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Occlusive mesenteric ischemia and its effects on jejunal intramucosal pH, mesenteric oxygen consumption and oxygen tensions from surfaces of the jejunum in anesthetized pigs

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Abstract *Objective*: To investigate the effects of superior mesenteric artery (SMA) flow reduction on the jejunal intramucosal pH (pH_i) and to compare these effects with corresponding changes of mesenteric oxygen transport variables and oxygen tensions on the surfaces of the jejunal serosa and mucosa.
Design: Prospective, randomized, controlled, experimental study.
Setting: Animal research laboratory.
Subjects: 20 domestic pigs.
Interventions: Mechanical flow reduction in the SMA. The animals were randomized to have an SMA flow of 0%, 25%, 38%, 50% or 100% (control).
Measurements and main results: Measurements (baseline, ischemia, reperfusion) consisted of hemodynamic and oxygen transport variables, SMA blood flow, mesenteric oxygen transport variables, pH_i and oxygen tensions of the jejunal serosa and mucosa. Flow reduction in the SMA resulted in a significant decrease of pH_i indicating ischemia earlier than mesenteric oxygen transport variables. The relationship between mesenteric oxygen delivery (DO_{2ms}) and pH_i during acute ischemia is best described by a sigmoid curve. There was a linear correlation between the changes of the jejunal surface oxygen tensions and pH_i due to SMA flow reduction.
Conclusion: The sigmoid relationship between pH_i and DO_{2ms} indicated that pH_i is a sensitive parameter for detecting ischemia at 50% of the baseline oxygen delivery and that below 25% there was no further decrease of pH_i. In contrast, mesenteric and whole body oxygen transport parameters were not indicative of impaired mucosal oxygen supply.

Key words Pig · Intramucosal pH · Occlusive mesenteric ischemia · Oxygen consumption · Oxygen delivery · Surface oxygen tension

Introduction

There is increasing evidence that mesenteric ischemia plays a central role in the development of shock, sepsis and multiple systems organ failure [1–3]. Unfortunately it is difficult to monitor adequate mesenteric oxygen supply. A viable method, therefore, is needed to detect and to treat mesenteric ischemia during its initial stages.

Hollow viscus tonometry [4] was used to determine intramucosal pH (pH_i) [5–7]. This method provides valid results under experimental conditions of endotoxemia and mesenteric occlusion in pigs [8]. Based on analysis of pH_i, there is clear evidence for gastrointestinal ischemia associated with experimental shock [9–12] and sepsis [13–15]. In clinical trials, low pH_i values are associated with more postoperative complications and higher mortality rates and costs [16–21]. A significant reduction in mortality occurred when therapy was guided by pH_i [22]. Despite the increasing use of pH_i measurements, basic questions about this method are unclear. In particular, pH_i starts to decrease after mesenteric oxygen consumption (VO_{2ms}) becomes supply-dependent [5, 23], a contradictory result in

view of the finding that pH_i is already reduced when VO_{2ms} is unchanged [24,25]. In addition, it is not clear if more than a qualitative relationship exists between ischemia and decreasing pH_i.

The goals of our investigation included determining the nature of the relationship between pH_i and mesenteric oxygen delivery (DO_{2ms}). A central point was the extent to which VO_{2ms} is maintained by an increase in mesenteric oxygen extraction (ERO_{2ms}) during decreased DO_{2ms}, and whether the pH_i values during this state of compensated reduction of DO_{2ms} are indicative of gut ischemia. In addition, pH_i values were compared with simultaneously obtained oxygen tensions from mucosal (P_sO_{2m}) and serosal (P_sO_{2s}) surfaces of the jejunum. Finally, we addressed the nature of intracellular acidosis developing during occlusive ischemia. Of particular interest was whether aerobic metabolism, through carbon dioxide accumulation, is responsible for mucosal acidosis or if anaerobic metabolism (dysoxia) also contributes to the overall intracelluar carbon dioxide content.

Materials and methods

The protocol of this study was approved by the Committee on Animal Research, Department of Research, University of Basel. We used 20 domestic pigs (Ellegard, Dalmose, Denmark) weighing 31.5± 0.5 kg (mean±SD).

Anesthesia

After overnight fasting, the pigs were premedicated with intramuscular ketamine (20 mg/kg) and atropine (0.05 mg/kg). Anesthesia was induced with thiopental (5–10 mg/kg i.v.). The trachea was intubated and the lungs were mechanically ventilated (Siemens, SV 900 B, Stockholm, Sweden) with fractional inspired oxygen (F_iO_2) of 0.5. Ventilation was facilitated by an intravenous bolus of pancuronium (0.1 mg/kg) followed by a continuous infusion (0.12 mg/kg per h). F_iO_2 was reduced to 0.21 after the end of the surgical preparation. Minute ventilation was adjusted to maintain an arterial carbon dioxide tension ($PaCO_2$) between 33 and 38 mmHg. Anesthesia was continued with an intravenous infusion of ketamine (4 mg/kg per h) and flunitrazepam (0.0125 mg/kg per h). Body temperature was monitored with the thermistor of a pulmonary artery thermodilution catheter (model 93A-131-7F, Edwards Laboratory, Santa Ana, Calif., USA) and kept constant at 38.5±0.5 °C using a warming blanket and overhead heating devices. All animals received a baseline infusion of Ringer's lactate (30 ml/kg per h). Intermittent boluses of 100–250 ml of hydroxyethyl starch (6% HES 70/0.5, Kabi Pharmacia GmbH, Erlangen, Germany) were infused when the hemoglobin content indicated hemoconcentration.

