwards Lifesciences); ΔPP, ΔrespPP, PPV, pulse pressure variation; PPVfina, pulse pressure calculated from Finapres™ (Ohmeda Monitoring Systems);TOE, transoesophageal echocardiography; PAC, pulmonary artery catheter; PAOP, pulmonary artery occlusion pressure; PVI, plethysmographic variability index; PVap, arterial pressure pulse variation; PVplt, plethysmographic pulse variation; ΔCI, changes in cardiac index; ΔCO, changes in cardiac output; SV, stroke volume; ΔSVI, changes in stroke volume index; SPV, systolic pressure variation; SVap, arterial pressure systolic variation; SVplt, plethysmographic systolic variation; GEDI, global end-diastolic index; ΔVAo, respiratory variability of peak aortic blood flow velocity; SVV, stroke volume variation; N/A, not applicable.

Table 4 Studies evaluating transthoracic echocardiography.

Study	Population	Patients (n)	Device	Fluid bolus	Response	Potential predictor	Level of evidence	ROC	Sensitivity (%)	Specificity (%)
Feissel et al. 2005 [13]	ICU-sepsis	20	PEP	8 ml.kg^{-1}	ΔCI ≥ 15%	ΔPP (man), ΔPEP (kt), ΔPEP (plet)	2b	0.96 ± 0.03, 0.97 ± 0.03, 0.94 ± 0.05	85,92,100	100,89,67
Lamia et al. 2007 [17]	Spontaneously breathing ICU patients	24	TTE	500 ml	SVI ≥ 15%	ΔVTIAo	2b	0.96 ± 0.04	77	100
Soubrier et al. 2007 [18]	Spontaneously breathing ICU patients	32	Radial catheter	500 ml	ΔCI ≥ 15%	ΔPP	2b	0.81 ± 0.08	63	92
Biais et al. 2008 [23]	Liver transplant	40	Flotrac/ Vigileo	20 ml × BMI	ΔCO > 15%	ΔSV	2b	0.96 ± 0.03	100	80
Keller et al. 2008 [24]	Healthy volunteers	25	PVI	PLR used instead	SV > 15%	PVI	2b	0.734 ± 0.01	82	57
Biais et al. 2009 [29]	ICU – Sepsis	30	Flotrac	500 ml	SV ≥ 15%	SVV	2b	0.95 (0.81–0.99)	94	94
Skulec et al. 2009 [30]	Spontaneously breathing volunteers	20	TTE	Volume diuresed in 90 min after furosemide	ΔCI ≥ 15%	ΔCI	2b	Not stated	89	100
Preau et al. 2010 [31]	ICU – Severe sepsis	34	TTE	500 ml	ΔSV ≥ 15%	ΔSV	2b	0.94 ± 0.4	86	90
Delerme et al. 2010 [32]	Spontaneously breathing volunteers	26	ΔPOP	PLR used instead	CI > 15%	ΔPOP	2b	0.67 ± 0.10	80	64
Guinot et al. 2011 [34]	ARDS – VVECMO	17	TTE	500 ml	SV > 15%	ΔSV	2b	0.88 ± 0.07	62	92
Muller et al. 2011 [35]	Ventilated ICU patients	39	TTE	100 ml in 1 min, then 400 in 14 min	VTIAo ≥ 15%	ΔVTI100	2b	0.92 (0.78–0.98)	95	78
Muller et al. 2012 [36]	Spontaneously breathing ICU patients	40	TTE-cIVC	500 ml	VTIAo ≥ 15%	cIVC	2b	0.77 (0.60–0.88)	70	80
Feissel et al. 2013 [38]	ED – Early septic shock	31	PVI	8 ml.kg^{-1}	VTIAo ≥ 15%	PVI	2b	0.97 (0.83–0.99)	94	87
Brun et al. 2013 [38]	Severe pre-eclampsia – oliguria	41	TTE	500 ml	SVI > 15%	ΔVTIAo	2b	0.93 (0.83–1)	75	100
Wu et al. 2014 [41]	ICU – Severe sepsis/shock	50	TTE	50 ml + 450 ml	ΔCO ≥ 15%	ΔCO50	2b	0.95 ± 0.03	93	91
Fischer et al. 2014 [42]	Elective Cardiac Surgery	54	esCCO	500 ml	CO ≥ 10%	esCCO	2b	N/A	N/A	N/A
Cinotti et al. 2014 [43]	Clinically brain-dead ventilated patients	25	PPV	500 ml	ΔCI ≥ 15%	PPV	2b	0.69 (0.47–0.88)	40	66

