British Journal of Anaesthesia **99 (3):** 343–8 (2007)
doi:10.1093/bja/aem179 Advance Access publication on July 9, 2007

BJA

Evaluation of corrected flow time in oesophageal Doppler as a predictor of fluid responsiveness

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Background. Corrected flow time (FTc) by oesophageal Doppler is considered to be a 'static' preload index. We evaluated the ability of FTc to predict fluid responsiveness and compared this with the abilities of other preload indices, such as pulse pressure variation (PPV), central venous pressure (CVP), and left ventricular end-diastolic area index (LVEDAI).

Methods. Twenty neurosurgical patients were studied. After induction of anaesthesia, FTc, PPV, LVEDAI, CVP, and stroke volume index (SVI) were measured before and 12 min after fluid loading with 6% hydroxyethyl starch solution (7 ml kg^{-1}). Responders and non-responders were defined as those patients with an SVI increase $\geq$10% or $<$10% after fluid loading, respectively. Pearson's correlation was used to assess correlations between changes in SVI and initial haemodynamic variables. Receiver operating characteristic (ROC) curves were constructed and compared to evaluate the overall performance of preload indices (FTc, PPV, LVEDAI, and CVP) in terms of predicting fluid responsiveness.

Results. FTc and PPV before fluid loading differed between responders (n=11) and non-responders (n=9), and correlated with changes in SVI (r=−0.515 and r=0.696, respectively), which was opposite to that observed for CVP or LVEDAI. Areas under ROC curves for FTc [0.944 (SD 0.058)] and PPV [0.909 (0.069)] were significantly greater than those for CVP [0.540 (0.133), P<0.001] and LVEDAI [0.495 (0.133), P<0.001]. The optimal threshold value given by ROC analysis was 357 ms for FTc.

Conclusions. In this study, FTc predicted fluid responsiveness. However, FTc should be used in conjunction with other clinical information.

Br J Anaesth 2007; **99**: 343–8

Keywords: fluid balance; heart, cardiac output; monitoring, arterial pressure; monitoring, cardiopulmonary; monitoring, intraoperative

Accepted for publication: May 17, 2007

Oesophageal Doppler (OED) is a non-invasive bedside monitor that allows continuous monitoring of haemodynamic variables.[1–3] In addition, OED is easy to use and avoids the complications associated with other monitoring devices.[4] Several studies have demonstrated that there is a good correlation between cardiac output measured by OED and that measured by thermodilution with pulmonary artery catheterization.[5 6] Of the OED variables, corrected flow time (FTc) has been used and evaluated as a preload index,[7–9] and the use of FTc for intraoperative volume optimization has been reported to reduce the incidence of complications and hospital stay after surgery.[10–12]

In many previous studies, FTc has been evaluated by comparing it with 'static' preload indices such as pulmonary artery wedge pressure (PAWP), and in two recent studies, it failed to predict the fluid response.[13 14] Considering that we usually use preload indices, including FTc, to guide fluid therapy in various clinical situations, more studies on FTc as a predictor of fluid responsiveness are warranted.

The aim of this study was to evaluate whether FTc as determined by OED can be a predictor of fluid responsiveness. Therefore, we evaluated whether FTc can predict fluid responsiveness by receiver operating characteristic

(ROC) curve analysis and compared the findings with those of other preload indices such as pulse pressure variation (PPV), central venous pressure (CVP), and left ventricular end-diastolic area index (LVEDAI) in patients undergoing neurosurgery.

Methods

After obtaining institutional review board approval and informed consent, 20 patients undergoing elective neurosurgery were enrolled in this study. Patients with known cardiac or respiratory disease (except controlled hypertension), preoperative arrhythmia, and contraindications to OED monitoring probe insertion (i.e. oesophageal stent, carcinoma of the oesophagus or pharynx, previous oesophageal surgery, oesophageal stricture, oesophageal varices, pharyngeal pouch, intra-aortic balloon pump, coarctation of the aorta, and severe coagulopathy) were excluded.

