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Ability of stroke volume variation measured by oesophageal Doppler monitoring to predict fluid responsiveness during surgery

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Editor's key points

- Changes in cardiovascular variables during respiration can be used to predict the response of the circulation to infused fluids.
- Most previous studies using oesophageal Doppler have used flow time to guide fluid therapy.
- In this study, changes in stroke volume with respiration predicted fluid responsiveness accurately during surgery.
- In contrast, changes in peak velocity and flow time assessed using oesophageal Doppler were not predictive.

Background. The objective of this study was to test whether non-invasive assessment of respiratory stroke volume variation (ΔrespSV) by oesophageal Doppler monitoring (ODM) can predict fluid responsiveness during surgery in a mixed population. The predictive value of ΔrespSV was evaluated using a grey zone approach.

Methods. Ninety patients monitored using ODM who required i.v. fluids to expand their circulating volume during surgery under general anaesthesia were studied. Patients with a preoperative arrhythmia, right ventricular failure, frequent ectopic beats, or breathing spontaneously were excluded. Haemodynamic variables and oesophageal Doppler indices [peak velocity (PV), stroke volume (SV), corrected flow time (FTc), cardiac output (CO), ΔrespSV, and respiratory variation of PV (ΔrespPV)] were measured before and after fluid expansion. Responders were defined by a $>15\%$ increase in SV after infusion of 500 ml crystalloid solution.

Results. SV was increased by $\geq 15\%$ after 500 ml crystalloid infusion in 53 (59%) of the 90 patients. ΔrespSV predicted fluid responsiveness with an area under the receiver-operating characteristic (AUC) curve of 0.91 [95% confidence interval (95% CI): 0.85–0.97, $P<0.0001$]. The optimal ΔrespSV cut-off was 14.4% (95% CI: 14.3–14.5%). The grey zone approach identified 12 patients (14%) with a range of ΔrespSV values between 14% and 15%. FTc was not predictive of fluid responsiveness (AUC 0.49, 95% CI: 0.37–0.62, $P=0.84$).

Conclusions. ΔrespSV predicted fluid responsiveness accurately during surgery over a ΔrespSV range between 14% and 15%. In contrast, FTc did not predict fluid responsiveness.

Keywords: anaesthesia; cardiac output measurement; Doppler ultrasonography; intraoperative monitoring; stroke volume

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Oesophageal Doppler monitoring (ODM) allows non-invasive continuous monitoring of cardiac output (CO) during surgery.[1–3] Several studies have demonstrated that ODM-guided intraoperative fluid optimization can have a significant impact on outcome in high-risk surgical patients.[4–7] Most of these studies have incorporated corrected flow time (FTc) as a target for fluid optimization. However, FTc is a complex variable affected by left ventricular preload, systemic vascular resistance, and the inotropic state of the heart.[8–10] Many studies over recent years have emphasized the superiority of respiratory variation of pulse pressure (ΔrespPP) and aortic blood flow (ΔrespABF) to predict fluid responsiveness in a wide range of clinical situations.[11–15] ΔrespABF can be evaluated by echocardiography or ODM.[16 17] Only one ODM study conducted in critically ill patients with acute circulatory failure has demonstrated the accuracy of ΔrespABF to predict fluid responsiveness.[17] No data are therefore available concerning ODM respiratory variation indices during surgical anaesthesia.

The primary objective of this study was to demonstrate that respiratory variation of SV (ΔrespSV) measured by ODM can predict fluid responsiveness more accurately than FTc. ΔrespSV was evaluated by using a grey zone approach and a risk–benefit assessment model of fluid administration.[15 18]

Methods

This study was approved by the Institutional Review Board (IRB) for human subjects. Informed consent was waived, as the IRB considered the protocol to be part of routine clinical practice.

We conducted a prospective observational study over a 5 month period (June–October 2011) in Amiens University Hospital. Inclusion criteria were: patients aged >18 yr and monitored by oesophageal Doppler (ODM), in whom the anaesthetist decided to infuse i.v. fluids to expand circulating volume. Exclusion criteria were: patients with a preoperative arrhythmia, right ventricular failure, frequent ectopic beats, patients breathing spontaneously during surgery, and contraindications to ODM probe insertion. Indications for ODM were visceral and gynaecological cancer surgery (n=49), peritonitis (n=12), radical prostatectomy (n=6), nephrectomy (n=9), renal transplantation (n=2), multiple trauma (n=4), haemostatic surgery (n=3), and vascular surgery (n=5).

