Strangulation Obstruction and the Release of Strangulation. Effects of Fluid Administration on Mucosal Blood Flow and Damage

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Abstract

Background/Purpose: This study evaluates bowel mucosa damage and the consequences of crystalloid fluid administration on mucosa damages upon release from strangulation obstruction. Secondary outcomes are metabolic and hemodynamic changes during and after release of strangulation obstruction.

Methods: Twenty-four anesthetized pigs were subject to strangulation of the distal ileum for 185 min. Variables and specimens were registered and collected during strangulation and for 25 min thereafter. Intravenous Ringer`s acetate infusion during strangulation obstruction and after release of strangulation was 15 mL·kg^{-1}·h^{-1} in group I (Standard infusion) and 55 mL·kg^{-1}·h^{-1} in group II (High infusion). Group III, (Sham) controls received 15 mL·kg^{-1}·h^{-1} throughout the experiment.

Results: Strangulation obstruction reduced bowel blood flow from baseline averages of 2.9-3.8 ml·min^{-1}·g^{-1} to 0.3-0.9 ml·min^{-1}·g^{-1}. Upon release of strangulation, the bowel blood flow remained low in the standard infusion group but increased significantly towards baseline levels in the high infusion group.

Strangulation damaged more mucosa with standard infusion (80% ± 13%) than high infusion (25% ± 6%) (p=0.032). Release of strangulation had no significant effect on the mucosa (72% ± 17% and 41% ± 15% damage, respectively). Mucosal cell proliferation fell during strangulation from 169 mm^{-1} ± 17 mm^{-1} in controls to 71 mm^{-1} ± 16 mm^{-1} in standard (p<0.05) and 120 mm^{-1} ± 16 mm^{-1} in high infusion group. Release of strangulation significantly increased cell proliferation towards control levels.

Serum base excess decreased significantly during strangulation and release of strangulation in both intervention groups. S-lactate increased significantly in blood from the strangulated loop, but only in peripheral blood of the standard infusion group.

Conclusion: Careful observation for hypotension, tachycardia and biochemical changes related to metabolic acidosis may contribute to early recognition of intestinal strangulation obstruction. Enhanced intravenous fluid administration reduces bowel damages and hemodynamic consequences of both strangulation and release of strangulation.

Reperfusion damages should not be expected upon release of strangulation in the strangulated bowel and signs of bowel restitution appear early.

Keywords: Animal model; Experimental model; Intestinal microcirculation; Mucosa; Reperfusion injury

Introduction

Strangulation obstruction occurs in 11% to 26% of cases with bowel obstruction [1, 2]. Recognition of the diagnosis may be challenging and a delayed diagnosis is associated with non-viable bowel, resection of wide areas of damaged bowel and increased risk of death [1]. Strangulation involves concomitant partial occlusion of arterial inflow and venous drainage of the bowel in contrast to complete mesenteric artery occlusion in ischemia [3]. The strangulation generates pronounced

bowel damage and the viability of the bowel is often difficult to determine [4]. The decision to resect wide areas of damaged bowel is often reached by the surgeon's subjective judgment and may leave the patient with a short bowel syndrome requiring long-term parenteral nutrition [5]. Reluctance to preserve bowel during surgical salvage procedures in strangulation obstruction is often justified by the progression of bowel damage by reperfusion. Reperfusion damages in the bowel are identified after release of arterial occlusion [6] and several strategies have been tested in order to reduce the ischemic reperfusion damages [7,8].

Whether release of strangulation obstruction also elicits reperfusion damages in the bowel is unclear. In contrast, partial restitution of bowel mucosa is observed 4 hr to 12 hr after the release of strangulation [4,9]. Therefore, any reperfusion damage after release of strangulation obstruction should be identified early after release of strangulation.

Strangulation obstruction generates loss of extracellular fluids and substitution with crystalloid fluids during strangulation modulates mucosal blood flow and mucosal damage in pigs [10]. This study evaluates bowel mucosa damage and the consequences of crystalloid fluid administration on mucosa damages upon release from strangulation obstruction. Secondary outcomes are metabolic and hemodynamic changes during and after release of strangulation obstruction.

Materials and Methods

Animal preparation

Twenty-four locally bred domestic pigs weighing 32 kg ± 3 kg (mean ± SD) were deprived of food overnight but had ad libitum access to water. The animals received an intramuscular injection of atropine 1 mg, diazepam 10 mg, and ketamine 300 mg prior to mask induction of anaesthesia with isoflurane. All animals were orotrachealy intubated and mechanically ventilated (Cato, Dräger, Lübeck, Germany) to an end tidal CO_2 concentration of 3.5 kPa to 6 kPa. Inspiratory oxygen level (FiO_2) was adjusted to keep arterial saturation above 98%. Anaesthesia was maintained with isoflurane (end tidal concentration below 1.7%) and a continuous infusion of fentanyl 8 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and midazolam 0.5 $mg \cdot kg^{-1} \cdot h^{-1}$, with minor adjustments). Bolus injections of fentanyl/midazolam were administered in case of reappearance of reflexes. Rectal temperature was monitored and adjusted by means of a heating pad. A Venflon 2 IV cannula (OD 1.0 mm) was inserted into a femoral artery for measurement of arterial blood pressure, heart rate and for sampling of peripheral arterial blood. Another catheter (OD 1.34 mm) inserted through the right carotid artery into the left ventricle of the heart demonstrating typical traces with low diastolic pressure was used for the injection of microspheres (see below). The catheters were connected to SensoNor 840 pressure transducers (SensoNor, Horten, Norway), HP 8805C pressure amplifiers, and a HP 7758A recorder (Hewlett Packard Company, Waltham, MA).

