Declaration of interest

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References

1 National Health Service. Consultant treatment outcomes. Available from http://www.nhs.uk/choiceintheNHS/Yourchoices/consultant-choice/Pages/consultant-data.aspx (accessed 15 September 2013)
2 National Health Service England. Press release 28/6/13: Major breakthrough in NHS Transparency as consultant mortality data goes online for first time. Available from http://www.england.nhs.uk/2013/06/28/mjr-brkthgh-nhs-transp-cons/ (accessed 15 September 2013)
3 Bristol Royal Infirmary. Learning from Bristol: the report of the public inquiry into children's heart surgery at the Bristol Royal Infirmary 1984–1995, 2001. Available from http://www.bristol-inquiry.org.uk (accessed 15 September 2013)
4 The *Guardian* Newspaper. Hospital's heart death figures face scrutiny, March 17, 2005. Available from http://www.theguardian.com/society/2005/mar/17/hospitals.nhs (accessed 15 September 2013)
5 *Report of the Mid Staffordshire NHS Foundation Trust Public Inquiry. Executive Summary*. London: The Stationery Office, 2013
6 Review into the quality of care and treatment provided by 14 hospital trusts in England: overview report, 2013. Available from http://www.nhs.uk/NHSEngland/bruce-keogh-review/Pages/published-reports.aspx (accessed 15 September 2013)
7 Bridgewater B, Grayson AD, Brooks N, *et al.* Has the publication of cardiac surgery outcome data been associated with changes in practice in northwest England: an analysis of 25 730 patients undergoing CABG surgery under 30 surgeons over eight years. *Heart* 2007; **93**: 744–8
8 Turgeon AF, Lauzier F, Simard JF, *et al.* Mortality associated with withdrawal of life-sustaining therapy for patients with severe traumatic brain injury: a Canadian multicentre cohort study. *Can Med Assoc J* 2011; **183**: 1581–8
9 Livingston DH, Mosenthal AC. Withdrawing life-sustaining therapy for patients with severe traumatic brain injury. *Can Med Assoc J* 2011; **183**: 1570–1
10 Stelfox HT, Hemmelgarn BR, Bagshaw SM, *et al.* Intensive care unit bed availability and outcomes for hospitalized patients with sudden clinical deterioration. *Arch Intern Med* 2012; **172**: 467–74
11 Aron D, Headrick L. Educating physicians prepared to improve care and safety is no accident: it requires a systematic approach. *Qual Saf Health Care* 2002; **11**: 168–73
12 Brindley PG. Patient safety and acute care medicine: lessons for the future, insights from the past. *Crit Care* 2010; **14**: 217–22
13 Haynes AB, Weiser TG, Berry WR, *et al.* A surgical safety checklist to reduce morbidity and mortality in a global population. *N Engl J Med* 2009; **360**: 491–9
14 World Alliance for Patient Safety. *Implementation Manual Surgical Safety Checklist*, 1st Edn. Geneva, Switzerland, World Health Organization, 2008
15 The Royal College of Surgeons of England. Outcomes data—patient Q & A. Available from http://www.rcseng.ac.uk/patients/surgical-outcomes/faq-outcomes-data (accessed 15 September 2013)

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EDITORIAL II

Fluid responsiveness: an evolution of our understanding

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Decisions regarding fluid therapy, whether this be in the operating theatre (OT), intensive care unit (ICU), emergency department (ED), or general ward, are among the most challenging and important tasks that clinicians face on a daily basis. Specifically, almost all clinicians would agree that both hypovolaemia and volume overload increase the morbidity and mortality of patients. What is not widely appreciated is that when a fluid challenge is given on 'clinical grounds', only 50% of haemodynamically unstable patients (in the OT, ICU, or ED) are volume responders [i.e. they will increase their stroke volume (SV) by >10–15%].[1] This emphasizes that clinicians have great difficulty in estimating the preload condition of their patients.

Fundamentally, the only reason to give any patient a fluid challenge is to increase their SV; if this does not happen, the fluid administration serves no useful purpose and is likely to be harmful.[2] Furthermore, the increase in SV (and thus cardiac output) must be judged to be beneficial. Fluid loading *per se* is not always the correct therapy for hypotension or a reduced urine production. Fluid therapy acts by increasing

the stressed venous volume, thereby increasing venous return to the heart. As the venous system has a much greater capacity for blood compared with the arterial system, it is a normal physiologic condition to be a fluid responder. However, being a fluid responder is not equal to being hypovolaemic. This suggests that not all patients who are fluid responders necessarily require volume expansion. Our homeostatic mechanisms have evolved (over thousands of years) to deal with hypovolaemia (tachycardia, vasoconstriction, and blood flow redistribution), whereas volume overload is a more recent, largely iatrogenic phenomenon (last 40 yr or so) for which the body is ill equipped to manage. An analysis of the overlapping Frank–Starling and extra-vascular lung water (EVLW) curves demonstrate that as patients become less fluid responsive, EVLW (and tissue oedema) increases markedly (see Fig. 1) because of the increased cardiac filling pressures and transmitted hydrostatic pressures.[3] This process is accentuated in patients with endothelial damage (sepsis, ARDS, pancreatitis, burns).[4] Increased cardiac filling pressures trigger the release of natriuretic peptides, presumably to assist in fluid removal. What is most troubling about this sequence of events is that natriuretic peptides cleave membrane-bound proteoglycans and glycoproteins (most notably syndecan-1 and hyaluronic acid) off the endothelial glycocalyx.[5 6] The endothelial glycocalyx plays a major role in regulating endothelial permeability.[7] Therefore, excessive volume expansion increases the release of natriuretic peptides, which in turn damages the endothelial glycocalyx, and this is followed by a rapid shift of intravascular fluid into the interstitial space, leading to a marked increase in EVLW and tissue oedema.[5 6] Increased EVLW has been demonstrated to be a very strong predictor of death.[8 9] Indeed in a cohort of patients with sepsis, Zhang and colleagues[10] demonstrated a strong correlation between the net fluid balance, the increase in brain natriuretic peptide, and the risk of death. This suggests that it may be beneficial to allow patients to be somewhat fluid responsive instead of fluid loading until they have reached the top of the Frank–Starling curve.

