EJA

Eur J Anaesthesiol 2017; **34:**755–763

ORIGINAL ARTICLE

Cardiac cycle efficiency and dicrotic pressure variations: new parameters for fluid therapy

An observational study

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BACKGROUND During a fluid challenge, the changes in cardiac performance and peripheral circulatory tone are closely related to the position of the ventricle on the Frank–Starling curve. Some patients have a good haemodynamic response to a fluid challenge, others hardly any response. The early haemodynamic effects of a fluid challenge could predict the final response before the entire fluid volume has been administered.

OBJECTIVE To assess whether a multivariate logistic regression model, including pulse pressure variation (PPV), cardiac cycle efficiency (CCE), arterial elastance and the difference between the dicrotic pressure and both systolic and mean arterial pressure ($SAP - P_{dic}$ and $MAP - P_{dic}$) can predict cardiac responsiveness early during a fluid challenge in comparison with the standard procedure described elsewhere.

DESIGN Observational study.

SETTING Elective surgical patients undergoing laparotomy, enrolled in two Italian University Hospitals.

PATIENTS Fifty adult surgical patients, ventilated with a lung protective strategy, were enrolled and data from 46 were analysed.

INTERVENTIONS A fluid challenge consisting of 500 ml of crystalloid infused over 10 min.

MAIN OUTCOME MEASURES AND ANALYSIS The changes in CCE, arterial elastance, $SAP - P_{dic}$ and $MAP - P_{dic}$ were compared using analysis of variance. A multivariate logistic regression analysis utilising baseline values and the first minute measuring a variation statistically significant for the considered variables.

RESULTS At baseline, PPV correctly identified 70% of patients (89% of non-responders; 42% of responders). The model, including baseline PPV, ΔCCE and $\Delta SAP - P_{dic}$, P_{dic}, correctly identified the efficiency of fluid challenge in 87% of patients (84.2% of responders; 92.5 of non-responders) after 5 min from fluid challenge infusion.

CONCLUSION In this pilot study conducted in a population of surgical patients mechanically ventilated with a V_T less than 8 ml kg^{-1}, a dynamic model of fluid challenge assessment, including PPV, ΔCCE and $\Delta SAP - P_{dic}$, enhances the prediction of fluid challenge response after 5 min of a 10-min administration.

TRIAL REGISTRATION ACTRN12616001479493.

Published online 19 June 2017

Introduction

Dynamic indices, such as systolic pressure variation and pulse pressure variation (PPV) (both derived from arterial waveform analysis) and stroke volume (SV) variation (derived from pulse contour analysis), have been shown to reliably predict fluid responsiveness during controlled mechanical ventilation.[1,2] Among these indices, when

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DOI:10.1097/EJA.0000000000000661

specific conditions are acknowledged, the PPV resulted in the most sensitive and specific index.[1]

However, in ICU patients who often need lung protective ventilation strategies, the accuracy of PPV in predicting fluid responsiveness is limited as the required conditions are rarely met.[3] Among these conditions, a low tidal volume ($V_T < 8\,ml\,kg^{-1}$) and high respiratory rate are known to affect PPV reliability,[4] and these patterns are now recommended as a beneficial strategy for ventilation during surgery.[5,6] PPV is automatically calculated and displayed by many of the available anaesthetic multiparametric monitors and has been used to guide goal-directed therapy algorithms in surgical patients with the purpose of maintaining PPV below a threshold ranging from 10 to 15%.[7–9]

As often baseline PPV cannot predict the outcome of fluid challenge reliably [i.e. an increase in cardiac index (*CI*) above a predetermined cut-off], the only way to evaluate preload dependence is to infuse the entire volume, usually consisting in 500 ml.[10] Depending on the position of the ventricular muscle function on the Frank–Starling curve, a fluid challenge may test either the steep part of the curve (when an increase in preload increases SV or cardiac output), or the flat part of the curve (when increase in preload will not increase *CI*).[11,12] In addition, fluid administration modifies the dynamic coupling between the left ventricle (LV) and the arterial system.[13,14] Instead of using the static baseline PPV, it is possible that the outcome of a fluid challenge could be evaluated dynamically, and, by considering both the cardiac efficiency and the peripheral response, this might predict the response to a fluid challenge, thus reducing the amount of infused fluids and thereby the risk of iatrogenic fluid overload.