The abdomen was opened in the midline and an infant blood pressure gasket (No.1, 3.1 cm to 5.7 cm, Hewlett-Packard, Andover, MD) was placed around a 250 cm long loop of the distal ileum. A catheter was inserted into the mesenteric vein proximal to the pressure gasket and the tip of the catheter was advanced into vein of the closed bowel loop for continuous recording of venous pressure and sampling of venous blood. The strangulated bowel loop was isolated from the abdomen in a plastic bag. A Foley catheter drained the urinary bladder during the experiment. To compensate for fluid loss during the operation the animals received Ringer`s acetate 15 $mL \cdot hour^{-1} \cdot kg^{-1}$ intravenously for the whole operation and stabilisation period. The animals were allowed 30 min of stabilisation after the surgical procedure before registration of Baseline variables.

Blood flow and cardiac output

Coloured microspheres (DyeTrak, Triton Technology, San Diego, CA) with a diameter of 15 μm and surface coated with a single dye were used for the measurement of Cardiac Output (CO) and tissue blood flow. The microspheres were injected into the left ventricle of the heart over a period of 30 seconds in a number of approximately 11.5×10^6 for eosin and yellow and 15×10^6 for violet and blue spheres. The sequence of colours was selected at random. A reference blood sample was drawn from the femoral artery with a constant rate extraction pump at a rate of 10 $mL \cdot min^{-1}$ during injection of spheres and 90s afterwards. Microspheres for blood flow and cardiac output measurement were injected at Baseline before strangulation, after 90 and 180 mins of strangulation, and 25 mins after release of strangulation obstruction.

The strangulated bowel loop was removed and a segment of approximately 30 cm was selected for measurement of whole wall tissue blood flow rate. Tissue samples were also taken from both kidneys in order to verify homogenous distribution of microspheres in paired organs. The tissue samples and reference blood samples were weighed and dissolved overnight in 20 mL of 4 M potassium hydroxide with 0.05% Tween 80 at 60°C. Each sample was filtered under vacuum through a 25 mm, 10 μm pore filter (Mitex Membrane Filters, Millipore, Ireland). The microspheres were washed with 0.05% Tween 80 and then with ethanol. The filters with their retained microspheres were centrifuged with 700 μL of dimethylformamide to elude the dyes. The solution of mixed dyes was scanned photometrical from 350 nm to 750 nm (Hewlett Packard 8452 A, Diode Array Spectrophotometer). The spectra obtained were quantified using partial least square single component analysis on commercial software (Advanced Chemstation Software, Hewlett Packard). A small segment of the strangulated bowel was weighed before and after being dried in an incubator in order to determine the tissue water content. The tissue blood flow rate expressed as $mL \cdot min^{-1} \cdot g^{-1}$ dry weight was computed according to standard formula [14]. The perfusion pressure in the strangulated bowel loop was calculated as the A-V pressure difference between the femoral artery and the vein of strangulated bowel.

Blood samples

Blood samples were collected from the femoral artery and the catheter in the vein of the strangulated bowel loop, just before induction of strangulation, at 90 and 180 mins of strangulation, and 2 and 25 mins after termination of the strangulation obstruction.

Lactate was analysed in plasma from blood collected in 5 mL containers with 20 mg of fluoresced heparin (BD Vacutainer, Belliver Industrial Estate, Plymouth, UK). The blood samples were immediately chilled, and the plasma was separated from cells within 15 mins in a chilled centrifuge (Megafuge 1.0R, Heraeus Instruments GmbH, Hanau, Germany). Samples with gross haemolysis were discarded. Lactate was quantified in an auto-analyser (aca® discrete clinical analyser, Du Pont Company, Wilmington, DE) by the Marbach and Weil method, which employs the oxidation of lactate to pyruvate, assay range 0 $mmol \cdot L^{-1}$ - 15 $mmol \cdot L^{-1}$. Arterial and venous blood pH, pCO_2, and pO_2 were analysed immediately by an automatic

Table 1: Heart rate, mean arterial blood pressure, and cardiac output during strangulation and termination of strangulation obstruction.

	n	(-5)	Strangulation (+90)	(+180)	Released (+2)	(+25)	minutes
Heart rate (beat/min)							
Strangulation Standard	6	123 ± 5	156 ± 9†*§	207 ± 12†*§	206 ± 13†§	192 ± 13†	Pw < 0.001
Strangulation High	8	115 ± 5	120 ± 8	144 ± 10	149 ± 11	147 ± 11	Pi = 0.006
Sham Standard	8	113 ± 5	119 ± 8	121 ± 10	125 ± 11	126 ± 11	Pb < 0.001
Cardiac output							
Strangulation Standard	6	6.4 ± 0.7	3.3 ± 0.9	2.7 ± 0.5		2.3 ± 0.5†	Pw < 0.001
Strangulation High	8	4.2 ± 0.6	3.5 ± 0.7	3.9 ± 0.5		4.1 ± 0.4	Pi < 0.001
Sham Standard	8	5.2 ± 0.6	5.2 ± 0.7	4.7 ± 0.5		4.7 ± 0.4	Pb = 0.254
Arterial Blood Pressure (mmHg)							
Strangulation Standard	6	73 ± 4	63 ± 3§	58 ± 3§	39 ± 3†*§	39 ± 3†§	Pw < 0.001
Strangulation High	8	75 ± 4	79 ± 3	70 ± 2	61 ± 3	64 ± 3	Pi < 0.001
Sham Standard	8	71 ± 4	70 ± 3	68 ± 2	64 ± 3	65 ± 3	Pb < 0.001

