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Original article

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Doppler-guided goal-directed fluid therapy does not affect intestinal cell damage but increases global gastrointestinal perfusion in colorectal surgery: a randomized controlled trial

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Abstract

Aim Individualized, goal-directed fluid therapy (GDFT), based on Doppler measurements of stroke volume, has been proposed as a treatment strategy in terms of reducing complications, mortality and length of hospital stay in major bowel surgery. We studied the effect of Doppler-guided GDFT on intestinal damage as compared with standard postoperative fluid replacement.

Method Patients undergoing elective colorectal resection for malignancy were randomized either to standard intra- and postoperative fluid therapy or to standard fluid therapy with additional Doppler-guided GDFT. The primary outcome was intestinal epithelial cell damage measured by plasma levels of intestinal fatty acid-binding protein (I-FABP). Global gastrointestinal perfusion was measured by gastric tonometry, expressed as regional (gastric) minus arterial CO_2-gap ($P_{r\text{-}a}CO_2$-gap).

Results I-FABP levels were not significantly different between the intervention group and the control group (respectively, 440.8 (251.6) pg/ml and 522.4 (759.9) pg/ml, $P = 0.67$). Mean areas under the curve (AUCs) of intra-operative $P_{r\text{-}a}CO_2$-gaps were significantly lower in the intervention group than in the control group ($P = 0.01$), indicating better global gastrointestinal perfusion in the intervention group. Moreover, the mean intra-operative $P_{r\text{-}a}CO_2$-gap peak in the intervention group was 0.5 (1.0) kPa, which was significantly lower than the mean peak in the control group, of 1.4 (1.4) kPa ($P = 0.03$).

Conclusion Doppler-guided GDFT during and in the first hours after elective colorectal surgery for malignancy increases global gastrointestinal perfusion, as measured by $P_{r\text{-}a}CO_2$-gap.

Keywords Fluid therapy, colorectal surgery, intestinal fatty acid-binding protein, perfusion

What does this paper add to this literature?
Doppler-guided goal-directed fluid therapy (GDFT) in colorectal surgery is a matter of debate. Intestinal cell damage and intestinal perfusion have never been investigated in this context. We showed no differences in intestinal cell damage, although we observed increased global gastrointestinal perfusion. This sheds new light on GDFT in clinical practice.

Introduction

Management of perioperative fluid in colorectal surgery is subject to some controversy. Although restrictive fluid regimens seem superior to liberal fluid treatment [1], euvolaemia has yet to be defined, particularly in relation to the ideal circulating volume in any given patient. Individualized, goal-directed fluid therapy (GDFT) might be one method to achieve euvolaemia. GDFT has been proposed as a treatment strategy in terms of reducing complications, mortality and length of hospital stay following major bowel surgery [1–6]. Studies indicate that GDFT is associated with shortened length of hospital stay of 2–3 days compared with controls, a

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(http://clinicaltrials.gov/ct2/show/NCT01175317)

reduction of major complications requiring intensive care admission and a lower incidence of gastrointestinal complications [3,4]. Typically, goal-directed fluid protocols are designed to optimize stroke volumes intraoperatively, guided by oesophageal Doppler monitoring and titration of colloid fluid boluses [7,8].

The effect of GDFT on gastrointestinal perfusion and subsequently on intestinal damage and wound healing is unknown. Furthermore, the effect of GDFT in the early postoperative period has not been investigated to date. It is suggested that Doppler-guided fluid optimization increases bowel perfusion [9], while liberal and restrictive treatment strategies may induce hypoperfusion by local oedema and hypovolemia, respectively [10]. Fluid management in the first hours following surgery may be as important as intra-operative fluid management in improving tissue perfusion and oxygenation [11]. In this period, hypovolemia may critically compromise perfusion [12]. In major bowel surgery, this may lead to the development of gut-associated complications (i.e. anastomotic leakage, intra-abdominal abscess and sepsis). GDFT may therefore also be related to a decreased risk of gut-associated complications. Although early studies on GDFT showed promising results, two recent randomized controlled trials could not prove a reduction in postoperative complications in general when GDFT was compared with restrictive fluid management [13,14].

The aim of the current study was to investigate, as a clinical proof of concept, whether oesophageal Doppler-guided GDFT, with the aim of optimizing circulating volume, reduces intestinal damage and improves gastrointestinal perfusion during colorectal surgery and during the first hours after colorectal surgery, compared with standard fluid therapy. It was hypothesized that GDFT decreased intestinal injury and improved gastrointestinal perfusion.

Method

Patients

Fifty-eight patients undergoing colorectal resection for malignancy were enrolled in this single-centre, parallel randomized clinical trial (ClinicalTrials.gov identification number: NCT01175317) between July 2010 and August 2013. Inclusion criteria were: elective colorectal cancer surgery with primary anastomosis; and a minimum age of 18 years. Written informed consent was obtained from all enrolled patients. Exclusion criteria were: nonmalignant causes of intestinal damage (e.g. inflammatory bowel diseases); use of steroids; history of oesophageal varices and other oesophageal disease; and aortic valve disease. History of oesophageal varices is a contraindication for the use of oesophageal Doppler monitoring, and aortic valve disease results in unreliable Doppler measurements. Before randomization, patients were stratified according to the type of surgery (i.e. laparoscopy or open surgery). For allocation of the participants, two computer-generated lists (for laparoscopy and open surgery, respectively) of random numbers were used following a simple randomization to one of two treatment groups. An investigator who did not take part in patient enrolment or data acquisition was in charge of these lists. The investigator responsible for patient enrolment, Doppler measurements and the fluid-optimization protocol, telephoned the investigator in charge of the lists after obtaining informed consent. The only other person aware of each patient's allocation was the anaesthetist responsible for the perioperative fluid management. The study was approved by the Medical Ethical Committee of Maastricht University Medical Centre (number 09-2-089) and was conducted according to the revised version of the Declaration of Helsinki (October 2008, Seoul). The study methods were not changed after trial registration.

