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ORIGINAL ARTICLE

Tidal volume challenge to predict fluid responsiveness in the operating room

An observational study

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BACKGROUND Pulse pressure variation (PPV) and stroke volume variation (SVV) do not predict fluid responsiveness when using a protective ventilation strategy: the use of functional haemodynamic tests can be useful to overcome this limitation.

OBJECTIVES We tested the use of a tidal volume challenge (V_TC), during 6 ml kg^{-1} [predicted body weight (PBW)] ventilation, and the end-expiratory occlusion test (EEOT) for prediction of fluid responsiveness.

DESIGN An interventional prospective study.

SETTING Supine elective neurosurgical patients.

INTERVENTIONS The study protocol was, first, the initial EEOT test was performed during baseline 6 ml kg^{-1} PBW ventilation; second, V_TC was performed by increasing the V_T up to 8 ml kg^{-1} PBW and PPV and SVV changes were recorded after 1 min; third, a second EEOT was performed during 8 ml kg^{-1} PBW ventilation; and V_T was reduced back to 6 ml kg^{-1} PBW and a third EEOT was performed. Finally, a 250 ml fluid challenge was administered over 10 min to identify fluid responders (increase in stroke volume index $\geq$10%).

RESULTS In the 40 patients analysed, PPV and SVV values at baseline and EEOT performed at 6 ml kg^{-1} PBW did not predict fluid responsiveness. A 13.3% increase in PPV after V_TC predicted fluid responsiveness with a sensitivity of 94.7% and a specificity of 76.1%, while a 12.1% increase in SVV after V_TC predicted fluid responsiveness with a sensitivity of 78.9% and a specificity of 95.2%. After EEOT performed at 8 ml kg^{-1} PBW, a 3.6% increase in cardiac index predicted fluid responsiveness with a sensitivity of 89.4% and a specificity of 85.7%, while a 4.7% increase in stroke volume index (SVI) with a sensitivity of 89.4% and a specificity of 85.7%.

CONCLUSION The changes in PPV and SVV obtained after V_TC are reliable and comparable to the changes in CI and SVI obtained after EEOT performed at 8 ml kg^{-1} PBW in predicting fluid responsiveness in neurosurgical patients.

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Introduction

Dedicated algorithms and protocols of anaesthetic care regarding fluid therapy are key factors to prevent perioperative hypovolaemia or hypervolaemia, which are both known to increase morbidity and length of hospital stay.[1–3] Fluid responsiveness [i.e. the increase in stroke volume (SV) after a fluid challenge] is limited to about 50% of critically ill or surgical patients.[4–8] For this reason, fluid challenge administration should be based on predictors of fluid responsiveness.[9] Static indexes, such as central venous pressure and pulmonary wedge pressure, are unsuited for this purpose,[10] but the dynamic indexes, such as pulse pressure variation (PPV) and stroke volume variation (SVV), reliably predict the effect of fluid challenge administration during controlled mechanical

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ventilation when a tidal volume (V_T) of at least 8 ml kg^{-1} is used.[11–13]

Use of an intra-operative lung-protective ventilation strategy (V_T of <8 ml kg^{-1} of predicted body weight, PBW) is associated with a better outcome[14] and is now suggested as standard practice in the operating room.[15] Such small V_Ts limit the assessment of fluid responsiveness in surgical patients by means of dynamic indexes. To overcome this V_T-related limitation of PPV and SVV, the prediction of fluid responsiveness can be achieved by applying functional haemodynamic tests[16] aimed at increasing venous return and enhancing right ventricle preload dependence.[10] Among these, the interruption of positive pressure ventilation (the so-called end-expiratory occlusion test, EEOT),[17] initially proposed in critically ill patients,[17–19] has been tested in two studies of elective surgical patients, with conflicting results. In patients ventilated with a mean V_T of 8.2 ml kg^{-1}, the EEOT was unable to reliably predict fluid responsiveness,[20] while the opposite was demonstrated in patients ventilated with a mean V_T of 6.8 ml kg^{-1}.[7]

More recently, in 20 critically ill patients with acute circulatory failure, Myatra *et al.*[21] successfully tested the hypothesis that fluid responsiveness could be reliably predicted by evaluating PPV and SVV changes after a 'V_T challenge' (V_TC), defined as a 1-min increase of V_T from 6 to 8 ml kg^{-1} PBW.[21]

We hypothesised that the baseline reliability of the dynamic indexes in elective surgical patients undergoing protective ventilation would be enhanced by the use of functional haemodynamic tests. Therefore, we designed this study to assess the sensitivity and specificity of PPV and SVV changes after a V_TC in predicting fluid responsiveness in a population of neurosurgical patients ventilated with 6 ml kg^{-1} PBW. We also the reliability of V_TC and EEOT performed at both 6 and 8 ml kg^{-1} PBW.

Materials and methods

Patients

A prospective study was conducted in the neurosurgery operating rooms at the University Hospital 'Maggiore della Carità' in Novara, Italy. The protocol was designed in accordance with the principles outlined in the Declaration of Helsinki; the study was approved by the local institutional ethics committee (Comitato Etico Interaziendale; Corso Mazzini n. 18, 28100 Novara, Italy; protocol number 192/17; approval date 15 December 2017; Chairperson Prof. Gian Carlo Avanzi) and registered (ACTRN12618000351213). Informed consent was obtained from all the participants.