The MostCare system, using a Pressure Recording Analytical Method (PRAM; Vygon Health, Padua, Italy), provides a measurement of cardiovascular performance status called cardiac cycle efficiency (CCE),[15] and two indices related to the vascular changes – the arterial elastance and the dicrotic arterial pressure (P_{dic}). The cardio-vascular system maintains homeostasis at different levels of energy expenditure as a result of the simultaneous interactions between heart function and the arterial system, venous return and the pulmonary circulation, and CCE is a promising parameter in assessing this.[15] Arterial elastance and P_{dic} variations are closely related to ventricular–arterial coupling, as recently showed in a clinical study enrolling septic patients.[16] In the present study, we tested both the difference between mean arterial pressure (MAP) and P_{dic} ($MAP - P_{dic}$)[16] and also a novel index: the difference between systolic arterial pressure (SAP) and P_{dic} ($SAP - P_{dic}$).

The aim of the present pilot study was to assess whether the changes in PPV, CCE, arterial elastance, P_{dic}, $MAP - P_{dic}$ and $SAP - P_{dic}$ during a fluid challenge could predict the outcome of the fluid challenge better than the standard assessment of baseline PPV.

Materials and methods

Patients

The study was performed in the operating rooms of the University Hospital 'Maggiore della Carità' in Novara and of the University Hospital 'Careggi' in Florence, in accordance with the principles outlined in the Declaration of Helsinki. The study was approved by the institutional ethics committees and registered (ACTRN12616001479493). Patient informed consent was obtained according to the Italian regulations. Patients were enrolled from December 2014 to December 2015 and the protocol was a part of routine clinical care (no randomisation).

The inclusion criteria were age at least 18 years; elective open abdominal surgery under general anaesthesia with mechanical ventilation using a volume controlled mode ($V_T < 8\,ml\,kg^{-1}$ ideal body weight); and the use of invasive blood pressure monitoring. Exclusion criteria were American Society of Anesthesiologists physical status classification (ASA) more than 3; a history of cardiac arrhythmia, known LV ejection fraction (LVEF) less than 30%,[17] or right ventricular dysfunction (systolic peak velocity of tricuspid annular motion $<0.16\,m\,s^{-1}$),[17] moderate-to-severe valvular heart disease,[18] or intra-cardiac shunt; chronic medication with beta-blockers; and any cause and type of arterial wave form distortion.[19]

Study protocol and measurements

Before induction of general anaesthesia, a 20-guage cannula was inserted into the radial artery and connected to the haemodynamic monitoring and data acquisition device (MostCare). A square-wave pressure test (bolus of 0.9% saline injected) was used in all patients to ensure that under-damping or over-damping of the pressure signal was excluded before starting the study protocol.[19]

The data acquired were saved to an external data card and imported into a spreadsheet by dedicated software (MostCare Data Card Reader 4.0.11). As recommended by manufactures the acquisition software was set to average all haemodynamic parameters over a 30-s period. The MostCare algorithm calculates SV and *CI* on a beat-by-beat basis by analyses of the systolic portion of the arterial wave form (sampling rate = 1000 Hz), without the need for external or internal calibration.[20,21] In addition, MostCare extracts SAP, diastolic arterial pressure, MAP and P_{dic} directly from the arterial pressure waveform and calculates the PPV and $MAP - P_{dic}$. MostCare evaluates the arterial pressure wave to identify the 'points of instability'. These points are distributed along the wave profile and represent the interaction between forward waves (due to cardiac systole) and backward waves coming from the periphery. Analysis of the waveform profile estimates the vascular impedance and the various

haemodynamic parameters. MostCare calculates arterial elastance automatically as the ratio between P_{dic}/SV, whereas SAP – P_{dic} was calculated *post hoc*.

CCE describes the haemodynamic performance in terms of energy expenditure and varies from −1 to +1, with a negative value indicating unfavourable energy expenditure conditions and positive values indicating beneficial energy expenditure conditions.[15] CCE is a quantitative measurement deriving from the dynamic interplay of all factors involved in the homeostasis of a single heartbeat and describes the cardiac haemodynamic performance, being the ratio between haemodynamic work and energy expenditure.[15] CCE is calculated as $CCE = \left(W_{sys}/W_{beat}\right) \times K(t)$, where W_{sys} and W_{beat} are power functions calculated from the systolic pressure wave and the complete cardiac cycle pressure wave, respectively, and $K(t)$ is defined as the ratio between the mean pressure expected and the mean pressure measured.[15]

Anaesthesia was maintained by an intravenous infusion of propofol (1.5 to 3.0 mg kg^{-1} h^{-1}) and remifentanil (0.1 to 0.5 μg kg^{-1} min^{-1}), according to clinical needs. The depth of anaesthesia was monitored with the bispectral index (BIS monitor; Covidien Medical, Boulder, Colorado, USA), and was targeted to the range 40 to 60.

