

CARDIOVASCULAR

# Dynamic preload markers to predict fluid responsiveness during and after major gastrointestinal surgery: an observational substudy of the OPTIMISE trial

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## Editor's key points

- This observational study investigated if stroke volume variation (SVV) and pulse pressure variation (PPV) may predict the response to i.v. fluid during and after major surgery.
- The performance of both SVV and PPV was on the borderline between poor and fair prediction of fluid responsiveness during surgery.
- After surgery, neither variable was a useful predictor of fluid responsiveness, primarily because of poor performance during spontaneous ventilation, which resulted in reduced specificity.
- The findings from this observational study should be confirmed prospectively.

**Background.** Stroke volume variation (SVV) and pulse pressure variation (PPV), termed dynamic markers of preload responsiveness, may predict the response to i.v. fluid in critically ill patients. However, the predictive accuracy of these variables during gastrointestinal surgery remains uncertain.

**Methods.** Observational study of patients aged  $\geq 50$  yr undergoing major gastrointestinal surgery, enrolled in the OPTIMISE trial. Patients received six 250 ml fluid challenges with i.v. colloid solution (three during and three after surgery), while SVV and PPV were measured using the LiDCOrapid monitor (LiDCO Ltd, UK). Fluid responsiveness was defined as a stroke volume increase  $\geq 10\%$ . Area under the receiver operating characteristic curve was calculated with 95% confidence intervals. Adjustment for covariates was performed by regression modelling and a clustering method was used to adjust for intra-patient correlation.

**Results.** One hundred patients were recruited between August 2010 and October 2012. Five hundred and fifty-six fluid challenges were administered and 159 (28.6%) were associated with increased stroke volume. The predictive value of both variables was poor during surgery [SVV 0.69 (0.63–0.77); PPV 0.70 (0.62–0.77)], and also after surgery [SVV 0.69 (0.63–0.78); PPV 0.64 (0.56–0.73)]. The findings were similar when analysed according to whether patients were mechanically ventilated [SVV 0.68 (0.63–0.77); PPV 0.69 (0.61–0.77)] or breathing spontaneously [SVV 0.69 (0.61–0.77); PPV 0.63 (0.56–0.72)]. Predictive value improved slightly in a sensitivity analysis excluding outlier values of SVV and PPV.

**Conclusions.** In this study, the predictive accuracy of SVV and PPV for fluid responsiveness was insufficient to recommend for routine clinical use during or after major gastrointestinal surgery.

**Keywords:** fluid therapy, methods; monitoring, physiological; observational study; surgery

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Estimates suggest that more than 230 million patients undergo surgery worldwide each year with mortality reported to be between 1% and 4%.<sup>1 2</sup> Complications and deaths are most frequent among high-risk patients, those who are older or have co-morbid disease, and undergo major gastrointestinal or vascular surgery. Importantly, patients who develop complications, but survive to leave hospital, suffer reduced long-term survival.<sup>3 4</sup> It is accepted that the dose of i.v. fluid has an important effect on patient outcomes, in particular after major

gastrointestinal surgery. However, fluid is widely prescribed according to subjective criteria leading to wide variation in clinical practice.<sup>5 6</sup>

One possible solution is the use of dynamic markers of preload responsiveness, such as stroke volume variation (SVV) and pulse pressure variation (PPV), which describe the degree of haemodynamic change which occurs during the respiratory cycle.<sup>7</sup> Larger values suggest hypovolaemia, but may also occur if the heart rhythm is irregular or the patient is

breathing spontaneously. Dynamic markers may simplify the approach to fluid therapy during the perioperative period, while reducing the number of fluid challenges administered simply to test the patients' volume status. SVV and PPV have both been used as endpoints for fluid therapy in two small randomized trials with promising results,<sup>8, 9</sup> while more recent studies of the predictive value of SVV and PPV for fluid responsiveness have yielded inconsistent findings.<sup>10–17</sup> This may relate to differences in patient populations, the specific methods used to test fluid responsiveness (in particular the volume of the i.v. fluid bolus), and to factors that introduce additional variation in cardiac output across the respiratory cycle. Commentaries have highlighted the need for further research to determine the appropriate use of haemodynamic endpoints provided by minimally invasive cardiac output monitoring.<sup>18</sup>

OPTIMISE is a recently completed multi-centre randomized trial of cardiac output-guided haemodynamic therapy in high-risk patients undergoing major gastrointestinal surgery.<sup>19</sup> The objective of the primary trial was to determine the clinical effectiveness of this approach in routine practice where the circumstances of patient care are less well controlled than in small efficacy trials. Given the potential value of SVV and PPV to simplify i.v. fluid therapy, we incorporated a substudy to determine the accuracy of these variables in predicting fluid responsiveness within the same context, in order to establish their utility in implementing the trial intervention into routine clinical practice. We hypothesized that SVV and PPV would accurately predict an increase in stroke volume of  $\geq 10\%$  in response to an i.v. fluid bolus.

