Gastric intramucosal pH, tissue oxygenation and acid–base balance

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It is widely accepted that global measurements of oxygen delivery, consumption and extraction do not provide reliable information on the adequacy of tissue oxygenation in patients who are, by all conventional clinical criteria, adequately resuscitated [13, 17, 29, 39, 51, 60, 103]. The indirect measurement of gastric intramucosal pH (pH\textsubscript{m}) is being widely evaluated as a minimally invasive and sensitive means of assessing the adequacy of tissue oxygenation in these circumstances.

Tissue acid–base balance is determined primarily by the balance between the protons released during the release of energy by ATP hydrolysis and consumed by the resynthesis of ATP by oxidative phosphorylation [64]. When the delivery of oxygen fails to resynthesize the ATP necessary to meet the energy demands of the tissue, the rate of ATP hydrolysis exceeds the rate of synthesis and pH decreases in proportion with the degree of unreversed ATP hydrolysis or dysoxia present [50, 91]. Measurement of gastric intramucosal pH provides a measure of tissue acid–base balance in a region of the body that is among the first to develop dysoxia in shock [25, 28, 59, 71, 79, 85, 88, 92]. Measurement of gastric intramucosal pH provides a measure of tissue acid–base balance in a region of the body that is among the first to develop dysoxia in shock [25, 28, 59, 71, 79, 85, 88, 92]. Use of the measurement suggests that approximately 50–60% of patients undergoing major surgery and 80% of ICU patients [22, 35, 56, 75] may develop transient and sometimes sustained episodes of dysoxia despite the conventional appearances of being adequately resuscitated.

The degree and duration of these episodes of gastric intramucosal acidosis are highly sensitive measures of the risk of developing injured and “leaky” gut [40, 45, 46, 89, 93] and its putative consequences, namely translocation [38, 45, 82], cytokine release [77, 83], organ dysfunction and failure [35, 70, 82, 83, 99], sepsis [37, 38] and death from organ failure [22, 34, 54, 57]. By providing an index of the adequacy of tissue oxygenation in one of the first parts of the body to exhibit dysoxia in shock, [25, 28, 59, 71, 79, 85, 88, 92], measurement of gastric intramucosal pH improves the opportunity to obtain advanced and accurate warning of the putative consequences of dysoxia and to intervene in time to prevent them. More importantly, timely therapeutic measures that restore the intramucosal pH to normality and “gut-directed” and “pH\textsubscript{m}-directed” therapies incorporating measures that reverse intramucosal acidosis are associated with improved outcome [6, 22, 56].

Measurements of gastric intramucosal pH have revealed what may be major deficiencies in accepted practices. It is apparent that empirical increases in global oxygen delivery may be redundant in the 50% of patients undergoing major cardiovascular surgery who do not develop gastric intramucosal acidosis during or immediately after surgery and whose prognosis is excellent [35, 89]. It is further apparent that the vogue of increasing global oxygen delivery to supranormal levels [95] cannot be relied upon to prevent and particularly to reverse [54, 97] intramucosal acidosis. Of concern is the intramucosal acidosis that may, on occasion, be induced by measures, notably transfusion of red blood cells and dobutamine [97], that increase global oxygen delivery in patients who do not have intramucosal acidosis and whose global oxygen delivery is considered inadequate by conventional criteria [30, 31]. Intramucosal acidosis may also be induced by some anaesthetic agents but not by others [81]. Of particular concern is the realization that therapeutic decisions are being based upon the false premise that current forms of monitoring are providing reliable information about the adequacy of tissue oxygenation.

In this review the theoretical basis of tonometric measurement of gastric intramucosal pH and its relationship to the adequacy of tissue oxygenation are reviewed, especially as it relates to the balance between the protons released by ATP hydrolysis and consumed in ATP resynthesis by oxidative phosphorylation and the buffering of “fixed” and “volatile” metabolic acids released into “open” and “closed” systems.

The tonometric method

Measurement of pH\textsubscript{m} in the most superficial layer of the mucosa is obtained indirectly by measuring PCO\textsubscript{2} in the lumen of the gut with a silicone balloon tonometer (Tonometrics, Inc., Worcester, MA, USA) and the bicarbonate concentration in arterial
Arterial $\text{HCO}_3^-$

$\text{pH}_{im} = 6.1 + \log \frac{[\text{HCO}_3^-]}{P_{\text{CO}_2} \times 0.031}$

Superficial mucosa

TRIP catheter

$P_{\text{CO}_2}$

Lumen

Figure 1 Intramucosal pH is derived from measurement of $P_{\text{CO}_2}$ in fluid with the TRIP (Tonometrics, Inc., Worcester, MA, USA) catheter (tonometer) that has been allowed to equilibrate with $P_{\text{CO}_2}$ in the superficial layers of the mucosa, and bicarbonate concentration $[\text{HCO}_3^-]$ in arterial blood. The primary assumption is that intramucosal bicarbonate is the same as that being delivered in arterial blood [26].

Figure 2 Top: Reduction in measured submucosal pH$_{im}$ (O) and in indirect pH (•) in the superficial layers of the mucosa during partial occlusion (0–60 min) and reperfusion [2]. Bottom: Reduction in measured submucosal pH$_{im}$ (O) and indirect pH$_{im}$ (•) in superficial mucosa in endotoxaemia while flow to the gut was maintained by resuscitation [2].

Figure 3 Top: Dissociation between measured submucosal pH$_{im}$ (O) and indirect superficial mucosal pH$_{im}$ (•) during no-flow (0–60 min) and reperfusion [2]. Bottom: Reduction in arterial bicarbonate ($\text{HCO}_3^-$) induced by endotoxin (•) and reperfusion after 60 min of no-flow (•) [2]. Note that arterial bicarbonate remains close to controls (O) during no-flow and decreases precipitously on reperfusion. Compare with changes in intramucosal pH in no-flow state shown above.

blood, and substituting these two values in the Henderson–Hasselbalch equation [26] (fig. 1). The measurement is based on the assumption that $P_{\text{CO}_2}$ in the most superficial layers of the mucosa is in equilibrium with that in the luminal contents with which it is in contact. It is further based on the assumptions that the bicarbonate concentration in the tissue is the same as that being delivered to it in arterial blood and that the $pK$ in tissue fluid is the same as that in plasma [2]. Technical details of the measurement are reviewed elsewhere [30, 31, 33].

The assumptions on which the indirect measurement of intramucosal pH are based are valid in adequately oxygenated and perfused tissues. In these circumstances the indirect measurement of intramucosal pH is identical to that measured directly in the submucosal space with a microprobe in the interstitial space [2] (figs 2, 3).

The indirect measure of pH$_{im}$ declines in parallel with the pH measured directly in the submucosal space when intramucosal acidosis is induced by endotoxaemia, low-flow or no-flow [2] (figs 2, 3). In those circumstances in which intramucosal acidosis is induced by endotoxin, and flow to the gut is maintained, the measurements are in close agreement ($r = 0.945$). When induced by low-flow and especially no-flow, the indirect measurements underestimate the severity of acidosis present in the submucosal space. The disparity between indirect and direct measurements observed in low-flow and no-flow states disappears when blood flow is re-established and the pH$_{im}$ is allowed to return towards normality. Inspection of the 20-min values obtained in the study of Antonsson and colleagues [2] reveals
occurs after administration of endotoxin [2] (fig. 3), arterial bicarbonate is unable to reduce the tissue bicarbonate in interstitial fluid. A reduction in the bicarbonate concentration in a no-flow state for it is generated when venous blood with its elevated $P_{CO_2}$ (fig. 4). Tissue bicarbonate decreases as a result of the buffering of metabolic acid in dysoxic tissue beds enters the pulmonary circulation, an "open" (lungs). Note that the decrease in bicarbonate was not significant in the closed system [49].

