# Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection

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**Background:** **Protocolized fluid administration using oesophageal Doppler monitoring may improve the postoperative outcome in patients undergoing surgery.**
**Methods:** **A total of 108 patients undergoing elective colorectal resection were recruited into a double-blind prospective randomized controlled trial. An oesophageal Doppler probe was placed in all patients. The control group received perioperative fluid at the discretion of the anaesthetist, whereas the intervention group received additional colloid boluses based on Doppler assessment. Primary outcome was length of postoperative hospital stay. Secondary outcomes were morbidity, return of gastrointestinal function and cytokine markers of the systemic inflammatory response. Standard preoperative and postoperative management was used in all patients.**
**Results:** **Demographic and surgical details were similar in the two groups. Aortic flow time, stroke volume, cardiac output and cardiac index during the intraoperative period were higher in the intervention group ($P < 0.050$). The intervention group had a reduced postoperative hospital stay (7 *versus* 9 days in the control group; $P = 0.005$), fewer intermediate or major postoperative complications (2 *versus* 15 per cent; $P = 0.043$) and tolerated diet earlier (2 *versus* 4 days; $P = 0.029$). There was a reduced rise in perioperative level of the cytokine interleukin 6 in the intervention group ($P = 0.039$).**
**Conclusion:** **A protocol-based fluid optimization programme using intraoperative oesophageal Doppler monitoring leads to a shorter hospital stay and decreased morbidity in patients undergoing elective colorectal resection.**

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## Introduction

Recent developments in multimodal care and enhanced surgical recovery programmes after colorectal surgery have identified potential improvement in outcomes after major bowel resection. Improved postoperative recovery may be reflected by a reduction in the surgical stress response[1]. The role of perioperative fluid management remains under debate.

In clinical practice it is common for large volumes of fluid to be administered during elective surgical procedures[2,3], based on the assumption that perioperative fluid redistribution leads to a net decrease in extracellular fluid volume[4]. In addition, aggressive resuscitation to achieve supranormal cardiovascular function using combinations of intravenous fluids with or without inotropes has been advocated on the basis that outcome is improved by increasing tissue oxygen delivery[5–7]. In contrast, other investigators have advised restriction of perioperative fluids, highlighting the risks of fluid overload and its associated complications[8–11].

In a large multicentre trial of 172 patients randomized to receive either a restricted or standard perioperative fluid regimen, Brandstrup *et al.*[12] showed that restriction of fluids (aiming at unchanged bodyweight) significantly reduced the number of complications after colorectal surgery. A recent review of intraoperative fluid restriction in gastrointestinal surgery concluded that judicious perioperative fluid therapy can improve outcome after major surgery, recommending a balanced approach to fluid management[13]. In thoracic surgery there is a trend towards a 'dry' regimen, with evidence to suggest that this reduces postoperative pulmonary complications[14].

With all regimens, however, the consensus is to avoid tissue hypoperfusion, activation of the systemic inflammatory response and multiple organ failure, yet at the same time prevent fluid overload.

Patients undergoing colorectal resection are particularly vulnerable to problems with fluid dynamics in the perioperative period. The patients are often elderly with multiple co-morbidities, putting them into a high-risk group. In addition, prolonged preoperative fasting and bowel preparation have a significant dehydrating effect[15].

Oesophageal Doppler monitoring is a minimally invasive method of accurately determining haemodynamic status in the perioperative period. Studies of patients undergoing orthopaedic procedures have shown shorter hospital stays and improved outcome following Doppler-guided fluid optimization in the intraoperative period[16,17]. In addition, Doppler optimization reduces the incidence of gut mucosal hypoperfusion and improves outcome in patients undergoing coronary artery bypass grafting[18].

Accurate guidance of intraoperative fluid administration using oesophageal Doppler monitoring may reduce the risk of perioperative hypovolaemia and subsequent tissue reperfusion injury. Importantly, it may allow the avoidance of gut mucosal hypoperfusion and its detrimental effects on gut wall barrier integrity, bacterial translocation and systemic inflammatory response. The aim of this study was to assess the effect of optimizing haemodynamic status, using a protocol-driven intraoperative fluid regimen, on outcome following elective colorectal resection.

## Patients and methods

### Study design

Following local ethics committee approval of the study, consecutive patients undergoing elective colorectal resection were recruited prospectively into a double-blind randomized controlled trial with written patient consent. Exclusion criteria were severe oesophageal disease, recent oesophageal or upper airway surgery, systemic steroid medication, moderate or severe aortic valve disease, bleeding diathesis and patient choice.

