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Volume Based Resuscitation and Intestinal Microcirculation after Ischaemia/Reperfusion Injury: Results of an Exploratory Aortic Clamping Study in Pigs

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WHAT THIS PAPER ADDS

The study provides further insight into the behaviour of intestinal microcirculatory blood flow after ischaemia/reperfusion injury. The results of the study emphasise that volume therapy should be titrated with meticulous care, particularly after ischaemia/reperfusion injury, and that unnecessary fluid load may impair microcirculatory flow and worsen tissue oedema. Effects on tissue oxygen supply, tissue viability, and patient outcome should be addressed in further studies.

Objectives: In the presence of ischaemia/reperfusion (I/R) induced endothelial injury, volume administration may not correlate with increased microcirculation. The aim of this study was to evaluate intestinal microcirculation after standardised sequential volume loading in an animal model of I/R injury following supracoeliac aortic clamping.

Methods: This was a prospective exploratory pilot animal study. Intestinal I/R injury was induced in eight pigs during experimental thoraco-abdominal aortic repair. After 6 h of I/R, microcirculatory blood flow (mFlux, measured in the ileum using direct laser speckle contrast imaging) and macrohaemodynamic parameters (using trans-cardiopulmonary thermodilution) were measured and measurements were repeated after each of four sequential volume loading steps (VLS1 − 4). Each load was administered over 5 min followed by another 5 min for equilibration.

Results: All animals survived until after VLS4. After 6 h of I/R cardiac output (CO) ($p < .001$) and mFlux ($p < .001$) had both decreased. CO increased again after VLS1 ($p < .001$) and VLS2 ($p = .036$), whereas mFlux did not change. In contrast, mFlux further decreased after VLS3 ($p < .01$) and VLS4 ($p < .001$), whereas CO did not change anymore. Extravascular lung water continued to increase after VLS2 ($p = .046$) and VLS4 ($p = .049$).

Conclusions: I/R leads to impaired intestinal microcirculation, which was not restored by volume administration in spite of improved CO. In contrast, further volume administration exceeding preload reserves was associated with additional decreases in the intestinal microcirculation. The potentially negative effect of excessive volume resuscitation after I/R injury should encourage further translational research.

Keywords: Aortic surgery, Haemodynamics, Ischaemia/reperfusion, Microcirculation, Volume management
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INTRODUCTION

Volume administration is a central element in the therapy of peri-operative and critically ill patients and is intended to maintain or re-establish an adequate macrocirculatory state. Nevertheless, several studies have shown that optimisation of the macrocirculation is not directly correlated with microcirculatory improvement and to some extent the microcirculation is uncoupled from macrohaemodynamic parameters.[1–3] However, as alternations in microcirculation lead to tissue oxygen deficits, multiple organ failure, and are associated with increased mortality,[4–7] it is crucial to know the effects of volume administration on microcirculatory blood flow.

Ischaemia/reperfusion (I/R) is often observed in peri-operative settings, such as aortic surgery, as well as thrombolytic therapy, organ transplantation, or cardiopulmonary

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bypass. I/R can also be found in intensive care and emergency patients undergoing resuscitation for shock and resuscitation therapy.[8] I/R induces the systemic inflammatory response syndrome, which accounts for 30—40% of intensive care mortality.[8] In spite of restoring perfusion and oxygenation, reperfusion can induce tissue damage and microcirculatory disturbances.[8—10] The small intestine is particularly sensitive to I/R induced damage. Intestinal ischaemia occurs in a number of scenarios seen in vascular or visceral surgery but also other medical fields and has a tremendous impact on patient outcome.[11—13] I/R induces impairment of microcirculatory blood flow caused by impaired endothelium dependent dilation of arterioles, increased vascular permeability and enhanced fluid extravasation caused by endothelial dysfunction, capillary occlusion caused by leucocyte plugging or interstitial oedema and consequently reduced numbers of perfused capillaries.[8,9,14] Therefore, in spite of the therapeutic approaches to optimise and restore macrocirculatory conditions during and after reperfusion, microcirculatory disturbances can persist, resulting in oxygen deficit and organ failure.

Although several studies have focused on microcirculatory impairment, measurements of intestinal microcirculation after volume administration under conditions of I/R have not been performed so far. Furthermore, there is a lack of studies using combined measurement of macrocirculation and microcirculation during volume administration in I/R conditions.

Using laser speckle contrast imaging (LSCI) for direct assessment of intestinal microcirculatory blood flow,[15,16] the aim of this study was to assess intestinal microcirculatory blood flow as well as macrohaemodynamic parameters after volume administration in an animal model of aortic surgery induced I/R.