The fluid challenge consisted of 500 ml of crystalloid solution (either 0.9% saline or Ringer's solution) infused over 10 min[22] and was utilised to improve haemodynamic instability according to the decision of the attending anaesthetist. The latter was unaware of the MostCare measurements. The start of the fluid challenge was recorded by the MostCare acquisition software when a flag-button included on the monitor was pressed. To avoid haemodynamic interferences caused by the induction of anaesthesia, all the fluid challenges were performed after a period of at least 15 min of haemodynamic stability. Only the first fluid challenge for each enrolled patient was considered. As our infusion pumps are limited to a maximum of 1200 ml h^{-1}, corresponding to 200 ml in 10 min, the infusion rate was standardised, as previously described, keeping the infusion bag 100 cm above the tip of the cannula and using a standard infusion set.[23] We infused the fluid challenge by means of 20-guage venflon cannula (Becton Dickinson; Via Enrico Cialdini, 16, 20161 Milano, Italy), which allows a flow of approximately 54 ml min^{-1}.[23] Patients were considered as responders to a fluid challenge if the *CI* increase was at least 15%.[24] All fluid challenges were timed and only those completed within the range of 9 to 11 min were considered for analysis.

Statistical analysis

The normality of data distribution was evaluated by means of the Kolmogorov–Smirnov test. All the variables were averaged over 1 min and average values were used for all comparisons. Receiver operating characteristic (ROC) curves [95% confidence interval (CI)] were constructed for percentage changes of PPV between baseline mean value vs. the response to the fluid challenge.

The variations of CCE and MAP – P_{dic}, arterial elastance and SAP – P_{dic} were compared using analysis of variance (ANOVA). For non-parametric data the Friedman test followed by Dunn multiple comparisons and for parametric data ANOVA with Bonferroni post-hoc tests adjusting for multiple comparisons were used. The Greenhouse–Geisser correction was used when sphericity could not be assumed.

A *t* test or χ^2 test (or Fisher's exact test, if indicated) was used to compare quantitative and qualitative variables, respectively. The prediction of fluid responsiveness was studied by constructing a multivariate logistic regression mathematical model.

We focused the multivariate analysis on the models, including baseline PPV and the variation of CCE, arterial elastance, MAP – P_{dic} and SAP – P_{dic} during the first 5 min of fluid challenge administration. We tested the models, including baseline PPV and the first minute, indicating a variation statistically significant for all the considered variables (ΔCCE, ΔEa, ΔMAP – P_{dic} and ΔSAP – P_{dic}). A Hosmer and Lemeshow test was calculated to evaluate the model fit. Statistical analyses were conducted using SPPS version 20.0 (SPSS, Inc., Chicago, Illinois, USA). For all comparisons, we considered significant *P* values less than 0.05.

Results

We enrolled 50 consecutive patients, 30 and 20 in Novara and Florence, respectively. However, the predetermined criteria for fluid challenge administration were not followed in four patients, and these results were excluded from the data analysis (Fig. 1). Volume expansion induced an increase in *CI* at least 15% in 19 of these 46 patients (41.3%). Demographic characteristics, comorbidities, ASA physical status classification or surgical procedures performed were comparable between responders and non-responders (Table 1).

As shown in Table 2, the baseline values of heart rate (HR), PPV, CCE and SAP – P_{dic} were significantly different between responders and non-responders. Also depicted in Table 2, in responders the fluid challenge significantly increased CCE, MAP and SAP – P_{dic} and decreased PPV and arterial elastance, whereas there was no effect in any of the variables in non-responders. After 5 min of infusion, the fluid challenge significantly increased CCE and SAP – P_{dic} and reduced PPV, arterial elastance and MAP – P_{dic} in responders only (Table 3 and Fig. 2).

The baseline area under the curve (AUC) of PPV was 0.80 (95% CI 0.66 to 0.94; sensitivity 80%, specificity

