BJA
British Journal of Anaesthesia
Volume 109, Number 3, September 2012

British Journal of Anaesthesia **109** (3): 299–302 (2012)
doi:10.1093/bja/aes277

EDITORIAL I

Minimal invasive cardiac output monitoring: get the dose of fluid right

R. A. Bouwman* and C. Boer

Department of Anaesthesiology, Institute for Cardiovascular Research VU University (ICaR-VU), VU University Medical Centre (VUmc), de Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

* E-mail: a.bouwman@vumc.nl

Cardiac output has long been considered the gold standard for the assessment of organ perfusion, but the validity of cardiac output measurement has, however, recently been of increasing research interest. The considerable risk of complications of invasive thermodilution techniques on the one hand,[1] and the ineffectiveness of traditional invasive haemodynamic measurements in improving patient care and outcome on the other,[2] were driving forces in the development of novel haemodynamic technologies and indices. The increasing interest in the use of dynamic haemodynamic measurements to guide fluid therapy and organ perfusion has changed the clinical demands for haemodynamic monitoring devices. It is, however, questioned whether these novel devices and indices provide a false sense of security in cases where clinical and physiological common sense is warranted.

The focus of perioperative fluid therapy has shifted from a fixed-dose approach based on static measures towards titration of fluids guided by dynamic indices of fluid responsiveness. This development can be attributed to the recognition that haemodynamic optimization by overzealous administration of i.v. fluids is associated with perioperative complications.[3] As a consequence, several historical assumptions regarding fluid management have been challenged. An important change is that infusion solutions should be considered as drugs with indications, contraindications, and side-effects, such as disruption of the endothelial glycocalyx, oedema formation, and electrolyte disturbances. This has contributed to the development of a rational approach for perioperative fluid therapy that consists of two components.[4] The first component consists of replacement of fluid deficits after fasting and insensible losses by crystalloids, which are estimated to be much lower than was previously believed. The second component concerns replacement of plasma losses resulting from surgery and bleeding in the context of maintaining organ perfusion and avoiding fluid overload.[4] Indeed, a recent meta-analysis of 29 studies involving 4805 patients showed that rational fluid management based on flow-directed haemodynamic goals significantly reduced perioperative mortality and morbidity.[5] An estimate of the possible impact of worldwide implementation of goal-directed haemodynamic strategies suggested that it could contribute to the yearly prevention of 3 million postoperative complications and 800 000 perioperative deaths.[6] This indicates that a lot can be gained with regard to patient safety and outcome even if only a small improvement in perioperative fluid management could be achieved. Despite the available evidence, it seems difficult to get to the 'right dose' for the right patient based on the right dynamic haemodynamic index. The problem was well summarized by Chappell and colleagues[4] who state that '... we must use the right kind of fluid in appropriate amounts at the right time to reduce collateral damage ...'.

How can we get the dose right? Here, we briefly touch on recent important developments.

The ultimate goal of i.v. fluid administration is optimizing the patient's haemodynamic status so that tissue perfusion closely matches the metabolic need. Cardiac output and its close relatives stroke volume variation and pulse pressure variation are usually optimized when stroke volume is only minimally increased after a fluid challenge. Until recently, cardiac output optimization was the cornerstone for

haemodynamic therapeutic guidance to ensure optimal oxygen delivery. However, in the last 5 yr, stroke volume variation and pulse pressure variation have evolved as more specific indices for goal-directed fluid therapy.

Ideally, haemodynamic monitoring devices should be minimally invasive, reliable, and provide continuous measurements. Although intermittent thermodilution derived from a pulmonary artery catheter meets almost none of these criteria, it is still considered the clinical 'gold standard'. Minimally invasive haemodynamic monitoring technologies can be divided into four methods: arterial waveform analysis, oesophageal Doppler, partial carbon dioxide rebreathing, and transthoracic bio-impedance. All these techniques are extensively reviewed elsewhere.[7–9] In a recent meta-analysis, none of the techniques was shown to be superior to thermodilution in accuracy and precision.[10] Although transoesophageal Doppler monitoring is the only method that is mentioned in patient management guidelines, there is an increasing focus on the accuracy and validity of arterial waveform analysis methods, either derived from an arterial line or non-invasively, to assess cardiac output.[7 9 10]

Dynamic analysis of haemodynamic variables, such as stroke volume variation and pulse pressure variation, may provide better prediction of fluid responsiveness than static variables such as central venous pressure, pulmonary artery occlusion pressure, or left ventricular end-diastolic area. The validity of these measures in spontaneously breathing patients is however limited, as they are based on the interaction between mechanical ventilation with large tidal volumes and stroke volume or pulse pressure.

Haemodynamic monitoring devices should be able to detect dynamic changes in order to assess variation in stroke volume or pulse pressure. However, there are only a limited number of studies available that address whether haemodynamic changes were reliably detected and reflected actual changes in haemodynamic variables.[9] A new approach was recently proposed using polar coordinates, that is, the angle and length of the vector of the cardiac output difference, to show the predictability of cardiac output changes.[9] The derived polar plots not only evaluate how well the evaluation method agrees, but also the reliability of trending and can be used in a manner similar to Bland and Altman plots to determine the limits of predictability. The authors recommended that full evaluation of a new device should involve three different phases: animal studies (phase 1), human/clinical studies (phase 2), and clinical utility/outcome studies (phase 3). This approach, and previous methodology considerations,[11] could contribute significantly to the quality and uniformity of validation studies.

Importantly, with any new treatments algorithm, the adverse effects should be explored. For example, Challand and colleagues[12] recently investigated the impact of a simplified goal-directed therapy algorithm aimed to improve cardiac output and oxygen delivery. Using the NICE protocol[13] in 176 patients undergoing colorectal surgery, they concluded that goal-directed therapy with the simplified algorithm provided no additional benefit for their primary endpoint: surgical readiness for discharge. However, in aerobically fit patients, goal-directed therapy had an unexpected adverse affect on the primary outcome. Stroke volume in patients treated with goal-directed therapy was indeed higher, but these patients also received, on average, 1.3 litre more colloids. The authors concluded from their study that stroke volume optimization solely by fluid treatment is an overly simplistic approach, which bears the risk of iatrogenic fluid overload. Was the dose of i.v. fluids not right, or is stroke volume no adequate indicator for fluid management? This study's findings were especially disappointing as the initial aim was to simplify the previous reported beneficial methods that also included central venous pressure and corrected flow time in the algorithm. In defining a fluid management strategy, it must be realized that haemodynamic optimization may not be simple after all, and may require integration of more than one clinical variable and identifying the right patient. This can be illustrated by a recent meta-analysis which compared liberal, restricted fluid management and goal-directed therapy.[14] Both restricted fluid management and goal-directed therapy proved beneficial for clinical endpoints, such as pneumonia, oedema, and first bowel movement. The interesting observation here was that patients treated with goal-directed therapy received considerably more fluids than the restricted- and non-goal-directed fluid therapy ones. In addition, large amounts of fluids were used for both goal-directed- and liberal fluid therapy patients, but the perioperative outcome was different. Based on these data, the authors concluded that it was not the amount of i.v. fluid *per se* that is related to complications of fluid management, but the use of specific haemodynamic goals to which fluid therapy is titrated. Because of data limitations, no clear conclusion could be made relating to the controversy of goal-directed therapy and restrictive fluid strategies. The authors conclude that an adequately powered randomized controlled trial is needed to answer this debate.[12]

Other approaches can be considered with the reducing perioperative fluid therapy. An intriguing example is a study of 70 patients undergoing minor surgery who had goal-directed therapy and were randomized to receive peristaltic pneumatic leg compression.[15] It was shown that patients in the intervention group received significantly less i.v. fluid (about 70%) and experienced fewer episodes of haemodynamic instability.

