Gut intramucosal pH and intraluminal PO₂ in a porcine model of peritonitis or haemorrhage

J B Antonsson, U H Haglund

Abstract

The tonometric method of detecting decreased gut intramucosal pH (pH_i) is based on the fact that carbon dioxide can diffuse through the wall of the silastic balloon of the tonometer. By using deoxygenated saline and measuring PO₂ as well as PCO₂, this study aimed to follow changes in mucosal PO₂ and relate them to changes in pH_i in peritonitis versus haemorrhage. Twenty five pigs were used. Five were controls, in 10 peritonitis was induced by the instillation of faeces in the abdominal cavity, and 10 were bled, half of them stepwise during three hours, and half of them rapidly down to a mean (SEM) arterial pressure of 30 (10) mm Hg. The drop in pH_i correlated well with decreasing intraluminal PO₂ ($r=0.63$ (0.13)) in haemorrhage. In peritonitis this drop occurred within a very limited change in intraluminal PO₂ ($r=0.06$ (0.17)). Thus oxygen seemed to be present in the mucosa at the same time as there were signs of anaerobic metabolism as evidenced by a low intramucosal pH. Impaired oxygen extraction or utilisation, or both, is proposed as an explanation to this seemingly paradoxical situation.

(Gut 1995; 37: 791-797)

Keywords: oxygen consumption, oxygen delivery, sepsis, small bowel, tonometry.

As the gut is an organ that suffers from early ischaemia during shock and as the ischaemic gut can act as a 'motor of shock' and thus aggravate the shock state, it has been shown to be of benefit to monitor gut ischaemia in experimental animals and patients in shock.^{1,2} This can be accomplished by the use of a tonometer, with which intramucosal pH (pH_i) can be calculated. Low pH_i is a sign of ischaemia, as anaerobic metabolism results in an accumulation of acid metabolites with increasing tissue acidity as a consequence. Ischaemia is mainly considered to be caused by an inadequate oxygen delivery to the gut, but earlier experiments show that in septic states other factors play an important part.³ Rasmussen and Haglund have shown that in the early stages of septic shock there is a drop in pH_i when oxygen delivery is still unaffected or even increased.⁴

It might seem more obvious to monitor gastrointestinal tissue oxygen tension directly, but technical difficulties have limited the use of methods for direct measurements in clinical practice.^{5,6} In 1964 Bergofsky could estimate PCO₂ and PO₂ in urinary and gall bladders by measuring PCO₂ and PO₂ in saline

that had been instilled in them. He could, by this method detect differences in PO₂ caused by different concentrations of O₂ in air inhaled.⁷ Dawson *et al* later used this technique in a loop of the small bowel.⁸ By measuring PO₂ intraluminally in a hollow viscus they could thus detect changes in tissue oxygen tensions. Using a gas permeable silastic tube inserted subcutaneously and flushing it slowly with anoxic saline to determine PO₂ of the perfusate Niinikoski and Hunt could estimate subcutaneous tissue PO₂.⁹ The tonometric method of determining gut intramucosal pH is a combination of these techniques. Here CO₂ of gut mucosa and lumen diffuses through the wall of a permeable balloon to its content of saline.¹⁰

The aim of this study was to monitor intramucosal pH in experimental animals (pigs) during peritonitis or haemorrhage. By using deoxygenated saline in the tonometer and measuring PO₂ of the fluid as well, intraluminal PO₂ could also be monitored. This will allow the relation between pH_i and intraluminal PO₂ to be studied and to find out if the relations differ in peritonitis versus haemorrhage.