Only patients who are likely to show a significant increase in SV with a fluid challenge and in whom the increased SV is considered to be beneficial should be given a fluid challenge. Furthermore, all attempts should be made to limit the volume of fluid administered. This begets the question of how to predict fluid responsiveness. After Hughes and Magovern[11] described the technique of central venous pressure (CVP) monitoring in 1959, this method became a standard tool for guiding fluid therapy. It has now been clearly established that there is a poor relationship between the CVP and the intravascular volume status, and no relationship between the CVP and fluid responsiveness.[1] In 1970, the flow-directed pulmonary artery catheter was developed by Swan and Ganz, allowing measurement of the pulmonary artery occlusion pressure (PAOP). However, the PAOP suffers from the same limitation as the CVP, and multiple studies have demonstrated that, like the CVP, the PAOP is unable to predict fluid responsiveness.[12 13]

After the 'widespread' recognition that the CVP/PAOP had no utility in guiding fluid resuscitation,[12] the idea that heart–lung interactions during mechanical ventilation could be used to predict fluid responsiveness was championed by Michard, Pinsky, Teboul, and others in the early 2000s.[14 15] The principles underling this technique are based on simple physiology.[2 3] Intermittent positive-pressure ventilation induces cyclic changes in the loading conditions of the left ventricle (LV) and right ventricle (RV). Mechanical insufflation decreases preload and increases afterload of the RV. The reduction in RV preload and the increase in RV afterload both lead to a decrease in RV SV, which is at a minimum at the end of the inspiratory period. The inspiratory reduction in RV ejection leads to a decrease in left ventricular filling after a phase lag of two or

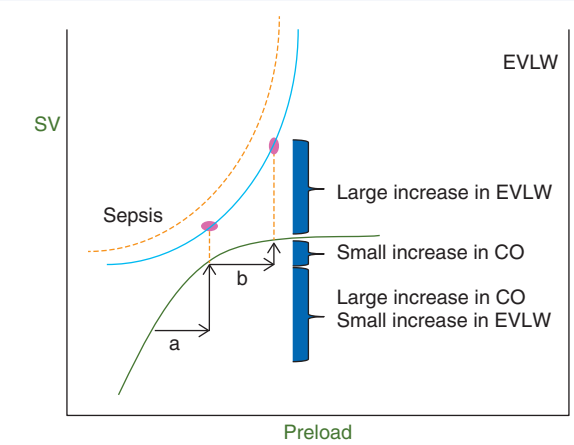

Fig 1 Superimposition of the Frank–Starling and Marik-Phillips curves demonstrating the effects of increasing preload on SV and lung water in a patient who is preload responsive (a) and non-responsive (b). With sepsis, the EVLW curve is shifted to the left. EVLW, extra-vascular lung water; CO, cardiac output; SV, stroke volume.

Table 1 Techniques for assessing fluid responsiveness. ROC, area under receiver operator characteristic curve; IVC, inferior vena cava; SVC, superior vena cava

Static pressure and volume parameters (ROC ~0.5–0.6)
CVP
PAOP
IVC/SVC diameter
Flow corrected time
Right ventricular end-diastolic volume
Left ventricular end-diastolic volume
SVC/IVC variation during mechanical ventilation
Dynamic techniques based on heart–lung interactions during mechanical ventilation (ROC ~0.7–0.8)
PPV
SVV
Pleth variability index
Aortic blood flow (Doppler or echocardiography)
Techniques based on real or virtual fluid challenge (ROC~0.9)
PLR
Rapid fluid challenge (100–250 cc)