Correct prediction of fluid responsiveness depends on the correct definition of the optimal threshold for each measure. For example, it was recently shown that a pulse pressure variation threshold of 12.5% had the highest sensitivity and specificity for fluid management.[16] However, it must be questioned whether this threshold can be used as a surrogate for our intuitive and physiological comprehension of perioperative haemodynamic challenges. Indeed, when confronted with a clinical problem in a patient, we come to a likely diagnosis by integrating information from patient history, physical examination, laboratory values, and radiological studies, if necessary. Coming to the right diagnosis

may not be straightforward in many cases, as symptoms can be ambiguous and results of laboratory tests, leading to a 'grey zone' of uncertainty. In clinical decision-making, it is essential to keep an open mind to these uncertainties, as they may indicate that our diagnosis is not entirely correct. In analogy, studies investigating the concept of fluid responsiveness usually discriminate between subjects in a binary approach (fluid responder or non-responder) based on a threshold in change of a haemodynamic measure after a fluid challenge. However, this may not reflect the clinical situation. For this reason, a multicentre study of 413 patients of the effect of volume expansion on pulse pressure variation applied the grey zone statistical approach to the data.[17] This identified that in their data set, a pulse pressure variation between 9% and 13% (accounting for 24% of the patients) fluid responsiveness was not reliably predicted. These results do not justify rejecting the clinical value of pulse pressure variation in determination of the fluids responsiveness, as the receiver operator curve analysis compared with central venous pressure confirmed the better predictive value of pulse pressure variation for fluid responsiveness. However, these findings expand the concept on rational fluid management to better fit within a clinical reality and at least start to quantify the area of uncertainty.

One-quarter of the patients fall in the grey zone and dynamic measurements in these patients are inconclusive with regard to fluid responsiveness. This could perhaps be explained by trivial patient- and measurement-related interactions that influence the assessment of dynamic indices, such as vasopressor therapy[18] or non-adherence to limitations of dynamic variables.[19] However, this explanation may be too easy and is unlikely in careful performed studies. It is important to remember that the cut-off value for pulse pressure variation does not take into account the physiological nature of the Starling curve.[20] The response to volume loading depends on the working point of the heart on the Starling curve and implies that the stroke volume response is continuous. Here, it should be noted that the working point of the heart is not solely determined by the cardiac function curve, but importantly also by venous function as described by the venous return curve.[21] This may explain why some hypovolaemic patients may not respond to fluid loading, as the working point of the heart is determined by the intersection of the cardiac function and venous return curve.[22] At the working point, cardiac output equals venous return and therefore parameters of venous return also determine cardiac output. The concept has not commonly been appreciated in clinical practice, as its main determinant, mean systemic filling pressure, is difficult to obtain clinically.[22] Maas and colleagues[23] recently described an approach to the mean systemic filling pressure in cardiac surgery patients. For this purpose, they reconstructed venous return curves by measuring arterial pressure, central venous pressure, and cardiac output during inspiratory hold manoeuvres with increasing plateau pressures from 5 to 35 cm H_2O. Venous return curves and the mean systemic filling pressure were obtained by linear regression and extrapolation to zero flow. In a subsequent study based on this simplified Guytonian model of the circulation, they simplified the approach and showed that PEEP-induced increases in central venous pressure predicted fluid responsiveness more reliably than stroke volume variation.[24] Although in its infancy, this approach of integrating the cardiac function curve and the venous return curve may especially be useful in the area of uncertainty, the grey zone, as it incorporates old-school physiology with clinical practice.

In conclusion, in keeping with the Hippocratic oath '... never do harm ...', we as clinicians are obliged to treat patients using the best available evidence. Although there are specific areas of uncertainty, a large body of evidence shows that a rational approach towards fluid management is beneficial to patient outcome. Whether this approach should be restrictive or goal-directed is yet to be determined. An approach without any defined goals however is outdated. How minimal invasive cardiac output monitoring techniques can be used to guide individualized fluid management[25] needs to be substantiated by validation studies that adhere to the proposed methodological considerations[9] as well as large-scale clinical outcome studies. To this end, integration of traditional physiological concepts with a clinically practicable approach based on minimal invasive cardiovascular management may be feasible. However, the impulse to rely on overly simplistic approaches should be resisted. This may especially be important in the grey zone that applies in almost one-quarter of our patients.

Declaration of interest

R.A.B. received travel support from Abbott to visit the 2011 ASA conference. C.B. was a lecturer during the Nexfin symposium at the ESA congress in Amsterdam, 2011.

Funding

R.A.B. is a clinical research fellow supported by a Dr E. Dekker research career grant of the Netherlands Heart Foundation (grant 2008T003), a research career grant of the Netherlands Society of Anaesthesiologists, and a ZonMW Clinical Fellow Stipendium (grant 40-00703-97-305). C.B. is supported by research support grant of the European Society of Anaesthesiology, a research grant of the European Association of Cardiothoracic Anaesthesthesiology, and the Netherlands Brain Foundation (grant F2010(1)-14).

References

1 Hadian M, Pinsky MR. Evidence-based review of the use of the pulmonary artery catheter: impact data and complications. *Crit Care* 2006; **10** (Suppl. 3): S8

2 Schwann NM, Hillel Z, Hoeft A, *et al.* Lack of effectiveness of the pulmonary artery catheter in cardiac surgery. *Anesth Analg* 2011; **113**: 994–1002

3 Brandstrup B, Tonnesen H, Beier-Holgersen R, *et al.* Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg* 2003; **238**: 641–8

4 Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. *Anesthesiology* 2008; **109**: 723–40
5 Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. *Anesth Analg* 2011; **112**: 1392–402
6 Michard F. The burden of high-risk surgery and the potential benefit of goal-directed strategies. *Crit Care* 2011; **15**: 447
7 de Waal EEC, Wappler F, Buhre WF. Cardiac output monitoring. *Curr Opin Anaesthesiol* 2009; **22**: 71–7
8 Schober P, Loer SA, Schwarte LA. Perioperative hemodynamic monitoring with transesophageal Doppler technology. *Anesth Analg* 2009; **109**: 340–53
9 Critchley LA, Lee A, Ho AM. A critical review of the ability of continuous cardiac output monitors to measure trends in cardiac output. *Anesth Analg* 2010; **111**: 1180–92
10 Peyton PJ, Chong SW. Minimally invasive measurement of cardiac output during surgery and critical care: a meta-analysis of accuracy and precision. *Anesthesiology* 2010; **113**: 1220–35
11 Squara P, Cecconi M, Rhodes A, Singer M, Chiche JD. Tracking changes in cardiac output: methodological considerations for the validation of monitoring devices. *Intensive Care Med* 2009; **35**: 1801–8
12 Challand C, Struthers R, Sneyd JR, *et al.* Randomized controlled trial of intraoperative goal-directed fluid therapy in aerobically fit and unfit patients having major colorectal surgery. *Br J Anaesth* 2012; **108**: 53–62
13 NICE. CardioQ-ODM oesophageal Doppler monitor. 2011. Available from http://guidance.nice.org.uk/MTG3/Guidance/pdf/English
14 Corcoran T, Emma Joy Rhodes J, Clarke S, Myles PS, Ho KM. Perioperative fluid management strategies in major surgery: a stratified meta-analysis. *Anesth Analg* 2012; **114**: 640–51
15 Kiefer N, Theis J, Putensen-Himmer G, Hoeft A, Zenker S. Peristaltic pneumatic compression of the legs reduces fluid demand and improves hemodynamic stability during surgery: a randomized, prospective study. *Anesthesiology* 2011; **114**: 536–44
16 Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med* 2009; **37**: 2642–7
17 Cannesson M, Le Manach Y, Hofer CK, *et al.* Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a 'gray zone' approach. *Anesthesiology* 2011; **115**: 231–41
18 Metzelder S, Coburn M, Fries M, *et al.* Performance of cardiac output measurement derived from arterial pressure waveform analysis in patients requiring high-dose vasopressor therapy. *Br J Anaesth* 2011; **106**: 776–84
19 Lansdorp B, Lemson J, van Putten MJ, de Keijzer A, van der Hoeven JG, Pickkers P. Dynamic indices do not predict volume responsiveness in routine clinical practice. *Br J Anaesth* 2012; **108**: 395–401
20 De Hert SG. Assessment of fluid responsiveness: insights in a 'gray zone'. *Anesthesiology* 2011; **115**: 229–30
21 Gelman S. Venous function and central venous pressure: a physiologic story. *Anesthesiology* 2008; **108**: 735–48
22 Jansen JR, Maas JJ, Pinsky MR. Bedside assessment of mean systemic filling pressure. *Curr Opin Crit Care* 2010; **16**: 231–6
23 Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, Jansen JR. Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. *Crit Care Med* 2009; **37**: 912–8
24 Geerts BF, Aarts LP, Groeneveld AB, Jansen JR. Predicting cardiac output responses to passive leg raising by a PEEP-induced increase in central venous pressure, in cardiac surgery patients. *Br J Anaesth* 2011; **107**: 150–6
25 Chikhani M, Moppett IK. Minimally invasive cardiac output monitoring: what evidence do we need. *Br J Anaesth* 2011; **106**: 451–3