Figure 4 Effect of increasing amounts of a fixed acid load on $P_{CO_2}$ and bicarbonate in a "closed" system (ECF) and changes induced by the loss of carbon dioxide when the system becomes "open" (lungs). Note that the decrease in bicarbonate was not significant in the closed system [49].

that the degree of dissociation observed between indirect and direct measurements is a linear function of the rate of decline in intramucosal pH induced, regardless of the experimental circumstances.

THE BICARBONATE ASSUMPTION

The primary assumption on which the validity of the tonometric measurements of the adequacy of tissue oxygenation is based is that the bicarbonate concentration in tissue fluid is the same as that being delivered to it in arterial blood. It has been said that this assumption is invalid in low-flow and especially no-flow states and that the dissociation between direct and indirect measurements in these circumstances is caused by a decrease in tissue bicarbonate below that present in arterial blood [30, 31]. On the contrary, the assumption appears to be valid in all circumstances examined in the validation experiments.

The law of mass action dictates that the reduction in bicarbonate concentration induced by the addition of a fixed acid load to a "closed system" from which carbon dioxide cannot escape, such as the extracellular fluid (ECF) compartment, is inhibited by accumulation of carbon dioxide. Indeed, the addition of even large amounts of fixed acid to ECF fails to produce a significant reduction in bicarbonate concentration but it does produce a significant increase in $P_{CO_2}$ [49] (fig. 4). Arterial bicarbonate decreases when venous blood with its elevated $P_{CO_2}$ generated by the buffering of metabolic acid in dysoxic tissue beds enters the pulmonary circulation, an "open system", from which carbon dioxide is able to escape (fig. 4). Tissue bicarbonate decreases as a result of the dilutional effect of the lowered arterial bicarbonate entering the tissue bed and equilibrating with the bicarbonate in interstitial fluid. A reduction in arterial bicarbonate is unable to reduce the tissue bicarbonate concentration in a no-flow state for it is unable to enter the tissue bed.

The highest rate of decline in arterial bicarbonate in the validation study of Antonsson and colleagues occurs after administration of endotoxin [2] (fig. 3), circumstances in which perfusion of the gut is maintained and the opportunity for blood to remove carbon dioxide from the tissue bed to be exhaled by the lungs is greatest [49]. Yet the correlation between indirect and direct measurements of intramucosal pH is closest in these circumstances ($r = 0.945$) (fig. 2), suggesting that tissue bicarbonate declines in parallel with the reduction in arterial bicarbonate. The dissociation between measured and calculated intramucosal pH is greatest in the no-flow state (figs 2, 3) in which carbon dioxide is unable to be removed by blood from the dysoxic tissue bed and the opportunity for tissue bicarbonate to be reduced is most limited (fig. 3). The dissociation of direct from indirect measurements in the no-flow states disappears on reperfusion, even though arterial bicarbonate and by inference tissue bicarbonate declines precipitously. Thus the assumption that tissue bicarbonate is the same as that being delivered to the tissue in arterial blood appears to be valid in all circumstances tested in the validation studies of Antonsson and colleagues.

The close correlation between the measured and indirect measurement of intramucosal pH made every 20 min in the study of Antonsson and colleagues indicates that the bicarbonate concentration in the tissue equilibrates with that in arterial blood within 20 min. However, $HCO_3^-/Cl^-$ exchange across cells that contain large amounts of carbonic anhydrase occurs within a fraction of a second [15, 104]. Indeed, by catalysing the dissociation of carbonic acid, the carbonic anhydrase present in red cells and mucosal cells [96], allows the bicarbonate in blood to equilibrate with that in ECF within the very short time flowing capillary blood is in contact with the tissue bed [15, 104]. Changes of this rapidity across capillary and cellular membranes are essential for the efficient transfer of carbon dioxide and $HCO_3^-$ between cells and capillary blood, especially in tissues that are metabolically very active. Thus equilibration between interstitial and arterial bicarbonate may be expected to occur extremely rapidly, possibly within seconds, in perfused capillary beds within the mucosa regardless of whether or not the bicarbonate in arterial blood is changed by pathophysiological events, or i.v. infusions of bicarbonate.

It has been reported that interstitial bicarbonate in the wall of the stomach may be dissociated from that in arterial blood in septic [20] and anaphylactic shock [102]. The bicarbonate concentration in these experiments is greater than 30 mmol litre$^{-1}$ and greater than that present in arterial blood when the dissociation between arterial and tissue bicarbonate occurs. The elevated tissue bicarbonate observed is almost certainly the consequence of the alkaline tide generated by a high rate of basal acid secretion, as interstitial bicarbonate in a non-secreting stomach should be the same as that in arterial blood, normally 25 mmol litre$^{-1}$ [96]. The basal rate of acid secretion is often high in animal experiments because the stomach invariably contains residual food that stimulates acid secretion. The dissociation observed in septic shock disappears as arterial bicarbonate decreases to less than 25 mmol litre$^{-1}$ with the pro-
gression of shock [20]. The development of intramucosal acidosis, which always accompanies arterial acidosis, prevents gastric secretagogues from stimulating acid secretion and hence generating an alkaline tide [62]. Thus acid secretion must be inhibited for the assumption that interstitial bicarbonate is the same as that in arterial blood to be valid. The secretion of acid and associated generation of an alkaline tide may be inhibited by an H₂ receptor antagonist [96]. The assumption appears to be valid in most of the circumstances likely to be encountered in clinical practice. It is, however, wise to delay making a measurement of intramucosal pH following a sudden change in arterial bicarbonate such as that induced by an i.v. infusion of bicarbonate. A delay of a few minutes should suffice. A delay of 20 min appears to be long enough for equilibration to occur in animals.

The severity of intramucosal acidosis might be overestimated in a no-flow state if arterial bicarbonate decreases below that present in the mucosa, but even large errors in the primary assumption should not confound the interpretation of the measurement in clinical practice as the measurement of intramural pH is so obviously abnormal in these circumstances (fig. 9). I.v. administration of bicarbonate diminishes the likelihood of overestimating the severity of tissue acidosis present in these circumstances by restoring arterial bicarbonate towards that present in the ischaemic tissue bed.

THE Pco₂ ASSUMPTION

A Pco₂ gradient of considerable magnitude may be created between arterial blood and luminal fluid in the dog by inducing a rapid increase in arterial Pco₂, while tissue oxygenation is maintained by rebreathing into a bag of oxygen [42]. An even larger Pco₂ gradient may be created in the opposite direction by buffering a pharmacological amount of exogenous acid with an equimolar amount of exogenous bicarbonate in the lumen of a closed stomach [42]. In both instances Pco₂ in the lumen equilibrates with that in arterial blood with the passage of time. This barrier, which should be a linear function of the thickness of the tissue layer, is also evident under physiological conditions. A gradient of modest size develops between lumen and arterial blood from the carbon dioxide generated by the buffering of the acid secreted in response to a meal [44]. A small Pco₂ gradient may even exist between the lumen of the stomach and arterial blood in the fasting state if basal acid secretion is not inhibited [61, 101]. Mucosal tissue does, therefore, present a definite barrier to the diffusion of carbon dioxide between lumen and blood.

The diffusional barrier between the submucosal space and lumen of the gut in the large animal model used in the validation studies of Antonsson and colleagues is relatively large. The diffusional barrier is much smaller in the rat. In this small animal model no Pco₂ gradient develops between mucosa and the lumen of the gut even in a no-flow state [5, 16].

