

## Comparison of lactated Ringer's, gelatine and blood resuscitation on intestinal oxygen supply and mucosal tissue oxygen tension in haemorrhagic shock

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**Objectives.** To evaluate the effects on intestinal oxygen supply, and mucosal tissue oxygen tension during haemorrhage and after fluid resuscitation with either blood (B; n=7), gelatine (G; n=8), or lactated Ringer's solution (R; n=8) in an autoperfused, innervated jejunal segment in anaesthetized pigs.

**Methods.** To induce haemorrhagic shock, 50% of calculated blood volume was withdrawn. Systemic haemodynamics, mesenteric venous and systemic acid–base and blood gas variables, and lactate measurements were recorded. A flowmeter was used for measuring mesenteric arterial blood flow. Mucosal tissue oxygen tension (PO<sub>2</sub>muc), jejunal microvascular haemoglobin oxygen saturation (HbO<sub>2</sub>) and microvascular blood flow were measured. Measurements were performed at baseline, after haemorrhage and at four 20 min intervals after fluid resuscitation. After haemorrhage, animals were retransfused with blood, gelatine or lactated Ringer's solution until baseline pulmonary capillary wedge pressure was reached.

**Results.** After resuscitation, no significant differences in macrohaemodynamic parameters were observed between groups. Systemic and intestinal lactate concentration was significantly increased in animals receiving lactated Ringer's solution [5.6 (1.1) vs 3.3 (1.1) mmol litre<sup>-1</sup>; 5.6 (1.1) vs 3.3 (1.2) mmol litre<sup>-1</sup>]. Oxygen supply to the intestine was impaired in animals receiving lactated Ringer's solution when compared with animals receiving blood. Blood and gelatine resuscitation resulted in higher HbO<sub>2</sub> than with lactated Ringer's resuscitation after haemorrhagic shock [B, 43.8 (10.4)%; G, 34.6 (9.4)%; R, 28.0 (9.3)%]. PO<sub>2</sub>muc was better preserved with gelatine resuscitation when compared with lactated Ringer's or blood resuscitation [20.0 (8.8) vs 13.8 (7.1) mm Hg, 15.2 (7.2) mm Hg, respectively].

**Conclusion.** Blood or gelatine infusion improves mucosal tissue oxygenation of the porcine jejunum after severe haemorrhage when compared with lactated Ringer's solution.

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Haemorrhagic shock is characterized by a critical decrease in organ perfusion and a primary reduction in tissue oxygen supply. This leads to end-organ hypoxia, accumulation of toxic metabolites and severe disturbances in cell metabolism. Without treatment, haemorrhagic shock results in

microcirculatory failure, breakdown of cell function and, finally, in the syndrome of multiple organ dysfunction.<sup>1</sup>

The intestinal tract is assumed to play an important role in this pathophysiological process. Inadequate splanchnic blood flow and oxygen supply may cause damage to the

bowel wall. As a physiologic barrier against intestinal bacteria and bacterial fragments, the mucosal layer has been the focus of scientific interest. Mucosal hypoperfusion during haemorrhage resulting in hypoxia can thus impair the integrity of the mucosal shield and weaken its barrier function.<sup>2,3</sup> Subsequent activation of gut-associated lymphatic tissue and, to some degree, translocation of bacteria or endotoxin has been demonstrated to occur in mucosal hypoxia.<sup>4,5</sup>

Although volume resuscitation is one of the primary therapeutic goals in haemorrhagic shock, data on effects of different fluid resuscitation regimens on gastrointestinal haemodynamics or tissue oxygen supply are sparse, and results of studies are heterogeneous. Existing meta-analysis comparing the effects of crystalloids and colloids on patient outcome suggest some beneficial effects of crystalloid resuscitation on patient mortality.<sup>6,7</sup> On the other hand, data exist that microcirculatory function, and the degree of tissue oedema improve with colloidal-based volume replacement.<sup>8–10</sup>

The aim of this study was to investigate tissue oxygen supply of the pathophysiologically and clinically most important cells of the gastrointestinal tract, the intestinal mucosa, after resuscitation with different regimens. We hypothesized that there was no difference in jejunal tissue oxygen supply and, in particular, mucosal tissue oxygen tension, when resuscitating haemorrhagic pigs with either gelatine or lactated Ringer's solution.

## Materials and methods

### *Animal preparation*

This study experiment was approved by the Federal Ministry of Science and Research. Twenty-three domestic pigs (34–44 kg) were fasted for 12 h with free access to water. After induction of anaesthesia with ketamine hydrochloride (20 mg kg<sup>-1</sup> i.m.), the animals were intubated and mechanically ventilated with a positive end-expiratory pressure of 5 cm H<sub>2</sub>O. Tidal volume and respiratory frequency were chosen to maintain normoventilation at baseline; fractional inspiratory oxygen concentration was constantly set at 0.3 throughout the study period. Anaesthesia was maintained with a continuous infusion of midazolam (0.5 mg kg<sup>-1</sup> h<sup>-1</sup>) and fentanyl (10 µg kg<sup>-1</sup> h<sup>-1</sup>). Muscle relaxation was achieved by hourly bolus injections of vecuronium (0.15 mg kg<sup>-1</sup>).

