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ORIGINAL ARTICLE

Multivariable haemodynamic approach to predict the fluid challenge response

A multicentre cohort study

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BACKGROUND Beat-to-beat stroke volume (SV) results from the interplay between left ventricular function and arterial load. Fluid challenge induces time-dependent responses in cardiac performance and peripheral vascular and capillary characteristics.

OBJECTIVE To assess whether analysis of the determinants of the haemodynamic response during fluid challenge can predict the final response at 10 and 30 min.

DESIGN Observational multicentric cohort study.

SETTING Three university ICUs.

PATIENTS 85 ICU patients with acute circulatory failure diagnosed within the first 48 h of admission.

INTERVENTION(S) The fluid challenge consisted of 500 ml of Ringer's solution infused over 10 min. A SV index increase at least 10% indicated fluid responsiveness.

MAIN OUTCOME MEASURES The SV, pulse pressure variation (PPV), arterial elastance, the systolic–dicrotic pressure difference (SAP-P_{dic}) and cardiac cycle efficiency (CCE) were measured at baseline, 1, 2, 3, 4, 5, 10, 15 and 30 min after the start of the fluid challenge. All haemodynamic data were submitted to a univariable logistic regression model and a multivariable analysis was then performed using the significant variables given by univariable analysis.

RESULTS The multivariable model including baseline PPV, and the changes of arterial elastance at 1 min and of the CCE and SAP-P_{dic} at 5 min when compared with their baseline values, correctly classified 80.5% of responders and 90.7% of nonresponders at 10 min. For the response 30 min after starting the fluid challenge, the model, including the changes of PPV, CCE, SAP-P_{dic} at 5 min and of arterial elastance at 10 min compared with their baseline values, correctly identified 93.3% of responders and 91.4% of nonresponders.

CONCLUSION In a selection of mixed ICU patients, a statistical model based on a multivariable analysis of the changes of PPV, CCE, arterial elastance and SAP-P_{dic}, with respect to baseline values, reliably predicts both the early and the late response to a standardised fluid challenge.

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Introduction

During circulatory failure, one of the first therapies used in the critically ill to correct arterial hypotension is the infusion of fluid.[1,2] Accurate prediction of the cardiovascular response may limit the risk of fluid overload, a factor associated with poor outcomes,[3–5] allowing fluid therapy to be tailored to the individual by applying the concept of

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'functional haemodynamics'.[6] Although fluid challenges are often given to reverse hypovolaemia and hypotension, only about 50% of ICU patients are fluid responsive.[7]

The stroke volume (SV) is determined by the interplay between cardiac function and arterial load. Diastolic filling depends on venous return, which is determined by the 'stressed volume' and venous compliance.[8,9] Systolic cardiac function depends on both cardiac factors and arterial load and is predominantly determined by arterial elastance and resistance.[10,11] The concept of arterial elastance, the inverse of the compliance,[10,11] has been incorporated as a net measure of ventricular afterload in the cardiovascular model of Sunagawa *et al.*,[12] who proposed an equilibrium point between both cardiac and arterial elastance.

When a fluid challenge is performed to increase SV, all other physiological variables influence the time and the amplitude of the response. The amount of fluid given, the rate of administration, the thresholds used to define the response and the time-point at which the response is checked are important to consider.[13,14] As a consequence, the prediction of fluid responsiveness in unstable ICU patients based on classic and simple prefluid challenge measurements, such as the dynamic index called pulse pressure variation (PPV), often fails.[15,16] In elective neurosurgical patients, we have previously demonstrated that the early haemodynamic effects during a fluid challenge can predict the final response.[17] In this study, we hypothesised that the response to a fluid challenge could be determined soon after the challenge onset by continuous analysis of the determinants of the haemodynamic response, and that this was achievable before the end of the fluid challenge. We tested whether changes in PPV, arterial elastance and two surrogate measures of ventriculo–arterial coupling, the cardiac cycle efficiency (CCE), and the difference between systolic and dicrotic pressure (SAP-P_{dic}), with respect to their baseline values, could predict the response to fluid administration observed 10 min after the onset of the challenge (early fluid responsiveness) and, second, and we hypothesised that this approach might predict the response to the fluid challenge at 30 min (late fluid responsiveness).

Materials and methods

Patients

The study was based in three ICUs in two University Hospitals. Two Italian ICUs were in Novara and Padova and a Turkish ICU in Ankara. The study was firstly approved by the Institutional Ethics Committee of Novara (co-ordinating centre – Comitato Etico Interaziendale; Corso Mazzini n. 18, 28100 Novara, Italy; protocol number CE160/16; approval date 19 December 2016) and then by the Institutional Ethics Committees of Padova (Via Giustiniani, 1, 35128 Padova, Italy; approval number 3208/AO/18) and Ankara (Taskent Cd. 77th street No: 11 pbx:06430 Bahcelievler/Ankara/Turkey; approval number KA17/). The trial was registered prior to patient enrolment at http://www.anzctr.org.au (ACTRN12617000076370; Principal Investigator AM; date of registration: 13 January 2017). Written consent was obtained from all participants in the trial, according to the local regulations.