After the patient arrived in the operating room, pulse oximetry, three-lead ECG, and non-invasive arterial pressure monitoring were applied. Anaesthesia was induced by propofol target-controlled infusion (TCI: orchestra® base intensive, Fresenius Kabi, Stans, Switzerland) using an initial effect-site target concentration of 5 μg ml^{-1}. After loss of consciousness, neuromuscular block was achieved with i.v. rocuronium (0.6 mg kg^{-1}). Remifentanil TCI was started with an initial effect-site target of 4 ng ml^{-1} and then a radial arterial cannula was inserted. After endotracheal intubation, lungs were mechanically ventilated using inspired oxygen 50% without PEEP. Ventilation was set at a tidal volume of 10 ml kg^{-1} with a ventilatory frequency adjusted to maintain end-tidal carbon dioxide at 4.6–5.3 kPa during the study period. Throughout the duration of study, anaesthesia was maintained with propofol and remifentanil (TCI targeting effect-site concentrations of 3.5 μg ml^{-1} and 3 ng ml^{-1}, respectively). A central venous catheter was placed through a right subclavian vein. Pressure transducers were zeroed at the midaxillary level to ambient pressure. An OED probe (Arrow® International, Everett, WA, USA) was also inserted into the oesophagus.

Fifteen minutes after induction of anaesthesia, values of heart rate (HR), mean arterial pressure (MAP), CVP, FTc, stroke volume index (SVI), and LVEDAI were measured before (T0) and 12 min (T1) after fluid loading. All measurements were taken in a haemodynamic steady state without the use of vasoactive drugs. Fluid loading was done using 6% hydroxyethyl starch solution (HES 130/0.4; Voluven®; Fresenius Kabi, Stans, Switzerland), at 7 ml kg^{-1} ideal body weight and at a rate of 1 ml kg $^{-1}$min^{-1}. OED measurements were obtained using the Hemosonic™ device (Arrow International). The same investigator, trained to use this technique, performed all measurements during the study. The position of the OED monitoring probe was confirmed by continuously measuring descending thoracic aorta blood velocity (Doppler transducer) and aortic diameter (M-mode echo transducer). After positioning, the OED probe continuously measured and displayed cardiac output, SVI, and FTc.

Transthoracic echocardiography (Vivid i Cardiovascular Ultrasound System, GE Healthcare, Milwaukee, WI, USA) was performed using a 1.5–3.5 MHz phased array probe (GE Healthcare, Model 3S); this was positioned to obtain the parasternal short-axis view of the left ventricle at the midpapillary level. Left ventricular end-diastolic area (LVEDA), which was defined as the largest left ventricular cross-sectional area after the electrocardiographic T-wave, was measured by manual planimetry of the area circumscribed by the leading edge of the endocardial border in this position. LVEDAI was calculated by dividing LVEDA by body surface area (BSA). All echocardiographic measurements were recorded by an experienced technician, and recorded data manipulations were performed by an investigator unaware of the haemodynamic measurements.

To calculate PPV, arterial and capnography waveforms were recorded over at least three breaths for offline analysis. After recording, pulse pressure (PP; defined as the difference between the systolic arterial pressure and the diastolic arterial pressure of the previous beat) was measured on a beat-to-beat basis using Adobe photoshop CS2 software (Adobe Systems Inc., San Jose, CA, USA). Maximal PP (PP_{max}) and minimal PP (PP_{min}) values were determined over a single respiratory cycle. PPV was calculated as:

$$PPV = 100 \times \frac{(PP_{max} - PP_{min})}{([PP_{max} + PP_{min}]/2)} (\%).$$

Statistical analysis was performed using SPSS 12.0 software (SPSS Inc., Chicago, IL, USA). All haemodynamic data were analysed as continuous variables and are expressed as mean (SD). BSA was calculated using the Du Bois formula (BSA=body weight [kg]$^{0.425}$×body length [m]$^{0.725}$×0.20247). χ^2 test was used to compare the types of operations in the responders with those in the non-responders. Comparisons of haemodynamic variables before and after volume expansion and between the responders and the non-responders were made using two-way analysis of variance. The correlation between changes in SVI and in initial haemodynamic variables was assessed using Pearson's correlation. Percentage differences in OED-derived SVIs before and after fluid challenge were used as principle indicators of fluid responsiveness. Patients were classified as the responders to fluid loading, when increases in SVI were $\geq$10%, or as the non-responders when increases were $<$10%.[14] To test the abilities of CVP, LVEDAI, PPV, and FTc to predict fluid responsiveness, areas under the ROC curves of the responders [area under the curve (AUC)=0.5: no better than chance, no prediction possible; AUC=1.0: best possible prediction] were calculated and compared using the Hanley–McNeil test. $P<0.05$ was considered statistically significant.