## Methods

### Study design

The OPTIMISE trial, is a multi-centre, observer-blinded, randomized controlled trial conducted in 17 hospitals in the UK.<sup>19</sup> The trial findings including the study protocol are presented in detail elsewhere. This substudy was conducted in two participating hospitals. Adult patients aged 50 yr or over undergoing major abdominal surgery involving the gastrointestinal tract of expected duration  $> 90$  min were eligible for recruitment, provided they satisfied one of the following criteria: age  $\geq 65$  yr, presence of a risk factor for cardiac or respiratory disease, acute or chronic renal impairment (serum creatinine  $\geq 130 \mu\text{mol litre}^{-1}$ ), diabetes mellitus, or non-elective surgery. Exclusion criteria were refusal of consent, pregnancy, acute arrhythmias, or myocardial ischaemia before enrolment and patients receiving palliative treatment only. Patients with chronic atrial fibrillation were eligible for inclusion. OPTIMISE was approved by the East London and City Research Ethics Committee (09/H0703/23) and the Medical and Healthcare products Regulatory Agency and registered with Controlled Trials (ISRCTN04386758). Written informed consent was obtained from all patients before surgery.

### Clinical management

The intervention period commenced with induction of anaesthesia and continued until 6 h after surgery was complete. All

patients received standard measures to maintain oxygenation ( $\text{SpO}_2 \geq 94\%$ ), haemoglobin ( $> 80 \text{ g litre}^{-1}$ ), core temperature ( $37^\circ\text{C}$ ), and heart rate ( $< 100 \text{ beats min}^{-1}$ ). 5% dextrose was administered at  $1 \text{ ml}^{-1} \text{ kg}^{-1} \text{ h}^{-1}$  to satisfy maintenance fluid requirements. Mean arterial pressure was maintained between 60 and 100 mm Hg using an  $\alpha$ -adrenoceptor agonist or vasodilator as required. In the control group, additional fluid was administered at the discretion of the clinician guided by heart rate, arterial pressure, urine output, core-peripheral temperature gradient, serum lactate, and base excess.

Patients randomized to the intervention received i.v. fluid and inotropic therapy guided by a haemodynamic therapy algorithm informed by cardiac output monitoring (LiDCOrapid, LiDCO Ltd, Cambridge, UK) as determined by the OPTIMISE trial protocol (Supplementary material). This algorithm included the use of 250 ml i.v. fluid challenges with colloid solution as required in order to achieve and maintain a maximal value of stroke volume. Fluid responsiveness was defined as an increase in stroke volume  $\geq 10\%$ . Patients also received an i.v. infusion of dopexamine at a fixed rate of  $0.5 \mu\text{g kg}^{-1} \text{ min}^{-1}$  (Cephalon, Welwyn Garden City, UK). The dose of dopexamine was reduced if the heart rate increased above 120% of baseline value or  $100 \text{ beats min}^{-1}$  (whichever was greater) for more than 30 min, despite adequate anaesthesia and analgesia. If the heart rate did not decrease despite dose reduction, the dopexamine infusion was discontinued.

Some additional measures were taken for substudy patients. During mechanical ventilation, the tidal volume was standardized to  $8 \text{ ml kg}^{-1}$  with a PEEP of 5 cm  $\text{H}_2\text{O}$  before fluid administration, as recommended by previous investigators.<sup>20, 21</sup> All fluid boluses were marked as an event on the monitor. Data describing the first three fluid challenges during surgery and the first three fluid challenges after surgery were recorded. The following baseline physiological data were recorded 1 min before administration of the fluid bolus: tidal volume ( $V_t$ ), respiratory rate (RR), spontaneous ventilation, heart rhythm, epidural infusion of local anaesthetic, i.v. infusion of vasoactive drugs, and recent bolus doses of vasoactive agents. Baseline data also included whether the patient was undergoing laparoscopy at the time of the fluid challenge and if so, the associated intra-abdominal pressure (IAP). A 250 ml i.v. colloid bolus was then administered within 60 s using a 50 ml syringe. Physiological and other data were then recorded again 5 min after the bolus was commenced.