The diffusional barrier between the lumen and the superficial layers of the mucosa is especially small. Moreover, carbon dioxide equilibrates extremely rapidly across cell membranes of tissues that contain large amounts of carbonic anhydrase, such as the gastric mucosa [14, 96]. It would seem, therefore, that Pco₂ in the lumen of the stomach is likely to be in equilibrium with Pco₂ in the most superficial layers of the mucosa, even in a rapidly changing state. Pco₂ in the lumen is not necessarily in equilibrium with Pco₂ in the deeper layers of the mucosa or submucosal space in the human stomach in which the mucosa is relatively thick.

VALIDITY OF THE MEASUREMENTS OF GASTRIC INTRAMUCOSAL pH

The assumptions on which the indirect measurement is based, and especially the bicarbonate assumption, appear to be valid even in a rapidly changing state. The indirect measurement appears, therefore, to provide a very accurate and reproducible measure of actual pH in the most superficial layers of the mucosa in contact with the luminal contents, but not of the submucosal space especially in rapidly changing states.

The validity of the indirect measurement of gastric intramucosal pH is not as well documented in animal studies as the validity of the measurement of intramucosal pH in the small intestine [2, 19, 40, 42]. Measuring the intramucosal pH in the stomach differs from measuring the pH in the small intestine because of the presence of residual food and large amounts of mucoid material in the stomachs of fasting animals. This makes it technically difficult to obtain accurate measurements in this part of the gastrointestinal tract. More importantly, stimulation of acid secretion by residual food generates an alkaline tide [96]. Acid secretion and associated generation of an alkaline tide must be inhibited for the assumption that the interstitial bicarbonate in the stomach is the same as that in arterial blood to be valid.

Fortunately, the fasting stomach is empty in humans and basal acid secretion low and easily aspirated. Measurement of intramucosal pH in the stomach of healthy patients whose acid secretion is inhibited is the same as that in arterial blood and the reproducibility of the measurement between subjects is excellent [61].

Determinants of gastric intramucosal acidosis

Gastric intramucosal acidosis might conceivably be caused by the back-diffusion of acid, carbon dioxide, or both, increased metabolic rate, impairment of mucosal perfusion, imbalance between ATP hydrolysis and resynthesis by oxidative phosphorylation, lactic acidosis or the presence of arterial acidosis.

BACK-DIFFUSION

Unlike the small and large intestine, the stomach is exposed to gastric acid and carbon dioxide generated by buffering of the gastric acid by pancreatic
bicarbonate. Back-diffusion of these substances may cause intramucosal acidosis [42, 66, 96]. Intramucosal acidosis induced by back-diffusion in vitro is attenuated by addition of bicarbonate to the fluid perfusing the serosal surface of the mucosa. Similarly, stimulation of acid secretion attenuates the severity of intramucosal acidosis induced by generating an alkaline tide within mucosal tissue.

In clinical practice back-diffusion of protons is insignificant as the hydrogen ion gradient in ICU patients is very small relative to that necessary to generate a back-diffusion of sufficient magnitude to cause a decrease in intramucosal pH in animal studies. Back-diffusion of carbon dioxide, generated by buffering of gastric acid by pancreatic bicarbonate, may be the cause of intramucosal acidosis in animals and patients, especially during stimulation of acid secretion by feeding [44]. The rate at which carbon dioxide is generated in the lumen of the stomach is a function of the amount of acid entering the duodenum [23, 41, 43, 106], and the concentration of acid and bicarbonate in pancreatic secretions. \( PCO_2 \) increases as the amount of acid entering the duodenum increases [106].

Inhibiting acid secretion with an \( H_2 \) receptor antagonist, and better yet, a proton pump inhibitor eliminates the contribution by back-diffusion to a decrease in intramucosal pH [61]. Inhibiting acid secretion also prevents the generation of an alkaline tide and is required to ensure that the assumption that interstitial bicarbonate is the same as that in arterial blood is valid. In so doing, inhibiting acid secretion improves the reproducibility of the measurement of gastric intramucosal pH between healthy subjects and facilitates the interpretation of the measurements in clinical practice. Preventing acid from entering the duodenum by aspirating the gastric contents should be as effective as an \( H_2 \) receptor antagonist in preventing intraluminal generation of carbon dioxide [106]. Conversely, reflux of duodenal secretions into the stomach should not be a significant cause of carbon dioxide generation in the lumen of the stomach when secretion of acid is prevented from entering the duodenum by aspiration of an \( H_2 \) receptor antagonist.

Feeding increases \( PCO_2 \) in the lumen of the stomach of healthy subjects [44] and causes a decrease in intramucosal pH by increasing back-diffusion of acid and carbon dioxide by stimulating acid secretion and the associated buffering of acid by pancreatic bicarbonate. The magnitude of the reduction in intramucosal pH is compounded by impairment of blood flow to the gut. Indeed, feeding has been used as a provocative test for the diagnosis of chronic intestinal ischaemia [9, 44]. The presence of food in the stomach may dampen the response to a change in intramucosal \( PCO_2 \) measured with an intraluminally located tonometer.

**LACTIC ACIDOSIS**

The production of lactic acid by anaerobic glycolysis is not, as commonly assumed, the cause of tissue acidosis present in dysoxic states [4, 64, 67]. The dissociation of lactic acid into lactate and \( H^+ \) occurs only when the pH is less than 6.0 or the pK is 3.9. In the pH range encountered in the critically ill, \( H^+ \) released by the dissociation of lactic acid is said to neither accumulate nor be depleted. Furthermore, development of tissue acidosis in hypoxic states cannot be prevented by inhibiting anaerobic glycolysis with iodoacetic acid [50].

**OXIDATIVE PHOSPHORYLATION AND ATP HYDROLYSIS**

The main sources of acid in normoxic tissues are the carbon dioxide generated by oxidative phosphorylation and the protons generated by the hydrolysis of ATP occurring with the release of energy to maintain the functional and structural integrity of the tissues [64, 67, 91]. In a resting 70-kg man, approximately 15000 mmol of volatile acid (\( H_2CO_3 \)) [49] is added by aerobic metabolism to tissue fluid each day and balanced by the exhalation of carbon dioxide from the lungs; an "open" system (table 1). Ten times as much fixed acid (150000 mmol \( H^+ \)) [64] is added by the hydrolysis of ATP and associated organic phosphates each day, one proton being generated for every inorganic phosphate liberated by hydrolysis. Only 0.1% of this enormous fixed acid load (150 mmol \( H^+ \)) is excreted by the kidneys; another "open" system [49]. The remaining 99.9% is balanced by the protons consumed in ATP resynthesis by oxidative phosphorylation, and the re-oxidation of reduced coenzymes and reduced cytochromes. Thus tissue acid–base balance is determined primarily by the balance between the protons produced by ATP hydrolysis in a "closed" system and consumed during resynthesis by oxidative phosphorylation in an adequately ventilated patient.