All elective supine neurosurgical patients (age >18 years) requiring invasive arterial monitoring and showing a reduction of more than 20% in systolic arterial pressure (SAP) with respect to the values observed before anaesthesia induction were considered eligible. The exclusion criteria were: any recurrent cardiac arrhythmia; reduced ventricular systolic function - left (ejection fraction <40%), right (systolic peak velocity of tricuspid annular motion <0.17 m s^{-1}); BMI more than 30; intra-operative use of vasopressors or inotropes before or during V_TC and EEOT applications; chronic lung disease; pre-operative use of beta blocking agents; and clinical or radiological signs of intracranial hypertension.

Perioperative management

All patients received standard intra-operative monitoring, including heart rate, peripheral oxygen saturation, continuous electrocardiography and noninvasive blood pressure monitoring. After pre-oxygenation, general anaesthesia was induced with propofol, remifentanil and cisatracurium besilate (0.15 to 0.2 mg kg^{-1}), and maintained with propofol (1.5 to 3.0 mg kg^{-1} h^{-1}) or sevoflurane (1to 2%) along with remifentanil (0.1 to 0.5 μg kg^{-1} min^{-1}). All patients received an intermittent bolus of cisatracurium 0.15 mg kg^{-1} every 40 to 50 min to guarantee a complete neuromuscular blockade throughout the intervention. Anaesthetic administration was targeted to maintain a bispectral index (BIS monitor; Medtronic, Brooklyn Park, Minnesota, USA) of 40 to 60 throughout the surgical procedure.[22] All patients received lactated Ringer's solution at 4 ml kg^{-1} per hour as a maintenance fluid infusion during surgery and were ventilated at baseline in volume-control mode with the following settings: V_T of 6 ml kg^{-1} PBW and positive end-expiratory pressure set between 3 and 6 cmH_2O (FLOW-I C40 ventilator; Maquet Critical Care, Sweden) to achieve and maintain a peripheral oxygen saturation of 96% and an end-tidal carbon dioxide concentration between 30 and 35 mmHg. The PBW (kg) was calculated as follows: X + 0.91[height (cm) - 152.4]; (X = 50 for men and 45.5 for women). After induction of general anaesthesia, invasive blood pressure monitoring was obtained by inserting a 20-G cannula into the radial artery. The pressure signal was then connected to both the operating room monitor (Mindray BeneView T8; Soma Technology, Inc., Bloomfield, Connecticut, USA) and to the MostCare device (Vyetech Health, Padua, Italy), by means of the manufacture's Y cable. A square-wave test was used in all patients to exclude under or overdamping of the pressure signal.[23]

Haemodynamic monitoring and tests

The MostCare works with a sampling rate of 1.000 points (Pt) per second, analysing both the systolic and the diastolic part of arterial waveform signal and calculates SV as the ratio between the area under the systolic component of the curve and the systemic vascular impedance by analysing the profile of the 'points of instability'. These points are generated by the mechanical interaction (i.e. pressure/time changes) between forward (due to cardiac systole) and backward pressure waves (coming from the peripheral vessels) and define the specific profile

of each arterial waveform, which is analysed by (MostCare) for the calculation of the vascular impedance.[24,25] Arterial pressures (systolic, diastolic, mean, dicrotic) and PPV are directly measured from arterial pressure waveform, while SVV is calculated by analysing the changes in SV over time. All the indexed values, including SV index, SVI and cardiac index, CI, are calculated using the patient's anthropometric measurements. All the haemodynamic variables recorded during each set of measurements were averaged according to the default time-setting (30 s) of MostCare and imported into a dedicated EXCEL (Microsoft, Redwood, Mississippi, USA) spreadsheet for further analysis.

Study protocol

Measurements were started during a period of haemodynamic stability (defined as changes in mean arterial pressure less than 10% over 5 min[7,26]).

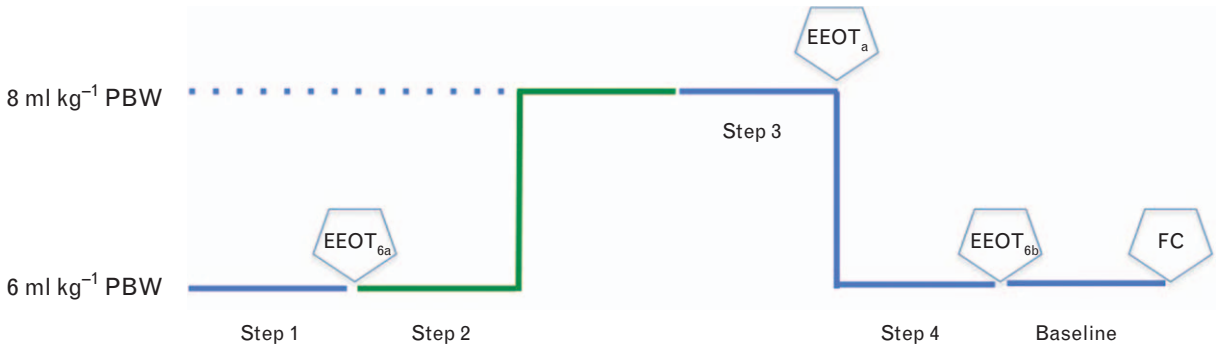
The study protocol (see Fig. 1) was, an initial recording of measurements (step1) and then the first EEOT test ($EEOT_{6a}$); second, after 1 min, a set of measurements was recorded (step 2); third, the V_TC was applied by increasing the V_T up to 8 ml kg^{-1} PBW and PPV and SVV changes were recorded (ΔPPV_{VTC} and ΔSVV_{VTC}, respectively, calculated as percentage of variations between the values of PPV and SVV recorded at step 2 and 1 min after the V_T increase); fourth, after 1 min, another set of measurements was recorded (step 3). Following this, a second EEOT ($EEOT_8$) was performed. Fifth, the V_T was reduced back to 6 ml kg^{-1} PBW and after 1 min, a set of measurements was recorded (step 4); sixth, a third EEOT was performed ($EEOT_{6b}$); seventh, after 1 min, a set of measurements was recorded (baseline) and the FC of 250 ml of Ringer's solution was infused over 10 min. Only the haemodynamic data obtained from the first fluid challenge administered to each enrolled patient were used for the analysis. Positive end-expiratory pressure was kept constant during the study period. Each EEOT was performed by interrupting mechanical ventilation for 30 s, using the software functionality 'expiratory hold' on the FLOW-I C40. For the safety of the patient, the interruption of the protocol was at discretion of the attending anaesthetist.