Mean ± SEM, Two animals died after release of strangulation in the Standard infusion group
† p<0.05, different from Sham group
* p<0.05, within group change from previous measurement
§ p<0.05, different from the other intervention group

blood gas analyser system and Base Excess (BE) was calculated (AVL 995-Hb, Graz, Austria).

Histology

Biopsies for histopathological examinations were obtained from the strangulated bowel loops after 180 mins of strangulation and after completion of experiments 25 mins after release of strangulation. The whole-wall tissue samples were kept in Bouin's solution (750 mL Picric acid, saturated aqueous solution, 250 mL 37% to 40% formaldehyde, 50 mL Glacial acetic acid) and stained with Haematoxylin-Eosin (H&E). Microscopic slides were coded and evaluated without revealing animal identity for the examiner. Intestinal tissue damage was semi-quantified as follows: Grade 0 = no damage to intestinal villi, Grade 1 = epithelial damage limited to distal half of the intestinal villi and Grade 2 = epithelial damage affecting more than distal half of the intestinal villi. Percent of grade 0, grade 1, and grade 2 damage were noted for each slide. Demonstration of the different grades of mucosal damage is published earlier [11].

Cell proliferation was evaluated in sections immunohistochemically stained for MIB-1 (Ki-67) and counterstained with Haematoxylin-Eosin (H&E). High power fields and intensely stained nuclei were chosen for MIB-1 counting. The mean number of proliferating cells per mm of mucosa was estimated.

Strangulation and reperfusion

The strangulation obstruction was initiated by inflation of the gasket until the venous pressure of the intestinal loop reached 50 mmHg. By adjusting the gasket pressure, the venous pressure was kept at 50 mmHg for the first 15 min of obstruction. Thereafter, gasket pressure was not altered independent of changes in venous pressure. A short segment of the strangulated intestine was resected just before termination of strangulation. The intestine was divided by TLC-55 Linear Cutters, Blue/Regular cartridge (Ethicon Endo-Surgery, LLC Johnson & Johnson, Guaynabo, Puerto Rico) and the corresponding mesentery was ligated. Strangulation obstruction was terminated after 185 mins by relieving the pressure and removing the gasket from the strangulated intestine. Haemodynamic variables and blood samples were obtained from systemic arterial blood and the

mesenteric vein of the strangulated intestine 5 mins before, and after 90 and 180 mins of strangulation. Another set of measurements and blood were sampled 2 and 25 mins after termination of strangulation obstruction.

Experimental groups

The animals were allocated at random into one of three experimental groups with eight animals in each group.

Group I (Standard infusion) received infusion of Ringer`s acetate at a constant rate of 15 mL·kg⁻¹·h⁻¹ during all phases of the experiment including the period of strangulation and after release of strangulation obstruction in order to compensate for loss of fluid related to the basal metabolism and laparotomy.

Group II (High infusion) received infusion of Ringer`s acetate at a rate of 15 mL·kg⁻¹·h⁻¹ during surgery and stabilisation and thereafter at a rate of 55 mL·kg⁻¹·h⁻¹ during strangulation obstruction and after release of strangulation. The enhanced fluid administration intended to compensate for loss of fluid related to the basal metabolism, laparotomy and strangulation obstruction.

Group III, the control group (Sham) was operated exactly as the two intervention groups but the gasket was not inflated. Thus, strangulation obstruction was not induced. Infusion of Ringer`s acetate was kept at a constant rate of 15 mL·kg⁻¹·h⁻¹ and evaluated the ability of base fluid infusion to compensate for fluid losses related to basal metabolism and laparotomy.

Ethics

The experiment was performed according to "Principles of laboratory animal care" [12] and the experimental animal board of the Norwegian Department of Agriculture approved the protocol. Approval number 200003. The responsible laboratory veterinarian supervised the experiments under the surveillance of the Norwegian Animal Research Authority. At the end of an experiment the animal was sacrificed with an intra-cardiac injection of 20-mL potassium chloride while still in the same narcosis.