Anaesthetic procedure

Anaesthesia was induced using propofol, sufentanil and rocuronium and was maintained using sevoflurane. In the majority of patients, an epidural catheter was inserted for additional analgesia with bupivacaine, which applied for both open and laparoscopic procedures. The epidural catheter was placed at Th8–10, tested with 3–5 ml of 0.25% bupivacaine with adrenaline, and continuous infusion of bupivacaine 0.25% was given for sufficient block. After induction of anaesthesia, a medically qualified investigator (KR) inserted an oesophageal Doppler probe (CardioQ; Deltex Medical, Chichester, UK) transnasally. In both the intervention and control groups, oesophageal Doppler measurements were performed every 15 min during surgery. The anaesthesiologist was blinded for Doppler measurements at all times; however, when additional fluid boluses based on Doppler readings were administered, the anaesthesiologist was informed. Therefore, the anaesthesiologist was not blinded to group allocation. The optimal Doppler signal was obtained according to the manufacturers' instructions, and stroke volume index (SVI; stroke volume normalized for body surface area) measurements were averaged over five beats. All patients received a radial artery line. Prophylactic antibiotics (metronidazole and cefazoline) were given to all patients.

Fluid treatment and study intervention

All patients were allowed to drink clear fluids until 2 h before surgery. Immediately after induction of anaesthesia,

SVI measurements were performed in all patients. In all patients, the volume of blood lost was replaced with an identical volume of Voluven (Fresenius Kabi, Utrecht, the Netherlands) was used to replace blood loss volume in a 1:1 ratio. Voluven and Ringer lactate were infused to maintain the mean arterial pressure (MAP) above 65 mmHg. Packed red blood cells (1U = 500 ml) were given to keep haemoglobin levels above 80–90 g/l, depending on patient age and the presence of cardiac disease. If the blood loss was large, plasma and thrombocytes were added. Ephedrine or phenylephrine was given if hypotension persisted despite fluid infusion. If inotropic support was needed over a longer time period, noradrenaline was given as a continuous infusion.

In the intervention group, standard fluid therapy was as described above. Furthermore, a fluid-optimization protocol (adapted from Wakeling and colleagues) was applied by the investigator (KR), without taking central venous pressure into account [4]. Immediately after induction of surgery, a 250-ml bolus of colloid fluid (Voluven) was administered. If the increase in SVI was 10% or more, patients were considered hypovolemic and a further 250-ml bolus of colloid fluid was given. This procedure was repeated until the increase in SV was <10%. The maximal SV was maintained during surgery and corrected if necessary with 250-ml boluses of Voluven. In the case of hypotension despite Doppler-guided volume therapy, vasoactive drugs were given as described above.

Postoperatively, patients in both control and intervention groups were admitted to a standard post-anaesthetic care unit for at least 6 h. The Doppler probe remained *in situ* for a maximum of 6 h or until the patient experienced significant discomfort. In all patients, basic postoperative fluid management consisted of administration of Ringer's solution at a rate of 2–4 ml/kg/h. Furthermore, intravascular volume was assessed every hour by the passive leg raising (PLR) test, which was performed with a standardized angle of 135° between the trunk and lower limbs, as described by Monnet *et al.* [15]. The optimal Doppler signal was obtained and SVI measurements were averaged over 5 beats. The same procedure was repeated after the PLR test. Doppler recordings were taken when the SVI reached its highest value (which was approximately 30 s after PLR). The maximum effect of PLR on SVI was seen within 1 min in all patients. In the control group, PLR was performed to record possible fluid deficits for study purposes, but no additional fluid interventions were carried out. In the intervention group, if the increase in SV during PLR was 10% or more, patients were considered hypovolemic and a 250-ml bolus of Voluven was given. In the control group, fluid boluses were administered based on standard haemodynamic and clinical parameters, such as heart rate and arterial blood pressure. At this stage, Doppler readings were also kept hidden from caregivers.

After discharge to a specialized colorectal surgery ward (at 6 h or more postoperatively), patients were treated according to a multimodal fast-track programme with early start of feeding and mobilization. Fluid therapy was equal in both groups: as soon as swallowing was considered safe, intake of fluids and nutrition was started, and a minimum fluid intake of 2 l per day was aimed for. If this could not be achieved by oral intake, supplementation with intravenous (i.v.) fluid was given. Pain management was achieved by patient-controlled analgesia via the epidural catheter or intravenously, for a maximum of 3 days postoperatively, and additional paracetamol or morphine was given if needed.

Haemodynamic parameters

The following haemodynamic parameters were monitored at 15-min intervals during surgery and hourly during the first 6 h after surgery: heart rate; SVI (Doppler); MAP (arterial line); and urinary output. Blood-soaked gauzes were weighed as they were passed off the surgical field, and the blood content of the suction system was measured to assess total blood loss at the end of surgery.

Blood sampling and processing

Arterial blood samples were obtained from the radial artery line at the following predefined time points: baseline; every 30 min during surgery; and every hour until 6 h postoperatively. Venous blood samples were taken daily until 3 days after surgery. Blood samples were collected in pre-chilled EDTA-containing vacuum tubes (BD vacutainer; Becton Dickinson Diagnostics, Aalst, Belgium) and immediately centrifuged at 4°C (2000 *g*, 15 min). Plasma samples were stored at −80°C until used in batch analysis.

Measurement of intestinal damage

The levels of intestinal fatty acid-binding protein (I-FABP) in plasma were determined using an in-house ELISA that selectively detects human I-FABP (lower detection limit: 25 pg/ml). I-FABP is a well-known plasma marker of enterocyte damage [16], and I-FABP levels correlate with gut hypoperfusion during hypotension in nonabdominal surgery [17].