Statistical analysis

A receiver operating characteristic (ROC) curve approach was used to evaluate the reliability of V_TC and EEOT tests in predicting fluid responsiveness. ROC [95% confidence interval (95% CI)] curves were constructed for PPV and SVV values before fluid challenge administration; for the percentage change in PPV and SVV between 6 and 8 ml kg^{-1} PBW ventilation after 1 min of V_TC application; and for the percentage change in SVI and CI after each EEOT application (ΔSVI and ΔCI, respectively). The haemodynamic data recorded at the end of each test were compared with baseline values from the minute before the application. A patient was considered fluid responsive if the SVI increased at least 10% after fluid challenge administration.[7,8] Cut-off values were chosen with the highest Youden index and, finally, statistically significant ROC curves ($P < 0.05$) were compared using the De Long test.[27] Considering the possibility of an overlap between responders and nonresponders, we determined a grey zone for ΔPPV_{VTC}, ΔSVV_{VTC}, ΔSVI and ΔCI, considering a low cut-off value including 90% of negative fluid challenge responses, and a high cut-off value predicting positive fluid challenge in 90% of cases.[7,28]

The sample size of the study was calculated by means of the comparison of the areas under the ROC curves test (AUC). For this purpose, we predicted an AUC of at least 0.75, which is the threshold for considering a diagnostic test as accurate,[29] and compared it with the null hypothesis (AUC = 0.50; no discriminating power). Accordingly, a sample size of 38 patients was calculated (type I error of 5% and type II error of 20%).

Fig. 1



Study protocol (see text for further explanations). EEOTs were performed by interrupting mechanical ventilation for 30 s. The V_TC was performed by increasing the tidal volume from 6 to 8 ml kg^{-1} PBW for 1 min (green line). EEOT, end-expiratory occlusion test; FC, fluid challenge; PBW, predicted body weight; V_TC, tidal volume challenge.

Normal distribution was evaluated by means of the d'Agostino-Pearson test and, accordingly, data are expressed as median with interquartile [IQR] range or mean (SD). Changes in continuous variables after V_TC were compared using a paired *t* test or Wilcoxon signed rank sum test, while an independent *t* test or Mann–Whitney *U* test was used for subgroup comparisons, as appropriate. For dichotomous or categorical variables, a Chi-square test for comparison of proportions were applied.

Statistical analyses were conducted using GraphPad PRISM V6 (GraphPad Software Inc., San Diego, California, USA) and Medcalc (Software 8.1.1.0; Mariakerke, Belgium). For all comparisons, we considered significant *P* values less than 0.05.