British Journal of Anaesthesia **109** (3): 302–304 (2012)
doi:10.1093/bja/aes278

EDITORIAL II

Prevention of opioid-induced hyperalgesia in surgical patients: does it really matter?

V. Martinez[1,2] and D. Fletcher[1,2,3]*

[1] Service d'anesthésie, Hôpital Raymond Poincaré, Garches, Assistance Publique Hôpitaux de Paris, F-92380 Garches, France
[2] INSERM, U-987, Hôpital Ambroise Paré, Centre d'Evaluation et de Traitement de la Douleur, Boulogne Billancourt F-92100, France
[3] Université Versailles Saint-Quentin, F-78035 Versailles, France

* E-mail: dominique.fletcher@rpc.aphp.fr

In a recent issue of the *British Journal of Anaesthesia*, Echevarría and colleagues[1] reported that nitrous oxide (N_2O) reduced postoperative opioid-induced hyperalgesia (OIH) after remifentanil–propofol anaesthesia. In their study, 50 adult ASA I–II patients undergoing elective open septorhinoplasty under general anaesthesia were assigned to receive N_2O (70%) or 100% oxygen. Mechanical pain thresholds were measured before surgery and 2 and 12–18 h after

British Journal of Anaesthesia **109** (3): 330–8 (2012)
Advance Access publication 26 June 2012 · doi:10.1093/bja/aes182

BJA

CARDIOVASCULAR

Prediction of fluid responsiveness by a continuous non-invasive assessment of arterial pressure in critically ill patients: comparison with four other dynamic indices

X. Monnet[1,2]*, M. Dres[1,2], A. Ferré[1,2], G. Le Teuff[4], M. Jozwiak[1,2], A. Bleibtreu[1,2], M.-C. Le Deley[4], D. Chemla[1,3], C. Richard[1,2] and J.-L. Teboul[1,2]

[1] EA4533, Université Paris-Sud 11, France
[2] Service de réanimation médicale, Hôpital de Bicêtre and [3] Service de physiologie, Hôpital Antoine Béclère, Hôpitaux universitaires Paris-Sud, Assistance Publique-Hôpitaux de Paris, Paris, France
[4] Unité de biostatistiques et d'épidémiologie, Institut Gustave Roussy, Villejuif, France

* Corresponding author: Service de réanimation médicale, Centre Hospitalier Universitaire de Bicêtre, 78, rue du Général Leclerc, 94 270 Le Kremlin-Bicêtre, France. E-mail: xavier.monnet@bct.aphp.fr

Editor's key points

- Research continues in finding appropriate ways of predicting fluid responsiveness in the critically ill.
- Non-invasive pulse pressure variation (PPV) was compared with invasive PPV, stroke volume, passive leg raising (PLR), and end-expiratory occlusion test.
- Importantly, non-invasive PPV was as good as invasive PPV in predicting fluid responsiveness.

Background. We evaluated the ability of an infrared photoplethysmography arterial waveform (continuous non-invasive arterial pressure, CNAP) to estimate arterial pulse pressure variation (PPV). We compared the ability of non-invasive PPV to predict fluid responsiveness with invasive PPV, respiratory variation of pulse contour-derived stroke volume, and changes in cardiac index induced by passive leg raising (PLR) and end-expiratory occlusion (EEO) tests.

Methods. We measured the responses of cardiac index (PiCCO) to 500 ml of saline in 47 critically ill patients with haemodynamic failure. Before fluid administration, we recorded non-invasive and invasive PPVs, stroke volume variation, and changes in cardiac index induced by PLR and by 15 s EEO. Logistic regressions were performed to investigate the advantage of combining invasive PPV, stroke volume variation, PLR, and EEO when predicting fluid responsiveness.

Results. In eight patients, CNAP could not record arterial pressure. In the 39 remaining patients, fluid increased cardiac index by $\geq$15% in 17 'responders'. Considering the 195 pairs of measurements, the bias (SD) between invasive and non-invasive PPVs was −0.6 (2.3)%. The areas under the receiver operating characteristic (ROC) curves for predicting fluid responsiveness were 0.89 (95% confidence interval, 0.78–1.01) for non-invasive PPV compared with 0.89 (0.77–1.01), 0.84 (0.70–0.96), 0.95 (0.88–1.03), and 0.97 (0.91–1.03) for invasive pulse pressure, stroke volume variations, PLR, and EEO tests (no significant difference). Combining multiple tests did not significantly improve the area under the ROC curves.

Conclusions. Non-invasive assessment of PPV seems valuable in predicting fluid responsiveness.

Keywords: arterial pressure, measurement; equipment, Finapress; equipment, monitors; fluid therapy; measurement techniques, arterial pressure; shock

Accepted for publication: 29 February 2012

In an attempt to predict fluid responsiveness in critically ill patients, several studies have consistently demonstrated that static preload markers, such as central venous pressure[1] and pulmonary artery occlusion pressure,[2] are ineffective.[3 4] Conversely, fluid responsiveness may be best predicted by using a functional approach relying on dynamic indices.[4] Among these indices, the respiratory variation of arterial pulse pressure induced by mechanical ventilation [pulse pressure variation (PPV), an estimate of stroke volume variation] has the largest evidence base.[5 6] The pulse contour analysis-derived stroke volume also exhibits respiratory variations that have been reported to correctly predict fluid responsiveness.[5 7–9] Passive leg raising (PLR) acts as a self-volume challenge.[10] Its effects on cardiac output or surrogates[11–17] predict fluid responsiveness with accuracy.[18] More recently, the changes in arterial pulse pressure or in pulse contour-derived cardiac index induced by an end-expiratory occlusion (EEO) were described as another valuable test to diagnose fluid responsiveness.[16] All these diagnostic indices of fluid responsiveness require a more or less invasive technique to estimate stroke volume.

Infrared plethysmography waveform analysis provides a non-invasive estimation of the arterial pressure curve.[19] The non-invasive PPV (PPVni) can thus be calculated. It has

already been demonstrated that PPVni can predict volume responsiveness with an accuracy similar to that of invasive PPV (PPVi) in patients undergoing major hepatic[20] or vascular surgery.[21] However, as far as we know, this technique has not been investigated in the specific population of critically ill patients.