Preparation

A catheter was placed into the carotid artery (Insyte 14G, Beckton-Dickinson, Sandy, Utah, USA), a flow-directed pulmonary-artery thermodilution catheter into the pulmonary artery and a double lumen catheter (Deltacath Bilumen, Beckton-Dickinson, Sandy, Utah, USA) into the superior vena cava via the left and right external jugular veins. A median laparotomy was performed and the superior mesenteric vein (SMV) was cannulated via the splenic vein (Seldiflex 1.7 mm, 20 cm, Plastimed, St-Leu-La-Foret Cedex, France). A tight fitting electromagnetic flow probe (Hellige, Germany) and a customized mechanical screw occluder were positioned around the superior mesenteric artery (SMA). A small jejunotomy was made 3 m proximal to the ileocecal valve and a tonometer (Tonomitor, Tonometrics, Worcester, Mass., USA) was advanced into the lumen of the small intestine; 50 cm distally from the tip of the tonometer a jejunostomy was prepared. The laparotomy was closed by sutures and clamps that allowed a small opening at the time of the readings. Finally, a urinary catheter was placed in the bladder by a minilaparotomy.

Measurements

Cardiac output was determined in triplicate by thermodilution technique (Edwards model 9520 A, Santa Ana, Calif., USA). The arterial line as well as the proximal and distal parts of the pulmonary artery catheter were connected to pressure transducers (Abbott Laboratories, North Chicago, Ill., USA). A calibrated electromagnetic flow probe was used to determine SMA blood flow. All pressures, the signal of the electrocardiogram and the SMA flow were recorded using a multichannel recorder (Hellige, Germany).

Blood gases (arterial, pulmonary arterial and superior mesenteric venous) were measured with a blood-gas analyzer (IL 1302, Instrumentation Laboratories, Middlesex, United Kingdom). Hemoglobin content and saturations were determined using a hemoximeter (OSM 3 Radiometer, Copenhagen, Denmark) calibrated for pig hemoglobin. Oxygen transport indices were calculated using standard formulas. Cardiac output, flow in the SMA and the oxygen transport variables were normalized to kilogram body weight.

Jejunal mucosal carbon dioxide tension ($P_{tono}CO_2$) was determined using a tonometer [7]. Jejunal pH_i was calculated using the formula supplied by the manufacturer. The balloon of the tonometer was filled with 3 ml 0.9% sodium chloride (NaCl). One measurement was made during each experimental period, and a period of 30 min was allowed for equilibration. To demonstrate that the changes of the arterial PCO_2 or metabolic derangements had no important effect on the pH_i values in our model, we calculated the tonometric minus the arterial PCO_2 difference (P_{tono}-aCO_2).

At the reading time points, the oxygen tensions on the jejunal surfaces were measured through the jejunostomy for the mucosa and through a small opening in the abdominal wall for the serosa. The same locations were used during the entire experiment. The measuring set-up contained a multiwire platinum electrode (Eschweiler, Kiel, Germany) connected via an interface (Eschweiler, Kiel, Germany) to a computer using a commercial software package (POWIN, Mussler, Aachen, Germany) designed for this purpose. Each P_sO_2 measurement was recorded in the form of a histogram. One histogram contains about 100 single P_sO_2 values from 15 electrode positions. The P_sO_2 value for a particular time and location is the arithmetic mean of a group of 100 P_sO_2 values for that time and location.

Experimental protocol

After the preparations had been completed, 1 h was allowed for stabilization before baseline readings were obtained. The animals were randomly allocated to have a SMA flow of 0% ($n=4$), 25% ($n=4$), 38% ($n=5$), 50% ($n=4$) or 100% ($n=3$; control) of their baseline SMA flow during the period of ischemia. At baseline, after 60 min of ischemia and after 60 min of reperfusion, the following data were collected: global hemodynamic measurements, SMA flow, pH_i, P_sO_{2m}, P_sO_{2s} arterial, SMV and pulmonary-artery hemoglobin content, hemoglobin saturation, PO_2, PCO_2, and pH. At the end of the experiment, a piece of the jejunum between the jejunostomy and the tonometer balloon was excised and immediately fixed in a 5% formalin solution; the animals were then killed.

Histologic examination

Histologic examination of the jejunum using standard techniques was performed by the same pathologist, who was blinded for the SMA flow rate of the particular animal. The histologic lesions were graded as follows: 1 = normal, 2 = necrosis of the tip of the villus, 3–5 = increasing necrosis of the villus, 6 = total necrosis of the villus, 7 = necrosis of part of the crypt, 8 = necrosis to the end of the crypt.

Data analyses

To describe the response of pH_i to DO_{2ms} we used the sigmoid Emax function [26]. Linear regression analysis was used to describe linear correlations between two variables: r is the correlation coefficient and p the probability that the slope equals zero. The correlation between SMA flow group and grade of histologic damage was tested with the Spearman rank correlation. Data were analyzed by one-way ANOVA, for repeated measurements where appropriate. Significant results were further evaluated by the Tukey-Kramer posthoc test. Values are expressed as means ± standard error (SE). Statistical significance was accepted at $p<0.05$.

Results

The degree of flow reduction in the SMA and the subsequent severity of mesenteric ischemia had only minor impact on global hemodynamic performance, blood gases and systemic oxygen transport variables. Marked changes occurred after reperfusion following total occlusion of the SMA (zero flow group): reduction of cardiac index, hypotension and a decrease of DO_{2tot} (Table 1).

