



# Changes in arterial blood pressure characteristics following an extrasystolic beat or a fast 50 ml fluid challenge do not predict fluid responsiveness during cardiac surgery

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## Abstract

Prediction of fluid responsiveness is essential in perioperative goal directed therapy, but dynamic tests of fluid responsiveness are not applicable during open-chest surgery. We hypothesised that two methods could predict fluid responsiveness during cardiac surgery based on their ability to alter preload and thereby induce changes in arterial blood pressure characteristics: (1) the change caused by extrasystolic beats and (2) the change caused by a fast infusion of 50 ml crystalloid (micro-fluid challenge). Arterial blood pressure and electrocardiogram waveforms were collected during surgical preparation of the left internal mammary artery in patients undergoing coronary artery bypass surgery. Patients received a fluid challenge (5 ml/kg ideal body weight). The first 50 ml were infused in 10 s and comprised the micro-fluid challenge. Predictor variables were defined as post-ectopic beat changes (compared with sinus beats preceding ectopy) in arterial blood pressure characteristics, such as pulse pressure and systolic pressure, or micro-fluid challenge induced changes in the same blood pressure characteristics. Patients were considered fluid responsive if stroke volume index increased by 15% or more after the full fluid challenge. Diagnostic accuracy was calculated by the area under the receiver operating characteristics curve (AUC). Fifty-six patients were included for statistical analysis. Thirty-one had extrasystoles. The maximal AUC was found for the extrasystolic change in pulse pressure and was 0.70 (CI [0.35 to 1.00]). The micro-fluid challenge method generally produced lower AUC point estimates. Extrasystoles did not predict fluid responsiveness with convincing accuracy in patients undergoing cardiac surgery and changes in arterial waveform indices following a micro-fluid challenge could not predict fluid responsiveness. Given a low number of fluid responders and inherently reduced statistical power, our data does not support firm conclusions about the utility of the extrasystolic method.

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**Keywords** Cardiac surgery · Fluid responsiveness prediction · Perioperative fluid therapy · Haemodynamic monitoring · Extrasystoles

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## 1 Introduction

Haemodynamic instability is often treated with fluids, but fluids have side effects and should only be considered in fluid responsive patients [1, 2], i.e. patients whose stroke volume will significantly increase with fluid infusion.

Static indicators for fluid responsiveness prediction (e.g. central venous pressure) have all proved unreliable [3–5]. Some protocols for major surgery dictate systematic fluid challenges of 100–500 ml to guide and titrate fluid administration [6, 7]. Such a fluid strategy entails a risk of overhydration, which is associated with increased postoperative complications [8]. In contrast, ventilator-induced dynamic variables such as pulse pressure variation (PPV) and stroke volume variation (SVV), and passive leg raising (PLR) [4, 9–11] have consistently proven reliable to predict fluid responsiveness. Common to these techniques is that preload fluctuations are utilized to predict fluid responsiveness.

However, during open-chest surgery, sternotomy and pericardiotomy during heart surgery changes the complex physiology of ventilator-induced heart–lung interactions by alterations to the interplay between preload, afterload and aortic compliance rendering dynamic preload variables less reliable [12, 13].

Thus, ventilator-induced indicators are less reliable in this setting and the classical PLR manoeuvre is hardly applicable during open-chest surgery [9, 13–17], although some studies altering the positioning of the patient have been performed at the end of cardiac surgery after chest closure [18, 19].

Therefore, a reliable technique for prediction of fluid responsiveness is missing for cardiac surgical patients during the open-chest condition. Still, the convincing results of PLR and dynamic variables in other settings indicate that the way forward is to look for alternative preload altering mechanisms.

Extrasystoles comprise a preload altering mechanism. The heartbeat following the extrasystolic beat, i.e. the post-ectopic beat, has a prolonged RR-interval (filling time) which results in increased preload compared with preceding sinus beats [20, 21]. Recent experimental and clinical studies have showed promising results using extrasystoles for fluid responsiveness prediction [22–24] but a study during general anaesthesia did not provide similar results [25]. Yet, the approach has not been investigated in general anaesthesia with thermodilution cardiac output as outcome. Furthermore, recently a micro-fluid challenge (MFC, 50 ml infused within 10 s) showed interesting results regarding fluid responsiveness prediction in the intensive care unit (ICU) when assessed by changes in echocardiographic measurements [26].

Accordingly, the present study aimed to validate the predictive value of both the extrasystoles and the

micro-fluid challenge methods in open cardiac surgery with closed pericardium. We hypothesised that these two different methods could predict fluid responsiveness in anaesthetized patients undergoing coronary artery bypass graft surgery.

## 2 Methods and materials

This prospective single-center study was approved by the Danish Data Agency (1-16-02-316-16), registered at clinicaltrials.gov (NCT02903316) prior to initiation and conducted at Aarhus University Hospital. The study is reported in alignment with STARD guidelines [27].

### 2.1 Patient selection and inclusion

Patients scheduled for elective on-pump coronary artery bypass graft surgery without additional surgical procedures were screened for exclusion criteria: ejection fraction < 35%, haemodialysis, major cognitive dysfunction, age < 18, pregnancy and cardiac arrhythmia, e.g. atrial fibrillation.

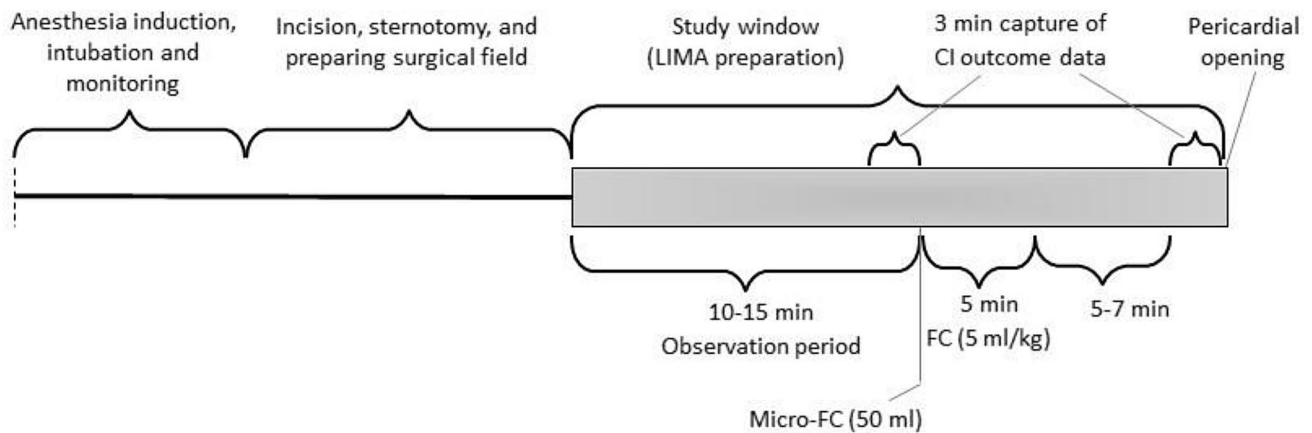
### 2.2 Perioperative monitoring and anaesthesia