All animals were infused with 10 ml kg<sup>-1</sup> h<sup>-1</sup> lactated Ringer's solution throughout the study period, independent of the type of fluid resuscitation. This amount of lactated Ringer's solution was not added to the final sum of fluid given. After preparation of the right carotid artery and the internal jugular vein, an arterial catheter and a 7.5-Fr pulmonary artery catheter (Baxter Healthcare, Irvine, CA, USA) were inserted. A 12-Fr large bore central venous

catheter (Arrows International Inc., Pennsylvania, USA) was inserted in the femoral vein to withdraw a specific blood volume from the animals, and to perform fluid resuscitation. A midline laparotomy was performed, and a 16-gauge catheter was placed in the superior mesenteric vein for intermittent blood sampling. The *A. mesenterica superior* was used to measure blood flow. To expose the mucosa for tissue oxygenation and laser-Doppler flow measurements, a 20 cm enterotomy opposite the mesenteric insertion was performed in the mid-jejunum. The edge of the enterotomized jejunum was sutured to the oval opening of a cork plate. The intestine was reintroduced into the abdominal cavity, with the exception of the exposed mucosa. The temperature of the preparation was maintained at 38°C by covering with a plastic box that included a temperature sensor and a servo-controlled heated water bath.

### *Measurement techniques*

Arterial, pulmonary arterial and central venous pressure were measured using three Statham P10EZ pressure transducers (Spectramed-Statham, Bithoven, The Netherlands). Cardiac output was determined by the thermodilution method. Heart rate, arterial pressure and core temperature were recorded continuously. Zero reference for all pressures was the mid-chest position. Arterial, central venous and mesenteric venous blood gases and acid–base status were analysed using an AVL 995 automatic blood gas analyser (AVL Biomedical Instruments, Graz, Austria). Haemoglobin oxygen saturation was measured with a haemoximeter (Cooximeter, AVL Biomedical Instruments, Graz, Austria). Haemoglobin concentration was assessed using the cyanomethaemoglobin method. Arterial and mesenteric venous lactate determinations were performed with a lactate analyser based on reflectance photometry (Accusport, Boehringer Mannheim, Mannheim, Germany). A Transonic Animal Research Flowmeter (Transonic, Ithaca, USA) was used for measuring mesenteric arterial blood flow. The measurement principle is based on the use of flowsensors, which are connected to the flow detection unit via a flexible cable. Two ultrasonic transducers within the flowsensor body transmit ultrasound through a rectangular sensing window, and sense volume flow passing through the window. The electronic flow detection unit automatically identifies the scaling factor and the individual calibration factor of the flowprobe connected to it.

### *Measurement of jejunal mucosal tissue oxygenation and microvascular blood flow*

The methodology for measuring mucosal tissue oxygen tension, microvascular haemoglobin oxygen saturation and jejunal microvascular blood flow has been described in detail in previous studies.<sup>11–13</sup> Briefly, mucosal oxygen tension (PO<sub>2</sub>muc) was measured by two Clark-type multi-wire surface electrodes (Eschweiler & Co., Kiel, Germany). These electrodes were calibrated using pure nitrogen and

room air in a water bath at 37°C. One electrode consisted of eight platinum wires, each of which had a diameter of 15 µm representing an individual measuring point and one Ag–AgCl reference electrode.

An Erlangen microlight guide spectrophotometer (EMPHO II, BGT, Überlingen, Germany) was used to determine jejunal microvascular haemoglobin saturation (HbO<sub>2</sub>). The measurement principle is based on the use of one illuminating and six detecting microlight guides (each 250 µm in diameter), and a rapidly rotating band-pass interference filter disk to generate monochromatic light in 2 nm steps within the spectral range of 502–628 nm representing 64 different wavelengths.

Jejunal microvascular blood flow was assessed by laser-Doppler velocimetry (Periflux 4001, Perimed, Järfälla, Sweden). Laser-Doppler measurements are based on the principle that light scattered by moving red blood cells experiences a frequency shift that is proportional to the velocity of red blood cells. The Periflux 4001 uses laser light with a wavelength of 770–790 nm. A fiberoptic guide-wire (PF407, Perimed) that conducts laser light to the tissue and carries back-scattered light to a photodetector was placed on the mucosal surface. Jejunal microvascular blood flow was recorded in relative perfusion units (PU). The probe was calibrated against a white surface (PU=0) and a standard latex solution [PU=250 (5)]. All sensors were kept in place by adhesion with small polyvinyl chloride caps, including the specific sensor surrounded by a transparent thin rubber patch, approximately 2 cm in diameter.