VO_{2ms} was maintained despite the SMA flow reduction and, consequently, VO_{2ms} was not yet dependent on either the SMA flow or DO_{2ms}. However, in the 25% flow group, mean VO_{2ms} was reduced by 24% from 0.80±0.07 to 0.61±0.04 ml/kg per min. This is an indication that in some animals flow dependency of VO_{2ms} might have been present. The reduction in DO_{2ms} was efficiently counterbalanced by a progressive increase in ERO_{2ms} (Fig. 1, Table 2). After reperfusion in the zero flow group, VO_{2ms} fell while ERO_{2ms} did not change compared to baseline.

The progressive reduction in SMA flow and oxygen delivery was associated with a significant decrease in pH_i in all groups (Fig. 2). The intergroup differences during ischemia were significant for control versus 0% flow and control versus 25% flow. After reperfusion pH_i increased in all groups, but only in the 38% and 50% flow groups were the pH_i values completely restored compared to baseline, while in the zero and 25% flow groups pH_i remained abnormal even after reperfusion. The same statistical results were derived from the data after the replacement of pH_i by P_{tono}-aCO_2 (Fig. 2).

Baseline P_sO_2 values were lower in the mucosa (27±1 mmHg) than in the serosa (68±2 mmHg; $p<0.0001$). The incremental SMA flow reduction caused progressive decreases of P_sO_{2s}, P_sO_{2m} and the mesenteric venous oxygen saturation ($Sv_{ms}O_2$), and an increase in the mesenteric venous PCO_2 ($Pv_{ms}CO_2$). After reperfusion, these parameters returned to baseline with the exception of P_sO_{2s} in the zero flow group (Table 2). During the experimental manipulation of the SMA flow pH_i showed a significant linear correlation with both P_sO_{2s} and P_sO_{2m} (Fig. 3). Moreover, there was a significant correlation between pH_i and DO_{2ms}. The scatter plot of individual data with DO_{2ms} as the independent and pH_i or P_{tono}-aCO_2 as the dependent variables suggested that there may be a sigmoid relationship between these variables (Fig. 1). This was confirmed by means of the Emax function model, which showed the best fit to the experimental data ($p<0.001$; Fig. 4). Finally, we found that $Sv_{ms}O_2$ was linearly correlated with the mesenteric venous carbon dioxide tension ($Pv_{ms}CO_2$). $P_{tono}CO_2$, however, had a biphasic relationship with $Sv_{ms}O_2$ (Fig. 5).

Histologic lesions were present only in the group of animals with total occlusion (one animal grade 8, one grade 5, two grade 4) of the SMA and in the 25% flow group (one grade 7, one grade 3, one grade 2, one normal). The lesions were limited to the mucosa, whereas the muscular and the serosal layers remained unchanged. The flow groups and the grade of histologic damage were correlated: Spearman $r = -0.81$, $p<0.0001$.

Discussion

Presently the measurement of gastric mucosal pH_i is the only bedside source of information regarding the adequacy of mesenteric oxygen supply. The validity of the method, however, still remains controversial. Therefore, we decided to study the indirectly derived changes in pH_i in an animal model of intestinal ischemia and reperfusion, and to relate the observed pH_i changes to directly measured parameters of intestinal oxygenation.

The changes in pH_i during varying levels of SMA flow reduction have not been studied before. Our data show that pH_i consistently responds to a decrease in SMA flow in the studied range of flow reduction (Fig. 2). Even with the moderate 50% flow reduction the group mean of pH_i fell to a highly abnormal value of 7.07. While the means of pH_i of the 0% and 25% flow groups differed significantly from the mean of the control group, the remaining groups did not. Beside the small number of animals, the marked scatter of the pH_i values, particularly in the 25–50% flow groups, may have been responsible for this lack of significance. Interestingly, measurements with intramucosal pH glass electrodes revealed standard deviations of the same magnitude [8]. The basis for this variability is unknown. One can speculate that during lesser degrees of mesenteric flow reduction a flow inhomogeneity develops and is reflected by variations in pH_i in different regions of the gut. In such situations a single pH_i value can never be used for the assessment of severity of ischemia.

Table 1 Global hemodynamic and oxygen transport variables (*HR* heart rate, *MAP* mean arterial pressure, *CI* cardiac index, DO_{2tot} total body oxygen delivery, VO_{2tot} total body oxygen consumption, ERO_{2tot} total body oxygen extraction, *pHa* arterial pH, *Hb* arterial hemoglobin)

