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Editorial

Editorial

Fluid therapy in 2015 and beyond: the mini-fluid challenge and mini-fluid bolus approach

The first description of the use of intravenous fluid in a human is attributed to Dr Thomas Latta during the cholera epidemic in London in 1831–2. Dr Latta described his experience in a letter to the editor of *The Lancet*.[1] Dr Latta first attempted to replace the lost fluid and salts 'by injecting copiously into the larger intestine warm water, holding in solution the requisite salts, and also administered quantities from time to time by mouth'.[2 3] He found there to be no permanent benefit and considered that the unfortunate sufferers' vomiting and purging were aggravated. Dr Latta wrote 'finding thus, that such, in common with all the ordinary means in use, was either useless or hurtful, I at length resolved to throw the fluid immediately into the circulation'. The injected solution was made up of 'two to three drachms of muriate of soda and two scruples of the subcarbonate of soda in six pints of water' (equivalent to approximately ½ Ringers lactate). His first patient was an elderly woman who had been given all the usual remedies and who had 'reached the last moments of her earthly existence.' Dr Latta inserted a tube into the basilic vein and 'injected ounce after ounce of fluid, closely observing the patient', at first with no visible effect, but then she began to breathe less laboriously and 'soon the sharpened features, and sunken eye, and fallen jaw, pale and cold, bearing the manifest imprint of death's signet, began to glow with returning animation; the pulse returned to the wrist . . .'. After 6 pints (2.8 litre) of fluid had been injected, the woman announced in a strong voice that she was now 'free from all uneasiness' and was cured.

The technique of fluid resuscitation described by Dr Latta nearly 200 yr ago has stood the test of time, and appears to be the only logical method to resuscitate patients—give repeated small boluses of fluid and observe the patient closely (what a remarkable concept!). This is best done by giving 200–500 ml boluses of Ringers lactate solution (or 4% human albumin solution) and closely monitoring the response. While the basic concept has not changed, the single most important advancement since the days of Dr Latta is the ability to measure stroke volume (SV) continuously by minimally invasive or non-invasive techniques.[4] This allows the clinician to assess the patient's fluid responsiveness and changes in SV over time. Fundamentally, only patients who are fluid responsive should be treated with fluids.[5] Physical examination, chest radiography, central venous pressure (CVP), urine output (particularly in septic patients), and ultrasonography, including the vena caval collapsibility index, have limited value in determining fluid responsiveness and guiding fluid management.[6–10] In the intensive care unit (ICU), fluid responsiveness can be determined by a passive leg raising (PLR) manoeuvre coupled with SV monitoring.[5] This manoeuvre is a good predictor of fluid responsiveness in both intubated and non-intubated patients.[11] The change in the pulse pressure variation (PPV) or stroke volume variation (SVV) following a mini-fluid challenge (100 ml), as elegantly described by Mallat and colleagues[12] in this issue of the *BJA*, is an alternative and/or complementary technique to determine fluid responsiveness in patients in the ICU or operating theatre who are receiving low tidal volume ventilation. However, as demonstrated by Mallat and colleagues and others, the 'non-challenged' PPV and SVV have limited diagnostic accuracy (and applicability in ICU patients) for determining fluid responsiveness.[13–15]

Although still widely recommended,[6 16] the idea of giving large boluses of crystalloids (20–30 ml kg^{-1}) is unphysiologic and likely to lead to severe volume overload.[17 18] The ability of crystalloids to increase intravascular volume is poor. In healthy volunteers, only 15% of a crystalloid bolus was reported to remain intravascular at 3 h.[19 20] In patients with sepsis, <5% of an infused bolus remains intravascular 1 h after the end of the infusion.[21] In a caecal ligation model, Bark and colleagues[22] demonstrated that the plasma volume expanding effect of normal saline was <1% of the infused volume 20 min after the end of the infusion. In critically ill medical, surgical, and trauma patients, the hemodynamic effects of a fluid bolus are likely to be short lived, with the net effect being the shift of fluid into the interstitial compartment with progressive tissue oedema. Tissue oedema impairs oxygen and metabolite diffusion, distorts tissue architecture, impedes capillary blood flow and lymphatic drainage and disturbs cell–cell interactions, leading to organ dysfunction.[23 24] In encapsulated organs such as the kidney, tissue oedema increases interstitial pressure, compromising renal blood flow, which may play a role in the aetiology of acute kidney injury.[25] Increased extravascular lung water (EVLW) impairs gas exchange, reduces lung compliance, increases the work of breathing, and is a strong independent predictor of death.[26 27]