Gastric tonometry

Gastric tonometry can be used to detect gastrointestinal hypoperfusion [18]. A gastric tonometry catheter (14F;

Medi-Line, Angleur, Belgium) was introduced transnasally for measurement of intramucosal carbon dioxide pressure (P_rCO_2, expressed in kPa) throughout the surgical procedure and during the 6 h following surgery, using the gas-automated capnograph (Tonocap TC-200; Datex-Ohmeda, Helsinki, Finland). Gastric tonometry measurements [P_rCO_2, and mucosal-arterial pCO_2 gap ($P_{r\text{-}a}CO_2$-gap)] were carried out at 15-min intervals during surgery and hourly during the first 6 h after surgery. The first measurement during surgery was performed 15 min after the start of surgery, because of the time taken to calibrate the device.

Statistical analysis

Statistical analysis was performed using PRISM 5.0 for Windows (GraphPad Software, Inc., San Diego, California, USA) and SPSS 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Normality was tested using the Kolmogorov–Smirnov test. The primary outcome was intestinal epithelial damage, which was measured by plasma I-FABP levels at 1 h postoperatively. Secondary outcomes were $P_{r\text{-}a}CO_2$-gap and the haemodynamic parameters MAP, SVI and urinary production. For all repeated measures, areas under the curve (AUC) were calculated for each patient separately, and missing data were handled using multiple imputations in SPSS. Average AUCs of the outcomes were compared using the Student's *t*-test. Except for length of hospital stay (median and range), all continuous variables are presented as mean and standard deviation (SD). Dichotomous variables were compared using the χ^2 test.

Sample size was calculated as follows. In a previous study, patients undergoing major nonabdominal surgery had mean ± SD I-FABP levels of 443 ± 309 pg/ml at the end of surgery [17]. In the current study, a reduction to 200 ± 150 pg/ml by haemodynamic optimization was estimated *a priori*, necessitating a sample size of 27 per group, with $\alpha = 0.05$ and $1\text{-}\beta = 0.95$. As a 5% dropout rate was expected because of inability to achieve adequate Doppler measurements, the sample size required was estimated at 29 for each group.

Results

Patients

Fifty-eight patients were randomized, 27 of whom were allocated to the intervention group (Fig. 1). The study protocol was completed in all patients and none was excluded from analysis. Baseline characteristics are summarized in Table 1. No differences were observed between intervention and control groups. Stratification for open and laparoscopic surgery was verified, and other operative characteristics are outlined in Table 2. Operative time was longer in the intervention group. A larger volume of colloid fluid was given in the intervention group (Table 3), while the total volume of fluids administered did not differ markedly between the groups. The mean length of time that the Doppler probe was tolerated postoperatively was 4 h.

Intestinal damage

Mean I-FABP levels 1 h after surgery were 488.6 ± 599.2 pg/ml in the total cohort. No significant differences of mean I-FABP levels between the intervention and control groups were observed at this time-point (respectively, 440.8 ± 251.6 pg/ml and 522.4 ± 759.9 pg/ml, $P = 0.67$) or at another time-point (Fig. 2). In addition, the levels of I-FABP did not increase during surgery in either group, indicating the absence of significant intestinal damage. The levels of I-FABP showed a significant decrease in both groups from the start of surgery to the first day postoperatively (respectively, from 600.5 ± 826.0 pg/ml to 384.2 ± 550.3 pg/ml, mean of all patients, $P = 0.03$). The mean AUC of the I-FABP concentration was not significantly different between the groups.

Haemodynamic changes

A significant increase in SVI from baseline to the start of surgery was accomplished by administration of colloid in the group receiving haemodynamic optimization (46.5 ± 12.0 ml/m² to 59.8 ± 15.7 ml/m², $P < 0.0001$, Fig. 3a). Of 27 patients in the intervention group, 24 (89%) needed fluid to establish a maximal SVI. A significant increase of SVI from baseline to the start of surgery was not observed in the control group. Furthermore, the mean AUC value of SVI during surgery was higher in the intervention group (12 631 ± 2568 ml/m² × min) compared with the control group (11 122 ± 2014 ml/m² × min, $P = 0.02$). The mean AUC values of postoperative SVI were not significantly different between groups (Fig. 3b).

There were no significant differences in MAP (Fig. 4) and urinary output (Fig. 5) between intervention and control groups.

Gastric tonometry

Intra-operative arterial CO_2 pressures were not markedly different between the intervention group (5.0 ± 0.4 kPa) and the control group (4.9 ± 0.3 kPa). Mean AUC of the $P_{r\text{-}a}CO_2$-gap during surgery was significantly lower in the intervention group (4.8 ± 98.9 kPa × min) than in