Doppler probe insertion and monitoring, and trial fluid administration were carried out by a medically qualified researcher who had no involvement in postoperative patient care or decision making. This allowed complete blinding of both surgical and anaesthetic clinical teams. Although the anaesthetist was blinded to Doppler readings and fluid administration, the researcher carrying out the optimization was aware of all anaesthetic activity. Fluid bolus administration in the intervention group was based solely on the Doppler-assessed parameters, following a strict algorithm (*Fig. 1*).

The primary outcome measure was length of hospital stay. Predefined discharge criteria were: toleration of oral diet, return of lower gastrointestinal function, adequate pain control on simple oral analgesics and mobilization to an appropriate level. Secondary outcomes studied were return of gastrointestinal function, morbidity, critical care stay and cytokine markers of the systemic inflammatory response.

### Operative procedures

All anaesthetic interventions were at the discretion of the consultant anaesthetist responsible for perioperative management of the patient. All patients received a standard volatile-based general anaesthetic; when instituted,

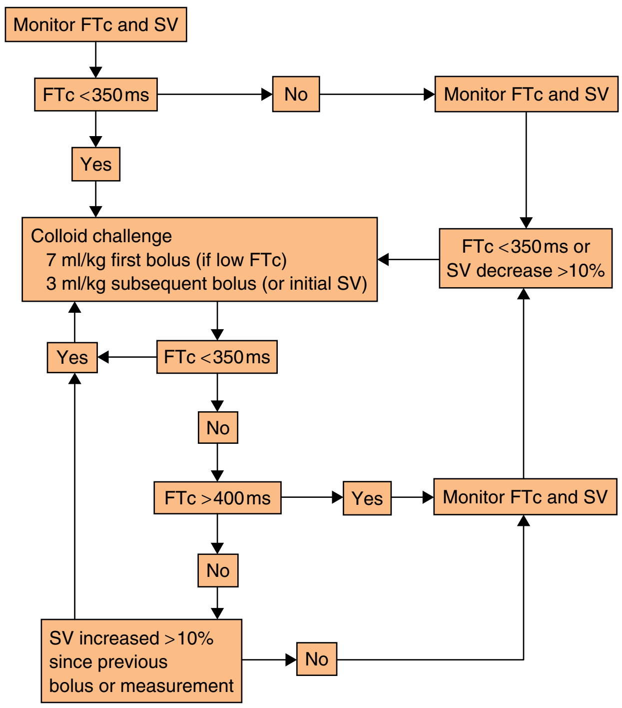


**Fig. 1** Fluid administration algorithm. FTc, descending aortic corrected flow time; SV, stroke volume

epidural analgesia was continued for 48 h after surgery. Routine perioperative monitoring included electrocardiography, pulse oximetry, end-tidal carbon dioxide monitoring, and non-invasive or invasive blood pressure monitoring. All patients had continuous oesophageal Doppler monitoring (Cardio-Q™; Deltex Medical, Chichester, UK). Crystalloid, colloid or blood products were administered by the anaesthetist based on intraoperative losses and standard haemodynamic parameters. No formal policy was instituted with regard to volume preloading; however, any fluid preload given in the anaesthetics room was included in the total volume administered. In addition, patients randomized to the intervention group received additional colloid (Volplex®; Cambridge Laboratories, Wallsend, UK) boluses to maintain a descending aortic corrected flow time (FTc) of more than 0·35 s (350 ms), and further boluses were given to optimize the stroke volume (SV). Once achieved, further fluid boluses were given only if the SV altered by more than 10 per cent or the FTc fell below 0·35 s. The colloid boluses followed a strict algorithm (*Fig. 1*), similar to that used by Gan *et al.*[19]. Haemodynamic parameters were recorded every 10 min. Both the surgical team in charge of postoperative patient care that determined fitness for discharge and the anaesthetist were blinded to the oesophageal Doppler readings and to patient randomization.

## Postoperative care

Postoperative care was standard for both groups of patients, and was undertaken by the same clinical and nursing teams using the same surgical wards. All patients were allowed free access to oral fluids from the evening of surgery, and normal oral diet was allowed from day 1 after operation. Postoperative intravenous fluid administration was based on clinical need assessed by blood pressure, urine output, losses and oral intake; no formal protocol was used. Early mobilization and daily physiotherapy was provided for all patients. Postoperative analgesia was given by epidural or patient-controlled analgesia for the first 48 h after surgery, with oral analgesics thereafter. Bowel function, dietary intake and fluid administration were recorded on each postoperative day. Complications (nature, severity and planned intervention) were recorded daily by the surgical team assistant; they were classified *post hoc* according to previously described criteria to aid analysis (see *Table 3*)[20]. Fitness for surgical discharge and total length of hospital stay were recorded.