In dysoxic states, in which oxygen delivery fails to generate the ATP necessary to meet the energy needs of the tissues at the time, the rate at which protons are generated by ATP hydrolysis exceeds the rate at which they are consumed by ATP resynthesis and protons accumulate in tissue fluids where they are buffered. The decrease in pH in isolated hepatocytes, induced by inhibiting anaerobic glycolysis and associated lactate production with iodoacetic acid and uncoupling oxidative phosphorylation with potassium cyanide, occurs in parallel with the degree of unreversed ATP hydrolysis or dysxia induced [50]. The reduction in intramucosal pH induced by no-flow in the small intestine also

<p>| Table 1 | The volatile acid load (( H_2CO_3 )) added to tissue by oxidative phosphorylation (Ox. phos.) is balanced by the amount exhaled from the lungs; the respiratory quotient of glucose being 1. The fixed acid load (( H^+ )) added by the hydrolysis of ATP and other organic phosphates is balanced by the ( H^+ ) consumed by ATP resynthesis, re-oxidation of reduced coenzymes and cytochromes (oxy- gen-dependent processes) and renal excretion. Estimates based on [49, 64] |</p>
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<th>&quot;Closed&quot; system</th>
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<td>Volatile acid (( H_2CO_3 )) load</td>
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<td>Ox. phos. +15000 mmol</td>
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Metabolic activity in this circumstance [65]. The production is increased to maintain the increased glycolytic rate. ATP turnover and hence rate of acid for the observed changes". Early sepsis is characterized by increased glucose uptake and glycolytic rate. ATP turnover and hence rate of acid production is increased to maintain the increased metabolic activity in this circumstance [65]. The intracellular pH is maintained, suggesting that supranormal levels [80] and an increase in blood may be prevented by increasing oxygen delivery to both sepsis and endotoxaemia may cause inadequacy of cellular oxygenation. The findings that the reduction in intramucosal pH induced by endotoxin in the small intestine of pigs (fig. 2) is accompanied by unreversed ATP hydrolysis and seems to be caused by the accumulation of protons [80]. Other investigators have also found evidence of unreversed ATP hydrolysis or dysoxia in sepsis [11, 12, 63, 78, 94]. As "the concentrations of high-energy phosphates and intracellular pH are sensitive indicators of the adequacy of cellular oxygenation, ATP depletion and mitochondrial functions" [65] both sepsis and endotoxaemia may cause inadequacy of cellular oxygenation. The findings that the reduction in intramucosal pH induced by endotoxin may be prevented by increasing oxygen delivery to supranormal levels [80] and an increase in blood lactate occurs in severe sepsis [65], are consistent with this conclusion.

In early sepsis ATP stores are not depleted and intracellular pH is maintained, suggesting that "cellular hypoxia or ischaemia are not responsible for the observed changes". Early sepsis is characterized instead by increased glucose uptake and glycolytic rate. ATP turnover and hence rate of acid production is increased to maintain the increased metabolic activity in this circumstance [65]. The increased amount of acid produced is balanced by an increased amount of protons consumed and accompanied by an increased consumption of oxygen.

**IMPAIRED PERFUSION**

Impairment of carbon dioxide removal by flowing capillary blood and exhalation from the lungs may contribute to the presence of intramucosal acidosis by causing an increase in PCO₂ (the Fick hypothesis—see below).

**SYSTEMIC ACIDOSIS**

Systemic acidosis is an additional cause of intramucosal acidosis. In determining the cause of an actual intramucosal acidosis, it is therefore necessary to consider systemic acid–base balance in addition to back-diffusion and the adequacy of tissue oxygenation. The actual intramucosal pH present may be determined from a pH-log PCO₂ diagram using the appropriate bicarbonate isobar (fig. 5). The base excess may also be determined from the Siggaard Andersen modification of the pH-log PCO₂ diagram [18]. The bicarbonate isobar shifts to the left with metabolic acidosis and to the right with metabolic alkaloisis.

**Stoichiometric analysis of determinants of tissue acidosis**

In normoxia the sole source of acid is the volatile acid (H₂CO₃) produced by oxidative phosphorylation. The protons released by aerobic metabolism are balanced exactly by the removal of protons by ATP resynthesis, re-oxidation of reduced coenzymes and cytochromes, and renal excretion, as adenosine nucleotides are primarily present in their unhydrolysed forms, the amount of free ADP in the cytosol being below the sensitivity of the typical magnetic resonance spectroscopy [65]. The principal source of acid in dysoxic states is the fixed acid (protons) released by unreversed ATP hydrolysis. Thus in the absence of flow, the pH of a given volume of tissue fluid is a function of the load of acid added to the fluid, the buffering capacity of the fluid, and whether the acid is buffered in a "closed" system from which carbon dioxide cannot escape or an "open" system (lungs) from which carbon dioxide can escape (the buffer hypothesis). In the presence of flow, pH may, in addition, be influenced by the ability of blood to remove carbon dioxide from the tissue bed to be exhaled from the lungs (Fick hypothesis).

The PCO₂ attained after buffering of the volatile and fixed acid loads present in ECF, a "closed system" (fig. 4), and the effects of carbon dioxide removal on entering the pulmonary circulation, an "open" system, may be calculated in the manner described by Gattinoni and Feriani [49].

**THE BUFFER HYPOTHESIS**

**Normoxia**

Let us assume that the energy requirements of normoxic tissue are met by 82.6 mmol of ATP.
Forty-six percent of the metabolic acid load produced enters ECF [49]. As 46% of the metabolic acid load entering ECF is equivalent to that generated by the aerobic metabolism of 1 mmol of glucose, 6 mmol of carbon dioxide and 38 mmol of ATP are generated for every 1 mmol of glucose metabolized. Only 13.5% of this volatile carbonic acid load remains after being buffered by proteins and determines \( P_{CO_2} \) present in ECF. Assuming that the bicarbonate concentration in ECF is 25 mmol litre\(^{-1} \), \( P_{CO_2} \) attained after buffering of this carbonic acid load in 1 litre of ECF is 27 mm Hg (6 x 0.135/0.03) (3.6 kPa). But resting healthy subjects with a bicarbonate concentration of 25 mmol litre\(^{-1} \) have a \( P_{CO_2} \) in normoxic ECF (i.e. arterial blood) of 40 mm Hg (5.3 kPa). A volatile acid load equivalent to that yielded by the aerobic metabolism of glucose 1.48 mmol litre\(^{-1} \) is necessary to yield a \( P_{CO_2} \) of 5.3 kPa (3.6 x 1.48 = 5.3 kPa); 56.2 mmol of ATP (38 x 1.48) are generated in the process. In normoxia the protons released by the hydrolysis of this ATP store in meeting the energy demands of the tissue at the time is balanced by the protons consumed in the resynthesis of ATP. The remaining 0.1% is excreted by the kidneys (table 1).

After entering the tissue bed arterial blood equilibrates with interstitial fluid. \( P_{CO_2} \) and bicarbonate in tissue ECF increase in proportion to the amount of oxygen extracted and utilized and the equimolar amount of carbon dioxide generated by oxidative phosphorylation. \( P_{CO_2} \) and bicarbonate leaving the tissue bed are thus both slightly elevated by buffering of the volatile acid load added. On entering the lungs, an “open” system, carbon dioxide is exhaled and \( P_{CO_2} \) and \( HCO_3^- \) return to the level originally present in arterial blood. As the respiratory quotient is 1 in these circumstances, the load of volatile acid added to ECF is balanced by the carbon dioxide exhaled from the lungs. Provided this balance is maintained, \( P_{CO_2} \) and \( HCO_3^- \), within arterial blood remain constant at 5.3 kPa and 25 mmol litre\(^{-1} \), respectively. Interstitial bicarbonate is thus maintained at 25 mmol litre\(^{-1} \) and intramucosal \( P_{CO_2} \) determined tonometrically, maintained at about 5.3 kPa [61] by perfusion of the tissue bed with arterial blood.

The amount of carbon dioxide generated by buffering of the volatile acid load released into a given volume of normoxic ECF should increase as the metabolic rate and the amount of oxygen consumed by oxidative phosphorylation increases. The number of protons released by ATP hydrolysis and the number consumed by ATP resynthesis should also increase as the metabolic rate and amount of oxygen consumed increases. The actual increase in \( P_{CO_2} \) should be insignificant for the increased metabolic demand for oxygen largely seen in septic patients is met by an increase in oxygen delivery, oxygen delivery being “demand-dependent” [91]. \( P_{CO_2} \) attained in a given volume of ECF by buffering of the volatile acid load generated by oxidative phosphorylation can only increase if the amount of oxygen extracted from a given volume of ECF and consumed by oxidative phosphorylation increases. Changes in extraction of the order seen in the critically ill do not appear to contribute significantly to intramucosal \( P_{CO_2} \) as intramucosal pH bears no relation to the extraction ratio [54].