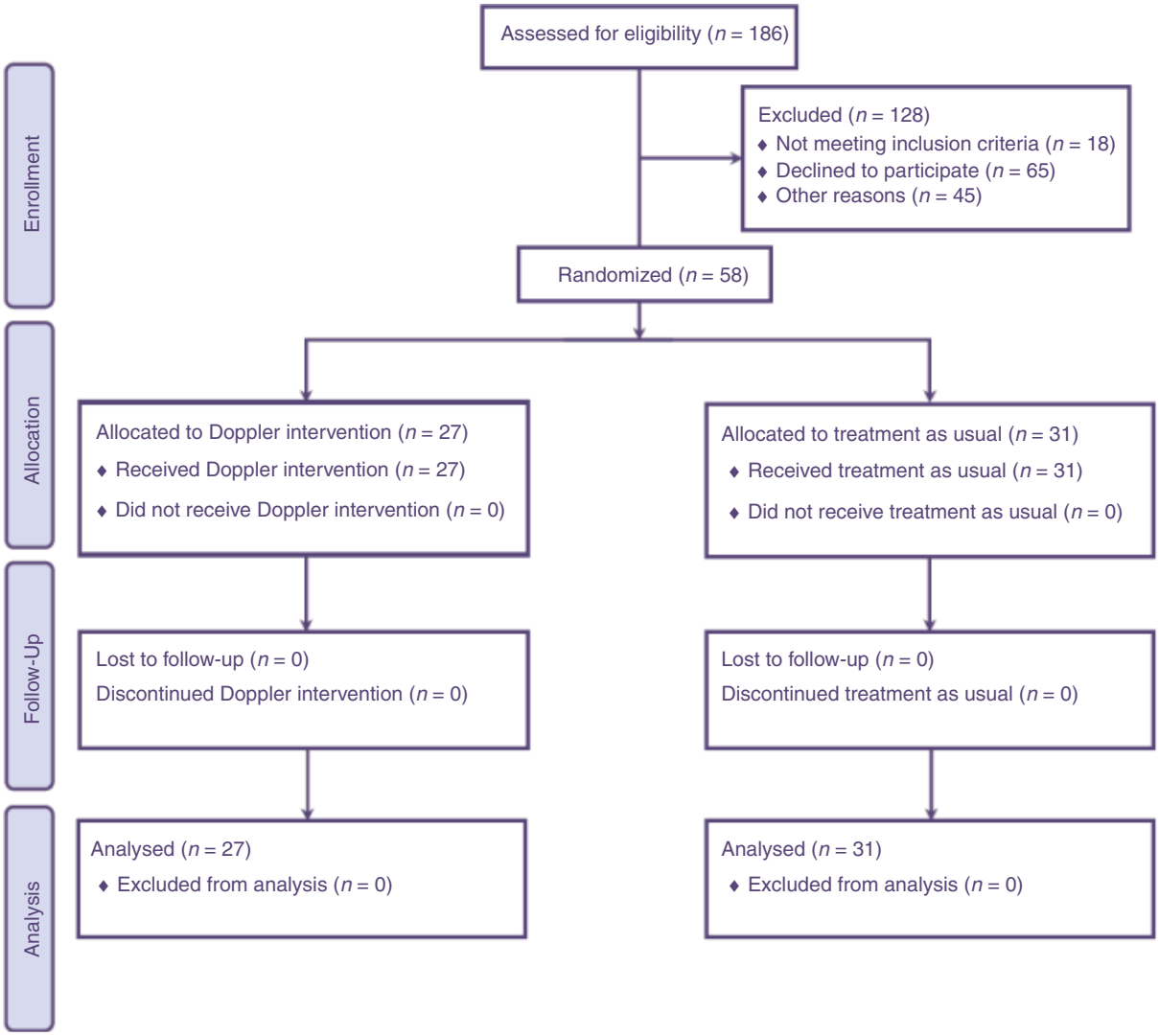

Figure 1 CONSORT diagram of the study.

the control group (91.7 ± 92.0 kPa × min, $P = 0.01$), indicating better global gastrointestinal perfusion in the intervention group (Fig. 6a). The mean intra-operative $P_{r\text{-}a}CO_2$-gap peak in the intervention group was 0.5 ± 1.0 kPa, which was significantly lower than the peak in the control group, of 1.4 ± 1.4 kPa ($P = 0.03$). However, no effect of SVI optimization on gastrointestinal perfusion was observed in the first 6 h after surgery in terms of $P_{r\text{-}a}CO_2$-gap AUC values or peak (Fig. 6b).

Postoperative arterial CO_2 pressures were not markedly different between the intervention group (5.6 ± 0.9 kPa) and the control group (5.4 ± 0.6 kPa). Mean AUC of the postoperative $P_{r\text{-}a}CO_2$-gap was elevated in patients with major blood loss during surgery (> 750 ml, $n = 10$); 6.7 ± 8.3 kPa × h compared with 0.6 ± 3.3 kPa × h in patients without major blood loss ($P = 0.005$, data not shown). In linear regression analysis, major blood loss was a significant independent predictor for increasing the $P_{r\text{-}a}CO_2$-gap postoperatively ($\beta = 0.55$, $P = 0.001$), and group (intervention) showed a trend towards significance ($\beta = -0.27$, $P = 0.07$).

When only patients without major blood loss were analysed, the mean postoperative AUC of the $P_{r\text{-}a}CO_2$-gap was lower in the intervention group (−0.7 ± 3.9 kPa × h) than in the control group (2.0 ± 2.3 kPa × h) ($P = 0.04$). Furthermore, the mean postoperative $P_{r\text{-}a}CO_2$-gap peak in the intervention group was 0.6 ± 0.7 kPa in this subgroup, which was significantly lower than the peak in the control group (1.4 ± 1.2 kPa) ($P = 0.04$).

Clinical outcome

Postoperative mortality, complications and length of hospital stay are summarized in Table 4. No statistical

Table 1 Patient characteristics.

Characteristic	Intervention group		Control group	
	n (%)	Mean ± SD	*n* (%)	Mean ± SD
Sex				
Male	21 (77.8)		20 (64.5)	
Female	6 (22.2)		11 (35.5)	
Age (years)				
> 70	10 (37.0)	68.6 ± 10.8	12 (38.7)	67.6 ± 100
BMI (kg/m²)				
> 25	12 (44.4)	25.9 ± 3.1	17 (54.8)	25.3 ± 3.0
ASA				
I	8 (29.6)		4 (12.9)	
II	14 (51.9)		24 (77.4)	
III	5 (18.5)		3 (9.7)	
Tumour location				
Colon	16 (59.3)		18 (58.1)	
Rectum	11 (40.7)		13 (41.9)	
Smokers	6 (22.2)		5 (16.1)	
Medical history				
Myocardial ischemia	1 (3.7)		1 (3.2)	
Stroke	4 (14.8)		3 (9.7)	
NIDDM	3 (11.1)		2 (6.5)	
COPD	1 (3.7)		2 (6.5)	

ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; NIDDM, non-insulin-dependent diabetes mellitus.

Table 2 Surgery characteristics.