## Cytokine analysis

Blood samples were obtained before surgery and at specific postoperative time points (at 0 (skin closure), 6, 24 and 48 h), and serum was stored at − 80°C for subsequent analysis of the inflammatory cytokine response to the surgical trauma.

Interleukin (IL) 6 levels were determined by cytometric bead array using a BD™ Human Th1/Th2 Cytokine Kit II (BD Biosciences, Oxford, UK). This method involves using a series of beads with discrete fluorescence intensities, which can be detected by flow cytometry. Each bead provides a capture surface for a specific protein and therefore allows simultaneous detection of multiple analytes. At the same time points, blood was also analysed for haemoglobin concentration and haematocrit. The plasma dilution factor was calculated.

## Statistical analysis

Power analysis on pilot data from 20 patients indicated that a sample size of 108 patients (54 per group) would be required to demonstrate statistical significance for a 3-day reduction in hospital stay, giving the study a power of 0·8 with a significance level of 0·050.

Kolmogorov–Smirnov tests were performed to assess normality of data. Normally distributed data were analysed with Student's $t$ test for unpaired samples, and other continuous data were compared with the Mann–Whitney $U$ test. Categorical data were compared using $\chi^2$ and Fisher's exact tests as appropriate. Haemodynamic parameters were analysed by means of summary measures. Data were analysed using the SPSS® version 10 for Windows® program (SPSS, Chicago, Illinois, USA). $P < 0{\cdot}050$ was considered statistically significant.

# Results

One hundred and eight patients undergoing elective colorectal resection were randomized (54 per group); five failed to complete the study (*Fig. 2*). In four patients the anaesthetist used oesophageal Doppler monitoring and therefore the trial fluid algorithm was not followed and blinding was not possible, and one patient withdrew from personal choice. In one patient in each group, the intervention did not proceed as planned. In one patient in the 'optimized' group, the intravenous line used to give the fluid boluses blocked during surgery, thus preventing the algorithm from being followed for the latter half of the procedure. One patient in the control group became haemodynamically unstable to the extent that the anaesthetist was unblinded as to the Doppler readings. All results were analysed on an intention to treat basis.

No differences between the two groups were found in patient demographics, risk indices, or duration and type of procedure (*Table 1*).

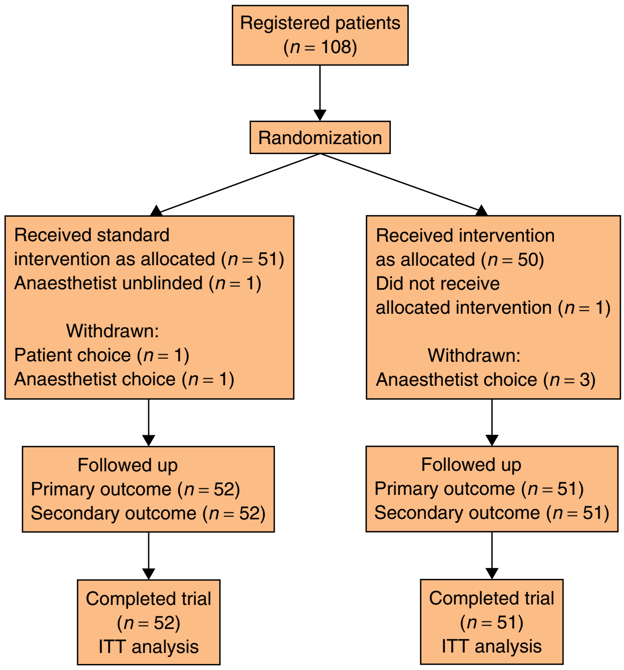


**Fig. 2** Flow chart depicting patients' progression through the randomized clinical trial. Patients shown as withdrawn through anaesthetist choice had anaesthetist-controlled oesophageal Doppler monitoring, not following the trial treatment algorithm. ITT, intention to treat

**Table 1** Demographic and surgical characteristics

| | Control | Intervention | *P*† |
|---|---|---|---|
| Age (years)* | 67·6(15·2) | 62·3(14·0) | 0·066 |
| Body mass index (kg/m$^2$)* | 26·4(4·5) | 25·9(5·3) | 0·635 |
| Colonic : rectal resection | 25 : 29 | 30 : 24 | 0·336 |
| Laparoscopic | 13 | 13 | 1·000 |
| Duration of surgery (min)* | 167·0(55·5) | 149·0(48·7) | |
| ASA grade* | 2·2(0·6) | 2·1(0·6) | 0·547 |
| POSSUM* | | | |
| Physiological Score | 16·4(3·6) | 16·0(3·5) | 0·434 |
| Operative Score | 16·1(3·7) | 15·4(4·2) | 0·326 |
| Predicted morbidity | 44·6(19·8) | 40·7(20·4) | 0·311 |
| Arterial line monitoring | 24 (46) | 20 (39) | 0·424 |
| CVP line | 21 (40) | 16 (31) | 0·271 |
| Epidural | 33 (63) | 32 (63) | 0·841 |

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.); ASA, American Society of Anesthesiologists; POSSUM, Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity; CVP, central venous pressure. †*t*-test/$\chi^2$ test.