### Statistical analysis

There is no standard approach to sample size calculations for comparing AUROC; instead, we planned to recruit 100 patients as the largest feasible sample size. Standard receiver operating characteristic (ROC) curves were constructed and area under these curves (AUROC) was calculated to quantify overall prognostic discrimination for fluid responsiveness. AUROC was then compared with the null value of 0.5 using a paired non-parametric technique. ROC curves were obtained by averaging 1000 populations bootstrapped from the original study population, as previously described.<sup>22</sup> This method limits the impact

of outlier values and allows for more robust calculations. To account for multiple fluid challenges given to each patient, a clustering method was used to adjust for the intra-patient correlation. The response to a fluid challenge can also be influenced by other factors such as baseline cardiovascular status. The ROC curves were adjusted using regression modelling for the following covariates: irregular cardiac rhythm (yes or no), heart rate, mean arterial pressure, central venous pressure, respiratory rate, epidural infusion of local anaesthetic (yes or no), vasoactive drug infusion (yes or no), vasoactive drug bolus within 20 min preceding fluid challenge (yes or no), closed abdomen or open abdomen or laparoscopy, and spontaneous ventilation (yes or no).<sup>23</sup> Two models were constructed to compare model fit before and after adjustment. The best threshold of an ROC curve was chosen as that which maximized the Youden index (sensitivity+specificity-1).<sup>24</sup> Predictive accuracy is described using the standard terms: poor (AUROC 0.6–0.7), fair (AUROC 0.7–0.8), good (AUROC 0.8–0.9), and excellent (AUROC 0.9–1.0). AUROC data are presented with 95% confidence intervals. Other data are presented as mean (SD) where normally distributed or median (IQR) where not normally distributed. Statistical analysis was performed using STATA MP 13.1 (STATA Corp., USA).

## Results

One hundred patients were recruited between August 2010 and October 2012, all of whom completed the study assessments and are included in the analysis. Baseline patient characteristics are presented in Table 1. Details of clinical management including i.v. fluid and vasoactive drug therapy are presented in Table 2. Two patients received fluid challenges

with hydroxyethyl starch solution, the remaining 98 with gelatin solution. In 44 instances, a fluid challenge was not indicated according to the trial intervention algorithm, two during surgery and 42 after surgery, giving a total of 556 fluid challenges all of which were included in the analysis. Overall, 28.6% (159 of 556) of fluid challenges were associated with an increase in stroke volume of  $\geq 10\%$ . During surgery, 29.8% (88 of 295) fluid challenges were positive and after surgery, 27.2% (71 of 261) were positive.

The distribution of SVV and PPV data is shown in Figure 1. Data describing sensitivity, specificity, AUROC, and optimal threshold values are shown in Table 3. During surgery, the performance of SVV and PPV was on the borderline between poor and fair predictive value (Fig. 2). After surgery, both variables were poor predictors of fluid responsiveness due to reduced specificity, although optimal threshold values changed only slightly (Fig. 3). For mechanically ventilated patients, the predictive value improved slightly and both were almost fair predictors of fluid responsiveness with minor changes in the optimal threshold value (Fig. 4). During spontaneous ventilation, SVV and PPV were both poor predictors of fluid responsiveness (Fig. 5). There was little change in AUROC after adjustment for pre-specified covariates, suggesting that these results are robust (Supplementary Tables S1 and S2). In order to understand the impact of high outlier values of SVV and PPV, we performed a sensitivity analysis excluding observations above the 95th centile (Supplementary Table S3). The predictive value of SVV and PPV improved slightly for measurements during surgery and mechanical ventilation but remained poor for measurements after surgery and during spontaneous ventilation. The optimal threshold values remained unchanged. We also performed a sensitivity analysis excluding 319 fluid challenges (53%) performed during laparoscopy, spontaneous ventilation, or any form of abnormal cardiac rhythm

**Table 1** Baseline patient characteristics. Data presented as mean (SD) or *n* (%). \*Baseline data missing on two patients