Characteristic	Intervention group		Control group	
	n (%)	Mean ± SD	*n* (%)	Mean ± SD
Surgical approach				
Open	20 (74.1)		21 (67.7)	
Laparoscopy	7 (25.9)		10 (32.3)	
Conversion	0 (0)		4 (40)	
Type of surgery				
Right colectomy	10 (37.0)		12 (38.7)	
Left colectomy	1 (3.7)		0 (0)	
Sigmoid resection	5 (18.5)		5 (16.1)	
Rectal resection	11 (40.7)		13 (41.9)	
Subtotal colectomy	0 (0)		1 (3.2)	
Epidural	21 (77.8)		22 (71.0)	
Ostomy	12 (44.4)		14 (45.2)	
Operative time (minutes)		256 ± 101		205 ± 77

analyses were performed on clinical outcome as the study was not powered for this purpose.

Discussion

This randomized controlled trial showed that Doppler-guided GDFT, during and after elective colorectal surgery for malignancy, increases global gastrointestinal perfusion. However, no significant differences in the levels of I-FABP in plasma were observed between the intervention group and the control group, which was the primary outcome of the study. In addition, neither group showed significant intestinal damage. A strong positive effect of Doppler-guided GDFT on

Table 3 Fluids during surgery.

	Intervention group		Control group	
Fluid	*n* (%)	Mean ± SD	*n* (%)	Mean ± SD
Total amount (ml)				
Crystalloids		3000 ± 1093		3026 ± 1307
Colloids		1526 ± 823		952 ± 687
Total fluid (ml/kg/h)		14.6 ± 4.7		16.2 ± 5.9
Blood loss (ml)		957 ± 1880		461 ± 1026
> 750 ml	6 (22.2)		4 (12.9)	
Blood transfusion	7 (25.9)		4 (12.9)	
Total fluid (ml/kg/h)*		15.8 ± 6.4		16.7 ± 6.5
Vasopressor use	12 (44.4)		15 (48.4)	

*Including blood transfusions.

gastrointestinal perfusion was seen during surgery. GDFT showed a marginally significant effect on postoperative gastrointestinal perfusion, and only when corrected for major intra-operative blood loss (> 750 ml). It was hypothesized that plasma I-FABP levels would peak, relative to baseline levels, at about 1 h after the end of surgery, as observed previously in nonabdominal surgery, with [19,20] and without [17] aortic cross-clamping. The latter study, investigating scoliosis repair in children, showed that low MAP values are associated with increased levels of I-FABP. In this previous study, average MAP values during surgery were 64 mmHg compared with 75 mmHg in the current study. It may therefore be speculated that patients undergoing elective colorectal surgery do not exhibit severe enough hypotension to develop intestinal damage. Nonetheless, increased gastrointestinal perfusion as a result of GDFT might indicate a euvolemic status in these patients because the gut is one of the organs that are primarily affected by the redistribution of blood to the vital organs in early hypovolemia [21].

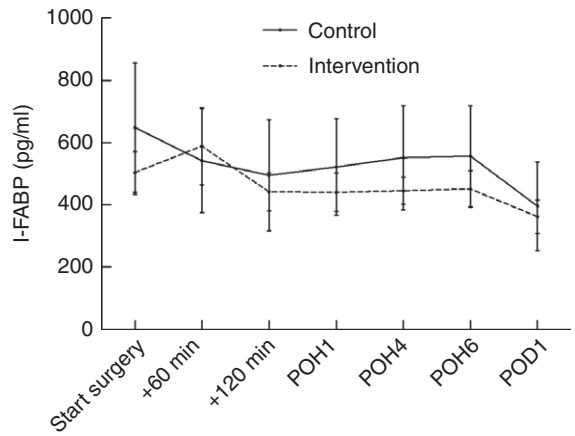

Figure 2 Intestinal fatty acid-binding protein (I-FABP) levels, during and after surgery. +60 min, 1 h after the start of surgery; +120 min, 2 h after the start of surgery; POHx, × hour (s) postoperatively.

The discrepancy between the effect of GDFT on intra-operative perfusion and postoperative perfusion may be explained by the methodological differences of fluid optimization during and after surgery. This was underlined by the higher mean SVI observed in the intervention group compared with the control group intra-operatively but not postoperatively. Just before and during surgery, the SVI was optimized by fluid challenges, while, after surgery, fluid responsiveness was assessed by PLR, and fluid challenges were only given when the PLR was positive. Although PLR represents good sensitivity (77%) for detecting fluid responsiveness, some patients (23%) who should receive a fluid bolus are inevitably missed [22]. In addition, recent evidence shows that response to PLR shows wide variation in normovolemic patients, indicating that PLR accuracy may be poor [23]. Moreover, other factors may be more important predictors of postoperative gastrointestinal perfusion, as indicated by the strong association between major intra-operative blood loss and decreased postoperative gastrointestinal perfusion.

Interestingly, the volume of fluid given did not differ between the intervention group and the control group, indicating that timing of fluid administration was the determinant of improving global and regional haemodynamics, thereby shedding new light on the concept of euvolemia. This observation is in line with previous work describing more stable haemodynamic parameters when SV-based optimization was applied, even though the total amount of fluid given in the intervention group was comparable with that given in the control group [24]. Another interesting finding was the need for fluid expansion in 89% of patients to establish maximal SVI, which is in line with a previous study showing

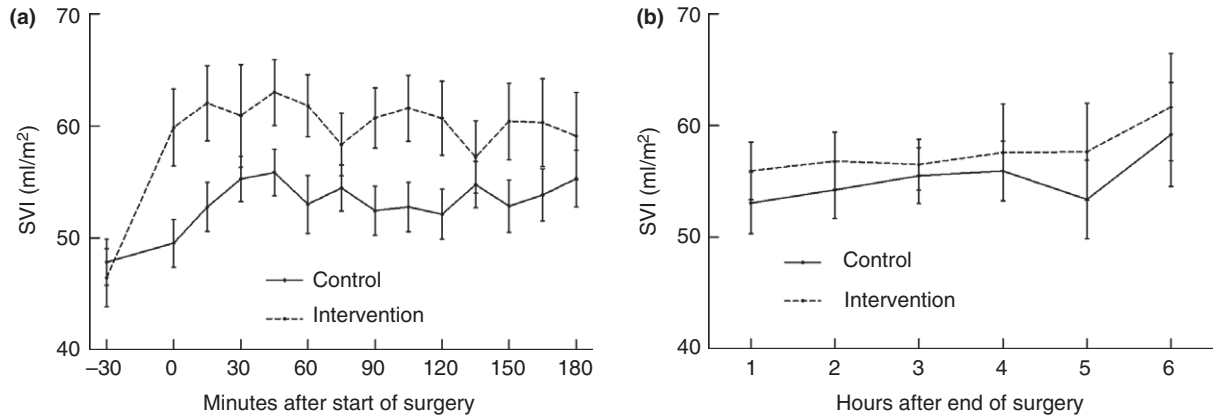

Figure 3 Mean indexed stroke volumes (SVI; corrected for body surface area) during surgery (a) and in the first 6 h after surgery (b). Error bars are standard error of the mean.

