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Crystalloids versus colloids for goal-directed fluid therapy in major surgery

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Abstract:

Introduction: Perioperative hypovolemia arises frequently and contributes to intestinal hypoperfusion and subsequent postoperative complications. Goal-directed fluid therapy (GDT) might reduce these complications. The aim of this study was to compare the effects of goal-directed administration of crystalloids and colloids on distribution of systemic, hepato-splanchnic and microcirculatory (small intestine) blood flow after major abdominal surgery in a clinically relevant pig model.

Methods: Twenty-seven pigs were anesthetized, mechanically ventilated and underwent open laparotomy. They were randomly assigned to one of three following treatment groups: the restricted Ringer's lactate group (R-RL, n=9) received 3 $ml \cdot kg^{-1} \cdot h^{-1}$ RL; the goal-directed RL group (GD-RL, n=9) received 3 $ml \cdot kg^{-1} \cdot h^{-1}$ RL and intermittent boluses of 250 ml RL and the goal-directed colloid group (GD-C, n=9) received 3 $ml \cdot kg^{-1} \cdot h^{-1}$ RL and boluses of 250 ml 6% hydroxyethyl starch (130/0.4). The two latter groups received a bolus infusion when mixed venous oxygen saturation (SvO_2) was below 60% (lock out time 30 min). Regional blood flow was measured in the superior mesenteric artery and the celiac trunk. In the small bowel microcirculatory blood flow was measured using laser Doppler flowmetry. Intestinal tissue oxygen tension was measured with intramural Clark-type electrodes.

Results: After 4 hours of treatment arterial blood pressure, cardiac output, mesenteric artery flow and mixed oxygen saturation were significantly higher in groups GD-C and GD-RL than in group R-RL. Microcirculatory flow in the intestinal mucosa increased by

50% in GD-C but remained unchanged in the other two groups. Likewise tissue oxygen tension in the intestine increased by 30% in GD-C but remained unchanged in GD-RL and decreased by 18% in the R-RL group. Mesenteric venous glucose concentrations were higher and lactate levels lower in group GD-C compared with the two crystalloid groups.

Conclusions: Goal-directed colloid administration markedly increased microcirculatory blood flow in the small intestine and intestinal tissue oxygen tension after abdominal surgery. In contrast, goal-directed crystalloid and restricted crystalloid administrations had no such effects. Additionally, mesenteric venous glucose and lactate concentrations suggest that intestinal cellular substrate levels were higher in the colloid-treated than in the crystalloid-treated animals. These results support the notion that perioperative goal-directed therapy with colloids might be beneficial during major abdominal surgery.

Introduction

Perioperative care of high risk surgical patients remains a challenge. Despite improvements in perioperative management, the rate of severe complications after major surgery remains high [1, 2]. It has been shown that perioperative decrease in oxygen transport is closely related to the development of organ failure and death [3, 4]. Failure of adequate fluid therapy is a common cause of decreased oxygen transport [3, 5, 6]. Intra-operative gut hypoperfusion was identified in 63% of major surgery patients and was associated with increased morbidity and hospital stay [3]. As a consequence low gastric pHi assessed by gastric tonometry was among the strongest predictors of various perioperative complications [3, 7].

While the importance of normovolemia is widely accepted, there is an ongoing debate about the right amount and the right type of fluid to be administered perioperatively in major surgery. Several recent publications have suggested goal-directed fluid therapy [8-10] with crystalloid or colloid administration a possible way to decrease morbidity and mortality in major surgery patients. Despite reporting decreased morbidity and mortality [5, 8, 11, 12] in these studies the actual effect of a perioperative goal-directed fluid therapy and in particular effects of the kind of fluid, namely crystalloid or colloid solution on the small intestinal tissue - the motor of multi organ failure - is still largely unknown. Goal-directed fluid therapy with colloids has been shown to improve gastric tonometry values in patients after cardiac surgery suggesting improved gastric perfusion [5]. On the other hand, distribution of blood flow after a fluid challenge is heterogeneous and increased cardiac output does not automatically result in increased hepato splanchnic blood flow [13].

Thus, the question remains unresolved in which way perioperative goal-directed fluid therapy influences regional and microcirculatory blood flow as well as tissue oxygen tension in the gastrointestinal tract. Additionally the type of fluid administered is likely to play an important role [14].

In the present study we hypothesize that goal-directed colloid fluid therapy in the setting of major abdominal surgery increases intestinal microcirculatory blood flow and tissue oxygen tension.

The main aim of this study was to investigate the influence of three different fluid management strategies on systemic blood flow (cardiac index), regional blood flow (hepatosplanchnic flow), local blood flow (microcirculatory flow in the small intestine) and intestinal tissue oxygen tension in a pig model of major abdominal surgery. An additional aim was to identify possible differences in effects between crystalloid and colloid based fluid treatments.

Materials and Methods:

This study was performed according to the National Institutes of Health guidelines for the care and use of experimental animals. The protocol was approved by the Animal Ethics Committee of Canton Bern, Switzerland.

27 domestic pigs (weight 28–32 kg) were fasted overnight but had free access to water. The pigs were sedated with intramuscular ketamine (20 $mg \cdot kg^{-1}$) and xylazine (2 $mg \cdot kg^{-1}$). Then a peripheral intravenous catheter was inserted in an ear vein for initial administration of fluids and medications. Anesthesia was induced with midazolam 0.4 $mg \cdot kg^{-1}$ and atropine 1mg. After induction the pigs were orally intubated and ventilated with oxygen in air (fraction of inspired oxygen = 0.3). Anesthesia was maintained with

midazolam 0.5 $mg \cdot kg^{-1} \cdot h^{-1}$, fentanyl 15 $\mu g \cdot kg^{-1} \cdot h^{-1}$, pancuronium 0.3 $mg \cdot kg^{-1} \cdot h^{-1}$ and low dose propofol 0.15 $mg \cdot kg^{-1} \cdot h^{-1}$. The animals were ventilated with a volume-controlled ventilator with a positive end-expiratory pressure of 5 cm H_2O (Servo 900C, Siemens, Solna, Sweden). Tidal volume was kept at 8 - 10 ml/kg and the respiratory rate was adjusted (22–26 breaths/min) to maintain end-tidal carbon dioxide tension ($PaCO_2$) at 5.3±0.5 kPa. Immediately after induction all animals received 1.5 g Cefuroxim intravenously as an antibiotic prophylaxis. The stomach was emptied with a large bore oro-gastric tube.

Surgical preparation

Through a left cervical cut-down, indwelling catheters were inserted into the left carotid artery and superior vena cava. A balloon-tipped catheter was inserted into the pulmonary artery through the right external jugular vein. Location of the catheter tip was determined by observing the characteristic pressure trace on the monitor as the catheter was advanced through the right heart into the pulmonary artery. Similarly a fiber-optic hepatic vein catheter was inserted through the right jugular vein. Correct positioning was verified by a 15 – 20% decrease in the continuously measured hepatic vein saturation versus the mixed venous saturation and by a significant decrease in lactate concentration compared to mixed venous blood. The right carotid artery was dissected free and a 4mm ultrasound transit time flow probe was placed around the vessel to measure carotid artery blood flow.

With the pig in supine position, a midline laparotomy was performed. A catheter was inserted into the urinary bladder for drainage of urine. A second catheter was inserted into the mesenteric vein for blood sampling. The superior mesenteric artery

(SMA), the celiac trunk and the hepatic artery were identified close to their origin. After dissection to free these vessels from the surrounding tissues precalibrated ultrasonic transit time flow probes (Transonic Systems, Ithaca, NY) were placed around the vessels and connected to an ultrasound blood flowmeter (T 207, Transonic Systems).

Through a small incision in the jejunum a custom-made laser Doppler flow probe (LDF, Oxford Optronix, Oxford, UK) was sutured to the jejunum mucosa for measurements of microcirculatory blood flow in the mucosa. A second laser Doppler flow probe was sutured to the adjacent jejunum muscularis. Both LDF probes were attached with six micro-sutures to ensure continuous and steady contact with the tissue under investigation, preventing motion disturbance from respiration and gastrointestinal movements throughout the experiment. The signals of the LDF probes were visualized on a computer monitor. If the signal quality of a probe was poor, the probe's position was corrected immediately. The incision in the jejunum also allowed controlled positioning of an air tonometer tube (TRIP Sigmoid catheter; Datex-Ohmeda, GE Health Care, Helsinki, Finland). The bowel incision was then closed with continuous sutures.

For intramural intestinal tissue oxygen tension measurement a polarographic tissue oxygen tension sensor was inserted into a section of healthy jejunum between the serosal and the mucosal tissue planes. The method has been described previously [15, 16]. Care was taken to minimize handling of the small intestine and to return the bowel to a neutral position.

After preparation the abdominal incision was closed and the animals were allowed to recover from instrumentation and stabilize for 60 min.

Throughout the entire study all animals received a basal infusion of $3ml \cdot kg^{-1} \cdot h^{-1}$ of Ringer's lactate, to avoid excessive fluid administration. This fixed fluid administration

resulted in a low central venous and pulmonary capillary wedge pressure between 2 and 4 mmHg at baseline. Body temperature of the animals was maintained at 38.0 ± 0.5 ^{o}C with a forced air patient air warming system (Warm Touch 5700, Mallinckrodt, Hennef, Germany).