Statistics

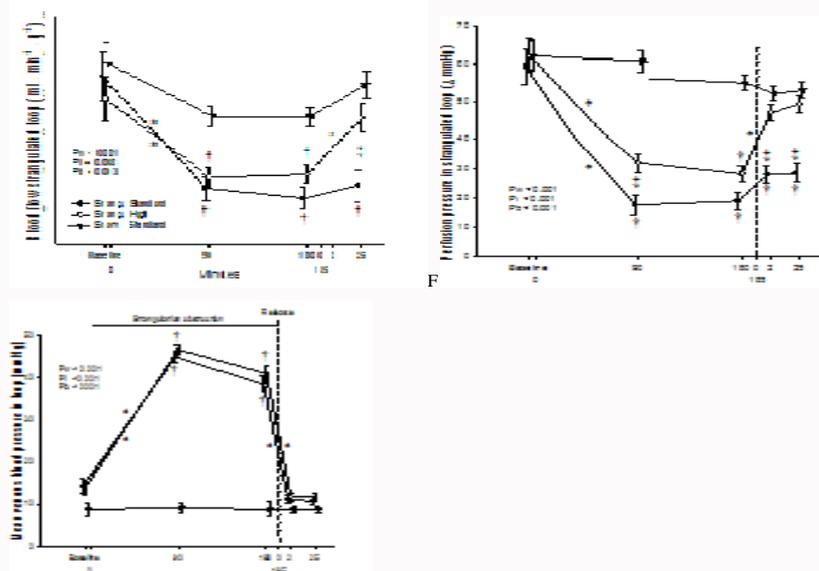The IBM SPSS Statistics ver.20 was used for the statistical analyses.

Figure 1: Circulatory changes in the bowel loop during strangulation obstruction and release of strangulation.
Upper panel: mean blood pressure in vein of strangulated loop; middle panel: perfusion pressure across vessels in strangulated loop (P_{art} - P_{vein}).
Lower panel: tissue blood flow rate. Bars are SEM. Pw, Pi and Pb denotes p-values from the RM-ANOVA for within group, interaction effect and between treatment groups, respectively.
† p<0.05, different from Sham group * p<0.05, within group change from previous measurement § p<0.05, different from the other intervention group.

Fluid administration (Standard or High) during the experiment was the intervention. Results are presented as mean with Standard Error of the Mean (SEM) unless stated otherwise. The degree of mucosal damage, arterial blood gases, blood flow rate and lactate were studied by two-way ANOVA for repeated measurements (RM-ANOVA) with Sham, Standard fluid and High fluid as grouping factor (Pb) and time as within factor (Pw). If the Mauchly's test of sphericity was significant, the p-value with a Greenhouse-Geisser adjustment of the degrees of freedom was noted. The interaction effect (Pi) was considered significant if p<0.10. In cases with significant interaction effect, differences between cell means were considered significant if 95% confidence intervals did not overlap. Otherwise, post hoc contrast tests between mean values were performed with the Tukey's multiple comparison tests and p<0.05 was considered significant.

Results

The hemodynamic consequences of small bowel strangulation and subsequent strangulation release are summarised in (Table 1). Briefly, standard infusion rate of Ringer acetate during strangulation obstruction was followed by increased heart rate, and a reduction of arterial blood pressure and cardiac output. Release of strangulation obstruction killed two of the animals. In the six surviving animals the arterial blood pressure and cardiac output decreased further. The hemodynamic of the sham group and the high volume group of fluid substitution were largely unaffected by strangulation and release of strangulation.

The blood pressure in the vein draining the bowel loop increased and remained stable at means of 38.5 mmHg to 46.5 mmHg in the intervention groups during strangulation. Release of strangulation reduced the venous blood pressure to baseline levels at means of 9 mmHg to 12 mmHg (Figure 1, upper panel).