**Dyoxia**

Aerobic glycolysis and associated generation of carbon dioxide by oxidative phosphorylation decreases as the availability of oxygen relative to demand decreases in dysoxic states. Thus the decrease in tissue pH in severely dysoxic states is, in terms of the buffer hypothesis, exclusively caused by the increase in \( P_{CO_2} \) induced by buffering of the protons released by unreversed organic phosphate hydrolysis [64, 67].

The ATP store generated by 1 mmol of glucose in normoxia together with the additional ATP generated by the conversion of pyruvate to lactate and the adenylate kinase reaction in anoxia, is hydrolysed to yield \( H^+ \) 80 mmol litre\(^{-1} \). This assumes that 1 proton is released per hydrolysed phosphate [64] and that the adenylate kinase reaction runs to completion [55]. The consumption of protons by the creatine kinase reaction, another anaerobic source of ATP, is matched by the numbers released by the subsequent hydrolysis of ATP generated and should not increase the acid load [55]. Gattinoni and Feriani have calculated that 7% of a fixed acid load added to ECF should be buffered by \( HCO_3^- /CO_2 \) and release carbon dioxide [49]. If it is assumed that the energy needs of the tissue remains the same as they are in normoxia, then the \( P_{CO_2} \) of ECF attained by buffering of the protons released into 1 litre\(^{-1} \) of ECF by the hydrolysis of 56.2 mmol of ATP in complete anoxia is 276 mm Hg (1.48 x 80 x 0.07/0.03) (36.8 kPa). Assuming the bicarbonate is 25 mmol litre\(^{-1} \), the pH in anoxia is 6.58 (fig. 6). During re-oxidation protons are consumed by ATP resynthesis and \( P_{CO_2} \) should decrease precipitously with the loss of the fixed acid load from the closed system and return to the volatile acid load generated by oxidative phosphorylation to normal levels. Inhibiting xanthine oxidase with allopurinol should enhance the reversal of the tissue acidosis present and increase the efficiency of ATP resynthesis by preventing the conversion of hypoxanthine to xanthine [90].

That portion of the ECF composed of capillary blood and in equilibrium with interstitial fluid is replaced by a new volume of capillary blood as each old volume of blood is replaced by a new volume by the flow of capillary blood. The bicarbonate concentration in the new volume of arterial blood entering the tissue bed equilibrates very rapidly with that in the old volume of interstitial fluid. The resulting bicarbonate concentration is determined by the new amount of bicarbonate present in the volume of ECF. The bicarbonate in interstitial fluid very rapidly approximates with that in arterial blood with successive changes of capillary blood with fresh arterial blood. The load of fixed and volatile acid buffered in each new volume of ECF together with the \( P_{CO_2} \) in arterial blood entering the tissue bed determines the new \( P_{CO_2} \) present. Changes in \( P_{CO_2} \) induced by changes in blood flow reflect changes in
the amounts of fixed (protons) and volatile \( (H_2CO_3) \) acid being buffered in each new volume of ECF present in the tissue bed at the time. They also reflect changes in arterial \( P_{CO_2} \). Thus the \( P_{CO_2} \) resulting from buffering of the metabolic acids by ECF is independent of the rate at which each volume of blood in the tissue is replaced by a fresh volume of arterial blood. The pH is determined by the \( P_{CO_2} \), attained and the new bicarbonate concentration in the interstitial fluid which is, in effect, the same as that in arterial blood perfusing the tissue.

The relative contributions by ATP hydrolysis and oxidative phosphorylation to \( P_{CO_2} \) in ECF and hence pH may be calculated for different degrees of dysoxia assuming a bicarbonate concentration of 25 mmol litre\(^{-1}\), as illustrated in figure 7. The difference between log \( P_{CO_2} \) in ECF theoretically induced by the combination of ATP hydrolysis and oxidative phosphorylation in the dysoxic state and the log of the normoxic value of 5.3 kPa is almost identical to that theoretically induced by ATP hydrolysis alone. (Log transformation of the changes in \( P_{CO_2} \) with different degrees of dyoxia provides the best fit with the changes in \( P_{CO_2} \) induced by ATP hydrolysis alone.) In theory, therefore, the difference between log \( P_{CO_2} \) present in ECF and log \( P_{CO_2} \) in normoxic ECF provides an index of the contribution by ATP hydrolysis alone to the \( P_{CO_2} \) present.

In terms of the buffer hypothesis, the intramucosal pH should remain constant as oxygen delivery is reduced, with or without a reduction in blood flow, until the point at which supply-dependency or dyoxia develops. It is only below the critical point that \( P_{CO_2} \) in ECF is expected to increase and intramucosal pH decreases with further reductions in oxygen delivery. This should be the case regardless of the actual level of oxygen delivery at which the critical point is reached. Furthermore, the pH in complete anoxia should be the same (6.58) regardless of the cause of anoxia (when bicarbonate concentration is 25 mmol litre\(^{-1}\)).

**THE FICK HYPOTHESIS**

Changes in intramucosal pH induced by a progressive reduction in oxygen delivery might alternatively be explained in terms of the Fick principle, a decrease in intramucosal pH reflecting an increase in \( P_{CO_2} \) induced by an impaired ability of flowing blood to transport carbon dioxide from the tissue to the lungs, the "open system", from which carbon dioxide can escape. In terms of this hypothesis, intramucosal \( P_{CO_2} \) should increase exponentially and intramucosal pH decrease to abnormally low levels as blood flow to the gut is reduced even if the critical point at which supply-dependency develops has not been reached. Conversely, intramucosal pH should remain constant when blood flow is maintained at control levels and oxygen content in blood reduced, or oxygen consumption, increased, or both, even though the critical point has been reached. Below the critical point at which supply-dependency develops, further reductions in blood flow should occur in parallel with the reduction in carbon dioxide generated by oxidative phosphorylation and buffering of protons released by unversed adenine nucleotide hydrolysis. In terms of the Fick hypothesis, intramucosal pH thus induced should approach zero and intramucosal \( P_{CO_2} \) approach infinity as the no-flow state of complete anoxia is approached.

**BUFFER VS FICK HYPOTHESES IN VIVO**

Indirect measurement of actual intramucosal pH\(_{im}\) in animal experiments remains within normal limits as oxygen delivery to the gut is reduced by either
These findings are consistent with both buffer and Fick hypotheses. Low intramucosal pH provides an index of the degree adequately oxygenated gut and that an abnormally flow is maintained. These findings confirm 36% of basal oxygen delivery with hypoxaemia below normal levels without inducing cardiovascular but not to those predicted by the Fick hypothesis. Intramucosal pH in anoxia are similar to the patterns consumption increases. The changes are consistent with the predictions of the buffer hypothesis but not of the Fick hypothesis. In both circumstances oxygen consumption by the intestine decreases in parallel with the reduction in pH to the measured nadir of 6.60 in no-flow observed in the study of Antonsson and colleagues [2] (fig. 3, table 1). These changes and intramucosal pH in anoxia are similar to the patterns and value (6.58) predicted by the buffer hypothesis but not to those predicted by the Fick hypothesis.

Intramucosal pH cannot be made to decrease below normal levels without inducing cardiovascular collapse by reducing oxygen delivery to as little as 36% of basal oxygen delivery with hypoxaemia while flow is maintained. These findings confirm that a normal intramucosal pH is indicative of adequately oxygenated gut and that an abnormally low intramucosal pH provides an index of the degree of inadequacy of mucosal oxygenation present. These findings are consistent with both buffer and Fick hypotheses.