	<i>n</i> =98*
Age (yr)	71 (51–93)
Sex	
Male	61 (62%)
Female	37(38%)
Elective surgery	91 (93%)
Non-elective surgery	7 (7%)
Renal impairment (creatinine $>130 \mu\text{mol litre}^{-1}$ )	10 (10%)
Diabetes mellitus	21 (79%)
Risk factor for cardiac or respiratory disease	38 (39%)
Chronic atrial fibrillation	2 (2%)
Upper gastrointestinal surgery	26 (26%)
Lower gastrointestinal surgery	36 (37%)
Small bowel $\pm$ pancreatic surgery	36 (37%)
ASA grade	
I	5 (5%)
II	48 (49%)
III	44 (45%)
IV	1 (1%)

**Table 2** Clinical management of patients during intervention period. Data presented as mean (SD), median (IQR), or *n* (%)

	<i>n</i> =98
Duration of surgery (min)	277 (93)
Anaesthetic technique	
General anaesthetic only	18 (19%)
General anaesthetic plus epidural	79 (81%)
I.V. crystalloid (ml)	
During surgery	2500 (1500–3000)
During 6 h after surgery	600 (435–800)
I.V. colloid (ml)	
During surgery	1250 (1000–1750)
During 6 h after surgery	750 (500–1000)
Blood products (ml)	
During surgery	556 (315–747)
During 6 h after surgery	313 (276–851)
Bolus vasopressor or inotrope agent used during intervention period	86 (88%)
Vasopressor or inotrope infusion (other than dopexamine) used during intervention period	22 (22%)

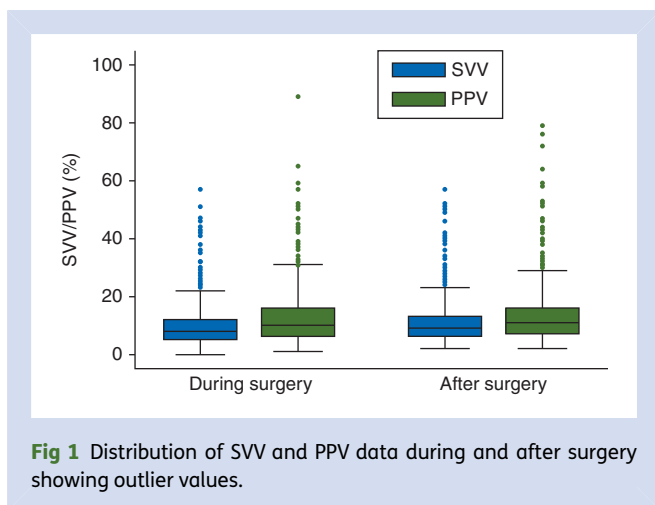
(Supplementary Table S4). The predictive values improved slightly for SVV and PPV in this sensitivity analysis. The optimal threshold values remained unchanged.

### Discussion

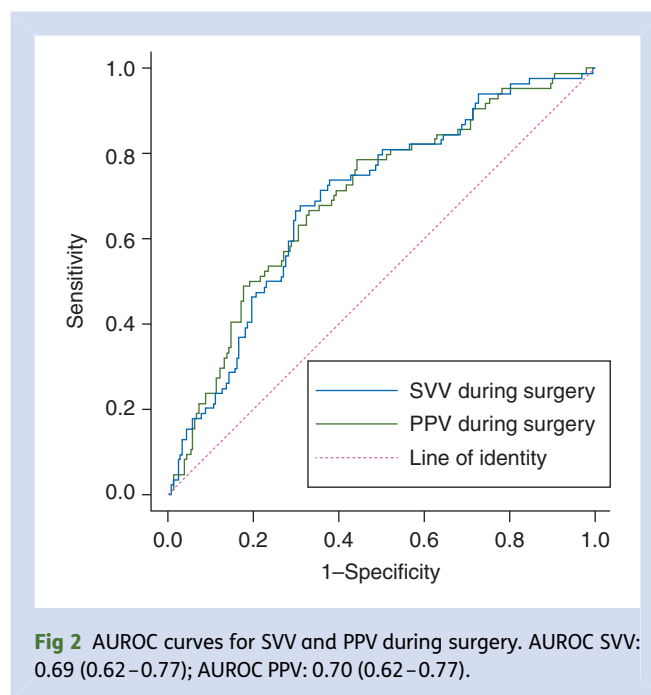
The principal finding of this study is that the performance of both SVV and PPV was on the borderline between poor and fair prediction of fluid responsiveness during surgery. After surgery, neither variable was a useful predictor of fluid responsiveness, primarily because of poor performance during spontaneous ventilation, which resulted in reduced specificity. These findings were essentially unchanged after adjustment for covariates and accounting for repeated measures taken during a series of six fluid challenges during and after surgery. Predictive value improved slightly in a sensitivity analysis excluding unusually high values of SVV and PPV.