Baseline measurements were performed after stabilization at t = 0 min. Subsequently all hemodynamic measurements were repeated every 30 min for four hours. Blood samples were drawn hourly, after the measurements of the hemodynamic parameters.

Immediately after baseline measurements the pigs were randomly assigned to one of three fluid treatment groups using a reproducible set of computer-generated random numbers. The assignments were kept in sealed, opaque and sequentially numbered envelopes until used. Once the fluid therapy was assigned the investigators were not blinded anymore. The assigned fluid therapy was started 15 min after the first measurement. The fluid treatment groups were:

Groups:

"Restricted Ringer's lactate (R-RL) group" (n=9): fixed administration of 3 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution throughout the experiment without additional fluids.

"Goal-directed Ringer's lactate group" (GD-RL) group (n=9): fixed administration of 3 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution throughout the experiment. Additionally administration of 250 ml lactated Ringer's solution as a bolus (within 3 – 4 min) if the mixed venous saturation (SvO_2) was < 60%. ("lockout" time between two boluses = 30 min).

"Goal-directed colloid group" (GD-C) group (n=9): fixed administration of 3 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution throughout the experiment. Additionally

administration of 250 ml hydroxyethyl starch (HES 130/0.4) as a bolus (within 3 – 4 min) if the mixed venous saturation (SvO_2) was < 60%. (“lockout” time between two boluses = 30 min).

Measurements:

Respiratory monitoring: Expired minute volume, tidal volume, respiratory rate, peak and other respiratory pressures, positive end-expiratory pressure, inspired and end-tidal carbon dioxide fraction, and inspired / expired oxygen fraction were monitored (S/5 Critical Care Monitor, Datex-Ohmeda, GE Health Care, Helsinki, Finland) throughout the study.

Hemodynamic monitoring: Mean arterial blood pressure (MAP, mmHg), central venous pressure (CVP, mmHg), mean pulmonary artery pressure (PAP, mmHg), hepatic vein (HVP, mmHg) and pulmonary capillary wedge pressure (PCWP,mmHg) were recorded with quartz pressure transducers. Puls pressure variation (PPV) and stroke volume (SV) were measured with a PiCCO plus hemodynamic monitor (Pulsion medical systems GmbH, Munich, Germany) connected to the arterial pressure transducer. Heart rate was measured from the electrocardiogram. Heart rate, MAP, pulmonary artery pressures and CVP were displayed continuously on a multi-modular monitor (S/5, Critical Care Monitor, GE Health Care, Helsinki, Finland). A thermodilution method was used to measure cardiac output at each measurement point. (Mean value of three consecutive manually performed measurements with 5ml of cold saline). Core temperature was measured form the thermistor in the pulmonary artery catheter.

Regional blood flow in the SMA, the celiac trunk and the hepatic artery was continuously measured throughout the experiments with ultrasonic transit time flowmetry

(TTF, ml min^{-1}) using two double channel HT 206 flowmeters (Transonic Systems Inc., Ithaca, NY, USA).

Microcirculatory blood flow was continuously monitored in the mucosa and the muscularis of the jejunum using a multi-channel laser Doppler flowmeter system (Oxford Optronix, Oxford, UK). A detailed description of the theory of laser Doppler flowmetry operation and practical details of laser Doppler flowmetry measurements have been published previously [17, 18]. The regional blood flow and the LDF data were acquired online with a sampling rate of 10 Hz via a multi-channel interface (MP 150; Biopac Systems Inc., Goleta, CA) with acquisition software (Acqknowledge 3.9., Biopac Systems Inc., Goleta, CA) and saved on a portable computer.

Laser Doppler flowmeters are not calibrated to measure absolute blood flow, but indicate microcirculatory blood flow in arbitrary perfusion units. Due to a relatively large variability of baseline values the results are usually expressed as changes relative to baseline [19-22] and that was also the case in the present study.

The jejunal intramucosal carbon dioxide pressure was measured with air tonometry (Tonocap® Monitor, Datex-Ohmeda, GE Health Care, Helsinki, Finland). The jejunal mucosal-to-arterial carbon dioxide pressure gap (CO_2 gap) was calculated at each measurement point.

Arterial, mixed venous, mesenteric and hepatic venous blood samples were withdrawn hourly from the indwelling catheters and immediately analyzed in a blood gas analyzer (ABL 620, Radiometer, Copenhagen, Denmark) for oxygen pressure (PO_2, kPa), carbon dioxide pressure (PCO_2, kPa), pH, lactate (mmol/l),and base excess (BE). Oxygen saturation (SO_2, %) and total hemoglobin concentration (Hb; g/dl) were measured with a analyzer, specially adjusted to porcine blood (OSM 3, Radiometer,

Copenhagen, Denmark). All values were adjusted to body temperature. Mixed and hepatic venous saturation were displayed continuously on two continuous cardiac output monitors (Vigilance, Edwards lifesciences, Baxter, Irvine CA)

Cardiac index (CI; $ml \cdot kg^{-1} \cdot min^{-1}$), superior mesenteric artery flow index (SMAI; $ml \cdot kg^{-1} \cdot min^{-1}$), and systemic vascular resistance index (SVRI; $mmHg \cdot kg^{-1} \cdot min^{-1}$) were indexed to body weight. Systemic vascular resistance index (SVRI) was calculated as: SVRI = (MAP – CVP) / CI [20, 23].

Systemic oxygen delivery index (sDO_2I; $ml \cdot kg^{-1} \cdot min^{-1}$), systemic oxygen consumption index (sVO_2I; $ml \cdot kg^{-1} \cdot min^{-1}$), as well as the correspondent mesenteric (splanchnic) variables (mDO_2I, mVO_2I; $ml \cdot kg^{-1} \cdot min^{-1}$) were calculated using the following formulas:

Systemic (total body) oxygen delivery index (sDO_2) = (CI x CaO_2), where CaO_2 is the arterial oxygen content.

Systemic (total body) oxygen consumption index (sVO_2) = (CI x (CaO_2 - CvO_2)) where CaO_2 is the arterial and CvO_2 is the mixed venous oxygen content, respectively.

Mesenteric (splanchnic) oxygen delivery index (mDO_2) = SMAI x CaO_2

Mesenteric (splanchnic) oxygen consumption index (mVO_2) = SMAI x (CaO_2 - CmO_2) where CmO_2 is the mesenteric vein oxygen content.

Oxygen content ($ml \cdot O_2$ / ml blood) = ((PO_2 x 0.0031) + (Hb x SO_2 x 1.36))/100

where Hb (g/dl) is the hemoglobin concentration and SO_2 is oxygen saturation.

Statistical analysis

Data was tested for normality by QQ-plot and Kolmogorow-Smirnow test. All baseline-data (i.e. before start of the respective treatment at t = 0 min) was compared

with analysis of variance (ANOVA) or Kruskall-Wallis test to exclude initial group discrepancies. Differences between the three fluid treatment groups were assessed by ANOVA for repeated measurements using group as between-subject factor and time as within-subject factor. If a significant difference between the groups was detected, a Tukey post-hoc test was performed to assess differences at individual timepoints. Additionally, the area under the variable-time curve (AUC) for each variable of interest was calculated and compared with ANOVA for group differences. A Tukey post-hoc test was performed to compare individual treatments if the ANOVA had detected significant differences between the groups. Measurements of microcirculatory blood flow (LDF) were transformed with baseline set to 100 % (t = 0 min) prior to statistical analysis. Absolute values were used for all other calculations.

Data are presented as means ± SDs unless otherwise specified. A p-value < .05 was considered significant. For statistical calculations SAS Version 8 (SAS Institute Inc., Cary, NC) was used.

Results:

All animals survived until the end of the experiment and were included in the final data analysis. The continuous intravenous infusion of basal Ringer's lactate administered during the entire experiments (induction until end of study) to groups R-RL, GD-RL and GD-C were 924 ± 44, 943 ± 68 and 917 ± 41 ml, respectively. Ringer's lactate administered as repeated bolus infusions (triggered by an SvO_2 < 60%) was 1794 ± 211 ml in group GD-RL while group GD-C received a total of 831 ± 267 ml of 6% hydroxyethyl starch (130/0.4) as bolus infusions.

Systemic hemodynamic data are presented in fig 1 and in table 1. At baseline there were no significant differences between the three groups in any parameter measured. In group R-RL SvO_2 was 49.5 ± 4.0 % at baseline and remained low (fig.1). The target value of 60% was not reached in any of the animals in this group at any time point. In group GD-RL SvO_2 increased over time and was 56 ± 5% after 4 hours. Only in three out of nine animals the target value was reached in this group. In group GD-C SvO_2 increased to 63 ± 4% after the first bolus and remained high. The target value for SvO_2 was reached in all nine animals in this group.