We investigated critically ill patients with acute circulatory failure diagnosed within the first 48 h after ICU admission, for whom the clinician in charge prescribed volume expansion. Acute circulatory failure was defined as SAP 90 mmHg or less (or a decrease >50 mmHg in hypertensive patients) or a mean arterial pressure (MAP) 70 mmHg or less or the use of vasopressors to maintain SAP more than 90 mmHg, associated with skin mottling; tachycardia at least 100 bpm; urinary flow 0.5 ml kg^{-1} or less for at least 2 h; blood lactate level at least 4 mmol l^{-1}. The exclusion criteria were severe myocardial or valvular dysfunction; cardiac arrhythmia; severe acute respiratory distress syndrome; on-going haemodialysis or continuous haemofiltration; modification of drug administration during fluid challenge (change in sedation, vasopressors or inotropic drugs infusion rate); prior treatment with beta-blockers.

Study design and measurements

The fluid challenge consisted of 500 ml of Ringer's solution infused over 10 min, administered either via a central or a peripheral line. Early and late fluid responsiveness were evaluated 10 and 30 min after the fluid challenge. Because pulse contour analysis requires a good quality arterial pressure signal from the radial or femoral arteries, the signal quality was checked on the monitor screen and the adequacy of the arterial pressure waveform was evaluated by performing a square-wave test before the fluid challenge. The pressure transducer was connected to the MOSTCARE™ system (Vytech Health, Padua, Italy), an uncalibrated device that analyses every heart beat at a rate of 1000 Hz digital sampling. This sampling rate allows accurate tracing and measurement of the dicrotic notch, which is essential to define the systolic component of the arterial pressure waveform. This point has been used to calculate SAP-P_{dic}, a variable related to SV ejection into the arterial vessels.[17] This device calculates the systemic vascular impedance by analysing the profile of the points of instability, related to arterial mechanics and backflow waves on a beat-to-beat analysis.[18] Arterial elastance is calculated as the ratio between P_{dic} and SV. SAP, MAP, P_{dic}, PPV and arterial elastance values were automatically stored on disc for further analysis. The CCE, as previously reported,[17] was used to evaluate the performance of the cardiovascular system. It was calculated as follows:

$$\mathrm{CCE} = \frac{W_{\mathrm{sys}}}{W_{\mathrm{beat}}} \times (K)t$$

where W_{sys} and W_{beat} are the systolic and complete beat power functions. $(K)t$ is the ratio between the expected and measured MAP.[19]

Statistical analysis

The distribution of the haemodynamic and personal variables was assessed using the D'Agostino–Pearson test. Data are expressed as mean ± SD or as median [IQR] as appropriate. Haemodynamic and personal variables were compared by using the unpaired (Mann–Whitney) and paired (Wilcoxon) tests, as required. The proportions of responders/nonresponders were compared using the χ^2 or Fisher exact test, as appropriate.

Within responder and nonresponders groups, data from PPV, CCE, arterial elastance and SAP-P_{dic} were averaged over a 30-s period at baseline and at 1, 2, 3, 4, 5, 10, 15 and 30 min and compared with baseline using the analysis of variance for repeated measurements with Bonferroni *post hoc* (for the normally distributed data), or the Friedman test followed by Dunn's test for multiple comparisons (for the nonparametric data).

The fluid challenge was assessed by evaluating the haemodynamic data before, during the fluid challenge, and 10 (early fluid responsiveness) or 30 min (late fluid responsiveness) after its start. An increase in stroke volume index (SVI) at least 10% was applied to define the responders; when SVI changes was below 10%, the patients were considered 'nonresponders'. A two-step statistical approach was used to define the best model to predict the fluid responsiveness.

(1) A univariable logistic regression model to test the association of the considered haemodynamic variables (PPV, CCE, arterial elastance and SAP-P_{dic}) with the primary outcome (fluid responsiveness at 10th minute). A multivariable analysis incorporating the significant ($P < 0.05$) variables was then performed (at baseline, 1, 2, 3, 4, 5 min), after testing the colinearity and interactions.
(2) A Hosmer and Lemeshow test was calculated to evaluate goodness of fit for the logistic regression model and the receiver operating characteristic (ROC) curve standard error (SE) analysis evaluated the performance of predictive items for fluid challenge response (Y = dependent variable = SVI increased by ≥10%) 10 min (Y_{10}) after challenge. The absence of a significant increase in the likelihood value after omission of each of the remaining variables was checked.

The same approach was used to define the best model to predict late fluid responsiveness (secondary outcome, Y = dependent variable = SVI increased by ≥10%; Y_{30}). For this purpose, only the subgroups of patients classified as responders or nonresponders at both 10 and 30 min were tested, excluding the patients who changed their classification between 10 and 30 min.

Cut-off values for all the statistically significant ROC curves were chosen with the highest Youden index. The relationship between SVI changes after fluid challenge and the expected arterial elastance reduction in fluid responders were tested with the Spearman rank method.

The sample size of the study was calculated by comparison of the predicted area under the ROC curves (AUC).[20] We compared the expected AUCs for the logistic model and baseline PPV. The reported AUC of PPV in mixed ICU patients ranged between 0.51 and 0.72.[15,21,22] We, therefore, predicted an AUC of 0.65 for PPV, which had to improve to 0.85 for the tested model, with a ratio of 1 : 2 between nonresponders and responders. A sample size of 80 patients was calculated (5% type 1 error rate; 90% power).

Statistical analyses were conducted using SPPS version 20.0 (SPSS, Inc., Chicago, Illinois, USA), Prism6 (GraphPad Software; La Jolla, California, USA) and MedCalc (software 12.5; Mariakerke, Belgium). For single comparisons, P values less than 0.05 were considered statistically significant.