Nunes and colleagues[28] assessed the time course of the hemodynamic response of a 500 cc fluid challenge in patients requiring vasopressor support. In this study, 65% of patients were fluid responders; however, the SV increase (in the responders) returned to baseline 60 min after the infusion. Fluid boluses are most frequently given for hypotension or oliguria. While the mean arterial pressure (MAP) may increase immediately following a fluid bolus, this effect is short lived. In a systematic review that investigated the hemodynamic response of fluid boluses in patients with sepsis, Glassford and colleagues[29] demonstrated that the MAP increased by 7.8 (3.8) mm Hg immediately following the fluid bolus, by 6.9 (2.7) mm Hg 30 min following the bolus, and by only 2 mm Hg at 1 h, with no increase in the urine output following the boluses. These data suggest, as described by Dr Latta more than 200 yr ago, that hemodynamically unstable patients who are fluid responsive should be treated with repeated mini-fluid boluses (200–500 cc) and guided by changes in their hemodynamic profile (including SV). Furthermore, the risk:benefit ratio should be assed prior to each fluid bolus. It is noteworthy that in the study by Wu and colleagues[30] a mini-fluid bolus of 50 ml crystalloid was associated with a 17% increase in SV. It is likely that the mini-fluid bolus approach will result in smaller increases in cardiac filling pressures with the attenuated release of atrial natriuretic factors and less tissue oedema with a lower cumulative positive fluid balance than large volume fluid resuscitation. In the study by Mallat and colleagues[12] there was a significant decrease in the systemic vascular resistance index in the fluid responders following the fluid bolus. This observation has been reported previously following fluid boluses in patients with sepsis.[31 32] This suggests that fluid boluses should be considered vasodilator therapy in patients with sepsis and that large volume fluid resuscitation may potentiate the hyperdynamic state. An emerging paradigm in critical care suggests that a 'less is more' approach improves patient outcomes,[33] and this approach appears to apply to fluid resuscitation.

Declaration of interest

The author has no financial interest in any of the products mentioned in this article.

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CRITICAL CARE

Decrease in pulse pressure and stroke volume variations after mini-fluid challenge accurately predicts fluid responsiveness†

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Abstract

Background: Dynamic indices, such as pulse pressure variation (PPV), are inaccurate predictors of fluid responsiveness in mechanically ventilated patients with low tidal volume. This study aimed to test whether changes in continuous cardiac index (CCI), PPV, and stroke volume variation (SVV) after a mini-fluid challenge (100 ml of fluid during 1 min) could predict fluid responsiveness in these patients.

Methods: We prospectively studied 49 critically ill, deeply sedated, and mechanically ventilated patients (tidal volume <8 ml kg^{-1} of ideal body weight) without cardiac arrhythmias, in whom a fluid challenge was indicated because of circulatory failure. The CCI, SVV (PiCCO™; Pulsion), and PPV (MP70™; Philips) were measured before and after 100 ml of colloid infusion during 1 min, and then after the additional infusion of 400 ml during 14 min. Responders were defined as subjects with a ≥15% increase in cardiac index (transpulmonary thermodilution) after the full (500 ml) fluid challenge. Areas under the receiver operating characteristic curves (AUCs) and the grey zones were determined for changes in CCI (ΔCCI_{100}), SVV (ΔSVV_{100}), and PPV (ΔPPV_{100}) after 100 ml fluid challenge.

Results: Twenty-two subjects were responders. The ΔCCI_{100} predicted fluid responsiveness with an AUC of 0.78. The grey zone was large and included 67% of subjects. The ΔSVV_{100} and ΔPPV_{100} predicted fluid responsiveness with AUCs of 0.91 and 0.92, respectively. Grey zones were small, including ≤12% of subjects for both indices.

Conclusions: The ΔSVV_{100} and ΔPPV_{100} predict fluid responsiveness accurately and better than ΔCCI_{100} (PiCCO™; Pulsion) in patients with circulatory failure and ventilated with low volumes.

Key words: cardiac output; fluid therapy; goal-directed therapy; haemodynamics; monitoring; pulse pressure

Fluid therapy is commonly used in critically ill patients with acute circulatory failure. The aim of volume expansion is to increase cardiac index and oxygen delivery and to improve tissue oxygenation. However, this occurs only in a situation of preload dependency. Moreover, giving fluids to a non-volume-responsive patient (preload independency) can result in detrimental pulmonary and interstitial oedema.[1] In this setting, identifying patients who will benefit from volume expansion remains difficult.[2] In this regard, the dynamic parameters pulse pressure variation (PPV) and stroke volume variation (SVV) can accurately predict fluid

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Editor's key points

- The ability of dynamic haemodynamic indices to predict fluid responsiveness was assessed in mechanically ventilated patients with circulatory failure.
- Reductions in pulse pressure variation or stroke volume variation after a mini-fluid challenge predicted fluid responsiveness better than increases in continuous cardiac index.
- In this single-centre study, a mini-fluid challenge of 0.1 litre colloid accurately predicted fluid responsiveness in patients ventilated with low tidal volume.

responsiveness in mechanically ventilated patients.[2–8] However, this approach has limitations in critically ill patients, especially with the use of tidal volumes <8 ml kg^{-1} of ideal body weight (IBW).[9–13] Fluid challenge, which consists of administering fluid to assess volume responsiveness, thus remains widely performed.[14 15] However, repeated fluid challenges, several times a day, can be harmful, especially in fluid non-responders.[1]

Interestingly, Muller and colleagues[16] showed that the response to 500 ml fluid challenge could be predicted by assessing the changes in aortic velocity–time index (VTI; by transthoracic echocardiography) after administration of a limited amount of fluid (100 ml during 1 min), known as the mini-fluid challenge technique. However, in clinical practice, major limitations of this technique include echograph availability, physicians' skills in echocardiography, and poor echogenicity, especially in mechanically ventilated patients. Therefore, we aimed to determine whether the effects of a mini-fluid challenge on continuous cardiac index (CCI; by pulse-contour method, using a PiCCO monitor) could also predict fluid responsiveness in patients with acute circulatory failure. In addition, because changes in PPV induced by volume expansion were recently shown to detect simultaneous changes in cardiac index in the perioperative period,[17] we tested the hypothesis that changes in PPV and SVV after the mini-fluid challenge could predict fluid responsiveness in deeply sedated patients, without spontaneous breathing and cardiac arrhythmias, even when ventilated with low tidal volume.