In group R-RL CI, SV, PPV, MAP, PAP, CVP, hepatic venous pressure (HVP) and PCWP remained largely unchanged. In Group GD-RL CI and MAP increased slowly (by 15%) over the four hours observation time. SV increased continuously (by > 30%) during the study. In group GD-C CI and MAP increased by 30% already after the first fluid bolus and remained significantly higher than in group GD-RL. SV increased by more than 50% after the first fluid bolus and decreased slightly thereafter resulting in almost identical stroke volume compared to the group GD-RL at the end of the study. PPV in group GD-C decreased sharply after the first bolus followed by an increase after 60 min. During the

remainder of the study PPV in both goal-directed groups were similar and decreased over time. Filling pressures, i.e. PAP, CVP, HVP and PCWP, increased similarly in groups GD-RL and GD-C.

Regional blood flow (fig 2 and table 1) in the carotid artery was unchanged in group R-RL but increased by 20% in group GD-RL and by almost 50% in group GD-C. On the other hand, blood flow in the celiac trunk and the hepatic artery remained virtually unchanged in all three groups throughout the experiment. Superior mesenteric artery flow decreased by 20% in group R-RL over time, while it remained nearly unchanged in group GD-RL. On the other hand SMAI flow increased significantly in group GD-C (by 20%).

Microcirculatory blood flow in the jejunum mucosa (fig 3) remained largely unchanged in groups R-RL and GD-RL throughout the four treatment hours while it rapidly increased by up to 50% in group GD-C and remained high until the end of the experiments. Microcirculatory blood flow in the jejunum muscularis (table 1) remained unchanged in group GD-C but decreased significantly in the other two groups.

Jejunum tissue oxygen tension (fig 3 & fig 4) decreased by 15% in the R-RL group but remained unchanged in the GD-RL group. In the GD-C group it increased by more than 40%, virtually in parallel with mucosal microcirculatory flow and remained high until the end. Jejunal mucosa carbon dioxide tension (fig 3) remained almost unchanged in the two crystalloid fluid groups while it decreased by 10% in the colloid group.

Systemic oxygen delivery increased by almost 40% in group GD-C and 20% in group GD-RL and systemic oxygen extraction ratio decreased by 25% in group GD-C and 15% in group GD-RL. Both parameters decreased in group R-RL (table 2). Hepatic venous oxygen saturation (fig 5) increased rapidly by 40% in group GD-C while it

increased slowly in group GD-RL and decreased in group R-RL. Mesenteric oxygen extraction ratio (fig 5) decreased by more than 20% in group GD-C, while it increased by 10% in the two crystalloid fluid groups. Lactate levels in the mesenteric vein (fig 5) remained unchanged in groups R-RL and GD-RL while they decreased by 50% in group GD-C. Hepatic vein lactate was similar in all groups. Glucose concentration in the mesenteric vein decreased in group R-RL by 15%, was virtually unchanged in group GD-RL and increased in group GD-C by 12%.

Arterial hemoglobin concentration (table 2) increased slightly in group R-RL while it decreased by approximately 10% in the two goal-directed groups.

Discussion:

In this study the effects of three different fluid regimens on systemic and regional blood flow as well as intestinal microcirculation and tissue oxygen tension were investigated during major abdominal surgery in pigs. The two groups receiving goal-directed fluid therapy (groups GD-RL and GD-C) had increased cardiac output and increased regional blood flow to the superior mesenteric artery compared to the group receiving a restricted fluid regimen (group R-RL). However, the effects of the two goal-directed fluid regimens were remarkably different in regard to microcirculatory blood flow, tissue oxygen tension and metabolic markers in the small bowel. Already the first bolus of goal-directed administration of colloids resulted in a 30% increase in microcirculatory blood flow in the small bowel mucosa with a concomitant increase in tissue oxygen tension (30%), an increase in mesenteric vein glucose (12%) and decreases in mesenteric lactate (50%), mesenteric oxygen extraction (20%) and intestinal CO_2 (fig 3, 4 and 5). On the other hand, even repeated boluses of RL in group GD-RL did not increase microcirculatory blood flow in the small bowel mucosa and showed virtually no effect on tissue oxygenation, intestinal CO_2, mesenteric lactate or glucose levels. Comparable pulse pressure variation (PPV), stroke volume (SV) and hemoglobin concentrations at the end of the study suggest similarly appropriate intravascular fluid volume in the two GDT groups.

Although systemic and regional blood flow increased significantly over time in group GD-RL, the goal of $SvO_2 \geq 60\%$ was not achieved in this group. It could be argued that if even larger amounts of crystalloids (more than 15 $ml \cdot kg^{-1} \cdot h^{-1}$) had been administered microcirculatory blood flow in the small bowel might have increased

comparably to the colloid group. However, dynamic systemic hemodynamic parameters such as PPV, SV and Hb concentration suggest that both goal-directed groups had similar intravascular fluid volume at the end of the study. Furthermore, despite increasing systemic and regional blood flow over time no trend of improvement in intestinal tissue oxygen tension or microcirculatory blood flow (fig 3) in the goal-directed crystalloid group was found. In addition, even larger amounts of crystalloids (over 20 $ml \cdot kg^{-1} \cdot h^{-1}$) did not increase perioperative small intestinal tissue oxygen tension [24].

Intestinal autoregulation does not explain the differences between the groups and suggests that the different pharmacological properties of the two fluid types, lactated Ringer's solution and 6% hydroxyethyl starch (130/0.4), were to a large extent responsible for the effects on the intestinal microcirculation. Ringer's lactate is distributed within the whole extra-celluar space i.e. three fourth of the administered amount leave the intravascular space within minutes [25], and thus expanding the extra-vascular space with interstitial fluid accumulation instead of increasing nutritive microcirculatory perfusion. Colloids on the other hand increase the intravascular volume as long as the endothelial glycocalix is competent [25] and thus may result in increased microcirculatory perfusion. The results are also in accordance with studies from Lang et. al. [26] and Mythen et al. [5]. Lang et al. [26] showed that only colloid administration resulted in increased skeletal muscle oxygen tension in patients but RL did not. Mythen et al. [5], measured indirectly gastrointestinal blood flow by gastric tonometry in patients undergoing cardiac surgery. They found improved gastric mucosa pH and outcome in patients receiving goal-directed administration of colloids compared with control patients [5]. In addition, several other clinical studies have reported improved outcome after major surgery in patients receiving goal-directed hydroxyethyl starch [8, 27-30]

compared with conventional fluid therapy. However, none of these studies measured directly microcirculatory blood flow, tissue oxygen tension or regional metabolic parameters in the gastrointestinal tract.

The strength of the present study is the combination of various methods to explore small intestinal microcirculation, oxygen transport and markers of oxygen metabolism simultaneously. Interestingly mesenteric vein glucose decreased in the fluid restricted animals while it increased in the colloid group. This is in accordance with a previous study from Krejci et al. where it was shown that a reduction in intestinal glucose levels was an early sign (earlier than increased lactate) of gastrointestinal hypoperfusion [31].

Considering the microcirculatory effects of colloid administration in the present study, intestinal tissue oxygen pressure as well as mesenteric metabolic markers indicate augmented oxygen supply and sufficient cellular substrate. These findings may be the basic, tissue-level mechanisms how goal-directed administration of colloids has beneficial impact on outcome.

The lack of effect of any of the fluid regimens used in this study on blood flow in the celiac trunk and the hepatic artery, compared with a marked increase in systemic, and superior mesenteric artery blood flows was a unanticipated finding and demonstrates once again the heterogeneous distribution of blood flow during different insults [13, 20, 32]. This underlines the fact that it is not appropriate to assume that changes in systemic, regional and microcirculatory blood flow occur in unison under non septic conditions.

The main limitation of this study is the relatively short (4 hours) observation time, which is too short to verify the effect of the respective fluid regimens on outcome. However, the aim of this study was to identify possible mechanisms and compare the

acute effects of restricted and goal-directed fluid therapy on microcirculatory blood flow as well as several markers of tissue oxygenation and metabolism in the gut.

The study was performed in an animal model because direct measurements of regional and local microcirculatory blood flow in patients are invasive, time-consuming, and require special skills and instruments that are not readily available at the bedside. This is also the reason why to our knowledge no clinical study has measured the direct effects of goal-directed fluid therapy with crystalloid and colloid fluids on intestinal microcirculation, tissue oxygen tension and metabolism. Therefore the pathophysiological background of improved outcome with goal-directed fluid therapy based on colloids was so far largely unknown. We chose the pig for this study because of its anatomical and physiologic similarity to humans with respect to the cardiovascular system and the digestive tract [33].

Another limitation of this experimental study concerns the choice of treatment target for fluid therapy. We do not suggest that the target of mixed venous saturation >60%, as used in this study, is valid for patients undergoing major surgery. Firstly, the target of 60% for mixed venous saturation seems rather low in patients, but it is ambitious in pigs, because normal mixed venous oxygen saturation in pigs is lower than in humans [33]. Secondly, mixed venous saturation measurements require a pulmonary artery catheter, which appears invasive for patients undergoing uncomplicated major surgery, particularly since other target parameters have been evaluated [8-10]. Last but not least based on the currently available data stroke volume optimization for i.v. fluid challenges is the best evaluated method for individualized goal directed fluid therapy and therefore seems preferable for human studies. However, for the purpose of this study we considered this method very reliable and our animals were all instrumented

with pulmonary artery catheters with continuous mixed venous oxygen saturation monitoring.