Patients were equipped with plethysmography, electrocardiogram and radial arterial blood pressure monitoring. Furthermore, patients were catheterized with a pulmonary artery catheter (Swan-Ganz CCOMbo CCO/SvO<sub>2</sub>, 744F75, Edwards Lifesciences, Irvine, California, US) for monitoring of continuous cardiac output (CO) and mixed venous oxygen saturation (SvO<sub>2</sub>).

Patients were anaesthetized with intravenous infusion of propofol and sufentanil and controlled mechanically ventilated.

### 2.3 Study design and data acquisition

Figure 1 shows the study timeline. Patients were observed for extrasystoles during preparation of the left internal mammary artery. Observation began after sternotomy and insertion of the sternal retractor and continued until approximately 10–15 min prior to pericardial opening estimated by the surgeon. Following the observation period, a pre-determined volume of 5 ml/kg (ideal body weight) fluid (Ringer's acetate, B. Braun, Melsungen, Germany) was manually infused with a 50-ml syringe in the central venous catheter. Ideal body weight was calculated from height and sex; men receiving 5 ml per cm above 100 cm and women 5 ml per cm above 105 cm. The first 50 ml of the total volume were infused within 10 s (the MFC; described below). A timing marker was added to the acquired waveform data simultaneously with infusion start. The rest of the total fluid



**Fig. 1** Outlines the different time periods during the study. *CI* cardiac index, *LIMA* left internal mammary artery, *FC* fluid challenge

challenge was subsequently infused within approximately 5 min. Three consecutive continuous cardiac index (CCI) and  $SvO_2$  measurements were read off the monitor trend data before and approximately 5–7 min after completion of the fluid challenge allowing for delay in response time for CCI [28]. Three consecutive CCI measurements were obtained from the STAT display on the Vigilance II monitor, Edwards Lifesciences, using the Swan-Ganz's continuous thermodilution method. Waveforms for arterial blood pressure, pulmonary artery pressure, plethysmography, electrocardiogram and central venous pressure were extracted from the patient's monitor (Philips MP70, Philips Healthcare) by commercially available software (ixTrend, iXellence GmbH, Wildau, Germany) for offline analysis. All waveforms were sampled at 125 Hz except the electrocardiogram, which was sampled at 500 Hz. During surgery, patients were excluded if (1) there were other haemodynamically significant changes during the study period e.g. changed infusion rates or boluses of sedatives, analgesics, inotropes, or vasopressor drugs or major changes of the bed position, (2) technical problems occurred e.g. placing of the pulmonary artery catheter (3) the attending anaesthesiologist deemed the scheduled fluid challenge inappropriate for any reason.

#### 2.4 Detection of eligible extrasystoles and extraction of haemodynamic indices

R spike detection was done semi-automatically in Kubios HRV (Kubios Oy, Finland) with visual inspection and correction. RR intervals were subsequently analysed in Matlab. Extrasystoles with at least 10 preceding sinus beats were included. Additionally, extrasystolic beats should at least have a 20% shortening of the RR interval (coupling interval) to induce a significant variation in cardiac preload compared to baseline RR intervals [22]. Potential eligible extrasystoles were visually examined by two investigators, who verified

that the simultaneous arterial waveform was not damped or presented with other artefacts. Differences between the post-ectopic beat and the median of the 10 preceding sinus beats were calculated for pulse pressure ( $\Delta PP_{ES}$ ), systolic blood pressure ( $\Delta SBP_{ES}$ ), maximal pressure upstroke slope ( $\Delta dP/dt_{ES}$ ) and pre-ejection period ( $\Delta PEP_{ES}$  = time from R spike in the electrocardiogram to arterial upstroke onset in arterial blood pressure). If multiple extrasystoles were eligible in the observation period, an average of the post-ectopic changes was calculated. Changes in PP, SBP and  $dP/dt$  were all calculated as relative changes whereas the  $\Delta PEP$  (decrease) was calculated as absolute change (in ms) to omit influence of variation in vascular transit time across patients [29]. Further details of signal processing and detection of PEP have been described previously [22].

Stroke volume index (SVI) was calculated before and after the fluid infusion by dividing CCI with heart rate. Heart rate was manually verified from the electrocardiogram and pressure curves in combination.

#### 2.5 Micro-fluid challenge

It was tested if a micro-fluid challenge could induce changes in PP, SBP,  $dP/dt$  and PEP that could be used for fluid responsiveness prediction.  $\Delta PP_{MFC}$ ,  $\Delta SBP_{MFC}$ ,  $\Delta dP/dt_{MFC}$  and  $\Delta PEP_{MFC}$  were calculated by subtracting the upper quartile of the 20 s following the fluid infusion from the corresponding median of the preceding 30 s to allow for capturing a peak change in the variables.

#### 2.6 Statistical analysis and classification

All patients without excluding factors were used to test the micro-fluid challenge. From this cohort, all patients with extrasystoles present before fluid infusion were identified.

Patients were classified as fluid responders if they had a 15% increase or more in SVI following the 5 ml/kg fluid challenge. Sample size for the extrasystole method (primary outcome) was calculated using previous data [23], assuming equal numbers of fluid responders and non-responders. Using a significance level of 0.05 and power of 0.9, we needed 30 patients with extrasystoles. Prior to initiating the study, the expected occurrence of extrasystoles was determined retrospectively inspecting ectopic activity as captured by the Philips® monitoring system from 59 cardiac surgeries. Approximately 70% of patients had at least one extrasystole, which was similar to a previous study [30]. Estimating conservatively, we therefore planned to include 60 patients.