three heartbeats. The cyclic changes in RV and LV SV are greater when the ventricles operate on the steep rather than the flat portion of the Frank–Starling curve.[2 3] A pulse pressure variation (PPV) or stroke volume variation (SVV) of >13% was shown to be predictive of fluid responsiveness.[14 15] In a meta-analysis published in 2009, it was demonstrated that the PPV was highly predictive of fluid responsiveness (ROC of 0.94).[16] Because of its sound physiological basis, good predictive ability, and apparent simplicity, this technique was met with great enthusiasm, and algorithms based on this principle were developed for use in the OT and ICU.[17 18] However, what was not fully appreciated when the meta-analysis was published was that almost all the studies were performed in a highly controlled environment (usually the OT) in a highly select group of patients.[16] It soon became apparent that a large number of clinical factors interacted to limit the accuracy of the PPV/SVV in predicting fluid responsiveness.[19 20] In a cohort of cardiac surgical patients Lansdorp and colleagues[21] demonstrated that PPV/SVV did not predict volume responsiveness in routine clinical practice. Multiple studies have now confirmed these findings.[22 23] In the largest study to date, Cannesson and colleagues[24] demonstrated that despite a strong predictive value, the PPV was inconclusive in predicting fluid responsiveness in 25% of patients during general anaesthesia. The utility of the PPV/SVV in the ICU appears significantly worse.[22 23] In a multicentre, point prevalence study published in this issue of the Journal, Mahjoub and colleagues[25] demonstrate that only 2% of ICU patients met the validity criteria for using the PPV to assess fluid responsiveness. Furthermore, only 3% of patients with an arterial line in place satisfied all the validly criteria. These data suggest that because of the frequency of confounding factors, the PPV/SVV should not be used as the primary technique for directing fluid management in the OT and ICU. Nevertheless, intravascular volume depletion should be suspected in patients who demonstrate marked PPV evident on either an arterial pressure waveform or a pulse oximetric waveform. However, in these situations, other tests should be performed to confirm fluid responsiveness.

Ultimately, only two techniques are currently available that can be used to determine fluid responsiveness with a high degree of accuracy, namely the passive leg raising (PLR) manoeuvre and the fluid challenge.[2 3 26 27] These techniques are best coupled with minimally invasive cardiac output monitors that can track changes in SV and cardiac output dynamically and in real time.[2 3] For obvious technical reasons, the fluid challenge technique is preferred during anaesthesia, while the PLR is preferred in the ICU and postoperatively.

In conclusion, the methods for assessing fluid responsiveness have evolved from static pressure and volume parameters, which are unable to predict fluid responsiveness, to dynamic indices based on heart–lung interactions during mechanical ventilation, which have a modest degree of accuracy, to those techniques based on either a virtual or a real fluid challenge, which have a high degree of accuracy in predicting fluid responsiveness (see Table 1). As our understanding of this complex topic evolves, it is likely that new and improved methods of assessing fluid responsiveness and more physiological targets of fluid therapy will emerge.

Authors' contributions

Both authors were responsible for writing this editorial, reviewing the final version, and approving it for publication.

Declaration of interest

P.E.M.: in the last 5 years, P.E.M. has received an honorarium from Pulsion Medical, manufacturer of the PiCCO haemodynamic device, for a lecture delivered at an international Critical Care Symposium (~1000 GBP) and an honorarium from Cheetah Medical, manufacturer of the NiCOM haemodynamic device, for a lecture delivered at medical grand rounds (~1500 GBP). J.L.: none declared.

References

1 Marik PE, Cavallazzi R. Does the central venous pressure (CVP) predict fluid responsiveness: an update meta-analysis and a plea for some common sense. *Crit Care Med* 2013; **41**: 1774–81

2 Marik PE, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. *Ann Crit Care* 2011; **1**: 1

3 Marik PE, Desai H. Goal directed fluid therapy. *Curr Pharm Design* 2012; **18**: 6215–24

4 Lee WL, Slutsky AS. Sepsis and endothelial permeability. *N Engl J Med* 2010; **363**: 689–91

5 Bruegger D, Jacob M, Rehm M, *et al.* Atrial natriuretic peptide induces shedding of endothelial glycocalyx in coronary vascular bed of guinea pig hearts. *Am J Physiol Heart Circ Physiol* 2005; **289**: H1993–99

6 Bruegger D, Schwartz L, Chappell D, *et al.* Release of atrial natriuretic peptide precedes shedding of the endothelial glycocalyx equally in patients undergoing on- and off-pump coronary artery bypass surgery. *Basic Res Cardiol* 2011; **106**: 1111–21

7 Jacob M, Chappell D. Reappriasing starling: the physiology of the microcircualtion. *Curr Opin Crit Care* 2013; **19**: DOI:10.1097/MCC.0b013e3283632d5e

8 Sakka SG, Klein M, Reinhart K, Meier-Hellmann A. Prognostic value of extravascular lung water in critically ill patients. *Chest* 2002; **122**: 2080–6

9 Chung FT, Lin SM, Lin SY, Lin HC. Impact of extravascular lung water index on outcomes of severe sepsis patients in a medical intensive care unit. *Respir Med* 2008; **102**: 956–61

10 Zhang Z, Zhang Z, Xue Y, Xu X, Ni H. Prognostic value of B-type natriuretic peptide (BNP) and its potential role in guiding fluid therapy in critically ill septic patients. *Scand J Trauma Resus Emerg Med* 2012; **20**: 86

11 Hughes RE, Magovern GJ. The relationship between right atrial pressure and blood volume. *Arch Surg* 1959; **79**: 238

12 Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest* 2002; **121**: 2000–8