Results

Twenty patients were included in this study. Indications for surgery included removal of tumour in 13 patients and clipping of intracranial aneurysm in seven patients. No complication occurred with OED probes or central venous catheters, and none of the patients required any pharmacological treatment with vasopressors during the study. Patients' characteristics and preoperative risk factors are presented in Table 1. Volume loading-induced SVI increases were $\geq$10% in 11 patients (the responders) and $<$10% in nine patients (the non-responders). The responders included four patients undergoing intracranial aneurysmal clipping and seven undergoing removal of brain tumour. There was no significant difference in the types of surgery among the responders and the non-responders (Table 2).

Haemodynamic variables before and after fluid loading in both the responders and the non-responders are presented in Table 3. In both the responders and the non-responders, CVP, FTc, and PPV changed significantly after volume expansion (all $P<0.01$) (Table 3). SVI increased only in the responders, and HR and LVEDAI increased only in the non-responders ($P<0.05$) (Table 3). FTc and PPV before fluid loading differed between responders and non-responders unlike the other haemodynamic variables ($P<0.01$ and $P<0.05$, respectively) (Table 3). Moreover, FTc and PPV before fluid loading, unlike CVP and LVEDAI, were found to correlate with changes in SVI (FTc, $R=-0.515$, $P<0.05$; PPV, $R=0.696$, $P<0.01$; CVP, $R=-0.126$, $P=0.596$; LVEDAI, $R=-0.081$, $P=0.734$) (Fig. 1).

The overall performances of preload indices for predicting fluid responsiveness were evaluated by constructing and comparing ROC curves (Fig. 2). Mean areas under ROC curves were 0.540 (0.133) for CVP [95% confidence interval (CI) between 0.307 and 0.761], 0.495 (0.133) for LVEDAI (95% CI between 0.268 and 0.723), 0.909 (0.069) for PPV (95% CI between 0.694 and 0.987), and 0.944 (0.058) for FTc (95% CI between 0.743 and 0.992). The area under the ROC curves for FTc and PPV was significantly greater than those of CVP ($P<0.001$) and LVEDAI ($P<0.001$). No significant difference was observed between the area under the ROC curves for FTc and PPV. The optimal threshold value given by ROC analysis was 357 ms for FTc.

Table 1 Patients' characteristics and preoperative risk factors. Data are presented as mean (SD) or number of patients

Patient characteristics	
Age (yr)	49 (11)
Sex (male/female)	8/12
Height (cm)	163 (9)
Weight (kg)	64 (10)
BSA (m^2)	1.69 (0.17)
Body mass index (kg m^{-2})	24 (3)
Preoperative risk factors	
Diabetes	1
Hypertension	5

Table 2 Types of surgery in the responders and the non-responders. Data are presented as number of patients

	Operations		Total
	Clipping of aneurysm (*n*)	Removal of tumour (*n*)	
Responders	4	7	11
Non-responders	3	6	9

Table 3 Changes of haemodynamic variables in the responders and in the non-responders before (T0) and after (T1) fluid loading. Data are presented as mean (SD). *$P<0.01$ in comparison with the values before fluid loading; †$P<0.05$ in comparison with the values before fluid loading; ‡$P<0.01$ in comparison with the values in the responders; §$P<0.05$ in comparison with the values in the responders. HR, heart rate; MAP, mean arterial pressure; SVI, stroke volume index; FTc, corrected flow time; PPV, pulse pressure variation; LVEDAI, left ventricular end-diastolic area index; CVP, central venous pressure

	T0	T1
HR (beat min^{-1})		
Responders	72 (15)	71 (16)
Non-responders	67 (8)	70 (9)*
MAP (mm Hg)		
Responders	79 (11)	84 (18)
Non-responders	82 (9)	86 (10)
CVP (mm Hg)		
Responders	3.36 (1.21)	6.55 (1.97)†
Non-responders	3.78 (1.48)	7.44 (1.01)†
LVEDAI (cm^2 m^{-2})		
Responders	31.89 (10.07)	31.97 (18.45)
Non-responders	32.56 (9.60)	40.15 (12.97)*
SVI (ml m^{-2})		
Responders	36.29 (12.00)	45.17 (17.11)†
Non-responders	31.96 (11.64)	31.83 (11.59)
FTc (s)		
Responders	337.18 (23.56)	356.45 (24.78)*
Non-responders	371.89 (14.11)‡	391.67 (5.10)†
PPV (%)		
Responders	11.29 (6.31)	5.65 (3.38)†
Non-responders	6.40 (1.80)§	3.43 (1.90)†

Discussion

In this study, ROC analysis demonstrated that FTc and PPV are better than CVP and LVEDAI in predicting fluid responsiveness. Moreover, FTc and PPV before fluid loading were lower in responders than in non-responders. In addition, changes in SVI caused by fluid loading correlated with FTc values before fluid loading.

