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ORIGINAL ARTICLE

Mini fluid chAllenge aNd End-expiratory occlusion test to assess flUid responsiVEness in the opeRating room (MANEUVER study)

A multicentre cohort study

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BACKGROUND The fluid challenge response in surgical patients can be predicted by functional haemodynamic tests. Two tests, the mini-fluid challenge (mini-FC) and end-expiratory occlusion test (EEOT), have been assessed in a few small single-centre studies with conflicting results. In general, functional haemodynamic tests have not performed reliably in predicting fluid responsiveness in patients undergoing laparotomy.

OBJECTIVE This trial is designed to address and compare the reliability of the EEOT and the mini-FC in predicting fluid responsiveness during laparotomy.

DESIGN Prospective, multicentre study.

SETTING Three university hospitals in Italy.

PATIENTS A total of 103 adults patients scheduled for elective laparotomy with invasive arterial monitoring.

INTERVENTIONS The study protocol evaluated the changes in the stroke volume index (SVI) 20 s ($EEOT_{20}$) and 30 s ($EEOT_{30}$) after an expiratory hold and after a mini-FC of 100 ml over 1 min. Fluid responsiveness required an increase in SVI at least 10% following 4 ml kg^{-1} of Ringer's solution fluid challenge infused over 10 min.

MAIN OUTCOME MEASUREMENTS Haemodynamic data, including SVI, were obtained from pulse contour analysis. The area under the receiver operating characteristic curves of the tests were compared with assess fluid responsiveness.

RESULTS Fluid challenge administration induced an increase in SVI at least 10% in 51.5% of patients. The rate of fluid responsiveness was comparable among the three participant centres ($P = 0.10$). The area under the receiver operating characteristic curves (95% CI) of the changes in SVI after mini-FC was 0.95 (0.88 to 0.98), sensitivity 98.0% (89.5 to 99.6) and specificity 86.8% (75.1 to 93.4) for a cut-off value of 4% of increase in SVI. This was higher than the SVI changes after $EEOT_{20,}$ 0.67 (0.57 to 0.76) and after $EEOT_{30,}$ 0.73 (0.63 to 0.81).

CONCLUSION In patients undergoing laparotomy the mini-FC reliably predicted fluid responsiveness with high-sensitivity and specificity. The EEOT showed poor discriminative value and cannot be recommended for assessment of fluid responsiveness in this surgical setting.

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Introduction

The titration of fluid administration in the operating room is a cornerstone of many peri-operative guidelines and pathways.[1,2] While the overall amount of intra-operative fluid that should be infused is still debated,[3] there is increasing evidence that suggests intra-operative fluid therapy should be guided by predefined physiologic targets.[4,5] Accordingly, recent research has been centred on the physiology of the individual with the purpose of tailoring and targeting fluid administration to that patient's needs.[4,6,7] In this context, the prediction of fluid responsiveness, the increase in stroke volume (SV) after a fluid challenge, is crucial for the optimisation of peri-operative fluid balance by avoiding unnecessary fluids, since roughly 50% of surgical patients do not respond to fluid challenge administration.[8]

Intra-operative fluid management can be guided by the prefluid challenge values of the dynamic indices of fluid responsiveness, such as pulse pressure variation (PPV) and SV variation (SVV). However, these indices predict the effect of fluid challenge only below or above the grey zone of uncertainty,[9] and only if specific validity criteria are respected.[10,11] A different intra-operative strategy relies on the application of manoeuvres that affect, to different extents, cardiac function and interactions between the heart and the lungs, in a way that might identify fluid responders and nonresponders, the so-called functional haemodynamic tests (FHTs).[12] Among them, the end-expiratory occlusion test (EEOT) aims at increasing venous return and SV by enhancing right ventricle (RV) preload dependence, after the interruption of mechanical ventilation for 15 to 30 s.[13] The mini-fluid challenge (mini-FC) is based on the assessment of the SV response to the rapid infusion of small aliquots of fluid, usually 100 ml over 1 min or less, to predict the final response to a full fluid challenge.[14,15]

A recent systematic review and meta-analysis from our group has demonstrated a good overall performance for EEOT and mini-FC in the operating room.[16] However, it also showed that these two FHTs had only been tested in a few studies and were potentially biased by the single-centre design, the selection criteria, the small number of patients enrolled and the reporting of conflicting results in different surgical settings.[17–20] To the best of our knowledge, the EEOT and mini-FC have only been previously tested during laparotomy in a few single-centre studies, showing that the EEOT was unable to accurately predict fluid responsiveness,[18,21] while the reliability of the mini-FC was only moderate, with 56% sensitivity and 87% specificity for distinguishing responders from nonresponders.[22]

We designed this study to address this issue by comparing the reliability of the EEOT and of the mini-FC in predicting fluid responsiveness in a multicentre trial on patients undergoing elective open abdominal surgery.

Materials and methods

Patients

The current multicentre study was conducted in the operating rooms of three Italian university hospitals: the Humanitas Research Hospital (Rozzano, Milano), the Maggiore della Carità (Novara) and the Azienda Ospedaliero-Universitaria Careggi (Firenze). The protocol was designed in accordance with the principles outlined in the Declaration of Helsinki and approved by the local institutional ethics committees (Humanitas Research Hospital Protocol number 91/19 – 19 February 2019; Maggiore della Carità Protocol number 6719 – 10 May 2019; Careggi Protocol number 22613/2019 – 12 June 2019) and was prospectively registered at https://clinicaltrials.gov (NCT03808753). Informed written consent was obtained from all the participants.

The inclusion criteria were: age more than 18 years, scheduled for elective laparotomy, need and availability of invasive arterial monitoring and operating room equipped with a ventilator having an expiratory-hold function.