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

14 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

15 Feissel M, Michard F, Mangin I, *et al.* Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. *Chest* 2001; **119**: 867–73
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 Benes J, Chytra I, Altmann P, *et al.* Intraopeartive fluid optimization using stroke volume variation in high risk surgical patients: results of prospective randomized study. *Crit Care* 2010; **14**: R118
18 McGee WT. A simple physiologic algorithm for managing hemodynamics using stroke volume and stroke volume variation: physiologic optimization program. *J Intensive Care Med* 2009; **24**: 352–60
19 De Backer D, Heenen S, Piagnerelli M, Koch M, Vincent JL. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med* 2005; **31**: 517–23
20 Mahjoub Y, Pila C, Friggeri A, *et al.* Assessing fluid responsiveness in critically ill patients: false-positive pulse pressure variation is detected by Doppler echocardiographic evaluation of the right ventricle. *Crit Care Med* 2009; **37**: 2570–5
21 Lansdorp B, Lemson J, van Putten MJ, *et al.* Dynamic indices do not predict volume responsiveness in routine clinical practice. *Br J Anaesth* 2012; **108**: 395–401
22 Lakhal K, Ehrmann S, Benzekri-Lefevre D, *et al.* Respiratory pulse pressure variation fails to predict fluid responsiveness in acute respiratory distress syndrome. *Crit Care* 2011; **15**: R85
23 Marik PE, Levitov A, Young A, Andrews L. The use of NICOM (Bioreactance) and Carotid Doppler to determine volume responsiveness and blood flow redistribution following passive leg raising in hemodynamically unstable patients. *Chest* 2013; **143**: 364–70
24 Cannesson M, Le MY, 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
25 Mahjoub Y, Lejeune V, Muller L, *et al.* Evaluation of pulse pressure variation validity criteria in critically ill patients: a prospective observational multicentre point-prevalence study. *Br J Anaesth* 2014; **112**: 681–5
26 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
27 Muller L, Toumi M, Bousquet PJ, *et al.* An increase in aortic blood flow after an infusion of 100 ml colloid over 1 minute can predict fluid responsiveness: the mini-fluid challenge study. *Anesthesiology* 2011; **115**: 541–7

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EDITORIAL III

Is it safe to use supraglottic airway in children with difficult airways?

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The supraglottic airway has a potential role in patients with difficult airways. There have been numerous reports of successful use of the supraglottic airway in patients in whom both tracheal intubation and facemask ventilation were difficult, and the device is now regarded as a 'rescue' device in cases of 'cannot intubate, cannot ventilate' scenario.[1 2] The supraglottic airway can also function as an aid to tracheal intubation, and studies have confirmed that this usage is highly effective in patients with difficult airways.[3 4] In addition, in adult patients with difficult airways, the supraglottic airways (without tracheal intubation) usually can provide clear airways during anaesthesia. In contrast, little is known about its efficacy in children with difficult airways. In this issue, Jagannathan and colleagues[5] report a retrospective analysis of the efficacy of sole of a supraglottic airway in children with difficult airways.

Jagannathan and colleagues[5] searched for children who had been predicted to have difficult airways caused by anatomical deformities (such as Treacher-Collins syndrome, subglottic stenosis, and pharyngeal masses), and those with history of difficult tracheal intubation and difficult facemask ventilation. Among 77 272 children who underwent general anaesthesia during a 4-yr period, the authors identified 459 children (0.6%) with difficult airways. In 109 of the 459 children, a supraglottic airway was used as a primary airway during anaesthesia, and it provided clear airways in 105 of the 109 children. In the remaining four children, reinsertion of a supraglottic airway (two patients) and tracheal intubation (two patients) became necessary.

Indications and contraindications

So, can we regard the supraglottic airway as being able to reliably provide a clear airway in a child with difficult airway? The answer would be 'yes', as the study by Janannathan and

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BJA

CRITICAL CARE

Evaluation of pulse pressure variation validity criteria in critically ill patients: a prospective observational multicentre point-prevalence study†

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Editor's key points

- Respiratory variation in pulse pressure is commonly used to predict fluid responsiveness in critically ill patients.
- The validity of this measure was assessed on a single day in a multicentre survey of French intensive care units.
- Very few patients satisfied all criteria for valid use of pulse pressure variation in this setting, in large part due to widespread use of low tidal volume ventilation.

Background. Respiratory variation in pulse pressure (ΔPP) is commonly used to predict the fluid responsiveness of critically ill patients. However, some researchers have demonstrated that this measurement has several limitations. The present study was designed to evaluate the proportion of patients satisfying criteria for valid application of ΔPP at a given time-point.

Methods. A 1 day, prospective, observational, point-prevalence study was performed in 26 French intensive care units (ICUs). All patients hospitalized in the ICUs on the day of the study were included. The ΔPP validity criteria were recorded prospectively and defined as follows: (i) mechanical ventilation in the absence of spontaneous respiration; (ii) regular cardiac rhythm; (iii) tidal volume $\geq$8 ml kg^{-1} of ideal body weight; (iv) a heart rate/respiratory rate ratio $>$3.6; (v) total respiratory system compliance $>$30 ml cm H_2O^{-1}; and (vi) tricuspid annular peak systolic velocity $>$0.15 m s^{-1}.

Results. The study included 311 patients with a Simplified Acute Physiology Score II of 41 (39–43). Overall, only six (2%) patients satisfied all validity criteria. Of the 170 patients with an arterial line in place, only five (3%) satisfied the validity criteria. During the 24 h preceding the study time-point, fluid responsiveness was assessed for 79 patients. ΔPP had been used to assess fluid responsiveness in 15 of these cases (19%).