In the present study, the ability of PPVni, PPVi, stroke volume variation (SVV), PLR, and EEO tests to predict fluid responsiveness were compared in a general population of critically ill patients.

Methods

Patients

As approved by the Institutional Review Board of our institution, patients' relatives were informed about the study when the patient was included, and could refuse the patient's participation at that time. If not, patients were informed as soon as their mental status enabled it and could withdraw from the study if they wanted. Forty-seven patients were prospectively included if they presented acute circulatory failure for which the attending physician had decided to administer fluid. This decision was based on inadequate tissue perfusion defined by the presence of at least one of the following signs:[11 16 22] (i) systolic arterial pressure $<$90 mm Hg (or a decrease of $>$50 mm Hg in previously hypertensive patients) or the need for norepinephrine, (ii) urine output $<$0.5 ml kg h^{-1} for at least 2 h, (iii) tachycardia $>$100 beats min^{-1}, (iv) skin mottling, or (v) blood lactate $>$2 mmol $litre^{-1}$. Patients were excluded if they presented cardiac arrhythmias, spontaneous triggering of the ventilator, as assessed by visual observation of the pressure curve of the ventilator, and obvious hydrostatic pulmonary oedema. Patients' characteristics are summarized in Table 1. All patients were ventilated with an Evita 4 (Dräger Medical Systems, Telford, PA, USA) in the volume-controlled mode. All patients received sedation and three patients were paralysed.

Table 1 Patient characteristics at baseline in volume responders (n=17) and non-responders (n=22). SAPS, simplified acute physiology score; ARDS, acute respiratory distress syndrome; Pa_{O_2}, partial pressure of arterial oxygen, $F_{I_{O_2}}$, inspired fraction of oxygen. No significant difference was observed between responders and non-responders

Age (range, yr)	
Responders	28–80
Non-responders	30–83
SAPS II [mean (SD)]	
Responders	62 (22)
Non-responders	70 (22)
Origin of shock (no. of patients)	
Septic	
Responders	15
Non-responders	13
Hypovolaemic	
Responders	4
Non-responders	3
Drug poisoning	
Responders	0
Non-responders	1
Acute respiratory distress syndrome (no. of patients)	
Responders	5
Non-responders	10
Tidal volume [mean (SD), ml kg^{-1} of predicted body weight]	
Responders	8.5 (2.1)
Non-responders	7.4 (2.8)
Total PEEP [mean (SD), cm H_2O]	
Responders	7 (3)
Non-responders	6 (3)
Compliance of the respiratory system [mean (SD), ml cm H_2O^{-1}]	
Responders	43 (23)
Non-responders	31 (10)
$Pa_{O_2}/F_{I_{O_2}}$ [mean (SD), kPa]	
Responders	31 (3)
Non-responders	32 (4)
Lactate [mean (SD), mmol $litre^{-1}$]	
Responders	2.3 (1.3)
Non-responders	2.2 (1.2)
Patients receiving norepinephrine (no. of patients)	
Responders	10
Non-responders	15
Dose of norepinephrine [mean (25–75% IQR), $\mu g\ kg^{-1}\ min^{-1}$]	
Responders	1.1 (0.6–2.0)
Non-responders	0.7 (0.1–2.4)

Continuous non-invasive arterial pressure measurement

With this technique, the arterial pressure in the finger is measured using the volume-clamp method.[23] This method is based on the development of the dynamic pulsatile unloading of the finger arterial walls.[24] The diameter of a digital artery under a cuff wrapped around the finger is kept constant in spite of the changes in arterial pressure during each heartbeat. Changes in diameter are detected by means of an infrared photoplethysmograph inserted into the finger cuff. When an increased arterial diameter is detected, the finger cuff pressure is immediately increased by a rapid pressure servo-controller system to prevent the diameter change. As a result, the finger cuff pressure is proportional to the intra-arterial pressure at the proper unloaded diameter of the finger artery. With the continuous non-invasive arterial pressure (CNAP, CNSystems, Graz, Austria) technology, the non-invasive arterial pressure (APni) is measured by an improved version of the vascular unloading principle using several concentrically interlocking control loops which enhance the accuracy and stability of the APni measurement.[25] The estimation of arterial pressure is calibrated by a measurement performed by sphygmomanometry with a brachial cuff. A typical APni waveform is displayed in Supplementary Figure S1.

Haemodynamic measurements

All patients had an internal jugular vein catheter and a thermistor-tipped arterial catheter (PV2024 Pulsion Medical Systems, Munich, Germany) in the femoral artery connected to the $PiCCO_2$ device (Pulsion Medical Systems, Munich, Germany) to measure cardiac index (through transpulmonary thermodilution and pulse contour analysis) and global end-diastolic volume (GEDV) (through transpulmonary thermodilution). The femoral arterial line was connected to the pressure sensor PV8115 (Pulsion Medical Systems) and the invasive arterial pressure (APi) was measured by the Infinity Delta XL monitor (Dräger Medical Systems). APni was measured through the CNAP device. Cardiac rhythm, APi, APni, and airway pressure were computerized continuously (HEM 3.5, Notocord Systems, Croissy-sur-Seine, France). From the computerized arterial pressure curve of APni and APi, PPVni and PPVi, respectively, were calculated using the standard formulae {PPV=(PPmax−PPmin)/[(PPmax+PPmin)/2], where PPmax and PPmin are the maximum and minimum values of PP during one respiratory cycle}.[26] For this purpose, the values of PPVni and PPVi of four consecutive respiratory cycles were averaged. The values of PPVi and PPVni were obtained offline, such that the investigators were blinded to these values. The value of SVV, as automatically calculated with a proprietary formula by the $PiCCO_2$ device, was also recorded.

Study design

At baseline, we measured heart rate, APi, APni, and transpulmonary thermodilution variables including cardiac index and GEDV. Immediately after, we performed the PLR and EEO tests (Fig. 1). The PLR test was performed by transferring the patient from the semi-recumbent position to a position in which the legs were elevated at 45°.[27] We calculated the change in pulse contour-derived cardiac index from its baseline value to the maximum value it reached within 1 min after starting PLR.[10 11] Patients were returned to the semi-recumbent position at the end of PLR. The EEO test was performed by interrupting ventilation at end-expiration for 15 s.[16] We calculated the change of pulse contour-derived cardiac index from its baseline value to the maximum value it reached during the last 5 s of EEO.[16] Immediately after the EEO and PLR tests, we recorded heart rate, APi, APni, PPVi, PPVni, SVV, and transpulmonary thermodilution variables including cardiac index and GEDV. Immediately afterwards, volume expansion was performed by infusing 500 ml of saline over 30 min.[28] After volume expansion, we again recorded heart rate, APi, APni, PPVi, PPVni, SVV, and transpulmonary thermodilution variables including cardiac index and GEDV. Patients in whom volume expansion increased cardiac index by more than 15% were defined as 'volume responders' and the remaining ones as 'non-volume responders'.[11 16 22 29] This cut-off is justified by the fact that the least significant change of cardiac index measured by transpulmonary thermodilution is 12% when three cold boluses are used when performing the measurement.[30] In each patient, one observation only was made.