MATERIALS AND METHODS

Ethics

The study was approved by the Governmental Commission on the Care and Use of Animals of the City of Hamburg (Reference-No. 101/15). The animals received care in compliance with the 'Guide for the Care and Use of Laboratory Animals' (NIH publication No. 86—23, revised 1996) and the study was carried out according to the ARRIVE guidelines.[17]

Study design

The study was conducted as a prospective exploratory pilot study in eight anaesthetised domestic pigs (German landrace). This study was performed in combination with a feasibility study for a new hybrid graft implantation in accordance with FELASA guidelines reducing animal number. Ischaemia/reperfusion was induced during aortic hybrid graft implantation. Microcirculation and macrocirculation were measured before (Before I/R) and 6 h after aortic hybrid graft implantation (After I/R). Thereafter four consecutive volume loading steps were performed followed by microcirculatory and macrocirculatory measurements, respectively (VLS1 — 4). No catecholamines were administered during the measurements. During graft implantation and over the 6 h period of observation, haemodynamic management was performed using a standardised algorithm. In detail, crystalloid (Sterofundin ISO 1/1 E, B. Braun, Melsungen, Germany) and colloidal (Voluven 6%, Fresenius Kabi, Bad Homburg, Germany) solutions were administered in the proportion of 2:1, and norepinephrine additionally administered for maintaining MAP above 60 mmHg. After 6 h catecholamine therapy was slowly reduced and terminated. Each volume loading step consisted of 6 mL kg^{-1} $bodyweight^{-1}$ colloids (Voluven 6%, Fresenius Kabi, Bad Homburg, Germany) and was performed over a time period of 5 min using pressurised infusions. After completion of each volume loading step, 5 min were allowed for equilibration.

Assessment of microcirculation

Microcirculatory blood flow was assessed directly using Laser Speckle Contrast Imaging (LSCI) (moorFLPI-2, moor instruments, Axminster, UK). LSCI has been used for measurements of microcirculatory blood flow in different organs and tissues including the ileum in various studies.[15,16,18—21] This method is based on the laser Doppler method, but has a much higher spatial and temporal resolution and allows for imaging of large surface areas contact free in real time.[18] LSCI uses full field laser measurements for estimation of tissue perfusion and detects mean microcirculatory blood flow (mFlux) up to a tissue depth of 3 mm. It is contact free, non-invasive and has good reproducibility.[22] To minimise measurement disturbances from organ movement,[18] the respiratory rate was held stable and a measurement period of several breathing cycles was used to reduce measurement variability.[23] The speckle laser was positioned 25 cm above the intestinal segment using a target laser. For each measurement step microcirculatory blood flow was assessed for a 30 s period. A blinded investigator defined the region of interest off line and calculated the mean Flux for the region of interest using dedicated software (moor FLPI-2 Review Software, v. 4.0, moor instruments, Axminster, UK).

Assessment of macrocirculatory conditions

Macrohaemodynamic measurements were performed following microcirculatory assessment. Trans-cardiopulmonary thermodilution providing cardiac output (CO), stroke volume (SV), global end diastolic volume (GEDV), and extravascular lung water (EVLW) were recorded and analysed using the PiCCO2 monitoring system (PiCCO2, Science edition, version 6.0, Pulsion, Munich, Germany). Thermodilution was performed using three consecutive injections of 15 mL cold saline at each measurement step. Thermodilution derived data were automatically calculated. Intrathoracic blood volume (ITBV) for calculation of EVLW was calculated with a correction factor for pigs using the following formula: $ITBV = a \times GEDV + b$, using $a = 1.10$ and $b = 99$ according to Nirmalan et al.[24]

Anaesthesia and surgical procedures

A detailed prescription of anaesthesia and surgical procedures is given in the online supplementary material. Experiments were performed in anaesthetised and mechanically ventilated animals. Surgical preparation was carried out according to standardised preparation techniques. A 15–20 cm segment of the terminal ileum was defined for measurement of intestinal microcirculatory blood flow. Aortic hybrid graft implantation was performed using a hybrid graft device with re-implantation of the coeliac trunk (TC), the superior mesenteric artery (SMA), and both renal arteries (LRA, RRA). Iliac arteries (right iliac artery [RIA] and left iliac artery [LIA]) were anastomosed to the graft device. Times of ischaemia for TC, SMA, RRA, LRA, RIA, and LIA are included in the online supplementary material. Problem free reperfusion was assessed by transit time flow measurements using a 6 mm flow measurement probe (Cardiomed, Medistim AS, Oslo, Norway). Flow measurements are included in the online supplementary material.

Euthanasia

After completion of the study protocol all animals were sacrificed during deep anaesthesia by fast injection of 40 mmol potassium chloride.