Conclusions. A very low percentage of patients satisfied all criteria for valid use of ΔPP in the evaluation of fluid responsiveness. Physicians must consider limitations to the validity of ΔPP before using this variable.

Keywords: fluid responsiveness; haemodynamic monitoring; pulse pressure variation

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† This article is accompanied by Editorial II.

Intravascular volume expansion is important in the treatment modality in hypotensive critically ill patients, but is not always effective, that is, fluid infusion is not always followed by an increase in stroke volume.[1 2] Given that ineffective volume expansion can even be harmful, it is essential to predict fluid responsiveness in guiding therapy.[3] Several static indices (such as central venous pressure, pulmonary artery occlusion pressure, and ventricular end-diastolic volume) have been studied, but none accurately predicts fluid responsiveness.[2] More recently, a dynamic index [respiratory variation in pulse pressure (ΔPP)] has been described as an accurate tool for predicting fluid responsiveness,[4] and confirmed by several studies over the last decade.[5] Thus, ΔPP and its surrogates (e.g. stroke volume variation) have been implemented in several devices for continuous monitoring of fluid responsiveness.[6] However, there are a number of limitations to this approach.[7–11] Unfortunately, the extent to which these limitations are actually encountered in intensive care units (ICUs) has not been evaluated in a large multicentre study. The aim of this prospective study was to evaluate the proportion of critically ill ICU patients meeting all validity criteria for the use of ΔPP (or a surrogate) in the prediction of fluid responsiveness.

Methods

Patients

This was a 1 day point-prevalence study of ΔPP validity criteria in 26 ICUs in 22 French hospitals. General, medical, and surgical ICUs for adults with eight or more beds were included. The independent ethics committee at Amiens University Hospital approved the study's objectives and procedures and waived the need for informed consent.

Data collection

Data were collected (using two questionnaires) by a clinician nominated as the principal investigator for each centre. A specific form was completed for each patient in each ICU. The investigators had a time window of 3 h in the morning to fill out the forms. Data were then entered into a database at the coordinating centre (Amiens University Hospital). The coordinating centre was available throughout the study to answer queries and provide feedback.

ICU data

The data collected for each ICU were: type of hospital (university or general), type of ICU (general or specialized), whether or not the ICU used a device to automatically calculate ΔPP (or a surrogate), and whether ΔPP was part of a written haemodynamic monitoring protocol.

Patient characteristic data

The patient's age, BMI, primary diagnosis, Simplified Acute Physiology Score II on admission, and Sequential Organ Failure Assessment score on inclusion were recorded.

Haemodynamic monitoring

The use of haemodynamic monitoring devices (especially arterial lines) and each patient's arterial pressure and heart rate (HR) values were recorded. Vasopressor use and the volume of fluid received over the previous 24 h were also recorded.

Ventilator settings

In mechanically ventilated patients, the type of ventilation, tidal volume (V_t), and respiratory rate (RR) were recorded. For patients on controlled mechanical ventilation in the absence of spontaneous breathing, total respiratory system compliance was calculated as V_t divided by the plateau pressure minus the positive end-expiratory pressure.

ΔPP validity criteria

The following ΔPP validity criteria were defined: regular cardiac rhythm[9] (defined as no arrhythmia or extrasystoles on the monitor screen); controlled mechanical ventilation in the absence of spontaneous breathing;[9 12] $V_t \geq 8$ ml kg^{-1} [7] of ideal body weight (IBW); HR to RR ratio >3.6;[8] total respiratory system compliance (C_{TRS}) >30 ml cm H_2O^{-1};[10] and tricuspid annular peak systolic velocity (S_t) >0.15 m s^{-1}.[11]

Fluid infusion

The need for an assessment of fluid responsiveness on inclusion and during the 24 h before the study time-point was recorded for each patient. The methods and parameters used to assess fluid responsiveness were also recorded.

Statistical analysis

Categorical variables were expressed as number (%). Continuous variables were expressed as mean (95% confidence interval, CI) or median (inter-quartile range), depending on their distribution. A Kolmogorov–Smirnov test was performed to assess the normality of distribution. Patients with an arterial line were compared with those without an arterial line. The data for categorical variables were analysed using the χ^2 test (with Yate's correction, if necessary) or Fisher's exact test. Continuous data were analysed in a two-sided *t*-test or a Mann–Whitney test (depending on the distribution). The threshold for statistical significance was set to $P<0.05$.

Results

The 26 participating ICUs included a total of 313 patients. Two patients were excluded because of missing data, so the final data set comprised 311 patients. There were 24 university hospital ICUs and two general hospital ICUs. Twelve ICUs admitted both non-surgical and surgical patients, 11 admitted only surgical patients, and three admitted only non-surgical patients. The mean number of beds was 13 (2). Although 23 (88%) of the ICUs were equipped with a device that automatically calculated ΔPP, this variable was a part of a written haemodynamic monitoring protocol in only three (12%) units.