Outcome measures are summarized in *Table 2*. Patients in the intervention group had a significantly reduced time to fitness for discharge (median 9 *versus* 6 days; $P = 0{\cdot}003$) and actual discharge (median 9 *versus* 7 days; $P = 0{\cdot}005$). There was no difference in lower gastrointestinal function as assessed by return of bowel activity. Patients in the intervention group were able to tolerate diet significantly earlier than those in the control group (toleration of diet was predefined as the patient consuming 50 per cent of each meal in a 24-h period) ($P = 0{\cdot}029$). A significant reduction in intermediate or major complications was observed in the patients who had Doppler-guided fluid optimization (one (2 per cent) *versus* eight (15 per cent) in the control group; $P = 0{\cdot}043$) (*Table 3*). There was one postoperative death in the control group from multiple organ failure secondary

**Table 2** Primary and secondary outcomes

| | Control | Intervention | *P*‡ |
|---|---|---|---|
| Surgical fitness for discharge (days)* | 9 (4–45) | 6 (3–35) | 0·003 |
| Total postoperative stay (days)* | 9 (4–45) | 7 (3–35) | 0·005 |
| Flatus (days)* | 2 (1–7) | 2 (1–8) | 0·923 |
| Bowel movement (days)* | 4 (1–21) | 3 (1–10) | 0·709 |
| Diet (days)* | 4 (1–19) | 2 (1–10) | 0·029 |
| Intraoperative colloid (ml)† | 1209(824) | 1340(838) | 0·397 |
| Intraoperative crystalloid (ml)† | 2625(1004) | 2298(863) | 0·077 |
| Blood loss (ml)* | 475 (100–2900) | 250 (40–2455) | 0·101 |
| Blood transfusion | 8 | 11 | 0·448 |
| Readmission rate | 1 (2) | 0 (0) | 0·990 |
| Mortality | 1 (2) | 0 (0) | 0·990 |
| Intraoperative inotrope | 26 (50) | 16 (31) | 0·048 |

Values in parentheses are percentages unless indicated otherwise; values are *median (interquartile range) and †mean(s.d.). ‡Mann–Whitney *U* test/$\chi^2$ test/Fisher's exact test.

**Table 3** Classification of postoperative complications[20] and complication rates in the two groups

| Grade | Definition | Control | Intervention | *P** |
|---|---|---|---|---|
| 1 | Any deviation from normal postoperative course with no need for pharmacological treatment or surgical, endoscopic or radiological intervention | 7 (13) | 6 (12) | 0·767 |
| 2 | Pharmacological treatment | 7 (13) | 6 (12) | 0·767 |
| 3 | Requiring surgical, endoscopic or radiological intervention | 2 (4) | 1 (2) | 0·558 |
| 4 | Life-threatening complication requiring HDU or ICU care | 4 (8) | 0 (0) | 0·042 |
| 5 | Death | 1 (2) | 0 (0) | |
| Suffix 'd' | Continuing complication at time of discharge | 1 (2) | 0 (0) | |

Values in parentheses are percentages. HDU, high-dependency unit; ICU, intensive care unit. *$\chi^2$ test/Fisher's exact test.

to methicillin-resistant *Staphylococcus aureus* pneumonia. Ileus, nausea and vomiting were recorded as complications in 12 control patients compared with three patients in the intervention group ($P = 0{\cdot}012$).

Significantly more patients in the control group required unplanned admission to the critical care unit (six versus no patients, $P = 0{\cdot}012$), due to pneumonia and sepsis-related multiple organ dysfunction syndrome (MODS) (one patient), anastomotic breakdown requiring reoperation and MODS (one), sepsis and intra-abdominal collection (treated by radiological drainage) (one), and pneumonia requiring non-invasive ventilatory support (one). No significant differences were found in the volume of fluid administered during surgery or in the first 48 h after operation in the two groups. The majority of protocol volume given was within the first 40 min of the initiation of surgery; 46 per cent of the total number of boluses (58 per cent of total volume) given can be accounted for in this period.