Routine monitoring consisted of a three-lead electrocardiogram, pulse oximetry, and non-invasive arterial pressure. All patients underwent balanced general anaesthesia with tracheal intubation and mechanical ventilation in volume-controlled mode. General anaesthesia was induced with propofol or etomidate and either remifentanil or sufentanil according to the anaesthetist's preference, and maintained with either propofol or an inhaled hypnotic (desflurane or sevoflurane) and the same opioid used at induction. All patients received neuromuscular block with i.v. cisatracurium (0.15 mg kg^{-1}) or rocuronium (0.6 mg kg^{-1}). Tidal volume was set to 7–9 ml kg^{-1} of ideal body weight with a ventilatory frequency adjusted to maintain end-tidal CO_2 at 3.99–4.7 kPa; PEEP of 0.74–1.24 kPa was applied.

The ventilator settings (tidal volume, plateau pressure, and end-expiratory pressure) were recorded at the baseline.

Oesophageal Doppler monitoring

The position of the oesophageal Doppler probe (CardioQ™, Deltex Medical, Gamida, France) was adjusted to obtain the best signal for descending aorta blood velocity.[9] To avoid artifacts concerning precise distinction of the beginning and end of aortic flow with each ventricular beat that may be distorted by wall thump and run-off, respectively, laminar flow was ensured with a narrow frequency range (blunt velocity profile). The reproducibility of SV measurement was tested before the study; the intraobserver and interobserver variability for SV measurements was 0.3 (0.1)% and 1.1 (3)%, respectively. Stroke volume (SV), FTc, and peak velocity (PV) were recorded continuously by the ODM software (beat by beat) from aortic blood flow velocity, and their mean values were calculated over 10 s. Respiratory variations (Δresp) of ODM values were calculated as described by Monet and colleagues, regardless of the respiratory cycle.[17] The respiratory variation of SV (ΔrespSV) was calculated as $\Delta respSV = [(SV_{max} - SV_{min})/(SV_{max} + SV_{min})/2] \times 100$, where SV_{max} and SV_{min} are the maximal and minimal SV values over one respiratory cycle, respectively. Respiratory variation of PV (ΔrespPV) was calculated using a similar formula. All values represented the mean of three measurements. All measurements were analysed off-line using a video sequence of the monitor.

Study protocol

Only the first fluid challenge infused during surgery was recorded for the study. All patients were studied after 5 min of stable haemodynamic variables with constant ventilator settings and drugs. A first set of measurements [heart rate (HR), systolic arterial pressure (SAP), mean arterial pressure (MAP), diastolic arterial pressure (DAP), SV, FTc, PV, ΔrespSV, and ΔrespPV] was recorded at the baseline. Volume expansion (VE) comprised the infusion of 500 ml crystalloid solution (Ringer or Ringer lactate) over 10 min. A second set of measurements (HR, SAP, MAP, DAP, SV, FTc, PV, ΔrespSV, and ΔrespPV) was recorded immediately after, at the end of VE.

Data analysis

Data are expressed as mean (SD), or proportion (percentage), as appropriate. SV measured before and after VE was used to define responders and non-responders. A positive response was defined as a ≥15% increase in SV. The Pearson rank method was used to test linear correlations between variables in responders and non-responders. The associations between cardiovascular variables (HR, SAP, MAP, DAP, SV, FTc, PV, CO, ΔrespSV, and ΔrespPV) and fluid responsiveness were assessed using a univariate logistic model. Variables with a P-value of <0.10 were then included in a multivariate logistic model with a backward selection procedure. A receiver-operating characteristic (ROC) curve was generated for ΔrespSV, ΔrespPV, and FTc. The ROC curves were obtained by averaging 1000 bootstrapped samples (sampling with replacement) from the original study population. The areas under the ROC curve (AUC) for each variable were compared using the test described by DeLong and colleagues. For clinical practice, it is preferable to avoid a single cut-off that dichotomizes the population (i.e. black or white distinction).[18] The predictive value of ΔrespSV was evaluated by using a grey zone approach. The grey zone approach indicated two cut-offs between which the diagnosis of fluid responsiveness remains uncertain; the physician must confirm the diagnosis by additional information.[18] The grey zone was calculated using two approaches previously described by Cannesson and colleagues.[15] The optimal cut-off was defined as the cut-point that maximized Youden's index (J=sensitivity+specificity−1=sensitivity−false-positive rate). The optimal cut-point was then determined for each bootstrapped sample, resulting in a set of 1000 values. The median value of the cut-points across 1000 bootstrap replications and its 95% confidence interval (CI) were then estimated. The grey zone was defined as the 95% CI of Youden's index. A second approach defined three classes of response: negative, inconclusive, and positive. Inconclusive responses were cut-off values with a sensitivity of <90% and a specificity of <90% (diagnostic