The pre-operative exclusion criteria were: any recurrent cardiac arrhythmia, known reduced left (ejection fraction <30%) or right (systolic peak velocity of tricuspid annular motion $<0.17\ m\ s^{-1}$) ventricular systolic function, BMI more than 35, chronic obstructive pulmonary disease classified as Global Initiative for Obstructive Lung Disease at least 2. Once enrolled the following exclusion criteria applied: significant bleeding (more than 500 ml in 30 min), persistent or recurrent extrasystoles, persistent low quality of the arterial signal despite optimisation.

Peri-operative management

All patients received standard intra-operative monitoring, including heart rate, peripheral oxygen saturation, continuous electrocardiography, and noninvasive blood pressure (BP) monitoring. General anaesthesia was induced, after preoxygenation, with propofol, remifentanil and rocuronium ($0.6\ mg\ kg^{-1}$), and maintained with propofol (1.5 to $3.0\ mg\ kg^{-1}\ h^{-1}$) or sevoflurane (1 to 2%) and remifentanil (0.1 to $0.5\ \mu g\ kg^{-1}\ min^{-1}$) to maintain a bispectral index (BIS monitor; Medtronic, Brooklyn Park, Minnesota, USA) target of 40 to 60 throughout surgery. Neuromuscular transmission was monitored using train-of-four supramaximal stimulations and neuromuscular blockade was ensured by intermittent boluses of rocuronium $0.10\ mg\ kg^{-1}$ every 40 to 50 min. The use of epidural anaesthesia and postoperative pain management was at the discretion of the attending anaesthetists.

Fluids, including the mini-FC, were infused peripherally through a dedicated 14 or 16-G cannula. All patients received lactated Ringer's solution at $4\ ml\ kg^{-1}\ h^{-1}$ as maintenance fluid during surgery and were ventilated in a volume-control mode with the following settings: tidal volume (V_T) $7\ ml\ kg^{-1}$ of predicted body weight and positive end-expiratory pressure set between 3 and 6 cmH_2O. After induction of general

anaesthesia, invasive BP was monitored via a 20-G cannula in the radial artery and the pressure signal was then connected to the MostCare device (Vygon, Padua, Italy). The arterial waveform was optimised to exclude under or overdamping, and a square-wave test was used in all patients to check the quality of the pressure signal.[23]

Haemodynamic monitoring and tests

The MostCare system works with a sampling rate of 1000 points (P/t) per second analysing both the systolic and the diastolic part of the arterial waveform signal. The SV is estimated 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' of the arterial waveform shape. These points are generated by the mechanical interaction between forward and backward pressure waves, and define the profile of each arterial waveform, which is analysed by MostCare for the calculation of the vascular impedance.[24] Systolic arterial pressure (SAP), diastolic, mean arterial pressure (MAP) and dicrotic arterial pressures 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.

Study protocol

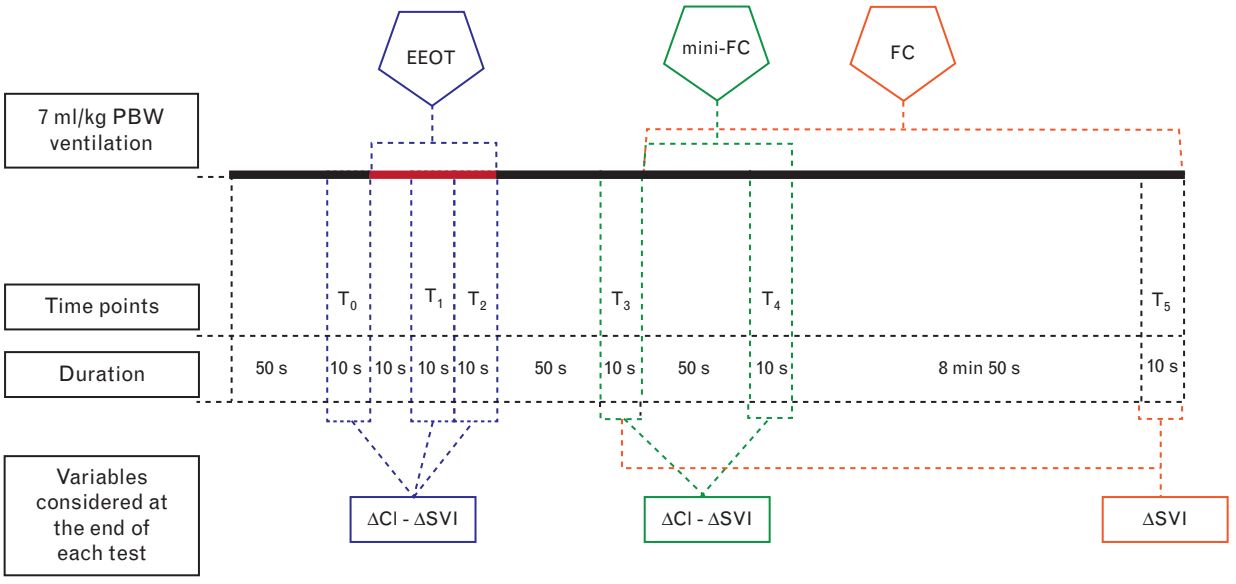
The protocol started during surgery before the administration of any vasopressor, epidural bolus or infusion, in a period of intra-operative haemodynamic stability as previously defined (change in MAP of less than 10% over 5 min),[20] while keeping the ventilatory settings constant. For the safety of the patient, the interruption of the protocol was at the discretion of the attending anaesthetist.