Before surgery (after induction of anaesthesia but before skin incision) there was no significant difference in pulse rate, mean arterial pressure (MAP), SV, FTc, cardiac index (CI) or cardiac output (CO) between the two groups (*Table 4*). However, at the end of surgery, despite no change in pulse rate or MAP, patients in the intervention group had a significantly increased SV, FTc and CO compared with values in the control group. Pulse and MAP were similar throughout surgery for each group, although CI was seen to rise in the intervention group early in the operating period and to remain raised throughout the operation in comparison with the control group (*Fig. 3*). FTc was

**Table 4** Cardiovascular variables before skin incision and after skin closure

| | Control | Intervention | *P** |
|---|---|---|---|
| Pulse rate (b.p.m.) | | | |
| Start | 66·6(15·0) | 72·8(18·4) | 0·068 |
| End | 73·5(13·4) | 77·2(18·5) | 0·245 |
| MAP (mmHg) | | | |
| Start | 74·9(15·5) | 73·0(17·3) | 0·541 |
| End | 74·1(15·2) | 76·1(14) | 0·477 |
| SV (ml) | | | |
| Start | 85·4(29·2) | 83·4(24·3) | 0·721 |
| End | 80·1(30·8) | 92·0(26) | 0·039 |
| FTc (ms) | | | |
| Start | 362·4(54) | 373·4(49) | 0·289 |
| End | 355·1(57) | 387·2(38) | 0·001 |
| CO (l/min) | | | |
| Start | 5·7(2·2) | 5·9(2·2) | 0·696 |
| End | 5·9(2·1) | 6·9(2·6) | 0·031 |
| CI (l/min/bsa) | | | |
| Start | 3·1(1·2) | 3·2(1·4) | 0·626 |
| End | 3·2(1·2) | 3·8(1·3) | 0·014 |

Values are mean(s.d.). b.p.m., Beats per minute; MAP, mean arterial pressure; SV, stroke volume; FTc, corrected flow time; CO, cardiac output; CI, cardiac index. *$\chi^2$ test/Fisher's exact.

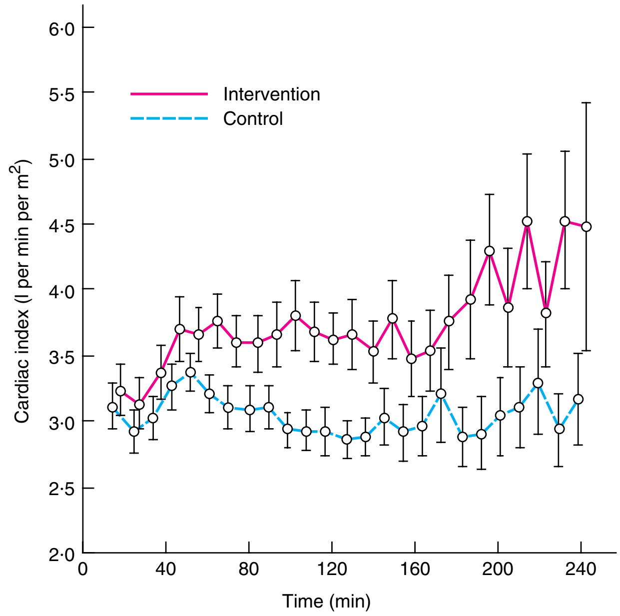


**Fig. 3** Cardiac index measured at 10-min intervals during surgery from induction of anaesthesia. Values are mean(s.d.), Mann–Whitney *U* test

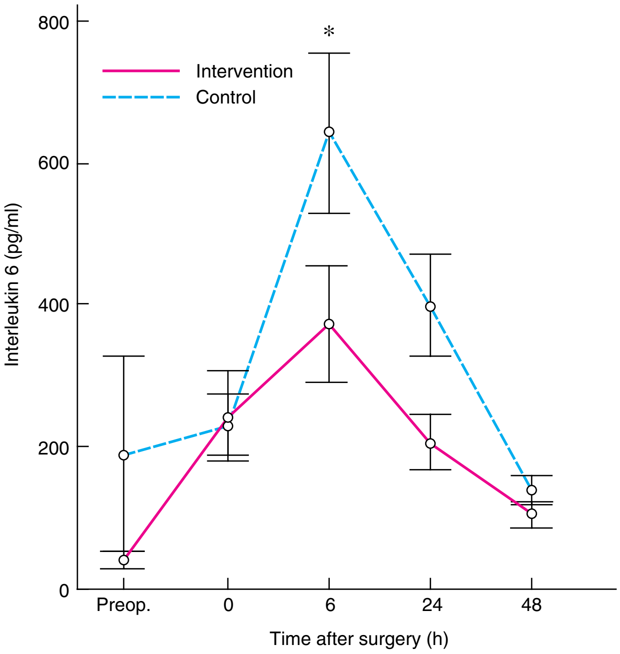


**Fig. 4** Interleukin 6 levels before and after surgery. Values are mean(s.d.). *$P = 0{\cdot}039$ (Mann–Whitney *U* test)

