British Journal of Anaesthesia **84 (1)**: 74–86 (2000)

BJA

REVIEW ARTICLE

Gastrointestinal luminal P_{CO_2} tonometry: an update on physiology, methodology and clinical applications

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Br J Anaesth 2000; **84**: 74–86

Keywords: gastrointestinal tract, pH; gastrointestinal tract, mucosal perfusion; measurement techniques, tonometry; partial pressure, carbon dioxide; carbon dioxide, partial pressure

Gastrointestinal mucosal pH (pHi), calculated from tonometrically measured P_{CO_2} in the gastrointestinal lumen and blood bicarbonate content using the Henderson–Hasselbalch equation, has been suggested to constitute an index of the adequacy of splanchnic mucosal perfusion. This may relate to the prognosis of critically ill patients, as bowel wall hypoperfusion may result in tissue injury, increased permeability, endotoxin–bacterial translocation and a harmful inflammatory (cytokine) response.[11 12 26 30 37 54 61 68 71 73 98 106 114 122 130 131] The theory is that hypoperfusion below a critical level causes tissue (mucosal) carbon dioxide accumulation and acidosis. As carbon dioxide diffuses easily across membranes, the P_{CO_2} in the gut lumen also increases, leading to widening of the tonometer–blood P_{CO_2} gradient. In fact, pHi has been used successfully to guide treatment and to improve the outcome of critically ill patients.[36 46 49 61 68] Nevertheless, tonometry has not yet become a routine intensive care monitoring technique. This may relate to uncertainties regarding its physiological background, methodology and clinical usefulness.[46] This review will therefore update current thoughts on these aspects.[36 46]

Physiological background

Gastrointestinal hypoperfusion

Several conditions may lead to altered gut perfusion (Table 1). Haemorrhagic hypotension, cardiac tamponade, cardiac bypass or vasopressin infusion for example, may lead to mucosal hypoperfusion along the entire gastrointestinal tract, and this may be assessed with the help of simultaneous tonometric measurements in various gastrointestinal segments.[1 82 84 101 117 118 134] In fact, the bowel P_{CO_2} gradient may increase and pHi decrease during hypoperfusion states, similar to changes in gastrically determined tonometric variables. This may also apply to sepsis and shock, even if the oxygen demands by the bowel wall increase,[101] and to cardiopulmonary bypass surgery, during which bowel wall oxygen demands may decrease following hypothermia and increase during rewarming.[3 11 29 53 106 110 111 129] Moreover, shock may result in early selective splanchnic vasoconstriction so that gastric tonometry may reveal an early indicator of general hypoperfusion.[33 36 46 55 101 134] The gastric tonometric P_{CO_2} gradient proved an early, sensitive indicator of hypovolaemia during haemorrhage in healthy volunteers.[55] An increase in the gastric P_{CO_2} gradient and decrease in pHi during general hypoperfusion in humans may relate to angiotensin II-induced selective splanchnic vasoconstriction.[67 109]

Experimental studies using vascular occlusion and reperfusion, induction of shock or pharmacological splanchnic vasoconstriction have revealed that changes in blood flow to the gut wall, as measured by microspheres, laser Doppler, electromagnetic or ultrasonic flow probes, or reflectance spectrophotometry, were paralleled by concordant changes in tonometric variables.[2 57 70 73 82 84 101 108 115 117–119 125 131 134] A decrease in blood flow to less than 50% of baseline during incremental hypoperfusion leads to an increased tonometric P_{CO_2} relative to supplying (and draining) blood values. This results in a decrease in pHi, in parallel with the decreasing blood flow and decrease in tissue P_{O_2} and oxygen consumption.[1 2 13 36 46 50 55 57 73 82 84 101 103 108 115 117–119 125 134] This may result in tissue damage and increased mucosal permeability.[1 11 12 26 71 73 106 122 131] In critically ill, septic and mechanically ventilated patients, laser Doppler (and reflectance spectroscopy) measurement of gastric mucosal blood flow, hepatosplanchnic blood flow measured by indocyanine green, or hepatic breakdown of injected lidocaine to monoethylglycinexylidide, were lower in