### Experimental protocol

Animals were randomized to a blood resuscitated group (B; *n*=7), a gelatine resuscitated group (G; *n*=8) and a lactated Ringer's solution resuscitated group (R; *n*=8). One animal in group G died immediately after initiation of haemorrhagic shock, and was therefore excluded from statistical analysis. After animal preparation and a 30 min resting period, we performed baseline measurements of systemic haemodynamics; arterial, mesenteric venous, and mixed venous blood gas analysis and haemoglobin oxygen saturation measurements; PO<sub>2</sub>muc; HbO<sub>2</sub>; and PU.

Total blood volume in the study animals was assumed as 70 ml kg<sup>-1</sup> body weight. After baseline measurements, 50% of the calculated blood volume was withdrawn via the femoral venous catheter. In group B animals, withdrawn blood was collected in citrate bags, which were placed on a cooled see-saw weighing machine, to avoid coagulation. Fluid resuscitation was started after systemic and regional measurements had been repeated 50 min after haemorrhage. Animals were retransfused with either gelatine (Gelofusine, B. Braun Melsungen AG, Melsungen, Germany. Gelofusine is prepared as a 4% solution of succinylated gelatine in saline; group G), lactated Ringer's solution (group R) or whole blood (group B) until baseline pulmonary capillary wedge pressures were reached. The fluid volume transfused

was recorded. After fluid resuscitation, systemic and regional measurements were repeated at 70, 90, 110 and 130 min after haemorrhage, without further intervention.

### Data analysis

Systemic and mesenteric oxygen delivery (DO<sub>2</sub>sys; DO<sub>2</sub>mes), oxygen consumption (VO<sub>2</sub>sys; VO<sub>2</sub>mes) and oxygen extraction ratio (ER<sub>sys</sub>; ER<sub>mes</sub>) were calculated according to standard formulae. PO<sub>2</sub>muc and HbO<sub>2</sub> were recorded for a period of at least 100 s. Laser-Doppler velocimetry measurements were performed for 300 s. Mean values of these variables were used for statistical comparison.

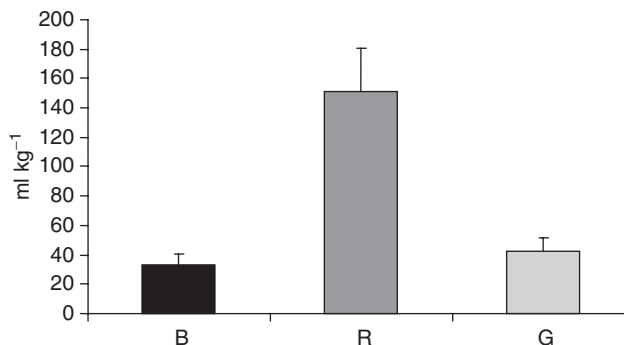
### Statistics

A Shapiro–Wilks's test was used to test for normal distribution of variables. Normality assumption was fulfilled in all main measurements. An ANOVA for repeated measurements was performed to analyse differences in mean values between and within groups for systemic haemodynamics, oxygen transport, systemic and mesenteric venous acid–base status, blood gas variables, arterial and mesenteric venous lactate concentrations, PO<sub>2</sub>muc, HbO<sub>2</sub>, PU, and intestinal oxygen extraction ratio. Global hypothesis was tested two-sided at the 0.05 significance level. In case of significant differences, further comparisons were made with paired *t*-tests within groups to baseline, and between groups at individual time points. The Bonferroni test was used to correct *P*-values, because of multiple comparisons. Data in text, tables and figures are presented as mean (SD), if not stated otherwise.

## Results

### Fluid volume

The amount of fluid volume infused after haemorrhage in the three different study groups is presented in Figure 1. Group R animals required over three times more volume than animals in group G [150.9 (30.6) ml kg<sup>-1</sup> vs 42.8 (11.5)



**Fig 1** Fluid volume infused after haemorrhage in blood resuscitated (B), gelatine resuscitated group (G) and Ringer's lactate resuscitated (R) animals in ml kg<sup>-1</sup>. Note that animals receiving lactated Ringer's solution required more than three times more volume compared with animals in group G (*P*<0.001).

**Table 1** Systemic haemodynamics and oxygen transport variables in blood resuscitated (B), gelatine resuscitated (G) and lactated Ringer's solution resuscitated (R) animals. \*Significant Bonferroni corrected *post hoc* group comparison. #Significant Bonferroni corrected *post hoc* baseline comparison. HR, heart rate; MAP, mean arterial blood pressure; PAP, mean pulmonary artery blood pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; DO<sub>2</sub>sys, systemic oxygen delivery; VO<sub>2</sub>sys, systemic oxygen consumption; ER<sub>sys</sub>, systemic oxygen extraction ratio. Values are mean (SD). Baseline is time 0 min. To convert mm Hg to kPa, multiply the value by 0.133