	Flow 0% (total occlusion; *n*=4)		
	Baseline	Ischemia	Reperfusion
HR (beats/min)	145 ±9	138 ±8	140 ±14
MAP (mmHg)	106 ±9	127 ±4	88 ±7 [c]
CI (mg/kg/min)	112 ±8	91 ±7	70 ±12 [b]
DO_{2tot} (ml/kg/min)	15.8 ±1.6	13.3 ±6	10.1 ±1.5 [a]
VO_{2tot} (ml/kg/min)	3.5 ±0.4	3.4 ±0.3	3.4 ±0.4
ERO_{2tot} (%)	23 ±2	26 ±2	35 ±7
pHa	7.42±0.02	7.41±0.02	7.39±0.02
Hb (mh/dl)	10.2 ±0.2	11 ±0.4	11.4 ±0.6
	Flow 25% (*n*=4)		
	Baseline	Ischemia	Reperfusion
HR (beats/min)	150 ±12	150 ±12	163 ±18
MAP (mmHg)	108 ±3	118 ±3	110 ±7
CI (ml/kg/min)	112 ±16	103 ±7	95 ±6
DO_{2tot} (ml/kg/min)	15.4 ±1.3	14.9 ±0.9	13.9 ±0.4
VO_{2tot} (ml/kg/min)	2.9 ±0.3	3.7 ±0.5	4.3 ±0.3
ERO_{2tot} (%)	19 ±1	25 ±4	31 ±2 [a]
pHa	7.43±0.01	7.45±0.02	7.45 ±0.02
Hb (mg/dl)	10.6 ±0.6	10.9 ±0.4	11.1 ±0.6
	Flow 38% (*n*=5)		
	Baseline	Ischemia	Reperfusion
HR (beats/min)	140 ±8	134 ±7	126 ±6
MAP (mmHg)	120 ±4	130 ±4 [a]	118 ±5 [d]
CI (ml/kg/min)	108 ±4	87 ±4 [b]	95 ±5
DO_{2tot} (ml/kg/min)	15.1 ±0.6	13.6 ±0.8	13.4 ±0.6
VO_{2tot} (ml/kg/min)	3.8 ±0.2	3.6 ±0.1	3.7 ±0.1
ERO_{2tot} (%)	25 ±1	26 ±1	28 ±2
pHa	7.42±0.03	7.44±0.02	7.47±0.01
Hb (mg/dl)	10.7 ±0.4	11.9 ±0.4 [a]	10.7 ±0.3 [d]
	Flow 50% (*n*=4)		
	Baseline	Ischemia	Reperfusion
HR (beats/min)	135 ±9	143 ±8	138 ±12
MAP (mm/Hg)	118 ±5	129 ±6	119 ±1
CI (ml/kg/min)	108 ±13	95 ±6	98 ±14
DO_{2tot} (ml/kg/min)	13.6 ±1	13.3 ±0.7	12.1 ±0.8
VO_{2tot} (ml/kg/min)	3.4 ±0.4	4 ±0.4	3.6 ±0.4
ERO_{2tot} (%)	25 ±2	30 ±2 [a]	30 ±1
pHa	7.42±0.02	7.43±0.03	7.46±0.04
Hb (mg/dl)	9.8 ±0.5	10.7 ±0.3 [a]	9.7 ±0.6 [d]
	Flow 100% (control; no flow reduction; *n*=3)		
	Baseline	Ischemia	Reperfusion
HR (beats/min)	176 ±3	157 ±12	143 ±7
MAP (mmHg)	112 ±8	118 ±6	115 ±3
CI (ml/kg/min)	109 ±13	99 ±16	89 ±9
DO_{2tot} (ml/kg/min)	15.1 ±1.2	13.6 ±1.3	12.5 ±0.5
VO_{2tot} (ml/kg/min)	3.6 ±0.2	3.2 ±0.3	3.4 ±0.1
ERO_{2tot} (%)	23 ±3	24 ±3	27 ±2
pHa	7.44±0.01	7.46±0.01	7.47±0.02
Hb (mg/dl)	10.9 ±0.8	10.5 ±0.8	10.5 ±0.8

[a] $p<0.05$ compared to baseline
[b] $p<0.01$ compared to baseline
[c] $p<0.05$ compared to ischemia, $p<0.05$ compared to group 38%, 50%, and to control
[d] $p<0.05$ compared to ischemia

Several studies have shown that intestinal ischemia may develop in the absence of abnormalities in systemic hemodynamics, systemic oxygen delivery, arterial lactate concentration and pH [11, 18–21]. These indices usually become abnormal when the ischemia is extended or severe and when therapeutic interventions are of limited value. Consistent with these data, we did not observe a change of global oxygen parameters during SMA flow reduction. This finding is in agreement with recent studies of pH_i in critically ill trauma patients [27] and in septic pediatric patients [28]. After reperfusion, however, in the group with total occlusion of the SMA we found a significant de-