Table 1 Patient characteristics: a comparison of patients with and without arterial lines. BMI, body mass index; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; ARDS, acute respiratory distress syndrome

	All patients ($n=311$)	Patients with an arterial line ($n=170$)	Patients without an arterial line ($n=141$)	*P*-value
Age (yr)	58 (56–60)	57 (54–59)	59 (58–62)	0.28
BMI (kg m^{-2})	25 (24–26)	26 (25–27)	25 (24–26)	0.5
SAPS II	41 (39–43)	44 (39–46)	37 (33–40)	0.02
SOFA score	4 (3–4)	4 (4–5)	2 (2–3)	0.001
Patients with ARDS [*n* (%)]	30 (10)	19 (11)	11 (8)	0.48
Patients with sepsis [*n* (%)]	100 (32)	51 (30)	49 (35)	0.41
Patients with septic shock [*n* (%)]	32 (10)	32 (19)	0 (0)	<0.0001
Patients on vasopressors [*n* (%)]	42 (14)	42 (25)	0 (0)	<0.0001
Patients who received colloid infusions [*n* (%)]	66 (21)	51 (30)	15 (11)	0.0001
Volume of colloids received during the previous 24 h (ml kg^{-1})	8 (6–10)	8 (6–10)	8 (6–15)	0.21
Patients who received crystalloid infusions [*n* (%)]	288 (93)	157 (92)	131 (93)	0.9
Volume of crystalloids received during the previous 24 h (ml kg^{1})	23 (21–26)	23 (20–26)	24 (19–29)	0.2
Patients who satisfied all ΔPP validity criteria [*n* (%)]	6 (2)	5 (3)	1 (0.7)	0.29

NB. 50% of patients breathed spontaneously, therefore excluded.

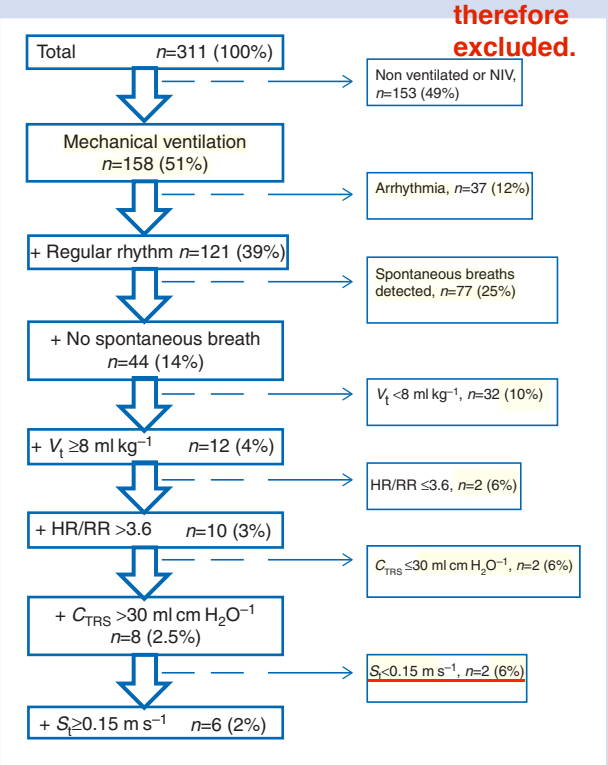

Fig 1 Flowchart showing the method used to calculate the final number of patients satisfying all ΔPP validity criteria. NIV, non-invasive ventilation; V_t, tidal volume; HR, heart rate; RR, respiratory rate; C_{TRS}, total respiratory system compliance; S_t, tricuspid annular peak systolic velocity.

Characteristics of the study population are shown in Table 1. Only six (2%) patients satisfied all ΔPP validity criteria (Fig. 1). Of the 170 (54%) patients with an arterial line, only five (3%) satisfied all ΔPP validity criteria (Table 1). One hundred and fifteen (37%) of the patients with an arterial line also received mechanical ventilation; of these, only five (4%) satisfied all ΔPP validity criteria.

During the 24 h immediately preceding the study time-point, fluid responsiveness was assessed for 79 patients (with 69 of the latter receiving fluids). Methods used to assess fluid responsiveness were as follows: ΔPP: $n=15$ patients (19%); clinical examination: $n=30$; fluid challenge: $n=24$; passive leg raising manoeuvre: $n=21$; central venous pressure: $n=1$; respiratory variations of the inferior vena cava: $n=8$; other echocardiographic parameters: $n=5$; a combination of two or more of these methods: $n=25$.

On inclusion, fluid responsiveness was assessed in 23 (7%) patients. Only one (4%) of these patients satisfied all six of the defined ΔPP validity criteria.

When comparing patients with and without arterial lines, we found that patients with an arterial line had higher severity scores and were more likely to have received vasopressors and colloids (Table 1).

Discussion

To the best of our knowledge, this is the first multicentre study to evaluate ΔPP validity criteria in a mixed ICU population. Our results show that of the 170 ICU patients who had an arterial line in place, only 3% satisfied all ΔPP validity criteria. When considering the ICU study population as a whole ($n=311$), only 2% satisfied all ΔPP validity criteria.