Methods

This prospective single-centre observational study was conducted in a general adult intensive care unit (ICU) after approval by our local institutional ethics committee (Lens Hospital, France). Informed consent was obtained from each subject's next of kin.

Subjects

We studied deeply sedated and mechanically ventilated patients without spontaneous breathing (as attested by the flow curve on the ventilator). Volume therapy was decided by the physician based on the presence of one or more of the following sign(s) of acute circulatory failure:[18] (i) systolic arterial pressure <90 mm Hg, mean arterial pressure <65 mm Hg, or the need for vasopressor infusion; (ii) skin mottling; and (iii) lactate concentrations >2 mM or (iv) urine output <0.5 ml kg^{-1} h^{-1} for ≥2 h. Subjects had also to be monitored by the PiCCO device (PiCCO; Pulsion Medical System, Munich, Germany) as part of routine management of persistent signs of tissue hypoperfusion. Exclusion criteria were as follows: tidal volume ≥8 ml kg^{-1} of IBW {with IBW (in kilograms) determined as follows: x+0.91[height (in centimetres)−152.4], where x=50 for males and x=45.5 for females}, pregnancy, age <18 yr, moribund, cardiac arrhythmias, and risk of fluid-loading-induced pulmonary oedema (IBW-indexed extravascular lung water >14 ml kg^{-1}).[19]

Measurements

Subject characteristics, the aetiology of acute circulatory failure, the Simplified Acute Physiology Score (SAPS) II, and the Sequential Organ Failure Assessment (SOFA) scores were obtained on the day of enrolment. Ventilator settings with airway pressures and inspiratory oxygen fraction were recorded. Static respiratory compliance (C_{rs}) was calculated as follows: C_{rs} (in millilitres per centimetre of water)=tidal volume/(plateau pressure − end-expiratory pressure). Driving pressure was determined as the difference between the plateau pressure and the end-expiratory pressure. The cardiac index was obtained with the PiCCO device by central venous injection of iced 0.9% saline solution (20 ml) in triplicate and then averaged. We also recorded CCI, which was measured by pulse-contour analysis after calibration. In addition, heart rate (HR), systemic arterial pressures, and end-expiratory central venous pressure (zero referenced to the mid-axillary line) were collected. The SVV and PPV were obtained online using the PiCCO monitor and the Philips® IntelliVue MP70 monitor (Philips Medical Systems, Suresne, France), respectively. Transthoracic echocardiography was performed before the beginning of the study (EnVisor® HD; Philips ultrasound system, Philips Healthcare, DA Best, The Netherlands), and left ventricular ejection fraction was determined by the Simpson method.[20]

Study protocol

The fluid challenge was administered via a separate venous line. A set of cardiovascular measurements was obtained at baseline, including HR, systemic arterial pressures, central venous pressure, SVV, PPV, CCI (pulse-contour) and cardiac index (transpulmonary thermodilution). A 100 ml colloid solution (4% human serum albumin, Vialebex®; LFB, Paris, France) was infused during 1 min, and cardiovascular measurements were repeated immediately after this bolus administration. The remaining 400 ml of colloid solution was then infused at a constant rate during 14 min, and cardiovascular measurements were repeated.

Changes in CCI (ΔCCI_{100}) induced by the mini-fluid challenge were expressed as relative changes. Changes in SVV (ΔSVV_{100}) and PPV (ΔPPV_{100}) were expressed as absolute differences (parameter after 100 ml minus parameter before 100 ml), as previously described.[17]

Statistical analysis

According to the changes in the thermodilution-derived cardiac index after 500 ml volume expansion, subjects were classified as responders (≥15% increase in cardiac index) or non-responders. Data are expressed as mean (SD), or as median [25–75% interquartile range (IQR)], as appropriate. Normality was evaluated using the Kolmogorov–Smirnov test. Differences between responders and non-responders were assessed by two-tailed Student's t-test or Mann–Whitney U-test, as appropriate. Comparisons within groups were assessed using Student's paired t-test or Wilcoxon test, as appropriate. Analysis of categorical data used the χ^2 or Fisher's exact test. Correlations were tested by using the Pearson or the Spearman test, as appropriate. To adjust for the phenomenon of regression to the mean, absolute changes in CCI, SVV, and PPV between baseline and after the mini-fluid challenge were also analysed by performing an analysis of covariance (ANCOVA), with the absolute changes in these variables

as dependent variables, the subject as a factor, and the baseline value of each variable as a covariate.

Receiver operating characteristic (ROC) curves were used to evaluate the capacity of each variable to predict fluid responsiveness after fluid challenge. The areas under the ROC curves (AUCs) were compared according to DeLong and colleagues.[21] The best cut-off of an ROC curve was chosen with the highest Youden index.[22] Usually, variables are considered as having good discriminative properties when the inferior limits of the 95% confidence interval (CI) of their AUC are >0.75.[22] For this purpose, 43 subjects would be sufficient for a power of 80% and an α risk of 0.05. Statistical analysis was performed using MedCalc 12.3.0.0 (MedCalc Software, Mariakerke, Belgium). A value of $P<0.05$ was considered statistically significant for single comparisons. All reported P-values are two sided.