greater than the target value of 350 ms for 84 per cent of the total operating time in the intervention group *versus* 61 per cent in the control group ($P < 0{\cdot}001$). This suggests a degree of hypovolaemia for 39 per cent of operating time in control patients. However, neither the intervention nor the control group exhibited prolonged systolic blood pressures below 90 mmHg (15 *versus* 13 per cent of operating time respectively; $P = 0{\cdot}152$) or tachycardia of more than 100 beats per min (6 *versus* 7 per cent of operating time; $P = 0{\cdot}593$).

Twenty-six patients in the control group received vasoconstrictor support during surgery, compared with 14 in the intervention group ($P = 0{\cdot}015$). Drugs used in control and intervention groups respectively were: metaraminol (ten *versus* seven patients; $P = 0{\cdot}482$), glycopyrrolate (three *versus* four patients; $P = 0{\cdot}696$), noradrenaline (one patient in each group) and ephedrine (12 *versus* two patients; $P = 0{\cdot}004$).

Circulating IL-6 concentration was seen to rise sharply immediately after surgery, peaking at 6 h as shown in *Fig. 4*, with a significant difference between control and intervention groups (mean 673·1 *versus* 369·4 pg/ml respectively; $P = 0{\cdot}039$). The plasma dilution factor was calculated using the equation described by Flordal[21]; no significant differences were found between the two groups at any of the five time points.

## Discussion

This study has shown that protocolized fluid administration guided by oesophageal Doppler monitoring decreases morbidity, allows earlier tolerance of diet and reduces postoperative hospital stay in patients undergoing elective colorectal resection. This evidence supports results from other studies in different patient groups regarding the importance of targeted intraoperative fluid administration, and confirms the utility of oesophageal Doppler monitoring.

Oesophageal Doppler monitoring is a minimally invasive method of determining cardiovascular status and response to fluid loading. It has been shown to be safe, to provide reliable and reproducible results, and to have comparable accuracy to the thermodilution method of measuring cardiovascular function[22,23]. In the present study no complications were observed relating to oesophageal Doppler probe insertion or perioperative monitoring. Doppler monitoring allowed protocol-driven fluid optimization based on continuous assessment of cardiovascular variables without subjecting patients to the hazards of pulmonary artery catheterization.

Sinclair *et al.*[16] studied the use of oesophageal Doppler optimization in 40 patients having orthopaedic surgery and found significant reductions in time to fitness for discharge and hospital stay[16]. A further study of patients undergoing hip surgery demonstrated a decrease in time to fitness for surgical discharge with no significant differences in hospital stay or overall morbidity[17]. In both of these studies, group sizes were small and, although the anaesthetists were blinded to Doppler readings, they were informed of fluid administration. Conway *et al.*[24] studied Doppler optimization in 57 patients undergoing bowel resection. Although differences in final CO and critical care admission were found, there was no significant difference in hospital stay, perhaps a reflection of the small sample size. The present results in patients undergoing colorectal resection represent a well powered study of a relatively homogeneous patient group. The use of a medically qualified researcher, independent of both anaesthetic and clinical teams, allowed blinding to a greater extent than in previous studies.

The primary outcome measure of the trial was length of postoperative hospital stay. Patients in the intervention group were fit for surgical discharge 3 days earlier than control patients, in keeping with the findings of other studies that used Doppler monitoring to optimize fluid administration[16–19]. Time to actual discharge was also reduced. Positive secondary outcomes were earlier return of oral intake, reduced unplanned critical care admission, reduced incidence of major or intermediate complications, increased CO parameters and dampened inflammatory cytokine release, a previously unreported finding.

No differences were found in the overall volume of fluid administered between the two groups. Even so, the intervention group had higher FTc, SV, CO and CI at the end of the procedure; 46 per cent of the boluses, accounting for more than 50 per cent of additional protocol volume given in the intervention group, were administered within the first quarter of the operating time. It may perhaps be the timing of these fluid boluses, early in the perioperative period, rather than the overall fluid volume that allowed a sustained increase in cardiovascular parameters. Brandstrup *et al.*[12] reported an improved outcome with a restricted perioperative fluid regimen. The overall volumes of fluid administered in both arms of the present trial were comparable with those received in the fluid-restricted arm of the Brandstrup study, suggesting that, although fluid restriction may improve outcome, other factors such as the timing of fluid intervention may also play an important role.