Statistical analysis

The dependent variables CO, SV, HR, mean arterial pressure (MAP), GEDV, EVLW, and mFlux were subjected to generalised linear mixed model analyses, using the SPSS v. 24 routine GENLINMIXED for continuous data with an identity link function. Models were specified assuming a fixed effect for measurement point and random intercepts for animals. Measurement points were considered as repeated measures within animals. For some dependent variables, these models did not converge or render a Hesse matrix that was not definitely positive. For such variables, either the random intercept term was omitted (dependent variable MAP) or the repeated measures specification (dependent variable EVLW). Marginal means with 95% CI were computed for all dependent variables at all measurement points, followed by pairwise comparisons of measurement point means by linear contrasts. As this was an exploratory pilot study, adjustments for multiple testing were not done. Statistical analyses were performed using the SPSS statistical software package, version 25 (IBM SPSS Statistics Inc., USA). Variables are expressed as mean (95% CI). Valid values of parameters for each measurement step are given in square brackets. Two tailed p values less than .05 were considered statistically significant. Additional data that may serve as inputs for future sample size calculations are included in the online supplementary material.

RESULTS

Study population

Eight animals were studied. Mean body weight was 78.13 kg (75.92–80.33). All animals survived until completion of VLS4.

Macrohaemodynamic parameters

Macrohaemodynamic parameters are shown in Table 1. A decrease in CO ($p < .001$), SV ($p < .001$), and MAP ($p < .001$) occurred 6 h after I/R. There was an increase in CO ($p < .001$), SV ($p < .01$), and MAP ($p < .001$) after VLS1. CO also increased after VLS2 ($p = .036$). GEDV decreased after I/R ($p < .01$) and increased after VLS2 ($p < .01$) and

Table 1. Macrohaemodynamic parameters throughout the protocol.

Hemodynamic parameter	Before I/R (CI 95%) valid values [n]	After I/R (CI 95%) valid values [n]	VLS1 (CI 95%) valid values [n]	VLS2 (CI 95%) valid values [n]	VLS3 (CI 95%) valid values [n]	VLS4 (CI 95%) valid values [n]
Cardiac output (l/min)	6.71 (5.27– 8.15) [8]	3.88^{z} (2.72–5.04) [8]	5.54^{z} (4.56–6.52) [8]	6.36* (5.29–7.42) [8]	6.51 (4.88–8.15) [8]	6.63 (4.68–8.58) [7]
Stroke volume (ml)	103.3 (88.82–117.85) [8]	42.03^{z} (27.52–56.55) [8]	68.10^{y} (53.59–82.62) [8]	81.66 (67.14–96.17) [8]	88.19 (73.67–102.70) [8]	90.93 (75.46–106.39) [7]
Heart rate (bpm)	66.65 (42.87–90.42) [8]	97.55* (74.65–120.46) [8]	83.32 (68.00–98.64) [8]	79.53 (63.83–95.22) [8]	73.66 (58.97–88.35) [8]	70.72 (56.12–85.32) [7]
Mean arterial pressure (mmHg)	76.56 (65.27–87.84) [8]	31.36^{z} (29.12–33.60) [8]	40.27^{z} (36.19–44.35) [8]	43.83 (38.65–49.01) [8]	43.95 (35.99–51.91) [8]	41.74 (33.16–50.31) [7]
Global end-diastolic volume (ml)	583.52 (493.79–673.26) [8]	487.43^{y} (407.00–567.86) [8]	515.55 (443.21–587.88) [8]	557.55^{y} (485.27–629.83) [8]	614.91^{z} (542.22–687.60) [8]	616.39 (536.52–696.26) [7]
Extravascular lung water (ml)	303.49 (254.07–352.90) [8]	335.96 (286.54–385.37) [8]	332.73 (283.32–382.14) [8]	368.82* (319.40–418.23) [8]	391.70 (342.28–441.11) [8]	428.73* (378.25–479.20) [7]

Data are presented as mixed model-estimated marginal means with 95% confidence intervals (CI). Valid values [n] included are shown in square brackets. Points of measurements are: Before I/R, 6h after I/R, at volume loading steps 1–4 during 6h after I/R (VLS1-4). *, $^{y, z}$ = statistically different from previous point of measurement at $p<0.05$, 0.01 and 0.001. I/R = ischemia reperfusion. BPM = beats per minute.

Table 2. Intestinal microcirculatory blood flow throughout the protocol.

Hemodynamic parameter	Before I/R (CI 95%) valid values [n]	After I/R (CI 95%) valid values [n]	VLS1 (CI 95%) valid values [n]	VLS2 (CI 95%) valid values [n]	VLS3 (CI 95%) valid values [n]	VLS4 (CI 95%) valid values [n]
Mean intestinal microcirculatory	726.46 (552.38–900.54) [8]	413.88[z] (287.61–540.14) [8]	434.84 (306.91–562.77) [8]	422.78 (306.69–538.87) [7]	371.40[y] (259.36–483.44) [8]	325.50[z] (211.45–439.56) [7]

Data are presented as mixed model-estimated marginal means with 95% confidence intervals (CI). Valid values [n] included are shown in square brackets. Points of measurements are: Before I/R, 6h after I/R, at volume loading steps 1–4 during 6h after I/R (VLS1-4). [y, z] = statistically different from previous point of measurement at 0.01 and 0.001. I/R = ischemia reperfusion.