Fig. 1

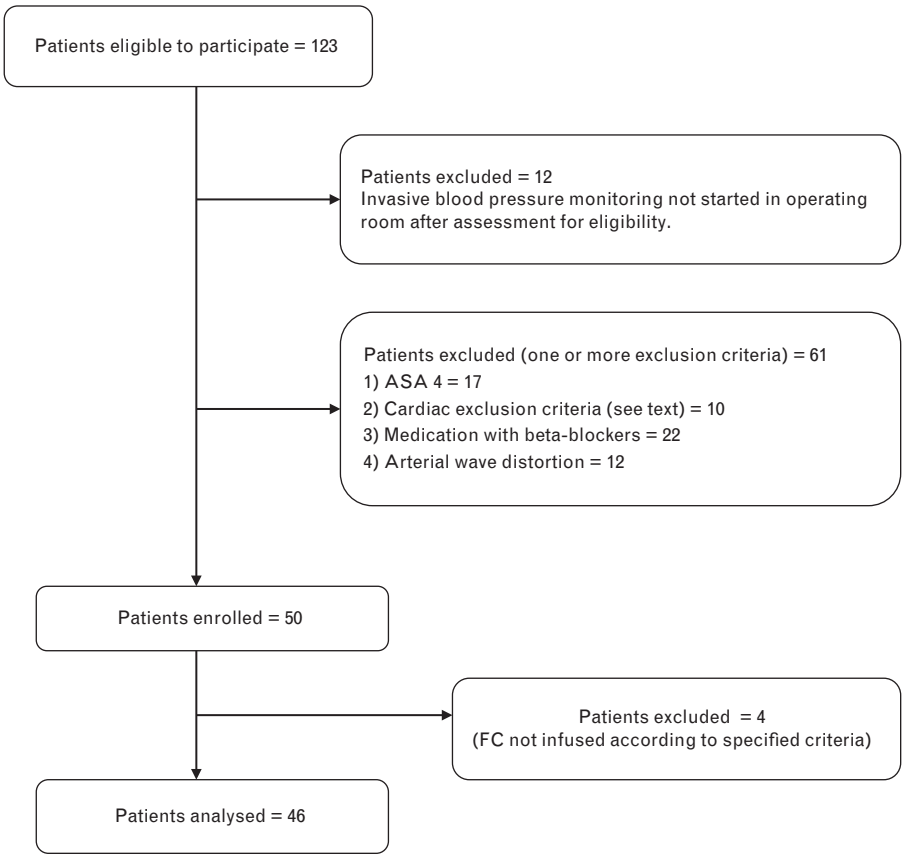


Diagram depicting the flow of patients in the study. ASA, American Society of Anesthesiologists physical status classification; FC, fluid challenge.

Table 1 **Patients characteristics at enrolment**

	Responders, $n = 19$	Non-responders, $n = 27$	*P* value
General characteristics			
Age (years)	68 ± 14	66 ± 11	0.68
Sex (M/F)	9/11	14/12	0.75
BMI (kg m^{-2})	24.1 ± 3.1	24.3 ± 2.9	0.66
ASA 1/2/3, *n* (%)	4/6/9 (21, 32, 47)	6/10/11 (22, 37, 41)	
Ventilator settings (baseline)			
PEEP (cmH_2O)	5.5 ± 1.6	5.8 ± 0.9	0.45
V_T (ml kg^{-1} ideal body weight)	6.8 ± 1.1	6.7 ± 0.7	0.55
PaO_2/FiO_2 (ratio)	415 ± 38	394 ± 40	0.06
Respiratory rate (breaths min^{-1})	12.3 ± 1.0	12.0 ± 1.2	0.53
Chronic disease			
Coronary heart disease	11 (55)	14 (54)	0.94
Hypertension	17 (85)	20 (77)	0.88
Peripheral artery disease	10 (50)	13 (50)	0.90
COPD/asthma	8 (40)	10 (38)	0.99
Cerebrovascular disease	7 (35)	7 (27)	0.62
Diabetes mellitus	6 (30)	8 (31)	0.88
Chronic kidney disease	3 (15)	5 (19)	0.67
Malignancy	12 (60)	12 (46)	0.43
Age > 70 years	12 (60)	11 (42)	0.30
Surgical procedures			
Colo-rectal surgery	12 (60)	15 (58)	0.15
Gastric surgery	2 (10)	3 (11.5)	0.48
Intra-abdominal vascular surgery	2 (10)	3 (11.5)	0.48
Other intra-abdominal surgery	4 (20)	5 (19)	0.32

Values are presented as number (percentage) or mean ± SD. ASA, American Society of Anesthesiologists physical status classification; COPD, chronic obstructive pulmonary disease; FiO_2, fractional inspired oxygen concentration; PaO_2, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure; V_T, tidal volume.