Table 1 Conditions in which tonometry is of potential clinical value

Perioperative monitoring in major surgery, including cardiopulmonary bypass, major (emergency) vascular surgery and liver transplantation
Myocardial infarction and shock
Heart failure
Pulmonary embolism and shock
Traumatic/hypovolaemic shock
Sepsis and shock
Pericardial tamponade
Fluid and drug therapy for shock
Infusion of vasopressin or other vasoconstrictors
Acute pancreatitis
Mesenteric thrombosis
Necrotizing enterocolitis
Ischaemic colitis
Bowel obstruction
Chronic coeliac and mesenteric vascular disease
Assessment of bowel viability
Intolerance to tube feeding
Weaning from mechanical ventilation
Haemodialysis

patients with an increased P_{CO_2} gradient and subnormal pHi than in those without these tonometric abnormalities, or in healthy controls.[35 93 102 127] In fact, drug-induced changes in blood flow assessed by these techniques can be paralleled by concordant changes in P_{CO_2} gradient and pHi.[34 93 101 102 127]

However, tonometric variables are indicators of the blood flow to demand ratio. Changes in splanchnic blood flow, as assessed by indocyanine green clearance or laser Doppler techniques, are not necessarily accompanied by changes in tonometric variables and vice versa, particularly when demand changes, for example with the variation in body temperature associated with cardiopulmonary bypass surgery and sepsis. During hypothermic cardiopulmonary bypass surgery, gastric mucosal (Doppler) blood flow may decrease, but neither the gastric luminal to blood P_{CO_2} gradient nor pHi may change.[3 106 114] The generally observed decrease in pHi during rewarming and in the postoperative phase may not concord with splanchnic blood flow changes and oxygen consumption, which may even increase, and this discrepancy suggests either increased oxygen demand or insufficient ability of pHi to reflect the balance between oxygen supply and demand.[53 106 109 110 114 129] Even during normothermic cardiopulmonary bypass surgery, bowel demands may increase and may be insufficiently met by an increase in blood flow, thereby lowering pHi.[53] Disconcordant changes in cardiac output and gut blood flow on the one hand and tonometric variables on the other during treatment with catecholamines, with an increase in the former but no improvement in the latter, may relate in part to redistribution of blood flow within the stomach or gut wall, away from the mucosa.[11 110 111 127 129] During endotoxaemic–septic shock, gut blood flow may not decrease and gut P_{O_2} and oxygen consumption may increase, but this may not prevent a subnormal gastrointestinal pHi developing, suggesting redistribution of blood flow, impaired oxygen use, or both.[131] Finally, it remains to be seen if deterioration in tissue oxygenation and increased anaerobic metabolism through severe hypoxaemia or anaemia also result in tonometry changes[70] as it is conceivable that a high blood flow but insufficient oxygen delivery may limit the increase in P_{CO_2} and decrease in pHi.[3]

Sublingual, oesophageal, gastric and bowel P_{CO_2} tonometry

Luminal production of carbon dioxide during buffering of gastric acid by bicarbonate or bacterial fermentation may limit the specificity of luminal P_{CO_2} and thus pHi as indicators of the adequacy of mucosal perfusion in the stomach and large bowel, respectively. This may not occur with tonometry in the oesophagus or sublingually as these areas are not supplied by splanchnic blood vessels. Thus the sensitivity of tonometry for early detection of general hypoperfusion may be inferior to that for detecting hypoperfusion in the stomach or small bowel, where selective vasoconstriction may occur.[33] During severe haemorrhage or sepsis in animals, sublingual, oesophageal and gastric P_{CO_2} nevertheless increased in parallel and simultaneously with the decrease in blood flow and increase in blood lactate concentration.[52 64 100 118 124] With regard to the value of small bowel *vs* gastric tonometry, widening of the tonometer–blood P_{CO_2} gradient in pigs may be earlier in the small bowel than in the stomach during haemorrhagic shock,[101] but not during cardiac tamponade.[1] The increase in jejunal P_{CO_2} during endotoxaemia in horses was less and occurred later than that of gastric P_{CO_2}.[123] Walley and colleagues,[134] however, showed that during haemorrhagic hypotension, widening of the tonometer–blood P_{CO_2} gradient was less and less variable in the jejunum than in the stomach, largely because of greater measurement error in the latter.