	0 min baseline	50 min haemorrhage	70 min retransfusion 1	90 min retransfusion 2	110 min retransfusion 3	130 min retransfusion 4	Time effect	Group effect
HR (mm Hg)								
B	98 (16)	150 (23) <sup>#</sup>	129 (18)	122 (20)	107 (18)	98 (17)	P=0.001	P=0.961
R	103 (22)	126 (30)	124 (32)	118 (27)	122 (31)	119 (25)		
G	116 (16)	115 (20)	121 (14)	123 (16)	119 (17)	117 (14)		
MAP (mm Hg)								
B	88 (21)	44 (19) <sup>#</sup>	73 (18)	92 (16)	97 (18)	99 (17)	P<0.001	P=0.906
R	93 (20)	52 (22) <sup>#</sup>	88 (34)	82 (33)	87 (34)	93 (35)		
G	97 (14)	55 (11) <sup>#</sup>	90 (10)	87 (11)	87 (13)	88 (17)		
PAP (mm Hg)								
B	26 (5)	14 (3) <sup>#</sup>	29 (5) <sup>#</sup>	27 (2)	26 (3)	26 (2)	P<0.001	P=0.978
R	22 (4)	13 (4) <sup>#</sup>	29 (6) <sup>#</sup>	28 (7) <sup>#</sup>	29 (5) <sup>#</sup>	29 (6) <sup>#</sup>		
G	23 (2)	14 (2) <sup>#</sup>	24 (7)	24 (3)	24 (3)	24 (3)		
PCWP (mm Hg)								
B	12 (2)	5 (1) <sup>#</sup>	13 (2)	13 (3)	12 (2)	11 (2)	P<0.001	P=0.306
R	12 (3)	4 (1) <sup>#</sup>	12 (3)	12 (3)	11 (3)	12 (3)		
G	11 (2)	5 (1) <sup>#</sup>	11 (2)	11 (1)	11 (2)	11 (1)		
CI (ml kg <sup>-1</sup> min <sup>-1</sup> )								
B	148 (25)	98.0 (33) <sup>#</sup>	149 (24)	150 (17)	138 (18)	128 (9)	P<0.001	P=0.078
R	159 (58)	86 (36) <sup>#</sup>	167 (50)	160 (47)	147 (40)	159 (54)		
G	158 (24)	98 (12) <sup>#</sup>	166 (14)	162 (11)	162 (12)	160 (16)		
DO <sub>2</sub> sys (ml kg <sup>-1</sup> min <sup>-1</sup> )								
B	11.4 (2.6)	6.1 (2.3) <sup>#</sup>	9.9 (2.1)	10.2 (1.2)	9.4 (1.2) <sup>#</sup>	8.7 (1.4) <sup>#</sup>	P<0.001	P=0.011
R	12.0 (5.4)	4.4 (2.4) <sup>#</sup>	5.1 (1.4) <sup>#,*</sup>	4.8 (1.2) <sup>#,*</sup>	4.5 (1.5) <sup>#,*</sup>	4.8 (1.5) <sup>#,*</sup>		
G	12.1 (3.1)	5.7 (2.3) <sup>#</sup>	6.7 (1.7) <sup>#,*</sup>	5.8 (1.5) <sup>#,*</sup>	5.3 (1.5) <sup>#,*</sup>	5.7 (1.6) <sup>#,*</sup>		
VO <sub>2</sub> sys (ml kg <sup>-1</sup> min <sup>-1</sup> )								
B	4.0 (0.3)	3.9 (0.4)	4.1 (0.4)	3.4 (0.3)	3.4 (0.2)	3.3 (0.3)	P<0.001	P=0.010
R	3.2 (0.3)	2.3 (0.4)	2.0 (0.2) <sup>#,*</sup>	1.8 (0.2) <sup>#,*</sup>	1.7 (0.2) <sup>#,*</sup>	2.2 (0.4) <sup>#</sup>		
G	4.7 (0.4)	3.7 (0.7)	3.4 (0.4) <sup>#</sup>	2.8 (0.6) <sup>#</sup>	2.8 (0.5) <sup>#</sup>	3.0 (0.6) <sup>#</sup>		
ER <sub>sys</sub>								
B	0.36 (0.04)	0.66 (0.09) <sup>#</sup>	0.42 (0.07)	0.34 (0.07)	0.36 (0.04)	0.38 (0.06)	P<0.001	P=0.882
R	0.3 (0.07)	0.57 (0.16) <sup>#</sup>	0.43 (0.15)	0.41 (0.23)	0.41 (0.18)	0.47 (0.19)		
G	0.34 (0.07)	0.52 (0.11) <sup>#</sup>	0.42 (0.08)	0.39 (0.15)	0.42 (0.14)	0.47 (0.10)		

ml kg<sup>-1</sup>;  $P<0.001$ ] to obtain baseline pulmonary capillary wedge pressure. The volume infused in group B animals was 33.4 (1.16) ml kg<sup>-1</sup>.

#### Systemic variables during haemorrhage

Haemorrhage caused significant changes in systemic haemodynamic parameters (Table 1). Mean arterial blood pressure, mean pulmonary arterial pressure, pulmonary capillary wedge pressure and cardiac index decreased significantly. In parallel with a decrease in cardiac index, DO<sub>2</sub>sys also decreased with a concomitant increase in systemic oxygen extraction ratio. Arterial pH (pHa) decreased and arterial lactate concentrations increased indicating some tissue hypoxia during haemorrhage in all study animals (Fig. 2).