One of the initial responses to a reduction in circulating volume is redirection of blood away from the splanchnic bed in favour of more vital organs. Pulse rate and blood pressure may remain within acceptable limits during this redistribution, and so hypovolaemia leading to splanchnic hypoperfusion may go uncorrected. Indeed, it has been shown that splanchnic hypoperfusion is an early consequence of hypovolaemia and inadequate CO, and is demonstrable before systemic blood pressure falls[25]. In the present study, although MAP and pulse rate remained similar throughout surgery in both groups, after a period of concordance at the start of operation SV, FTc, CO and CI all increased in the intervention group compared with values in the control group. Thus, blood pressure monitoring alone may not be sufficient to assess circulatory status accurately.

The splanchnic vasculature plays an essential role in circulatory regulation, but the gut mucosa itself is particularly susceptible to hypoxia. Gut mucosal hypoperfusion may lead to bacterial translocation, endotoxaemia and activation of inflammatory cascades, all of which may contribute to the systemic inflammatory response after surgery[26]. In this study, a reduction in peak systemic inflammatory cytokine (IL-6) levels was found in the intervention group, suggesting the Doppler intervention may have reduced the systemic inflammatory response to surgical trauma. Early achievement and maintenance of a higher CI in the intervention group may have preserved splanchnic perfusion and thereby reduced gut-related inflammatory responses. Mythen and Webb[18] studied fluid optimization and gastric pH during coronary artery bypass surgery, and found that perioperative plasma volume expansion guided by oesophageal Doppler monitoring preserved gut mucosal perfusion. Perioperative vasoconstrictors may affect splanchnic blood flow and oxygen supply/uptake ratios[27,28]. In the present study a greater number of patients in the control group received perioperative vasopressors; this may have further altered splanchnic haemodynamics attributing to the increase in inflammatory response.

The reduced increase in IL-6 levels in the intervention group suggests that maintenance of a stable CO in the perioperative period reduces the resultant systemic inflammatory response to surgical trauma. Similarity in plasma dilution factors between the groups confirms that differences observed in systemic cytokine levels cannot be due simply to variations in plasma volume. The increase in IL-6 concentration in response to injury is proportional to the severity of trauma[29,30]. Studies comparing IL-6 levels in mesenteric or portal blood and the systemic circulation suggest that the IL-6 release seen after surgery may originate from the gut[31,32]. Early achievement and maintenance of a normovolaemic state may reduce splanchnic hypoperfusion, reduce inflammatory mediator release and have beneficial effects on patient outcome.

It is apparent that, although excess fluid administration may lead to complications, the inadequate treatment of occult hypovolaemia is also a factor in postoperative morbidity. Oesophageal Doppler monitoring is a minimally invasive method of determining haemodynamic status in the perioperative period, allowing protocol-led fluid management. The regimen used in this study resulted in beneficial effects on postoperative recovery and morbidity, with a reduction in the systemic inflammatory cytokine response to surgery and an overall reduction in hospital stay.

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## References

1 Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth* 1997; **78**: 606–617.
2 Cohn LH, Powell MR, Seidlitz L, Hamilton WK, Wylie EJ. Fluid requirements and shifts after reconstruction of the aorta. *Am J Surg* 1970; **120**: 182–186.
3 Lang K, Boldt J, Suttner S, Haish G. Colloids *versus* crystalloids and tissue oxygen tension in patients undergoing major abdominal surgery. *Anesth Analg* 2001; **93**: 405–409.
4 Shires T, Williams J, Brown F. Acute changes in extracellular fluids associated with major surgical procedures. *Ann Surg* 1961; **154**: 803–810.
5 Shoemaker WC, Appel P, Bland R. Use of physiologic monitoring to predict outcome and assist in clinical decisions in critically ill post-operative patients. *Am J Surg* 1983; **146**: 43–50.
6 Stone MD, Wilson RJT, Cross J, Williams BT. Effect of adding dopexamine to intraoperative volume expansion in patients undergoing major elective abdominal surgery. *Br J Anaesth* 2003; **91**: 619–624.
7 Wilson J, Woods I, Fawcett J, Whall R, Dibb W, Morris C *et al*. Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery. *BMJ* 1999; **318**: 1099–1103.
8 Moore FD. *Metabolic Care of the Surgical Patient*. WB Saunders: Philadelphia, 1959.
9 Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SA. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet* 2002; **359**: 1812–1818.
10 Lowell JA, Schifferdecker C, Driscoll DF, Benotti PN, Bistrian BR. Postoperative fluid overload: not a benign problem. *Crit Care Med* 1990; **18**: 728–733.
11 Holte K, Sharrock NE, Kehlet H. Pathophysiology and clinical implications of perioperative fluid excess. *Br J Anaesth* 2002; **89**: 622–632.