An additional limitation of the study is that both goal-directed groups received the same size of fluid bolus with identical lock out times. Thus the GDT-RL group may have needed more time to receive a hemodynamically equally effective amount of fluid. The aim of goal-directed therapy in the present study was to achieve a physiologic goal over a certain time period. The size of the intravenous fluid bolus administered in this study corresponds to 580 ml in a 70 kg patient and reflects clinical practice at our institution in hemodynamically stable patients (bolus infusion of about 500ml). After such a bolus a reevaluation of the patient's hemodynamics is mandatory. Thus, it was not considered advisable to have shorter lock out time than 30 min also because fluid distribution after a rapid bolus administration needed some time. A slight delay in achieving the goal parameter in group GD-RL was, under the circumstances, found acceptable. Particularly since it has been shown in a previous study that early aggressive fluid administration during surgery with crystalloids (> 20 ml/kg/h) did not improve intestinal tissue oxygen tension compared to fluid restriction [24].

The present study indicates that in the small bowel fluid restriction as reflected by the data from group R-RL results in impaired microcirculation, decreased tissue oxygen tension and cellular oxygen metabolism. Goal-directed fluid therapy with crystalloids had virtually no beneficial effects either on the intestinal microcirculation or the tissue oxygen tension but requires considerable amounts of fluids. However, excessive fluid administration may result in interstitial fluid accumulation and weight gain. Significant perioperative weight gain results, however, in increased mortality [34].

Conclusion:

The results from this animal study show for the first time directly that goal-directed fluid therapy with colloids increases intestinal microcirculatory blood flow and tissue oxygen tension compared to goal-directed therapy with lactated Ringer´s solution or fluid restriction. Neither goal-directed crystalloid treatment nor fluid restriction had beneficial effects on intestinal microcirculation or on tissue oxygen tension. In addition, mesenteric venous glucose and lactate concentrations suggest that intestinal cellular substrate levels were increased in the colloid group compared to the other groups. Consequently the presented data supports the notion that perioperative goal-directed fluid therapy with colloids might be beneficial to restore intravascular volume depletion, intestinal microcirculatory blood flow and tissue oxygen delivery during major abdominal surgery.

Key messages:

- Colloids (HES 130/0.4) markedly increased microcirculatory blood flow and tissue oxygen tension in the small intestinal mucosa.
- Colloids decreased intestinal carbon dioxide gap, decreased mesenteric venous lactate and increased mesenteric venous glucose concentration suggesting improved intestinal cellular substrate levels.
- Colloids significantly increased mixed venous saturation with less fluid administered compared to Crystalloids.
- Different fluid therapy regimens had no apparent effects on hepatic arterial blood flow indicating sufficient liver tissue oxygenation even during restricted fluid administration.
- The results of this animal study suggest possible mechanisms for improved outcome after goal directed therapy with colloids in major abdominal surgery in patients. This hypothesis requires, however, further studies.

Abbreviations

BE = arterial standard base excess; CaO_2 = arterial oxygen content; CI = cardiac index; CvO_2 = mixed venous oxygen content; CVP = central venous pressure; GD-C = goal directed colloid fluid therapy; GD-RL = goal directed Ringer's lactate fluid therapy; Hb = hemoglobin concentration; HES = Hydroxyethyl starch; HR = heart rate; HVP = hepatic vein pressure; LDF = laser Doppler flowmetry; MAP = mean arterial blood pressure; MBF = microcirculatory blood flow; mDO_2I = mesenteric oxygen delivery index; PAP = pulmonary artery pressure; pCO_2 = carbon dioxide partial pressure; pO_2 = oxygen partial pressure; PPV = pulse pressure variation; PU = laser Doppler perfusion units; PCWP = pulmonary capillary wedge pressure; RL = Ringer's lactate solution; R-RL = restricted Ringer's lactate fluid therapy; sDO_2I = systemic oxygen delivery index; SO_2 = arterial oxygen saturation; SV = cardiac stroke volume; SvO_2 = mixed venous oxygen saturation; SVRI = systemic vascular resistance index; TTF = ultrasonic transit time flowmetry.

Competing Interests

The authors declare that they have no competing interests.

Authors' contributions

LBH: Experimental design. Animal preparation, performance and supervision of experimental work. Preliminary analysis of the data. Writing of the manuscript. Supervision and overview of entire project. OK: Experimental design. Animal

preparation, performance and supervision of experimental work. Analysis of the data. Helped to draft the manuscript. MA: Animal preparation, performance and supervision of experimental work. Preliminary analysis of the data. Helped to draft the manuscript. SB: Animal preparation, performance and supervision of experimental work. Preliminary analysis of the data. AK: Consulting of experimental design, assistance with statistics and in drafting the manuscript. GHS: Assistance and consulting of experimental design. Substantial contribution to the manuscript, in particular the discussion section, Senior advisor.

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References:

1. Bozzetti F, Gianotti L, Braga M, Di Carlo V, Mariani L: **Postoperative complications in gastrointestinal cancer patients: the joint role of the nutritional status and the nutritional support**. *Clin Nutr* 2007, **26**:698-709.
2. Law WL, Choi HK, Lee YM, Ho JW, Seto CL: **Anastomotic leakage is associated with poor long-term outcome in patients after curative colorectal resection for malignancy**. *J Gastrointest Surg* 2007, **11**:8-15.
3. Mythen MG, Webb AR: **Intra-operative gut mucosal hypoperfusion is associated with increased post-operative complications and cost**. *Intensive Care Med* 1994, **20**:99-104.
4. Bland RD, Shoemaker WC: **Probability of survival as a prognostic and severity of illness score in critically ill surgical patients**. *Crit Care Med* 1985, **13**:91-95.
5. Mythen MG, Webb AR: **Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery**. *Arch Surg* 1995, **130**:423-429.
6. Theodoropoulos G, Lloyd LR, Cousins G, Pieper D: **Intraoperative and early postoperative gastric intramucosal pH predicts morbidity and mortality after major abdominal surgery**. *Am Surg* 2001, **67**:303-308; discussion 308-309.
7. Ivatury RR, Simon RJ, Islam S, Fueg A, Rohman M, Stahl WM: **A prospective randomized study of end points of resuscitation after major trauma: global oxygen transport indices versus organ-specific gastric mucosal pH**. *J Am Coll Surg* 1996, **183**:145-154.
8. Gan TJ, Soppitt A, Maroof M, el-Moalem H, Robertson KM, Moretti E, Dwane P, Glass PS: **Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery**. *Anesthesiology* 2002, **97**:820-826.
9. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED: **Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]**. *Crit Care* 2005, **9**:R687-693.
10. Lopes MR, Oliveira MA, Pereira VO, Lemos IP, Auler JO, Jr., Michard F: **Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery: a pilot randomized controlled trial**. *Crit Care* 2007, **11**:R100.
11. 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.
12. Wakeling HG, McFall MR, Jenkins CS, Woods WG, Miles WF, Barclay GR, Fleming SC: **Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery**. *Br J Anaesth* 2005, **95**:634-642.
13. Ali SZ, Bracht H, Krejci V, Beck M, Stalder M, Hiltebrand L, Takala J, Brandt S, Jakob SM: **The immediate and sustained effects of volume challenge on regional blood flows in pigs**. *Anesth Analg* 2008, **106**:595-600, table of contents.
14. Grocott MP, Mythen MG, Gan TJ: **Perioperative fluid management and clinical outcomes in adults**. *Anesth Analg* 2005, **100**:1093-1106.
15. Fleischmann E, Herbst F, Kugener A, Kabon B, Niedermayr M, Sessler DI, Kurz A: **Mild hypercapnia increases subcutaneous and colonic oxygen tension in patients given 80% inspired oxygen during abdominal surgery**. *Anesthesiology* 2006, **104**:944-949.
16. Ratnaraj J, Kabon B, Talcott MR, Sessler DI, Kurz A: **Supplemental oxygen and carbon dioxide each increase subcutaneous and intestinal intramural oxygenation**. *Anesth Analg* 2004, **99**:207-211.