Statistical analysis

All the continuous variables except the dose of norepinephrine were normally distributed (Kolmogorov–Smirnov test). Results are expressed as mean [standard deviation (SD)], median (25–75% inter-quartile range, IQR), or mean (95% confidence interval, CI), as appropriate. Values of APi and APni were compared by the Bland–Altman analysis. The percentage error was calculated as 2 × SD divided by the mean of the reference method.[31] Comparisons of haemodynamic variables between the different study times were assessed using a paired Student *t*-test. Comparisons of responders *vs* non-responders were assessed using a two-sample Student *t*-test or a Mann–Whitney *U*-test, as appropriate. Correlations were assessed by the Pearson coefficient. Receiver operating characteristic (ROC) curves were constructed to test the ability of the following variables to predict fluid responsiveness: GEDV, PPVni, PPVi, SVV, effects of PLR, and effects of EEO tests on cardiac index.[32] The areas under the ROC curves (AUC) were compared using DeLong and colleagues'[33] test. The optimal cut-off of each variable was estimated by maximizing the Youden index (=sensitivity+specificity−1). For each variable, the median and the standard error of the optimal cut-off were estimated using 1000 bootstrapped samples; the derived 95% CI [cut-off (1.96 SE)] defines the 'grey zone'.[34] Multivariable logistic regressions were performed by entering PPVi, SVV, PLR, and/or EEO tests to determine the best model of combined diagnostic tests for predicting fluid responsiveness. The combination of all four diagnostic tests could not be studied due to the limited number of observations. PPVni was not entered in these models since, in clinical practice, PPVni would not be used in combination with PPVi, SVV, the PLR, and EEO tests, which all require an arterial catheter. A difference between two AUCs was considered statistically significant when the *P*-value of DeLong and colleagues' test was <0.05. The statistical analysis was performed with the MedCalc8.1.0.0 (Mariakerke, Belgium) and SAS software (9.1).

Results

Patients

Among the 47 patients of study population, eight (17%) were excluded because the arterial curve could not be obtained by the CNAP device. All these patients exhibited clinical signs of severe skin hypoperfusion. In these patients, the mean APi was 45 (10) mm Hg and the dose of norepinephrine was 5.1 (25–75% IQR: 3.1–6.3 $\mu g\ kg^{-1}\ min^{-1}$). In the remaining 39 patients, volume expansion significantly increased cardiac index by more than 15% [34 (18)%] in 18 volume responders (Table 2). In non-volume responders, volume expansion did not significantly change cardiac index (Table 2).

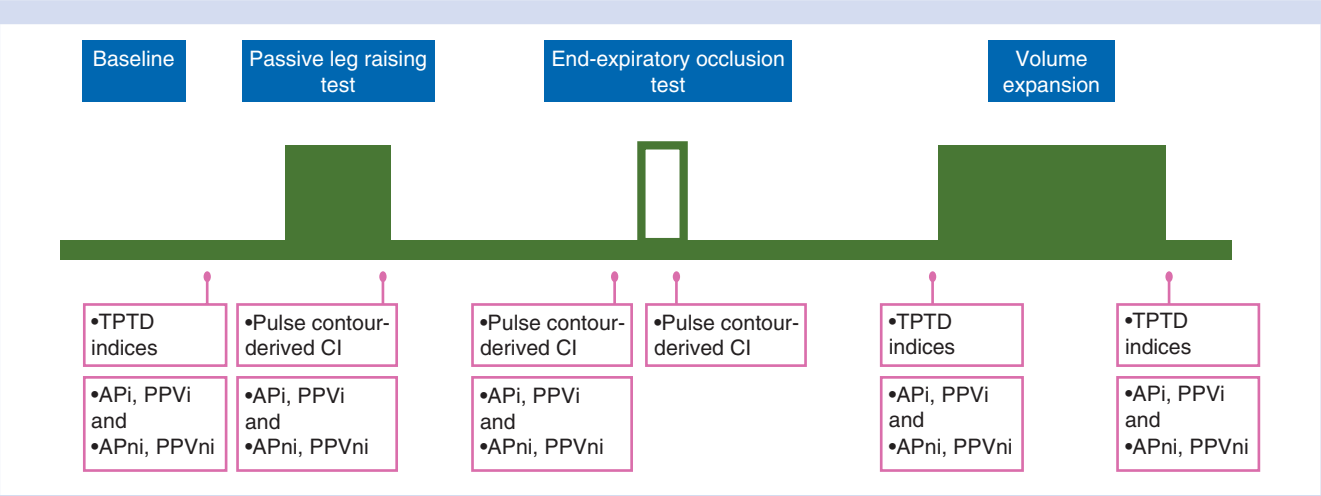

Fig 1 Study protocol with the corresponding haemodynamic measurements. TPTD, transpulmonary thermodilution; APi, invasive arterial pressure; APni, non-invasive arterial pressure; PPV, respiratory variation of APi; PPni, respiratory variation of APni; CI, cardiac index.

Non-invasive measurement of arterial pressure

Considering all study times (baseline, during PLR, before EEO test, before, and after volume expansion), a total of 195 pairs of measurements of APi and APni were performed. The mean APni and the mean APi were significantly correlated ($r=0.81$, $P<0.0001$). The bias was 5 (11) mm Hg (Supplementary Fig. S2). The percentage error was 29%. The PLR- and fluid-induced changes in the mean APni [+20 (29)%] and the mean APi [+20 (36)%] were significantly correlated ($r=0.69$, $P<0.001$). The results of the comparison between systolic and diastolic values of APni and APi are provided as Supplementary data. PPVni and PPVi were significantly correlated ($r=0.88$, $P<0.001$, $n=195$). The bias was −0.6 (2.3)% (Fig. 2). The percentage error was 46%.

Prediction of fluid responsiveness

In volume responders, PPVni, PPVi, and SVV were significantly higher than the respective values of PPVni, PPVi, and SVV in non-responders. In responders, all these values significantly decreased with fluid administration (Table 2).

A PPVni ≥11% was associated with a sensitivity of 82% (95% CI, 57–96%) and a specificity of 91% (95% CI, 71–99%) (Table 3, Fig. 3). Using the Bayesian approach, the PPVni ≥11% predicted a positive response to fluid administration in 88% of cases in our cohort, whereas a value lower than 11% was associated with a negative predictive value of 87%. The positive likelihood ratio was estimated to 9.1, meaning that a PPVni ≥11% is 9.1 times more frequent in responders than in non-responders. Based on the positive and negative likelihood ratios (9.1 and 0.19, respectively), the diagnostic value of PPVni can be classified as good. The grey zone around the optimal cut-off ranges from 8% to 14%, with 10 patients (26% of the sample) falling in this grey zone.

A PPVi ≥10% predicted a positive response to fluid administration with a sensitivity of 88% (95% CI, 64–98%) and a specificity of 91% (95% CI, 71–99%), with 21% of patients falling in the grey zone (Table 3, Fig. 3). An SVV ≥14% enabled prediction of a positive response to fluid administration with a sensitivity of 76% (95% CI, 50–93%) and a specificity of 82% (95% CI, 71–99), with 46% of patients in the grey zone (Table 3, Fig. 3).

Two patients were false-negative for both PPVni and PPVi. These patients were also false-negative for SVV. Both patients were ventilated with a tidal volume of 5 ml kg^{-1} of predicted body weight. The compliance of the respiratory system in these patients was the lowest of the population (19 ml cm H_2O^{-1}). The two false-negative cases using PPVni, PPVi, or SVV were correctly classified by both the PLR and the EEO tests.

In volume responders, PLR induced a greater increase in cardiac index than in non-volume responders (Table 2). An increase in cardiac index ≥11% during PLR predicted a positive response to fluid administration with a sensitivity of 100% (95% CI, 81–100%) and a specificity of 91% (95% CI, 71–99%), with 13% of patients in the grey zone (Table 3, Fig. 3). The two patients of the original population who were false-positive using the PLR test were correctly classified by the EEO test, PPVni, PPVi, and SVV.