**Intramucosal pH, tissue oxygenation and acid-base balance**

**Figure 8** Changes in oxygen consumption and indirect measurement of intramucosal pH induced in the small intestine of a dog by a progressive decrease in oxygen delivery [26]. pH decreases as the degree of supply dependent oxygen consumption increases. The changes are consistent with the predictions of the buffer hypothesis but not of the Fick hypothesis (see text).

ischaemia, or the combination of hypoxia and ischaemia, until the critical point is reached at which supply-dependency develops. The critical point at which intramucosal pH decreases after induction of ischaemia (60% basal oxygen delivery) (fig. 8) is higher than that induced by the combination of hypoxaemia and ischaemia (51% basal oxygen delivery) [52]. In both circumstances oxygen consumption by the intestine decreases in parallel with the reduction in pH to the measured nadir of 6.60 in no-flow observed in the study of Antonsson and colleagues [2] (fig. 3, table 1). These changes and intramucosal pH in anoxia are similar to the patterns and value (6.58) predicted by the buffer hypothesis but not to those predicted by the Fick hypothesis.

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**Table 2** Comparison between the theoretical pH in ECF during 95% dysoxia and anoxia in tissue calculated in terms of the buffer hypothesis and actual intramucosal pH observed in the small intestine during no-flow [2], and in isolated hepatocytes in which 95% unreversed ATP hydrolysis was induced independently of flow by “chemical hypoxia”, induced by iodoacetic acid (IAA), to inhibit lactate production and potassium cyanide (KCN) to uncouple oxidative phosphorylation [50].

<table>
<thead>
<tr>
<th>Circumstances</th>
<th>Normoxia</th>
<th>Hypoxia</th>
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<tbody>
<tr>
<td>ECF (theoretical)</td>
<td>7.40</td>
<td>6.58</td>
</tr>
<tr>
<td>Intramucosal</td>
<td>7.35</td>
<td>6.60</td>
</tr>
<tr>
<td>ECF (theoretical)</td>
<td>7.40</td>
<td>6.60</td>
</tr>
<tr>
<td>Hepatocytes</td>
<td>7.40</td>
<td>6.33-6.57</td>
</tr>
</tbody>
</table>

In sepsis the critical point at which supply-dependency is induced by ischaemia occurs at a higher level of oxygen delivery than that induced in the absence of sepsis [24]. Similarly, endotoxin induces a decrease in intramucosal pH while flow to the gut is maintained at control levels [47]. The reduction in intramucosal pH induced by endotoxin is prevented by increasing oxygen delivery to supranormal levels [48]. That tissue oxygen demand is an important determinant of dysoxia is well established [91]. These observations are consistent with the buffer hypothesis but not with the Fick hypothesis.

**OTHER WAYS OF LOOKING AT THE PROBLEM**

The stoichiometric analysis performed above is simplistic and some of the assumptions made clearly invalid. The tissue concentration of ATP, for example, is much lower than that required in terms of the stoichiometric analysis to generate the fixed acid load necessary to yield the pH observed in dysoxic and anoxic states [50]. Furthermore, although occurring in parallel with ATP hydrolysis, ATP hydrolysis alone accounts for only half of the observed acidosis induced by hypoxia. The remaining half is attributed to the hydrolysis of other organic phosphates. Conversely, the protons generated by aerobic metabolism are removed by re-oxidation of reduced coenzymes and cytochromes in addition to being removed by ATP resynthesis [64].
The quantitative aspects of the stoichiometric analysis may be changed by changing the assumptions. The ATP requirements could, for example, be derived from the increase in $P_{CO_2}$ of 0.8 kPa occurring in the tissue bed during aerobic metabolism. If in addition it is assumed that half the fixed acid load is generated by ATP hydrolysis and the remaining half by the hydrolysis of other organic phosphates, the pH derived for the anoxic state is higher than the 6.58 derived in the stoichiometric analysis. A different value is obtained when instead the fixed acid load generated is derived from the knowledge that 8 protons are generated for every 1 molecule of oxygen consumed [64].

In reality the origin and amount of the fixed acid load generated in aerobic metabolism and the mechanisms by which it is consumed by oxidative phosphorylation are not fully understood. What is known is that a fixed acid load is released into the tissue by metabolism and that acid–base balance is primarily dependent on the adequacy of tissue oxygenation (table 1). Regardless of the assumptions made in computing the fixed acid load released into the tissues in dysoxic and anoxic states, the in vivo findings reviewed above are consistent in pattern and, depending on the assumptions made, the magnitude of those predicted by the buffer hypothesis. They are inconsistent with those predicted by the Fick hypothesis. There is no reason to invoke even a partial role for the Fick hypothesis in accounting for the in vivo observations in terms of the buffer hypothesis.

It is concluded that intramucosal pH in an ICU patient with a given concentration of tissue bicarbonate is determined by the $P_{CO_2}$ attained after buffering of the load of metabolic acid released into the tissue in normoxic, dysoxic and anoxic states regardless of the rate of blood flow at the time. It is further concluded that blood flow is a determinant of intramucosal pH primarily, insofar as it relates to the adequacy of oxygen delivery and tissue oxygenation rather than as it relates to carbon dioxide removal.

**Quantifying the Degree of Dysoxia Present**

The pH of ECF at any given concentration of tissue bicarbonate may be determined from the tissue $P_{CO_2}$ on the pH–log $P_{CO_2}$ diagram (fig. 5). As mucosal bicarbonate is the same as that being delivered to the tissue in arterial blood and $P_{CO_2}$ in the superficial layers of the mucosa is the same as that in the lumen of the gut, the actual intramucosal pH may be derived from the intramucosal $P_{CO_2}$ measured with a tonometer ($P_{CO_2}^i$) using the isobar corresponding to the concentration of bicarbonate present in arterial blood:

$$\text{actual intramucosal } pH = 6.1 + \log \frac{HCO_3^-}{P_{CO_2}^i \times 0.03}$$

In dysoxia the pH predicted in terms of the buffer hypothesis decreases as the degree of dysoxia increases (fig. 6). The isobar shifts to the right as bicarbonate increases and to the left as it decreases. It may be seen from the pH–log $P_{CO_2}$ diagram that

<table>
<thead>
<tr>
<th>Table 3 Different mathematical expressions of the degree of dysoxic acidosis or un reversed ATP hydrolysis</th>
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<tr>
<td>$\text{pH-gap} = \text{pHa} - \text{pH}_{\text{in}}$</td>
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<tr>
<td>$\log P_{CO_2}^i - \log P_{aCO_2} = \log \frac{P_{CO_2}^i}{P_{aCO_2}}$</td>
</tr>
<tr>
<td>standard intramucosal pH = $7.4 - \log \frac{P_{CO_2}^i}{P_{aCO_2}}$</td>
</tr>
</tbody>
</table>

the actual intramucosal pH may be determined independently of bicarbonate from the difference between arterial pH and pH-gap or log $P_{CO_2}$-gap (i.e. log $P_{CO_2}^i$–log $P_{aCO_2}$). This is to be expected as arterial bicarbonate is a derivative of $P_{CO_2}$ and pH:

$$\text{actual intramucosal } pH = \text{pHa} - (\log P_{CO_2}^i - \log P_{aCO_2})$$

$$= \text{pHa} - \log \frac{P_{CO_2}^i}{P_{aCO_2}}$$

where $P_{CO_2}^i = P_{CO_2}$ in the mucosa measured with a tonometer and $P_{aCO_2} = P_{CO_2}$ in arterial blood.