Table 2 Effects of fluid challenge on haemodynamic parameters in responders ($n = 19$) and non-responders ($n = 27$)

	Pre-FC	Post-FC	*P* value R vs. NR at baseline	*P* value pre-FC vs. post-FC
CI (l min^{-1} m^{-2})				
R	2.2 ± 0.4	3.0 ± 0.5	0.14	<0.0001
NR	2.4 ± 0.3	2.4 ± 0.2		0.98
MAP (mmHg)				
R	70 ± 12	80 ± 14	0.51	0.0006
NR	73 ± 15	76 ± 17		0.39
HR (beats min^{-1})				
R	74 ± 13	69 ± 11	0.01	0.20
NR	63 ± 17	62 ± 14		0.82
PPV (%)				
R	20.3 ± 10.3	12.3 ± 8.3	0.003	0.01
NR	9.7 ± 6.7	8.4 ± 6.1		0.43
CCE (−1 to +1)				
R	−0.08 ± 0.30	0.05 ± 0.28	0.002	0.0006
NR	0.25 ± 0.32	0.14 ± 0.34		0.19
Ea (mmHg ml^{-1})				
R	2.4 ± 0.9	2.1 ± 0.8	0.11	0.002
NR	1.9 ± 0.9	2.0 ± 0.9		0.65
MAP − P_{dic} (mmHg)				
R	−0.7 ± 5.5	−0.3 ± 5.1	0.66	0.99
NR	1.8 ± 9.8	1.4 ± 10.1		0.45
SAP − P_{dic} (mmHg)				
R	28 ± 9	37 ± 13	0.003	0.04
NR	40 ± 14	40 ± 15		0.92

Data are expressed as means ± SD. CCE, cardiac cycle efficiency; *CI*, cardiac index; Ea, arterial elastance; Ea_{dyn}, dynamic arterial elastance; FC, fluid challenge; HR, heart rate; MAP, mean arterial pressure; MAP − P_{dic}, mean − dicrotic pressure; NR, non-responders; PPV, pulse pressure variation; R, responders; SAP − P_{dic}, systolic − dicrotic pressure.

85%). At baseline, PPV correctly identified 70.0% of patients (89% of non-responders and 42% of responders) with a threshold value at 12.7%. Baseline AUC of CCE was 0.77 (95% CI 0.63 to 0.90; sensitivity 56%, specificity 95% with a threshold value at 0.26). Baseline AUC of SAP − P_{dic} was 0.75 (95% CI 0.61 to 0.89; sensitivity 40%, specificity 95% with a threshold value at 40.0). Baseline AUCs of arterial elastance (0.59) and MAP − P_{dic} (0.54) were very small.

As CCE significantly increased in responders after 5 min, all the multivariate models were constructed, including baseline PPV, ΔCCE, ΔEa and ΔSAP − P_{dic}, between baseline and minute 5. The model, including ΔMAP − P_{dic}, was not constructed because the fluid challenge did not modify ΔMAP − P_{dic} after minute 1 (Table 3).

The model, including baseline PPV, ΔEa and ΔCCE, showed an AUC of 0.88, a Hosmer and Lemeshow value of 0.05 and correctly identified the efficacy of the fluid challenge in 80.4% of patients (73.7% of responders and 85.2% of non-responders). The comparison between the AUC of this model and the AUC of the baseline PPV alone was not statistically significant ($P = 0.13$).

The model, including baseline PPV, ΔSAP − P_{dic} and ΔCCE, showed the greatest AUC (0.92), a Hosmer and Lemeshow value of 0.91 and correctly identified the efficacy of the fluid challenge in 87% of patients (84.2% of responders and 92.5 of non-responders). The comparison between the AUC of this model and the AUC of the baseline PPV was statistically significant ($P = 0.03$). The following formula describes this latter model:

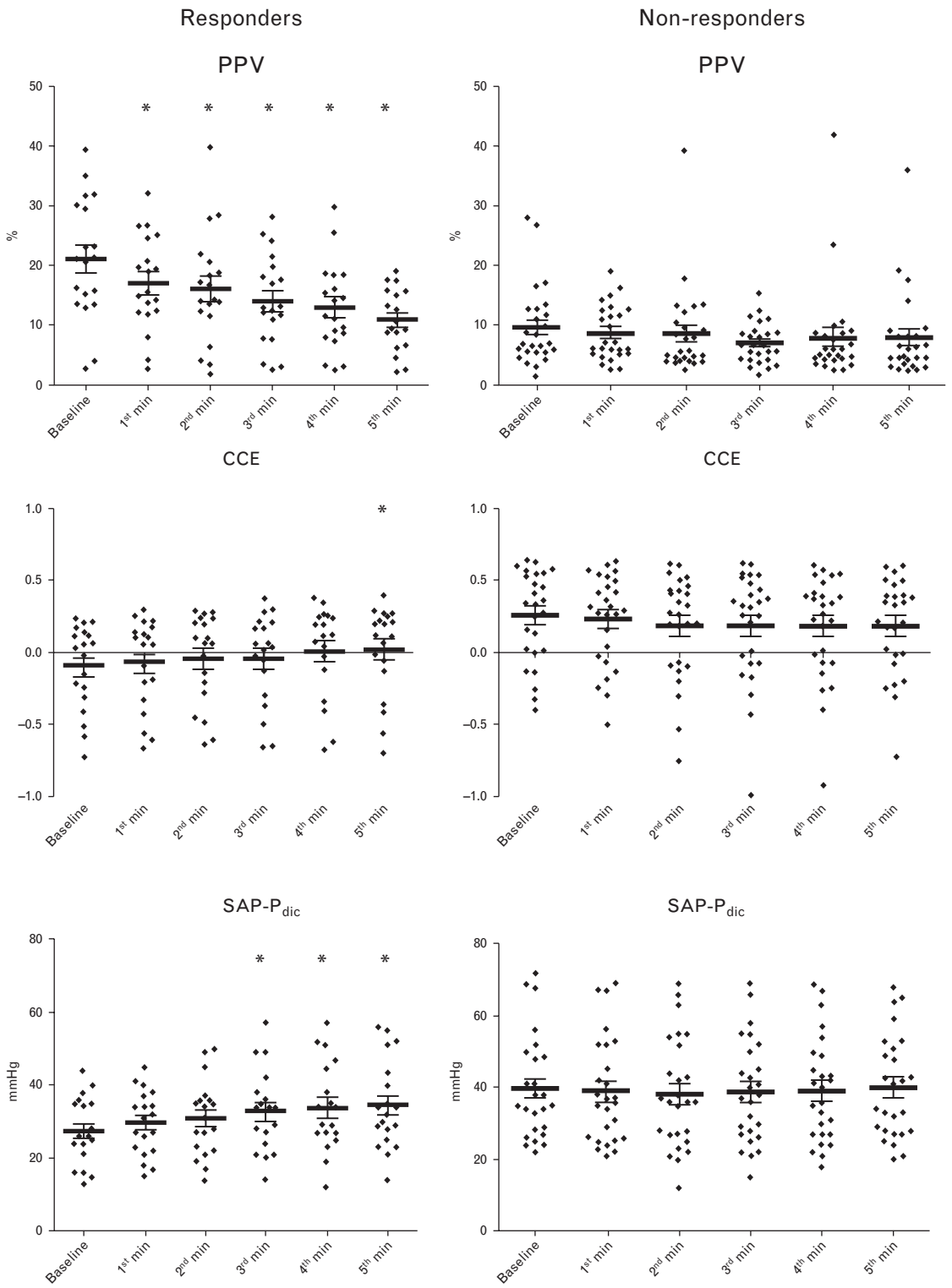
$$0.039 + (1.042 \times \Delta(\mathrm{SAP} - \mathrm{P_{dic\ 5\,min}})) + (1.278 \times \Delta\mathrm{CCE_{5\,min}}) + 1.159 \times \mathrm{PPV_{baseline}}$$

Discussion

Compared with the baseline haemodynamic variables in a population of surgical patients, a fluid challenge reduced PPV and increased CCE and SAP − P_{dic} in patients who responded to the fluid challenge with an increase in *CI* at least 15%. A multivariate model, including these three variables, reliably predicts the outcome of fluid challenge in a population of surgical patient ventilated with a V_T less than 8 ml kg^{-1}.

The reliability of PVV to predict fluid responsiveness is reduced by several clinical conditions, patient–ventilator asynchronies[25] or spontaneous respiratory efforts,[2] and a low respiratory rate/V_T ratio.[26] Although these clinical conditions are quite common in ICU patients, none were present in the patients whose data was analysed in this study. A protective lung strategy in patients with volume-controlled ventilation is known to affect PPV reliability.[4] Recently, Cannesson *et al.*[27] found that in surgical patients ventilated with an average V_T of 7.9 ± 1.3 ml kg^{-1} 1 up to 25% had a PPV between 9 and 13%, a range of values that usually cannot help to predict fluid responsiveness (the so-called grey zone). However, in our study, despite the threshold of PPV related to hypovolaemia

Fig. 2



Changes of the variables included in the multivariate analysis (pulse pressure variation, cardiac cycle efficiency and systolic – dicrotic pressure) during administration of a fluid challenge in responders and non-responders. Mean values of each minute are depicted by the thick black line, the thinner whiskers are the SD. In responders, pulse pressure variation is progressively reduced, whereas cardiac cycle efficiency and systolic – dicrotic pressure increase. Non-responders did not show any significant variation in the variables. $^{*}P < 0.05$ (for the exact P value please refer to Table 3). CCE, cardiac cycle efficiency; PPV, pulse pressure variation; SAP – P_{dic}, systolic – dicrotic pressure.