Methods

Medication and instrumentation

After 12 hours of starvation but with full access to water, 25 Landrace pigs of both sexes with a mean weight of 19.1 kg (range 15-22), were premedicated with ketamine (Ketalar, Parke-Davis, NJ), 7 mg/kg. They were then anaesthetised with an intravenous injection of pentobarbital, 20 mg/kg. The animals were intubated through a tracheostomy and connected to a respirator (Servo Ventilator System, Siemens-Elema, Sweden) and ventilated with a mixture of oxygen and room air to give an O₂ concentration of 40% in air inhaled. Respiration was adjusted to give an arterial PCO₂ of 40 (5) mm Hg. Anaesthesia was maintained with a continuous infusion of pentobarbital, 18 mg/h; this drug was given in 2.5% glucose (Rehydrex, Pharmacia, Uppsala, Sweden) at a rate of 15 ml/kg/h. Furthermore, an infusion of Ringer's acetate, 30 ml/kg/h, was given from the induction of anaesthesia. Thus, the total amount of fluid infusion was 45 ml/kg/h.

Bilateral neck cutdowns were performed: a polyethylene catheter was positioned through the carotid artery in the thoracic aorta and connected to a pressure transducer (PDCA 75, Druck Ltd, Groby, Leicestershire, UK) for recording of arterial pressure. One cephalic

Department of
Surgery, University
Hospital, Uppsala,
Sweden
J B Antonsson
U H Haglund

Correspondence to:
Dr J Antonsson, Department
of Surgery, University
Hospital, S-751 85 Uppsala,
Sweden.

Accepted for publication
21 April 1995

vein was used for infusion and the other cannulated for injection of saline for determination of cardiac output; the thermodilution method was used and the results are the calculated means from three consecutive measurements (Oximetrix 3 computer, Abbott Laboratories, North Chicago, IL). A Swan-Ganz catheter was positioned in the pulmonary artery through a jugular vein and connected to the pressure transducer, its position being secured by the typical pressure pattern.

Through a skin incision the left femoral artery was cannulated for blood sampling and bleeding.

A midline laparotomy was performed. The superior mesenteric artery was identified close to its origin from the aorta and was cleaned from the surrounding tissue. An ultrasonic flow probe (Transsonic Systems, Ithaca, NY) was placed around the vessel and connected to a blood flow meter (T 201, Transsonic Systems, Ithaca, NY). A vein in the mesenterium of jejunum was cannulated and a catheter was positioned with its tip in the superior mesenteric vein. A small anti-mesenteric incision was made in the mid-ileum and a tonometer (Tonometor, Tonometrics Inc, Bethesda, MD) was placed in the lumen of the gut and secured with a purse string suture. In 10 animals autologous faeces were secured from a colostomy, which thereafter was closed with a purse string suture. The laparotomy was then closed, and the animals were allowed to rest for a period of one hour.

Experimental design

The animals were allocated into five groups ($n=5$ in all groups). One group served as controls (group C). In 10 animals the laparotomy was reopened after the resting period and peritonitis was induced by the instillation of autologous faeces immersed in 50 ml of saline into the abdominal cavity, whereafter the laparotomy wound was closed. In five of these $1 \text{ g} \times \text{kg}$ bw of faeces was used; in five $2 \text{ g} \times \text{kg}$ bodyweight. All these animals were infused with 45 ml/kg/h of fluid, as described above, from the start of anaesthesia till the end of the experiment. In group B I blood was withdrawn: 25% of the estimated blood volume at time=0, 15% at $t=1$ hour, 5% at $t=2$ hours, and 5% at $t=3$ hours. Blood volume was calculated on body weight.¹¹ From $t=0$ these animals were given only 15 ml/kg/h of 2.5% glucose with pentobarbital, no Ringer's acetate was given. Group B II was bled over a period of half an hour down to an arterial pressure of 30 mm Hg. If needed, additional bleedings were performed to keep the arterial pressure at 30 ± 10 mm Hg. The same fluid regimen as in group B I was used. These two different models of haemorrhage were chosen to ensure one group with milder response (B I) and one with severe response (B II) within a limited time scope.