Grey zones were calculated using two methods. The first method consisted of the determination of the 1000 bootstrapped (sampling with replacement) 95% CI of Youden's index by the bias-corrected and accelerated (BCa) bootstrap method.[23] The second method defined three levels of response: positive, uncertain, and negative. Uncertain responses were cut-off values with a sensitivity of <90% or a specificity of <90% (diagnosis tolerance of 10%).[24] Two-curve (sensitivity and specificity) representations were used to illustrate this analysis adequately.

The grey zones were determined for each variable from the values that did not allow having 10% of diagnosis tolerance. However, if the Bca-bootstrapped 95% CI was larger than the inconclusive zone, the values obtained with the first approach were kept for grey zone determination.

Reproductibility of PPV, SVV, and CCI was calculated from data obtained in 15 subjects. We collected five consecutive values of PPV, SVV, and CCI (one value each minute) displayed on the monitor at times when the haemodynamic status was stable. The coefficient of variation was then calculated for each collection and averaged for the series of 15 sets. The precision was calculated as two times the coefficient of variation, and the least significant change (LSC) as precision time $\sqrt{2}$. The LSC characterizes the minimal change that a device needs to measure in order to detect a real change.

Results

We studied 49 subjects, whose characteristics are summarized in Table 1. The major cause of acute circulatory failure was septic shock (94%). All subjects were sedated and mechanically ventilated, without spontaneous breathing. Sedation level and vasopressor infusion were kept constant during volume expansion. No subjects had right ventricular dilatation (defined by the ratio of right-to-left ventricular diameter >0.6) or paradoxical septal motion by echocardiography.

There were 22 (45%) responders defined by an increase in the thermodilution cardiac index of >15% after volume expansion of 500 ml. No significant differences were found in subject characteristics, heart rate-to-respiratory rate ratio, or tidal volume between responders and non-responders except for driving pressure, plateau pressure, and lactate concentrations, which were higher, and C_{rs}, which was lower in non-responders (Table 1).

Effect of volume expansion on haemodynamic variables

At baseline, central venous pressure was significantly higher and PPV lower in non-responders, whereas other haemodynamic

Table 1 Characteristics of the population and comparison between responders and non-responders. C_{rs}, respiratory system compliance; FI_{O_2}, inspired oxygen fraction; HR, heart rate; IBW, ideal body weight; ICU, intensive care unit; IQR, interquartile range; LVEF, left ventricular ejection fraction; Pa_{CO_2}, arterial carbon dioxide partial pressure; Pa_{O_2}, arterial oxygen partial pressure; RR, respiratory rate; SAPS, Simplified Acute Physiology Score; SBE, standard base excess; SOFA, Sequential Organ Failure Assessment; V_T, tidal volume. Data are expressed as mean (SD), median (25–75% interquartile range), or count (%)

Characteristic	All subjects (n=49)	Responders (n=22)	Non-responders (n=27)	P-value
Age [median (range); yr]	64 (26–79)	61 (26–79)	66 (47–78)	0.53
BMI [mean (SD); kg m^{-2}]	26.6 (4.6)	25.8 (4.40)	27.3 (4.8)	0.23
Sex (male/female)	29/20	16/6	13/14	0.08
SAPS II score [mean (SD)]	66 (20)	64 (17)	67 (22)	0.58
SOFA score [median (IQR)]	10 (6–14)	10 (6–11)	10 (6–14)	0.34
ICU mortality [n (%)]	24 (49)	10 (45)	14 (52)	0.12
V_T/IBW [median (IQR); ml kg^{-1}]	6.8 (6.4–7.3)	6.8 (5.6–7.3)	6.8 (6.4–7.6)	0.55
Total PEEP [median (IQR); cm H_2O]	8 (6–10)	6 (5–10)	8 (7–10)	0.10
Plateau pressure [median (IQR); cm H_2O]	22 (17–25)	17 (14–25)	23 (20–27)	0.008
C_{rs} [median (IQR); ml (cm H_2O)$^{-1}$]	32.3 (25.1–46.9)	45.2 (26.7–55.9)	28.8 (23.7–35.7)	0.009
C_{rs}≤30 ml (cm H_2O)$^{-1}$ [n (%)]	24 (49)	6 (27.3)	18 (66.7)	0.006
Driving pressure [mean (SD); cm H_2O]	13.8 (4.6)	12.0 (4.6)	15.3 (4.2)	0.012
HR/RR ratio [median (IQR)]	4.4 (3.3–5.4)	4.4 (3.4–6.0)	4.2 (3.2–5.0)	0.28
LVEF [mean (SD); %]	55 (9)	57 (9)	52 (9)	0.90
pH [median (IQR)]	7.35 (7.23–7.38)	7.32 (7.23–7.38)	7.36 (7.21–7.39)	0.84
Pa_{CO_2} [median (IQR); kPa]	5.05 (4.26–5.32)	4.79 (4.26–5.32)	5.05 (4.26–5.45)	0.24
Pa_{O_2}/FI_{O_2} [mean (SD); kPa]	30.2 (14.8)	34.0 (17.8)	26.6 (10.4)	0.1
SBE [median (IQR); mequiv litre^{-1}]	−6.2 (−9.8 to −1.5)	−7.8 (−9.8 to −1.9)	−5.0 (−11.9 to −1.1)	0.39
Lactate [median (IQR); mmol litre^{-1}]	2.1 (1.2–3.6)	1.9 (1.0–3.1)	2.3 (1.4–4.8)	0.06
Norepinephrine [n (%)]	45 (92)	20 (91)	25 (93)	1.00
Norepinephrine [median (IQR); μg kg^{-1} min^{-1}]	1.0 (0.3–1.6)	1.0 (0.4–1.6)	1.2 (0.3–1.7)	0.78
Type of shock [n (%)]				
Septic	46 (94)	21 (95)	25 (93)	1.00
Hypovolaemic	3 (6)	1 (5)	2 (7)	1.00

variables were similar between the two groups (Table 2). Volume expansion decreased SVV and PPV only in responders. Nevertheless, HR did not change significantly after volume expansion. The AUCs for baseline SVV and PPV, when predicting fluid responsiveness, were 0.52 [(95% CI: 0.34–0.66); P=0.84] and 0.62 [(95% CI: 0.48–0.76); P=0.12], respectively.