In addition to using  $\Delta$ SVI as the outcome variable, we also secondarily in retrospect analysed our data with  $\Delta$ SvO<sub>2</sub> as outcome because SvO<sub>2</sub> may reflect changes in CO more rapidly during metabolic stable conditions. Patients were classified as fluid responders if  $\Delta$ SvO<sub>2</sub> > 0 to catch subtle changes in tissue perfusion.

The researcher analysing the arterial waveforms and extracting predictors (STV) was blinded for the outcome,  $\Delta$ SVI, whereas the researcher (JMB) calculating the  $\Delta$ SVI was blinded for predictor indices. Data are reported as area under the receiver operating characteristics (ROC) curve (AUC) together with confidence intervals (95% CI) using deLong method. Optimal sensitivity and specificity were

found using Youden Index. Spearman Rank Correlation  $\rho$  is reported. Demographic and clinical variables are presented as mean  $\pm$  standard deviation (SD) except ventilation parameters, which are presented as median (interquartile range). Wilcoxon Mann–Whitney U Test was used to compare responders with non-responders. Categorical data was compared with Fisher’s Exact Test due to low number of observations. All statistical calculations and figures were done with StataMP (version 13, StataCorp., College Station, TX, USA).

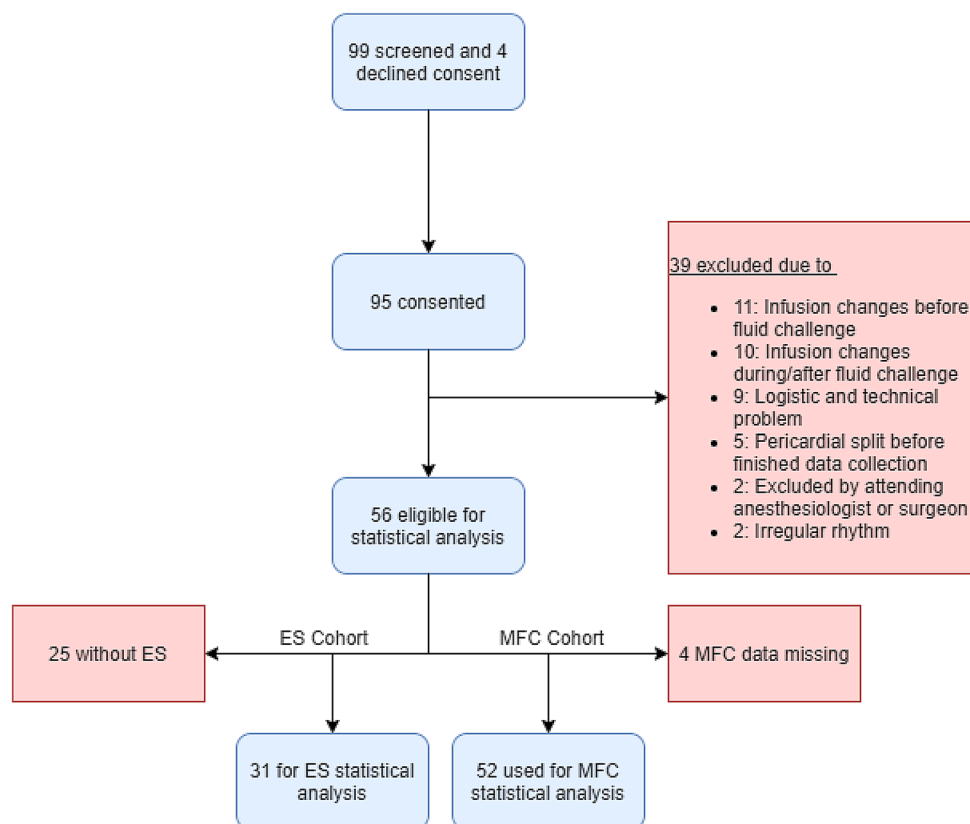
### 3 Results

Patient inclusion is shown in Fig. 2. Demographics and baseline cardio-respiratory characteristics are shown in Table 1 for the extrasystolic cohort (n = 31) and in Table 2 for the micro-fluid challenge cohort (n = 52). In both cohorts, fluid responders are compared with non-responders.

#### 3.1 Extrasystole method results

Out of 56 eligible patients, 31 had extrasystoles (55%). Responders and non-responders had similar background characteristics. Three patients out of the 31 (10%) were fluid responders. Patients received 385 (SD: 47) ml infusion.

**Fig. 2** Flowchart of patient inclusion. *ES* extrasystole, *MFC* micro-fluid challenge



**Table 1** Background characteristics the extrasystole cohort

	All participants (n=31)	Responders (n=3)	Non-responders (n=28)	p-value
General characteristics				
Age	66 (9)	64 (6)	66 (10)	0.57
Gender, female/male	2/29	0/3	2/26	1.00
Weight, kg	87 (12)	99 (6)	86 (12)	0.02*
Height, cm	177 (7)	181 (10)	176 (7)	0.37
Disease severity				
2-vessels disease	6	0	6	
3-vessels disease	25	3	22	
Number of grafts				
1	2	1	1	
2	11		11	
3	14	1	13	
4	3	1	2	
5	1		1	
Baseline vital signs				
HR, beats/min	58 (10)	62 (4)	58 (10)	0.40
SBP, mmHg	105 (14)	100 (8)	105 (14)	0.37
MAP, mmHg	73 (10)	71 (7)	73 (10)	0.59
SvO <sub>2</sub> , %	77.2 (5.3)	76 (6.1)	77.3 (5.3)	0.59
Flow measurements				
CCI, L/min*m <sup>2</sup>	2.31 (0.54)	1.73 (0.26)	2.37 (0.52)	0.03*
Preoperative LVEF, %	55 (8)	52 (8)	55 (8)	0.40
Ventilation median (interquartile)				
Tidal volume	500 (450; 530)	500 (450; 550)	500 (440; 525)	0.73
Tidal volume (ml/ideal body weight)	6.4 (5.7; 6.8)	6.4 (5.6; 6.6)	6.4 (5.8; 6.9)	0.79
Respiratory rate	12 (12; 15)	14 (12; 16)	12 (12; 15)	0.62
FiO <sub>2</sub> (%)	50 (50; 60)	60 (60; 60)	50 (50; 60)	0.09
Ventilation modus (n)				
Volume controlled	30	3	27	
Pressure controlled	1		1	

Data are presented as mean ± standard deviation (SD) except ventilation parameters, which are presented as median (interquartile range)

HR heart rate, SBP systolic blood pressure, MAP mean arterial pressure, CCI continuous cardiac index, LVEF left ventricle ejection fraction, FiO<sub>2</sub> fraction of inspiratory oxygen

\*p < 0.05 responders compared to non-responders

Post-ectopic changes in haemodynamic indices are plotted against  $\Delta$ SVI in Fig. 3 and corresponding ROC curves can be seen in Fig. 4.