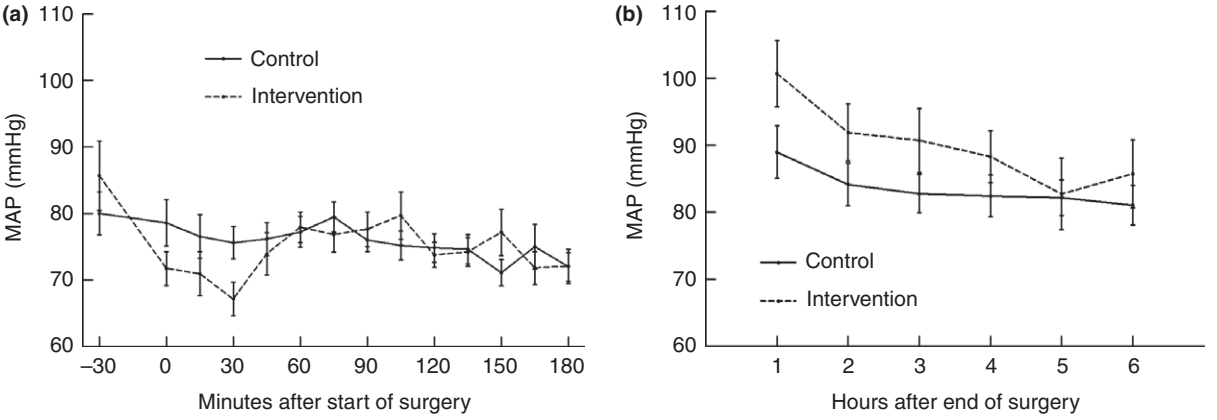

Figure 4 Mean arterial pressures (MAP) during surgery (a) and in the first 6 h after surgery (b). Error bars are standard error of the mean.

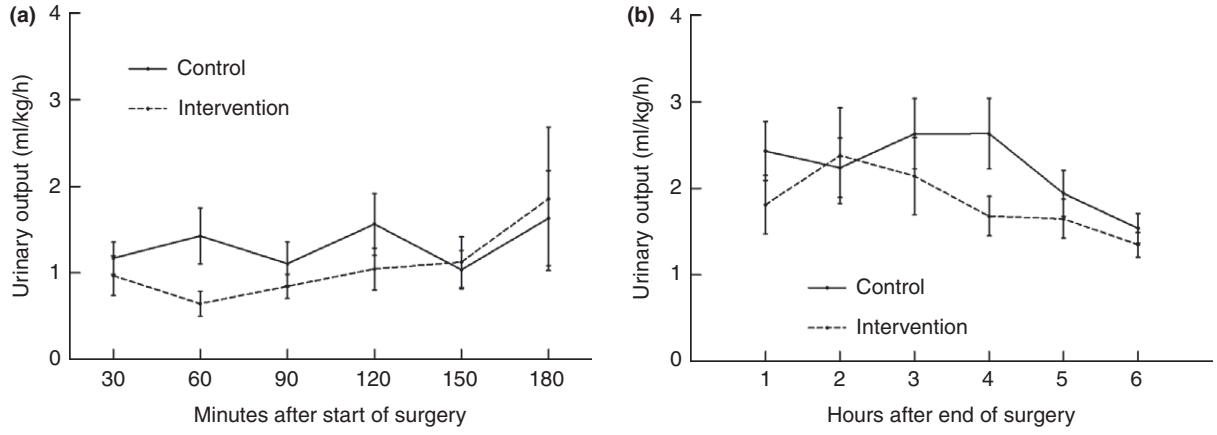

Figure 5 Mean urinary output per hour corrected for body weight during surgery (a) and in the first 6 h after surgery (b). Errors bars are standard error of the mean.

a functional volume deficit in 70% of patients undergoing different types of surgery [25]. This underlines the possible benefits of patient-tailored GDFT. However, it remains unclear whether such deficits represent actual susceptibility to complications or rather increased physiological reserves.

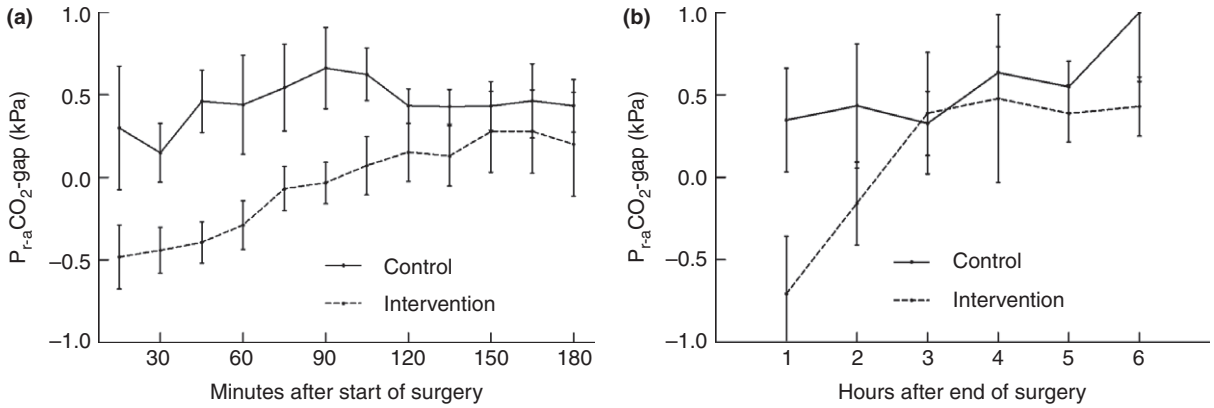

Figure 6 Regional (gastric) minus arterial CO_2-gap ($P_{r\text{-}a}CO_2$-gap) during surgery (a) and in the first 6 h after surgery (b). Error bars are standard error of the mean.