All animals were followed up for five hours with hourly haemodynamic measurements and sampling from arterial, central mixed venous, and mesenteric venous blood. The samples were analysed for blood gases (ABL 300,

Figure 1: Mean (SEM) values of mean arterial pressure (MAP – open circles and full line) and cardiac index (CI – filled circles and broken line). For description of groups, see text. *Values significantly ($p < 0.05$) different from baseline; †significant ($p < 0.05$) difference from controls.

Radiometer, Copenhagen, Denmark) and oxygen saturation and haemoglobin (OSM 3 HemoximeterTM, Radiometer, Copenhagen, Denmark).

Gut intramucosal pH (pH_i) and gut intraluminal PO₂

The tonometric method for calculation of gut intramucosal pH (pH_i) has been described before.^{10,12} The balloon of the tonometer placed in the mid-ileum was filled with 2.5 ml of saline. After one hour of equilibration through the wall of the balloon the saline was aspirated and PCO₂ and PO₂ of the sample determined in the blood gas machine. PCO₂ from the tonometer and simultaneously obtained arterial [HCO₃⁻] were used in the Henderson-Hasselbalch equation for calculation of pH_i.

The saline was flushed with nitrogen for at least one hour before the start of the experiment. PO₂ of the saline was tested on four separate occasions during these procedures with three samples at each time: mean (SEM) PO₂ was 173.9 (7.4) mm Hg before, and 23.4 (1.6) mm Hg after one hour of nitrogen flushing.

Calculation of oxygen delivery (DO₂) and consumption (VO₂)

Oxygen content (Co₂) was determined according to the equation: Co₂ = (PO₂ × 0.003) + (Hgb × So₂ × 1.36), where Hgb is haemoglobin and So₂ is oxygen saturation. DO₂ = Cardiac index × C_aO₂, where C_aO₂ is oxygen content of arterial blood.

VO₂ = Cardiac index × (C_aO₂ - C_vO₂), where C_vO₂ is oxygen content of central mixed venous blood.

Gut DO₂ = (SMA flow kg⁻¹) × C_aO₂.

Gut VO₂ = (SMA flow kg⁻¹) × (C_aO₂ - C_{smv}O₂), where C_{smv}O₂ is oxygen content of blood from the superior mesenteric vein.

Statistical methods

Data were analysed using a two way (group and time) analysis of variance (ANOVA) for repeated measures with Duncan's new multiple range test. Differences with respect to baseline within a group were analysed by using a one way ANOVA with Duncan's new multiple range test. Differences with respect to controls at matched time points were assessed by Mann-Whitney U test. p Values < 0.05 were considered significant. All results are given as mean (SEM).

Figure 2: Mean (SEM) values of gut oxygen delivery (gut DO₂ - open squares and full line) and gut oxygen consumption (gut VO₂ - filled squares and broken line). For description of groups, see text. *Values significantly (p < 0.05) different from baseline; †significant (p < 0.05) difference from controls.

TABLE I Changes in mean (SEM) packed cell volume (%) at baseline, three hours, and end point

	Baseline	Three hours	Five hours
Controls	28.0 (1.4)	28.4 (1.2)	29.0 (1.1)
P I	29.0 (0.5)	38.3 (2.2)*†	38.0 (2.5)*†
P II	28.8 (1.3)	36.5 (2.5)*†	37.2 (2.2)*†
B I	29.6 (1.0)	27.8 (1.6)	22.8 (2.0)*
B II	28.4 (0.7)	21.2 (2.0)*†	20.5 (2.8)*†

*Values significantly ($p < 0.05$) different from baseline; †values significantly ($p < 0.05$) different from controls.

In establishing the relation between pH_i and intraluminal PO_2 in peritonitis and haemorrhage correlation coefficients were calculated for each animal separately, based on all six measure points in every animal. The slopes presented in Fig 5 are the means of the correlation coefficients for animals with peritonitis and haemorrhage, respectively.¹³

Ethics

This study was approved by the Institutional Review Board for the Care of Animal Subjects, and the care and handling of the animals was in accord with National Institutes of Health guidelines for the use of experimental animals.