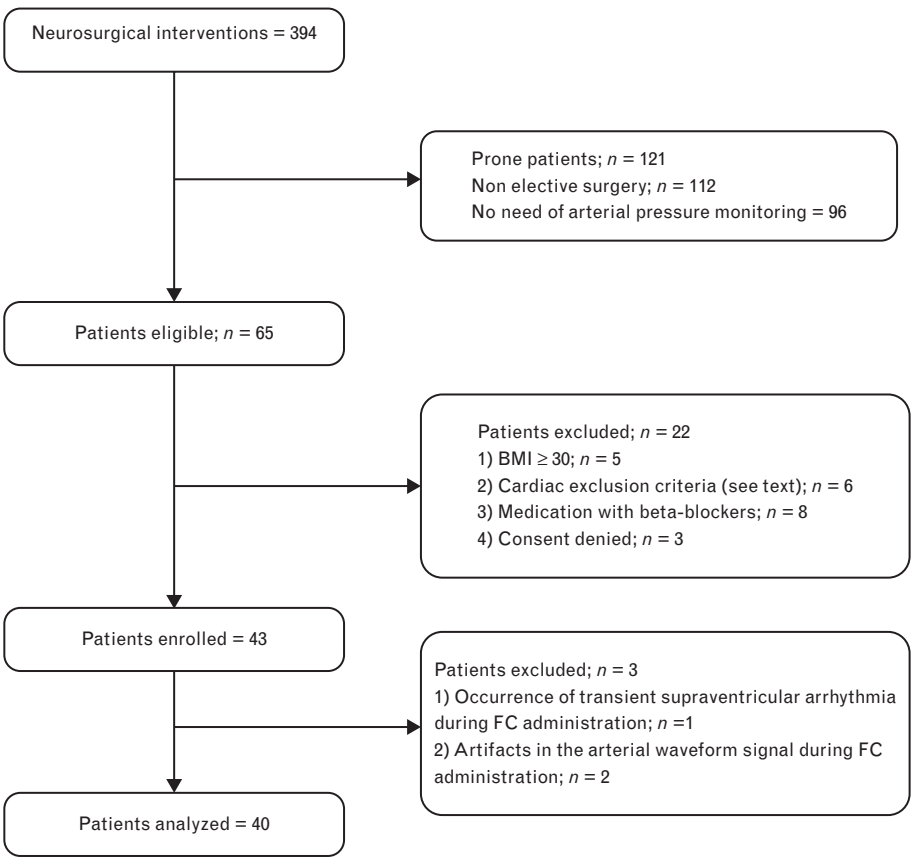
Results

From January 2018 to May 2018, 65 consecutive neurosurgical patients were considered eligible for inclusion. However, 22 were excluded before and three after the enrolment (see Fig. 2). Finally, 40 patients were analysed. The study protocol was never interrupted by the attending anaesthetist and no adverse effects were reported after EEOT or V_TC use. The study protocol was applied within the first hour after skin incision in all the enrolled patients. Fluid challenge administration induced an increase in SVI at least 10% in 21 patients (52.5%, fluid challenge responders). Demographic characteristics, comorbidities, surgical procedures, risk scores and ventilatory variables were comparable between responders and nonresponders and are reported in Table 1.

The measurements from each step of the study protocol are reported in Table 2. The haemodynamic values of responders and nonresponders before fluid challenge administration were comparable, except for SVV, which was significantly higher in responders as compared to nonresponders. Fluid challenge administration significantly increased CI, SVI and SAP in responders, while it reduced PPV and SVV. In nonresponders, fluid challenge administration reduced CI and SVI and did not affect any of the other considered variables.

PPV and SVV values recorded at baseline, before fluid challenge administration were poor at discriminating fluid responsiveness (see Table 3).

Fig. 2



Flow of patients in the study. FC, fluid challenge.

Table 1 Patients' characteristics at enrolment

	Whole population	R ($n=21$)	NR ($n=19$)	Comparison between R and NR (P)
General characteristics				
Age (years)	58 [49 to 67]	57 [48 to 63]	64 [54 to73]	0.06
Sex (M/F)	16/24	8/13	8/11	0.90
BMI ($kg\,m^{-2}$)	24.7 [22.0 to 26.2]	23.6 [21.5 to 25.1]	25.0 [22.8 to 28.5]	0.07
ASA score	2 [1 to 2]	2 [1 to 2]	2 [2 to 2]	0.28
NSQIP score for any complication (%)	6.9 [4.8 to 12.3]	6.3 [4.9 to 8.5]	7.8 [4.7 to 15.2]	0.26
NSQIP score for serious complication (%)	6.2 [4.5 to 9.3]	5.9 [4.5 to 8.4]	7.0 [4.2 to 13.2]	0.50
Duration of surgery (min)	240 [180 to 300]	240 [150 to 300]	240 [180 to 360]	0.42
Pre-operative haemoglobin ($g\,dl^{-1}$)	12.9 [11.5 to 13.6]	12.8 [11.2 to 13.4]	13.2 [12.4 to 13.9]	0.17
Pre-operative creatinine ($mg\,dl^{-1}$)	0.7 [0.6 to 0.8]	0.6 [0.5 to 0.7]	0.7 [0.6 to 0.8]	0.05
Fluids infused before the protocol start (ml)	379 [314 to 426]	348 [314 to 415]	390 [370 to 450]	0.08
Lactate ($mmol\,l^{-1}$)	0.6 [0.5 to 0.6]	0.6 [0.5 to 0.8]	0.6 [0.5 to 1.0]	0.33
Ventilator settings				
pH	7.40 [7.37 to 7.43]	7.43 [7.42 to 7.46]	7.39 [7.43 to 7.48]	0.34
Total PEEP (cmH_2O)	5 [5.0 to 5.5]	5 [5.0 to 5.5]	5 [5.0 to 5.0]	0.90
V_T (ml)	400 [350 to 440]	400 [330 to 445]	400 [360 to 440]	0.82
Total respiratory compliance $6\,ml\,kg^{-1}$ VCV ($ml\,cmH_2O^{-1}$)	65 [58 to 73]	65 [57 to 74]	66 [60 to 72]	0.87
Driving pressure $6\,ml\,kg^{-1}$ VCV (cmH_2O)	6 [5 to 8]	6 [5 to 7]	6 [5 to 8]	0.75
Total respiratory compliance $8\,ml\,kg^{-1}$ VCV ($ml\,cmH_2O^{-1}$)	83 [69 to 91]	79 [68 to 95]	83 [71 to 91]	0.89
Driving pressure $8\,ml\,kg^{-1}$ VCV (cmH_2O)	11 [10 to 12]	11 [10 to 12]	11 [10 to 12]	0.59
paO_2/FiO_2 (ratio)	392 [302 to 538]	466 [325 to 548]	362 [251 to 476]	0.10
$paCO_2$ (mmHg)	36.1 [30.0 to 38.8]	38.2 [34.8 to 42.2]	38.9 [36.8 to 43.8]	0.59
RR (breaths/min)	15 [14 to 18]	15 [13 to 16]	16 [14 to 18]	0.15
Chronic pre-operative disease (n, %)				
Hypertension	17	7 (33.3)	10 (52.6)	0.33
Coronary heart disease	3	2 (9.5)	1 (5.2)	0.99
COPD/Asthma	3	2 (9.5)	1 (5.2)	0.99
Cerebrovascular disease	3	1 (4.7)	2 (10.5)	0.99
Diabetes mellitus	7	4 (19)	3 (15.7)	0.98
Chronic kidney disease	2	1 (4.7)	1 (5.2)	0.99
Malignancy	7	5 (23.8)	2 (10.5)	0.41
Surgical procedures				
Craniotomy for intracranial masses	27	14 (66.6)	13 (68.4)	0.90
Craniotomy for vascular diseases	5	2 (9.5)	3 (15.7)	0.59
Cervical spine surgery	8	5 (23.8)	3 (15.7)	0.63