Our findings contrast with those of the widely quoted systematic review undertaken by Marik and colleagues<sup>7</sup> in 2009. The findings of this previous review, which included trials

primarily of mechanically ventilated patients in intensive care, suggested good or excellent predictive value for both SVV and PPV. Importantly, the incidence of fluid responsiveness was >50% among the component studies in this systematic review but <30% in the study presented here. This difference may in turn relate to the size of fluid challenge, which was 500 ml or greater in many previous studies but only 250 ml in the current work. The findings of studies published since Marik's review have been inconsistent, with widely differing results in terms of predictive accuracy.<sup>10-17</sup> The largest study to date reported a good predictive value of PPV to predict fluid responsiveness in 413 patients undergoing surgery.<sup>11</sup> There are several key differences between this previous study



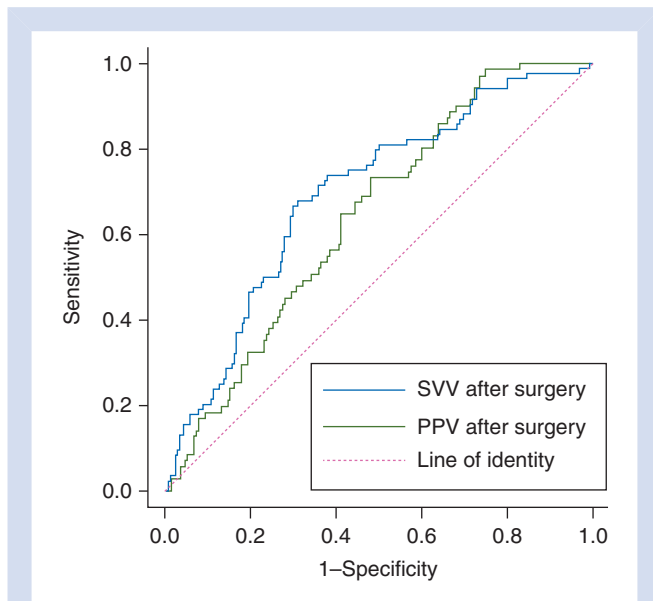
**Fig 1** Distribution of SVV and PPV data during and after surgery showing outlier values.



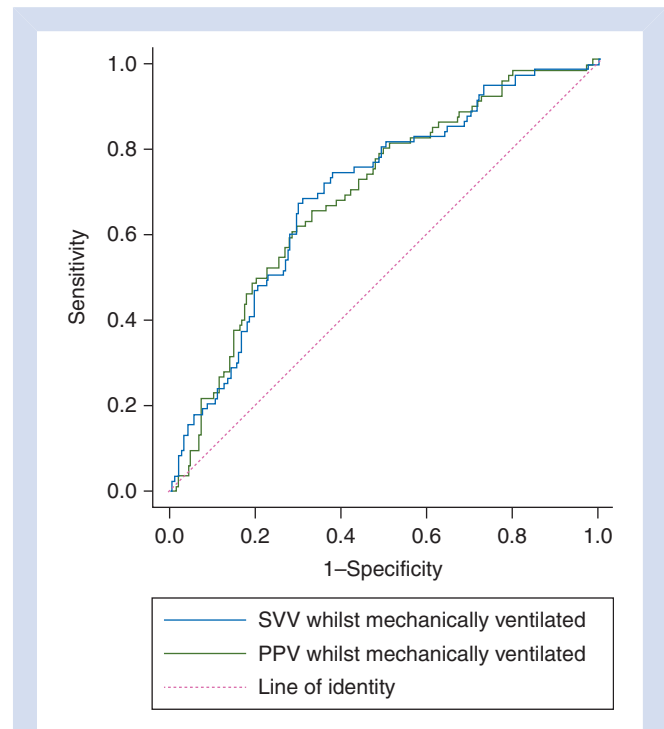
**Fig 2** AUROC curves for SVV and PPV during surgery. AUROC SVV: 0.69 (0.62–0.77); AUROC PPV: 0.70 (0.62–0.77).