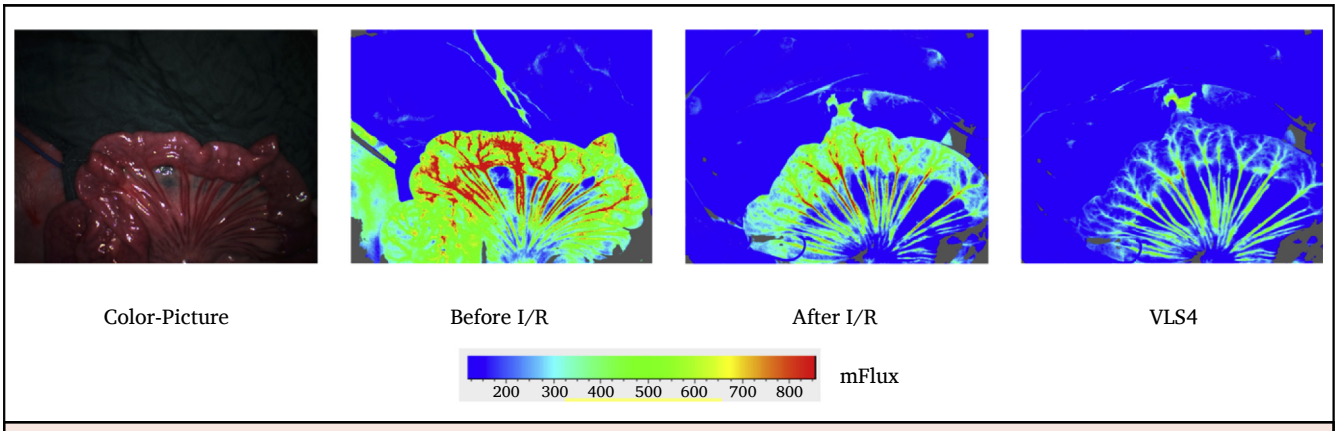

Figure 1. Example for visualisation of intestinal microcirculatory blood flow. Color Picture = Color picture of ileum segment at baseline. mFlux = mean microcirculatory blood flow of ilieal loop. Before I/R = Color coded mFlux prior to induction of I/R. After I/R = Color coded mFlux 6 h after I/R. VLS4 = Color coded mFlux after volume loading step 4. I/R = ischemia reperfusion.

VLS3 ($p < .001$). There was an increase of EVLW after VLS2 ($p = .046$) and VLS4 ($p = .049$).

Intestinal microcirculation

Mean microcirculatory blood flux is shown in Table 2. Color coded example pictures of mFlux are shown in Fig. 1. There was a reduction of mean intestinal flux (mFlux) 6 h after I/R ($p < .001$). There were no significant changes in mFlux after VLS1 and 2. There were reductions of mFlux after VLS3 ($p < .01$) and VLS4 ($p < .001$).

Comparison of macrohaemodynamic parameters and intestinal microcirculation

Simultaneous examination of macrohaemodynamic parameters and intestinal microcirculation during volume administration shows dissociation between micro- and macrocirculatory blood flow. The percentage differences compared with baseline values before I/R for CO and mFlux are shown in Fig. 2. While CO improved towards baseline values, baseline mFlux values could not be restored. Instead mFlux remained reduced and was further reduced after VLS3 and 4.

DISCUSSION

This study presents first data on intestinal microcirculatory blood flow after volume administration in an animal model of I/R during thoraco-abdominal aortic repair. Impairment of the intestinal microcirculation occurred after I/R injury. Despite macrocirculatory improvement resulting from initial volume administration, the microcirculation could not be fully restored to baseline conditions. Instead, the intestinal microcirculation was impaired and aggravated during volume administration while CO was stable. This was accompanied by an increase in extravascular lung water indicating volume overload. This emphasises the potential risk associated with volume administration after I/R on intestinal microcirculation despite macrocirculatory improvement.