Results

The response to the introduction of faeces into the abdominal cavity differed considerably from animal to animal and was not correlated to the amount used. Our aim was to have one group with mild and one with a more severe peritonitis, and this was not accomplished by

increasing the amount of faeces. This can be caused by individual differences in the response to faecal challenge and by differences in the amount of bacteria in each faecal sample. Therefore, the results from the animals with peritonitis are presented in two groups independently of the amount of faeces used. Those with the five lowest pH_i – values at end point form a group with more 'severe' peritonitis (P I) whereas those remaining five with higher pH_i at end point constitute the group with 'mild' peritonitis (P II).

The packed cell volume remained unchanged in the control group, whereas a haemoconcentration was noted in the septic groups (P I and P II), and a haemodilution in the haemorrhagic groups (B I and B II) (Table I).

Mean arterial pressure remained stable in controls after an initial rise, probably because of the large amount of fluids given; in the experimental groups there was a continuous decrease in mean arterial pressure (mean arterial pressure in group B II of course had a rapid drop as an arterial pressure of 30 (10) mm Hg was a guideline for the amount of blood to be shed) (Fig 1). A progressive decrease in cardiac index was noted in group C, probably as a result of the cardiodepressing effects of anaesthesia. The decrease in CI was, however, more profound in all experimental groups (Fig 1).

Figure 2 shows the changes in gut oxygen delivery (gut DO_2) and consumption (gut VO_2). Peritonitis as well as haemorrhage resulted in a significant drop in gut DO_2 , whereas no changes in gut VO_2 were noted.

Figure 3: Mean (SEM) values of gut intramucosal pH (pH_i – open triangles and full line) and changes in intraluminal PO_2 (filled triangles and broken line). For description of groups, see text. *Values significantly ($p < 0.05$) different from baseline; †significant ($p < 0.05$) difference from controls.

Both these parameters were unaffected in controls.

pH_i did not change during the experiment in controls. In peritonitis there was a significant drop in both groups: from 7.35 to 7.08 in P I and from 7.31 to 7.18 in P II. It should, however, be noted that pH_i at end point was used to group these animals. There was a drop from 7.32 to 7.02 in B I and from 7.32 to 7.09 in B II (Fig 3). A drop in pH_i can result from either increased gut lumen PCO₂, or decreased [HCO₃⁻], or both. Table II shows [HCO₃⁻] at baseline, three hours, and at end point. From this it can be seen that [HCO₃⁻] showed a significant decrease from baseline only in group B II.

Intraluminal PO₂ did not change in controls and peritonitis (C, P I, and P II). A progressive drop was seen in B I. The rapid bleeding in B II resulted in a rapid drop of intraluminal PO₂ at t=one hour, followed by a plateau and then by a slight decrease (Fig 3).

Figure 4 illustrates the correlation between pH_i and intraluminal PO₂ in controls, haemorrhage, and peritonitis, respectively. Each line represents an individual animal. Based on

TABLE II Changes in mean arterial bicarbonate concentration (mmol/l) at baseline, three hours, and end point

	Baseline	Three hours	Five hours
Controls	26.8	28.9*	29.2*
P I	25.4	24.2†	24.0†
P II	25.9	24.5†	24.0†
B I	25.0	23.8†	23.7†
B II	25.6	19.0*†	22.5*†

*Values significantly (p<0.05) different from baseline; †values significantly (p<0.05) different from controls.

calculations using each measure point in every animal a good correlation was noted in haemorrhage (r=0.63 (0.13)) whereas there was no correlation at all in peritonitis (r=0.06 (0.17)). The difference between them was significant (p<0.002) (Fig 5).