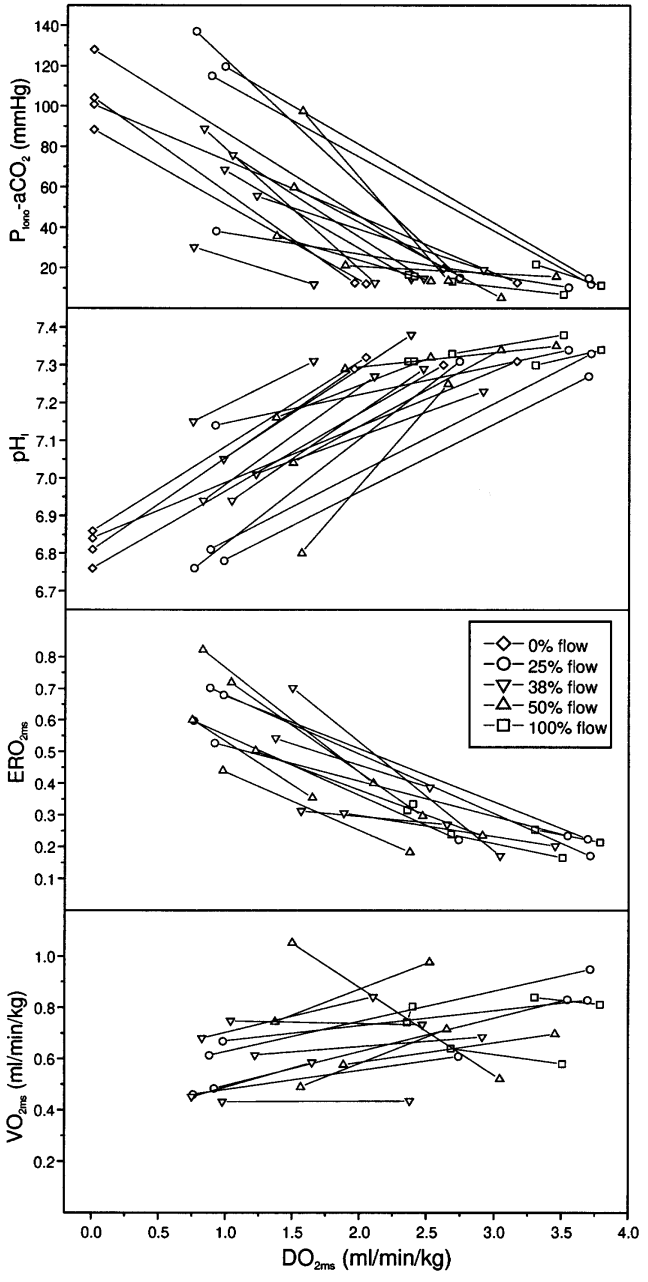

Fig. 1 Relationship between DO_{2ms}, VO_{2ms}, ERO_{2ms}, pH_i and P_{tono}-aCO_2 at baseline and after flow reduction in the SMA. The corresponding data for baseline and flow reduction in individual animals are linked

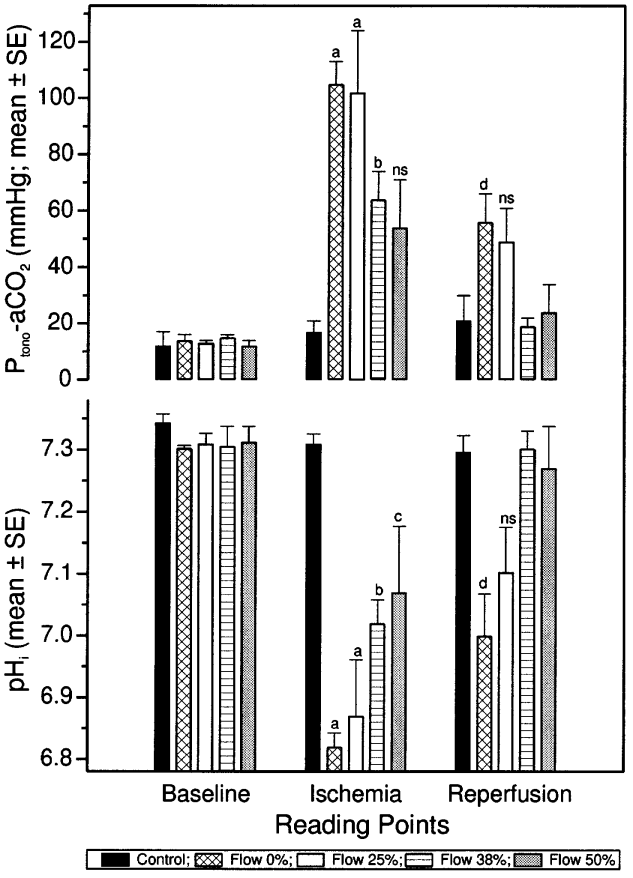

Fig. 2 Effects of SMA flow reduction (% of baseline) and reperfusion on jejunal intramucosal pH (pH_i) and tonometric minus arterial carbon dioxide tension (P_{tono}-aCO_2)
[a] $p<0.01$ to baseline and to control; [b] $p<0.01$ to baseline; [c] $p<0.05$ to baseline; [d] $p<0.01$ to baseline and to group 38%, $p<0.05$ to group 50% and to control; [ns] not significant

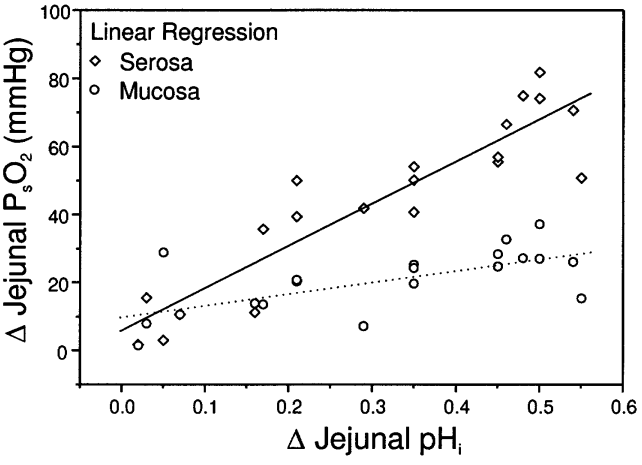

Fig. 3 Linear regression of the changes from baseline to SMA flow reduction for jejunal pH_i and polarographic oxygen tensions from the jejunal serosa and mucosa (Serosal regression line: y=6+124x; $p<0.0001$; $r=0.92$; $n=20$. Mucosal regression line: y=10+33x; $p<0.01$; $r=0.65$; $n=20$)

crease in cardiac index, blood pressure and oxygen delivery that may be due to a release of cardiodepressant mediators and peripheral pooling.