The post-ectopic change in PP, SBP, dP/dt and PEP predicted fluid responsiveness with AUCs between 0.62 and 0.70.  $\Delta$ PP<sub>ES</sub> predicted fluid responsiveness with an AUC of 0.70 (CI [0.35 to 1]). The optimal threshold for  $\Delta$ PP<sub>ES</sub> was 25% resulting in sensitivity of 67% and specificity of 86% ( $\rho = 0.23$ ,  $p = 0.21$ ).  $\Delta$ SBP<sub>ES</sub> had an AUC of 0.65 (CI [0.23 to 1]).  $\Delta$ dP/dt<sub>ES</sub> and  $\Delta$ PEP<sub>ES</sub> had lower AUCs (see detailed data in Fig. 4 and Table 3).

### 3.2 Micro-fluid challenge results

The micro-fluid challenge cohort was based on the 56 eligible patients but four of these datasets were uncertain regarding exact indication of start of fluid infusion in the curve data and were thus excluded. Out of the 52 remaining patients, 29 were in the extrasystolic cohort as well. Seven of the 52 patients (13%) were fluid responders. The haemodynamic changes following the micro-fluid challenge are plotted against  $\Delta$ SVI in Fig. 5. All micro-fluid challenge measures had ROC curves following the identity line (Fig. 6). All

**Table 2** Background characteristics for micro-fluid challenge cohort

	All participants (n = 52)	Responders (n = 7)	Non-responders (n = 45)	p-value
General characteristics				
Age	66 (9)	64 (6)	66 (9)	0.46
Gender, female/male	6/46	2/5	4/41	0.18
Weight, kg	85 (13)	86 (19)	84 (12)	0.23
Height, cm	175 (9)	174 (12)	175 (8)	0.70
Disease severity				
2-vessels disease	13	1	12	
3-vessels disease	39	6	33	
Number of grafts				
1	1	1		
2	21	1	20	
3	25	4	21	
4	4	1	3	
5	1		1	
Vital signs (min; max)				
HR, beats/min	58 (12)	66 (17)	57 (11)	0.17
SBP, mmHg	107 (14)	110 (12)	106 (14)	0.66
MAP, mmHg	73 (9)	77 (9)	73 (9)	0.29
SvO <sub>2</sub> , %	77.3 (5.0)	78.1 (5.5)	77.2 (5.0)	0.50
Flow measurements				
CCI, L/min*m <sup>2</sup>	2.15 (0.52)	1.67 (0.22)	2.23 (0.52)	0.0028*
LVEF, %	55 (7)	56 (6)	55 (8)	0.51
Ventilation median (interquartile)				
Tidal volume	500 (455; 515)	500 (410; 500)	500 (470; 520)	0.36
Tidal volume (ml/ideal body weight)	6,6 (6,2; 6,9)	6,4 (6,3; 6,8)	6,7 (6,1; 6,9)	0.79
Respiratory rate	12 (12; 14)	12 (12; 14)	12 (12; 14)	0.92
Fio <sub>2</sub> (%)	50 (50; 60)	60 (60; 60)	50 (50; 60)	0.03*
Ventilation modus (n)				
Volume controlled	51	8	43	
Pressure controlled	1		1	

Data are presented as mean ± standard deviation (SD) except ventilation parameters, which are presented as median (interquartile range)

HR heart rate, SBP systolic blood pressure, MAP mean arterial pressure, CCI continuous cardiac index, LVEF left ventricle ejection fraction, Fio<sub>2</sub> fraction of inspiratory oxygen

\*p < 0.05 responders compared to non-responders

indices included 0.5 in their confidence interval. Optimal cut-off values and corresponding sensitivity and specificity are presented in Table 3 for indices with AUCs above 0.5.

### 3.3 Results using $\Delta\text{SvO}_2$ and static variables

AUCs for baseline static variables (central venous pressure, mean arterial pressure and SvO<sub>2</sub>) are presented in Table 3.