Effect of mini-fluid challenge on haemodynamic variables

We found significant changes between responders and non-responders after the first infusion of 100 ml for all tested haemodynamic variables except for HR (Table 3). In responders, mini-fluid challenge increased CCI by 8.6% and decreased PPV and SVV by 4 and 3%, respectively. The mini-fluid challenge induced absolute changes in CCI, PPV, and SVV that were significantly greater in responders than in non-responders (ANCOVA, P=0.001, P<0.001, and P<0.001, respectively). Furthermore, after adjusting to static respiratory compliance and plateau pressure, these change were still significantly different between the two groups (ANCOVA, P=0.005, P<0.001, and P<0.001, respectively).

Relationship between mini-fluid challenge-induced changes in haemodynamic variables

The correlation between ΔCCI_{100} and changes in cardiac index after the 500 ml fluid infusion (ΔCI_{500}) in all subjects was significant but weak (r=0.47, P=0.001; Supplementary Fig. S1). We also observed a closer negative relationship between ΔSVV_{100} and ΔCI_{500} (r=−0.74, P<0.001) and between ΔPPV_{100} and ΔCI_{500} (r=−0.74, P<0.001; Supplementary Fig. S1).

Ability of mini-fluid challenge-induced changes in haemodynamic variables to predict fluid responsiveness

The AUC for ΔCCI_{100} was 0.78 (95% CI: 0.68–0.88). The ability of ΔSVV_{100} and ΔPPV_{100} to predict fluid responsiveness was excellent, with AUCs of 0.91 (95% CI: 0.80–0.97) and 0.92 (95% CI: 0.81–0.98), respectively (Fig. 1 and Table 4). There were significant differences between the AUCs for ΔPPV_{100} and ΔCCI_{100} (P=0.04) and between the AUCs for ΔSVV_{100} and ΔCCI_{100} (P=0.05).

The best AUC cut-off values, when predicting fluid responsiveness, were 5.2% for ΔCCI_{100} [sensitivity=77% (95% CI: 55–92%); specificity=74% (95% CI: 54–89%)], −2% for ΔSVV_{100} [sensitivity=86% (95% CI: 65–97%); specificity=89% (95% CI: 71–98%)], and −2% for ΔPPV_{100} [sensitivity=86% (95% CI: 64–96%); specificity=85% (95% CI: 65–95%); Supplementary Fig. S2].

Grey zone limits

Table 4 and Figure 1 show the limits of the inconclusive zone for the changes in haemodynamic parameters induced by the mini-fluid challenge. A large grey zone was found for ΔCCI_{100}, and 67% of the subjects were within this inconclusive zone. Conversely, we observed small grey zones for ΔSVV_{100} and ΔPPV_{100}, which included only 8 and 12% of subjects, respectively (Table 4 and Fig. 1).

Reproducibility of PPV, SVV, and CCI

The precision was 3.0 (3.2)% for PPV and 3.5 (3.3)% for SVV. The LSC was 4.2 (4.5)% for PPV and 5.0 (4.7)% for SVV. Such coefficients correspond to absolute changes ≤1% for initial PPV or SVV values of 10–12%, as recorded at baseline in our subjects. For CCI, precision and LSC were 3.0 (1.8) and 4.2 (2.6)%, respectively.

Table 2 Haemodynamic variables before and after 500 ml of volume expansion. Data are expressed as mean (SD) or median (25–75 interquartile range; IQR). Responders n=22; Non-responders n=27. *P<0.05 compared with responders. †P<0.05 compared with before volume expansion

Variable	Before volume expansion	After volume expansion
Heart rate [mean (SD); beats min^{-1}]		
Responders	103 (28)	101 (22)
Non-responders	100 (24)	99 (23)
Systolic arterial pressure [mean (SD); mm Hg]		
Responders	101 (24)	123 (21)†
Non-responders	102 (23)	114 (25)†
Diastolic arterial pressure [mean (SD); mm Hg]		
Responders	55 (14)	63 (8)†
Non-responders	55 (10)	62 (11)†
Mean arterial pressure [mean (SD); mm Hg]		
Responders	70 (16)	83 (12)†
Non-responders	70 (14)	80 (16)†
Pulse pressure [mean (SD); mm Hg]		
Responders	45 (19)	59 (16)†
Non-responders	47 (17)	52 (17)†
Central venous pressure [mean (SD); mm Hg]		
Responders	11 (5)	13 (5)†
Non-responders	15 (5)*	18 (6)*†
Intrathoracic blood volume index [median (IQR); ml m^{-2}]		
Responders	819 (672–946)	954 (858–1079)†
Non-responders	872 (676–1052)	952 (693–1008)†
Extravascular lung water index [median (IQR); ml kg^{-1}]		
Responders	7.2 (5.9–8.8)	7 (5.9–8.9)
Non-responders	8.8 (6.9–11.3)*	8.4 (7.5–11.1)*
Systemic vascular resistance index [median (IQR); dynes.second m^{-2} cm^{-5}]		
Responders	1870 (1500–2350)	1590 (1420–2030)†
Non-responders	1710 (1200–2030)	1756 (1160–2060)
Central venous oxygen saturation [mean (SD); %]		
Responders	61 (14)	64 (13)†
Non-responders	61 (15)	61 (14)
Cardiac index [median (IQR); litre min^{-1} m^{-2}]		
Responders	2.51 (1.91–3.33)	3.48 (2.43–4.13)†
Non-responders	2.60 (2.34–3.24)	2.72 (2.36–3.46)
Stroke volume index [median (IQR); ml m^{-2}]		
Responders	27.6 (18.6–35.9)	38.4 (25.8–43.9)†
Non-responders	32.4 (20.2–39.3)	32.1 (22.6–41.6)
Stroke volume variation [median (IQR); %]		
Responders	12 (7–17)	6 (4–8)†
Non-responders	13 (7–17)	11 (7–19)*
Pulse pressure variation [median (IQR); %]		
Responders	11 (8–21)	5 (3–12)†
Non-responders	10 (4–16)*	10 (7–17)*