To our knowledge this is the first study that relates different DO_{2ms} values elicited by occlusive SMA flow reduction to pH_i. The relationship between DO_{2ms} and pH_i seems to be expressed best by a sigmoid curve corresponding to a Emax function (Fig. 4). The Emax function

Table 2 Mesenteric oxygen transport variables and surface oxygen tensions (DO_{2ms} mesenteric oxygen delivery, VO_{2ms} mesentric oxygen consumption, ERO_{2ms} mesenteric oxygen extraction, P_sO_{2s} serosal surface oxygen tension (jejunum), P_sO_{2m} mucosal surface oxygen tension (jejenum), $Pv_{ms}CO_2$ mesenteric venous carbon dioxide tension, $Sv_{ms}O_2$ mesenteric venous oxygen saturation)

	Flow 0% (total occlusion; n=4)		
	Baseline	Ischemia	Reperfusion
DO_{2ms} (ml/kg/min)	2.44±0.28	0 ±0	2.18±0.34 [n]
VO_{2ms} (ml/kg/min)	0.64±0.01		0.41±0.05 [o]
ERO_{2ms} (%)	27 ±3		21 ±5
P_sO_{2s} (mmHg)	70 ±3	3 ±1 [b]	54 ±3 [j]
P_sO_{2m} (mmHg)	28 ±3	0 ±2 [c]	23 ±4
$Pv_{ms}CO_2$ (mmHg)	44 ±1		43 ±2
$Sv_{ms}O_2$ (%)	71 ±3		76 ±5
	Flow 25% (n=4)		
	Baseline	Ischemia	Reperfusion
DO_{2ms} (ml/kg/min)	3.42±0.23	0.97±0.05 [d]	3.85 ±0.53
VO_{2ms} (ml/kg/min)	0.8 ±0.07	0.61±0.04	0 .75±0.08
ERO_{2ms} (%)	23 ±1	63 ±4 [e]	21 ±3
P_sO_{2s} (mmHg)	68 ±5	4 ±6 [f]	58 ±2
P_sO_{2m} (mmHg)	23 ±3	–2 ±2 [g]	20 ±8
$Pv_{ms}CO_2$ (mmHg)	44 ±2	67 ±7 [k]	41 ±2
$Sv_{ms}O_2$ (%)	74 ±1	36 ±4 [k]	77 ±3
	Flow 38% (n=5)		
	Baseline	Ischemia	Reperfusion
DO_{2ms} (ml/kg/min)	2.3 ±0.21	0.96±0.08 [h]	2.55 ±0.20
VO_{2ms} (ml/kg/min)	0.66±0.07	0.58±0.06	0.63 ±0.02
ERO_{2ms} (%)	29 ±4	62 ±7 [i]	26 ±3
P_sO_{2s} (mmHg)	64 ±4	20 ±4 [a]	63 ±5
P_sO_{2m} (mmHg)	28 ±3	7 ±3 [k]	24 ±2
$Pv_{ms}CO_2$ (mmHg)	44 ±1	54 ±3 [j]	40 ±1
$Sv_{ms}O_2$ (%)	68 ±4	37 ±7 [k]	73 ±3
	Flow 50% (n=4)		
	Baseline	Ischemia	Reperfusion
DO_{2ms} (ml/kg/min)	2.92±0.21	1.58 ±0.11 [l]	2.85 ±0.29
VO_{2ms} (ml/kg/min)	0.73±0.09	0.72 ±0.12	0.81 ±0.09
ERO_{2ms} (%)	26 ±5	47 ±10	30 ±6
P_sO_{2s} (mmHg)	68 ±5	37 ±13 [k]	63 ±4
P_sO_{2m} (mmHg))	31 ±1	16 ±4 [m]	30 ±2
$Pv_{ms}CO_2$ (mmHg)	49 ±3	54 ±2	45 ±2
$Sv_{ms}O_2$ (%)	72 ±5	52 ±9	67 ±6
	Flow 100% (control; no flow reduction; n=3)		
	Baseline	Ischemia	Reperfusion
DO_{2ms} (ml/kg/min)	3.22±0.44	2.79 ±0.27	2.65 ±0.21
VO_{2ms} (ml/kg/min)	0.71±0.07	0.76 ±0.06	0.65 ±0.02
ERO_{2ms} (%)	23 ±4	28 ±3	25 ±3
P_sO_{2s} (mmHg)	76 ±2	70 ±4	64 ±3
P_sO_{2m} (mmHg)	33 ±8	26 ±6	31 ±3
$Pv_{ms}CO_2$ (mmHg)	45 ±2	43 ±2	42 ±1
$Sv_{ms}O_2$ (%)	76 ±5	72 ±4	75 ±3

[a] p<0.01 to baseline and to control
[b] p<0.01 to baseline, p<0.05 to group 50%, and control
[c] p<0.01 to baseline to group 50%, and to control
[d] p<0.01 to baseline, to group 0%, 50% and control
[e] p<0.01 to baseline and p<0.05 to control
[f] p<0.01 to baseline, to group 50%, and to control
[g] p<0.05 to baseline and to group 50%, p<0.001 to control
[h] p<0.01 to baseline, to 0% and to control
[i] p<0.01 to baseline, p<0.05 to control
[j] p<0.01 to baseline
[k] p<0.05 to baseline and to control
[l] p<0.01 to baseline and all groups
[m] p<0.05 to baseline
[n] p<0.05 to group 25%
[o] p<0.01 to baseline and to group 25%, p<0.05 to group 50%