Discussion

From a theoretical point of view some objections can be raised against the tonometric method of measuring intraluminal PO₂. Firstly, when using the tonometric method subcutaneously, the silastic tube is in full contact with the surrounding tissue,⁹ but the tonometer in the small bowel may not necessarily be in full contact with the mucosa, parts of it may be in free lumen. Secondly, CO₂ diffuses easily through tissue planes and it has been shown that intramucosal PCO₂ is in equilibrium with that of the lumen.¹⁴ Whether this is also the case with oxygen, has not been investigated. Thirdly, the time to reach an equilibrium between the gut lumen and the contents of the tonometer balloon is not known and no correlation factor has been established. Finally, the implication of the counter-current exchange and its impacts on the diffusion of oxygen in the mucosal villi has to be studied.¹⁵ It could be argued that the method in itself needs more investigation and validation and we therefore present our data as per cent of baseline, as we are confident that changes in intraluminal PO₂ reflect changes in mucosal PO₂. Probably it is not necessary to detoxify the saline in the tonometer as the oxygen most probably will equilibrate irrespective of direction of flow. It should also be emphasised that this method is very sensitive to errors caused by negligent handling. Even a small amount of air, accidentally sucked into the syringe, may give falsely high values.

Figure 4: Relation between gut intramucosal pH (pH_i) and changes in intraluminal PO₂ in each animal in controls (C), peritonitis (P I and P II), and haemorrhage (B I and B II).

Figure 5: Relation between gut intramucosal pH (pH_i) and gut intraluminal PO₂ in peritonitis and haemorrhage. r=0.06 (0.17) in peritonitis and r=0.63 (0.13) in haemorrhage (p<0.002).

The mean (SEM) value for all tonometric measurements of PO_2 at baseline ($n=25$) was 71.9 (1.83) mm Hg. Bergofsky found a PO_2 of 48 mm Hg in saline instilled in the urinary bladder after three hours of equilibration; this value increased after the breathing of pure oxygen.⁷ Dawson *et al* estimated mucosal PO_2 in the small bowel of dogs to range between 35 and 45 mm Hg. In one normal volunteer it was found to be 45 mm Hg.⁸ Hamilton *et al* found a wide range of PO_2 values in dogs using a tonometric method with fluids instilled in loops of the bowel. Their maximum value was 57 mm Hg.¹⁶ Korsbäck measured PO_2 in deoxygenated saline slowly flushed through a gas permeable catheter implanted subserosally in the jejunum of pigs and found a mean at baseline of 35 mm Hg.¹⁷ In Korsbäck's experiment the O_2 of the tissue equilibrated over the wall of the implanted tube to saline flushed through the tube, whereas, in our experiment, intraluminal O_2 could equilibrate with saline that was kept in the balloon of the tonometer for a full hour. Bohlen, using oxygen micro-electrodes in the mucosa of rats, found a PO_2 of only 14.8 in the villus apex.¹⁸ The tissue PO_2 is, however, known to increase towards the base of the villus, and it can be assumed that intraluminal PO_2 is influenced by that of the crypts, or, more specifically, by PO_2 in the fluid of the crypts.

In all of the above experiments, as well as in experiments by Sheridan *et al* on rats¹⁹ and on humans²⁰ using a Clark oxygen electrode on the serosal surface of the bowel, changes in gut tissue oxygen tension occurred simultaneously with changes in arterial PO_2 . The animals in the present series had 40% oxygen in their breathing air and consequently a high arterial PO_2 , 183 (4.9) mm Hg ($n=25$) at baseline. This, together with our long equilibration time (one hour), might explain our seemingly high PO_2 values.

When comparing the mean values for changes in intraluminal PO_2 in the separate groups no statistical differences were found in controls and peritonitis. In haemorrhage values were different from baseline from $t=4$ hours in B I and from $t=2$ hours in B II; a difference from controls was noted only at end point in B II. This can be explained by a considerable overlap because of the individual differences in the response to the challenge of intraperitoneal faeces or haemorrhage. It might be assumed that, if an individual animal in, for example, haemorrhage only developed a minor change in pH_i , it would also show only a minor change in intraluminal PO_2 as well as in other variables. More profound changes in pH_i would, on the other hand, be accompanied by more profound changes in intraluminal PO_2 . To test this and to establish the relation between mucosal ischaemia (that is, a fall in pH_i) and intraluminal PO_2 each individual measurement of PO_2 was plotted against the measurement of pH_i at the same timepoint. The slope was then calculated for the animals with peritonitis (groups P I and P II) and for those with haemorrhage (groups B I and B II) (Fig 5).