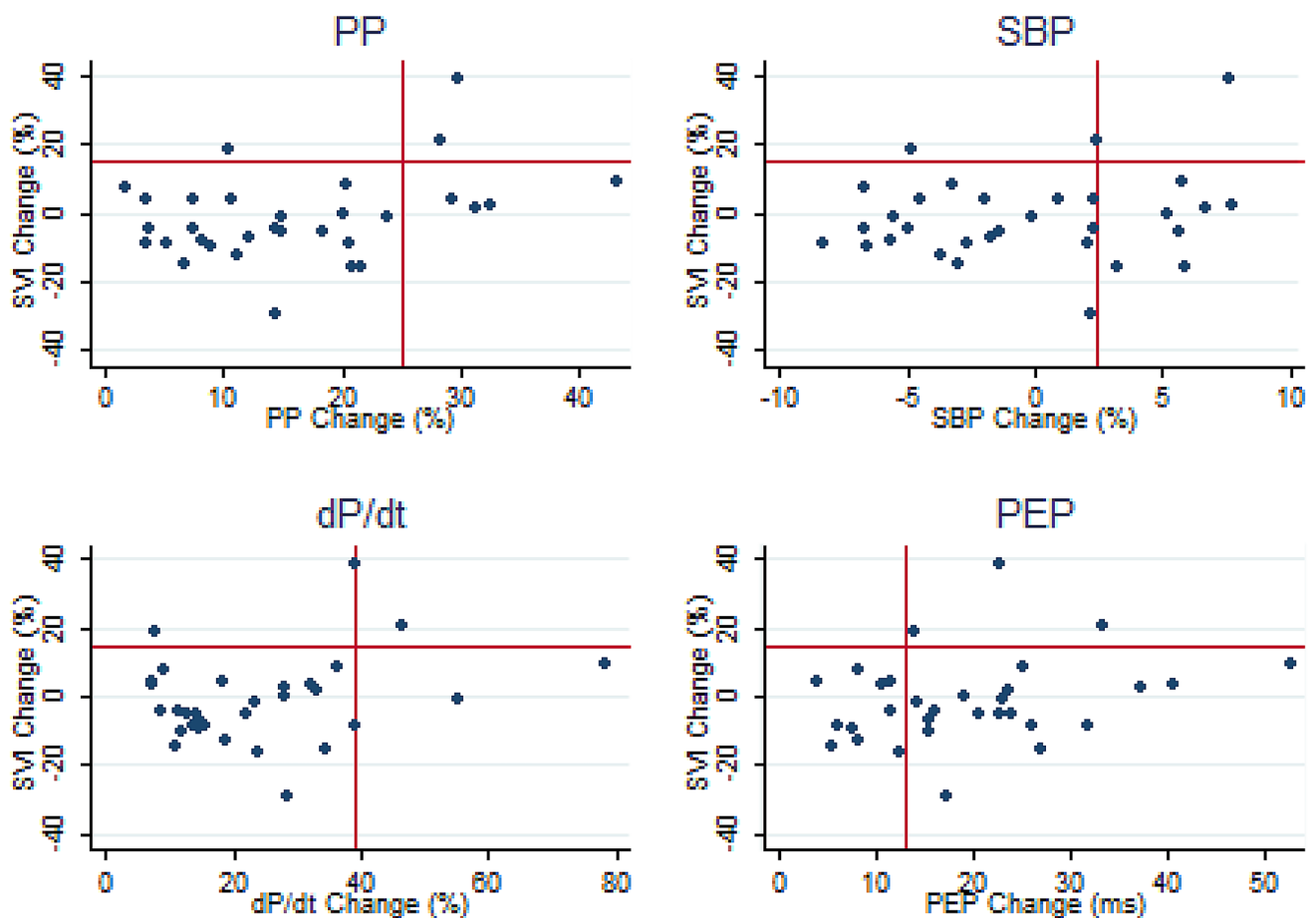
SvO<sub>2</sub> rose modestly (0.6%) but significantly following the fluid infusion in the entire group (p < 0.0122, n = 54). There was no significant difference in  $\Delta\text{SvO}_2$  between fluid responders compared with non-responders defined by  $\Delta\text{SVI}$  (p < 0.183).

ROC curves for all measures of the extrasystole method and micro-fluid challenge using  $\Delta\text{SvO}_2$  as the outcome variable did not show better classification (for detailed classification data see supplementary material).

## 4 Discussion

The post-ectopic changes in four blood pressure characteristics did not provide a clinically satisfactory prediction of fluid responsiveness. The best predictive indicator was  $\Delta\text{PP}_{\text{ES}}$  with AUC of 0.70 (0.35 to 1). All other indices tested ( $\text{SBP}_{\text{ES}}$ ,  $\text{dP/dt}_{\text{ES}}$  and  $\text{PEP}_{\text{ES}}$ ) had similar findings with lower AUCs. Although we did not find any significant results





**Fig. 3** Indices for post-ectopic changes (*PP* pulse pressure, *SBP* systolic pulse pressure,  $\Delta dP/dt$  maximal pressure upstroke slope and *PEP* pre-ejection period) plotted against change in stroke volume index ( $\Delta$ SVI). *Red vertical line* best cut-off, *Horizontal line* fluid responsiveness cut-off

for the extrasystole method, all AUC point estimates were slightly above 0.5. This may support the physiological concept, but in a specific patient during cardiac surgery, the extrasystolic method does not seem applicable. Still, only three patients in the extrasystolic cohort (10%) responded with at least 15% increase in SVI following the fluid challenge. This proportion was not anticipated and not in accordance with the assumptions for our power calculation.

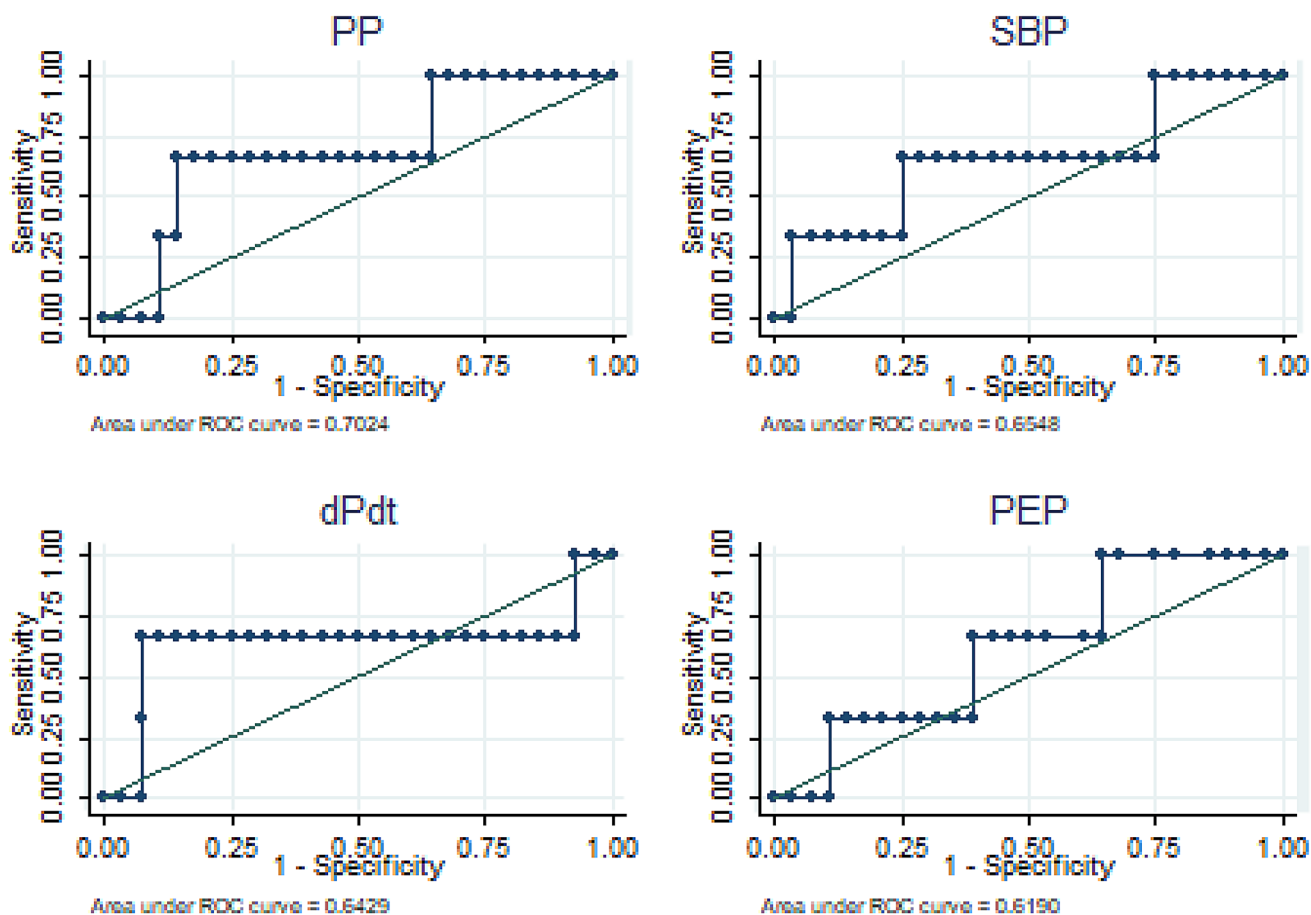
The micro-fluid challenge combined with velocity time integral measures was a reliable method to predict fluid responsiveness in an ICU study [26]. We wanted to make the micro-fluid challenge method less operator dependent and more applicable in the operating theatre by analysing arterial blood pressure characteristics as predictors instead of using echocardiography. None of our four arterial blood pressure derived indices revealed a predictive value as all of them had AUC point estimates around 0.5 or less.