These findings appear to contradict those of two recent studies,[13 14] where FTc was not a predictor of fluid responsiveness. Moreover, Singer and colleagues[9 10 15] have reported many studies on FTc and have recently warned about the risk associated with FTc when it is used inadequately to guide fluid therapy.[16] To explain the causes of these differences, the specific characteristics of FTc must be understood. FTc is affected not only by left ventricular

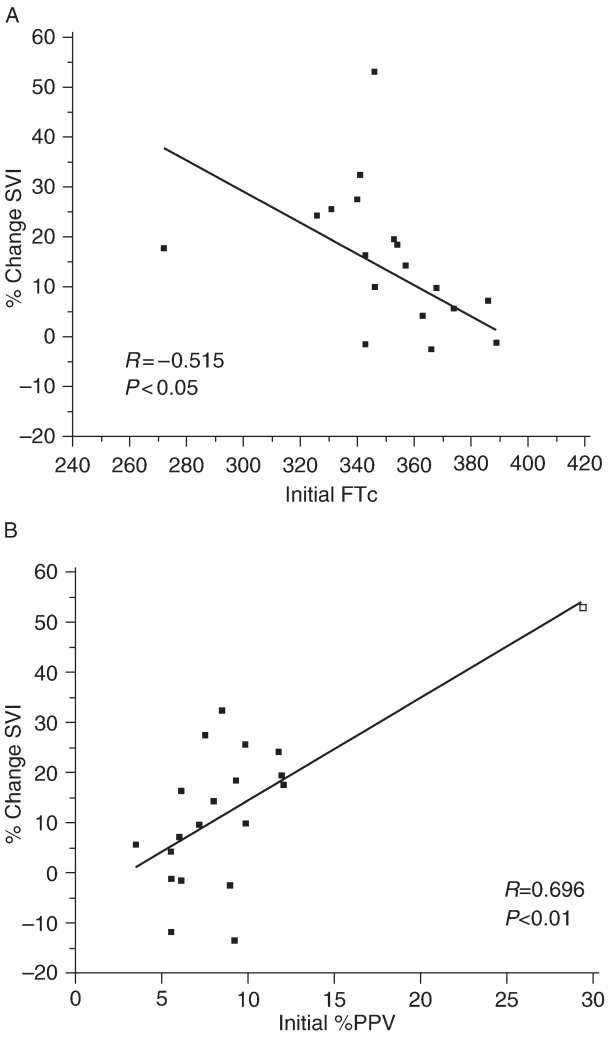

Fig 1 Relationships between the percentage changes in SVI (% Change SVI) and the initial values of PPV (% PPV; B) or initial corrected flow time (FTc; A).

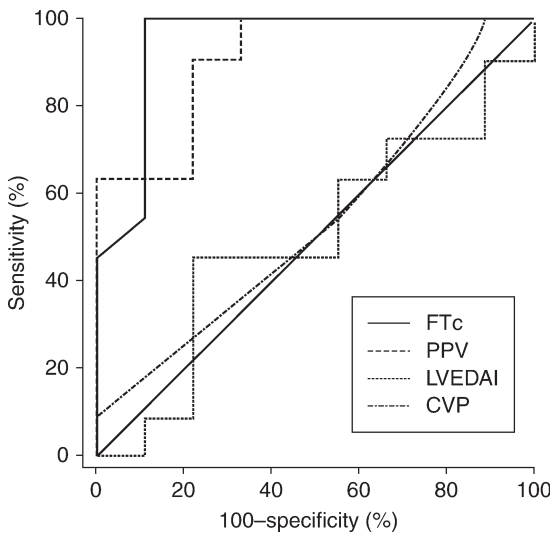

Fig 2 ROC comparing the ability of FTc, PPV, CVP, and LVEDAI to discriminate the responders and the non-responders.

preload but also by other haemodynamic factors, and it is inversely proportional to afterload.[15] Moreover, hypotensive patients with a low FTc may not respond to a fluid challenge in a pathological condition, which prevents adequate filling of the left ventricle (e.g. pericardial tamponade, massive pulmonary embolus, and tight mitral stenosis).[16] Consequently, low FTc does not always correspond to low left ventricular preload; low FTc can even represent a volume overload state.[9] This means that simple fluid challenge guided by only FTc could further aggravate deterioration in haemodynamic conditions.