12 Brandstrup B, Tonnesen H, Beier-Holgersen R, Hjortso E, Ording H, Lindorff-Larsen K *et al*. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens. A randomized assessor-blinded multicenter trial. *Ann Surg* 2003; **238**: 641–648.
13 Joshi GP. Intraoperative fluid restriction improves outcome after major elective gastrointestinal surgery. *Anesth Analg* 2005; **101**: 601–605.
14 Slinger P. Perioperative fluid management for thoracic surgery: the puzzle of postpneumonectomy pulmonary edema. *J Cardiothorac Vasc Anesth* 1995; **9**: 442–451.
15 Sanders G, Mercer SJ, Saeb-Parsey K, Akhavani MA, Hosie KB, Lambert AW. Randomized clinical trial of intravenous fluid replacement during bowel preparation for surgery. *Br J Surg* 2002; **88**: 1363–1365.
16 Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. *BMJ* 1997; **315**: 909–912.
17 Venn R, Steele A, Richardson P, Poloniecki J, Grounds M, Newman P. Randomised controlled trial to investigate influence of the fluid challenge on duration of hospital stay and perioperative morbidity in patients with hip fractures. *Br J Anaesth* 2002; **88**: 65–71.
18 Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. *Arch Surg* 1995; **130**: 423–429.
19 Gan TJ, Soppitt A, Maroof M, El-Moalem H, Robertson KM, Moretti E *et al*. Goal-directed intraoperative fluid administration reduces length of stay after major surgery. *Anesthesiology* 2002; **97**: 820–826.
20 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205–213.
21 Flordal A. The plasma dilution factor: predicting how concentrations in plasma and serum are affected by blood volume variations and blood loss. *J Lab Clin Med* 1995; **126**: 353–357.
22 DiCorte CJ, Latham P, Greilich PE, Cooley MV, Grayburn PA, Jessen ME. Esophageal Doppler monitor determinations of cardiac output and preload during cardiac operations. *Ann Thorac Surg* 2000; **69**: 1782–1786.
23 Shaw A, Weavind L, Parmley L. Comparison of thermodilution, esophageal Doppler and transoesophageal echocardiography data in the hemodynamic assessment of critically ill cancer patients. *Crit Care Med* 2000; **28**(Suppl): 159; M65.
24 Conway DH, Mayall R, Abdul-Latif MS, Gilligan S, Tackaberry C. Randomised controlled trial investigating the influence of intravenous fluid titration using oesophageal Doppler monitoring during bowel surgery. *Anaesthesia* 2002; **57**: 845–849.
25 Singer M. Haemodynamic management: are we doing it right? *International Proceedings Journal* 1994; **1**: 1–3.
26 Jakob SM, Takala J. Splanchnic hemodynamics in critical illness. *Curr Opin Crit Care* 2000; **6**: 123–129.
27 Priebe HJ, Noldge GFE, Armbruster K, Geiger K. Differential effects of dobutamine, dopamine, and noradrenaline on splanchnic haemodynamics and oxygenation in the pig. *Acta Anaesthesiol Scand* 1995; **39**: 1088–1096.
28 De Backer D, Vincent JL. Pharmacological modulation of splanchnic blood flow. *Curr Opin Crit Care* 1998; **4**: 104–110.
29 Biffl WL, Moore EE, Moore FA, Peterson VM. Interleukin-6 in the injured patient: marker of injury or mediator of inflammation? *Ann Surg* 1996; **224**: 647–664.
30 Cruickshank A, Fraser WD, Burns HJ, Van Damme J, Shenkin A. Response of serum interleukin-6 in patients undergoing elective surgery of varying severity. *Clin Sci* 1990; **79**: 161–165.
31 Wortel CH, van-Deventer SJ, Aarden LA, Lygidakis NJ, Buller HR, Hoek FJ *et al*. Interleukin-6 mediates host defense responses induced by abdominal surgery. *Surgery* 1993; **114**: 564–570.
32 Baigrie RJ, Lamont PM, Whiting S, Morris PJ. Portal endotoxin and cytokine responses during abdominal aortic surgery. *Am J Surg* 1993; **166**: 248–251.