Discussion

The main findings were as follows: (i) ΔCCI_{100} after a rapid infusion of 100 ml of colloid solution has a reasonable accuracy to predict a 15% increase in cardiac index after a 500 ml infusion; (ii) this approach, however, has limited clinical application as reflected by a large grey zone including 67% of subjects; and (iii) the ability of ΔSVV_{100} and ΔPPV_{100} induced by mini-fluid challenge to detect fluid responsiveness was excellent and higher than ΔCCI_{100}, with smaller inconclusive zones.

Two recent studies, using echocardiography, suggested that infusion of a very limited amount of fluid during a very short

Table 3 Changes in haemodynamic parameters between after and before mini-fluid challenge (100 ml of colloid). Data are expressed as median (25–75 interquartile range; IQR) or mean (SD). All changes in haemodynamic parameters are expressed as relative changes, except for stroke volume variation and pulse pressure variation, for which absolute differences are reported (see Methods)

Parameter	Responders (*n*=22)	Non-responders (*n*=27)	*P*-value
Stroke volume variation [median (IQR); %]	−3 (−5 to −2)	0 (−1 to 1)	<0.001
Pulse pressure variation [median (IQR); %]	−4 (−4 to −2)	0 (0–1)	<0.001
Continuous cardiac index [median (IQR); %]	8.6 (4.5–16.2)	0 (0.0–5.4)	<0.001
Continuous stroke volume index [median (IQR); %]	9.5 (5.1–14.0)	0 (0.0–6.0)	<0.001
Heart rate [mean (SD); %]	−1.8 (4.1)	−1.9 (4.3)	0.93
Pulse pressure [median (IQR); %]	3.7 (−1.5 to 19.8)	0 (−7.0 to 10.6)	0.08
Systolic arterial pressure [median (IQR); %]	4.6 (0.3–14.6)	2.0 (−5.7 to 6.5)	0.051
Diastolic arterial pressure [median (IQR); %]	6.2 (0–10.9)	−2.1 (−4.9 to 4.0)	0.020
Mean arterial pressure [median (IQR); %]	5.1 (0–11.5)	−1.4 (−7.7 to 4.0)	0.017