Results

From July 2017 to March 2018, 121 adult ICU patients were enrolled and 85 were included in the final analysis (Fig. 1). Personal data, sedation, vasopressor support, ventilation and source of haemodynamic instability are shown in Table 1. Personal data were similar between groups. Twenty-eight volume responders (68.2%) vs. 26 volume nonresponders (59.1%) were receiving controlled ventilatory support, the remaining being under partial ventilatory support. Vasopressors were used in 30.8% of responders and 32.9% nonresponders ($P = 0.79$). Eleven responders vs. 14 nonresponders ($P = 0.64$) were not receiving any sedation.

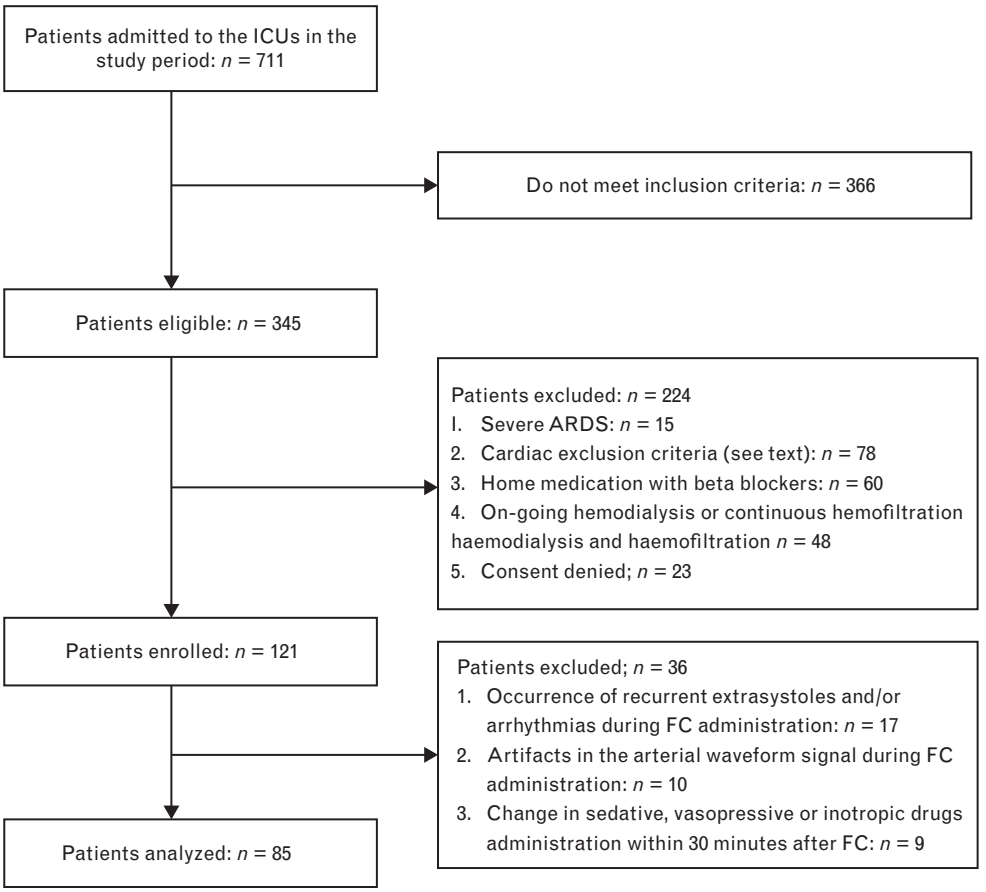
Haemodynamic effect of fluid challenge

Overall, 41/85 (48.2%) were fluid responsive and they had a lower baseline value for cardiac index (*CI*) and SVI as compared with the nonresponders, with a higher baseline arterial elastance and PPV. In these patients, in addition to increases in SVI and *CI*, the fluid challenge increased SAP, P_{dic} and CCE, with a concomitant reduction in arterial elastance, heart rate, PPV and stroke volume variation (Table 2). In the nonresponders, the fluid challenge significantly increased only the pressure values; SAP and P_{dic} (Table 2). Baseline values of all the considered haemodynamic variables poorly predicted early fluid responsiveness (Table S1 in the Supplemental Digital Content, http://links.lww.com/EJA/A351). At baseline, a PPV of 14.2%, as single predictor, accurately estimated fluid responsiveness after 10 min in 68.2% of patients (51/85) with an AUC (SE) of 0.69 (0.06), a sensitivity of 73.1% [95% confidence interval (CI) 57.0 to 85.7%] and a specificity of 65.9 (95% CI 50.0 to 79.5%).

Effect of fluid challenge on arterial elastance

An inverse linear correlation between ΔSVI and Δarterial elastance after the fluid challenge was observed at 5 min

Fig. 1. Flow diagram of the study



(r −0.65, 95% CI −0.77 to −0.47; $P < 0.000$) at 10 min (r −0.62, 95% CI −0.76 to −0.44; $P < 0.0001$) and at 30 min (r −0.57, 95% CI −0.72 to −0.37; $P < 0.0001$) (Fig. 2).