However, the two studies in which FTc could not predict the fluid responsiveness[13 14] involved patients in acute circulatory failure.[13 14] Although in the study by Monnet and colleagues[13] patients with hypoxaemia or volume overload by chest radiography were excluded, both studies did not present exact causes of circulatory failure, and consequently, it is possible that patients with haemodynamic conditions that would prevent FTc from predicting fluid responsiveness were not excluded. In the study by Vallee and colleagues,[14] acute circulatory failure was defined as a systolic pressure of $<$90 mm Hg or requiring norepinephrine infusion. Considering that vasoconstriction by norepinephrine may cause low FTc regardless of left ventricular preload state, this could be why FTc failed to predict fluid responsiveness in the study. In our study, elective neurosurgical patients were included, and patients with cardiac disease were excluded. Moreover, as 13 of our 20 patients underwent surgery for a brain tumour, patients in the present study might have been be in a relatively hypovolaemic state induced by measures taken to control intracranial pressure (ICP), and maintain low CVPs [responders 3.36 (1.20), non-responders 3.78 (1.48)]. Therefore, the majority of haemodynamic conditions that prevent FTc from predicting fluid responsiveness were avoided in the present study.

Evaluation of preload status is important in neurosurgical patients. Many patients were taking diuretics for ICP control, and there are numerous factors, such as intraoperative bleeding, preoperative fasting, and induction of anaesthesia, which influence the preload status.

Previously investigated preload indices have been known to have certain limitations. For example, PAWP, a golden standard of static preload index, failed to predict the fluid responsiveness.[17 18] In the presence of diastolic dysfunction, higher than normal PAWP is required to maintain adequate left ventricular filling. Echocardiography is considered as the best tool for bedside haemodynamic evaluations, but is expensive and needs experienced personnel. Moreover, echocardiographic measurements of LVEDAI failed to predict preload responsiveness in previous studies[17 19] as in the present study. Although PPV has been reported to be successful in predicting the fluid responsiveness,[18 19] several limitations have been reported. First, the response of the arterial monitoring system may be affected by some technical factors, such as air bubbles, kinks, clot formation, compliant tubing, and excessive

length of tube.[20] Secondly, PPV can vary from one patient to another according to arterial compliance for a given change in stroke volume, because not only stroke volume but also arterial compliance directly affects PP.[21] Thirdly, PPV may be unreliable in predicting fluid responsiveness in patients with cardiac arrhythmias. Moreover, a decrease in HR itself may decrease the respiratory variation in arterial pressure during mechanical ventilation.[22 23] To this extent, it must be noted that the cut-off value of PPV to predict fluid responsiveness has been demonstrated mainly in septic patients who are usually tachycardic.[18 24] A relatively lower value of initial PPV in our study than that in other studies [18 24] may be explained by this limitation of PPV. Fourthly, increased intrathoracic pressure by large tidal volume[25 26] or PEEP[27] may also increase stroke volume and arterial pressure variation. In our study, absence of PEEP may be another cause of a relatively low level of PPV.

Consequently, there may be no single parameter that can guide fluid therapy under all situations. Therefore, every clinical finding and all haemodynamic data should be applied whenever required. In the present study, we measured CVP in conjunction with FTc. When the patient shows low FTc with high CVP, we can suspect the pathological conditions such as heart failure, pericardial tamponade, massive pulmonary embolism, and tight mitral stenosis where low FTc cannot represent a low preload state. Therefore, although CVP cannot predict fluid responsiveness, by simultaneously monitoring CVP and FTc, fluid therapy can be safer than by monitoring FTc alone. Moreover, because central venous catheters are frequently inserted not only to measure CVP but also for other purposes, such as the infusion of total parenteral nutrition and the administration of the fluid to treat hypovolaemia in the operating room or intensive care unit, the simultaneous monitoring of CVP and FTc can be easily performed.

In summary, FTc successfully predicted fluid responsiveness. Considering that the enrolled patients were 20 elective neurosurgical patients with normal heart function, the generalization of these results may be limited. However, FTc may be extremely useful when interpreted in conjunction with other clinical information, and measurements such as CVP.

Acknowledgement

This article was supported by a grant no. 04-2006-032-0 from the Seoul National University Hospital Research Fund.

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