Perfusion pressure across the strangulated bowel loop (Figure 1, middle panel) decreased significantly during strangulation in both i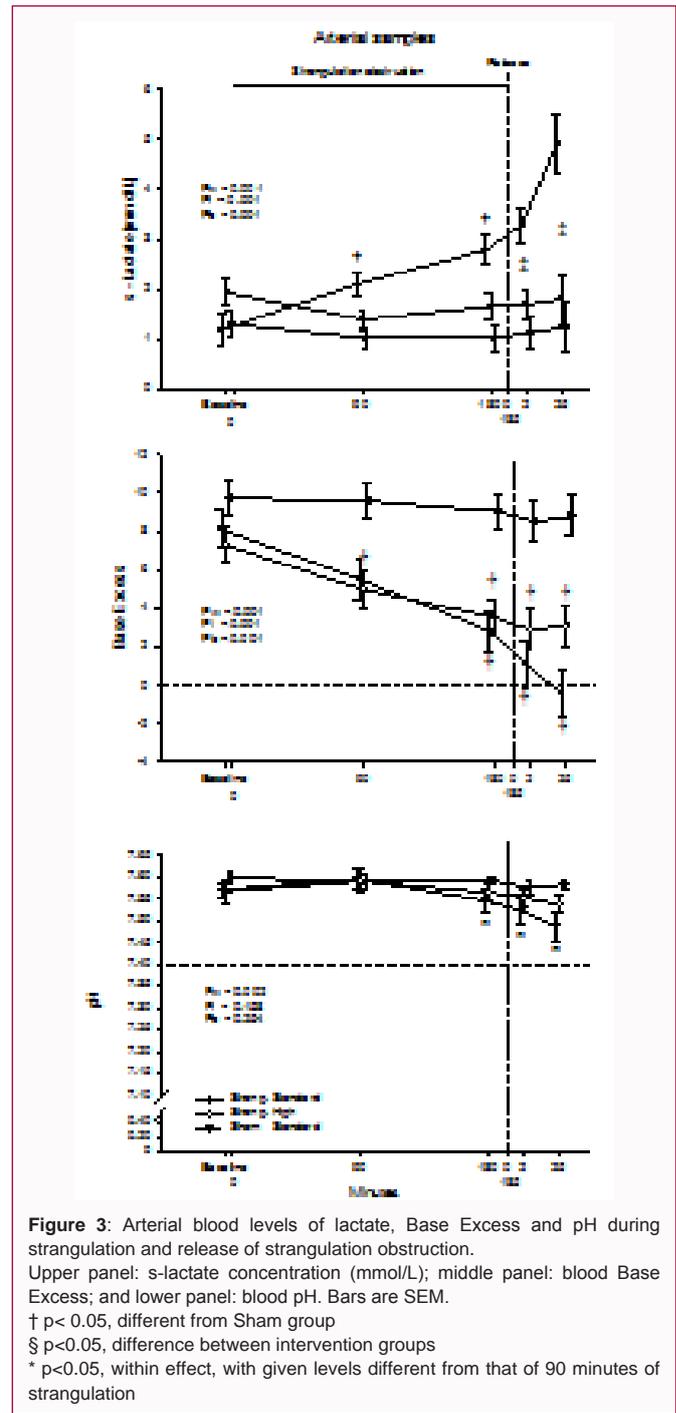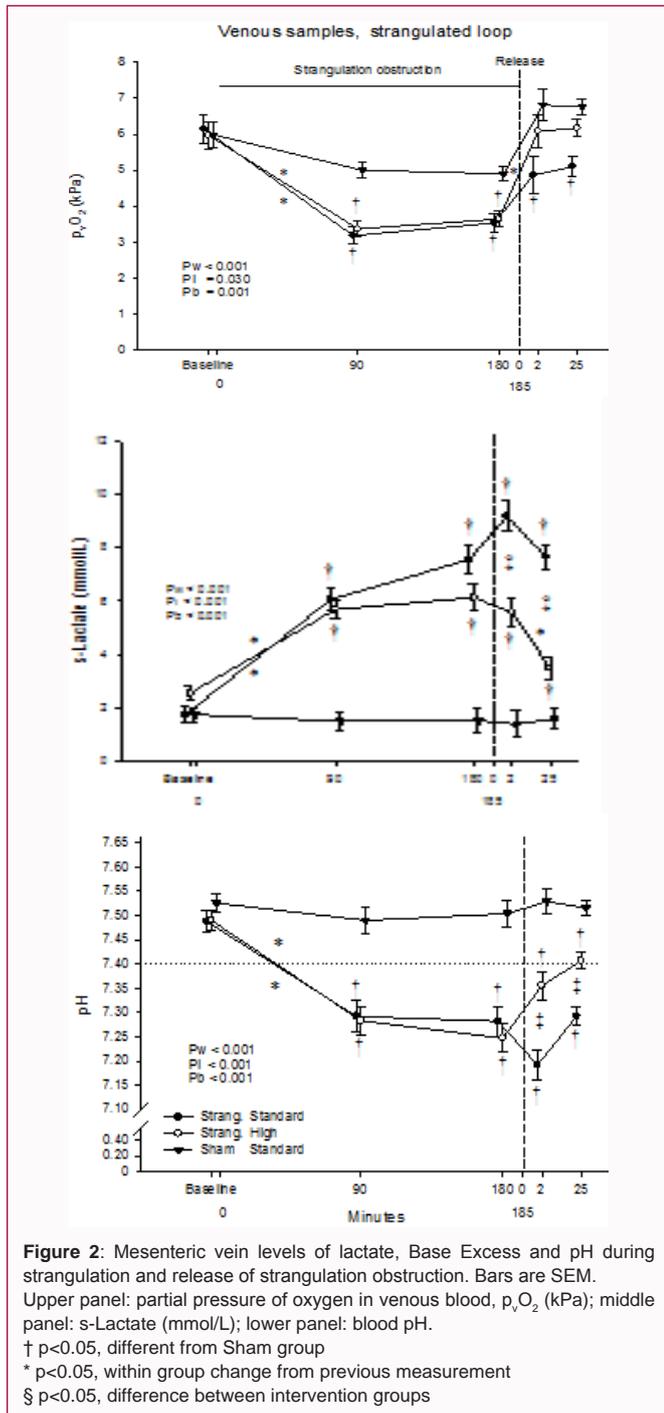ntervention groups to means of 18 mmHg to 28 mmHg, when compared to both baseline and sham operated animals (range of means: 59 mmHg to 62 mmHg). Animals with standard rate of fluid administration experienced the lowest perfusion pressure in the strangulated loop and the perfusion pressure remained low upon release of strangulation. The high infusion group demonstrated an increase of perfusion pressure towards baseline and sham group of animals upon release of strangulation.

There was a clear reduction in tissue blood flow during bowel strangulation in both intervention groups from baseline averages of 2.9 ml·min⁻¹·g⁻¹ - 3.8 ml·min⁻¹·g⁻¹ to 0.3 ml·min⁻¹·g⁻¹ - 0.9 ml·min⁻¹·g⁻¹ (Figure 1, lower panel). Upon release of strangulation, the blood flow remained very low in the strangulated bowel loop of the standard infusion group, whereas the tissue blood flow increased towards baseline levels in the high infusion group.