ICU, intensive care unit; ARDS, acute respiratory distress syndrome; VVECMO, veno-venous extracorporeal membrane oxygenation; ED, emergency department; BMI, body mass index; FloTrac/Vigileo, FloTrac™/Vigileo™ system (Edwards Lifesciences); PLR, passive leg raise; PVI, plethysmographic variability index; TTE, transthoracic echocardiography; esCCO, estimated continuous cardiac output; cIVC, respiratory variation of inferior vena cava diameter; PPV, pulse pressure variation; ΔPOP, respiratory variations in pulse oximetry plethysmographic waveform amplitude; CO, cardiac output; CI, cardiac index; SV, stroke volume; SVV, stroke volume variation; PPV, pulse pressure variation; ΔCI, changes in cardiac index; ΔCO, changes in cardiac output; ΔSV, changes in stroke volume; VTIAo, velocity–time integral of aortic valve blood flow; ΔVTIAo, variation of velocity–time integral of aortic valve blood flow; ΔCO50, cardiac output variations after 50 ml crystalloid fluid infusion over 10 s; ΔVTI100, subaortic velocity–time index variation after infusion of 100 ml hydroxyethyl starch; N/A, not applicable; PEP, Pre-ejection period defined as the time interval between the beginning of the R wave on the electrocardiogram and the upstroke of the radial arterial pressure curve or the pulse plethysmographic waveforms and cardiac index (transthoracic echocardiography–Doppler).

providing information on device performance, we have been able to review in detail the various physiological and methodological underpinnings and assumptions within the literature on this topic. These include: the definition of 'fluid responsiveness'; the precision of measurements made; and measurement issues relating to changes over time. These are dealt with below.

The definition of fluid responsiveness in most studies included in our review was based on the assumption that thermodilution is the only method validated to detect a 10–15% increase in cardiac output, cardiac index or stroke volume to define fluid responsiveness. However, this definition lacks consensus, as the quantity and type of fluid administered, and the timing and cut-off values for defining 'responders' varied considerably between the included studies. Furthermore, among the transthoracic and transoesophageal echocardiography studies we included, only five used thermodilution as a reference standard. The significance of definitional and other methodological issues is underlined by the conflicting findings of two recent systematic reviews of transthoracic echocardiography. Wetterslev et al. [44] evaluated the predictive value of transthoracic echocardiography-derived variables for fluid responsiveness, defined as change in cardiac output or stroke volume measured by thermodilution after a fluid challenge or a passive leg raise test. Only one study out of 4294 fulfilled their inclusion criteria for valid assessment of fluid responsiveness. This one study examined the predictive value of variations in inferior vena cava diameter (> 16%) for fluid responsiveness (ROC 0.90, 95% CI 0.73–0.98), and yielded a sensitivity and specificity of 71% and 100%, respectively. The authors concluded that further evaluation was required before committing to transthoracic echocardiography as a fluid responsiveness tool. In the same year, Mandeville et al. [8] also assessed the value of transthoracic echocardiography in predicting fluid responsiveness in critically ill patients. In contrast to the Wetterslev review, the authors concluded that transthoracic echocardiography accurately predicted fluid responsiveness, and its discriminatory power was unaffected by the reference technique used to evaluate transthoracic echocardiography. The assessment of changes in the inferior vena cava diameter, stroke volume or cardiac output by transthoracic echocardiography provided highly predictive values for fluid responsiveness. However, the studies included in this review were not limited to those using thermodilution techniques as an established reference standard, in our view reducing the validity of its conclusions.