From this graph, where the correlation between pH_i and intraluminal PO_2 in haemorrhage was 0.63 (0.13), it can be seen that a drop in pH_i from 7.42 to 6.46 was concomitant with a change in PO_2 from 100 at baseline down to 59%, or vice versa. If it is accepted that intraluminal PO_2 mirrors the PO_2 of the gut mucosa, it follows that a drop in mucosal PO_2 is accompanied by a drop in pH_i , indicating increasing anaerobic metabolism. This becomes even more clear if we look at the decreasing DO_2 in these two haemorrhagic groups. The chain of events in haemorrhage thus seems to be as follows: DO_2 dropped because of a decreased mesenteric blood flow and decreased oxygen carrying capacity, as a result of a fall in the packed cell volume. The result of this was a drop in tissue oxygen tension to the extent that aerobic metabolism could not be maintained and was therefore replaced by anaerobic processes. As a consequence tissue acidity increased, which here was shown by a fall in pH_i .

The pattern for the septic animals was different, however, and less straight forward. The drop in pH_i preceded that in gut DO_2 – that is, at a timepoint where no statistically significant decrease had appeared in DO_2 , pH_i had decreased significantly. It can therefore not be assumed that low DO_2 was the sole, or even the most important, cause for gut mucosal acidity. This is in accordance with the findings by Fink *et al*.³ When pH_i dropped from 7.42 to 7.06 only a minor, insignificant, change in PO_2 was noted, from 100 to 96.1 (the haemorrhagic animals had a lower pH_i at end point but at a pH_i of 7.06 in this group the corresponding PO_2 was 84.1). Although a significant drop in DO_2 takes place in both groups with peritonitis only minor changes are detected in intraluminal PO_2 . Furthermore, these minor changes are accompanied by a significant drop in pH_i . Thus we have a seemingly paradoxical situation where decreased DO_2 only results in minor, or even no, changes in intraluminal PO_2 but still there is a drop in pH_i , implying anaerobic metabolism. As the animals with peritonitis did not have as low pH_i at end point as those with haemorrhage, we cannot determine the relation between pH_i and intraluminal PO_2 at pH_i below 7.06, which was our lowest calculated pH_i value in this series of peritonitis. The possibility cannot be excluded that, with pH_i values in a lower range, the correlation curve would reach a deflection point where a further drop in pH_i would be accompanied by a steeper drop in PO_2 . Furthermore, the difference between peritonitis and haemorrhage might be questioned as the range was wider in haemorrhage, with pH_i values below 7.0, whereas the single lowest value in peritonitis was 7.06. We, therefore, recalculated the correlation between pH_i and changes in PO_2 in haemorrhage excluding those three animals that had a pH_i value at any timepoint below 7.0. We still found a correlation ($r=0.55$ (0.17)).

Earlier experiments have shown that the drop in pH_i , seen in septic states, is not solely dependent upon decreased oxygen delivery.

Rasmussen and Haglund recently found that, in the early stages of septic shock, pH_i was decreasing even when DO₂ was still normal or increased – that is, during the hyperdynamic phase of shock.⁴ Fink *et al* found that endotoxaemia in pigs resulted in a decrease of gut DO₂ and of pH_i. If, however, the blood flow in the superior mesenteric artery was mechanically decreased to the same values as in the septic animals no change in pH_i was noted.³ It, thus seems justified to conclude that low DO₂ alone cannot account for the gut intramucosal acidity seen in sepsis.