A series of measurements made up the study protocol (Fig. 1). The first set of measurements (T_0) was recorded and then the EEOT test was performed by using the 'expiratory hold' function on the ventilator for 30 s. Two sets of measurements (T_1 and $T_{2)}$ were recorded after 20 ($EEOT_{20}$) and 30 ($EEOT_{30}$) s. After 1 min a further set of measurements (T_3) was recorded, the mini-FC (100 ml of Ringer's solution over 1 min) was applied, and another set of measurements (T_4) was recorded. Subsequently the residual aliquot of the fluid challenge consisting of 4 ml kg^{-1} of Ringer's solution was administered in 9 min and a set of measurements (T_5) was recorded at the end of the fluid challenge. All the haemodynamic variables during the entire study protocol were averaged every 10 s by the MostCare and imported into a dedicated EXCEL (Microsoft, Redwood, Mississippi, USA) spreadsheet for further analysis.

Statistical analysis

The sample size of the study was calculated by means of the comparison of the area under the receiver operating characteristic (ROC) curves (AUC). In keeping with previous findings,[16,18,21] we predicted an AUC of 0.91

Fig. 1 Study protocol: the end-expiratory occlusion test was performed by interrupting the 7mlkg−1 volume-controlled mechanical ventilation for 30s (red line)



The mini-fluid challenge consisted of 100 ml infused over 1 min, while the rest of the 4 ml kg^{-1} fluid challenge was infused over 9 min. T_0 to T_5 are the time-points used to assess the changes in stroke volume index after each test. CI, cardiac index; EEOT, end-expiratory occlusion test; FC, fluid challenge; PBW, predicted body weight; SVI, stroke volume index.

for the mini-FC and 0.78 for the EEOT. Accordingly, we calculated a sample size of 102 patients (type I error of 5% and type II error of 20%, ratio of responders/non-responders = 1). Each centre planned to enroll at least 20% of the overall sample size (20 patients).

Normal distribution was evaluated by the d'Agostino-Pearson test, and the results were expressed as mean ± SD or median [IQR]. Proportions were compared using the χ^2 test or the Fisher exact test while continuous variables were compared with an unpaired *t* test or the Mann–Whitney *U* test, as appropriate. The haemodynamic values of responders and nonresponders at each step of the protocol were analysed with Friedman repeated measures analysis of variance (ANOVA) on ranks. Post hoc testing was performed using Tukey's test.

The reliability of the EEOT and the mini-FC in predicting fluid responsiveness were assessed using a ROC curve approach. A patient was considered fluid responsive if the SVI increased at least 10% after fluid challenge administration (T_5), when compared with T_0 value. The areas under the ROC curves (95% CI) were calculated: first, for PPV and SVV values recorded at T_0; second, for the EEOT, considering SVI changes after 20 (T_1 – $EEOT_{20}$) and 30 (T_2 – $EEOT_{30}$) s from expiratory hold, with respect to haemodynamic values recorded at T_0; third, for the mini-FC, considering SVI changes in the last 10 s of the test application (T_4) with respect to haemodynamic values recorded at T_3 (Fig. 1).

The ROC curves were also built by using a bootstrap methodology, which creates multiple samples (1000) by randomly drawing instances with replacement from the original study cohort, limiting the impact of outliers and providing more robust representations.[25]

Cut-off values for all the preload-dependency indexes were chosen to correspond to the best respective Youden's index,[26] and statistically significant ROC curves were compared using the De Long test.[27] To avoid the limitation of the binary response imposed by the ROC curve approach and accounting for overlapping results between responders and nonresponders, the grey zones for all the statistically significant ROC curves were computed, with the low cut-off value, including 90% of negative fluid challenge responses, and the high cut-off value predicting positive fluid challenge in 90% of cases.[9]

Considering the small SVI thresholds reported in previous studies for the EEOT and the mini-FC,[16] we calculated the least significant change (LSC) of the SVI, which sets the minimum percentage change between successive measurements considered associated with a random error and representing then a real change in SVI.[28] LSC was calculated as follows: first, the coefficient of variation (SD/mean) of SVI measurements was calculated from three consecutive measurements retrieved from the first 50 enrolled patients (25 nonresponders and 25 responders) during the EEOT; second, the precision was calculated as 2 × coefficient of variation; third, the LSC was calculated as precision $\sqrt{2}$.

Statistical analyses were conducted using GraphPad PRISM V8 (GraphPad Software Inc., San Diego, California, USA) and Medcalc (Software 8.1.1.0; Mariakerke, Belgium). A two-tailed *P* value less than 0.05 was considered statistically significant.

Results

From 27 February 2019 to 16 January 2020, 223 consecutive adults underwent an elective laparotomy, but 56 did not meet the inclusion criteria, and 64 were excluded after the enrolment. Finally, data obtained from 103 patients were analysed (52 from Milan, 25 from Florence and 26 from Novara). However, one $EEOT_{20}$ record was considered unsuitable for the analysis because of an altered arterial signal and, therefore, excluded (Fig. 2). Patient characteristics, comorbidities, surgical procedures, risk scores and ventilatory variables are reported in Table 1 (Table s1 in the Supplementary Digital Content, http://links.lww.com/EJA/A444).

Overall, fluid challenge administration induced an increase in SVI at least 10% in 53 patients (51.5%, fluid challenge responders). The rate of fluid responsiveness was comparable among the three centres ($P = 0.10$; Table s1 in the Supplementary Digital Content, http://links.lww.com/EJA/A444). The fluid challenge in responders and nonresponders was 276 ml [240 to 316 ml] and 272 ml [231 to 332 ml], respectively ($P = 0.75$).