Venous partial pressure of oxygen (pvO_2) decreased in the bowel loop during strangulation from a baseline of 5.9 kPa to 6.1 kPa to a level of 3.1 kPa to 3.6 kPa in both intervention groups (Figure 2, upper panel). Release of strangulation improved blood pvO_2 within minutes towards baseline levels in the high infusion group, whereas pvO_2 remained lower in the standard infusion group. Changes in pvO_2 of sham-operated animals were statistically insignificant.

Lactate concentrations from the vein in the strangulated loop increased significantly from a baseline of 1.7 mmol·L⁻¹ to 2.5 mmol·L⁻¹ towards a level of 5.7 mmol·L⁻¹ to 7.5 mmol·L⁻¹ in both intervention groups (Figure 2, middle panel). Release of strangulation rapidly reduced venous lactate level in animals with high volume administration but still the level was higher than in controls after 2 and 25 mins. In animals with standard fluid administration, the lactate concentration remained at a level of 7.7 mmol·L⁻¹ - 9.2 mmol·L⁻¹ and significantly higher than in the control and in the high infusion group.

The venous pH decreased during strangulation from mean baseline levels of 7.48 to 7.52 to a level of 7.25 to 7.29 in both

Figure 2: Mesenteric vein levels of lactate, Base Excess and pH during strangulation and release of strangulation obstruction. Bars are SEM.
Upper panel: partial pressure of oxygen in venous blood, p_vO_2 (kPa); middle panel: s-Lactate (mmol/L); lower panel: blood pH.
† p<0.05, different from Sham group
* p<0.05, within group change from previous measurement
§ p<0.05, difference between intervention groups

Figure 3: Arterial blood levels of lactate, Base Excess and pH during strangulation and release of strangulation obstruction.
Upper panel: s-lactate concentration (mmol/L); middle panel: blood Base Excess; and lower panel: blood pH. Bars are SEM.
† p< 0.05, different from Sham group
§ p<0.05, difference between intervention groups
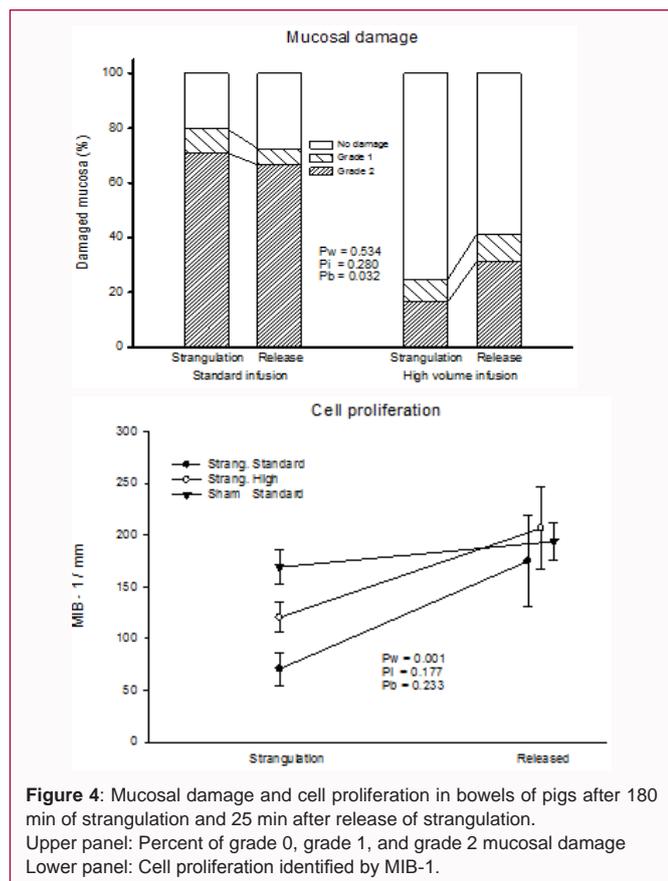* p<0.05, within effect, with given levels different from that of 90 minutes of strangulation

intervention groups (Figure 2, lower panel). After release of strangulation the venous pH remained low in standard infusion group (pH: 7.19 to 7.29) and increased somewhat in the high infusion group to an intermediate level (pH 7.35 to 7.4) statistically different from both the control and standard infusion group.

Results of arterial blood samples are summarised in (Figure 3). A statistical increase in serum lactate level during strangulation and even more after release of strangulation was noticed in the standard infusion group, only (Figure 3 upper panel).

Base excess decreased gradually during the experiment from baseline levels of 7.3 mmol·L^{-1} to 9.8 mmol·L^{-1} and remained significantly lower than in sham-operated controls during strangulation (5.0 mmol·L^{-1} to 3.5 mmol·L^{-1} and 5.5 mmol·L^{-1} to 2.8 mmol·L^{-1}) and following release of strangulation (2.9 - 3.1 and - 0.4 - 1.1) both in animals with high and standard infusion rate (Figure 3, middle panel). Changes in arterial pH were modest, but a statistically significant decrease was noticed by the end of strangulation and after release of strangulation (within main effect) (Figure 3, lower panel).