17. Kiel JW, Riedel GL, DiResta GR, Shepherd AP: **Gastric mucosal blood flow measured by laser-Doppler velocimetry**. *Am J Physiol* 1985, **249**:G539-545.
18. Shepherd AP, Riedel GL: **Continuous measurement of intestinal mucosal blood flow by laser-Doppler velocimetry**. *Am J Physiol* 1982, **242**:G668-672.
19. Krejci V, Hiltebrand LB, Sigurdsson GH: **Effects of epinephrine, norepinephrine, and phenylephrine on microcirculatory blood flow in the gastrointestinal tract in sepsis**. *Crit Care Med* 2006, **34**:1456-1463.
20. Hiltebrand LB, Krejci V, Banic A, Erni D, Wheatley AM, Sigurdsson GH: **Dynamic study of the distribution of microcirculatory blood flow in multiple splanchnic organs in septic shock**. *Crit Care Med* 2000, **28**:3233-3241.
21. Banic A, Krejci V, Erni D, Wheatley AM, Sigurdsson GH: **Effects of sodium nitroprusside and phenylephrine on blood flow in free musculocutaneous flaps during general anesthesia**. *Anesthesiology* 1999, **90**:147-155.
22. Hiltebrand LB, Krejci V, tenHoevel ME, Banic A, Sigurdsson GH: **Redistribution of microcirculatory blood flow within the intestinal wall during sepsis and general anesthesia**. *Anesthesiology* 2003, **98**:658-669.
23. Hiltebrand LB, Krejci V, Jakob SM, Takala J, Sigurdsson GH: **Effects of vasopressin on microcirculatory blood flow in the gastrointestinal tract in anesthetized pigs in septic shock**. *Anesthesiology* 2007, **106**:1156-1167.
24. Hiltebrand LB, Pestel G, Hager H, Ratnaraj J, Sigurdsson GH, Kurz A: **Perioperative fluid management: comparison of high, medium and low fluid volume on tissue oxygen pressure in the small bowel and colon**. *Eur J Anaesthesiol* 2007, **24**:927-933.
25. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M: **A rational approach to perioperative fluid management**. *Anesthesiology* 2008, **109**:723-740.
26. Lang K, Boldt J, Suttner S, Haisch G: **Colloids versus crystalloids and tissue oxygen tension in patients undergoing major abdominal surgery**. *Anesth Analg* 2001, **93**:405-409.
27. 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.
28. Venn R, Steele A, Richardson P, Poloniecki J, Grounds M, Newman P: **Randomized 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.
29. Price J, Sear J, Venn R: **Perioperative fluid volume optimization following proximal femoral fracture**. *Cochrane Database Syst Rev* 2002:CD003004.
30. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED: **Changes in central venous saturation after major surgery, and association with outcome**. *Crit Care* 2005, **9**:R694-699.
31. Krejci V, Hiltebrand L, Buchi C, Ali SZ, Contaldo C, Takala J, Sigurdsson GH, Jakob SM: **Decreasing gut wall glucose as an early marker of impaired intestinal perfusion**. *Crit Care Med* 2006, **34**:2406-2414.
32. Krejci V, Hiltebrand L, Banic A, Erni D, Wheatley AM, Sigurdsson GH: **Continuous measurements of microcirculatory blood flow in gastrointestinal organs during acute haemorrhage**. *Br J Anaesth* 2000, **84**:468-475.
33. Hannon JP, Bossone CA, Wade CE: **Normal physiological values for conscious pigs used in biomedical research**. *Lab Anim Sci* 1990, **40**:293-298.

34. Lowell JA, Schifferdecker C, Driscoll DF, Benotti PN, Bistrian BR: **Postoperative fluid overload: not a benign problem**. *Crit Care Med* 1990, **18**:728-733.

Figure Legends:

Fig 1: Systemic hemodynamic parameters

Fig 1a: Changes in mixed venous oxygen saturation (mean ± SD) before (baseline) and during the different fluid treatment strategies. Mixed venous saturation was the target parameter for fluid administration.

Fig 1b: Changes in mean arterial pressure (mean ± SD) before (baseline) and during the different fluid treatment strategies.

Fig 1c: Changes in cardiac index (mean ± SD) before (baseline) and during the different fluid treatment strategies.

Group R-RL received 3 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution throughout the entire experiment.

Group GD-RL received 3 ml $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution plus 250 ml lactated Ringer's solution if SvO_2 was < 60%.

Group GD-C received 3 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution plus 250 ml hydroxyethyl starch (130/0.4) if SvO_2 was < 60%.

Significant differences ($p < 0.05$) for area under the curve (AUC): # R-RL vs. GD-RL, † R-RL vs. GD-C, $ GD-RL vs. GD-C

Significant differences ($p < 0.05$) for ANOVA for repeated measurements (Tukey post-hoc test): * R-RL vs. GD-RL, ≠ R-RL vs. GD-C, § GD-RL vs. GD-C.

Fig 2: Regional blood flow parameters

Fig 2a: Changes in superior mesenteric artery flow index (mean ± SD) before (baseline) and during the different fluid treatment strategies.

Fig 2b: Changes in hepatic artery flow index (mean ± SD) before (baseline) and during the different fluid treatment strategies.

Fig 2c: Changes in carotid artery flow index (mean ± SD) before (baseline) and during the different fluid treatment strategies.

Group R-RL received 3 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution throughout the entire experiment.

Group GD-RL received 3 ml $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution plus 250 ml lactated Ringer's solution if SvO_2 was < 60%.

Group GD-C received 3 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution plus 250 ml hydroxyethyl starch (130/0.4) if SvO_2 was < 60%.

Significant differences ($p < 0.05$) for area under the curve (AUC): # R-RL vs. GD-RL, † R-RL vs. GD-C, $ GD-RL vs. GD-C

Significant differences ($p < 0.05$) for ANOVA for repeated measurements (Tukey post-hoc test): * R-RL vs. GD-RL, ≠ R-RL vs. GD-C, § GD-RL vs. GD-C.

Fig 3: Intestinal perfusion and oxygenation parameters

Fig 3a: Relative changes in microcirculatory blood flow in the jejunum mucosa (mean ± SD) before (baseline) and during the different fluid treatment strategies. Blood flow was set at 100% at baseline.

Fig 3b: Changes in jejunum wall tissue oxygen tension (mean ± SD) before (baseline) and during the different fluid treatment strategies.

Fig 3c: Changes in mucosal carbon dioxide tension in the jejunum (mean ± SD) before (baseline) and during the different fluid treatment strategies.

Group R-RL received 3 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution throughout the entire experiment.

Group GD-RL received 3 ml $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution plus 250 ml lactated Ringer's solution if SvO_2 was < 60%.

Group GD-C received 3 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution plus 250 ml hydroxyethyl starch (130/0.4) if SvO_2 was < 60%.

Significant differences ($p < 0.05$) for area under the curve (AUC): # R-RL vs. GD-RL, † R-RL vs. GD-C, $ GD-RL vs. GD-C

Significant differences ($p < 0.05$) for ANOVA for repeated measurements (Tukey post-hoc test): * R-RL vs. GD-RL, ≠ R-RL vs. GD-C, § GD-RL vs. GD-C.

Fig 4: Relative changes in intestinal microcirculation and tissue oxygen tension

Black squares GD-C MBF: relative changes in microcirculatory blood flow in group GD-C

Open squares GD-C $ptiO_2$: relative changes in tissue oxygen tension in group GD-C

Black triangles GD-RL MBF: relative changes in microcirculatory blood flow in group GD-RL

Open triangles GD-RL $ptiO_2$: relative changes in tissue oxygen tension in group GD-RL

Black circles R-RL MBF: relative changes in microcirculatory blood flow in group R-RL

Open circles R-RL MBF: relative changes in tissue oxygen tension in group R-RL

Group R-RL received 3 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution throughout the entire experiment.

Group GD-RL received 3 ml $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution plus 250 ml lactated Ringer's solution if SvO_2 was < 60%.

Group GD-C received 3 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution plus 250 ml hydroxyethyl starch (130/0.4) if SvO_2 was < 60%.

Baseline was set = 100% for all parameters

Significant differences ($p < 0.05$) for area under the curve (AUC): # R-RL vs. GD-RL, † R-RL vs. GD-C, $ GD-RL vs. GD-C

Significant differences ($p < 0.05$) for ANOVA for repeated measurements (Tukey post hoc test): * R-RL vs. GD-RL, ≠ R-RL vs. GD-C, § GD-RL vs. GD-C.

Fig 5: Splanchnic oxygenation parameters

Fig 5a: Changes in hepatic vein oxygen saturation (mean ± SD) before (baseline) and during the different fluid treatment strategies.

Fig 5b: Changes in mesenteric vein glucose (mean ± SD) before (baseline) and during the different fluid treatment strategies.

Fig 5c: Changes in mesenteric oxygen extraction ratio (mean ± SD) before (baseline) and during the different fluid treatment strategies.

Fig 5d: Changes in mesenteric vein lactate (mean ± SD) before (baseline) and during the different fluid treatment strategies.

Group R-RL received 3 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution throughout the entire experiment.

Group GD-RL received 3 ml $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution plus 250 ml lactated Ringer's solution if SvO_2 was < 60%.

Group GD-C received 3 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution plus 250 ml hydroxyethyl starch (130/0.4) if SvO_2 was < 60%.

Significant differences ($p < 0.05$) for area under the curve (AUC): # R-RL vs. GD-RL, † R-RL vs. GD-C, $ GD-RL vs. GD-C

Significant differences ($p < 0.05$) for ANOVA for repeated measurements (Tukey post-hoc test): * R-RL vs. GD-RL, ≠ R-RL vs. GD-C, § GD-RL vs. GD-C.