Values are presented as absolute (percentage) or median [interquartile range], as appropriate. ASA, American Society of Anaesthesiologists classification; COPD, chronic obstructive pulmonary disease; NR, nonresponders; NSQIP; national surgical quality improvement programme; $paCO_2$, arterial partial pressure of carbon dioxide; paO_2/FiO_2, arterial partial pressure of oxygen/fraction of inspired oxygen; PEEP, positive end-expiratory pressure; R, responders; RR, respiratory rate; VCV, volume-controlled ventilation; V_T, tidal volume.

Effect of V_TC on pulse pressure variation and stroke volume variation

V_TC application increased both PPV and SVV in responders (from 6.3% [4.1 to 7.5] to 10.3% [7.6 to 12.7], $P<0.0001$, and from 7.3% [5.3 to 9.4] to 10.8% [7.8 to 12.8], $P<0.0001$, for PPV and SVV, respectively), but not in nonresponders (see Table 2 and Supplemental Figure 1 in the Supplemental Digital Content, http://links.lww. com/EJA/A201). These changes reliably predicted fluid responsiveness (see Table 3 and Fig. 3).

After V_TC application, ΔPPV_{VTC} predicted fluid responsiveness with a sensitivity of 94.7% (95% CI 73.9 to 99.8) and a specificity of 76.1% (95% CI 52.8 to 91.7) for a PPV_{VTC} increase cut-off of 13.3%, while ΔSVV_{VTC} predicted fluid responsiveness with a sensitivity of 78.9% (95% CI 54.4 to 93.9) and a specificity of 95.2% (95% CI 76.1 to 99.8) for a SVV_{VTC} increase cut-off of 12.1%.

Effect of end-expiratory occlusion test on stroke volume index and cardiac index

$EEOT_6$ did not predict fluid responsiveness when performed at $6\,ml\,kg^{-1}$ PBW ventilation. On the contrary, the changes in CI and SVI after EEO_8 reliably predicted fluid responsiveness (see Table 3 and Fig. 3).

After EEO_8, ΔCI predicted fluid responsiveness with a sensitivity of 89.4% (95% CI 66.8 to 98.7) and a specificity of 85.7% (95% CI 63.6 to 96.5), with a CI increase cut-off of 3.6%, while ΔSVI predicted fluid responsiveness with a sensitivity of 89.4% (95% CI 66.8 to 98.7) and a specificity of 85.7% (95% CI 63.6 to 96.9), with a SVI increase cut-off of 4.7%.

Receiver operating characteristic comparisons

The comparisons with $EEOT_6$ were not performed, as the ROC curve for the test was not significant. The AUCs of V_TC and $EEOT_8$ were all significantly greater than the AUCs of baseline PPV and SVV ($P<0.001$ for all the