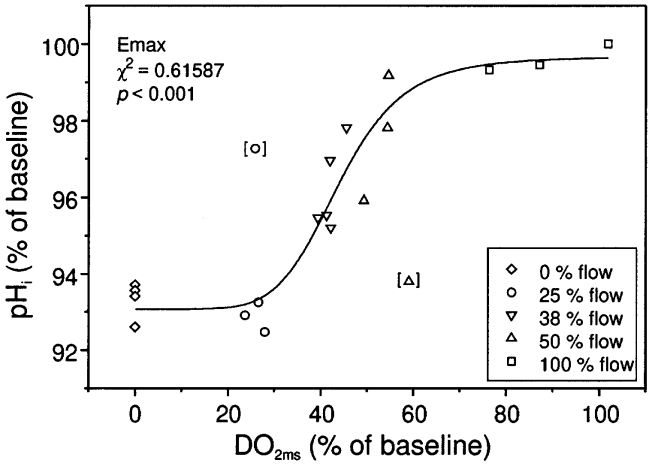

Fig. 4 Relationship between DO_{2ms} and jejunal pH_i after SMA flow reduction. The values are expressed as a percentage of their baseline. The Emax model was used to calculate the sigmoid curve. The outliers in brackets [ ] were excluded from the Emax analysis.

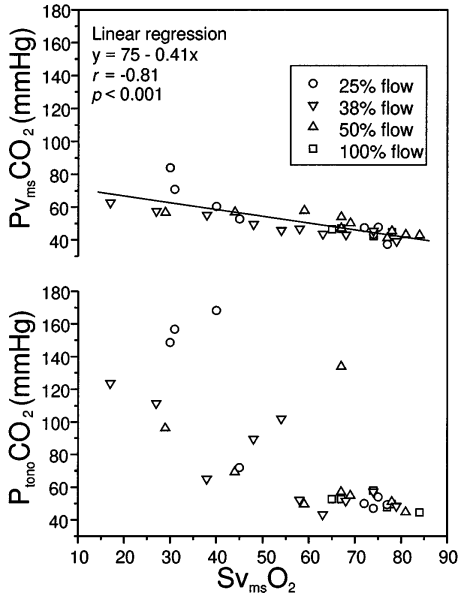

Fig. 5 Relationship between $Pv_{ms}CO_2$, $P_{tono}CO_2$ and $Sv_{ms}O_2$ for individual animals at baseline and after SMA flow reduction. $Sv_{ms}O_2$ and $Pv_{ms}CO_2$ (*upper graph*) were analyzed by linear regression. The figure shows the exaggerated increase of the carbon dioxide tension in the tonometer balloon (*lower graph*) compared with that in the mesenteric vein (*upper graph*) as a function of the mesenteric venous oxygen saturation

is able to illustrate extremes of response [26]. Because we wanted to model the extreme of the pH_i response to DO_{2ms} reduction, we used Emax in our animal model. This three-phase relationship can be explained as follows: over a wide range of DO_{2ms}, pH_i does not change because the decreasing DO_{2ms} is fully compensated by an increase in ERO_{2ms} (upper plateau). At a given critical value of DO_{2ms}, pH_i starts to decrease rapidly with any further reduction of DO_{2ms} (steep portion). The low pH_i reflects the accumulation of carbon dioxide due to low flow and buffered hydrogen ions from anaerobic metabolism. The presence of the countercurrent exchanger of the mucosal villi [29], which produces an important oxygen gradient between the base and the tip of the villus, and the high oxygen demand of the mucosa explain the vulnerability of the mucosal layer to DO_{2ms} reduction. Consequently, the mucosa becomes ischemic at DO_{2ms} values that are still adequate for neighboring tissues. Hence, pH_i reflecting only mucosal perfusion reaches its lowest values at a DO_{2ms} above zero (lower plateau). Although other investigators did not observe a plateau of pH_i at low DO_{2ms} values [5, 23], these results cannot be compared with our findings because of methodological differences: the reduction of DO_{2ms} was effected by different means, the previous study designs resulted in last analysis time points with low but unstable DO_{2ms} values, and, finally, different animal models were used. Our three-phase relationship, however, is supported by the first report to validate tonometric analysis [8]; we note that these investigators also found the same pH_i for a group with a flow reduction to 25% of baseline and the zero flow group.

It might be difficult to understand why pH_i should stop decreasing below a DO_{2ms} of 25% baseline. However, there is still another way to look at the problem: it might also be possible that the pH_i values of the 25% flow group derived from a mucosa that was almost completely ischemic. If this is true for our experiments, it would not be astonishing that the pH_is of the 25% and the zero flow groups are in the same magnitude. This view is supported by the fact that the grades of the histologic lesions were nearly the same in the zero and in the 25% flow group. We believe, therefore, that it is important to realize that the sigmoid relationship that we found between pH_i and DO_{2ms} cannot be explained only by pathophysiologic mechanisms. But, in addition to the general discussion on the tissue production of carbon dioxide during low flow states, which consists of several hypotheses [30], methodological reasons also might be responsible for the sigmoid relationship between pH_i and DO_{2ms} in our study.