Table 1: Systemic, regional and local hemodynamic variables

	Heart rate [#†]	SV [†]	SVRI [#†]	CVP	HVP	PCWP [†]	CeliacusI	MBF JM [#†]
	(beats/min)	(ml/beat)	($mmHg \cdot kg^{-1} \cdot min^{-1}$)	(mmHg)	(mmHg)	(mmHg)	($ml \cdot kg^{-1} \cdot min^{-1}$)	(% of baseline)
Restricted Ringer's lactate solution (R-RL)								
0 min	117 ± 2	28.1 ± 8.4	732 ± 84	2.8 ± 1	3.8 ± 1.4	3.1 ± 0.6	4.0 ± 0.9	100 ± 0
30 min	117 ± 4	26.6 ± 6.7	744 ± 123	3.1 ± 0.8	4.5 ± 1	3.3 ± 0.7	4.1 ± 1.0	93 ± 20
180 min	123 ± 15	23.7 ± 5.7	868 ± 161	3.3 ± 0.7	3.9 ± 1.4	3.2 ± 0.9	4.9 ± 1.2	74 ± 24
240 min	128 ± 14	24.2 ± 5.2	835 ± 149	2.8 ± 1.1	3.9 ± 0.9	2.9 ± 0.7	5.1 ± 1.1	71 ± 18
Goal directed Ringer's lactate solution (GD-RL)								
0 min	110 ± 11	25.4 ± 6.6	705 ± 140	3 ± 1.1	4.3 ± 1.4	3.3 ± 1.1	3.8 ± 1.4	100 ± 0
30 min	101 ± 4	28.3 ± 7	652 ± 157	3.3 ± 1.1	4.6 ± 1.1	3.6 ± 1	3.9 ± 1.5	97 ± 22
180 min	106 ± 15[#]	30.8 ± 6.5	666 ± 147	3.8 ± 1.1	5.5 ± 0.9	3.9 ± 1.2	6.2 ± 1.7	54 ± 18
240 min	103 ± 18[*#]	33.2 ± 6.7	646 ± 90[#]	4 ± 0.9	5.6 ± 1	4.4 ± 1.2	5.8 ± 1.1	49 ± 11
Goal directed Colloid solution (GD-C)								
0 min	113 ± 7	25.2 ± 9.8	682 ± 155	3 ± 0.7	4.1 ± 0.9	3.3 ± 0.5	4.3 ± 1.3	100 ± 0
30 min	98 ± 9	38.7 ± 7.3[≠]	589 ± 76	4.3 ± 0.7[≠]	5.4 ± 1	4.6 ± 0.8	5.0 ± 1.5	122 ± 19
180 min	106 ± 16[≠]	35.1 ± 11[≠]	622 ± 109[≠]	3.8 ± 1.1	5.1 ± 1	3.9 ± 1.1	5.4 ± 1.5	101 ± 19[§≠]
240 min	109 ± 20[≠]	33.9 ± 12	563 ± 53[≠]	4.2 ± 0.9[≠]	5.7 ± 0.9	3.7 ± 0.9	5.4 ± 1.5	94 ± 22[§≠]

Data presented as mean ± SD.

SV: cardiac stroke volume; SVRI: systemic vascular resistance index; CVP: central venous pressure; HVP: hepatic venous pressure; PCWP: pulmonary capillary wedge pressure; CeliacusI: truncus celiacus flow index; MBF JM: microcirculatory blood flow in the muscularis of the jejunum.

Microcirculatory blood flow was set at 100% at t = 0 min. t=0 baseline values before start of the respective fluid therapy.

At t = 30 min effects of one fluid bolus, 250 ml lactated Ringer's solution in group GD-LR or hydroxyethyl starch GD-C are presented. At t = 240 min effects after additional 1794 ± 211 ml of lactated Ringer's solution in group GD-LR and additional 831 ± 267 ml of hydroxyethyl starch (130/0.4) in group GD-C are presented.

Significant differences ($p < 0.05$) for Area under the curve (AUC): # R-RL vs. GD-RL, † R-RL vs. GD-C, $ GD-RL vs GD-C

Significant differences ($p < 0.05$) for ANOVA for repeated measurements (Tukey post-hoc test): * R-RL vs. GD-RL, ≠ R-RL vs. GD-C, § GD-RL vs GD-C.

Group R-RL received 3 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution throughout the entire experiment.

Group GD-RL received 3 ml $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution plus 250 ml lactated Ringer's solution if SvO_2 was < 60%.

Group GD-C received 3 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution plus 250 ml hydroxyethyl starch (130/0.4) if SvO_2 was < 60%.

Table 2 : Oxygen delivery, extraction and other variables

	sDO_2I #†	sER #†$	mDO_2I †	mesent Lac	art Hb †	art pH	art pO_2	art pCO_2	art BE
	($ml \cdot kg^{-1} \cdot min^{-1}$)	(%)	($mmHg \cdot kg^{-1} \cdot min^{-1}$)	($mmol \cdot l^{-1}$)	(g/l)		(mmHg)	(mmHg)	($mmol \cdot l^{-1}$)
Restricted Ringer's lactate solution (R-RL)									
0 min	109 ± 11	49 ± 5	25 ± 2	1.5 ± 0.4	101 ± 7	7.51 ± 0.02	138 ± 9	36 ± 2	5.4 ± 0.9
60 min	103 ± 11	48 ± 6	26 ± 2	1.4 ± 0.6	102 ± 6	7.51 ± 0.02	135 ± 10	36 ± 3	5.3 ± 1.2
180 min	97 ± 12	50 ± 6	21 ± 2	1.2 ± 0.3	105 ± 9	7.5 ± 0.02	134 ± 15	36 ± 2	4.5 ± 1.7
240 min	97 ± 12	50 ± 4	20 ± 1	1.3 ± 0.2	104 ± 6	7.49 ± 0.04	135 ± 12	37 ± 2	4.3 ± 2.0
Goal directed Ringer's lactate solution (GD-RL)									
0 min	109 ± 17	51 ± 4	26 ± 6	1.4 ± 0.2	100 ± 10	7.52 ± 0.05	132 ± 11	37 ± 3	6.3 ± 1.9
60 min	116 ± 19	50 ± 4	30 ± 8	1.2 ± 0.2	99 ± 10	7.52 ± 0.04	132 ± 10	36 ± 2	6.4 ± 2.0
180 min	134 ± 26	44 ± 4	27 ± 6	1.2 ± 0.3	96 ± 6	7.49 ± 0.037	127 ± 10	38 ± 2	5.6 ± 2.0
240 min	130 ± 18	42 ± 7	26 ± 7	1.2 ± 0.3	90 ± 8	49 ± 0.03	126 ± 9	38 ± 3	5.1 ± 2.1
Goal directed Colloid solution (GD-C)									
0 min	116 ± 18	50 ± 6	26 ± 6	1.4 ± 0.4	97 ± 12	7.52 ± 0.03	135 ± 12	37 ± 3	5.8 ± 1.2
60 min	141 ± 22$^{\$}$	38 ± 5$^{\$\dagger}$	35 ± 8	0.9 ± 0.2	86 ± 10	7.5 ± 0.02	132 ± 17	38 ± 3	5.7 ± 1.4
180 min	151 ± 33$^{\neq}$	38 ± 4$^{\S\neq}$	29 ± 6$^{\neq}$	0.8 ± 0.3	89 ± 11$^{\neq}$	7.49 ± 0.02	131 ± 14	38 ± 1	5.0 ± 1.3
240 min	158 ± 38$^{\neq}$	37 ± 5$^{\neq}$	27 ± 5$^{\neq}$	0.8 ± 0.3	87 ± 12$^{\neq}$	7.49 ± 0.02	128 ± 16	37 ± 1	4.6 ± 1.0

Data presented as mean ± SD.

sDO_2: systemic oxygen delivery index; sER: systemic oxygen extraction ratio; mDO_2I: mesenteric oxygen delivery; mesent Lac: mesenteric venous lactate; arterial Hb: arterial hemoglobin content; arterial pO_2: arterial oxygen tension; arterial pCO_2: arterial carbon dioxid tension; arterial BE: arterial standard base excess.

t=0 baseline values before start of the respective fluid therapy. The measurements were performed hourly for 4 hours.