#### Small intestinal variables during haemorrhage

Similar observations were detected in jejunal-derived variables (Table 2). Blood loss resulted in a significant decrease in mesenteric arterial blood flow and DO<sub>2</sub>mes with an increase in mesenteric oxygen extraction ratio. Mesenteric venous pH decreased and mesenteric venous lactate increased significantly after initiation of haemorrhage (Fig. 2).

#### Haemorrhage and small intestinal mucosal tissue oxygenation

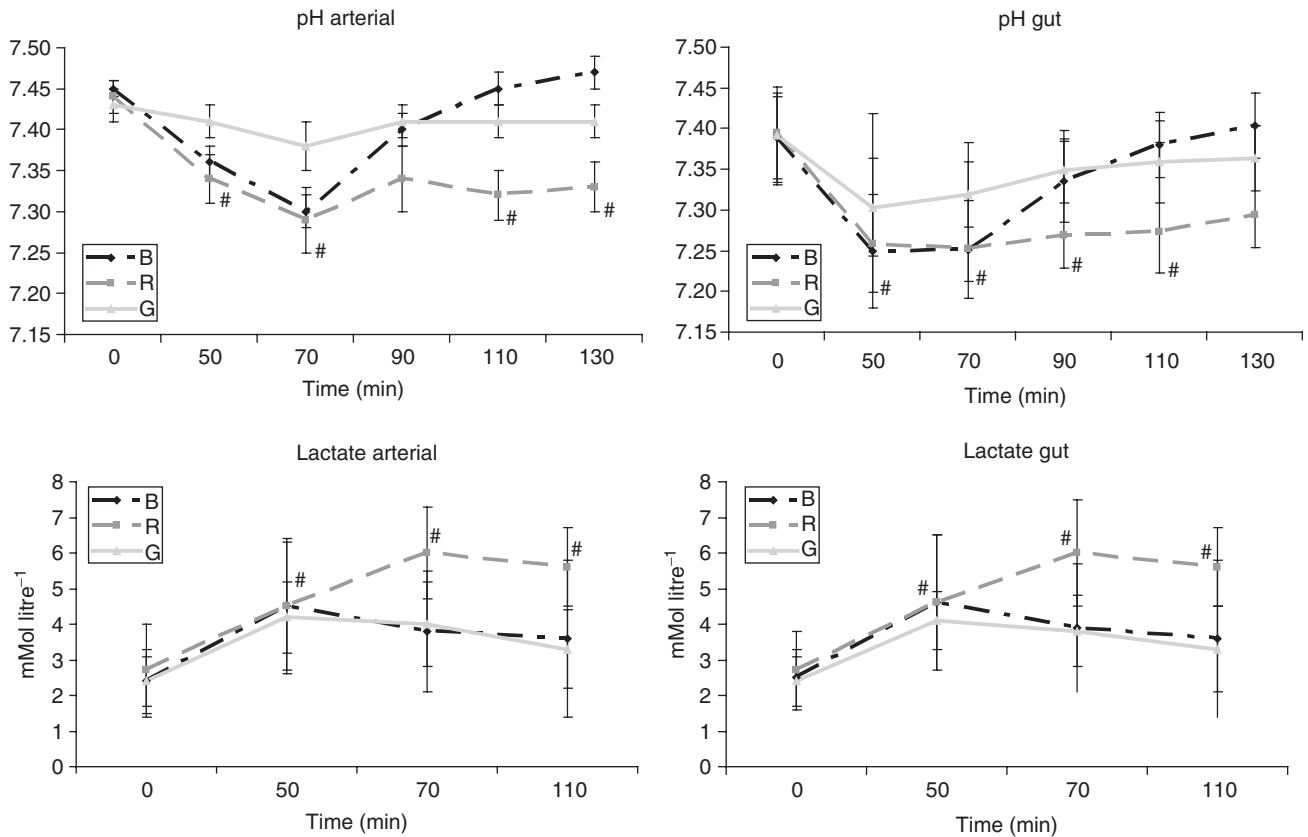
Haemorrhage resulted in a significant decrease in mucosal tissue oxygen tension and chemically bound oxygen in the jejunal microcirculation (Fig. 3).

#### Fluid resuscitation and systemic variables

Systemic haemodynamic parameters were restored after wedge-guided volume resuscitation in all three groups (Table 1). A sustained significant elevation of mean pulmonary arterial pressure was found in group R animals. A short-term significant elevation was also detectable in group B animals. DO<sub>2</sub>sys was only restored in group B animals, whereas it remained low in groups G and R animals. Furthermore, VO<sub>2</sub>sys was significantly impaired and arterial lactate concentrations remained high in group R animals.