In volume responders, the EEO test induced a greater increase in cardiac index than in non-volume responders (Table 2). In non-volume responders, cardiac index did not change during EEO. An increase in cardiac index of ≥5% during EEO predicted a positive response to fluid administration with a sensitivity of 100% (95% CI, 81–100%) and a specificity of 91% (95% CI, 71–99%), with 15% of patients in the grey zone (Table 3, Fig. 3). The two patients of the original population who were false-positive using the EEO test were correctly classified by the PLR test, PPVni, PPVi, and SVV.

The AUCs established for PPVni, PPVi, SVV, the PLR-induced, and the EEO-induced changes in cardiac index were not significantly different (Table 3, Fig. 3). The AUC for GEDV was significantly lower than that for PPVni, PPVi, SVV, the PLR, and the EEO tests (Table 3).

Table 2 Haemodynamic variables before and after volume expansion in volume responders ($n=17$) and non-responders ($n=22$). APni, non-invasive arterial pressure; APi, invasive arterial pressure; PPVni, respiratory variation of pulse APni; PPVi, respiratory variation of pulse APi; SVV, respiratory variation of stroke volume estimated by pulse contour analysis, PLR, passive leg raising; EEO, end-expiratory occlusion. *$P<0.05$ *vs* responders; #$P<0.05$ *vs* before volume expansion

	Before volume expansion	After volume expansion
Heart rate [mean (SD), beats min^{-1}]		
Responders	107 (28)	101 (25)#
Non-responders	83 (21)*	84 (20)*
Cardiac index [mean (SD), litre min^{-1} m^{-2}]		
Responders	3.5 (1.3)	4.5 (1.6)#
Non-responders	3.4 (1.2)	3.6 (1.2)
Systolic APni (finger) [mean (SD), mm Hg]		
Responders	105 (24)	136 (36)#
Non-responders	107 (24)	115 (25)
Systolic APi (femoral) [mean (SD), mm Hg]		
Responders	100 (25)	137 (40)#
Non-responders	116 (32)	119 (32)
Mean APni (finger) [mean (SD), mm Hg]		
Responders	77 (18)	94 (24)#
Non-responders	81 (19)	85 (16)
Mean APi (femoral) [mean (SD), mm Hg]		
Responders	70 (18)	91 (26)#
Non-responders	76 (18)	79 (18)
Diastolic APni (finger) [mean (SD), mm Hg]		
Responders	64 (17)	74 (23)#
Non-responders	66 (18)	67 (16)
Diastolic APi (femoral) [mean (SD), mm Hg]		
Responders	55 (15)	67 (19)#
Non-responders	56 (14)	57 (14)
PPVni (finger) [mean (SD), %]		
Responders	16 (8)	7 (7)#
Non-responders	5 (3)*	5 (4)
PPVi (femoral) [mean (SD), %]		
Responders	16 (6)	9 (6)#
Non-responders	6 (4)*	5 (4)
SVV [mean (SD), %]		
Responders	18 (7)	12 (6)#
Non-responders	10 (7)	9 (6)
Changes in cardiac index during PLR [mean (SD), %]		
Responders	29 (29)	—
Non-responders	6 (7)*	—
Changes in cardiac index during EEO [mean (SD), %]		
Responders	11 (4)	—
Non-responders	2 (4)*	—
Global end-diastolic volume [mean (SD), ml m^{-2}]		
Responders	782 (355)	927 (496)#
Non-responders	683 (163)	800 (281)#

Considering results of multivariable logistic regressions, the AUCs ranged from 0.89 (95% CI, 0.76–1.01) to 0.98 (95% CI, 0.95–1.01) for the models including two tests and from 0.98 (95% CI, 0.95–1.01) to 0.99 (95% CI, 0.98–1.01) for the models including three tests. Concerning these tests including several predictors, the only significant difference between AUCs was observed when comparing SVV alone with the models including two or three predictors, except for the model including PPVi and SVV (Table 3).

Discussion

This study shows that PPV measured by non-invasive infrared plethysmography technology (PPVni) predicts fluid responsiveness with an accuracy comparable with that of PPV recorded at the femoral artery (PPVi). It was also found that the predictive value of the PLR and EEO tests was excellent. PPVi demonstrated lower predictive cut-offs than previously reported in patients ventilated with non-low tidal volumes and non-low compliance of the respiratory system.[6]

The first goal of our study was to investigate a non-invasive estimation of PPV. The advantage of the volume-clamp method, which was developed some years ago, is to provide a non-invasive estimation of continuous arterial pressure.[19] The older device (Finapress) using this technique was shown to provide an unreliable estimation of arterial pressure in critically ill patients.[35] The technique we used in this study (CNAP) was recently proposed to enable a more continuous estimation of arterial pressure than the older technologies.[25] This device was investigated by a few studies[20 21] in the operating theatre setting, but has not been tested in the specific population of critically ill patients. In this regard, a first important result of the present study is that APni could not be assessed by the CNAP device in 17% of critically ill patients because of excessive finger hypoperfusion. These patients were severely ill, since their mean arterial pressure remained low in spite of high doses of norepinephrine. It cannot be excluded that the high dose of norepinephrine was responsible for marked finger vasoconstriction, even though other mechanisms (sympathetic stimulation, distal microthrombi) could also contribute to the inability of the CNAP device to provide the APni signal. Solus-Biguenet and colleagues[20] and Biais and colleagues[21] did not report such limitations of the technique in the operating theatre. This suggests that the technique might be more suitable for the perioperative setting than for the intensive care unit context in which both disease and treatment might induce significant finger vasoconstriction.

Considering the population of patients for which the APni signal could be obtained, the great advantage of photoplethysmography over a simple brachial pressure cuff is obviously that it provides a beat-to-beat estimation of AP and allows for the calculation of PPVni. In the present study,

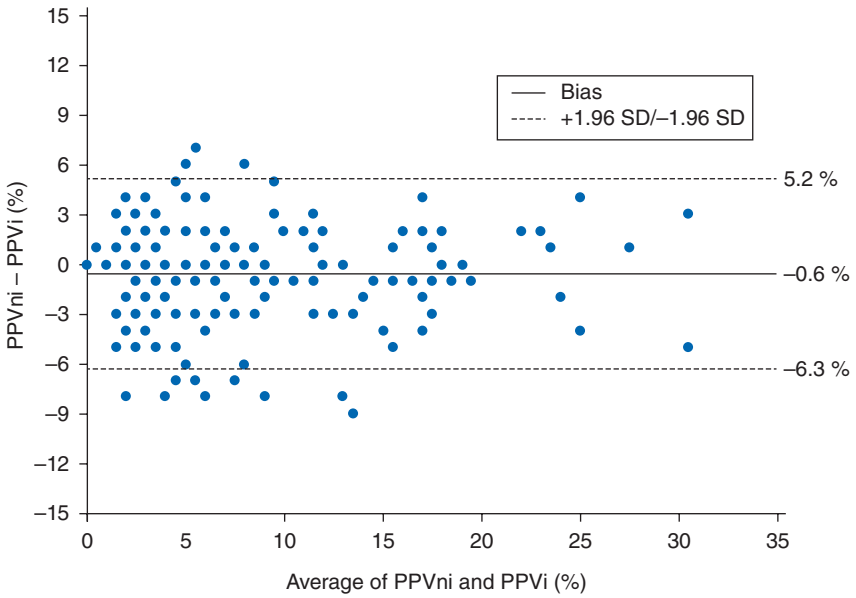

Fig 2 Bland–Altman plot between PPV measured through a femoral catheter (PPVi) and by the CNAP system (PPVni) for all the pairs of measurements performed during the study (n=195).