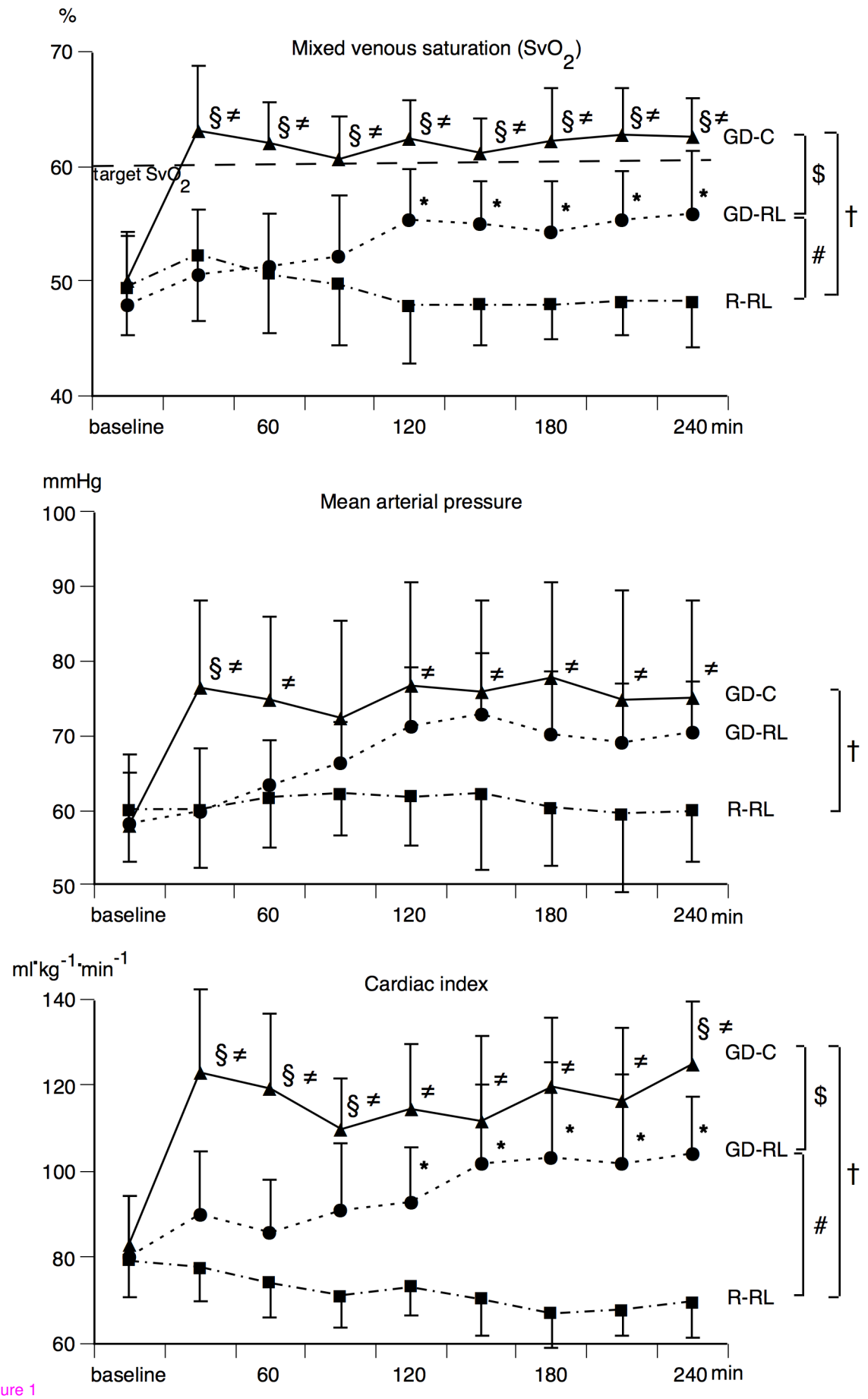
Significant differences ($p < 0.05$) for Area under the curve (AUC): # R-RL vs. GD-RL, † R-RL vs. GD-C, $ GD-RL vs GD-C

Significant differences ($p < 0.05$) for ANOVA for repeated measurements (Tukey post-hoc test): * R-RL vs. GD-RL, ≠ R-RL vs. GD-C, § GD-RL vs GD-C.

Group R-RL received 3 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution throughout the entire experiment.

Group GD-RL received 3 ml $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution plus 250 ml lactated Ringer's solution if SvO_2 was < 60%.

Group GD-C received 3 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution plus 250 ml hydroxyethyl starch (130/0.4) if SvO_2 was < 60%.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§ ≠
GD-C
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Mean arterial pressure
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Cardiac index
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120
100
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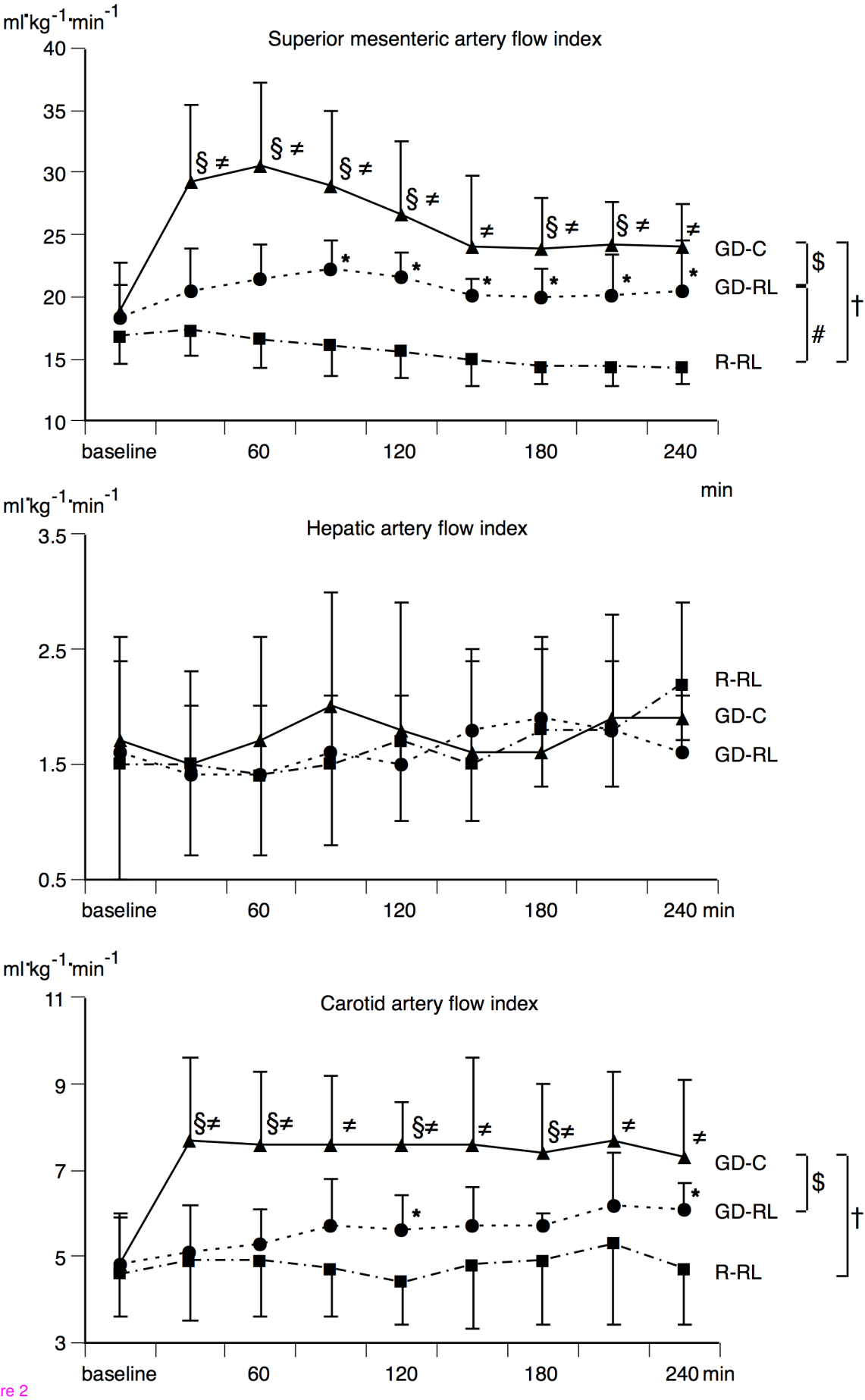
Figure 1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Hepatic artery flow index
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ml·kg-1·min-1
Carotid artery flow index
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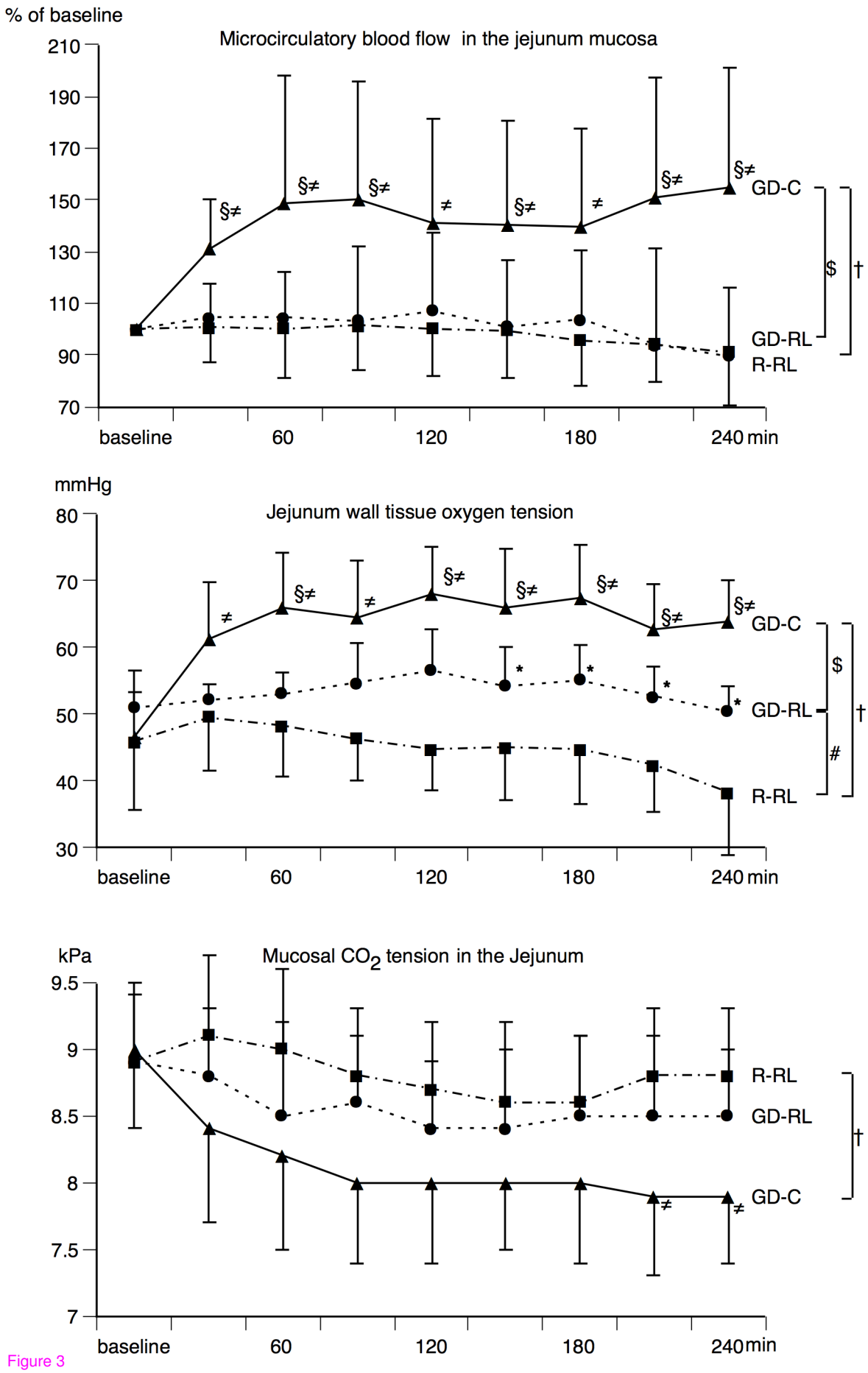
Figure 2