Table 3 Variation of pulse pressure variation, cardiac cycle efficiency, arterial elastance, mean pressure − dicrotic pressure and systolic pressure − dicrotic pressure between baseline and each of the first 5 min after fluid challenge administration in responders

PPV	Mean diff.	95% CI	*P* value	CCE	Mean diff.	95% CI	*P* value	Ea	Mean diff.	95% CI	*P* value
Min 1 vs. baseline	−3.95	0.21 to −7.70	<0.05	Min 1 vs. baseline	0.02	0.12 to −0.08	NS	Min 1 vs. baseline	−3.95	−0.20 to 7−.70	<0.05
Min 2 vs. baseline	−4.92	−1.53 to −8.30	<0.01	Min 2 vs. baseline	0.05	0.15 to −0.05	NS	Min 2 vs. baseline	−4.92	−1.5 to −8.30	<0.01
Min 3 vs. baseline	−6.77	−2.65 to −10.89	<0.001	Min 3 vs. baseline	0.05	0.15 to −0.04	NS	Min 3 vs. baseline	−6.77	−2.6 to −10.89	<0.001
Min 4 vs. baseline	−7.99	−2.93 to −13.05	<0.001	Min 4 vs. baseline	0.10	0.21 to 0.01	0.05	Min 4 vs. baseline	−7.99	−2.9 to −13.05	<0.001
Min 5 vs. baseline	−8.40	−3.26 to −13.55	<0.001	Min 5 vs. baseline	0.11	0.21 to 0.01	<0.05	Min 5 vs. baseline	−8.40	−3.2 to −13.55	<0.001

MAP − P_{dic}	Mean Diff.	95% CI	*P* value	SAP − P_{dic}	Mean Diff.	95% CI	*P* value
Min 1 vs. baseline	−7.18	−4.34 to −10.02	<0.0001	Min 1 vs. baseline	2.15	5.88 to 1.58	NS
Min 2 vs. baseline	−0.41	0.95 to −1.78	NS	Min 2 vs. baseline	3.31	7.04 to 0.41	NS
Min 3 vs. baseline	0.03	2.31 to −2.25	NS	Min 3 vs. baseline	5.68	9.41 to 1.95	<0.001
Min 4 vs. baseline	−0.31	2.12 to −2.76	NS	Min 4 vs. baseline	6.56	10.29 to 2.82	<0.0001
Min 5 vs. baseline	−0.47	2.29 to −3.23	NS	Min 5 vs. baseline	7.44	11.18 to 3.71	<0.0001

CCE, cardiac cycle efficiency; CI, confidence interval; Ea, arterial elastance; MAP − P_{dic}, mean pressure − dicrotic pressure; Min, minute; PPV, pulse pressure variation; SAP − P_{dic}, systolic pressure − dicrotic pressure.

being 12.7%, the baseline AUC of PPV was 0.80 with a sensitivity of 80% and specificity of 85%. Applying these values, in only 24.0% of patients could the response to a fluid challenge not be predicted.

As MAP and *CI* were similar between responders and non-responders, and PPV values were in a grey zone for some patients, more discriminating parameters are warranted. Such discriminating parameters would be important to avoid volume overtreatment as that is associated with poorer outcomes.[28,29] In our population, the decisions made by the anaesthetists based on clinical judgement led to an overall inappropriate infusion of 13.5 l of crystalloid in the whole cohort of the patients. The use of a predictive model that includes baseline PPV, CCE and SAP − P_{dic} after 5 min of fluid challenge, as confirmed by the ROC curve comparison, increased both the sensitivity and specificity of the prediction compared with baseline PPV alone. The latter failed to detect eight out 19 responders, but predicted 24 out of 27 non-responders. The multivariate model had a greater impact on the sensitivity of PPV rather than its specificity, correctly predicting 16/19 responders and 25/27 non-responders at 5 min compared with 8/19 responders and 24/27 non-responders with PPV alone. This predictive ability at 5 min might be useful as a 'warning' to guide the fluid challenge when baseline PPV values are within the grey zone range, thus avoiding the risk of fluid overload.

After the fluid challenge, CCE increased progressively in responders, whereas it did not change in non-responders (Tables 2 and 3). The increase in CCE became significant after 5 min, a reasonable time to detect the impact of a significant fluid volume on the cardiovascular system.