The measurements and the comparisons from each step of the study protocol are reported in Table 2 (Table s2 in the Supplementary Digital Content, http://links.lww.com/EJA/A444). In responders, fluid challenge administration increased SAP ($P = 0.01$), CI ($P < 0.001$) and SVI ($P < 0.001$), while it reduced heart rate ($P < 0.001$). In nonresponders, fluid challenge administration did not significantly affect any of the measured haemodynamic variables.

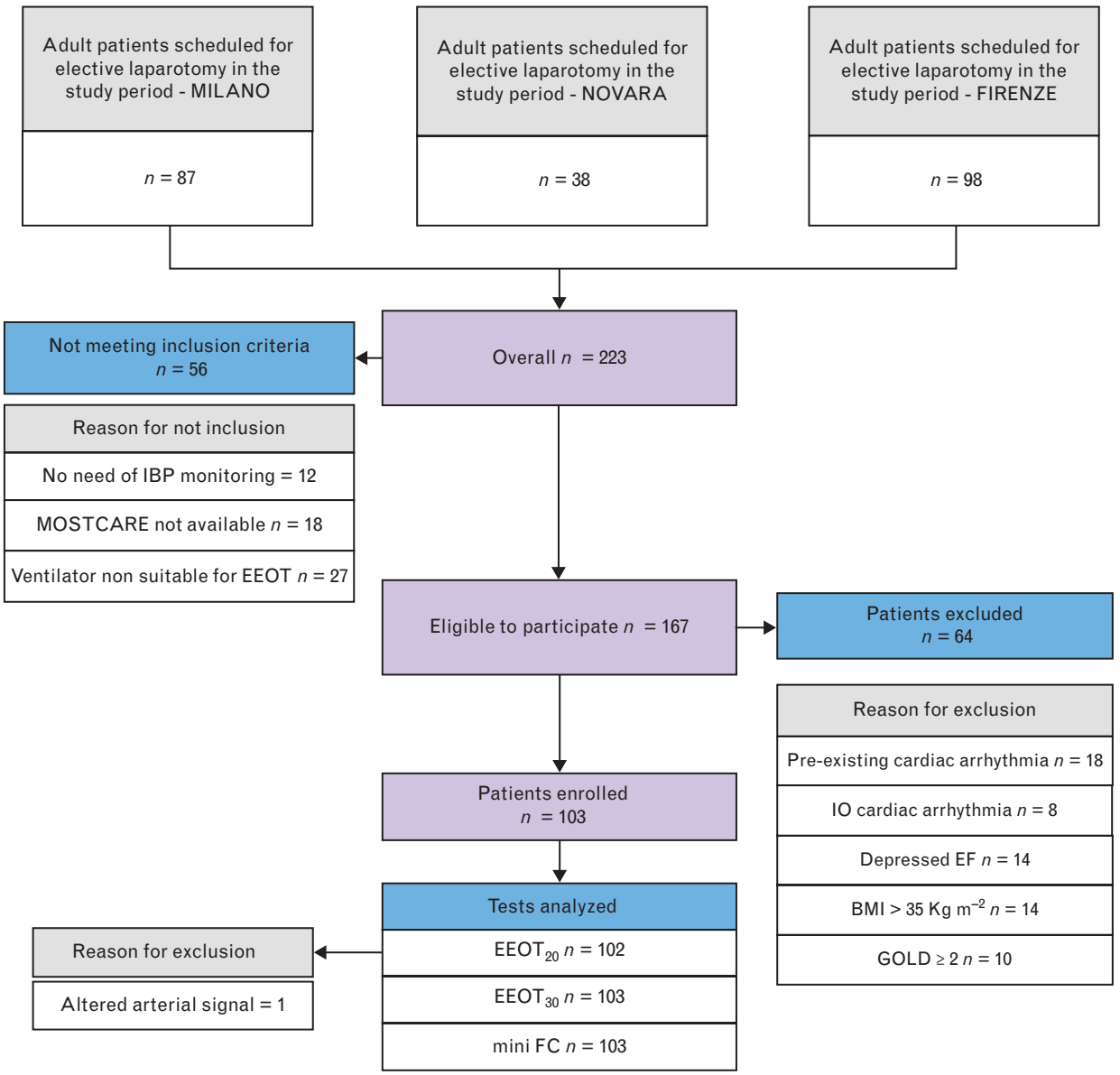
Baseline dynamic indexes of fluid responsiveness

The PPV showed an AUC of 0.77 (95% CI; 0.67 to 0.84; $P < 0.0001$), a best threshold of 10.8% with 48.5% of patients included in the grey zone [11.1 to 5.2%]. The SVV showed an AUC of 0.71 (95% CI; 0.61 to 0.80; $P = 0.0002$), a best threshold of 10.0% with 57.3% of patients included in the grey zone [12.0 to 5.0%].

Effect of end-expiratory occlusion test and mini-fluid challenge on systolic arterial pressure

Neither SAP changes after the mini-FC (AUC of 0.62; $P = 0.07$), or SAP changes after the $EEOT_{20}$ or the $EEOT_{30}$ (AUC = 0.50; $P = 0.97$ and AUC = 0.54; $P = 0.54$, respectively) predicted fluid responsiveness.

Fig. 2 Flow of patients in the study



BMI, body mass index; EEOT, end-expiratory occlusion test; EF, ejection fraction; FC, fluid challenge; GOLD, Global Initiative for Obstructive Lung Disease classification; IBP, invasive blood pressure; IO, intra-operative.