#### Fluid resuscitation and small intestinal variables

Mesenteric artery blood flow was restored after fluid resuscitation in all three groups (Table 2). In group R animals DO<sub>2</sub>mes values remained low and VO<sub>2</sub>mes decreased with no change in ER<sub>mes</sub> between groups. Mesenteric venous pH



**Fig 2** Arterial and mesenteric venous pH and lactate levels in blood resuscitated (B), gelatine resuscitated (G) and Ringer's lactate resuscitated (R) animals. Mesenteric venous and arterial pH decreased, and mesenteric venous and arterial lactate increased significantly after initiation of haemorrhage in all animals. After resuscitation, these parameters did not recover in group R animals in contrast to groups B and G animals. pH arterial: time effect,  $P < 0.001$ ; group effect,  $P = 0.122$ . pH gut: time effect,  $P < 0.001$ ; group effect,  $P = 0.254$ . Arterial lactate: time effect,  $P < 0.001$ ; group effect,  $P = 0.083$ . Gut lactate: time effect,  $P < 0.001$ ; group effect,  $P = 0.085$ . #Significant Bonferroni corrected *post hoc* baseline comparison.

was lowered and mesenteric venous lactate levels increased over time in group R animals (Fig. 2).

#### Fluid resuscitation and small intestinal mucosal tissue oxygenation

In group R animals jejunal  $\text{HbO}_2$  significantly decreased by nearly 50% at 130 min (Fig. 3).  $\text{PO}_2\text{muc}$  values in group G animals were better preserved when compared with groups R and B animals after volume resuscitation, although there was no difference in jejunal  $\text{PO}_2\text{muc}$  between groups during the experiment.

## Discussion

Systemic haemodynamic parameters were restored after severe haemorrhage, regardless of the type of fluid used. Blood and gelatine resuscitation resulted in higher oxygen saturation of jejunal microvascular haemoglobin, when compared with resuscitation using lactated Ringer's solution, after severe haemorrhagic shock. Mucosal tissue oxygen tension was better preserved with gelatine compared with lactated Ringer's solution.

#### Haemorrhage and small intestinal mucosal tissue oxygenation

In this study, loss of 50% of the calculated blood volume significantly impaired jejunal mucosal tissue oxygenation in the pig. Although intestinal oxygen delivery decreased, systemic and intestinal oxygen consumption was maintained as a result of compensatory increases in systemic and intestinal oxygen extraction ratio, respectively. Both intestinal oxygen delivery and spectrophotometrically determined microcirculatory  $\text{HbO}_2$  decreased by nearly 50% after haemorrhage. This observation is in agreement with previous reports, as mucosal  $\text{HbO}_2$  reflects oxygen delivery to the mucosal and, to a lesser extent, the submucosal cell layer of the intestinal wall, and has been shown to be linearly related to changes in mucosal blood flow during bleeding.<sup>14-16</sup>

During haemorrhagic shock, there was evidence of anaerobic metabolism, reflected by increased intestinal lactate production and decreased mesenteric venous pH levels. In addition, mucosal tissue  $\text{PO}_2$  within the small intestine decreased by more than 50% during bleeding. Our data is in line with results by Dubin and colleagues,<sup>17</sup> in which haemorrhage-induced hyperlactataemia and intramucosal acidosis indicate anaerobic metabolism. Interestingly,

**Table 2** Mesenteric artery blood flow, intestinal oxygen supply and oxygen extraction ratio, and jejunal microcirculatory blood flow in blood resuscitated (B), gelatine resuscitated (G), and lactated Ringer's solution resuscitated (R) animals. \*Significant Bonferroni corrected *post hoc* group comparison. #Significant Bonferroni corrected *post hoc* baseline comparison. BFmes, mesenteric artery blood flow; DO<sub>2</sub>mes, intestinal oxygen delivery; VO<sub>2</sub>mes, intestinal oxygen consumption; ERmes, intestinal oxygen extraction ratio; MBFj, jejunal microvascular blood flow. Values are mean (SD). Baseline is time 0 min. To convert mm Hg to kPa, multiply the value by 0.1333