In our model of peritonitis, we thus have obtained evidence that normal concentrations of oxygen are present in the mucosa and yet there is anaerobic metabolism as evidenced by a drop in pH_i. An explanation of this seemingly paradoxical situation could be that the uptake of oxygen in the individual cell is blocked in sepsis, or that the utilisation of oxygen in the intracellular metabolism is somehow limited. The most probable function to be disturbed in sepsis seems to be the oxidative phosphorylation taking place in the mitochondria, as a lack of oxygen here leads to an anaerobic pathway with production of an excess of [H⁺] explaining the acidity detected in the mucosa as well as in other tissues in septic states.

Although Dawson *et al* assessed that mitochondrial function is enhanced by sepsis,²¹ there are abundant data supporting the idea that mitochondrial function is impaired in sepsis, either by bacterial endotoxins directly or, more probably, by toxic mediators released by them. Mela *et al*, in 1971, could show defects in liver mitochondrial energy linked functions in haemorrhagic and endotoxin shock. They proposed the destruction of mitochondrial membranes by lysosomal enzymes as an explanation.²² Astiz and coworkers, in an experiment using caecal ligation in rats, showed an impaired oxidative metabolism and energy production in muscle tissue, expressed as increased lactate/pyruvate ratio and decreased high energy phosphates. This was the case even if blood circulation was kept at control values by albumin infusion and tissue PO₂ was unchanged.²³ Hotchkiss *et al* could not detect signs of cellular hypoxia in septic rats using [¹⁸F]fluoromisonidazole. Yet there was increased blood lactate concentrations in their experimental settings indicating anaerobic metabolism. However, the gut was not examined in their experiment.²⁴ Schaefer and coworkers have recently shown that cellular oxidative phosphorylation in endotoxic rats was impaired. In the brain they noted that these changes were correlated to the decreased blood flow induced by endotoxaemia, but in the small bowel they found this defect to be disproportionally great and independent of maintenance of normal blood flow.^{25–27}

In conclusion, we found a drop in mucosal pH to correlate well with a drop in gut intraluminal PO₂ in haemorrhage. In peritonitis, on the other hand, a significant drop in pH_i occurred within a very limited and insignificant change of intraluminal PO₂. This can be

explained by a limited oxygen uptake in the individual cell, possibly resulting from an impairment of mitochondrial function, as has been seen in sepsis by earlier investigators.

This study was sponsored by grants from the Swedish Medical Research Council, project 4502, the Swedish Medical Society, and Trygg Hansa.