Volume administration remains an integral part of most resuscitation protocols for peri-operative and critically ill patients to improve macrohaemodynamic parameters. This is reflected by the fact that most studies investigating the effect of volume administration have focused on assessment of macrohaemodynamic changes. Monitoring of microcirculation remains experimental and therefore therapeutic approaches are not included in actual guidelines. Only a handful of studies have also investigated the changes in microcirculatory blood flow during volume administration. Deterioration of the microcirculation leads to oxygen deficits, multiple organ failure, and is associated with increased mortality.[4–7] Therefore, therapeutic interventions to improve the microcirculation appear promising. Typically, microcirculatory disturbances are accompanied by interstitial fluid oedema, endothelial dysfunction, and capillary occlusion.[8–10,14] Thus, especially therapeutic interventions based on volume administration do have the risk of further

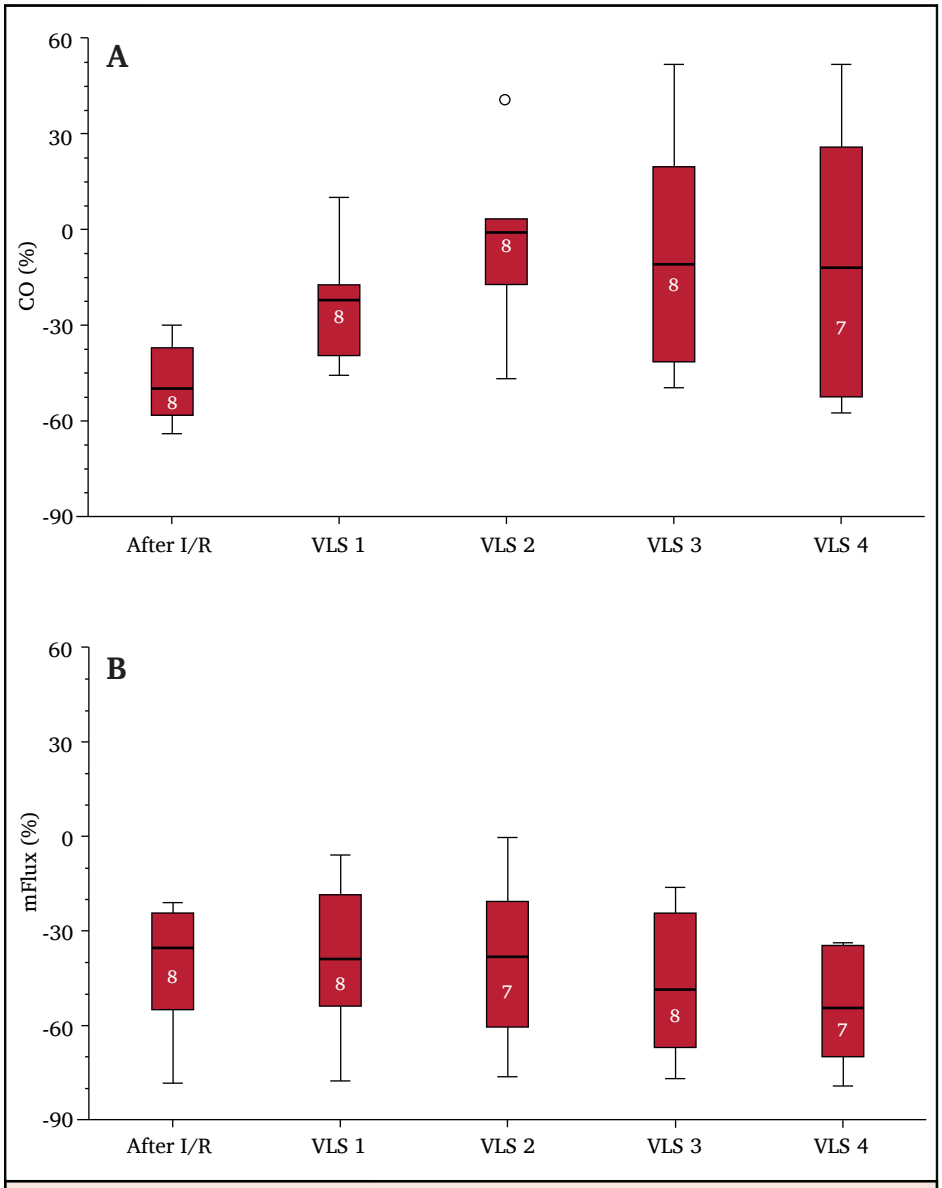

Figure 2. Percentage changes of cardiac output and mean intestinal microcirculatory blood flow compared with baseline value before I/R. Percentage changes were calculated for each animal. Boxes represent values between 25th and 75th percentiles, whiskers the upper and lower values adjacent within a 1.5 box length distance, and the horizontal lines represent the median values. Outliers are displayed as circles. Number of valid values is given inside the boxes. After I/R = 6 h after I/R, VLS 1−4 = volume loading steps 1−4 6 h after I/R. CO = cardiac output, mFlux = mean intestinal microcirculatory blood flow. I/R = ischemia reperfusion.

impeding microcirculatory blood flow caused by volume overload, even if macrohaemodynamic optimisation occurs.