Effect of end-expiratory occlusion test and mini-fluid challenge on stroke volume index

The AUC of the SVI changes after the mini-FC was 0.95 (95% CI; 0.88 to 0.98; $P < 0.0001$), with a best cut-off value of 4.0 and 3.8% of patients included in the grey zone [2.3 to 4.1%]. The AUC of the SVI changes after EEO_{20} was 0.67 (95% CI; 0.57 to 0.76; $P = 0.004$), with a best cut-off value of 3.4 and 60.8% of patients included in the grey zone [−4.3 to 5.1%]. The AUC of the SVI changes after EEO_{30} was 0.73 (95% CI; 0.63 to 0.81, $P < 0.0001$), with a best cut-off value of 3.4%, and 53.3% of patients included in the grey zone [−3.8 to 3.2%] (Fig. 3).

The LSC obtained for SVI measurements was 4.5% (2.9 to 6.6%). Since all the obtained cut-offs were lower than the median LSC of the SVI measurement, we give the first threshold reported by the ROC analysis above the LSC, and the associated sensitivity and specificity (Table 3).

Receiver operating characteristic comparisons and bootstrapping analysis

The AUC of the mini-FC for both SVI and CI were significantly higher than the AUCs of baseline PPV and SVV ($P < 0.001$ for both) and than the AUCs of baseline $EEOT_{20}$ and $EEOT_{30}$ ($P < 0.001$). After $EEOT_{20}$ and

Table 1 Patients' characteristics at enrolment

Variables		Total cohort	Responders, *n*=53	Nonresponders, *n*=50	*P* value
General characteristics					
Age (years)		69 [59 to 76]	69 [56 to 76]	67.5 [60 to 76]	0.84
Male		60 (59)	34 (64)	26 (53)	0.26
BMI (kg m^{-2})		24 [22 to 27]	24 [22 to 27]	24 [22 to 28]	0.94
NSQIP score for serious complications		20.9 (7.1)	21.5 (7.3)	20.3 (6.8)	0.39
NSQIP score for all complications		24.1 (7.8)	24.6 (8.1)	23.6 (7.4)	0.52
ASA score					
1		8 (7.8)	4 (7.6)	4 (8.0)	0.39
2		65 (63.1)	30 (56.6)	35 (70.0)	
3		29 (28.2)	18 (34.0)	11 (22.0)	
4		1 (1.0)	1 (1.9)	0 (0.0)	
Pre-operative comorbidities					
Hypertension		45	25	20	0.46
Cardiovascular disorders (including cerebrovascular)		34	22	12	0.06
Diabetes		22	12	10	0.75
COPD		13	6	7	0.68
Renal dysfunction		3	1	2	0.53
Cancer		91	52	39	0.002
Other metabolic disorders		22	11	11	0.88
Duration of surgery (min)		422 [250 to 545]	430 [260 to 548]	417 [245 to 535]	0.41
Time from anaesthesia induction to protocol start (min)		63 [36 to 100]	65 [35 to 115]	60 [37 to 87]	0.51
Pre-operative haemoglobin (mg dl^{-1})		12.4 ± 2.1	12.4 ± 2.2	12.4 ± 2.1	0.99
Pre-operative creatinine (mg dl^{-1})		0.78 [0.66 to 0.90]	0.80 [0.67 to 0.90]	0.76 [0.65 to 0.90]	0.45
Surgical procedures					
Intervention	Duodenocefalopancreatectomy	38 (36.9)	19 (35.9)	19 (38.0)	0.12
	Pancreatectomy	17 (16.5)	9 (17.0)	8 (16.0)	
	Gastrectomy	7 (6.8)	5 (9.4)	2 (4.0)	
	Hemicolectomy	5 (4.9)	1 (1.9)	4 (8.0)	
	Retroperitoneal sarcoma resection	4 (3.9)	4 (7.6)	0 (0.0)	
	Cholecystectomies	3 (2.9)	0 (0.0)	3 (6.0)	
	Hepatectomies	2 (1.9)	2 (3.8)	0 (0.0)	
	Esophagectomy	2 (1.9)	2 (3.8)	0 (0.0)	
	Others	25 (24.2)	11 (20.7)	14 (28.0)	
Intra-operative ventilator settings and blood gases at T_0					
V_T, (ml)		459 ± 65	466 ± 48	452 ± 79	0.28
Total PEEP (cmH_2O)		5 [5 to 6]	5 [5 to 6]	5 [5 to 6]	0.44
Driving pressure (cmH_2O)		9.3 ± 2.7	9.0 ± 2.4	9.7 ± 2.9	0.24
RR (bpm)		12 [12 to 14]	12 [12 to 14]	12 [12 to 14]	0.64
PaO_2/FiO_2 (ratio)		414 ± 142	445 ± 120	382 ± 157	0.03
C_t (ml cmH_2O^{-1})		50 [42 to 62]	55 [43 to 65]	50 [42 to 57]	0.12
pH		7.41 [7.43 to 7.38]	7.41 [7.43 to 7.36]	7.41 [7.42 to 7.38]	0.88
$PaCO_2$ (mmHg)		41 ± 5	41 ± 5	41 ± 4	0.86
Lactate (mmol l^{-1})		0.7 [0.5 to 0.9]	0.8 [0.6 to 0.9]	0.6 [0.5 to 0.7]	0.04
Base excess, (mEq l^{-1})		1.4 [−1 to 3.0]	1.6 [−0.6 to 2.8]	0.8 [−1.4 to 3.3]	0.56

Values are presented as number (%); mean ± SD or median [IQR] as appropriate. ASA, American Society of Anesthesiologists classification; BMI, body mass index; COPD, chronic obstructive pulmonary disease; C_t, total respiratory compliance; NSQIP; National Surgical Quality Improvement Program; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2/FiO_2, arterial partial pressure of oxygen/fraction of inspired oxygen; PEEP, positive end-expiratory pressure; RR, respiratory rate; V_T, tidal volume.