PPVni predicted fluid responsiveness with an accuracy similar to that of PPVi. Thus, we confirmed the positive results already obtained with the Finapress[20] and the CNAP[21] devices in the setting of the operating theatre. In our study, the percentage error for PPVni as an estimate of PPVi was large (46%), which could at first glance appear to contradict the ability of PPVni to predict fluid responsiveness. In fact, this is clearly explained by the fact that the highest limits of agreement were observed for the lowest value of PPVi, as showed by the Bland–Altman representation. In contrast, the limits of agreement were narrower when the average of PPVi and PPVni was 15% and above.

The CNAP device provided an estimation of the mean APi with a 29% error and this confirms results already obtained with an older device using the same technology.[36] Our finding was expected as the estimation of APni by the CNAP device is calibrated by a measurement of arterial pressure by a brachial pressure cuff. Thus, by comparing APi and APni, we in fact compared the pressure cuff *vs* the invasive measurement of AP. The only moderate ability of sphygmomanometry to measure arterial pressure compared with invasive measurement is already well known.[37] Thus, the clinical utility of the CNAP device is not that it estimates the absolute values of arterial pressure (which can be done by a simple brachial cuff), but that it provides a continuous measurement of PPVni.

The second goal of the present study was to compare the different indices that have been developed to predict fluid responsiveness. Although the volume responders had a lower cardiac preload than the non-responders, as assessed by a lower value of GEDV, the latter index, as a static marker of preload, could not predict volume responsiveness with an acceptable accuracy, thus confirming previous studies.[7 38] It is noteworthy that PPVi exhibited a lower cut-off diagnostic value than previously reported.[6] This was explained by the fact that tidal volume and compliance of the respiratory system were low in some of our patients.[39] When tidal volume is low, the changes in intrathoracic pressure might be low, such that the changes in cardiac preload could be too low to challenge the preload-dependence of stroke volume. This might be particularly true if a low lung compliance prevents transmission of the change in alveolar pressure to the vessels and cardiac chambers.[39] According to this hypothesis, we observed that the two false-negative cases of PPVi were the two volume responders in whom the tidal volume was below 7 ml kg^{-1} and the compliance of the respiratory system was low as well.

The ability of the PLR test to predict fluid responsiveness has now been demonstrated by several studies[11–17 27 40] and confirmed by a recent meta-analysis.[18] Unlike PPVni, PLR might allow testing for fluid responsiveness even in patients ventilated with low tidal volume and lung compliance. Accordingly, the volume responders who were false-negative for PPVi were positive in the PLR test. A novelty of the present study was the investigation of the predictive value of the PLR tests with a 'grey zone' approach.[34] The grey zone of the PLR test was relatively narrow, ranging from 9% to 13%. In other words, if the PLR-induced increase in cardiac index was below 9% or above 13%, then the fluid unresponsiveness/responsiveness could be predicted with 95% certainty. The EEO test was introduced more recently. Occluding the respiratory circuit for a few seconds at end-expiration precludes the tidal interruption of venous return that occurs at each mechanical inspiration. The

Table 3 Diagnostic ability of the different indices of fluid responsiveness. AUC, area under the ROC curve; PPVi, respiratory variation of invasive arterial pulse pressure; PPVni, respiratory variation of non-invasive arterial pulse pressure; SVV, respiratory variation of stroke volume; PLR, passive leg raising; EEO, end-expiratory occlusion; GEDV, global end-diastolic volume indexed for body area. *The standard error of the optimal cut-off was estimated using 1000 bootstrapped samples; the derived 95% CI [cut-off (1.96 SE)] defines the 'grey zone'. †The AUC of GEDV is significantly different from the AUCs of other tests alone ($P<0.05$) but not from AUC=0.50. ‡The AUCs of models with at least two predictors (except the model including PPVi and SVV) are significantly higher than that of the model with SVV alone ($P<0.05$)

	AUC (95% CI)	Sensitivity	Specificity	Youden index	Optimal cut-off	'Grey zone'*	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio
Predictors of fluid responsiveness considered alone										
SVV	0.84 (0.71–0.97)	0.76	0.82	0.58	14%	9–19%	0.76	0.82	4.21	0.29
PPVi	0.89 (0.77–1.01)	0.88	0.91	0.79	10%	7–13%	0.88	0.91	9.71	0.13
PPVni	0.89 (0.78–1.01)	0.82	0.91	0.73	11%	8–14%	0.88	0.87	9.06	0.19
PLR	0.95 (0.88–1.03)	1.00	0.91	0.91	11%	9–13%	0.89	1.00	11.00	0.00
EEO	0.97 (0.91–1.03)	1.00	0.91	0.91	5%	4–6%	0.89	1.00	11.00	0.00
GEDV	0.52 (0.51–0.63)†									
Predictors of fluid responsiveness considered in combination‡										
PPVi–SVV	0.89 (0.76–1.01)	0.88	0.91	0.79			0.88	0.91	9.70	0.13
SVV–PLR	0.97 (0.92–1.01)	0.94	0.91	0.85			0.89	0.95	10.35	0.06
SVV–EEO	0.97 (0.93–1.02)	1.00	0.91	0.91			0.89	1.00	11.00	0.00
PLR–EEO	0.98 (0.94–1.01)	1.00	0.91	0.91			0.89	1.00	11.00	0.00
PPVi–PLR	0.98 (0.94–1.01)	0.94	0.95	0.89			0.94	0.95	20.70	0.06
PPVi–EEO	0.98 (0.95–1.01)	1.00	0.91	0.91			0.89	1.00	11.00	0.00
PPVi–SVV–PLR	0.98 (0.95–1.01)	0.94	0.95	0.89			0.94	0.95	20.70	0.06
PPVi–SVV–EEO	0.98 (0.95–1.01)	1.00	0.91	0.91			0.89	1.00	11.00	0.00
PPVi–PLR–EEO	0.99 (0.97–10.1)	1.00	0.91	0.91			0.89	1.00	11.00	0.00
SVV–PLR–EEO	0.99 (0.98–1.01)	0.94	1.00	0.94			1.00	0.96	—	0.06

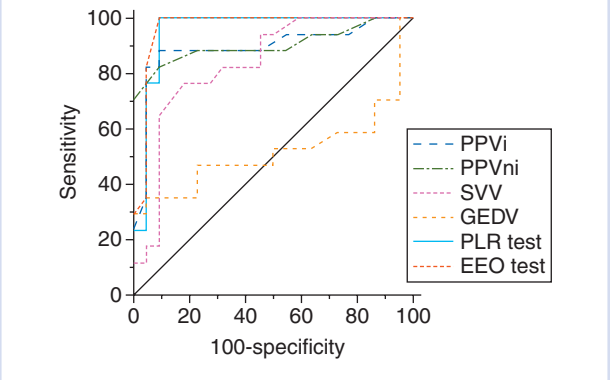

Fig 3 ROC curves showing the ability of non-invasive PPV (PPVni), invasive PPV (PPVi), SVV, changes in cardiac index induced by PLR, and changes in cardiac index induced by EEO to predict fluid responsiveness.

resulting increase in cardiac preload allows for accurate prediction of fluid responsiveness.[16] In the present study, the grey zone observed for the EEO test, which has never been described, was between 4% and 6%, which might be considered as narrow. We confirm that the EEO test and the PLR test perform accurately even when tidal volume and compliance of the respiratory system are low.[39]

At the present time, several indices are available at the bedside to predict fluid responsiveness. One of the strengths of this study was that it examines the ability of test combinations to perform better than diagnostic tests alone. We found that the combination of multiple tests did not significantly improve the prediction of fluid responsiveness when compared with the model including only one test, except for the SVV test. However, the limited sample size does not allow for a powerful comparison of the diagnostic performance of the different tests. Further investigations would help test whether PPVni could replace the invasive tests.