Several other randomized clinical trials have been performed on Doppler-guided GDFT in major bowel surgery [2–6,13,14]. Although some trials showed a significantly shortened length of hospital stay, decreased morbidity and increased gut function [3,4], the largest [6,13] and most recent [14] trials showed no advantage of Doppler-guided GDFT over standard or restrictive fluid therapy. Recently, Pearse *et al.* [26] showed no beneficial effect in terms of complications and mortality of a cardiac output optimization protocol using arterial pressure waveform analysis compared with standard of care. However, when they added their results to a meta-analysis of different strategies optimizing global blood flow in surgery, a reduction of postoperative infectious complications and hospital stay was observed. Challand and coworkers showed that GDFT increases length of hospital stay in aerobically fit patients [6]. This supports the hypothesis that sub-maximal SVI reflects physiological reserves instead of a pathological deficit, and SVI optimization, although improving gut perfusion, can actually lead to fluid overload in these patients. The present study adds the application of Doppler-guided GDFT in the early postoperative phase. However, only marginally significant effects of the intervention were seen postoperatively in terms of gastrointestinal perfusion or SVI. Therefore, based on the current results, GDFT has no additional effect compared with standard fluid treatment in the postoperative phase.

Table 4 Clinical outcome.

	Intervention group		Control group	
Variable	*n* (%)	Median (range)	*n* (%)	Median (range)
Mortality	0 (0)		1 (3.2)	
Anastomotic leakage	3 (11.1)		2 (6.5)	
Intra-abdominal abscess	2 (7.4)		1 (3.2)	
SSI	2 (7.4)		3 (9.7)	
Fascial dehiscence	0 (0)		2 (6.5)	
Pneumonia	3 (11.1)		1 (3.2)	
Urinary tract infection	2 (7.4)		5 (16.1)	
POI	3 (11.1)		2 (6.5)	
Gastroparesis	0 (0)		3 (9.7)	
Cardiac decompensation	0 (0)		1 (3.2)	
Unplanned ICU admission	1 (3.7)		4 (12.9)	
Readmission within 30 days	1 (3.7)		3 (9.7)	
Length of hospital stay (days)		11 (4–50)		8 (5–26)
Clavien-Dindo score		2.5 (1–4)		2 (1–5)

ICU, intensive care unit; POI, postoperative ileus; SSI, surgical site infection.

The present study was not designed to detect differences in clinical outcome. Although we show that stroke volume optimization improves gastrointestinal perfusion, it remains to be determined in which patients this approach leads to better clinical outcome. Yet, the current data suggest increased surgical time, blood loss and length of stay in the intervention group, although no statistical analyses were performed. Increased blood loss as a result of increased perfusion cannot be completely ruled out. As noted in the Challand trial [6], patients who have low oxygen-consumption levels may benefit from GDFT; however, large numbers of such a

selected population are needed and are difficult to recruit. Moreover, caution should be taken when interpreting the gut tonometry data, as the measurements were performed in the stomach as a reflection of overall gastrointestinal perfusion. In colorectal surgery, an important target of fluid therapy is to establish adequate perfusion of the gut and the anastomosis in particular, to diminish the risk of postoperative complications such as anastomotic leakage and gut-derived sepsis. It is not known whether gastric tonometry accurately correlates with colonic perfusion. Other techniques, such as *in vivo* microscopy [27], could be accurate tools for detecting local perfusion.

A possible limitation of the current study is that the sample size calculation was based on a rather different study population [17]. However, this was the only applicable study for calculating sample size. The study might therefore be underpowered to detect I-FABP differences, although the data suggest that intestinal cell damage does not occur in this population, as all I-FABP levels were within the normal range and no increase in levels of I-FABP was seen after surgery.

Theoretically, fluid overload is impossible in Frank-Starling-based fluid optimization protocols. However, as significant SV increase in response to PLR was observed in a substantial proportion of healthy and therefore normovolaemic subjects, it is questionable whether increases in SV always represent hypovolemia in surgical patients [23,28]. Therefore, patients in optimized groups may have experienced fluid overload in the current and previous studies. It may be hypothesized that fluid optimization should be reserved for genuinely high-risk surgical patients, which demands future research to test this hypothesis.

In conclusion, Doppler-guided GDFT increased global gastrointestinal perfusion in this study in patients undergoing elective colorectal surgery, indicating a euvolemic state in these patients. We accept, however, that the clinical significance of this finding seems limited as no intestinal damage was observed in the group with 'impaired' fluid status. This study sheds new light on GDFT, although an appropriately powered randomized clinical trial with matched groups, based on surgical technique measuring clinical outcomes, would be required.

Conflicts of interest

None declared.

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Author contributions

Kostan W. Reisinger: study design, analysis and interpretation of data, manuscript drafts and revisions; Henriette M. Willigers: study concept and design, interpretation of data, manuscript revisions; Jochen Jansen: study design, interpretation of data, manuscript revisions; Wim A. Buurman: study concept and design, interpretation of data, manuscript revisions; Maarten F. Von Meyenfeldt: study concept and design, interpretation of data, manuscript revisions; Geerard L. Beets: study concept and design, analysis and interpretation of data, manuscript revisions; Martijn Poeze: study concept and design, analysis and interpretation of data, manuscript revisions.Trial registry number: NCT01175317(http://clinicaltrials.gov/ct2/show/NCT01175317)

References

1 Rahbari NN, Zimmermann JB, Schmidt T *et al.* Meta-analysis of standard, restrictive and supplemental fluid administration in colorectal surgery. *Br J Surg* 2009; **96:** 331–41.