Using LSCI for microcirculatory blood flow evaluation of the terminal ileum together with macrohaemodynamic measurements, impairment of intestinal microcirculation was observed accompanied by a decline in MAP, SV, and CO 6 h after I/R. This microcirculatory behavior is in line with the results of Siegemund et al.,[25] who showed a reduction of serosal microcirculatory oxygenation and perfused ileal capillaries 3 h after I/R and has been reported for other organs as well.[18,26]

Simultaneous examination of macrohaemodynamic parameters and intestinal microcirculation during volume administration shows dissociation between micro- and macrocirculatory blood flow. While initial volume administration improved CO as well as SV and MAP, there was no significant improvement of mean intestinal microcirculatory blood flow. This is in line with several studies showing an uncoupling of macrohaemodynamic parameters from the microcirculation and emphasises the impact of direct microcirculatory evaluation.[3,27,28] Thus, in a comparable clinical setting, even when using advanced macrohaemodynamic monitoring, the microcirculatory response to volume administration is most likely to be unpredictable. Moreover, further volume administration without further macrohaemodynamic improvement promptly resulted in a

decline of intestinal microcirculation. While saturation of the volume effect has already been described,[2,29] deleterious effects of volume overload on intestinal microcirculation have so far not been reported. The decrease of microcirculatory perfusion, being accompanied by an absence of further improvement of CO, SV, or MAP in response to volume, highlights the differential response of macro- and microcirculation to the volume challenge. Regarding CO and SV, this indicates that cardiac preload reserve was already fully used and volume administration does not further increase CO. At this point, further volume administration is potentially harmful as it can result in volume overload. While a strictly goal directed volume therapy is widely used for resuscitation of septic patients,[30,31] the amount of fluid given in the peri-operative period is often highly variable.[32] As it is known that volume overload will result in worsening of outcome,[33,34] a recently proposed approach to peri-operative fluid therapy was based on the idea of goal directed fluid restriction.[35] This approach led to improved outcome and with regard to the present findings. Possible benefits for intestinal microcirculation after I/R using restrictive fluid strategies should be investigated in future studies.

Global end diastolic volume (GEDV) is a volumetric parameter of preload and represents the end diastolic volume of all heart chambers.[36] It decreased after I/R indicating a reduction in preload. During volume loading, GEDV was increased compared with the baseline value before I/R. This suggests a potential for using GEDV as a tool to guide volume therapy following I/R.

A rise in extravascular lung water (EVLW) during volume load was also indicative of volume overload and formation of tissue oedema. Although the association between EVLW and volume overload has been demonstrated in several previous studies,[37] the relationship between ELVW and microcirculation is not well known. In this study increases of EVLW were observed in parallel with reductions of mean intestinal microcirculatory blood flow. Although tissue oedema in the ileum was not directly assessed, EVLW may prove to be a suitable safety parameter for preventing microcirculatory impairments during peri-operative care.

This study has certain limitations. As it was an exploratory pilot study for generating hypotheses rather than confirmatory testing pre specified hypotheses, alpha error adjustment for multiple testing was not done. Moreover, sensible a priori input data to be used for sample size and power calculations were not available, hence, a sample size was chosen that appeared feasible with respect to the size of the study protocol and in accordance with FELASA guidelines reducing animal numbers to a reasonable sample size while being able to address the scientific topic properly. However, the data gathered in this study may serve as inputs for future sample size calculations. In addition, experiments were not performed in control animals without I/R or volume administration. While the surgical preparations were standardised, the time intervals for ischaemia of the different vessels were not standardised and were dependent on the duration of surgical preparation for vessel anastomoses. However, as I/R is known to be a severe systemic syndrome,[25,38] the sum of ischaemic events and reperfusion in the present model should be feasible for studying the effects of volume administration on intestinal microcirculatory blood flow in I/R conditions. Times of ischaemia for different vessels are included in online supplementary material. Nevertheless, randomised controlled animal trials as well as human trials are needed to confirm these results before changing clinical practice for volume therapy in ischaemia/reperfusion. In addition, organ function was not measured, for example intestinal barrier function, and further outcome measures were not evaluated, nor was histological analysis of tissue viability performed. Moreover, mFlux is an arbitrary unit and the clinical relevance of reductions of absolute values therefore cannot be predicted. Therefore, it is not possible to connect microcirculatory reductions to changes in either tissue viability or organ function, nor to present data on the formation of intestinal tissue oedema caused by volume administration. However, the clinical impact of microcirculatory impairment in vital organs has been demonstrated in the literature. Edul et al. reported that while alterations of sublingual microcirculation revealed no differences between non-survivors and survivors, changes in intestinal microcirculation had a distinct impact on clinical outcome.[39] The fact that microcirculation of the intestine, as assessed in the present study, has a relevant impact on outcome after I/R has been shown in several studies.[8,9,13,40] Nevertheless, the clinical relevance of the microcirculatory decline could not be determined in the present study setting and should be assessed in future studies. Another limitation is that this study was conducted in young healthy pigs without comorbidities, which would not be the case in a clinical setting in which comorbid diseases may exist and might affect microcirculatory behavior following I/R.[8–10] Nonetheless, the present animal model has the advantage of enabling clinical standardisation and direct assessment of microcirculation in an organ of interest using laser speckle contrast imaging (LSCI) rather than sublingual microcirculation.