Precision is also relevant. In most of the studies included in this review, bias comparison, precision and limits of agreement (bias ±1.96 SD) between determinants of fluid responsiveness measured by different devices (pulmonary artery catheter, transthoracic echocardiography, transoesophageal echocardiography, LidCO, PiCCO, etc.) were not evaluated. The percentage error for determining the acceptable limits of agreement between devices was not calculated either. Understanding of the precision of a device used to measure fluid responsiveness before it is accepted into clinical practice and utilised for any therapeutic intervention is of paramount importance. In order for a monitor to detect the response to a fluid challenge, it must have a level of precision (standard deviation (SD) of bias) that can detect this change; this is customarily done with 95% certainty. Bland–Altman analysis is used for assessing agreement between two measurements of the same clinical variable. When comparing monitors, one must make allowances for the imprecision of the reference standard and the imprecision of the comparison monitor. In terms of bias and limits of agreement, a cut-off of 30% in the percentage error is used to decide whether a new technique may be considered a good alternative [45]. The pulmonary artery catheter has long been regarded as the standard clinical reference method for cardiac output monitoring, against which other devices are compared. Stetz et al., when investigating the accuracy of the pulmonary artery catheter, reported a precision of 15%; that is, a minimal difference of 15% is required between determinations of cardiac output (three measurements per determination) to imply clinical significance [46]. This precision has been adopted both as the reference value for the pulmonary artery catheter, and more widely in studies assessing fluid responsiveness.

Repeated measurements over time bring their own potential problems; detecting a change in a parameter such as cardiac index or stroke volume does not necessarily mean that the patient's physiological status has

Table 5 Studies evaluating transoesophageal echocardiography.

Publication	Population	Patients (n)	Device	Fluid bolus	Response	Potential predictor	Level of Evidence	ROC	Sensitivity (%)	Specificity (%)
Lattik et al. 2002 [10]	Cardiac	14	TOE	500 ml	SV > 20%	E/A Ratio	2b	0.71 (0.54-0.88)	75	60
Wiesenack et al. 2005 [11]	Cardiac	21	CCOmboV, TOE	7 $ml.kg^{-1}$	SVItd ≥ 10%	ΔVAo	2b	Not done – correlation index used instead	N/A	N/A
Wiesenack et al. 2005 [12]	Cardiac	20	PiCCO	7 $ml.kg^{-1}$	SVItd ≥ 20%	SVV	2b	Not done – correlation index used instead	N/A	N/A
Cannesson et al. 2006 [16]	Cardiac	18	TOE	PLR used instead	CO > 15%	ΔSA	2b	0.958 ± 0.043	92	83
Solus-Biguenet et al. 2006 [15]	Hepatic Surgery	8	Finapres	250 ml	ΔSVI ≥ 10%	LVEDAI	2b	0.70 (0.53-0.88)	N/A	N/A
Belloni et al. 2008 [19]	Cardiac	19	LidCOplus	7 $ml.kg^{-1}$	ΔCI > 15%	LVEDA	2b	N/A	N/A	N/A
Ranucci et al. 2009 [26]	Cardiac	65	PAC	7 $ml.kg^{-1}$	SV ≥ 20%	ΔVAo	2b	0.71 (0.56-0.87)	77.3	75
Chin et al. 2013 [40]	Laparoscopic prostatectomy	45	FloTrac/Vigileo	500 ml	SV ≥ 15%	SVV	2b	0.81 (0.68-0.94)	77.3	75

TOE, transoesophageal echocardiography; PAC, pulmonary artery catheter; Lidco, lithium dilution cardiac output; CCOmboV, 7.5 Fr right-heart ejection fraction pulmonary artery catheter (CCOmboV 774HF75; Edwards Lifesciences); FloTrac/Vigileo, FloTrac™/Vigileo™ system (Edwards Lifesciences); Fianpres, Finapres™ non-invasive monitor (Ohmeda, Englewood, CO, USA); PiCCO, pulse contour continuous cardiac output; PLR, passive leg raise; CO, cardiac output; SV, stroke volume; SVV, stroke volume variation; ΔCI, changes in cardiac index; ΔSVI, changes in stroke volume index; SVItd, volume-induced increase in thermodilution-derived stroke volume index; ΔSA, respiratory variations in left ventricular stroke area; E/A Ratio, velocity of the E wave/velocity of the A wave in cm/s recorded by pulse Doppler in the apical four-chamber view at the distal extremity of the mitral leaflets; LVEDA, left ventricular end-diastolic area; LVDAI, left ventricular end-diastolic area index; ΔVAo, respiratory variability of peak aortic blood flow velocity; N/A, not applicable.

changed. The error of the measuring technique is directly related to the magnitude of the minimum change that needs to be measured in order for the device to recognise a real change [45]. Roeck et al. [47] measured the change in stroke volume in response to a fluid challenge with pulmonary artery catheter and oesophageal Doppler measured by two independent examiners. While the overall correlation between the two methods was relatively good both before and after the fluid challenge (correlation coefficients between 0.6 and 0.9, $p < 0.01$), individual differences between the methods and the examiners using oesophageal Doppler were obvious. The Bland–Altman analysis showed that the bias was small (overall bias for cardiac output 0.3 $l.min^{-1}$) but the precision was poor (1.8 $l.min^{-1}$).