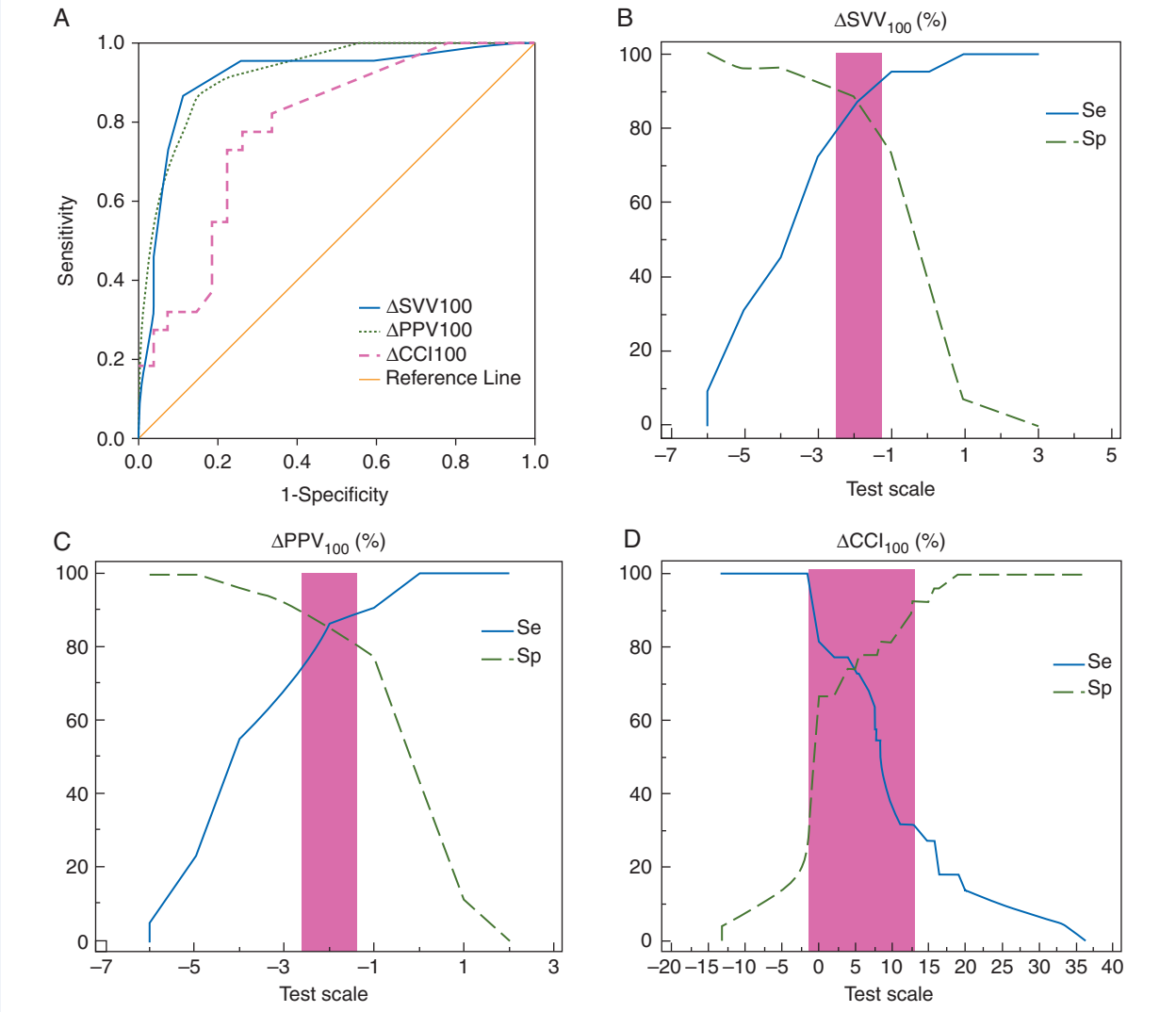

Fig 1 (A) Receiver operating characteristic (ROC) curves for ΔSVV_{100} (%), ΔPPV_{100} (%), and ΔCCI_{100} (%) after infusion of 100 ml fluid during 1 min. Two-graph ROC curves: sensitivity (Se) and specificity (Sp) of mini-fluid challenge-induced changes in stroke volume variation (SVV; B), pulse pressure variation (PPV; C), and continuous cardiac index (CCI; D) according to the value of the cut-off for the detection of more than 15% increase in cardiac index after volume expansion. The inconclusive zone, which is >10% of diagnosis tolerance, is represented as a shaded rectangle. ΔSVV100 is the changes in stroke volume variation after 100 ml of fluid challenge. ΔPPV100 is the changes in pulse pressure variation after 100 ml of fluid challenge. ΔCCI100 is the changes in continuous cardiac index variation after 100 ml of fluid challenge.

Table 4 Predictive values of 100 ml of fluid challenge-induced changes in haemodynamic parameters to detect a more than 15% increase in cardiac index. AUC, area under the curve; CCI, continuous cardiac index; DAP, diastolic arterial pressure; MAP, mean arterial pressure; PP, pulse pressure; PPV, pulse pressure variation; SAP, systolic arterial pressure; SVV, stroke volume variation

Parameter	AUC	95% Confidence interval	P-value	Cut-off (%)	Sensibility (%)	Specificity (%)	Grey zone	Patients in the grey zone (%)
Absolute change in SVV (%)	0.91	0.80–0.97	<0.001	−2	86	89	−2.5 to −1.4	4 (8%)
Absolute change in PPV (%)	0.92	0.81–0.98	<0.001	−2	86	85	−2.6 to −1.3	6 (12%)
Relative change in CCI (%)	0.78	0.64–0.88	<0.001	5.2	77	74	−1.56 to 12.6	33 (67%)
Relative change in SAP (%)	0.66	0.52–0.82	0.038	2.4	86	44	−5.6 to 12.2	32 (65%)
Relative change in DAP (%)	0.70	0.55–0.82	0.013	4.7	62	81	−6.2 to 10.0	29 (60%)
Relative change in MAP (%)	0.70	0.55–0.82	0.001	1.7	81	55	−4.6 to 11.6	28 (57)
Relative change in PP (%)	0.65	0.48–0.76	0.12	5.2	95	40	−4.8 to 11.3	28 (57)

period could be sufficient to predict fluid responsiveness among mechanically ventilated patients.[16 25] We found that ΔCCI_{100} using the pulse-contour analysis technique (PiCCO device) had a lower accuracy to predict fluid responsiveness (AUC=0.78) than that obtained with echocardiographic measurements [cardiac output (CO) and VTI] in these latter studies.[16 25] Moreover, using a grey zone approach, we found a wide range for an inconclusive zone, which included 67% of the subjects in whom fluid responsiveness remained uncertain (Table 4). These discrepancies are likely to be attributable to the techniques used for assessing the response to mini-fluid challenge. Pulse-contour analysis uses the relationship between stroke volume, area under the arterial pressure waveform (systolic portion), and shape of the waveform according to a proprietary algorithm.[26] As the pressure waveform also depends on arterial resistance and compliance, the precision of the pulse-contour CO has been questioned in patients with haemodynamic instability, especially with therapeutic manoeuvres.[27–31] In our study, the pulse-contour CO was recalibrated immediately before the beginning of the mini-fluid challenge. In these conditions, pulse-contour CO reliably assessed changes in CO induced by volume expansion (500 ml of saline during a 30 min period).[30] However, the precision of pulse-contour CO has not been assessed for mini-fluid challenge. The small amplitude of CCI changes after 100 ml fluid (between 0 and 10% in most subjects) in our study is likely to explain our results. Indeed, the LSC for CCI (4.2%) that we found, which is in agreement with the findings of previous studies (4.5 and 5.1%),[30 31] was close to the best cut-off value of CCI changes induced by mini-fluid challenge (5.2%). Accordingly, evaluation of the ability of CO monitors to quantify trends in CO usually excludes CO changes <10–15%.[32]