Despite the low number of responders, our AUC estimates for the extrasystole method shows similar predictive values as reported in a comparable general anaesthesia study [25] but inferior value compared with previous studies in

the post-operative cardio-thoracic ICU and a more general ICU, where sensitivities and specificities around 80% were found for  $\Delta PEP_{ES}$ , and  $\Delta SBP_{ES}$  [23, 24]. All our patients had low heart rates during anaesthesia (mean: 58 beats/min), likely related to anaesthesia and possibly the prevalent use of  $\beta$ -blockers before surgery. This is similar to a comparable general anaesthesia study [25] also associated with mediocre classification, but contrasted by the heart rates generally encountered in the ICU, where the method has been more reliable. Prolongation of the RR interval might entail relatively less preload increase at the post-ectopic beat due to the relatively long passive filling time already present for the regular sinus beats.

The micro-fluid challenge method did not show any predictive value, which was surprising considering Wu et al.'s results [26]. Wu et al. studied another patient population and used velocity time integrals to assess the micro-fluid challenge induced fluid response as opposed to our use of arterial blood pressure characteristics.

A limitation for our study is the low proportion of fluid responders, which is not in alignment with previous studies.



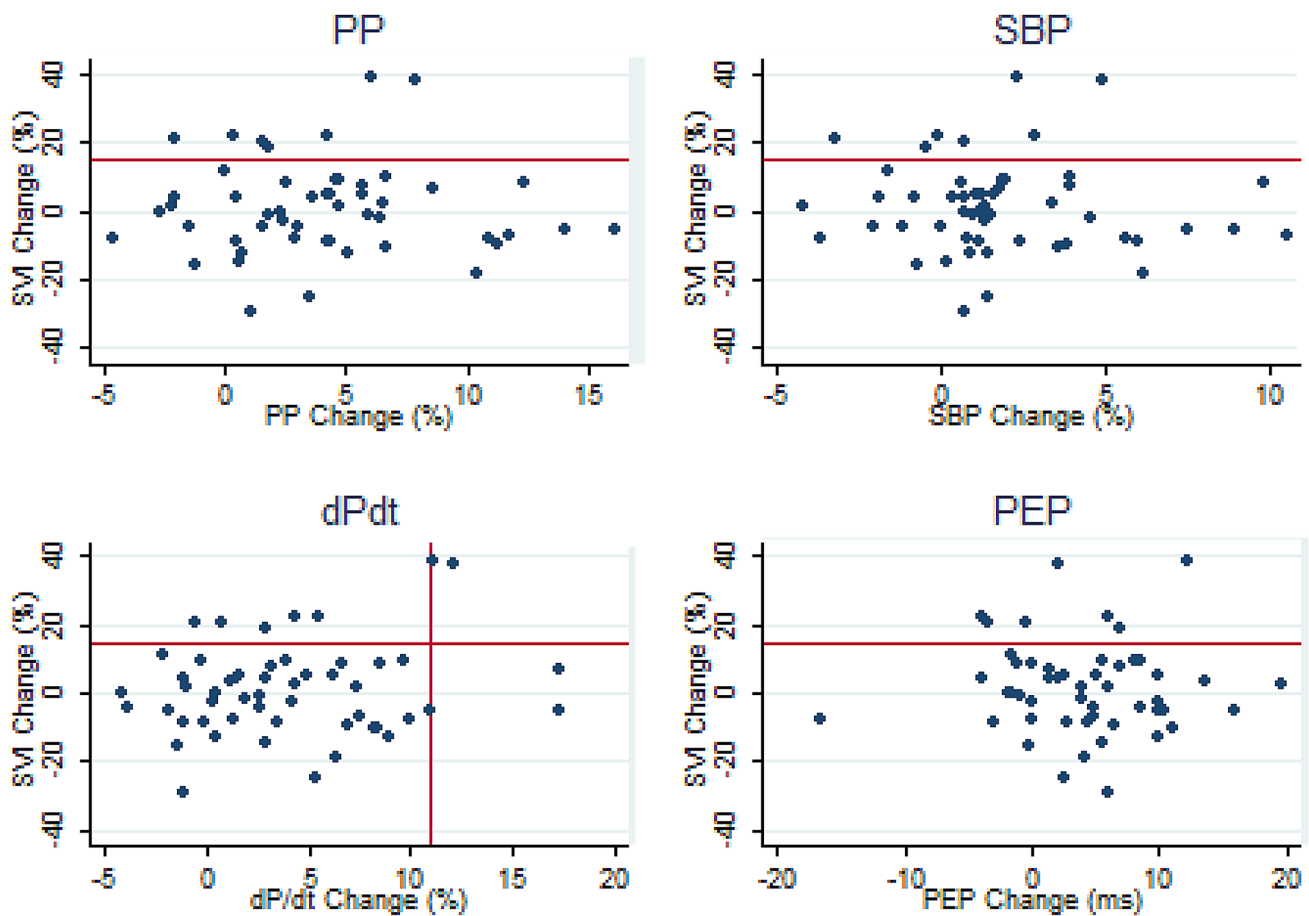
**Fig. 4** Receiver operating characteristic (ROC) curves for post-ectopic indices (*PP* pulse pressure, *SBP* systolic pulse pressure,  $\Delta dP/dt$  maximal pressure upstroke slope and *PEP* pre-ejection period). Area under the ROC-curve (AUC) are presented below each panel