tolerance of 10%). Sensitivity and specificity were then plotted on two curves. The grey zone was defined as the largest 95% CI of these two approaches. The physician is therefore able to give preference to either sensitivity or specificity, as the consequence of false-positive or false-negative results is not equivalent in terms of the cost–benefit relationship. The grey zone was assessed on a benefit–risk assessment model of fluid administration: ratio of cost (R) defined as: R=cost (false-positive)/cost (false-negative). $R<1$ represents a 'liberal' fluid strategy (not treating a false-negative is worse than treating a false-positive). $R>1$ denotes a 'restrictive' fluid management (not treating a false-positive is worse than missing a false-negative).[14] $R=1$ is equivalent to maximizing Youden's index. Differences with a P-value of <0.05 were considered statistically significant. Statistical analyses were performed using IBM® SPSS® Statistics 18 (IBM) and R software with the ROCR package.

Results

We studied 90 patients in whom the anaesthetist decided to administer i.v. fluids to expand circulating volume (Table 1).

Fifty-three of the 90 patients (59%) were defined as responders because SV increased by >15% with VE. Baseline SV and CO were lower, and ΔrespSV and ΔrespPV were higher in responders compared with non-responders (Table 2). VE increased SAP, PV, SV, and CO and decreased ΔrespSV and ΔrespPV only in responders (Table 2). There was a significant correlation between ΔrespSV and ΔrespPV ($r=0.57$, $P<0.001$). VE increased FTc in both groups. There was a correlation between increases in FTc and SV in response to VE ($r=0.36$, $P<0.01$).

The ability of ΔrespSV to predict fluid responsiveness was excellent, with an AUC of 0.91 (95% CI: 0.83–0.97, $P<0.0001$) (Fig. 1). The ability of ΔrespPV to predict fluid responsiveness was poor with an AUC of 0.68 (95% CI: 0.54–0.80, $P=0.01$) (Fig. 1). The AUC of ΔrespSV was higher than that of ΔrespPV ($P<0.001$). FTc was not predictive of fluid responsiveness [AUC 0.49 (95% CI: 0.37–0.62), $P=0.84$] (Figs 1 and 2). When analysed using multivariate logistic regression, ΔrespSV was the only factor associated with fluid responsiveness [odds ratio (OR) 1.25 (95% CI: 1.13–1.4), $P<0.0001$].

Table 1 Patient characteristics presented as mean (range), mean (SD), or number (%)

Age (yr)	54 (20–90)
Height (cm)	165 (9)
Weight (kg)	74 (15)
Sex (female:male)	74:26
Type of surgery, *n* (%)	
Gynaecological	47 (52)
Digestive	17 (19)
Urologic	17 (19)
Orthopaedic	4 (4)
Vascular	5 (6)
Tidal volume (ml kg^{-1} of predicted body weight)	8.5 (0.9)
Respiratory rate (min^{-1})	13 (2)
Pressure plateau (cm H_2O)	14 (4)

Grey zone limits of ΔrespSV

Using resampling, the median cut-off was 14.4% with a 95% CI of the distribution of optimal cut-offs ranging between 14.3% and 14.5%. The sensitivity and specificity curves identified a zone between 13.8% and 14.7%. These two approaches therefore defined a grey zone between 14% and 15% (Fig. 3). Twelve patients (14%) were situated in the inconclusive zone in relation to these values. The grey zone for liberal fluid

Table 2 Cardiovascular variables in responders and non-responders expressed as mean (SD). HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; FTc, flow time corrected; SV, stroke volume; PV, peak velocity; CO, cardiac output; ΔrespSV, respiratory stroke volume variation; ΔrespPV, respiratory peak velocity variation. The independent predictive value of ΔrespSV was validated after adjustment with other clinical factors in a multivariable logistic model. ΔrespSV was the only variable predictive for response/no response [OR 1.25 (95% CI: 1.13–1.4), $P=0.0001$]. *$P=0.0001$