	0 min baseline	50 min haemorrhage	70 min retransfusion 1	90 min retransfusion 2	110 min retransfusion 3	130 min retransfusion 4	Time effect	Group effect
BF mes (ml min <sup>-1</sup> kg <sup>-1</sup> )								
B	33.0 (6.1)	25.1 (8.1) <sup>#</sup>	34.1 (7.4)	33.9 (8.7)	30.6 (7.4)	29.3 (7.3)	P<0.001	P=0.079
R	33.4 (6.8)	18.6 (6.3) <sup>#</sup>	38.0 (10.2)	35.3 (9.9)	35.7 (12.1)	34.9 (12.6)		
G	40.4 (8.8)	26.8 (6.6) <sup>#</sup>	42.8 (7.8)	42.7 (8.8)	43.6 (8.0)	43.2 (7.6)		
DO <sub>2</sub> mes (ml min <sup>-1</sup> kg <sup>-1</sup> )								
B	2.5 (0.2)	1.6 (0.2) <sup>#</sup>	2.2 (0.2) <sup>#</sup>	2.3 (0.2)	2.1 (0.2) <sup>#</sup>	2.0 (0.2) <sup>#</sup>	P<0.001	P=0.010
R	2.5 (0.2)	0.9 (0.1) <sup>#</sup>	1.2 (0.1) <sup>#,*</sup>	1.1 (0.1) <sup>#,*</sup>	1.1 (0.1) <sup>#,*</sup>	1.2 (0.2) <sup>#</sup>		
G	3.0 (0.3)	1.6 (0.2) <sup>#</sup>	1.8 (0.2) <sup>#</sup>	1.6 (0.2) <sup>#</sup>	1.5 (0.2) <sup>#</sup>	1.6 (0.2) <sup>#</sup>		
VO <sub>2</sub> mes (ml min <sup>-1</sup> kg <sup>-1</sup> )								
B	0.89 (0.07)	0.946 (0.11)	0.77 (0.07) <sup>#</sup>	0.87 (0.10)	0.89 (0.08)	0.87 (0.09)	P<0.001	P=0.001
R	0.90 (0.08)	0.52 (0.07) <sup>#</sup>	0.48 (0.07) <sup>#</sup>	0.41 (0.07) <sup>#,*</sup>	0.41 (0.1) <sup>#,*</sup>	0.43 (0.04) <sup>#,*</sup>		
G	1.09 (0.10)	0.81 (0.12)	0.66 (0.05) <sup>#</sup>	0.61 (0.07) <sup>#</sup>	0.56 (0.06) <sup>#,*</sup>	0.58 (0.06) <sup>#</sup>		
ER mes								
B	0.35 (0.04)	0.60 (0.07) <sup>#</sup>	0.34 (0.05)	0.38 (0.06)	0.43 (0.08)	0.44 (0.09)	P<0.001	P=0.830
R	0.37 (0.06)	0.57 (0.06) <sup>#</sup>	0.41 (0.12)	0.39 (0.16)	0.40 (0.11)	0.40 (0.10)		
G	0.36 (0.06)	0.52 (0.04) <sup>#</sup>	0.40 (0.10)	0.42 (0.09)	0.40 (0.07)	0.39 (0.10)		
MBFj (PU)								
B	253 (66)	157 (66)	212 (94)	212 (41)	214 (32)	188 (84)	P<0.001	P=0.871
R	264 (91)	178 (68)	219 (17)	187 (49)	174 (29)	161 (53)		
G	251 (57)	173 (49)	214 (56)	253 (40)	235 (51)	220 (26)		

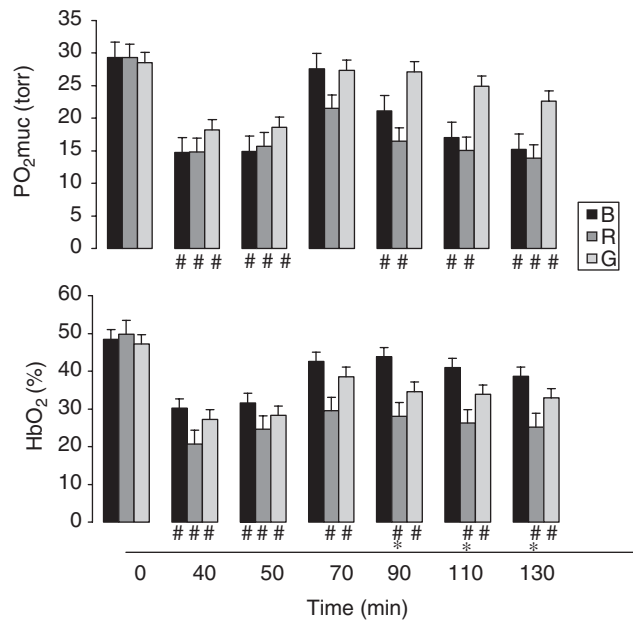
intestinal oxygen consumption was neither dependent on blood flow nor on oxygen transport, respectively. A possible explanation for this phenomenon may be a pathologic redistribution of blood flow, giving rise to hidden hypoxic microcirculatory units next to well-perfused, or even overperfused normoxic units.<sup>18 19</sup>

#### Fluid resuscitation and mucosal tissue oxygenation

In the present experiment, study animals showed only minor differences in mean arterial blood pressure, heart rate, pulmonary capillary wedge pressure or cardiac index between different fluid agents. Despite normalization of these traditionally used endpoints of resuscitation, we observed significant changes in mucosal tissue oxygen tension and microvascular haemoglobin oxygen saturation. Neither PO<sub>2</sub>muc nor HbO<sub>2</sub> recovered after resuscitation with shed blood, gelatine or lactated Ringer's solution. Nevertheless, we observed a better jejunal oxygen supply in animals resuscitated with gelatine. This difference in splanchnic perfusion between colloid and crystalloid is in line with a previous report. Marik and colleagues<sup>20</sup> showed that, during elective aortic aneurysm repair, patients resuscitated with hydroxyethyl starch (HES) required significantly less intraoperative fluid, and had a significantly smaller decrease in pH<sub>i</sub> than patients resuscitated with crystalloid. Other reports on tissue oxygenation during different fluid resuscitation regimens are sparse, but also favour colloids with respect to tissue oxygenation.<sup>9 21–23</sup>