$EEOT_{30}$, the AUCs of baseline PPV and SVV, compared with SVI changes, did not differ significantly (Table s3 in the Supplementary Digital Content, http://links.lww.com/EJA/A444). The bootstrapped ROC curves for the listed tests produced almost identical results to those not applying this statistical approach (Table s4 in the Supplementary Digital Content, http://links.lww.com/EJA/A444).

Discussion

The main findings of this three-centre study regarding the use of FHTs during a laparotomy are: first, the mini-FC predicts fluid responsiveness better than the EEOT; second, in this context the EEOT, with both a 20 or a 30-s expiratory hold, showed a moderate discriminatory ability comparable with that of the dynamic indices PPV and SVV.

Hundreds of thousands of elective and emergency laparotomies are performed every year all over the world,[29,30] all requiring appropriate fluid administration. Attempts to get this right might include the assessment of preload dependency, which is often challenging.[4,7,16] In our study, haemodynamic improvement after fluid administration was found in only 51.5% of the patients, which is in agreement with previous findings.[8] Since the reliability of the PPV and SVV is low in surgical patients,[9] the use of FHTs, such as the EEOT and mini-FC, have gained in popularity, despite being tested only in small-sized and potentially biased studies.[16]

Table 2 Haemodynamic variables at protocol steps T_0 to T_5

	Variables	T_0	T_1	T_2	T_3	T_4	T_5	*P* value All steps
Responders, *n*=53	MAP (mmHg)	71 [62 to 81]	73 [63 to 83]	73 [63 to 79]	71 [62 to 79]	71 [66 to 79]	75 [64 to 81]	0.21
	SAP (mmHg)	105 [91 to 113]	106 [95 to 116]	106 [94 to 113]	103 [88 to 114]	104 [96 to 114]	109 [91 to 125]	0.04[1]
	CI ($l\,min^{-1}\,m^{-2}$)	2.3 [2.0 to 2.6]	2.3 [2.1 to 2.7]	2.3 [2.0 to 2.6]	2.2 [2.0 to 2.5]	2.4 [2.2 to 2.8]	2.6 [2.3 to 2.8]	<0.0001[2]
	SVI ($ml\,min^{-1}\,m^{-2}$)	33 [25 to 39]	33 [27 to 401]	34 [26 to 40]	31 [25 to 38]	37 [30 to 42]	37 [32 to 44]	<0.0001[3]
	HR (bpm)	72 [63 to 79]	72 [64 to 78]	71 [62 to 78]	74 [63 to 80]	68 [60 to 77]	69 [62 to 76]	<0.0001[4]
	PPV (%)	11 [6 to 17]	8 [5 to 14]	7 [3 to 12]	11 [6 to 18]	9 [7 to 19]	11 [5 to 17]	<0.0001[5]
	SVV (%)	10 [7 to 13]	10 [7 to 13]	8 [6 to 11]	10 [7 to 15]	11 [7 to 13]	9 [7 to 15]	0.02[6]
Nonresponders, *n*=50	MAP (mmHg)	71 [64 to 81]	70 [64 to 81]	70 [64 to 79]	70 [63 to 78]	69 [63 to 76]	72 [66 to 78]	0.14
	SAP (mmHg)	105 [92 to 119]	104 [95 to 120]	102 [91 to 119]	103 [91 to 115]	104 [91 to 117]	105 [97 to 115]	0.16
	CI ($l\,min^{-1}\,m^{-2}$)	2.5 [2.3 to 2.8]	2.5 [2.3 to 2.9]	2.5 [2.3 to 2.7]	2.5 [2.2 to 2.9]	2.6 [2.2 to 2.9]	2.5 [2.3 to 2.8]	0.14
	SVI ($ml\,min^{-1}\,m^{-2}$)	38 [31 to 47]	38 [31 to 48]	38 [38 to 47]	38 [33 to 47]	39 [33 to 47]	39 [32 to 45]	0.45
	HR (bpm)	65 [59 to 77]	66 [58 to 76]	67 [58 to 76]	65 [59 to 74]	64 [56 to 72]	66 [60 to 74]	<0.0001[7]
	PPV (%)	7 [3 to 9]	7 [4 to 10]	5 [3 to 10]	7 [5 to 11]	7 [5 to 10]	8 [5 to 11]	0.01[8]
	SVV (%)	8 [4 to 10]	8 [6 to 12]	8 [5 to 12]	9 [6 to 12]	9 [6 to 12]	9 [5 to 12]	0.33

Median [IQR] values of haemodynamic variables at each step of the protocol (T_0 to T_5). *P* value shows multiple comparisons among haemodynamic variables at each step of the study protocol, using Friedman test for repeated measures. CI, cardiac index; HR, heart rate; MAP, mean arterial pressure; PPV, pulse pressure variation; SAP, systolic arterial pressure; SVI, stroke volume index; SVV, stroke volume variation. [1]T_0 vs. T_5 *P* value = 0.01. [2]T_0 vs. T_1 *P* value = 0.003; T_0 vs. T_2 *P* value = 0.04; T_0 vs. T_4 *P* value <0.001; T_0 vs. T_5 *P* value <0.001. [3]T_0 vs. T_1 *P* value = 0.01; T_0 vs. T_2 *P* value = 0.006; T_0 vs. T_4 *P* value <0.001; T_0 vs. T_5 *P* value <0.001. [4]T_0 vs. T_4 *P* value <0.001; T_0 vs. T_5 *P* value <0.001. [5]T_0 vs. T_1 *P* value = 0.01; T_0 vs. T_2 *P* value <0.001. [6]Differences between T_0 and the other time-points NS. [7]T_0 vs. T_4 *P* value = 0.007. [8]Differences between T_0 and the other time-points NS.