Despite its strengths, our review is limited to some extent by the small sample size of the studies included (only 4 of 34 studies enrolled more than 50 patients). In addition, we were not able to perform a meta-analysis due to heterogeneity of the methods and patient characteristics. The available studies evaluating monitors measuring cardiovascular response to a fluid challenge are heterogeneous in terms of the clinically accepted criterion standard method used, study methodology and patient population [48]. Most of the studies included in our review were conducted in selected patient groups, from single centres, which might limit their wider applicability. In addition, most used a ROC curve approach, which does not take into account the existence of an overlap between 'fluid-responders' and 'non-responders'. This dichotomous approach does not square with observations in clinical practice, where the overlap of a dynamic parameter value, such as pulse pressure variation between 'responders' and 'non-responders' has been interpreted as a 'grey zone' in which clinical decisions regarding fluid responsiveness cannot be made with certainty (approximately 25% of patents under general anaesthesia fall into this category) [23, 49, 50]. The 'grey zone' methodology proposes two thresholds for fluid responsiveness that constitute the borders of the 'grey zone' avoiding the binary response proposed by ROC curve methodology. In the presence of an intermediate dynamic parameter value within the 'grey zone', one may expect a mild increase in cardiac output, stroke volume or cardiac index in response to a fluid challenge [49, 50]. This is clinically valuable when assessing the benefit/risk ratio and trying to avoid hypo- or hypervolaemia before giving a fluid bolus.

In the majority of studies included in our review, the volume of the fluid bolus given was 500 ml or more. In six studies, passive leg raising was used to assess the cardiovascular response to volume expansion. Passive leg raise mimics a fluid challenge by transferring a volume of around 300 ml from the lower body (venous reservoir) into the right heart, but avoids the risks of fluid overload as the haemodynamic effects produced are rapidly reversible. However, pain, coughing, discomfort and awakening during the manoeuvre could cause adrenergic stimulation, resulting in wrong interpretation of cardiovascular response; this potentially misleading sympathetic stimulation should be suspected when passive leg raising is accompanied by significant tachycardia; this should not normally occur [51–53]. More recently, smaller fluid boluses have been tested; Wu et al. showed that a mini-fluid challenge of 50 ml crystalloid in mechanically ventilated critically ill patients was associated with a 17% increase in stroke volume [41]. Guinot et al. demonstrated that a mini-fluid challenge of 100 ml crystalloid in spontaneously breathing patients under spinal anaesthesia 'predicted' fluid responsiveness, with a 'grey zone' ranging between 3 and 8% [54]. This could potentially decrease the cardiac filling pressures and limit the deleterious effects of fluid among non-responders [55]. In addition, because of the form of the Frank-Starling curve, the increase in stroke volume would be greater at the beginning (first 100 ml) of the fluid challenge (steep portion of the curve).

To conclude, this review demonstrates that, among a vast range of scientific papers over the last decade, only a limited number have attempted to validate newer technology by comparing it with an established reference standard, and in most cases the quality of the evidence is relatively poor. Different technologies used to measure the cardiovascular response to a fluid challenge should be appropriately evaluated focusing on the statistical methods applied in comparison studies and measurement of the precision of the reference technique. There is a need for uniformity in defining fluid responsiveness; in this regard, both mini-fluid

challenge and passive leg raising are promising techniques which fulfil many desirable criteria and could provide new research perspectives for effectively and rapidly assessing fluid responsiveness taking into account the 'grey zone' concept. Future research should also focus on clinically important outcomes using mini-fluid challenge and passive leg raise to guide fluid titration.

In the meantime, we hope that by outlining the problematic areas within this topic, we have helped clinicians understand the importance of methodology when appraising studies on 'fluid responsiveness'. In clinical practice, it is important that the risks and benefits to an individual patient are balanced before fluid loading, and that a fluid challenge is given to those patients who are likely to have a significant increase in stroke volume in response, bearing in mind that smaller volume boluses may be sufficient for this purpose.

Competing interests

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