	Baseline	Volume expansion
HR (beats min^{-1})		
Responders	73 (18)	72 (16)
Non-responders	66 (17)	66 (17)
SAP (mm Hg)		
Responders	105 (20)	110 (16)
Non-responders	105 (17)	102 (22)
DAP (mm Hg)		
Responders	57 (13)	58 (15)
Non-responders	64 (13)	63 (13)
MAP (mm Hg)		
Responders	70 (13)	73 (16)
Non-responders	78 (14)	79 (13)
FTc (ms)		
Responders	345 (58)	383 (49)
Non-responders	350 (43)	364 (48)
PV (cm s^{-1})		
Responders	71 (23)	80 (33)
Non-responders	75 (26)	74 (27)
SV (ml)		
Responders	71 (20)	90 (22)
Non-responders	89 (19)	91 (21)
CO (ml min^{-1})		
Responders	4.9 (1.4)	6.4 (2.1)
Non-responders	5.7 (2)	5.8 (2)
ΔrespSV (%)		
Responders	22 (9)	12 (8)
Non-responders	10 (5)*	8 (3)
ΔrespPV (%)		
Responders	12 (6)	8 (4)
Non-responders	9 (5)	6 (3)

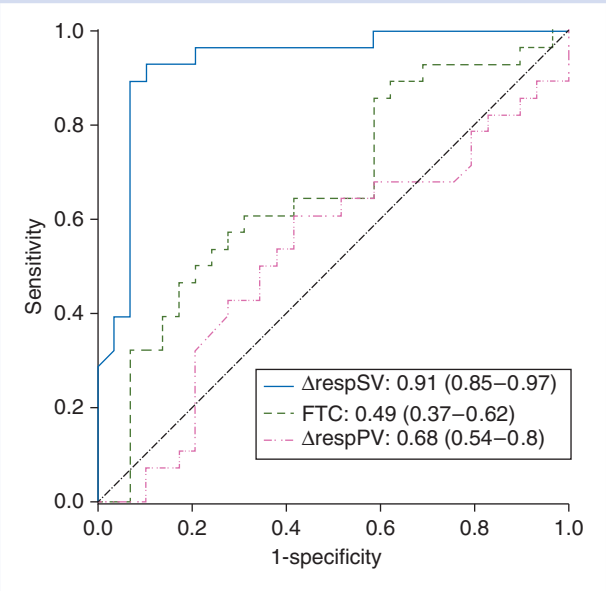

Fig 1 ROC curves of FTc, ΔrespSV, and ΔrespPV to discriminate responders and non-responders to VE. Area under ROC appears in cartouche with 95% confidence interval (95% CI).

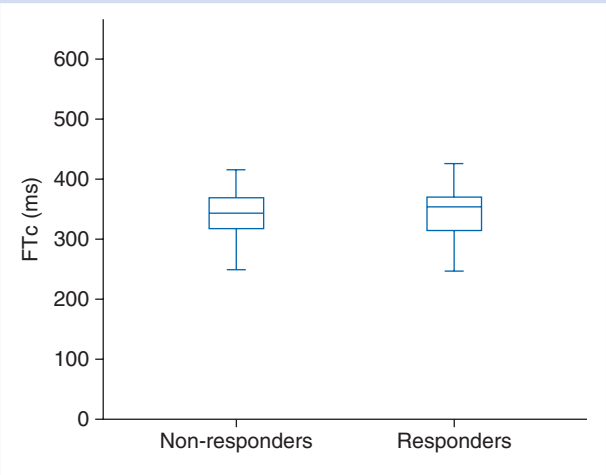

Fig 2 Box and whisker plot represents the distribution of baseline FTc according to each group (responders and non-responders). Baseline FTc was not statistically different between the two groups. FTc, corrected flow time expressed as ms.

control (cost ratio=0.5) ranged between 13% and 14%, with a median of 13.9%. The grey zone for restrictive fluid control (cost ratio=2) ranged between 14% and 15%, with a median of 14.6%.

Discussion

This is the first study to evaluate the predictive value of ΔrespSV measured by ODM during surgery using a grey zone approach. We found that ΔrespSV predicted fluid responsiveness accurately, with a grey zone ranging between 14% and 15%. In contrast, ΔrespPV and FTc were not reliable markers of response to fluid expansion.