In contrast to our findings, Monnet and colleagues[33] have shown that an increase in pulse-contour cardiac index ≥5% (obtained with a PiCCO device) during an end-expiratory occlusion predicted fluid responsiveness with a sensitivity and a specificity of 91 and 100%, respectively. However, the increase in cardiac index induced by the end-expiratory occlusion was greater than that induced by the mini-fluid challenge in our study (12 *vs* 8.6%, respectively). Moreover, their coefficient of variation for the pulse-contour cardiac index was 1.76%, resulting in an LSC of 5%, which was the best cut-off value of the end-expiratory occlusion test.[33] Thus, according to their findings, an increase of 5% in pulse-contour cardiac index cannot be considered as a real change.

It has been well established that measurement of both PPV and SVV allows accurate prediction of fluid responsiveness in patients under controlled mechanical ventilation with no inspiratory efforts and sinus cardiac rhythm.[2–4 6–8] However, in instances of low tidal volume (<8 ml kg^{-1} of IBW), these dynamic indices are no longer reliable predictors of fluid responsiveness in relationship with reduced variations in intracardiac pressure, and thus, low PPV/SVV values even in fluid-responsive patients (false negatives).[10 11 16] Recently, Biais and colleagues[34] found that PPV values between 2 and 17% did not predict fluid responsiveness in ICU patients who were mechanically ventilated with tidal volume <8 ml kg^{-1} of IBW. Accordingly, in our study, the median tidal volume was 6.8 ml kg^{-1} of IBW, and median PPV and SVV values in responders before volume expansion were 11 and 12%, respectively, explaining the poor performance of both indices before volume expansion. Nevertheless, ΔSVV_{100} and ΔPPV_{100} predicted fluid responsiveness accurately (Table 4). The decreases in PPV/SVV observed after the 100 ml bolus in responders were larger than the LSC values determined for both indices, suggesting that volume expansion could be performed by repeated administration of such boluses, as previously discussed by Muller and colleagues[16] using echocardiography. Interestingly, ΔSVV_{100} and ΔPPV_{100} presented narrow inconclusive areas, and only few subjects were in these grey zones, which indicates that these indices have significant clinical applicability. Moreover, we found strong relationships between ΔSVV_{100}, ΔPPV_{100}, and ΔCI_{500} (Supplementary Fig. S1).

It was previously shown in patients ventilated with larger tidal volumes [7.9 (1.3) ml kg^{-1} body weight] that changes in PPV after volume expansion (500 ml) could be used to detect changes in cardiac index.[16] To the best of our knowledge, our study is the first to demonstrate the following: (i) the usefulness of changes in SVV and PPV after a mini-fluid challenge (100 ml) to predict fluid responsiveness; and (ii) the validity of this approach in ICU patients ventilated with low tidal volumes. Furthermore, we provided grey zone boundaries that may be more helpful to decision-making than only a single cut-off in clinical practice.[22]

We acknowledge particular circumstances in which our study was conducted that may limit the clinical relevance of our results. First, because patients with cardiac arrhythmia and spontaneous ventilation were not included, our findings cannot be extrapolated to such patients. Nowadays, partial spontaneous ventilation and light sedation, which are well-established limits of the use of dynamic indices, are common practice in the ICU. However, applicability of dynamic indices is likely to be higher in the early stages of critical states where patients are usually deeply sedated with mandatory ventilation,[35] which was the situation for our subjects. Second, few subjects had severe ventricular dysfunction; thus, we do not know whether our results can be applied to that setting. Third, as a result of the study design, the interpretation of our results could theoretically be obscured by the phenomenon of regression to the mean. However, at baseline, there were no differences in haemodynamic

variables between the two groups. Furthermore, changes in CCI, SVV, and PPV induced by the mini-fluid challenge were still significantly different using a statistical method that adjusts to their baseline values (ANCOVA). Therefore, we believe that the effect of regression to the mean did not affect the interpretation of our findings. Finally, it is a single-centre study, which may limit its external validity.

Conclusion

In spite of a relatively fair predictive value, ΔCCI_{100}, as measured with the pulse-contour analysis technique (PiCCO device), may be inconclusive in two-thirds of patients and should not be used routinely as a predictor of fluid responsiveness in the ICU in patients with acute circulatory failure. However, ΔSVV_{100} and ΔPPV_{100} are able to detect fluid responders in mechanically ventilated patients with low tidal volume with excellent sensitivity and specificity and grey zones of ~10% of the subjects.

Supplementary material

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

Authors' contributions

Study conception: J.M., L.T., D.T.
Study design: J.M., M.M., E.D.
Patient recruitment and data collection: J.M., M.M., E.D., M.L., F.P., J.T., N.V.
Acquisition, analysis, and interpretation of data: all authors.
Statistical analysis: J.M.
Drafting the manuscript: J.M., B.T.
Revising the draft, reading, and approval of the final manuscript for publication: all authors.

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Declaration of interest

None declared.

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