As indicated above, the dysoxic component of $P_{CO_2}$ in ECF may be computed by subtracting log $P_{CO_2}$ generated in normoxic ECF by oxidative phosphorylation alone from that present in dysoxic ECF (fig. 7). As arterial blood is, in effect, normoxic ECF, the differences between log $P_{CO_2}^i$ and log $P_{aCO_2}$, log $P_{CO_2}/P_{aCO_2}$ and pH-gap provide different mathematical expressions of the dysoxic component of actual intramucosal pH for any given tissue bicarbonate. In the majority of patients whose acid secretion is inhibited by an H$_2$ receptor antagonist and whose arterial pH is normal, the actual intramucosal pH per se provides a measure of the severity of the dysoxic acidosis present in the mucosa.

Thus in adequately oxygenated mucosa the actual intramucosal pH is equal to arterial pH and both pH-gap and log $P_{CO_2}^i/P_{aCO_2}$ are zero. In dysoxia, $P_{CO_2}$ increases above that present in arterial blood, the actual intramucosal pH decreases below that in arterial blood, and the pH-gap and log $P_{CO_2}^i/P_{aCO_2}$ increase (fig. 5).

Arterial pH decreases in respiratory acidosis and increases in respiratory alkalosis. Provided perfusion of the tissue is maintained, the changes in arterial $P_{CO_2}$ should be reflected in the tissue bed, and the dysoxic component should still be log $P_{CO_2}^i/P_{aCO_2}$ or pH-gap. Arterial pH may also decrease when bicarbonate decreases in metabolic acidosis and increase when it increases in metabolic alkalosis. Both normoxic and dysoxic isobars shift to the left and right, respectively, in these circumstances. The dysoxic component of intramucosal pH may still be determined from log $P_{CO_2}^i/P_{aCO_2}$ and pH-gap, independently of changes in arterial bicarbonate or pulmonary ventilatory rate provided that time is allowed for equilibration of carbon dioxide and especially bicarbonate to occur within the tissue bed (figs 5, 7, table 3). The degree of dysoxia present may alternately be expressed as standardized intra-
Gastric intramucosal pH, tissue oxygenation and acid-base balance

mucosal pH, a measurement that eliminates the confounding effects of disturbances in systemic acid-base balance:

\[ \text{standard intramucosal pH} = 7.40 - \log \frac{P_{CO_2}}{P_{aCO_2}} \]

The standard intramucosal pH is the same as the actual pH in the majority of patients whose arterial pH is normal (7.40), but differs from actual pH when arterial pH is abnormal because of a systemic disturbance in acid-base balance.

Some have advocated using \( P_{CO_2} \) alone as a measure of the severity of shock or inadequacy of tissue oxygenation [105]. \( P_{CO_2} \) dissociates from the adequacy of tissue oxygenation on rebreathing into a bag containing enough oxygen to maintain tissue oxygenation [42] and also on hyperventilation. More importantly \( P_{CO_2} \) is confounded by shifts in the bicarbonate isobar, especially when close to the normal range (fig. 5). Indeed, the assumption that tissue bicarbonate is the same as that being delivered to the tissue in arterial blood is fundamental to the determination of the degree of dysoxia present from measurements of \( P_{CO_2} \), be this determined from the standard intramucosal pH, pH-gap or log \( P_{CO_2}/P_{aCO_2} \). Of these different mathematical expressions of the degree of dysoxia present, the standard pH is the preferred, as all clinical staff appreciate that a pH of 7.40 is normal and that a pH less than 7.40 may be abnormal. The standard pH provides a conventional expression of the pathophysiological abnormality present in dysoxic states, namely the imbalance between the protons released by ATP hydrolysis and those consumed in ATP resynthesis by oxidative phosphorylation.

The theoretical changes in intramucosal pH which occur with different degrees of dysoxia suggest that the actual gastric intramucosal pH may be capable of detecting the presence of dysoxia whenever the delivery of oxygen fails to meet more than 20% of the tissue’s needs, regardless of the presence of even severe disturbances in systemic acid-base balance (fig. 6). The stoichiometric analysis of the effects of dysoxia further suggests that the standard intramucosal pH may improve the sensitivity and accuracy of the measurement of the degree of dysoxia present, currently determined with measurements of actual intramucosal pH.

**ACTUAL VS STANDARD INTRAMUCOSAL pH IN VIVO**

The possibility that the accuracy of the indirect measurement of intramucosal pH in detecting the presence of mucosal dysoxia might be improved by using a theoretically more accurate measure of the degree of dysoxic tissue acidosis present has been examined in animals. In these studies the abilities of the actual intramucosal pH and pH-gap to detect the presence of mucosal ischaemia were compared. The pH-gap is a better diagnostic test for ischaemia (\( P < 0.001 \)) than actual intramucosal pH (\( P < 0.01 \)) [32]. The same should apply for the other mathematical expressions of the dysoxic component, including standard intramucosal pH. An abnormal pH-gap, and hence standard intramucosal pH, may be present in patients whose actual intramucosal pH is normal [3] and the addition of pH-gap to pH\(_m\) in a study of patients undergoing cardiac surgery improves the sensitivity of the prediction of impending complications from 87.5% to 100% [35].

Benjamin and colleagues [7, 8] administered carbicarb in a bolus of 5 ml kg\(^{-1}\) followed by 5 ml kg\(^{-1}\) h\(^{-1}\) to reverse tissue acidosis induced in a haemorrhagic shock and resuscitation model. Carbicarb increased arterial bicarbonate from 14 to 38 mmol litre\(^{-1}\) during shock and increased the actual gastric intramucosal pH from 6.9 to 7.36 thus masking the dysoxia present. Arterial bicarbonate increased to 41 mmol litre\(^{-1}\) and intramucosal pH to 7.51 with replacement of the blood lost. Gastric acid secretion was inhibited in this model. The standard gastric intramucosal pH, computed from their results, increased from 7.10 to 7.20 after administration of carbicarb during shock and to 7.31 after replacement of blood. Thus i.v. infusions of pharmacological amounts of carbicarb may mask the presence of mucosal dysoxia when assessed with actual intramucosal pH but not when assessed with standard intramucosal pH.

**Clinical implications**

**MONITORING THE ADEQUACY OF TISSUE OXYGENATION**

The indirect measurement of actual intramucosal pH provides an accurate diagnostic test for the presence of macroscopic and clinical evidence of gastric, small intestinal and large intestinal ischaemia in patients [36, 40, 44, 89]. The sensitivity of intramucosal pH as a diagnostic test for gastric ischaemia in humans is reported to be 95% and the specificity 100% [44]. For severe ischaemic colitis after abdominal aortic surgery, the sensitivity is reported to be 100% and the specificity 87% [89]. Of particular relevance to patients who are critically ill is the inability of those with an actual intramucosal acidosis to secrete acid in response to pentagastrin [62]. The inability to secrete acid in patients with an intramucosal acidosis may be because of an energy deficit characteristic of the dysoxic state. An energy deficit is a known cause of stress ulceration in animals [76] and impairment of gastric mucosal oxygenation is the likely cause of stress ulceration in the critically ill [27, 40].

The actual gastric intramucosal pH, measured after administration of an H\(_2\) receptor antagonist to avoid the confounding influence of back-diffusion of acid, carbon dioxide, or both, is inversely related to the hepatic venous lactate concentration in patients undergoing cardiac surgery (\( r = -0.71 \)) [68, 69] and correlates closely with this and other indices of splanchnic tissue oxygenation (\( r = 0.92 \)). Gastric intramucosal pH may, therefore, provide an index of the adequacy of splanchnic tissue oxygenation.