Table 2 Haemodynamic variables at each step of the protocol

Variable	Step 1	$EEOT_{6a}$	Step 2	V_TC	Step 3	$EEOT_8$	Step 4	$EEOT_{6b}$	Baseline	Post FC	*P* Baseline vs. post FC
Responders											
MAP	73 [61 to 87]	69 [64 to 77]	72 [60 to 77]	74 [59 to 78]	72 [65 to 76]*	72 [65 to 76]	71 [60to 73]	72 [63 to 77]	68 [59 to 73]	68 [59 to 73]	0.12
CI	2.5 [2.2 to 2.9]	2.4 [2.3 to 3.0]	2.4 [2.3 to 2.8]	2.4 [2.2 to 2.7]	2.4 [2.1 to 2.7]	2.6 [2.4 to 2.8]	2.5 [2.2 to 2.8]	2.5 [2.1 to 2.7]	2.4 [2.2 to 2.8]	2.7 [2.4 to 3.2]	< 0.0001
SVI	44 [32 to 53]	43 [53 to 35]	42 [33 to 49]	44 [34 to 50]	41 [32 to 51]	46 [35 to 54]	47 [35 to 53]	43 [32 to 51]	40 [35 to 49]	48 [39 to 56]	< 0.0001
HR	62 [55 to 70]	61 [55 to 67]	62 [56 to 67]	61 [54 to 64]	61 [55 to 65]	60 [56 to 67]	59 [56 to 68]	60 [55 to 68]	60 [55 to 65]	59 [52 to 65]	0.17
PPV	8.4 [6.0 to 12.0]	6.6 [4.8 to 10.7]	6.3 [4.1 to 7.5]	10.3 [7.6 to 12.7]	10.8 [7.4 to 14.2] *	9.4 [6.9 to 12.5]	8.7 [6.1 to 11.8]	7.1 [4.8 to 9.7]	8.1 [6.0 to 12.0]	6.8 [5.8 to 9.2]	0.02
SVV	9.9 [8.8 to 11.3]	8.7 [5.6 to 10]	7.3 [5.3 to 9.4]	10.8 [7.8 to 12.8]	9.0 [7.8 to 12.9]	10.6 [7.4 to 13.7]	8.4 [4.7 to 11.1]	7.2 [5.6 to 13.0]	11.0 [6.4 to 13.7]*	7.4 [5.4 to 9.2]	0.04
Nonresponders											
MAP	67 [62 to 77]	64 [61 to 77]	64 [61 to 74]	68 [59 to 72]	65 [59 to 69]	65 [59 to 69]	63 [58 to 65]	63 [58 to 65]	68 [59 to 73]	66 [60 to 72]	0.72
CI	2.5 [2.4 to 2.7]	2.5 [2.3 to 2.9]	2.6 [2.4 to 2.7]	2.6 [2.4 to 2.8]	2.5 [2.3 to 2.8]	2.4 [2.3 to 2.7]	2.4 [2.2 to 2.7]	2.5 [2.4 to 2.7]	2.5 [2.2 to 2.8]	2.3 [2.2 to 2.5]	0.01
SVI	44 [38 to 53]	44 [41 to 54]	48 [40 to 55]	45 [41 to 55]	43 [38 to 55]	42 [38 to 54]	44 [38 to 54]	45 [39 to 55]	46 [37 to 55]	41 [32 to 53]	0.01
HR	59 [48 to 67]	59 [48 to 66]	58 [47 to 65]	59 [49 t0 66]	58 [46 to 66]	59 [47 to 66]	56 [47 to 69]	57 [48 to 63]	56 [46 to 69]	60 [46 to 69]	0.17
PPV	6.4 [4.5 to 7.9]	5.3 [4.2 to 7.1]	5.6 [4.4 to 7.2]	5.7 [4.7 to 6.7]	7.1 [5.8 to 9.2]	7.6 [5.7 to 8.8]	6.0 [4.2 to 9.1]	8.1 [4.3 to 10.8]	6.1 [4.0 to 8.3]	6.4 [4.3 to 10.4]	0.90
SVV	7.7 [5.6 to 11.7]	8.7 [5.1 to 10.5]	7.8 [6.9 to 9.9]	7.8 [6.0 to 10.1]	6.7 [5.5 to 9.2]	7.6 [5.7 to 11.2]	6.8 [5.5 to 9.0]	5.9 [4.2 to 12.3]	4.8 [3.5 to 10.0]	7.0 [3.7 to 8.7]	0.20

Median [25th to 75th IQR] values of haemodynamic variables at each step of the protocol. PPV (*$P = 0.03$) and MAP (*$P = 0.03$) were significantly higher in responders than in nonresponders at step 3. SVV (*$P = 0.04$) was significantly higher in responders than in nonresponders at baseline. CI, cardiac index; EEOT, end-expiratory occlusion test (please refer to Methods section for further explanations regarding the study protocol); FC, fluid challenge; MAP, mean arterial pressure; PPV, pulse pressure variation; SVI, stroke volume index; SVV, stroke volume variation; V_TC, tidal volume challenge.

comparisons). The AUCs of V_TC and $EEOT_8$ were not different (see Table 4).

Discussion

The main findings of our study conducted in elective neurosurgical patients are first, the use of a V_TC increases both PPV and SVV in fluid responders and these changes accurately predict fluid responsiveness; second, the changes in SVI and CI after an EEOT are reliable only when the test is performed at 8 ml kg^{-1} PBW ventilation; third, the sensitivity and specificity of V_TC and $EEOT_8$ in revealing preload dependency are not significantly different; and fourth, baseline PPV and SVV in elective neurosurgical patients undergoing protective ventilation do not predict fluid responsiveness.

The reliability of dynamic indexes in predicting fluid responsiveness is affected by several clinical variables,[18,30–34] which are unfortunately present in the vast majority of critically ill patients.[11,12] Moreover, in the operating room, PPV values ranging between 9 and 13% are poorly predictive of fluid responsiveness,[28] and require additional haemodynamic tests to assess preload dependence and to avoid inappropriate fluid administration.[8,21]

Our results confirm that a protective ventilation strategy precludes the use of baseline PPV and SVV in the assessment of the volume status, even if all other validity criteria are respected. Moreover, the percentage of fluid responsive patients was about 50% (consistent with previous findings in elective surgical patients[7,8,35,36]), suggesting that functional haemodynamic tests should be used in patients undergoing protective ventilation in the operating room, to enhance the predictive value of PPV and SVV.

Recently, Myatra *et al.*[21] successfully tested the hypothesis in critically ill patients that increasing the V_T from 6 to 8 ml kg^{-1} for only 1 min would correct baseline PPV and SVV to values discriminating responders from nonresponders. In fact, as protective ventilation causes false-negative values of the dynamic indexes,[37] raising V_T and intrathoracic pressure should increase PPV and SVV to a different extent in responders and nonresponders.