In 2000, Michard and colleagues reported the value of ΔPP for prediction of fluid responsiveness. In a population of 40 patients, they showed that a cut-off of 13% was able to discriminate between responders and non-responders with a sensitivity of 94% and a specificity of 96%.[4] This was a significant step forward in fluid management of the critically ill. Since then, several studies have confirmed these results in various settings.[5] Although ΔPP can only be used in patients on mechanical ventilation with no spontaneous breathing activity and no arrhythmia,[9 12 13] several research reports have shown

that this parameter has other limitations in this situation. When studying 60 mechanically ventilated ICU patients with no spontaneous breathing or cardiac arrhythmia, De Backer and colleagues[7] showed that ΔPP was not a reliable predictor of fluid responsiveness in patients with $V_t < 8$ ml kg^{-1} of IBW. These results were subsequently confirmed.[14 15] Mechanical ventilation with low V_t (<6 ml kg^{-1}) for acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) has been shown to decrease mortality.[16] For patients free of ALI/ARDS, some studies have suggested that the use of $V_t > 7$ ml kg^{-1} was an independent risk factor for developing ARDS.[17 18] The use of low V_t in ICUs has therefore become common practice and some researchers recommend using low V_t for the majority of patients.[19] In the present study, only 12 of 44 mechanically ventilated patients without spontaneous breathing or arrhythmia had $V_t \geq 8$ ml kg^{-1}.

De Backer and colleagues[8] also demonstrated that ΔPP was unreliable when the HR/RR ratio was <3.6, a value that is frequently encountered in the ICU (especially in ARDS patients). For example, the mean RR in the ARDS Net study was around 30 bpm,[20] such that the HR/RR ratio will be <3.6 if HR is <108 beats min^{-1}. Another limitation of ΔPP relates to low chest wall compliance. In a study of 54 patients with circulatory shock, Monnet and colleagues[10] demonstrated that the area under the receiver operating characteristic (ROC) curve of ΔPP for predicting fluid responsiveness was low [0.69 (0.10)] for patients with total respiratory system compliance below 30 ml cm H_2O^{-1}. Lastly, right ventricular failure (as assessed by Doppler tissue imaging) can be responsible for false-positive ΔPP values.[11] Unfortunately, tissue Doppler imaging requires a level of expertise that might not be available in all ICUs.[21]

All these limitations must be taken into account when using ΔPP to predict fluid responsiveness. The present study shows that when these limitations are taken into account, this index can only be correctly applied in a very low proportion of patients (2%). We found that patients with an arterial line had higher severity scores and were more likely to be on vasopressors. Even when only patients with an arterial line in place were taken into account, the percentage of patients satisfying all ΔPP validity criteria was just 3%.

This percentage of ICU patients meeting criteria for ΔPP monitoring is much lower than that observed in an anaesthesia setting. In a single-centre retrospective study of 12 308 procedures, Maguire and colleagues[22] found that 38.9% of patients satisfied ΔPP validity criteria. However, in this general anaesthesia study, patients were more heavily sedated (only 13% showed spontaneous breathing), ventilated with a higher V_t (41% had $V_t > 8$ ml kg^{-1}), and had a lower prevalence of ARDS and cardiac arrhythmia. Moreover, Maguire and colleagues did not use the same validity criteria, since neither C_{TRS} nor S_t was assessed.

Our findings do not appear to agree with the conclusions of Marik and colleagues' systematic review of the literature on dynamic changes in arterial waveform variables. These researchers found that ΔPP is highly accurate for predicting fluid responsiveness in the ICU [with an area under the ROC curve of 0.95 (0.93–0.96)].[5] However, their analysis encompassed six studies of highly selected patient populations (heavily sedated patients under mechanical ventilation, with no arrhythmia and $V_t > 7$ ml kg^{-1}).[5] Other validity criteria (HR/RR, respiratory system compliance, and S_t) were published after this systematic review and thus were not studied. However, the last three validity criteria have not been extensively studied and are subject to debate.[23] In contrast, mechanical ventilation without spontaneous breathing or arrhythmia and $V_t > 7$ ml kg^{-1} are well accepted. Nevertheless, only 12 (4%) of our patients satisfied these three well-accepted validity criteria.

We also found that although ΔPP was part of a written protocol in just one ICU, this parameter was used in 19% of fluid responsiveness assessments. Moreover, we observed that despite its known poor reliability, clinical examination alone was the most frequently used technique for evaluating fluid responsiveness.[24 25]

This study has a number of limitations. As this was a 1 day study based on a snapshot at a given time-point, results might have been different at other time-points. Secondly, our study took place primarily in tertiary hospitals in a single country (France). This might represent a source of selection bias that would have to be addressed in larger, international studies. Thirdly, some of the validity criteria studied here are still subject to debate.[10 23 26–29] Nevertheless, all these criteria have been previously studied in ICUs in this context. Fourthly, other criteria that limit the applicability of ΔPP have been described and need to be investigated further: vasopressors appear to decrease ΔPP,[30] whereas intra-abdominal hypertension appears to increase ΔPP.[31] Lastly, the study's design prevented us from investigating the sensitivity and specificity of a ΔPP cut-off value in the assessment of fluid responsiveness in patients who satisfied all validity criteria.[32] Further studies are needed to investigate this issue.

In conclusion, a very small proportion of ICU patients satisfied all validity criteria for the use of ΔPP. Caution is therefore advised when using ΔPP to assess fluid responsiveness.

Authors' contributions

Y.M., E.L., H.D.: study design. Y.M., V.L., L.M., E.L., M.S., H.D.: data analysis. Y.M., V.L., L.M., S.P., L.Z., F.B., B.V., C.P.-B., S.J., A.A., E.Z., S.L., A.V.-B., H.Q., O.J.-B., G.P., P.M., S.D., M.L., N.A., M.S.: data collection. Y.M., S.P., L.Z., F.B., B.V., C.P.-B., S.J., A.V.-B., H.Q., O.J.-B., G.P., P.M., S.D., M.L., N.A.: writing the manuscript.