- Gutierrez G, Palizas F, Doglio G, Wainsztein N, Gallesio A, Pacin J, *et al*. Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. *Lancet* 1992; **339**: 195–9.
- Maynard N, Bihari D, Beale R, Smithies M, Baldock G, Mason R, *et al*. Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory failure. *JAMA* 1993; **270**: 1203–10.
- Fink MP, Antonsson JB, Wang H, Rothschild HR. Increased intestinal permeability in endotoxic pigs. Mesenteric hypoperfusion as an etiologic factor. *Arch Shock* 1991; **126**: 211–8.
- Rasmussen I, Haglund U. Early gut ischemia in experimental fecal peritonitis. *Circ Shock* 1992; **38**: 22–8.
- Gottrup F. Measurement and evaluation of tissue perfusion in surgery (to optimize wound healing and resistance to infection). In: Leaper DJ, Branicki FJ, ed. *International surgical practice*. Oxford: Oxford University Press, 1992: 15–39.
- Hunt TK, Rabkin J, Jensen JA, Jonsson K, von Smitten K, Goodson III WH. Tissue oximetry: an interim report. *World J Surg* 1987; **11**: 126–32.
- Bergofsky EH. Determination of tissue O₂ tensions by hollow visceral tonometers: effect of breathing enriched O₂ mixtures. *J Clin Invest* 1964; **43**: 193–200.
- Dawson AM, Trenchard D, Guz A. Small bowel tonometry: assessment of small gut mucosal oxygen tension in dog and man. *Nature* 1965; **206**: 943–4.
- Niinikoski J, Hunt TK. Measurement of wound oxygen with implanted Silastic tube. *Surgery* 1972; **71**: 22–6.
- Grum CM, Fiddian-Green RG, Pittenger GL, Grant BJB, Rothman ED, Dantzer DR. Adequacy of tissue oxygenation in intact dog intestine. *J Appl Physiol* 1984; **56**: 1065–9.
- von Engelhardt W. Swine cardiovascular physiology – a review. In: Bustad CK, McClellan RO, ed. *Swine in biomedical research*. Seattle: Frayn Printing Co, 1966.
- Antonsson JB, Boyle III CC, Kruthoff KL, Wang H, Sacristan E, Rothschild HR, *et al*. Validation of tonometric measurement of gut intramural pH during endotoxemia and mesenteric occlusion in pigs. *Am J Physiol* 1990; **259**: G519–23.
- Källén R, Borgström A, Fält K. Pancreatic enzymes in serum and urine as indicators of pancreatic allograft rejection in the pig. *Transplantation* 1989; **48**: 376–81.
- Cunningham JA, Cousar CD, Jaffin JH, Harmon JW. Extraluminal and intraluminal pCO₂ levels in the ischemic intestines of rats. *Curr Surg* 1987; **44**: 229–32.
- Lundgren O, Haglund U. The pathophysiology of the intestinal countercurrent exchanger. *Life Sci* 1978; **23**: 1411–22.
- Hamilton JD, Dawson AM, Webb JPW. Observations upon small gut 'mucosal' pO₂ and PCO₂ in anesthetized dogs. *Gastroenterology* 1968; **55**: 52–60.
- Korsbäck C. Tissue pO₂ and pCO₂ in the gastrointestinal tract and liver during intravenous vasopressin infusion. An experimental study in pigs. *Acta Chir Scand* 1984; **150**: 593–7.
- Bohlen HG. Intestinal tissue PO₂ and microvascular responses during glucose exposure. *Am J Physiol* 1980; **238**: H164–71.
- Sheridan WG, Lowndes RH, Williams GT, Young HL. Determination of a critical level of tissue oxygenation in acute intestinal ischaemia. *Gut* 1992; **33**: 762–6.
- Sheridan WG, Lowndes RH, Young HL. Intraoperative tissue oximetry in the human gastrointestinal tract. *Am J Surg* 1990; **159**: 314–9.
- Dawson KL, Geller ER, Kirkpatrick JR. Enhancement of mitochondrial function in sepsis. *Arch Surg* 1988; **123**: 241–4.
- Mela L, Bachalzo LV, Miller LD. Defective oxidative metabolism of rat liver mitochondria in hemorrhagic and endotoxin shock. *Am J Physiol* 1971; **220**: 571–7.
- Astiz M, Rackow EC, Weil MH, Schumacher W. Early impairment of oxidative metabolism and energy production in severe sepsis. *Circ Shock* 1988; **26**: 311–20.
- Hotchkiss RS, Rust RS, Dence CS, Wasserman TH, Song S-K, Hwang D-R, *et al*. Evaluation of the role of cellular hypoxia in sepsis by the hypoxic marker [¹⁸F]fluoromisonidazole. *Am J Physiol* 1991; **261**: R965–72.
- Schaefer CF, Biber B, Lerner MR, Jöbbsis-VanderVliet FF, Fagraeus L. Rapid reduction of intestinal cytochrome a₃ during lethal endotoxemia. *J Surg Res* 1991; **51**: 382–91.
- Schaefer CF, Lerner MR, Biber B. Dose-related reduction of intestinal cytochrome a₃ induced by endotoxin in rats. *Circ Shock* 1991; **33**: 17–25.
- Schaefer CF, Biber B. Effects of endotoxemia on the redox level of brain cytochrome a₃ in rats. *Circ Shock* 1993; **40**: 1–8.