Many studies have reported the ability of Δresp indices to predict fluid responsiveness in the operating theatre (vascular, cardiac, visceral, neurosurgical surgery).[14–16] Monnet and colleagues[17] demonstrated that ΔrespABF measured by ODM accurately predicted fluid responsiveness in critically ill patients with acute circulatory failure. Similarly, we demonstrated that ΔrespSV accurately predicted fluid responsiveness in the operating theatre. ΔrespSV was found to be more accurate than ΔrespPV. SV is approximated by aortic blood flow velocity (VTI) of the descending aorta and the use of a nomogram using the patient's height and weight multiplied by a correction factor, whereas PV is measured automatically from the peak value of aortic blood velocity, which is not equivalent to SV. Unlike respiratory changes in VTI, ΔrespPV may not accurately reflect ΔrespSV, as ΔrespPV may vary in different proportions from ΔrespSV, which may explain the different results obtained for these two indices.

Cannesson and colleagues recently introduced the grey zone approach to ΔrespPP. By defining two cut-offs between which the diagnosis of fluid responsiveness remains uncertain; the grey zone is more representative of the difficulties in clinical practice that may occur in up to one-quarter of the patients.[15] Moreover, the boundaries of this grey zone change according to the fluid management strategy applied.[15] Such limits have been observed for ΔrespSV. Using a grey zone approach, we demonstrated an inconclusive zone ranging between 14% and 15%, which concerned 14% of the patients studied. Equally, cut-off values changed according to the cost ratio approach (restrictive or liberal fluid management). The main goal of dynamic indicators of fluid responsiveness is to predict an increase in CO in response to fluid expansion.[19] In clinical practice, fluid responsiveness does not necessarily mean that the patient requires fluid expansion, as CO optimization by fluid administration may be beneficial in some patients and in some surgical procedures, but fluid overload can increase perioperative morbidity.[4–7 20–22] Moreover, depending on their medical status (poor left ventricular function, diastolic heart failure, risk of acute lung injury), some patients would derive greater benefit from a restrictive fluid strategy.[23 24] Knowledge of the grey zone of ΔrespSV and its variation according to the cost ratio chosen would help physicians adapt fluid management to the surgical procedure and the patient. High values of ΔrespSV (above the upper limit of the grey zone) indicate fluid responsiveness. Conversely, low values of ΔrespSV (below the lower limit of the grey zone) indicate fluid non-responsiveness and that fluid expansion would be ineffective. In the grey zone of ΔrespSV, the anaesthetist can choose various strategies depending on the patient and the type of surgery. When a liberal strategy is preferred, cardiac index optimization can be tested by fixed fluid expansion. Two studies have demonstrated that a 10% increase in SV during limited fluid loading was predictive of subsequent fluid responsiveness.[25 26] According to a restrictive fluid management strategy, the anaesthetist can