In conclusion, this study showed that the volume-clamp method with the CNAP device could not detect arterial pressure in 17% of our population of critically ill patients. When measured, the PPVni predicted fluid responsiveness with an accuracy that differed non-significantly from that of PPVi.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Declaration of interest

J.-L.T. and X.M. are members of the Medical Advisory Board of Pulsion Medical Systems.

Funding

This study was supported by the Paris-Sud University and the Assistance Publique-Hôpitaux de Paris. CNSystems kindly provided the CNAP device.

References

1 Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest* 2008; **134**: 172–8

2 Osman D, Ridel C, Ray P, *et al.* Cardiac filling pressures are not appropriate to predict haemodynamic response to volume challenge. *Crit Care Med* 2007; **35**: 64–8

3 Monnet X, Teboul JL. Volume responsiveness. *Curr Opin Crit Care* 2007; **13**: 549–53

4 Marik PE, Monnet X, Teboul JL. Haemodynamic parameters to guide fluid therapy. *Ann Intensive Care* 2010; **1**: 1

5 Cannesson M. Arterial pressure variation and goal-directed fluid therapy. *J Cardiothorac Vasc Anesth* 2010; **24**: 487–97

6 Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med* 2009; **37**: 2642–7

7 Hofer CK, Muller SM, Furrer L, Klaghofer R, Genoni M, Zollinger A. Stroke volume and pulse pressure variation for prediction of fluid responsiveness in patients undergoing off-pump coronary artery bypass grafting. *Chest* 2005; **128**: 848–54

8 Hofer CK, Senn A, Weibel L, Zollinger A. Assessment of stroke volume variation for prediction of fluid responsiveness using the modified FloTrac and PiCCOplus system. *Crit Care* 2008; **12**: R82

9 Berkenstadt H, Margalit N, Hadani M, *et al.* Stroke volume variation as a predictor of fluid responsiveness in patients undergoing brain surgery. *Anesth Analg* 2001; **92**: 984–9

10 Monnet X, Teboul JL. Passive leg raising. *Intensive Care Med* 2008; **34**: 659–63

11 Monnet X, Rienzo M, Osman D, *et al.* Passive leg raising predicts fluid responsiveness in the critically ill. *Crit Care Med* 2006; **34**: 1402–7

12 Lamia B, Ochagavia A, Monnet X, Chemla D, Richard C, Teboul JL. Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneously breathing activity. *Intensive Care Med* 2007; **33**: 1125–32

13 Maizel J, Airapetian N, Lorne E, Tribouilloy C, Massy Z, Slama M. Diagnosis of central hypovolemia by using passive leg raising. *Intensive Care Med* 2007; **33**: 1133–8

14 Preau S, Saulnier F, Dewavrin F, Durocher A, Chagnon JL. Passive leg raising is predictive of fluid responsiveness in spontaneously breathing patients with severe sepsis or acute pancreatitis. *Crit Care Med* 2010; **38**: 989–90

15 Thiel SW, Kollef MH, Isakow W. Non-invasive stroke volume measurement and passive leg raising predict volume responsiveness in medical ICU patients: an observational cohort study. *Crit Care* 2009; **13**: R111

16 Monnet X, Osman D, Ridel C, Lamia B, Richard C, Teboul JL. Predicting volume responsiveness by using the end-expiratory occlusion in mechanically ventilated intensive care unit patients. *Crit Care Med* 2009; **37**: 951–6

17 Biais M, Vidil L, Sarrabay P, Cottenceau V, Revel P, Sztark F. Changes in stroke volume induced by passive leg raising in spontaneously breathing patients: comparison between echocardiography and Vigileo/FloTrac device. *Crit Care* 2009; **13**: R195

18 Cavallaro F, Sandroni C, Marano C, *et al.* Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies. *Intensive Care Med* 2010; **36**: 1475–83

19 Bogert LW, van Lieshout JJ. Non-invasive pulsatile arterial pressure and stroke volume changes from the human finger. *Exp Physiol* 2005; **90**: 437–46

20 Solus-Biguenet H, Fleyfel M, Tavernier B, *et al.* Non-invasive prediction of fluid responsiveness during major hepatic surgery. *Br J Anaesth* 2006; **97**: 808–16

21 Biais M, Stecken L, Ottolenghi L, *et al.* The ability of pulse pressure variations obtained with CNAPTM device to predict fluid responsiveness in the operating room. *Anesth Analg* 2011; **113**: 523–8

22 Monnet X, Rienzo M, Osman D, *et al.* Esophageal Doppler monitoring predicts fluid responsiveness in critically ill ventilated patients. *Intensive Care Med* 2005; **31**: 1195–201

23 Penaz J. Photoelectric measurement of blood pressure, volume and flow in the finger. *Digest of the 10th International Conference on Medical and Biological Engineering*. Dresden, 1973

24 Wesseling KH. Finapres, continuous noninvasive finger arterial pressure based on the method of Peňáz. In: Meyer-Sabellek W, Anlauf M, Gotzen R, Steinfeld L, eds. *Blood Pressure Measurement*. Darmstadt: Steinkopff Verlag, 1990; 161–72

25 Fortin J, Marte W, Grullenberger R, *et al.* Continuous non-invasive blood pressure monitoring using concentrically interlocking control loops. *Comput Biol Med* 2006; **36**: 941–57

26 Michard F, Chemla D, Richard C, *et al.* Clinical use of respiratory changes in arterial pulse pressure to monitor the haemodynamic effects of PEEP. *Am J Respir Crit Care Med* 1999; **159**: 935–9

27 Jabot J, Teboul JL, Richard C, Monnet X. Passive leg raising for predicting fluid responsiveness: importance of the postural change. *Intensive Care Med* 2009; **35**: 85–90

28 Vincent JL, Weil MH. Fluid challenge revisited. *Crit Care Med* 2006; **34**: 1333–7

29 Michard F, Boussat S, Chemla D, *et al.* Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med* 2000; **162**: 134–8

30 Monnet X, Persichini R, Ktari M, Jozwiak M, Richard C, Teboul JL. Precision of the transpulmonary thermodilution measurements. *Crit Care* 2011; **15**: R204

31 Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. *J Clin Monit Comput* 1999; **15**: 85–91

32 Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; **143**: 29–36

33 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; **44**: 837–45

34 Cannesson M, Le Manach Y, Hofer CK, *et al.* Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a 'gray zone' approach. *Anesthesiology* 2011; **115**: 231–41

35 Farquhar IK. Continuous direct and indirect blood pressure measurement (Finapres) in the critically ill. *Anaesthesia* 1991; **46**: 1050–5

36 Philippe EG, Hebert JL, Coirault C, Zamani K, Lecarpentier Y, Chemla D. A comparison between systolic aortic root pressure and finger blood pressure. *Chest* 1998; **113**: 1466–74

37 Bur A, Hirschl MM, Herkner H, *et al.* Accuracy of oscillometric blood pressure measurement according to the relation between

cuff size and upper-arm circumference in critically ill patients. *Crit Care Med* 2000; **28**: 371–6

38 Preisman S, Kogan S, Berkenstadt H, Perel A. Predicting fluid responsiveness in patients undergoing cardiac surgery: functional haemodynamic parameters including the respiratory systolic variation test and static preload indicators. *Br J Anaesth* 2005; **95**: 746–55

39 Monnet X, Bleibtreu A, Ferré A, *et al.* Passive leg raising and end-expiratory occlusion tests perform better than pulse pressure variation in patients with low respiratory system compliance. *Crit Care Med* 2012; **40**: 152–7

40 Lafanechere A, Pene F, Goulenok C, *et al.* Changes in aortic blood flow induced by passive leg raising predict fluid responsiveness in critically ill patients. *Crit Care* 2006; **10**: R132