% of baseline
Microcirculatory blood flow in the jejunum mucosa
210
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Jejunum wall tissue oxygen tension
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Mucosal CO_2 tension in the Jejunum
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Figure 3

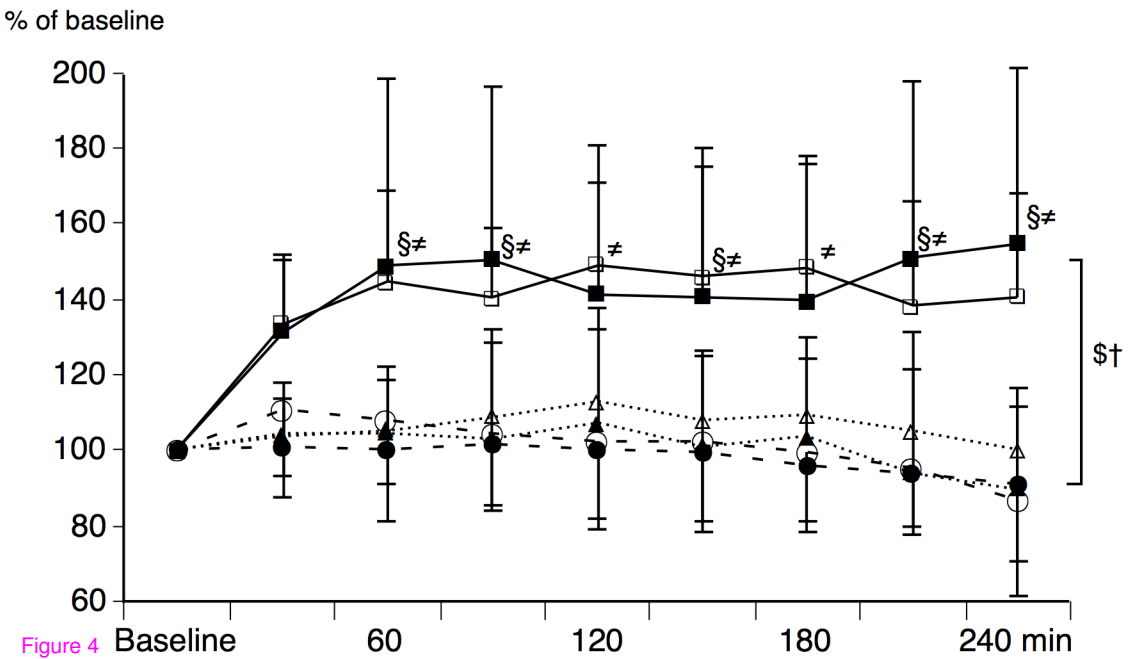
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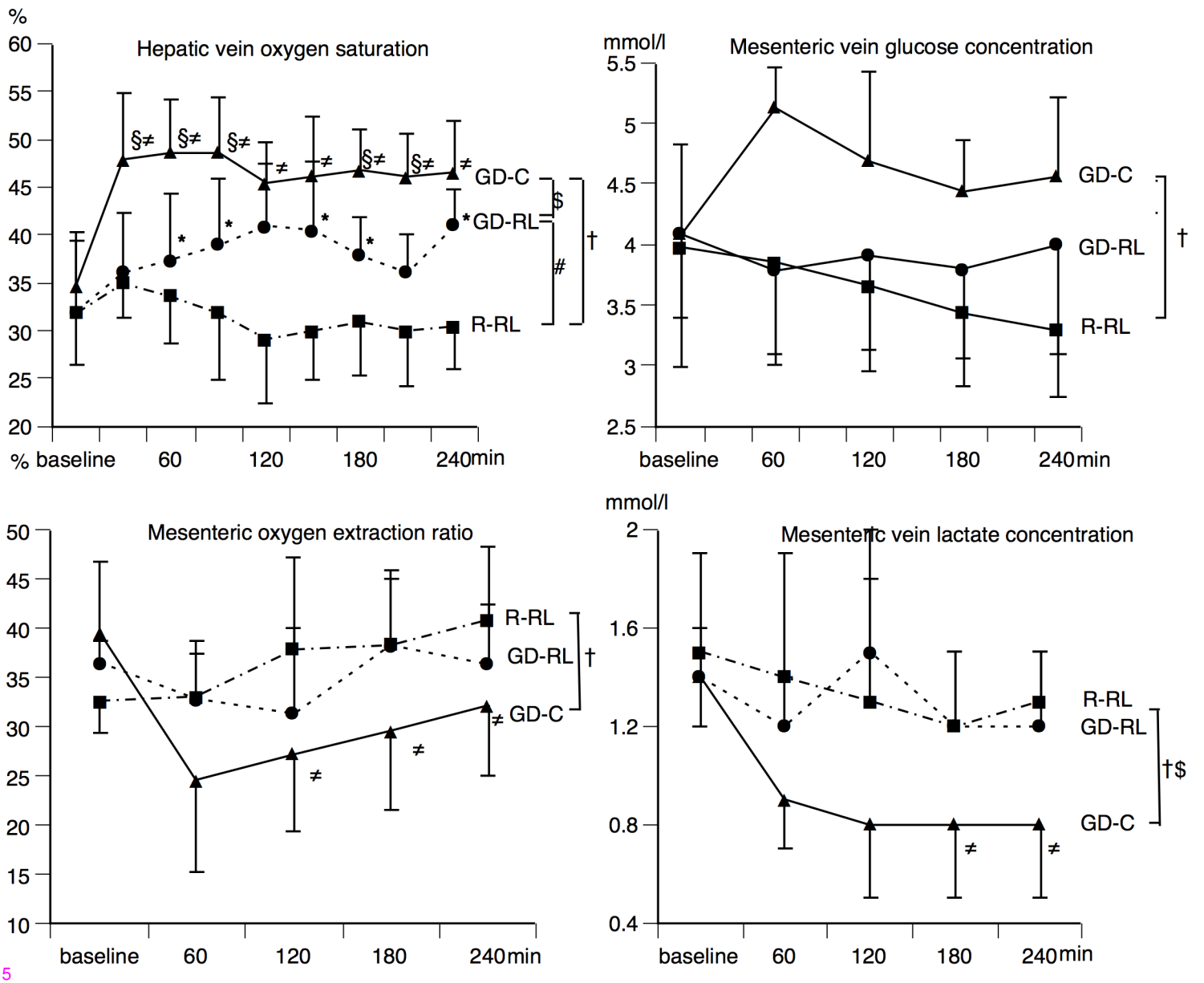
Figure 4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GD-RL
R-RL
$
#
†
% baseline
60
120
180
240min
mmol/l
Mesenteric vein glucose concentration
5.5
5
4.5
4
3.5
3
2.5
GD-C
GD-RL
R-RL
†
baseline
60
120
180
240min
Mesenteric oxygen extraction ratio
50
45
40
35
30
25
20
15
10
R-RL
GD-RL
GD-C
†
≠
≠
≠
baseline
60
120
180
240min
mmol/l
Mesenteric vein lactate concentration
2
1.6
1.2
0.8
0.4
R-RL
GD-RL
GD-C
†$
≠
≠
baseline
60
120
180
240min

Figure 5