**Table 3** Comparison of AUROC before and after adjustments, sensitivity, specificity, and optimal threshold value for SVV and PPV. CI, 95% confidence intervals

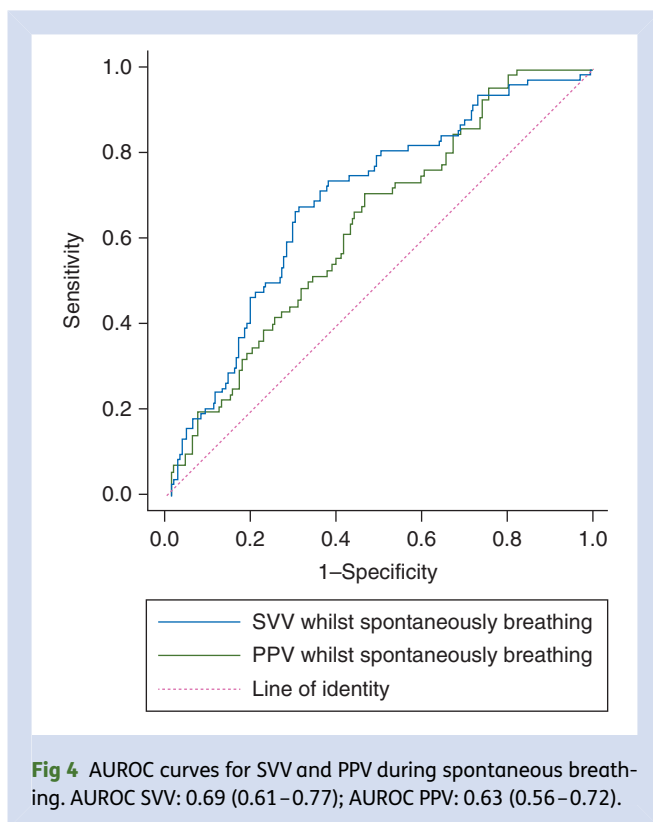
	AUROC (CI)	AUROC after adjustment (CI)	Sensitivity	Specificity	Optimal threshold	Positive predictive value	Negative predictive value
<b>During surgery</b>							
SVV	0.69 (0.62–0.77)	0.69 (0.62–0.77)	76%	66%	10%	73%	69%
PPV	0.70 (0.62–0.77)	0.70 (0.62–0.77)	75%	61%	12%	82%	54%
<b>After surgery</b>							
SVV	0.69 (0.63–0.78)	0.69 (0.63–0.78)	69%	56%	11%	73%	52%
PPV	0.64 (0.56–0.73)	0.64 (0.56–0.73)	84%	41%	10%	83%	54%
<b>Spontaneously breathing</b>							
SVV	0.69 (0.61–0.77)	0.69 (0.61–0.77)	69%	56%	11%	74%	52%
PPV	0.63 (0.56–0.72)	0.63 (0.56–0.72)	85%	41%	10%	83%	43%
<b>Mechanically ventilated</b>							
SVV	0.68 (0.63–0.76)	0.68 (0.63–0.76)	76%	66%	10%	73%	69%
PPV	0.69 (0.61–0.77)	0.69 (0.61–0.77)	74%	61%	12%	82%	54%



**Fig 3** ROC curves for SVV and PPV after surgery. AUROC SVV: 0.69 (0.63–0.78); AUROC PPV: 0.64 (0.56–0.73).



**Fig 5** AUROC curves for SVV and PPV during mechanical ventilation (with no spontaneous breathing). AUROC SVV: 0.68 (0.63–0.76); AUROC PPV: 0.69 (0.61–0.77).



**Fig 4** AUROC curves for SVV and PPV during spontaneous breathing. AUROC SVV: 0.69 (0.61–0.77); AUROC PPV: 0.63 (0.56–0.72).