The actual gastric intramucosal pH also correlates very well and inversely with systemic blood lactate when it is abnormally elevated. In many circumstances, however, blood lactate is normal when intramucosal pH is low and no correlation between the variables can be demonstrated [86, 92]. Changes in actual pH influence the pH-dependent enzymes...
regulating carrier-mediated efflux of lactate from muscle and the pH-dependent enzyme phosphofructokinase which regulates the rate of anaerobic glycolysis [64]. In addition, blood lactate is the net effect of production and consumption by tissues. The change in blood lactate may also be dissociated from the change in adequacy of tissue oxygenation on reperfusion of ischaemic gut. In these circumstances blood lactate increases from tissue washout while intramucosal pH increases from the improvement in tissue oxygenation [92]. The overall correlation between the two variables is thus rather poor ($r = -0.40$) but nevertheless statistically significant ($P = 0.026$) [21].

The indirect measurement of actual intramucosal pH provides a measure of the adequacy of tissue oxygenation in the most superficial layer of the mucosa, a region of the gut rendered relatively hypoxic by the countercurrent exchange system within the mucosal vasculature and hence especially sensitive to alterations in the adequacy of tissue oxygenation [71]. It also provides a measure of the adequacy of tissue oxygenation in a region of the body that is among the first to develop an inadequacy of tissue oxygenation or dysoxia in shock and the last to be restored to normality by resuscitation. The splanchnic vasculature is selectively constricted by the endogenous vasoconstrictors released in shock [88]. For these reasons a decrease in intramucosal pH may occur hours to days in advance of an increase in blood lactate [92].

It is concluded that the indirect measurement of actual gastric intramucosal pH provides a very sensitive and specific index of the adequacy of tissue oxygenation. Blood lactate provides neither a sensitive nor a specific index of the adequacy of tissue oxygenation.

CORRELATIONS WITH ACID–BASE BALANCE AND CLINICAL EVENTS

The indirect measurement of actual gastric intramucosal pH may correlate very closely with arterial pH ($r = 0.67$) and other systemic indices of acid–base balance such as arterial bicarbonate ($r = 0.50$), the base deficit in extracellular fluid ($r = 0.60$) and base deficit in blood ($r = 0.63$) [10]. This is consistent with the conclusion that gastric intramucosal pH provides an index of the balance between the protons released by ATP hydrolysis and consumed in the resynthesis of ATP by oxidative phosphorylation, the major determinants of acid–base balance in adequately ventilated patients. As with global measurements of blood lactate, changes in systemic acid–base balance provide a very dampened signal of disturbances in the adequacy of tissue oxygenation. A reduction in actual gastric intramucosal pH often precedes a reduction in arterial pH or base excess by hours or even days [30, 31, 92] (fig. 9). As with lactate, these systemic indices of acid–base balance may be dissociated from gastric intramucosal pH and adequacy of tissue oxygenation on reperfusion [2, 28, 92] (fig. 10).

The predictive value of measurements of actual gastric intramucosal pH for outcome is superior to those of the systemic measures of tissue oxygenation and acid–base balance [74, 84, 92]. Maynard and colleagues [72], for example, compared the predictive...
value of measurement of gastric intramucosal pH with those of blood lactate, arterial pH and base excess for death in ICU patients. The likelihood ratio for pH<sub>int</sub> was 2.32, for blood lactate 1.70, for arterial pH 1.52 and base excess 1.47. Logistic regression showed only pH<sub>int</sub> to independently predict outcome.

Furthermore, clinical experience has shown that changes in gastric intramucosal pH correlate better with the passage of clinical events than either blood lactate, arterial pH or base excess [74, 84, 92]. Indeed abnormal systemic measures of blood lactate and acid–base balance often appear only as the inadequacy of tissue oxygenation and associated intramucosal acidosis is being reversed and the patient’s condition is improving (fig. 10).

Thus the actual gastric intramucosal pH correlates with systemic indices of tissue oxygenation and acid–base balance only when they are grossly abnormal and may be dissociated from the systemic indices on reperfusion of dysoxic tissue beds. The actual gastric intramucosal pH correlates more closely with the adequacy of tissue oxygenation and clinical events than these systemic indices, especially on reperfusion of dysoxic tissue beds. By eliminating the confounding effect of changes in systemic acid–base balance, measurements of standard gastric intramucosal pH may improve the sensitivity of the regional measurements to changes in the adequacy of tissue oxygenation [32] and increase the dissociation between tissue and systemic measures of tissue oxygenation and acid–base balance.

**INTRAMUCOSAL pH AS A THERAPEUTIC TARGET**

As a reduction in intramucosal pH is such a sensitive and early measure of dysoxia, the indirect measurement provides clinicians with an opportunity of limiting the degree and duration of dysoxia hours to days earlier than ever before and averting its possible consequences (fig. 9).

“Gut-directed” and “pH<sub>int</sub>-directed” therapies improve outcome. These therapies use a “normal” pH, or pH, greater than 7.35 as a supplementary therapeutic goal in the resuscitation of patients [39]. This pH was chosen to ensure that gastric intramucosal pH was maintained well within normal limits. The normal limits may, however, differ from institution to institution with the use of different blood–gas analysers [33]. It is furthermore possible that an end-point other than 7.35 might be more appropriate.

While it would seem desirable to maintain a normoxic state by maintaining the standard intramucosal pH at 7.40, it is not necessarily desirable to maintain the actual intramucosal pH at 7.40. There is a considerable body of evidence indicating that a mild degree of cellular acidosis protects cells by limiting the activity of the autolytic enzymes responsible for cell injury and death [1, 64]. Furthermore, the addition of bicarbonate to the extra-cellular environment attenuates the reduction in intracellular pH during ATP depletion and accelerates cell death. The presence of an actual intramucosal acidosis may, therefore, be desirable and efforts to correct metabolic acidosis with bicarbonate potentially harmful. Indeed, the practice of correcting metabolic acidosis induced by cardiac arrest by administration of bicarbonate is no longer recommended [4].

Experience with monitoring of intramucosal pH has helped to identify new therapeutic options in patients with severe sepsis. These options include restriction of red cell transfusions in anaemic patients as they may increase the severity of the intramucosal acidosis present [97]. They also include pharmacological agents that may reverse intramucosal acidosis refractory to increases in global oxygen delivery. These drugs include dobutamine [86], dopexamine [73, 98, 107], prostacyclin [87] and N-acetylcysteine [100]. Further studies are required to establish whether the withholding of blood, or the reversal of dysoxia, or both, induced by these or other drugs improves outcome in severe sepsis.

**Conclusion**

It is concluded that acid–base balance is intimately related to the adequacy of tissue oxygenation insofar as it relates to the balance between the protons released by ATP hydrolysis and consumed by ATP synthesis from oxidative phosphorylation. Tissue pH appears to be determined largely by the P<sub>CO<sub>2</sub></sub> attained following buffering of the volatile and fixed acid loads entering the intramucosal ECF and the bicarbonate concentration in the ECF at the time—the “buffer hypothesis”. Intramucosal pH appears to be related to blood flow only insofar as it relates to the adequacy of tissue oxygenation. The assumption that gastric intramucosal bicarbonate is the same as arterial bicarbonate is only valid in the absence of an alkaline tide and associated secretion of acid. The indirect measurement of actual gastric intramucosal pH is the sum of the effects of several determinants of intramucosal acidosis, including back-diffusion, systemic acid–base balance and the degree of unreversed ATP hydrolysis present. By eliminating the confounding effects of disturbances of acid–base balance, the standard gastric intramucosal pH provides a more specific measure of the degree of unreversed ATP hydrolysis or dysoxia present at the time. The addition of standard to actual values improves the clinical utility of measurements of gastric intramucosal pH. Systemic measures of acid–base balance and blood lactate provide delayed and very dampened signals of inadequacies of tissue oxygenation relative to those provided by the gastric intramucosal pH. The systemic measures of acid–base balance and blood lactate may be dissociated from the adequacy of tissue oxygenation on reperfusion of a dysoxic tissue bed and correlate poorly with clinical events relative to the measurement of gastric intramucosal pH.

**References**