The strangulated bowel had macroscopic signs of severe damage with intestinal oedema and a bluish discolouration of varying intensity in both intervention groups. The microscopy results of bowel mucosa is summarised in (Figure 4). The sham-operated control group was omitted from the analyses due to absence of mucosal damage. In biopsies obtained after 180 min of strangulation, mucosal damage in

Figure 4: Mucosal damage and cell proliferation in bowels of pigs after 180 min of strangulation and 25 min after release of strangulation.
Upper panel: Percent of grade 0, grade 1, and grade 2 mucosal damage
Lower panel: Cell proliferation identified by MIB-1.

the standard infusion group was extensive (80% ± 13% of examined mucosa) when compared to the high infusion group (25% ± 6%). After release of strangulation, 72% ± 17% and 41% ± 15% of the mucosa was damaged in the standard and the high infusion groups, respectively. Despite an apparent numeric increase of grade 2 damage after release of strangulation in the high infusion group, release of strangulation produced no statistical increase in mucosal damage. Over all, the mucosal damage was more pronounced in the standard than in the high infusion group (p<0.032).

The average number of MIB - 1 stained cell was low in the mucosa during strangulation (Figure 4, lower panel). The number of MIB - 1 cells was also statistically lower in the standard infusion group (71 mm^{-1} ± 16 mm^{-1}) than in the sham group (169 mm^{-1} ± 17 mm^{-1}) (p<0.05 by Tukey HSD). The high infusion group demonstrated an intermediate level of MIB - 1 stained cell (120 mm^{-1} ± 16 mm^{-1}). Release of strangulation increased significantly the number of MIB - 1 stained cells towards the level in the sham group.

Discussion

This study shows that increased crystalloid fluid administration improves central haemodynamic and perfusion pressure in a strangulated bowel segment and protects against mucosal damage during strangulation and release of strangulation obstruction. Release of strangulation imposes no additional damaging effect on the bowel mucosa. Instead, signs of cell proliferation increase immediately as an indication of viable bowel and early onset of restitution.

Signs of anaerobe metabolism in peripheral arterial blood are modest and only noticed in case of insufficient volume substitution. Release of strangulation obstruction under such circumstances may

be deleterious as two animals succumbed immediately.

Hemodynamic/anaerobe metabolism

The standard infusion rate of Ringer`s acetate is sufficient to compensate for fluid loss due to basal metabolism and laparotomy throughout the experiment in the control group (Table 1). The hemodynamic changes during strangulation are therefore most likely a consequence of excess fluid loss during strangulation [3]. Insufficient volume substitution with hypovolemia renders the animals susceptible to vasodilation, drop in blood pressure and even death after release of strangulation (Table 1). The effect of insufficient crystalloid substitution on the hemodynamic is particularly clear upon release of strangulation (Figure 1). Experiments with strangulation obstruction in rats suggest infusion of hypertonic saline is superior to identical volume of Ringer lactate [13]. Hypertonic saline effectively mobilize cellular water into the blood volume and the volume expansion by hypertonic saline may reach 10 times of what is obtained by lactated Ringer's solution [14]. Sufficient substitution of fluid with crystalloids is therefore important to avoid hemodynamic changes during both strangulation and release of strangulation obstruction.

The mechanisms

Bacterial translocation occurs even in simple intestinal obstruction in humans [15]. In experiments, high weight hydrophilic marker molecules continue to translocate from bowel to venous blood after release of strangulation and during restitution of mucosal damage as indication of a continuous barrier deficit in strangulation obstruction [4]. Bacterial translocation is not evaluated in this study but hypertonic saline as volume substitution significantly reduce bacteraemia in rats [13]. This may be one of the effects of sufficient volume substitution in strangulation obstruction.

Although strangulation of bowel facilitates bacterial translocation, other substances from the strangulated bowel may modify vascular tone upon release of strangulation. Distinct traces of anaerobe metabolism in peripheral arterial blood and hypotension after release of strangulation in the standard volume substitution group (Figure 3, Table 2) suggest a vicious circle of prolonged low flow state with anaerobe metabolism, acidosis, or release of vasoactive substances from the strangulated bowel [16,17]. The effect of such substances is probably modest since high volume substitution easily prevents most of the effects (Figure 1 and 2, Table 1).

Mucosal/Bowel damage

There is a striking difference in mucosal damage between the standard and the high volume infusion group (Figure 4) which is related to mucosal blood flow [10] although differences in perfusion pressure and blood flow are modest (Figure1 and 4). Improved blood flow alone is therefore not a satisfactory explanation of reduced mucosal damage in the high infusion group. The parallel reduction in pvO$_2$ and pH, and increase of lactic acid in the mesenteric vein during strangulation obstruction in the two groups (Figure 2) are also somewhat inconsistent with different degree of mucosal damage. Thus, both intestinal blood flow and metabolic changes detected in the mesenteric vein during strangulation obstruction seem unable to predict the degree of intestinal damage. A modulation of leukocyte endothelial interactions by hypertonic saline described by Luiz Zanoni et al. [13] May be the missing link in the explanation of reduced bowel damage in the high infusion group.