and the current work. We analysed three fluid challenges during and three fluid challenges after major gastrointestinal surgery giving 556 study episodes. We used a rapid 250 ml fluid bolus administered within 1 min and a positive fluid challenge was defined as an increase in stroke volume of 10% or

more within 5 min. In the previous work, 413 patients were included but only 12% underwent gastrointestinal surgery. Each patient was studied only once giving 413 fluid challenge episodes consisting of a 500 ml bolus administered over 10–20 min with a positive fluid challenge defined as an increase in cardiac output of 15% or more. In the previous study, PPV was calculated manually while in the current work, this measurement was made using the LiDCOrapid system. The method of calculating SVV and PPV may differ between proprietary monitors. These differences may help to explain the contrasting findings of the two studies. In accordance with previous work, we standardized mechanical ventilation with a tidal volume of 8 ml kg<sup>-1</sup> during the fluid challenge.<sup>20 21</sup> There is ongoing debate about the most appropriate tidal volume for mechanical ventilation during surgery, with contrasting findings from recent studies.<sup>25 26</sup> While the tidal volume used in this study is on the borderline of the contrasting ranges recommended in these recent studies,<sup>25 26</sup> concerns regarding the safety of ventilation at higher tidal volumes may further limit the utility of SVV and PPV.

In terms of individual fluid challenges, this is the largest study of the predictive accuracy of dynamic markers of preload responsiveness we are aware of, and the second largest in terms of numbers of patients recruited. We utilized a cardiac output monitoring technology which can be used both during and after surgery (in awake, extubated patients), which has been extensively evaluated in terms of accuracy, and has been in widespread

clinical use for more than 10 yr.<sup>27</sup> It is the only study of which we are aware, to make adjustments for important covariates encountered in routine clinical practice, relating to baseline physiological status, surgical procedure, and respiratory management. We also take account of the multiple fluid challenges performed in each patient as part of our statistical analysis. However, there are also some potential limitations to this work. The volume of i.v. colloid used in each fluid challenge may be considered by some to be insufficient to result in a measurable change in stroke volume, although the approach to fluid challenge used does reflect normal practice in the UK. We also included patient data regardless of possible confounding factors such as irregular heart rhythm, or pneumoperitoneum. The findings of recent studies have suggested that midline thoracotomy and changes in IAP may affect the predictive value of SVV and PPV.<sup>28 29</sup> In a few cases, SVV and PPV values were unusually high and some commentators argue that clinicians would not use high outlier values to guide fluid therapy. However, we note that exclusion of high outliers in our sensitivity analysis did not substantially alter our findings. We also conducted a sensitivity analysis which excluded all measurements taken during laparoscopy, spontaneous ventilation, or any form of abnormal cardiac rhythm. While this did result in some improvement in predictive accuracy, the exclusion of more than half the fluid challenges clearly limits the utility of SVV and PPV in guiding i.v. fluid therapy. While we took several steps to account for sources of measurement error in our analysis, it is possible that our findings do not represent the optimal performance which could be achieved when using these variables as predictors of fluid responsiveness. However, our objective was to study these variables as they will be used in routine clinical practice, rather than in a carefully controlled and standardized environment which does not reflect usual clinical care. The measures we took to standardize the fluid challenge process may more closely reflect those that a busy clinician is able to take in a normal working environment. Nonetheless, it is possible that predictive accuracy could be improved with clinical training to better recognize the circumstances under which SVV and PPV measurement is likely to be inaccurate. A number of haemodynamic endpoints have been proposed for i.v. fluid therapy and it is possible that alternative endpoints may have greater predictive accuracy than those studied in this work.

## Conclusions

In this study, the predictive accuracy of SVV and PPV for fluid responsiveness was not adequate for routine use during or after major gastrointestinal surgery. Our findings also confirm the established view that these variables should not be used for predicting fluid responsiveness in spontaneously breathing patients. While it may be possible to make valid use of these variables in more specific patient groups, under more controlled physiological circumstances, this may limit the convenience and simplicity of these variables. A much larger study would be needed to define the circumstances under which SVV and PPV could be recommended to guide i.v. fluid therapy in routine clinical practice.

## Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

## Authors' contributions

R.M.P., I.M., N.M., and C.J.H. were responsible for study design. Patient recruitment and data collection were performed by N.M. and O.M. T.A. performed the data analysis with input from R.M.P. and N.M. The manuscript was drafted by R.M.P., N.M., and T.A., and revised following critical review by all authors.

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## Declaration of interest

R.M.P. has received equipment loans from LiDCO Ltd, a research grant from Circassia Holdings Ltd, and has performed consultancy work for Edwards Lifesciences, Covidien, and Massimo Inc. I.M. is a member of the editorial board of the *British Journal of Anaesthesia*. R.M.P. is a member of the editorial advisory board of the *British Journal of Anaesthesia*.

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## Data sharing

The authors are happy to consider data sharing requests from bona fide researchers. These should be addressed to the senior author at: r.pearse@qmul.ac.uk.

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