Factors associated with fluid responsiveness at 10 min

To detect potential early predictors among variables used for univariate analysis at 10 min, the model was built to include data collected at baseline and at 1, 2, 3, 4 and 5 min. The best-fitting model associated with response to fluid challenge included baseline PPV, Δarterial elastance at 1 min and ΔCCE and $\Delta\text{SAP-P}_{dic}$ at 5 min. The AUC (SE) was 0.87 (0.04) and the Hosmer–Lemeshow goodness-of-fit χ^2 was 5.78 (df = 8, $P = 0.67$). The model equation was:

$$Y_{10} = 0.113 + 1.088 \times \text{PPV}_{\text{baseline}} + 1.005 \times \Delta\text{CCE}_{\text{baseline}-5\,\text{min}} + 0.902 \times \Delta\text{SAP-P}_{\text{dic baseline}-5\,\text{min}} + 1.009 \times \Delta\text{Ea}_{\text{baseline}-5\,\text{min}}$$

Y_{10} = SVI increased by at least 10% after the fluid challenge at 10 min (early fluid responsiveness).

At the 5th minute, this model adequately classified 86.0% of the patients (80.5% responders vs. 90.7% of nonresponders). Twelve of 85 patients (14.1%) were misclassified (eight responders and four nonresponders). The AUC of each variable included in the model is reported in the Table S2, in the Supplemental Digital Content, http://links.lww.com/EJA/A351.

Factors associated with fluid responsiveness at 30 min

The selected subgroup of 65 patients having a coherent response to the fluid challenge at 10 and 30 min (30 responders and 35 nonresponders) were used to establish the best predicting model for the response at 30 min. The best-fitting model included ΔPPV, ΔCCE and $\Delta\text{SAP-P}_{dic}$ at 5 min and Δarterial elastance at 10 min. The AUC was 0.94 (0.03) and the Hosmer–Lemeshow goodness-of-fit χ^2 test was 0.83 (df = 7, $P = 0.99$). The following formula

Table 1 Patient characteristics

General characteristics	Responders, *n*=41	Nonresponders, *n*=44	*P* value
Age (year)	62 ± 17	63 ± 16	0.84
Sex (M/F)	19/22	27/17	0.19
BMI ($kg\,m^{-2}$)	25 ± 3	25 ± 4	0.35
SAPS II	40 ± 19	38 ± 14	0.50
SOFA	6 [5 to 8]	6 [4 to 8]	0.89
Temperature (°C)	36.5 ± 1.0	36.5 ± 0.9	0.92
Fluid balance at enrolment (ml)	340 ± 1620	620 ± 1504	0.40
RASS	−3.0 [−4.0 to −2.0]	−3.0 [−4.0 to −1.0]	0.36
Propofol (*n*; $mg\,kg^{-1}\,h^{-1}$)	26; 1.2 ± 0.4	29; 1.4 ± 0.1	0.12
Remifentanil (*n*; $\mu g\,kg^{-1}\,min^{-1}$)	27; 0.06 [0.05 to 0.07]	23; 0.06 [0.05 to 0.1]	0.15
Norepinephrine (*n*; $\mu g\,kg^{-1}\,min^{-1}$)	25; 0.0 [0.0 to 0.25]	28; 0.0 [0.0 to 0.23]	0.88
Ventilation			
Totally controlled ventilatory support, *n* (%)	28 (68.2)	26 (59.1)	0.50
PCV, *n* (%)	5 (12.2)	4 (9.1)	0.65
VCV, *n* (%)	23 (56.1)	22 (50.0)	0.88
PEEP (cmH_2O)	8 [5 to 10]	8 [5 to 9]	0.80
V_T ($ml\,kg^{-1}$ ideal body weight)	6.5 ± 1.4	6.3 ± 1.5	0.74
PaO_2/FiO_2 (ratio)	224 ± 84	187 ± 47	0.06
RR (bpm)	16 ± 3	17 ± 4	0.25
HR/RR ratio	5.7 [4.0 to 6.8]	4.5 [4.2 to 5.3]	0.15
Partially controlled ventilatory support, *n* (%)	13 (31.8)	18 (40.9)	0.50
PSV, *n* (%)	13 (31.8)	18 (40.9)	0.50
PEEP (cmH_2O)	7.2 ± 2.8	7.8 ± 2.1	0.40
Pressure support (cmH_2O)	9.2 ± 3.5	8.2 ± 2.2	0.33
V_T ($ml\,kg^{-1}$ ideal body weight)	6.4 ± 1.3	6.7 ± 2.5	0.65
PaO_2/FiO_2 (ratio)	186 [172 to 233]	190 [159 to 260]	0.78
RR (bpm)	20 ± 6	21 ± 5	0.59
HR/RR ratio	4.9 ± 1.3	4.7 ± 1.1	0.64
Source of haemodynamic instability			
Sepsis/Septic shock, *n* (%)	23 (56.0)	26 (59.1)	0.82
Haemorrhagic shock, *n* (%)	5 (12.2)	3 (6.8)	0.47
Trauma, *n* (%)	5 (12.2)	5 (11.3)	0.98
Vasoplegic shock/SIRS, *n* (%)	8 (19.6)	10 (18.1)	0.79