In our study, the V_TC increased both PPV and SVV only in fluid responders, but to a smaller extent than the previous results of Myatra *et al.*[21]

Moreover, the thresholds of ΔPPV_{VTC} and ΔSVV_{VTC} identified by the ROC curve analysis are different in our study compared with the study by Myatra *et al.*[21] This finding could be explained by the different extent of the haemodynamic effect of V_TC application in a population of elective supine surgical, not obese patients as compared to the population of Myatra *et al.*,[21] showing a median compliance of the respiratory system of about 28 ml cmH_2O^{-1} in critically ill patients with acute respiratory disease.[21] Chest wall and respiratory system compliances affect the transmission of the intrathoracic

Table 3 Reliability of dynamic indexes, tidal volume challenge and end-expiratory occlusion tests in predicting fluid responsiveness

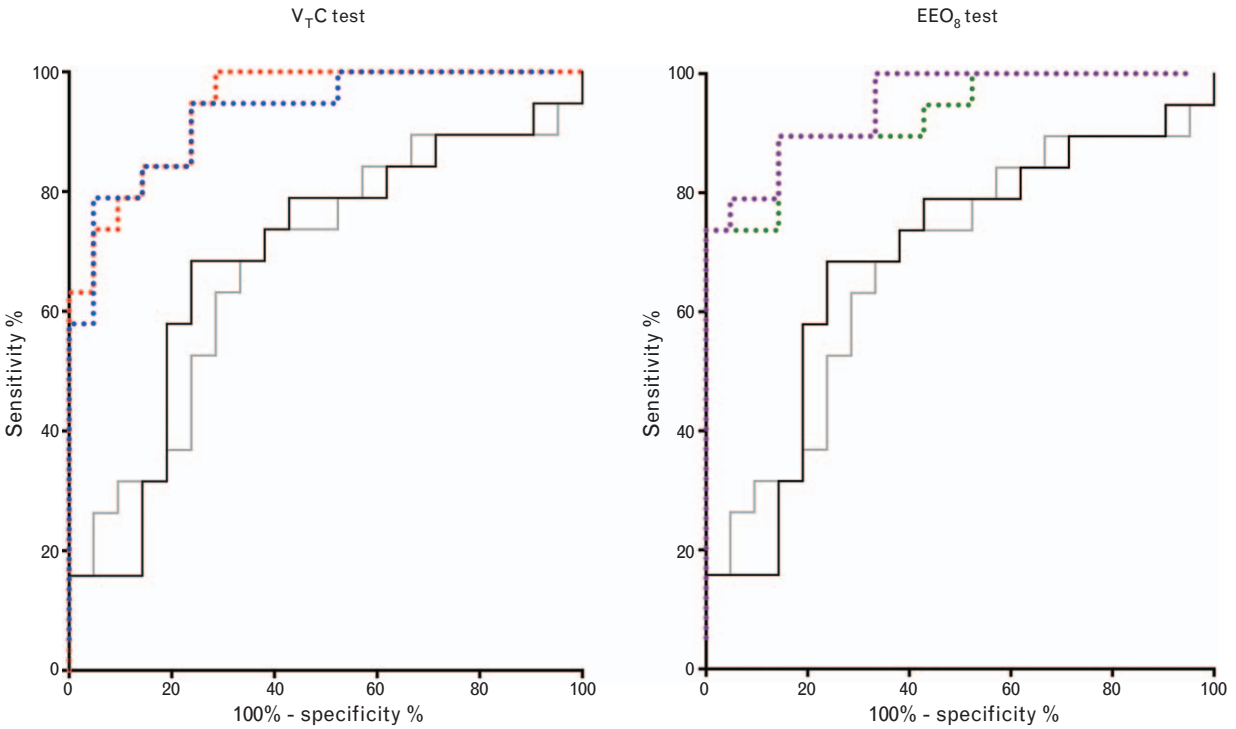
	AUC (95%CI)	Best threshold (%)	Youden index	Grey zone (%)	Patients in the grey zone (%)
Baseline PPV	0.68 (0.50 to 0.85)	7.2	0.34	5 to 17	62.5
Baseline SVV	0.68 (0.52 to 0.86)	6.6	0.44	3 to 16	88.5
ΔPPV_{VTC}	0.94 (0.82 to 0.99)	13.3	0.71	10 to 15	27.5
ΔSVV_{VTC}	0.93 (0.80 to 0.98)	12.1	0.75	8 to 20	20
ΔCI after $EEOT_6$	0.53 (0.35 to 0.71)	NA	NA	NA	NA
ΔSVI after $EEOT_6$	0.52 (0.33 to 0.70)	NA	NA	NA	NA
ΔCI after $EEOT_8$	0.93 (0.84 to 1.00)	3.6	0.75	2 to 6	27.5
ΔSVI after $EEOT_8$	0.95 (0.88 to 1.00)	4.7	0.75	2 to 6	27.5

AUC area under the curve and 95% confidence interval (95% CI). CI, cardiac index; $EEOT_6$/$EEOT_8$, end-to-expiratory occlusion tests performed at 6 and 8 ml kg^{-1} of predicted body weight ventilation; NA, not applicable; PPV, pulse pressure variation; PPV_{VTC}, changes in pulse pressure variation after tidal volume challenge; SVI, stroke volume index; SVV, stroke volume variation; SVV_{VTC}, changes in stroke volume variation after tidal volume challenge; (ROC curve not significant).

pressure to the pleural and atrial pressure and, in turn, the dynamic indexes.[38] In fact, only about one-third of the applied airway pressure is transmitted to the pericardium and the vena cava, and this effect is enhanced by a reduced chest wall compliance,[38] which is present in about 30% of critically ill patients.[39]

EEOT did not predict fluid responsiveness when performed during a 6 ml kg^{-1} PBW ventilation, as previously reported in the literature.[21] It showed a sensitivity and specificity comparable to the V_TC when performed during a 8 ml kg^{-1} PBW ventilation with a cut-off of about 5% of increase in CI and SVI. The increase in right ventricle preload and, in turn, in CI and SVI after the EEOT manoeuvre is related to the changes in intrathoracic pressure during mechanical ventilation. The effect on venous return of a lung protective ventilatory strategy could be insufficient and the consequent changes in CI and SVI after the occlusion manoeuvre too small to discriminate between responders and nonresponders.