In the present study, there was multiple evidence of anaerobic metabolism, such as acidosis and hyperlactataemia in animals resuscitated with Ringer's solution

when compared with group B or G animals. Interestingly, this observation, combined with the decrease in mucosal tissue oxygenation in group R animals, was present despite restored blood flow in the *A. mesenterica superior*, and no significant differences in jejunal microvascular blood flow between groups. There may be several reasons for the differences in intestinal tissue oxygenation between groups. First, animals receiving lactated Ringer's solution required over three times more volume as animals in group G, resulting in haemodilution with a subsequent decrease in both, DO<sub>2</sub>sys and DO<sub>2</sub>mes, as a result of reduced oxygen carrying capacity. Second, the high molecular weight molecules from gelatine solution remain largely intravascular, in contrast to crystalloid fluids, which are mostly distributed in the interstitium, resulting in tissue swelling.<sup>22</sup> Volume replacement with lactated Ringer's solution to maintain intravascular volume and cardiac output may be accompanied with progressive tissue oedema, thereby resulting in impairment of tissue oxygenation.<sup>24</sup> Similarly, in a hamster model, capillary perfusion and tissue oxygenation were significantly depressed in lactated Ringer's haemodiluted animals, because of interstitial oedema.<sup>22</sup> These observations have not only been seen in animal experiments but also in human studies.<sup>9</sup> As a result of an almost unrestricted passage of lactated Ringer's solution into the interstitial space, the Starling forces establish a new pressure balance across the capillary wall. The interstitial hydrostatic pressure increases by fluid accumulation, and the increasing dilution lowers interstitial oncotic pressure to a greater extent than intravascular oncotic pressure. Furthermore, the compensation for increased fluid filtration by lymphatic drainage as in the lung is insufficient in soft tissues.<sup>25</sup> In addition,



**Fig 3** Mucosal tissue oxygen tension (PO<sub>2</sub>muc) and microvascular haemoglobin oxygen saturation (HbO<sub>2</sub>) of the jejunum in blood resuscitated (B), gelatine resuscitated (G) and Ringer's lactate resuscitated (R) animals. There were no significant differences in PO<sub>2</sub>muc and HbO<sub>2</sub> between groups at baseline. Both PO<sub>2</sub>muc and HbO<sub>2</sub> decreased significantly after haemorrhage. Blood and gelatine resuscitation resulted in higher HbO<sub>2</sub> than lactated Ringer's solution. PO<sub>2</sub>muc: time effect,  $P < 0.001$ ; group effect,  $P = 0.110$ . HbO<sub>2</sub>: time effect,  $P < 0.001$ ; group effect,  $P = 0.041$ . \*Significant Bonferroni corrected *post hoc* group comparison. #Significant Bonferroni corrected *post hoc* baseline comparison.

endothelial and erythrocyte oedema may also occur and further compromise oxygen diffusion from end-arterioles and capillaries to tissues.<sup>26</sup>

#### Clinical relevance and limitations of the study

Our data suggest that gelatine infusion may be useful in improving intestinal mucosal tissue oxygenation during haemorrhage and subsequent resuscitation, when compared with lactated Ringer's solution. However, these results can only be extrapolated to humans, and especially to critically ill patients, with great caution. When using a specific fluid solution for resuscitation, one has to consider possible side-effects such as anaphylactic reactions, increased bleeding tendency, increased formation of tissue oedema, alterations in immune function or renal dysfunction, which have all been reported for colloid solutions.<sup>1</sup>

The lactated Ringer's solution is a weak acid of pH 5.0–7.0 and contains 28 mmol litre<sup>-1</sup> lactate which is metabolized in the liver. The byproducts of lactate metabolism in the liver counteract acidosis as a result of lactated Ringer's solution infusion. In patients with normal liver function, lactate as a result of infusion of lactated Ringer's solution is easily metabolized. In our experiment we cannot exclude some derangement of liver function leading to a decrease in lactate metabolism and to a secondary increase in lactate levels.

Succinylated gelatine was chosen for this experiment, as it is the most commonly used colloidal solution in our institution. Furthermore, gelatine solution usage in other countries such as the UK is still remarkably high.<sup>27</sup> The intravascular persistence of gelatin is relatively low (2–3 h), and gelatin can be given without dose-limitation. Traditional estimates on anaphylactoid reactions caused by gelatine are based on relatively old data from Ring and Messmer.<sup>28</sup> Recent data suggest that gelatin remain the most likely colloid to induce an anaphylactoid reaction.<sup>29</sup> Furthermore, gelatine solutions are generally considered to have little effect on clotting and are inexpensive.

#### Conclusion

In summary, we observed that restoration of systemic haemodynamic parameters can be achieved after severe haemorrhage with either lactated Ringer's solution, blood or succinylated gelatine. But only gelatine and blood infusion improved intestinal oxygen supply in the porcine jejunum after severe haemorrhage, when compared with lactated Ringer's solution. A possible explanation for this observation may be the more pronounced interstitial oedema formation, associated with an increased diffusion distance for oxygen in tissue.

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