To the best of our knowledge, this is the first multicentre study assessing the discriminatory ability of FHTs in the operating room. Our results suggest that the mini-FC should be considered as the first choice, showing high-sensitivity, 98.0% [89.5 to 99.6] and specificity, 86.8% [75.1 to 93.4] in predicting fluid responsiveness for a 4% increase in the SVI. This cut-off is close to that reported in the literature (5%).[16] After correcting the cut-off (5.1%) for the LSC of SVI measurements, the overall performance of the test was not affected and led only to a minimal reduction in the specificity of the test.

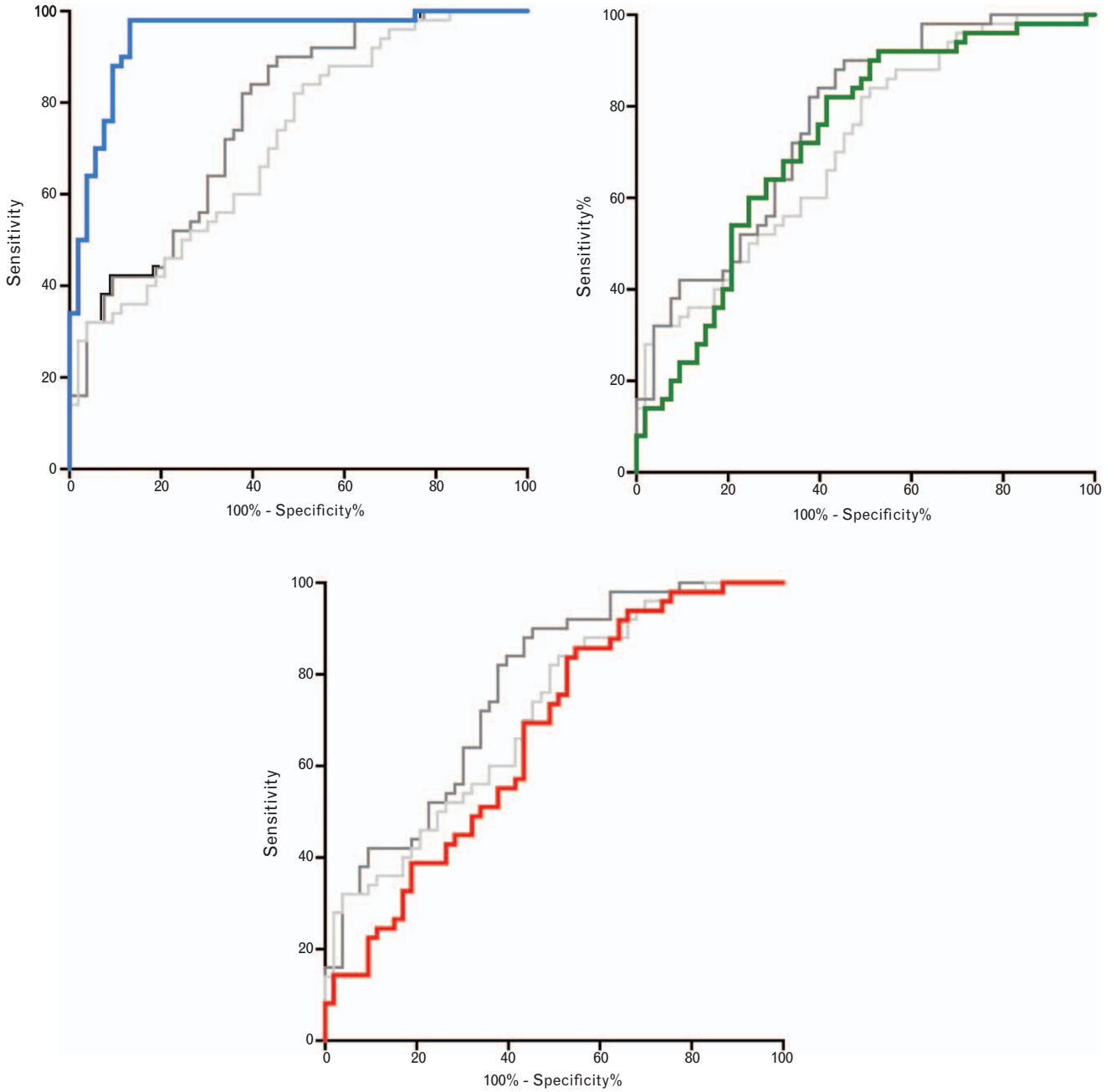
The good performance of the mini-FC may be partially attributed also to the methodology used in our study. Both the final response to the entire aliquot of the fluid challenge and to the first 100 ml (the mini-FC) have been calculated with respect to the same baseline value (T_3). This approach may artificially boost the true predictive power of the mini-FC, since the predictor variables are not independent (a different approach would consider the final response with respect to a 'new' baseline after the mini-FC), as previously pointed out by Vistisen and Scheeren[31] Moreover, the volume adopted for the fluid challenge, which is not standardised in previous reports, may influence the final haemodynamic response and, in turn, the predictability the FHTs.[32] However, we minimised this bias by adopting the dose of 4 $ml\,kg^{-1}$, which has been described as the minimal required to adequately challenge the haemodynamic system during a fluid challenge.[33]

Our results show that laparotomy affects the discriminatory ability of the EEOT, confirming previous findings from studies predominantly[18] or entirely[21] performed in this surgical setting. The interruption of the mechanical inspirations during the EEOT is associated with a rather small increase in the right SV (about 5%)[16] only in fluid responders. This transient effect on the preload may be somewhat affected by laparotomy, due to the physiological interactions between vascular abdominal and cardiothoracic compartments. More than 20 years ago, Takata *et al.*[34] described the relationship between abdominal pressure and venous return as a waterfall phenomenon at the level of inferior vena cava before getting through the diaphragm. Abdominal opening affects the transdiaphragmatic pressure gradient by reducing abdominal pressure[21] and, in turn, may potentially alter the effect on the RV preload of the end-expiratory hold, making the EEOT unreliable. Significantly, with a closed abdomen, the EEOT successfully predicted fluid responsiveness in supine neurosurgical patients,[35] but not when the prone position compressed the inferior cava,[36] confirming that, to be reliable, the EEOT requires specific physiological conditions related to venous return. In contrast, the mini-FC acts as a quick and transient increase of the RV preload via the superior cava, which is independent of the interplay between intrathoracic and abdominal pressure and therefore, less affected by laparotomy.