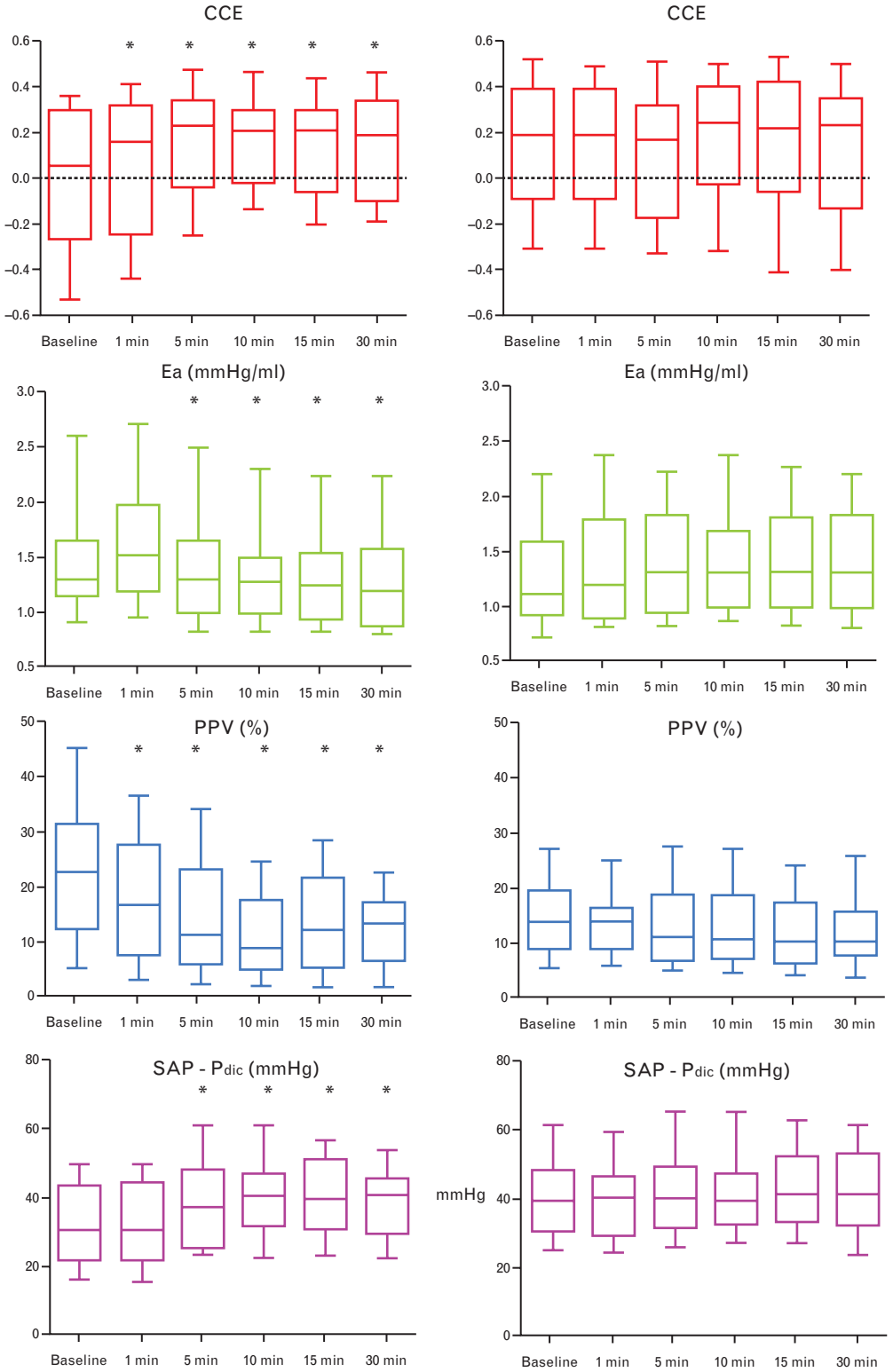
Data presented as mean ± SD or median [IQR], as appropriate. Fluid balance refers to the 24 h before fluid challenge administration. HR, heart rate; PaO_2/FiO_2, arterial partial pressure of oxygen/fraction of inspired oxygen; PCV, pressure-controlled ventilation; PEEP, positive end-expiratory pressure; PSV, pressure support ventilation; RASS, Richmond agitation-sedation scale; RR, respiratory rate; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; VCV, volume-controlled ventilation; V_T, tidal volume.

Table 2 Effects of fluid challenge on haemodynamic values in volume responders (*n*=41) and volume nonresponders (*n*=44) after 10 min

Haemodynamic variables	Pre challenge	Post challenge	Pre challenge comparison (*P* value)	Post challenge comparison (*P* value)	Pre–post challenge comparison (*P* value)
SAP (mmHg) responders	90 ± 18	104 ± 17	0.11	0.75	<0.0001
Nonresponders	98 ± 23	103 ± 23			0.01
P_{dic} (mmHg)					
Responders	60 ± 14	66 ± 15	0.99	0.27	<0.0001
Nonresponders	60 ± 16	62 ± 15			0.02
CI ($l\,min^{-1}\,m^{-2}$)					
Responders	1.9 ± 0.37	2.4 ± 0.51	0.02	0.005	<0.0001
Nonresponders	2.2 ± 0.44	2.1 ± 0.48			0.40
SVI ($ml\,m^{-2}$)					
Responders	21 [16 to 28]	27 [23 to 36]	0.04	0.09	<0.0001
Nonresponders	26 [19 to 32]	26 [18 to 32]			0.34
HR (bpm)					
Responders	91 ± 20	87 ± 19	0.27	0.75	0.02
Nonresponders	86 ± 17	86 ± 17			0.80
CCE (−1/1)					
Responders	0.07 [−0.27 to 0.27]	0.2 [−0.03 to 0.31]	0.14	0.98	<0.0001
Nonresponders	0.15 [−0.09 to 0.33]	0.16 [−0.07 to 0.35]			0.73
Ea ($mmHg\,ml^{-1}$)					
Responders	1.5 [1.2 to 1.9]	1.2 [1.0 to 1.5]	0.04	0.53	<0.0001
Nonresponders	1.2 [0.9 to 1.6]	1.3 [1.0 to 1.7]			0.05
PPV (%)					
Responders	21.6 [13.1 to 27.4]	9.0 [5.05 to 18.9]	0.0007	0.69	<0.0001
Nonresponders	13.0 [8.3 to 16.9]	10.1 [6.2 to 19.0]			0.48
SVV (%)					
Responders	15.8 [10.3 to 20.8]	12.2 [7.2 to 16.6]	0.31	0.47	0.02
Nonresponders	12.7 [7.2 to 22.1]	12.6 [8.1 to 17.1]			0.65