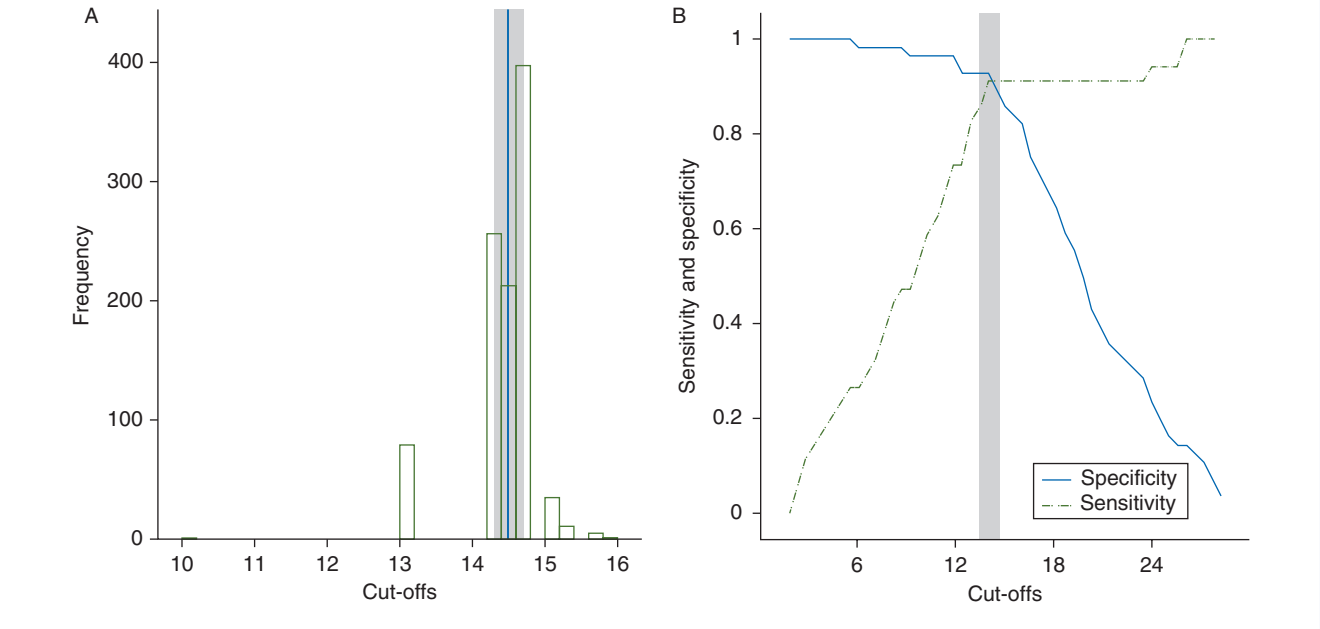

Fig 3 Determination of the grey zone for ΔrespSV according to an optimal threshold (cost ratio: $R=1$). The grey zone approach indicated two cut-offs between which the diagnosis of fluid responsiveness remains uncertain. The grey zone was calculated using two approaches. (A) Histograms represent the distribution of the optimal cut-offs for each of the 1000 resampled population. The black line indicates the median of the distribution of optimal thresholds. The inconclusive zone (95% CI) is represented as a shaded zone. (B) Two graph ROC curves: sensitivity (Se) and specificity (Sp) of ΔrespSV according to the value of the cut-off. The inconclusive zone, which is more than 10% of diagnosis tolerance, is represented as a shaded zone.

observe the spontaneous course of ΔrespSV and CO and can then titrate fluids in the presence of a further increase (decrease) in ΔrespSV (CO).

In contrast to ΔrespSV, FTc did not predict haemodynamic response to fluid infusion. Baseline FTc was not statistically different between the two groups (Fig. 1). Moreover, regardless of the cut-off, FTc did not predict fluid responsiveness. These findings contradict those reported by Lee and colleagues,[27] who demonstrated a good predictive value of FTc. Lee and colleagues studied a small, specific population of neurosurgical patients who may have been in a preload dependency state. Furthermore, FTc increased in both responders and non-responders.[25 27] FTc is a complex static indicator influenced by preload, afterload, and inotropic state that can be integrated in a multimodal ODM approach to evaluate the effect of the treatments administered, such as fluid expansion, inotropic drugs, or vasoconstrictor drugs.[8 9] Sinclair and colleagues[7] integrated an upper limit of FTc to optimize CO while avoiding excessive fluid loading.

This study has a number of limitations. Respiratory-derived indices (and ΔrespSV) are only reliable predictors of fluid responsiveness under strict conditions.[28] Nevertheless, we excluded patients with cardiac arrhythmia, multiple extrasystoles, spontaneous ventilation, or right ventricular failure. The magnitude and cut-off of ΔrespSV are altered by tidal volume and intrathoracic pressure.[29] Patients had normal lung compliance and were mechanically ventilated with a mean tidal volume of 8 ml kg^{-1}. Consequently, our results cannot be extrapolated to patients not meeting these conditions. Another limitation of this study was that the OD device (CardioQ^{TM}, Deltex Medical) does not measure instantaneous aortic diameter. As aortic diameter varies with aortic pressure, accurate measurement of SV and PV could be influenced by this variable. Compared with the results reported by Monnet and colleagues, our results indicated that the absence of the measurement of aortic diameter did not affect the accuracy of ΔrespSV.[17] The discriminative power of ΔrespSV was assessed by using a resampling procedure from the original study population. As this method was not equivalent to a study based on a population comprising the same number of patients, our results must therefore be validated by further studies under other clinical conditions.

In conclusion, we found that dynamic measures of preload responsiveness (ΔrespSV) measured using ODM predicted fluid responsiveness, with an inconclusive range of values of ΔrespSV between 14% and 15%. The data were obtained in surgical patients undergoing mechanical ventilation and with sinus rhythm. Although FTc increased with VE, it could not be used to predict fluid responsiveness. FTc could however be integrated into a multimodal ODM approach to evaluate the effect of therapy.

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Declaration of interest

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