Some limitations of this trial should be acknowledged. First, the results of our study are primarily applicable to laparotomy procedures. Second, the enrolment was limited by the concurrent availability in the operating room of a ventilator equipped with an expiratory hold function, to perform the EEOT. This technical limitation could have partially biased the selection of those patients simultaneously eligible for the study, since that choice was at the discretion of the principal investigator of each centre.

Third we did not randomise the sequence of application of the two tests, and we used 1 min of delay between the

Fig. 3 Receiver operating characteristic curves of the changes of stroke volume index after the mini-fluid challenge – blue line, upper panel; 0.95 (0.88 to 0.98), after the end-expiratory occlusion test20 – green line, middle panel; 0.67 (0.57 to 0.76) and after the end-expiratory occlusion test30 – red line, lower panel; 0.73 (0.63 to 0.81), compared with the receiver operating characteristic curves of pulse pressure variation – dark grey line; 0.77 (0.67 to 0.84) and stroke volume variation – light grey line; 0.71 (0.61 to 0.80) at baseline (T0 time point; see Fig. 1)



EEOT, end-expiratory occlusion test; FC; fluid challenge; PPV, pulse pressure variation; ROC; receiver operating characteristic (curve); SVV, stroke volume variation.

EEOT and the mini-FC to guarantee the return to steady-state before the application of the subsequent test of the protocol. These choices may add a risk of bias due to a carry-over effect, which cannot be excluded. However, the ANOVA analysis of the protocol steps showed few significant changes that seem not to have any clinical relevance. Moreover, the reliability of the EEOT in predicting fluid responsiveness is also known to be affected by the low V_T. We have previously demonstrated that in the operating room and ICU the EEOT performed better when the mean V_T was higher than 6.8 ml kg^{-1}.[16] Accordingly, we adopted a 7 ml kg^{-1} baseline V_T to minimise the risk of this bias.

Table 3 Discriminatory ability of dynamic indices, end-expiratory occlusion and mini-fluid challenge tests in predicting fluid responsiveness

	AUC (95% CI)	Best threshold (%)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Youden index
Baseline PPV	0.77 (0.67 to 0.84)	10.8	54.7 (40.4 to 68.4)	90.0 (78.2 to 96.7)	0.45
Baseline SVV	0.71 (0.61 to 0.80)	10.0	49.1 (35.1 to 63.2)	84.0 (70.9 to 92.8)	0.33
ΔSVI $EEOT_{20}$	0.67 (0.57 to 0.76)	3.4	85.7 (72.8 to 94.1)	45.3 (31.6 to 59.6)	0.31
ΔSVI $EEOT_{30}$	0.73 (0.63 to 0.81)	3.4	92.0 (81.2 to 96.8)	45.3 (32.6 to 58.5)	0.41
ΔSVI mini-FC	0.95 (0.88 to 0.98)	4.0	98.0 (89.5 to 99.6)	86.8 (75.1 to 93.4)	0.85
	AUC (95% CI)	**Thresholds considering LSC (%)**	**Sensitivity (%) (95% CI)**	**Specificity (%) (95% CI)**	**Youden index**
ΔSVI $EEOT_{20}$	0.67 (0.57 to 0.76)	4.9	87.7 (75.2 to 95.3)	23.1 (35.8 to 50.2)	0.24
ΔSVI $EEOT_{30}$	0.73 (0.63 to 0.81)	4.7	92.0 (81.1 to 96.8)	35.8 (24.3 to 49.1)	0.28
ΔSVI mini-FC	0.95 (0.88 to 0.98)	5.1	98.0 (89.5 to 99.6)	84.9 (72.9 to 92.1)	0.83

The median [IQR] LSC for SVI measurements was 4.5% [2.9 to 6.6] and the reported thresholds are those above the LSC retrieved from the receiver operating characteristic curve analysis of each test. ΔSVI, changes in the stroke volume index; AUC, area under the receiver operating characteristic curve; $EEOT_{20}$/$EEOT_{30}$, end-expiratory occlusion lasting 20 or 30 s; LSC; least significant change of the SVI, which sets the minimum percentage change between successive measurements that can be considered not due to random error and therefore representing a real change in SVI; mini-FC, mini-fluid challenge; PPV, pulse pressure variation; SVV, stroke volume variation.

Finally, in agreement with previous findings,[16] SVI changes associated with both FHTs are relatively small, raising concerns about the ability to track real changes by haemodynamic monitoring, which is usually uncalibrated in the operating room.[16] The reliability of the MostCare is highly dependent on the quality of the arterial waveform signal,[24] and the centres involved in the study are highly trained in the use of this device.

Conclusion

In patients undergoing laparotomy the mini-FC reliably predicted fluid responsiveness with high-sensitivity and specificity. The EEOT showed poor discriminative value and cannot be recommended for the assessment of fluid responsiveness in this surgical setting.

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