**Table 3** Summary of all results

	AUC	CI (95%)	Best cut-off	Sensitivity (%)	Specificity (%)
<b>ES</b>					
$\Delta PP$	0.70	0.35 to 1.00	25%	67	86
$\Delta SBP$	0.65	0.23 to 1.00	2.4%	67	75
$\Delta dP/dt$	0.64	0.08 to 1.00	39%	67	93
$\Delta PEP$	0.62	0.29 to 0.95	13 ms	100	36
<b>MFC (75%)</b>					
$\Delta PP$	0.42	0.20 to 0.65			
$\Delta SBP$	0.43	0.18 to 0.68			
$\Delta dP/dt$	0.60	0.36 to 0.83	11%	29	96
$\Delta PEP$	0.40	0.13 to 0.67			
<b>Static variables</b>					
CVP	0.48	0.22 to 0.74			
SvO <sub>2</sub>	0.58	0.31 to 0.85	79	71	51
MAP	0.63	0.38 to 0.87	79	57	74

*ES* extrasystole, *MFC* micro-fluid challenge,  $\Delta PP$  pulse pressure change,  $\Delta SBP$  systolic blood pressure change,  $\Delta dP/dt$  maximal pressure upstroke slope change,  $\Delta PEP$  pre-ejection period change, *CVP* central venous pressure, SvO<sub>2</sub> mixed venous oxygen saturation, *MAP* mean arterial pressure, *AUC* area under the receiver operating characteristics curve, *CI* confidence interval (95%)





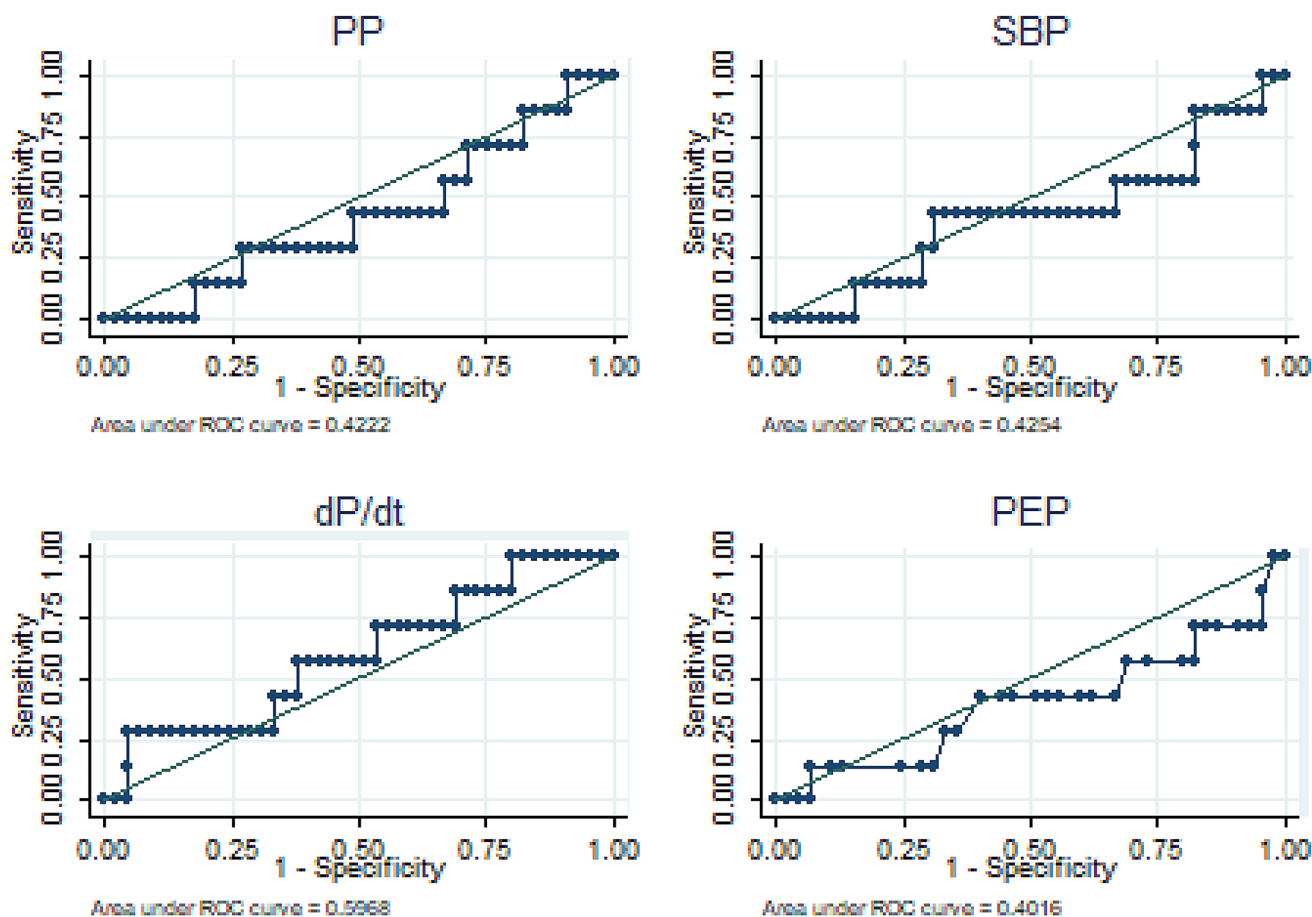
**Fig. 5** Indices for micro-fluid challenge upper quartile changes (*PP* pulse pressure, *SBP* systolic pulse pressure,  $\Delta dP/dt$  maximal pressure upstroke slope and *PEP* pre-ejection period) plotted against change in

stroke volume index ( $\Delta$ SVI). *Red vertical line* best cut-off, *Horizontal line* fluid responsiveness cut-off