2 Conway DH, Mayall R, Abdul-Latif MS *et al.* Randomised controlled trial investigating the influence of intravenous fluid titration using oesophageal Doppler monitoring during bowel surgery. *Anaesthesia* 2002; **57:** 845–9.

3 Noblett SE, Snowden CP, Shenton BK *et al.* Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. *Br J Surg* 2006; **93:** 1069–76.

4 Wakeling HG, McFall MR, Jenkins CS *et al.* Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. *Br J Anaesth* 2005; **95:** 634–42.

5 Senagore AJ, Emery T, Luchtefeld M *et al.* Fluid management for laparoscopic colectomy: a prospective, randomized assessment of goal-directed administration of balanced salt solution or hetastarch coupled with an enhanced recovery program. *Dis Colon Rectum* 2009; **52:** 1935–40.

6 Challand C, Struthers R, Sneyd JR *et al.* Randomized controlled trial of intraoperative goal-directed fluid therapy in aerobically fit and unfit patients having major colorectal surgery. *Br J Anaesth* 2012; **108:** 53–62.

7 Klotz KF, Klingsiek S, Singer M *et al.* Continuous measurement of cardiac output during aortic cross-clamping by the oesophageal Doppler monitor ODM 1. *Br J Anaesth* 1995; **74:** 655–60.

8 Donati A, Munch C, Marini B *et al.* Transesophageal Doppler ultrasonography evaluation of hemodynamic changes during videolaparoscopic cholecystectomy. *Minerva Anestesiol* 2002; **68:** 549–54.

9 Roy N, Maw A, Stuart-Smith K. Fluid optimization guided by oesophageal Doppler significantly improves bowel perfusion. *Br J Anaesth* 2011; **107:** 1012–3.

10 Holte K, Sharrock NE, Kehlet H. Pathophysiology and clinical implications of perioperative fluid excess. *Br J Anaesth* 2002; **89:** 622–32.
11 Poeze M, Ramsay G, Greve JW *et al.* Prediction of postoperative cardiac surgical morbidity and organ failure within 4 hours of intensive care unit admission using esophageal Doppler ultrasonography. *Crit Care Med* 1999; **27:** 1288–94.
12 Brandstrup B. Fluid therapy for the surgical patient. *Best Pract Res Clin Anaesthesiol* 2006; **20:** 265–83.
13 Brandstrup B, Svendsen PE, Rasmussen M *et al.* Which goal for fluid therapy during colorectal surgery is followed by the best outcome: near-maximal stroke volume or zero fluid balance? *Br J Anaesth* 2012; **109:** 191–9.
14 Srinivasa S, Taylor MH, Singh PP *et al.* Randomized clinical trial of goal-directed fluid therapy within an enhanced recovery protocol for elective colectomy. *Br J Surg* 2013; **100:** 66–74.
15 Monnet X, Rienzo M, Osman D *et al.* Passive leg raising predicts fluid responsiveness in the critically ill. *Crit Care Med* 2006; **34:** 1402–7.
16 Veerkamp JH, Paulussen RJ, Peeters RA *et al.* Detection, tissue distribution and (sub)cellular localization of fatty acid-binding protein types. *Mol Cell Biochem* 1990; **98:** 11–8.
17 Derikx JP, van Waardenburg DA, Thuijls G *et al.* New insight in loss of gut barrier during major non-abdominal surgery. *PLoS One* 2008; **3:** e3954.
18 Otte JA, Geelkerken RH, Huisman AB *et al.* What is the best diagnostic approach for chronic gastrointestinal ischemia? *Am J Gastroenterol* 2007; **102:** 2005–10.
19 Vermeulen Windsant IC, Hellenthal FA, Derikx JP *et al.* Circulating intestinal fatty acid-binding protein as an early marker of intestinal necrosis after aortic surgery: a prospective observational cohort study. *Ann Surg* 2012; **255:** 796–803.
20 Hanssen SJ, Derikx JP, Vermeulen Windsant IC *et al.* Visceral injury and systemic inflammation in patients undergoing extracorporeal circulation during aortic surgery. *Ann Surg* 2008; **248:** 117–25.
21 Moore FA. The role of the gastrointestinal tract in postinjury multiple organ failure. *Am J Surg* 1999; **178:** 449–53.
22 Lamia B, Ochagavia A, Monnet X *et al.* Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneously breathing activity. *Intensive Care Med* 2007; **33:** 1125–32.
23 Godfrey GE, Dubrey SW, Handy JM. A prospective observational study of stroke volume responsiveness to a passive leg raise manoeuvre in healthy non-starved volunteers as assessed by transthoracic echocardiography. *Anaesthesia* 2014; **69:** 306–13.
24 Rinehart J, Chung E, Canales C *et al.* Intraoperative stroke volume optimization using stroke volume, arterial pressure, and heart rate: closed-loop (learning intravenous resuscitator) versus anesthesiologists. *J Cardiothorac Vasc Anesth* 2012; **26:** 933–9.
25 Bundgaard-Nielsen M, Jorgensen CC, Secher NH *et al.* Functional intravascular volume deficit in patients before surgery. *Acta Anaesthesiol Scand* 2010; **54:** 464–9.
26 Pearse RM, Harrison DA, MacDonald N *et al.* Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. *JAMA* 2014; **311:** 2181–90.
27 Goedhart PT, Khalilzada M, Bezemer R *et al.* Sidestream Dark Field (SDF) imaging: a novel stroboscopic LED ring-based imaging modality for clinical assessment of the microcirculation. *Opt Express* 2007; **15:** 15101–14.
28 Minto G, Struthers R. Stroke volume optimisation: is the fairy tale over? *Anaesthesia* 2014; **69:** 291–6.