We were unable to detect a relationship between pH_i and VO_{2ms}. This was unexpected because a decreasing intracellular pH is an indication that oxygen consumption is supply-dependent and, therefore, should decrease with decreasing oxygen delivery [5]. However, previous studies showed that this association is not easily demonstrable because the supply dependency of VO_{2ms} is not manifest until DO_{2ms} becomes relatively low [2]. In our study, VO_{2ms} in the 25% flow group was not statistically different from the higher flow groups. However, the decrease of 24% of VO_{2ms} from baseline to flow reduction in the 25% flow group indicates that, in some animals, flow dependency was present, and we speculate that overall flow depen-

dency starts at about 75% flow reduction from baseline. Also, different methods of DO_{2ms} reduction (SMA flow reduction, SMA flow reduction combined with hypoxia) elicit distinct critical points of DO_{2ms} at which VO_{2ms} begins to decrease [5]. The situation is more complex in studies with induced sepsis. Fink et al. showed that the infusion of endotoxin in pigs induced a decrease of DO_{2ms} and pH_i but VO_{2ms} was maintained [13, 24, 31]. Very recently, it was shown that VO_{2ms} remained stable during heavy bleeding with decreasing DO_{2ms} and pH_i [25]. These diverging results minimally demonstrate that the relationship of DO_{2ms} and pH_i is not comparable to DO_{2ms} and VO_{2ms}. There appear to be mechanisms responsible for the early decrease of pH_i other than inadequate oxygen supply. One possibility might be related to the accumulation of carbon dioxide [32]. Alternatively, the relationship between DO_{2ms} and pH_i may be more sensitive to impaired mucosal oxygen supply than that between DO_{2ms} and VO_{2ms}.

Intestinal polarographic oxygen tensions have been used in patients intraoperatively [33] and in animals experimentally [34–36] to assess the adequacy of intestinal perfusion. These studies have shown that the P_sO_2 of the gut correlates well with oxygen delivery [35] and SMA artery flow [36]. In our study, the changes of P_sO_{2s} and P_sO_{2m}, obtained at the same part of the gut as the pH_i values, correlated well with the change of pH_i (Fig. 3). Our study also confirmed the marked difference of the P_sO_{2m} and P_sO_{2s} [34]. This is consistent with the presence of a countercurrent exchanger in the villi and may explain, in part, why the mucosa is more susceptible to ischemia. Another, perhaps more important, mechanism is the higher mucosal oxygen demand relative to blood flow, which is caused by the high metabolic activity of the mucosa compared to the serosa. The responses of the mucosa and the serosa to flow reduction were similar, thus permitting the P_sO_{2s} values to be related to P_sO_{2m} values. This relationship could be of clinical interest, although it will be important to determine if a corresponding relationship exists in humans.

The increase in mucosal PCO_2 assessed by tonometry as $P_{tono}CO_2$ and the consequent decrease in pH_i can be caused by two different mechanisms. First, the increased PCO_2 results from buffering protons released by unreversed phosphate hydrolysis in a severely dysoxic state. Second, PCO_2 can increase because of the reduced blood flow's being incapable of transporting carbon dioxide [23, 30]. It is important to distinguish between these alternatives because the presence of dysoxia means that the oxygen supply no longer meets the needs of the tissue and cell damage is imminent. In our study, the correlation between $Sv_{ms}O_2$ and $Pv_{ms}CO_2$ was linear (Fig. 5). This negative linear relationship implicates a carbon dioxide increase due to flow reduction but not due to dysoxia [23]. In contrast, the correlation between $Sv_{ms}CO_2$ and P_{tono}-CO_2 was biphasic (Fig. 5) with a disproportional increase in $P_{tono}CO_2$ at low flows. This phenomenon is likely to reflect inadequate carbon dioxide transport and production due to dysoxia, which is in accordance with the results of Schlichtig and Bowles [23], who demonstrated that the tonometer is capable of detecting mucosal acidosis produced by dysoxia in dogs.

There are some important limitations of the model which have to be addressed. First, we measured jejunal and not gastric pH_i, the latter being used mostly in clinical situations. Our intention was to investigate the effects of occlusion of the SMA. Because the SMA mainly supplies the gut with blood and not the stomach, it was necessary to measure pH_i in the gut. Second, we evaluated the effects of the regional impairment of blood supply and the results are not necessarily valid for systemic disorders such as hemorrhage or sepsis. Third, our model does not permit conclusions about the influence of metabolic derangements on pH_i. We calculated P_{tono}-aCO_2 in order to eliminate the effects of arterial carbon dioxide and the arterial bicarbonate concentration. We found that replacement of pH_i by P_{tono}-aCO_2 did not change the statistical results or the characteristics of the graphs. Therefore, we concluded that our model was sufficiently stable. However, elucidation of the influence of metabolic and respiratory derangements on pH_i, P_{tono}-aCO_2 or other calculated tonometric indices requires further investigations. Further studies are also needed to clarify the sigmoid relationship between pH_i and DO_{2ms} and to elucidate its clinical relevance.

In summary, pH_i, assessed by gut tonometry, had a three-phase relationship with DO_{2ms}. The variability of the mean pH_i values of the flow groups indicates the difficulty in correlating pH_i with the severity of gut ischemia. SMA flow markedly affected P_sO_{2m} and P_sO_{2s}; both of these parameters were linearly related to pH_i. In contrast, whole body oxygen transport variables did not show a relationship with gut ischemia. In the investigated flow range of 25–50% of SMA baseline flow, VO_{2ms} did not detect impaired oxygen supply. Finally, our data demonstrate that a tonometer can be used to measure acidosis caused by both carbon dioxide accumulation and dysoxia.

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