CCE has been used to assess the cardiac energy status when ultra-filtration was used in congestive heart failure patients,[30] when levosimendan (a calcium sensitiser) was administered to patients with decompensated heart failure,[31] and after electrical cardioversion of atrial fibrillation was successful.[32] More recently, in a mixed population of critically ill patients, Scolletta *et al.*[20] demonstrated a good correlation between CCE and the LVEF obtained with echocardiography. A CCE less than 0.07 predicted a LVEF less than 40% with a sensitivity of 0.93 and a specificity of 0.96, whereas a CCE more than 0.12 predicted a LVEF at least 50% with a sensitivity of 0.96 and a specificity of 0.82.[20]

To our knowledge, the present study is the first to investigate variations in CCE in relation to the preload responsiveness of the cardiovascular system. Interestingly, baseline CCE was significantly different between responders and non-responders [-0.08 ± 0.30 vs. 0.25 ± 0.32, respectively ($P = 0.002$)]. This may result from a combination of higher HR, and more sympathetic reflex activity to maintain MAP in responders at baseline, leading to an unfavourable coupling between heart function and peripheral arterial load (Table 2). CCE is an adimensional number combining several haemodynamic variables related to the coupling between the heart and the arterial system. Although a single number is appealing, it could be a problem as it limits the ability of CCE to identify a specific disorder or single identifiable factor causing change.

The interaction among SAP, MAP and P_{dic} was studied many years ago to investigate their relationship with SV ejection into the arterial vessels.[33,34] MAP − P_{dic} is usually low in healthy patients and becomes higher during resuscitated septic shock because of the reduced arterial tone.[16] In patients with normal arterial tone and normal P_{dic}, a fluid challenge induces variations in SAP − P_{dic} mainly related to SAP increase secondary to SV elevation. In our *CI* responders, as HR did not change

significantly the increase in $SAP - P_{dic}$ reflects an increase in SV, a sign of adequate cardiac function.[35]

Although arterial elastance values at baseline were similar between responders and non-responders, after a fluid challenge arterial elastance changed only in responders: a decrease of some 12.5%. This is consistent with previous findings reported by Monge Garcia *et al.*[13] in septic shock patients. These authors showed that arterial elastance (calculated as 90% of SAP/SV) reduction resulted from both a reduced vascular tone (as assessed by peripheral resistance) and a reduced pulsatile component (as evaluated by net compliance). It has been shown that a fluid challenge frequently triggers a flow-mediated vascular relaxation reflex.[13] This short-term mechanism of arterial adaptation could partially explain arterial elastance reduction after a fluid challenge infusion in patients with septic shock, which indirectly reduces arterial load.[36]

The current study has some limitations. First, infusion pumps capable of administering 500 ml of crystalloids in 10 min are not a standard of care, but significant variations in the infusion rate among the patients are unlikely as patients having the fluid infused outside the 9 to 11 min window were excluded. Second, the accuracy of the data collected and calculated by the MostCare monitor is totally dependent on the quality of the arterial pulse wave signal. Artefacts related to signal damping and inadequate pressure wave transmission reduce the reliability of the MostCare monitor,[20] and a level of expertise is required to identify such artefacts.[19] Although we performed a square-wave pressure test to detect low-quality arterial signals before each data collection period, the accuracy of haemodynamic assessment by the MostCare monitor remains operator-dependent.

Conclusion

In a population of surgical patients mechanically ventilated with a V_T less than $8\,ml\,kg^{-1}$, using a dynamic model, which includes PPV, ΔCCE and $\Delta SAP - P_{dic}$, enhances the ability to predict the haemodynamic response to a fluid challenge 5 min after the start of 500 ml infusion given over 10 min. The preliminary results of this model are promising but should be confirmed in larger cohort of patients as well as from different medical populations such as patients in ICU or who have septic shock.

Acknowledgements relating to this article

Assistance with the study: none.

Financial support and sponsorship: the work has not been funded by any external source. Specifically, there was no support in terms of monitor provision from Vygon–Vytech as all the participating centres already used the MostCare monitor in daily practice.

Conflicts of interest: In the past 5 years, DP and SR received travel expenses and registration for meetings, congresses and courses and lecture fees from Vygon. DP has a consultant contract with Vygon–Vytech. DP received funding from Vytech, Italy, and BBraun Melsungen, Melsungen, Germany. SMR is owner of the PRAM method patent. Disclosure of potential conflicts of interest unrelated to the present study: PN's research laboratory has received equipment and grants from Maquet Critical Care, Draeger, Biotest, Fisher & Pykel, Hillrom and Intersurgical S.p.A. He also received honoraria/speaking fees from Maquet Critical Care, Draeger, Breas, Philips, Resmed and Hillrom. PN contributed to the development of the helmet Next, whose licence for patent belongs to Intersurgical S.p.A., and receives royalties for that invention.

Presentation: preliminary data from the present study were presented during the 29th European Society of Intensive Care Medicine Annual Congress, 1 to 5 October 2016, Milan, Italy.

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