Fig. 3



Receiver operating characteristic curves of pulse pressure variation and stroke volume variation variations after tidal volume challenge application [ΔPPV_{VTC} (red line) and ΔSVV_{VTC} (blue line), left] and after the EEOT performed at 8 ml kg^{-1} of PBW ($EEOT_8$) [ΔCI (green line) and ΔSVI (purple line), right]. The ROC curves of PPV (black line) and SVV (grey line) at baseline (before fluid challenge) are also reported in each figure. Both V_TC and $EEOT_8$ performed better than baseline PPV and SVV in predicting fluid responsiveness (see Table 4). EEOT, end-expiratory occlusion test; PBW, predicted body weight; PPV, pulse pressure variation; SVV, stroke volume variation; V_TC, tidal volume challenge.

Table 4 Receiver operating characteristic curve comparisons

Tests	*P*
AUC ΔPPV_{VTC} vs. AUC ΔSVV_{VTC}	0.73
AUC ΔCI after $EEOT_8$ vs. AUC ΔSVI after $EEOT_8$	0.59
AUC ΔPPV_{VTC} vs. AUC ΔCI after $EEOT_8$	0.91
AUC ΔPPV_{VTC} vs. AUC ΔSVI after $EEOT_8$	0.79
AUC ΔSVV_{VTC} vs. AUC ΔCI after $EEOT_8$	0.96
AUC ΔSVV_{VTC} vs. AUC ΔSVI after $EEOT_8$	0.74

ROC curves were compared using the De Long test. ΔCI, changes in cardiac index; ΔSVI, changes in stroke volume index; AUC, area under the curve; $EEOT_8$, end-expiratory occlusion test performed at 8 ml kg^{-1} of predicted body weight ventilation; PPV_{VTC}, changes in pulse pressure variation after tidal volume challenge; SVV_{VTC}, changes in stroke volume variation after tidal volume challenge.

As suggested by Myatra *et al.*,[21] the V_TC could potentially be used in resource-limited settings, as PPV measurement can be achieved without a dedicated cardiac output device. Nevertheless, 27.5% of patients were included in the grey zone analysis of ΔPPV_{VTC}, suggesting caution in the sole use of this parameter. A simultaneous increase of PPV more than 15% and SVI more than 6% after V_TC and $EEOT_8$ would identify the vast majority of responders. However, the assessment of these haemodynamic changes requires both a ventilator equipped with the end-expiratory occlusion function, which are not widely available in operating rooms, and a continuous cardiac output monitoring.

Some limitations of this work should be acknowledged. First, fluid responsiveness and fluid challenge assessment are closely related. Changing the amount of fluid infused, the rate of administration and the thresholds to define the response would affect the number of fluid responders and, as a consequence, the ROC curve analysis. We chose a 250-ml fluid challenge administered over 10 min, as proposed during intra-operative goal-directed fluid therapy and now suggested by international statements,[2,40] and SVI at least 10% as target, while Myatra *et al.*[21] adopted 7 ml kg^{-1} bolus in 10 min and CI more than 15%.[22] This discrepancy would limit the comparability of the studies. Second, EEOT has been proposed as a 15-s hold in critically ill patients.[17–19] We used a 30-s interruption as previously described in surgical patients,[7] which corresponds to the MostCare default time-setting modality for averaging haemodynamic data. Although the haemodynamic effect of EEOT could change between the two time-points, the best thresholds for both ΔCI and ΔSVI (about 4%) are consistent with those reported in surgical and critically ill patients for a 30-s or a 15-s EEOT (4% to 5%) and the ROCs are comparable.[7,18,21] Thirdly, the accuracy of MostCare is highly dependent on the quality of the signal obtained from the arterial catheter.[25] Artefacts related to under/overdamping and to the transmission of the signal may influence the reliability of the device and some expertise is needed to correctly recognise these erroneous patterns.[23] For this reason, the reliability of the MostCare remains operator-dependent and the centre involved in the study is highly trained in the use of this device. Fourthly, at least two exclusion criteria for this study (i.e. the chronic use of beta-blocking agents and obesity) would limit the external validation of the results in high-risk surgical patients, requiring further specific investigations in this subgroup of patients. Finally, we used a 1-min delay between the EEOTs and the V_TC to guarantee the return to the steady state before the application of the subsequent test in the protocol and to minimise the risk of bias due to a carry-over effect, which, cannot be completely excluded.

Conclusion

In neurosurgical patients undergoing protective ventilation, the baseline values of dynamic indexes are unsuitable in assessing preload dependence. In this setting, the changes in PPV and SVV obtained after V_TC are reliable and comparable to the changes in CI and SVI obtained after EEOT performed at 8 ml kg^{-1} in predicting fluid responsiveness. These tests should be considered as adjuctive, well tolerated and useful methods to guide intra-operative fluid therapy.

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