CONCLUSION

I/R injury as occurs during aortic repair leads to impairment of intestinal microcirculation. Despite initial macrocirculatory improvement from volume administration, intestinal microcirculatory blood flow was not restored with volume administration after I/R injury. Instead, it was observed that the intestinal microcirculation was reduced during advanced volume administration. This was accompanied by an increase in extravascular lung water indicating a volume overload. The results of this exploratory pilot study on intestinal microcirculatory blood flow after I/R suggest the potential risk of volume administration after I/R on intestinal microcirculation and should encourage further research on this topic.

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CONFLICTS OF INTEREST

Constantin J.C. Trepte has received honorarium for lectures by Maquet. All other authors declare no conflicts of interest.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2018.08.055.

REFERENCES

1 Ospina-Tascon G, Neves AP, Occhipinti G, Donadello K, Büchele G, Simion D, et al. Effects of fluids on microvascular perfusion in patients with severe sepsis. *Intensive Care Med* 2010;**36**:949–55.
2 Pottecher J, Deruddre S, Teboul JL, Georger JF, Laplace C, Benhamou D, et al. Both passive leg raising and intravascular volume expansion improve sublingual microcirculatory perfusion in severe sepsis and septic shock patients. *Intensive Care Med* 2010;**36**:1867–74.
3 De Backer D, Ortiz JA, Salgado D. Coupling microcirculation to systemic hemodynamics. *Curr Opin Crit Care* 2010;**16**:250–4.
4 De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med* 2002;**166**:98–104.
5 De Backer D, Creteur J, Dubois MJ, Sakr Y, Vincent JL. Microvascular alterations in patients with acute severe heart failure and cardiogenic shock. *Am Heart J* 2004;**147**:91–9.
6 Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Crit Care Med* 2004;**32**:1825–31.
7 Trzeciak S, Dellinger RP, Parrillo JE, Guglielmi M, Bajaj J, Abate NL, et al. Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: relationship to hemodynamics, oxygen transport, and survival. *Ann Emerg Med* 2007;**49**:e1–2.
8 Granger DN. Ischemia-reperfusion: mechanisms of microvascular dysfunction and the influence of risk factors for cardiovascular disease. *Microcirculation* 1999;**6**:167–78.
9 Carden DL, Granger DN. Pathophysiology of ischaemia-reperfusion injury. *J Pathol* 2000;**190**:255–66.
10 Granger DN, Stokes KY, Shigematsu T, Cerwinka WH, Tailor A, Krieglstein CF. Splanchnic ischaemia-reperfusion injury: mechanistic insights provided by mutant mice. *Acta Physiol Scand* 2001;**173**:83–91.
11 Di Eusanio M, Trimarchi S, Patel HJ, Hutchison S, Suzuki T, Peterson MD, et al. Clinical presentation, management, and short-term outcome of patients with type A acute dissection complicated by mesenteric malperfusion: observations from the International Registry of Acute Aortic Dissection. *J Thorac Cardiovasc Surg* 2013;**145**:385–90.
12 Jarvinen O, Laurikka J, Sisto T, Tarkka MR. Intestinal ischemia following surgery for aorto-iliac disease. A review of 502 consecutive aortic reconstructions. *Vasa* 1996;**25**:148–55.
13 Haglund U, Bergqvist D. Intestinal ischemia – the basics. *Langenbecks Arch Surg* 1999;**384**:233–8.
14 Kurose I, Argenbright LW, Anderson DC, Tolley J, Miyasaka M, Harris N, et al. Reperfusion-induced leukocyte adhesion and vascular protein leakage in normal and hypercholesterolemic rats. *Am J Physiol* 1997;**273**:H854–60.
15 Wu Y, Ren J, Zhou B, Ding C, Chen J, Wang G, et al. Laser speckle contrast imaging for measurement of hepatic microcirculation during the sepsis: a novel tool for early detection of microcirculation dysfunction. *Microvasc Res* 2015;**97**:137–46.
16 Ding C, Ren J, Zhou B, Wu Y, Shao X, Wang G, et al. Laser speckle contrast imaging for assessment of abdominal visceral microcirculation in acute peritonitis: does sequential impairments exist? *Microvasc Res* 2014;**95**:26–30.
17 Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. *Osteoarthritis Cartilage* 2012;**20**:256–60.
18 Li CH, Wang HD, Hu JJ, Ge XL, Pan K, Zhang AQ, et al. The monitoring of microvascular liver blood flow changes during ischemia and reperfusion using laser speckle contrast imaging. *Microvasc Res* 2014;**94**:28–35.
19 Yeh YC, Wu CY, Cheng YJ, Liu CM, Hsiao JK, Chan WS, et al. Effects of dexmedetomidine on intestinal microcirculation and intestinal epithelial barrier in endotoxemic rats. *Anesthesiology* 2016;**125**:355–67.
20 Eriksson S, Nilsson J, Lindell G, Sturesson C. Laser speckle contrast imaging for intraoperative assessment of liver microcirculation: a clinical pilot study. *Med Devices (auckl)* 2014;**7**:257–61.
21 Yeh YC, Wang MJ, Lin CP, Fan SZ, Tsai JC, Sun WZ. Ko WJ Enoxaparin sodium prevents intestinal microcirculatory dysfunction in endotoxemic rats. *Crit Care* 2012;**16**:R59.
22 Eriksson S, Nilsson J, Sturesson C. Non-invasive imaging of microcirculation: a technology review. *Med Devices (auckl)* 2014;**7**:445–52.
23 Rousseau P, Mahe G, Haj-Yassin F, Durand S, Humeau A, Leftheriotis G, et al. Increasing the "region of interest" and "time of interest", both reduce the variability of blood flow measurements using laser speckle contrast imaging. *Microvasc Res* 2011;**82**:88–91.
24 Nirmalan M, Niranjan M, Willard T, Edwards JD, Little RA, Dark PM. Estimation of errors in determining intrathoracic blood volume using thermal dilution in pigs with acute lung injury and haemorrhage. *Br J Anaesth* 2004;**93**:546–51.
25 Siegemund M, van Bommel J, Stegenga ME, Studer W, van Iterson M, Annaheim S, et al. Aortic cross-clamping and reperfusion in pigs reduces microvascular oxygenation by altered systemic and regional blood flow distribution. *Anesth Analg* 2010;**111**:345–53.
26 Sturesson C, Milstein DM, Post IC, Maas AM, van Gulik TM. Laser speckle contrast imaging for assessment of liver microcirculation. *Microvasc Res* 2013;**87**:34–40.
27 Saugel B, Trepte CJ, Heckel K, Wagner JY, Reuter DA. Hemodynamic management of septic shock: is it time for "individualized goal-directed hemodynamic therapy" and for specifically targeting the microcirculation? *Shock* 2015;**43**:522–9.
28 Ince C. Hemodynamic coherence and the rationale for monitoring the microcirculation. *Crit Care* 2015;**19**:S8.
29 De Backer D, Orbegozo Cortes D, Donadello K, Vincent JL. Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. *Virulence* 2014;**5**:73–9.
30 Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;**345**:1368–77.