Data presented as mean ± SD or median [IQR] as appropriate. Data were compared with Wilcoxon or Mann–Whitney tests, as required. AUC, area under the curve; CCE, cardiac cycle efficiency; *CI*, cardiac index; Ea, arterial elastance; HR, heart rate; P_{dic}, dicrotic pressure; PPV, pulse pressure variation; SAP, systolic arterial pressure; SE, standard error; SVI, stroke volume index; SVV, stroke volume variation.

Fig. 2. Changes of the variables included in the multivariable analysis (cardiac cycle efficiency, arterial elastance, pulse pressure variation and systolic–dicrotic pressure) during fluid challenge in responders (left panels) and nonresponders (right panels) from baseline to minute 30



Box-and-whisker plots represent the mean (10th to 90th percentile) of the included variables at each predefined time-points. Cardiac cycle efficiency and systolic–dicrotic pressure progressively increased while pulse pressure variation and arterial elastance decreased in responders. Nonresponders did not show any significant variation of the considered variables. $*P < 0.05$; for the exact P values please refer to Table 3. CCE, cardiac cycle efficiency; Ea, arterial elastance; PPV, pulse pressure variation; SAP-P_{dic}, systolic–dicrotic pressure.

describes this model:

$$Y_{30} = 0.009 + 1.353 \times \mathrm{PPV}_{\mathrm{baseline}} + 0.645 \times \Delta\mathrm{CCE}_{\mathrm{baseline-5\,min}} + 1.034 \times \Delta\mathrm{SAP\text{-}P}_{\mathrm{dic\ \ baseline-5\,min}} + 1.020 \times \Delta\mathrm{Ea}_{\mathrm{baseline-5\,min}}$$

Y_{30} = SVI increased by at least 10% after the fluid challenge at 30 min (late fluid responsiveness).

At the 10th minute, this model identified 92.3% of patients (93.3% of responders and 91.4% of nonresponders) as having a coherent response at 10 and 30 min. Overall, five out of 65 patients were wrongly classified (two responders and three nonresponders). The AUC of the model at 30 min was significantly greater than the AUC of baseline PPV ($P = 0.015$). The AUC of each variable included in the model is reported in Table S2, in the Supplemental Digital Content, http://links.lww.com/EJA/A351. In late responders, the percentage variation of arterial elastance from baseline to 10 min predicted the SV response at 30 min with an AUC of 0.85 (0.05), with 65.7% sensitivity and 83.3% specificity (Fig. S1 in the Supplemental Digital Content, http://links.lww.com/EJA/A351). Considering the cut-offs obtained by the ROC curve analysis of this variable, a 5.5% decrease in arterial elastance at the 10th minute predicted the late fluid responsiveness in more than 90% of patients. Conversely, a 5.5% increase in arterial elastance at the 10th minute predicted unresponsiveness in more than 90% of patients.

Discussion

The current study shows that an approach that uses multiple indices to evaluate the dynamic changes of the determinants of heart function and vascular status can predict the response at 10 and 30 min after a fluid challenge. The debate regarding fluid responsiveness relies on the selection of suitable indices to define a positive response, on the volume and infusion rate required to obtain a response to the challenge, and on the variables that might predict the response and indicate a reduction in fluid administration to nonresponders. In our study, the different baseline values, including PPV, were poor predictors for a response to the fluid challenge in both responders and nonresponders, in keeping with previous studies.[15,16] The reliability of baseline PPV can be enhanced by the use of functional haemodynamic tests, from 'passive leg raising'[23] to the more recent 'tidal volume challenge',[24,25] which are both rarely used clinically[26] and have specific limitations in their clinical applicability.[27] The differences between responders and nonresponders after fluid challenge were observed for PPV, arterial elastance, CCE and SAP-P_{dic}, as we have previously reported in elective neurosurgical patients.[17] In preload-dependent patients, although PPV decreases after fluid challenge in responders, it poorly predicts the response at baseline. The significant changes in arterial elastance, SAP-P_{dic} and CCE might add predictability.

Ability to predict a response to a fluid challenge seems to be achievable earlier than 10 min, as the best multivariable model for prediction included values at baseline, 1 and 5 min. Significantly, a failure to respond to a fluid challenge is associated with a persistent absence of significant changes in variables related to pressure and volume. The model identified 90.9% of the nonresponders, potentially limiting the amount of volume given, and decreasing their cumulative positive fluid balance. By applying this principle in our cohort, potentially some 10 l of crystalloid would not be infused in nonresponders, limiting the risk of accumulated fluid overload.