The majority of the mucosal damage associated with ischemia occurs during reperfusion and not during the ischemic period

[6]. Reperfusion by release of strangulation inflicts no additional damage to the mucosa within the first 25 mins (Figure 4). Laws et al. [18] notice similar results. The already extensive mucosal damage induced by strangulation obstruction seen in the standard infusion group suggests that any additional or progressive mucosal damage by release of strangulation may be impossible to identify. The slight but statistically insignificant increase of grade 2 damage after release of strangulation in high volume group indicates that some mucosal damage may occur upon release of strangulation, but not to the extent seen in reperfusion after an arterial occlusion. Thus, further mucosal or bowel damage should not be expected upon release of strangulation obstruction.

It can be argued that the time of reperfusion (25 mins) in this study is short compared to that of experiments with complete arterial occlusion demonstrating mucosal damage after the 60 mins of reperfusion [6]. However, suppressed cell proliferation as evaluated by MIB - 1 is already reactivated to control levels 25 mins after release of strangulation (Figure 4) and strangulation studies in horse bowel show no changes 90 mins after release of venous occlusion [18]. Moreover, 4-hrs after release of strangulation the bowel mucosa approaches complete restitution [4]. Thus, a relative short observation time from release of strangulation seems sufficient for the detection of early signs of reperfusion damage and restitution in damaged bowel mucosa.

Restitution is time consuming and involves migration of cuboid cells along the basement membrane towards the tip of the villi [19], and is strongly associated with the extent of strangulation [4]. High volume fluid substitution may therefore reduce mucosal damage, predispose to expeditious recovery of the mucosa and reduce bacterial translocations from the bowel to the blood [4,13].

Clinical implications

Parameters contributing to the identification of strangulation obstruction are of great interest in non-operative management and triage of small bowel obstruction by for instance water-soluble contrast [20]. Decline in peripheral blood level of Base Excess (BE) occurs during strangulation obstruction and identify metabolic acidosis at a level that may be consistent with reversible bowel ischemia (Figure 3). This is a new observation, since earlier studies show that BE reduction is associated with bowel gangrene and bowel resection with a sensitivity and specificity of 75% and 80%, respectively [21,22].

Lactate in peripheral blood is also a marker of nonviable bowel strangulation [23,24]. However, release of lactic acid to the mesenteric vein during strangulation (Figure 2) is easily masked in peripheral blood by extensive crystalloid fluid administration (Figure 3). Elevated lactic acid in peripheral blood may therefore characterize the general circulatory status rather than the anaerobe metabolism of a strangulated bowel. Although not easily available, peritoneal fluid lactate may be more precise in detection of intestinal strangulation and abdominal catastrophes [25]. The modest changes in arterial pH seen in the present study are consistent with the poor predictive value of peripheral blood pH in clinical studies [22].

The hazard of fluid loss, intravascular volume depletion, and hemodynamic changes (Table 1) is probably related to systemic effect of metabolic acidosis or other factors released from the bowel both during and following the release of strangulation [3] [26-28]. The effect of substances be from the strangulated bowel is, nevertheless, modest as crystalloid fluid administration alone appears

to compensate for the effect (Table 1). Sufficient fluid administration cannot be overrated in strangulation obstruction as it enables the pigs to withstand changes in vascular tone, cardiac function, and death.

The recovery of suppressed cell proliferation to control level within 25 mins of release from strangulation (Figure 4) suggests that the strangulated bowel may be viable and the bowel should be assessed for preservation. Clinically, an attitude towards conservation of bowel and second look strategies may be justified in situations with risk of extensive bowel loss.

Metabolic changes detected in mesenteric vein of the two intervention groups' reveal similar reductions in pO_2 and pH, and a similar rise in lactic acid during strangulation obstruction (Figure 2). Thus, an increase in oxygen extraction and anaerobe metabolism during surgery for strangulation obstruction is unable to predict the degree of mucosal and bowel damage. Intraoperative near-infrared fluorescence angiography predicts survival of ischaemic bowel with greater accuracy than clinical evaluation in animal experiments [29]. This technique may also prove helpful in predicting viability of strangulated bowel in the future.

Experiment evaluation

Changes in sham-operated animals (Figure 1 and 2) are probably due to handling and positioning of the un-inflated gasket around the bowel segment. Nevertheless, the lack of bowel damage in the control group confirms that standard infusion rate of Ringer`s acetate is sufficient to compensate for fluid loss due to basal metabolism and laparotomy in this experimental model.

A single point of evaluation after release of strangulation may inflict study limitations. However, the rapid improvements of blood flow (Figure 1), metabolism (Figure 2), hemodynamic, and suppressed cell proliferation encourage early evaluation upon release from strangulation. Similarly, Juel et al. [4] show that hemodynamic and tissue blood flow returns close to baseline and few changes are observed in these parameters beyond the first hr of release from strangulation [4]. Moreover, restitution of ischemic mucosa commence within 60 mins of reperfusion [30] and restitution of damaged mucosa is well in progress with villi covered by normal columnar or cuboidal cells four hours after release of strangulation [4]. Thus, evaluation of reperfusion damages in strangulation obstruction must occur very early.

Conclusion

Careful observation for hypotension, tachycardia and biochemical changes related to metabolic acidosis may contribute to early recognition of intestinal strangulation obstruction. Reperfusion damages in the strangulated bowel should not be expected upon release of strangulation. Enhanced intravenous fluid administration during preparation to operation and during the surgical procedure may reduce bowel damage and hemodynamic consequences of strangulation obstruction.

Acknowledgment

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