31 Osborn TM. Severe sepsis and septic shock trials (ProCESS, ARISE, ProMISe): what is optimal resuscitation? *Crit Care Clin* 2017;**33**: 323–44.
32 Lilot M, Ehrenfeld JM, Lee C, Harrington B, Cannesson M, Rinehart J. Variability in practice and factors predictive of total crystalloid administration during abdominal surgery: retrospective two-centre analysis. *Br J Anaesth* 2015;**114**:767–76.
33 Shin CH, Long DR, McLean D, Grabitz SD, Ladha K, Timm FP, et al. Effects of intraoperative fluid management on postoperative outcomes: a hospital registry study. *Ann Surg* 2018; **267**:1084–92.
34 Thacker JK, Mountford WK, Ernst FR, Krukas MR, Mythen MM. Perioperative fluid utilization variability and association with outcomes: considerations for enhanced recovery efforts in sample US surgical populations. *Ann Surg* 2016;**263**:502–10.
35 Luo J, Xue J, Liu J, Liu B, Liu L, Chen G. Goal-directed fluid restriction during brain surgery: a prospective randomized controlled trial. *Ann Intensive Care* 2017;**7**:16.
36 Pinsky MR. Functional hemodynamic monitoring. *Crit Care Clin* 2015;**31**:89–111.
37 Jozwiak M, Teboul JL, Monnet X. Extravascular lung water in critical care: recent advances and clinical applications. *Ann Intensive Care* 2015;**5**:38.
38 Stallion A, Kou TD, Latifi SQ, Miller KA, Dahms BB, Dudgeon DL, et al. Ischemia/reperfusion: a clinically relevant model of intestinal injury yielding systemic inflammation. *J Pediatr Surg* 2005;**40**:470–7.
39 Edul VS, Ince C, Navarro N, Previgliano L, Risso-Vazquez A, Rubatto PN, et al. Dissociation between sublingual and gut microcirculation in the response to a fluid challenge in postoperative patients with abdominal sepsis. *Ann Intensive Care* 2014;**4**:39.
40 Haglund U. The splanchnic organs as the source of toxic mediators in shock. *Prog Clin Biol Res* 1988;**264**:135–45.