At the point of completion of the challenge (10 min), responders increased SVI and *CI* as expected, but with a significantly larger fall in arterial elastance compared with the modest changes observed in nonresponders (Table 3 and Fig. 3). Despite a large amount of evidence regarding the method of fluid administration and the bedside assessment of the response to a fluid challenge, the majority of ICU physicians still use an increase in blood pressure (BP) during and after the challenge rather than an increase in SV, to indicate fluid responsiveness.[26] Although hypotension is frequently the trigger for a fluid challenge, BP is not a reliable method of assessing the adequacy of fluid resuscitation.[2] BP can change for a variety of reasons, so using it solely to decide whether to perform a fluid challenges may lead to unnecessary fluid administration.[2]

Significantly, 30 out of 41 volume responders (73.1%) demonstrated a persistent increase in SVI at 30 min after the fluid challenge. Among the hypotheses for this, the arterial elastance variations in responders to the challenge point to a modification in the arterial system. Arterial elastance reduction induced by the challenge may then favour left ventricular ejection facing a reduced arterial load, as suggested by Fig. 2, which shows the correlation between the amplitude of SV increase and the decrease in arterial elastance. When arterial elastance (P_{dic}/SV) was introduced in the proposed predictive models, more than 90% of the patients were suitably classified. Moreover, especially in the subgroup of septic shock patients, norepinephrine infusion may increase cardiac preload and thus SV,[28] having an additive effect on the persistence of the haemodynamic effect of the fluid challenge on the SV.

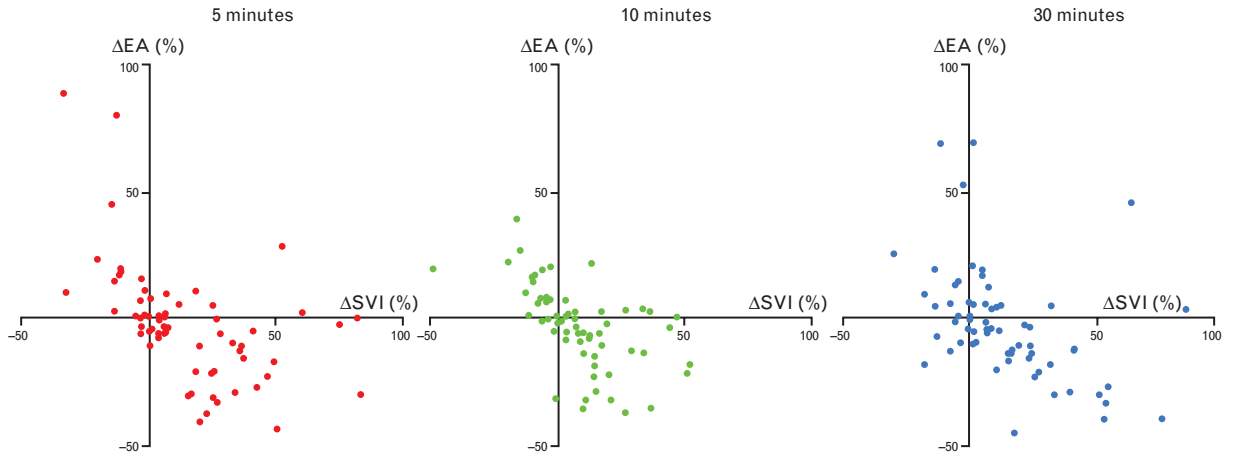
As shown in Table 2, baseline arterial elastance (a net measure of the arterial load)[29,30] was higher in responders compared with nonresponders, and decreased significantly by approximately 20% after the fluid challenge, as previously shown in septic patients.[31] These findings suggest a key role of the reactive vascular components related to recruitment of previously closed vessels, which is a short-term nitric oxide-mediated adaptive

Table 3 Variation of cardiac cycle efficiency, stroke volume index arterial elastance, pulse pressure variation and systolic–dicrotic pressure between baseline values and each of the predefined time-points after fluid challenge in responders and nonresponders