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None declared.

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References

1 Task Force of the American College of Critical Care Medicine, Society of Critical Care Medicine. Practice parameters for hemodynamic support of sepsis in adult patients in sepsis. *Crit Care Med* 1999; **27**: 639–60

2 Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest* 2001; **121**: 2000–8

3 National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR, *et al.* Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; **354**: 2564–75

4 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

5 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

6 Cannesson M, Desebbe O, Piriou V, Lehot JJ. Automatic and continuous monitoring of preload dependence in the perioperative period: interests and limits. *Ann Fr Anesth Reanim* 2010; **29**: 452–63

7 De Backer D, Heenen S, Piagnerelli M, Koch M, Vincent JL. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med* 2005; **31**: 517–23

8 De Backer D, Taccone FS, Holsten R, Ibrahimi F, Vincent JL. Influence of respiratory rate on stroke volume variation in mechanically ventilated patients. *Anesthesiology* 2009; **110**: 1092–7

9 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

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

11 Mahjoub Y, Pila C, Friggeri A, *et al.* Assessing fluid responsiveness in critically patients: positive pulse pressure variation is detected by Doppler echocardiographic evaluation of the right ventricle. *Crit Care Med* 2009; **37**: 2570–5

12 Soubrier S, Saulnier F, Hubert H, *et al.* Can dynamic indicators help the prediction of fluid responsiveness in spontaneously breathing critically ill patients? *Intensive Care Med* 2009; **33**: 1117–24

13 Micharf F, Teboul J-L. Using heart–lung interactions to assess fluid responsiveness during mechanical ventilation. *Crit Care* 2000; **4**: 282–9

14 Lansdorp B, Lemson J, van Putten MJ, *et al.* Dynamic indices do not predict volume responsiveness in routine clinical practice. *Br J Anaesth* 2012; **108**: 395–401

15 Charron C, Fessenmeyer C, Cosson C, *et al.* The influence of tidal volume on the dynamic variables of fluid responsiveness in critically ill patients. *Anesth Analg* 2006; **102**: 1511–7

16 [No author listed.] Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury. *N Engl J Med* 2000; **342**: 1301–8

17 Gajic O, Dara SI, Mendez JL, *et al.* Ventilator associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med* 2004; **32**: 1817–24

18 Gajic O, Frutos-Vivar F, Esteban A, Hubmatr RD, Anzueto A. Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. *Intensive Care Med* 2005; **31**: 922–6

19 Schultz MJ, Haitsma JJ, Slutsky AS, Gajic O. What tidal volume should be used in patients without acute lung injury? *Anesthesiology* 2007; **106**: 1226–31

20 The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; **342**: 1301–8

21 Mayo PH, Beaulieu Y, Doelken P, *et al.* American College of Chest Physician/La société de réanimation de langue française statement on competence in critical care ultrasonography. *Chest* 2009; **135**: 1050–60

22 Maguire S, Rinehart J, Vakharia S, Cannesson M. Technical communication: respiratory variation in pulse pressure and plethysmographic waveforms: intraoperative applicability in a North American academic center. *Anesth Analg* 2011; **112**: 94–6

23 Vieillard-Baron A, Charron C. Preload responsiveness or right ventricular dysfunction? *Crit Care Med* 2009; **37**: 2662–3

24 McGee S, Abernethy WB III, Simel DL. The rational clinical examination. Is this patient hypovolemic? *J Am Med Assoc* 1999; **281**: 1022–9

25 Stéphan F, Flahault A, Dieudonné N, Hollande J, Paillard F, Bonnet F. Clinical evaluation of circulating blood volume in critically ill patients—contribution of a clinical scoring system. *Br J Anaesth* 2001; **86**: 754–62

26 Lakhal K, Ehrmann S, Benzekri-Lefèvre D, *et al.* Respiratory pulse pressure variation fails to predict fluid responsiveness in acute respiratory distress syndrome. *Crit Care* 2011; **15**: R85

27 Huang CC, Fu JY, Hu HC, *et al.* Prediction of fluid responsiveness in acute respiratory distress syndrome patients ventilated with low tidal volume and high positive end-expiratory pressure. *Crit Care Med* 2008; **36**: 2810–6

28 Muller L, Louart G, Bousquet PJ, *et al.* The influence of the airway driving pressure on pulsed pressure variation as a predictor of fluid responsiveness. *Intensive Care Med* 2010; **36**: 496–503

29 Wiklund CU, Morel DR, Orbring-Wiklund H, *et al.* Influence of tidal volume on pulse pressure variations in hypovolemic ventilated pigs with acute respiratory distress-like syndrome. *Anesthesiology* 2010; **11**: 630–8

30 Nouira S, Elatrous S, Dimassi S, *et al.* Effects of norepinephrine on static and dynamic preload indicators in experimental hemorrhagic shock. *Crit Care Med* 2005; **33**: 2339–44

31 Duperret S, Lhuillier F, Piriou V, *et al.* Increased intra-abdominal pressure affects respiratory variations in arterial pressure in normovolaemic and hypovolemic mechanically ventilated healthy pigs. *Intensive Care Med* 2007; **33**: 163–71

32 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

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