During open thoracic surgery a study found 37% fluid responders [31] and for a heterogeneous surgical population, the proportion was even higher [32]. Several reasons might explain the low proportion of fluid responders. First, our patients received less fluid ( $385 \pm 47$  ml) compared with other fluid responsiveness studies [32]. However, this amount should be enough for increasing preload [6] as goal directed therapy studies often use 250 ml as their intervention [33]. Another explanation could be related to protocol timing with the open-chest condition induced immediately prior to our observation window. Open-chest results in decreased central venous pressure [13, 34], thus increasing the venous return flow, which might reduce preload responsiveness probably due to a rightward shift on the Frank-Starling relation between ventricular preload and stroke volume [11, 12]. Indeed, we observed a higher response rate in similar patients in the subsequent post-operative setting [23]. This, together with the fact that our patients were not extremely hypovolemic might cause the low number of

fluid responders. Additionally, the low fluid response rate may be related to the observational nature of the study: The attending anaesthesiologist changed infusion rates or gave boluses of vasodilating agents in some excluded patients (Propofol, Sevoflurane or Sufentanil), in some cases due to a blood pressure increase before aortic cannulation. Although speculative, these few cases may have been fluid responders if not excluded during infusion. In addition, we cannot exclude that due to the nature of cardiac procedures and high dose opioid anaesthesia, SVI in itself might decrease over observation time.

Finally, the use of Swan-Ganz for CO measurements might partly explain the low proportion of fluid responders. Swan-Ganz is the gold standard when precise CO measurements are needed. However, when using the continuous CO modality, Haller et al. showed that following an intervention, the detection of the change in CO is delayed [28]. The proprietary algorithm reducing thermal noise in the vigilance II system might have stabilised our



**Fig. 6** Receiver operating characteristic (ROC) curves for micro-fluid challenge indices (*PP* pulse pressure, *SBP* systolic pulse pressure,  $\Delta P/dt$  maximal pressure upstroke slope and *PEP* pre-ejection period). Area under the ROC-curve (AUC) are presented below each panel

CO measurements and delayed the detection of the fluid response. The delay confirmed by Edwards Tech support should be 6–10 min following an intervention. Our data collection was designed to account for this, and only if the response time was longer than 10 min, would a partial and not the entire fluid response have been detected. Alternatively, if a (positive) stroke volume/cardiac output response was very transient (i.e. few minutes), we would deem our study design to be problematic but in a previous study, the response to much slower fluid infusions lasted and was captured by the CCO method [29]. We therefore speculate that clinical rather than technical circumstances gave rise to a limited number of fluid responders.

Using  $\Delta SvO_2$  as the outcome variable instead of  $\Delta SVI$  in our analyses showed similar classification results and thus did not indicate better prediction with either of the two fluid responsiveness monitoring concepts under investigation. This, supports our interpretation of a low predictive value of the methods during cardiac surgery and also an actual, albeit unexpected, low number of fluid responders.

Considering the basis of our power calculation, we calculated in retrospect the power of the present study based on the extrasystolic results for pulse pressure (with ROC area at 0.70). The power is 0.21. We also did a new power calculation based on this data set (AUC = 0.70,  $\alpha = 0.05$ , power = 0.8 and a distribution of responders/non-responders similar to this study). A study would then need to include approximately 180 patients to show that the ROC area is indeed different from 0.5. Given the observed distribution of responders and non-responders (3 and 28), the minimal detectable AUC could also be calculated, and it is 0.927 (and 0.813 for the micro-fluid challenge method). If an acceptable AUC range is defined between 0.8 and 0.9, then, strictly speaking, the present study can only conclude that the micro-fluid challenge based methods are probably not acceptable. As a consequence, firm conclusions for the extrasystole method are not possible to draw from this statistical point of view. Yet, this statistical aspect should also be seen in the context of the remaining results and the clinical expectations to a fluid responsiveness test. All of the variables (morphologic

extrasystolic and micro-fluid challenge features) under investigation were producing a point estimate for the ROC area far from acceptable for clinical application. Also, as opposed to our existing extrasystole studies, more patients with e.g. an  $SBP_{ES}$  beyond 5% were non-responders in this study compared with the previous studies. This strongly indicates that the previously suggested threshold of e.g. 5% for  $SBP_{ES}$  in other clinical contexts is not optimal in this context of cardiac surgery—despite the low statistical power to make overall firm conclusions about the extrasystole method.

In conclusion, post-extrasystolic and micro-fluid challenge induced changes in the arterial blood pressure curve had low predictive values for predicting fluid responsiveness. Given a low number of fluid responders and inherently reduced statistical power, our data does not support firm conclusions about the utility of the extrasystolic method. Still, our point estimates, supports the evidence that dynamic preload indicators are inappropriate to predict fluid responsiveness in the open-chest condition. Thus, systematic administration and evaluation of a fluid challenge remains the best way to assess—but not predict—fluid responsiveness in patients undergoing cardiac surgery.

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**Author contributions** JMB: Designed and planned the study, collected data, made statistical analysis, wrote the first manuscript draft and approved the final version. DVN: Designed and planned the study, collected data, and approved the final version. VA: Helped designing the study, collected data and approved the final version. NEH: Helped designing the study, collected data and approved the final version. STV Designed and planned the study, waveform data analysis, statistical analysis and approved the final version.

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**Data availability** Raw data sets are not available due to lack of patient consent and lack of approval from the Danish Data Agency. Statistic codes used to process data can be requested from the corresponding author upon reasonable request.

## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. The Danish regional ethics committee classified the study as observational because the fluid infusion was considered a systematic framework of clinical practice.

**Informed consent** Written informed consent for the use of data was obtained before surgery for all individual participants included in the study.

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