	Responders				Nonresponders			
Variables	**Comparisons**	**Mean (baseline)**	**Mean (min)**	***P* value**	**Comparisons**	**Mean (baseline)**	**Mean (min)**	***P* value**
CCE (−1/1)	Baseline vs. 1 min	−0.01	0.06	≤0.0001	Baseline vs. 1 min	0.16	0.14	NS
	Baseline vs. 2 min	−0.01	0.10	≤0.01	Baseline vs. 2 min	0.16	0.13	NS
	Baseline vs. 3 min	−0.01	0.12	≤0.01	Baseline vs. 3 min	0.16	0.13	NS
	Baseline vs. 4 min	−0.01	0.13	≤0.05	Baseline vs. 4 min	0.16	0.13	NS
	Baseline vs. 5 min	−0.01	0.17	≤0.01	Baseline vs. 5 min	0.16	0.09	NS
	Baseline vs. 10 min	−0.01	0.16	≤0.01	Baseline vs. 10 min	0.16	0.16	NS
	Baseline vs. 15 min	−0.01	0.14	≤0.01	Baseline vs. 15 min	0.16	0.17	NS
	Baseline vs. 30 min	−0.01	0.13	≤0.05	Baseline vs. 30 min	0.16	0.13	NS
Ea (mmHg ml^{-1})	Baseline vs. 1 min	1.64	1.51	NS	Baseline vs. 1 min	1.27	1.36	NS
	Baseline vs. 2 min	1.64	1.51	NS	Baseline vs. 2 min	1.27	1.36	NS
	Baseline vs. 3 min	1.64	1.52	NS	Baseline vs. 3 min	1.27	1.37	NS
	Baseline vs. 4 min	1.64	1.39	≤0.001	Baseline vs. 4 min	1.27	1.37	NS
	Baseline vs. 5 min	1.64	1.43	≤0.01	Baseline vs. 5 min	1.27	1.36	NS
	Baseline vs. 10 min	1.64	1.37	≤0.01	Baseline vs. 10 min	1.27	1.39	NS
	Baseline vs. 15 min	1.64	1.40	≤0.05	Baseline vs. 15 min	1.27	1.41	NS
	Baseline vs. 30 min	1.64	1.34	≤0.0001	Baseline vs. 30 min	1.27	1.41	NS
PPV (%)	Baseline vs. 1 min	23.21	18.30	≤0.01	Baseline vs. 1 min	13.95	14.05	NS
	Baseline vs. 2 min	23.21	15.41	≤0.01	Baseline vs. 2 min	13.95	15.10	NS
	Baseline vs. 3 min	23.21	18.02	NS	Baseline vs. 3 min	13.95	14.39	NS
	Baseline vs. 4 min	23.21	17.27	NS	Baseline vs. 4 min	13.95	14.04	NS
	Baseline vs. 5 min	23.21	14.94	≤0.001	Baseline vs. 5 min	13.95	13.50	NS
	Baseline vs. 10 min	23.21	11.89	≤0.0001	Baseline vs. 10 min	13.95	13.15	NS
	Baseline vs. 15 min	23.21	14.73	≤0.01	Baseline vs. 15 min	13.95	12.19	NS
	Baseline vs. 30 min	23.21	13.18	≤0.001	Baseline vs. 30 min	13.95	12.65	NS
SAP-P_{dic} (mmHg)	Baseline vs. 1 min	31.60	32.63	NS	Baseline vs. 1 min	39.91	39.77	NS
	Baseline vs. 2 min	31.60	34.80	NS	Baseline vs. 2 min	39.91	39.40	NS
	Baseline vs. 3 min	31.60	35.77	NS	Baseline vs. 3 min	39.91	40.43	NS
	Baseline vs. 4 min	31.60	38.37	≤0.01	Baseline vs. 4 min	39.91	40.66	NS
	Baseline vs. 5 min	31.60	38.93	≤0.01	Baseline vs. 5 min	39.91	41.40	NS
	Baseline vs. 10 min	31.60	40.63	≤0.0001	Baseline vs. 10 min	39.91	41.66	NS
	Baseline vs. 15 min	31.60	40.13	≤0.001	Baseline vs. 15 min	39.91	42.80	NS
	Baseline vs. 30 min	31.60	38.03	≤0.01	Baseline vs. 30 min	39.91	42.03	NS

Comparisons between the mean baseline values of the considered variables vs. each minute of assessment after the fluid challenge. For all the comparisons, *P* values refer to the analysis of variance for repeated measures. CCE, cardiac cycle efficiency; Ea, arterial elastance; NS, not significant; PPV, pulse pressure variation; SAP-P_{dic}, systolic–dicrotic pressure.

Fig. 3. Linear correlation between changes in stroke volume index and arterial elastance (Δarterial elastance), after 5 (red), 10 (green) and 30 (blue) min after fluid challenge



mechanism to the downstream dilatation induced by shear stress.[31,32] Moreover, monitoring the adaptive changes of vascular tone during fluid resuscitation would result in better individualisation of fluid therapy, and a reduction in the amount of fluid administered to non-responders.[33,34] Our prediction model might be improved by the addition of an assessment of ventriculo–arterial coupling, as the pressure and SV are defined by the interaction between the heart and the arterial system.

Study limitations

The main limitation of this study is that our model has not been externally validated with a separate set of patients. This first algorithm retrospectively predicted the final effect of the fluid challenge (responder/nonresponder) within the cohort.

A second limitation is that our model is constructed on a predefined volume of fluid that may vary in clinical practice, although our protocol is frequently used.[7] However, the amount and the rate of fluid infused during a fluid challenge affect the proportions of responders and nonresponders.[14,35] Moreover, the type of fluid used could influence the haemodynamic response to the challenge, as the intravascular persistence of colloids could affect the late response to it. These aspects limit the generalisability of our results.

In addition, although the reliability of the MOSTCARE has recently been assessed by a large multicentre study enrolling a mixed group of 400 ICU patients,[18] the use of an uncalibrated tool in haemodynamically unstable critically ill patients is still questionable.[36] The response to a fluid challenge should also be assessed by another calibrated haemodynamic tool to compare the variations in the SV tracked by the MOSTCARE. The reliability of the MOSTCARE relies on the quality of the arterial pressure signal and the physicians involved in this study were highly trained in the quality assessment of arterial pressure waveforms. Finally, the strict selection of our cohort precludes the generalisation of our results to all ICU patients.

Future directions

Recent research showed that fluid challenge causes complex systemic interactions between heart function and vascular response, based on the pharmacodynamic effect on the SV,[14] the persistence of fluid responsiveness[37] and the changes in the arterial elastance during the infusion.[31] If confirmed by larger trials, the integration of haemodynamic signals obtained from cardiac cycles and the vascular response could potentially help guide and tailor fluid therapy, especially to nonresponders for whom a fluid challenge will be stopped early.

Conclusion

In a selected group of haemodynamically unstable ICU patients receiving a standardised fluid challenge, our model built on the basis of a multivariable analysis found that changes in arterial elastance, PPV, SAP-P_{dic} and CCE reliably predicted the early and late response to the challenge.

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