P_{CO_2} gradient vs pHi as an indicator of mucosal hypoperfusion

It has been argued repeatedly that pHi is a composite variable, consisting of a systemic and locally derived variable, and should be replaced by the tonometer–blood P_{CO_2} (or perhaps pH) gradient. This is especially so if tonometry is being done to yield a sensitive and specific measure of the adequacy of gastrointestinal mucosal perfusion, independent of systemic metabolic and respiratory alterations.[26 42 46 51 55 61–64 73 87 120 134] Indeed, the major pitfall in the calculation of pHi from gastric P_{CO_2} and arterial bicarbonate content is the assumption that the latter equals mucosal content. In humans, the mucous layer of the acid-secreting stomach also contains bicarbonate, which is secreted by non-parietal cells and helps to protect the underlying mucosa from the gastric acid secreted by parietal cells.[69] Mild hypovolaemia in human volunteers decreases gastric bicarbonate secretion more than acid secretion, and this may be associated with alterations in tissue bicarbonate concentration.[69] Hence the bicarbonate content of the mucosa may normally be higher than in blood, while

hypoperfusion may result in a dissimilar decrease in blood and mucosal bicarbonate content, depending on the balance between general and regional hypoperfusion, diminished bicarbonate secretion and the degree of buffering of lactic acid in the hypoperfused stomach wall.[73 115 119 125] Conversely, changes in arterial blood bicarbonate content may lead to alterations in calculated pHi, independent of changes in the degree of mucosal hypoperfusion and the increase in P_{CO_2} gradient.[120] I.v. bicarbonate administration to a patient with mesenteric thrombosis resulted in an increase in gastric tonometer pHi to normal values, despite a necrotic bowel found at laparotomy, but the stomach may not have represented the small bowel.[10] Conversely, in cardiac surgery patients, a rapid decrease in arterial bicarbonate content by volume loading during surgery may contribute to a lowered gastric pHi, independent of luminal P_{CO_2}.[6]

Moreover, gastric P_{CO_2} closely parallels local arterial (and draining venous) blood P_{CO_2} values during changes in alveolar ventilation, as demonstrated in animals and human volunteers with (presumably) normal perfusion, so that changes in pHi may result from changes in alveolar ventilation, independent of mucosal hypoperfusion.[13 27 31 79 117] Conversely, changes in alveolar ventilation in patients undergoing mechanical ventilation resulted in changes in tonometric variables similar to blood P_{CO_2}, if gastric mucosal blood flow remained adequate.[13 31] The dependency of pHi on arterial blood bicarbonate content and P_{CO_2} may underlie the observed concurrent changes or correlations between calculated pHi on the one hand and arterial blood pH and acid–base variables, including lactate concentration, on the other.[19 31 41 49 61 83 135]

It is still unclear as to the threshold for anaerobic metabolism, but the upper limit of a normal gradient would be approximately 1.2 kPa.[79 87 115 126] The increased luminal P_{CO_2} during hypoperfusion is assumed to stem from two sources. With a moderately gradual reduction in perfusion, mucosal P_{CO_2} accumulates after a reduced washout and an increase in tissue and venous P_{CO_2}. A further decrease in blood flow results in a steep increase in tissue (luminal) and to a lesser extent venous P_{CO_2} and this may be caused by buffering of anaerobically produced lactate and protons by mucosal bicarbonate.[57 73 115 119 134] Hence a gradient between tissue and draining venous P_{CO_2}, in spite of allegedly high diffusibility of carbon dioxide, may be a marker of anaerobic tissue metabolism. It seems that a decrease in tissue oxygen consumption and tension and development of anaerobic metabolism and production of lactic acid occurs at a P_{CO_2} gradient of 3.3 kPa or greater, a value that can be regarded as the critical gradient.[2 36 115 119 134] A lower gradient, however, does not exclude a focal oxygen deficit in the mucosa.[79] The baseline P_{CO_2} tonometer–blood gradient in patients with gastric erosions or ulcerations and stenotic or occluded coeliac and mesenteric vessels at angiography was approximately 0.4 kPa and increased to 2.5 kPa during submaximal exercise, whereas no such increase was observed in patients with normal angiography.[80] Thus some patients had lesions in the stomach attributable to hypoperfusion in spite of a resting P_{CO_2} gradient presumably below the critical value of approximately 3.3 kPa.[80] The lesions may relate to intermittent or patchy hypoperfusion rendering the mucosa susceptible to damage by other factors.

Methodological considerations

Comparison of tonometric with directly measured variables

In the control state, tonometric pHi may agree with directly measured tissue pH in the stomach and bowel.[38] Some authors have shown that directly measured P_{CO_2} is higher than tonometrically derived P_{CO_2}, and that the response time of the latter is slower.[36 103] This may result in tonometric pHi overestimating directly measured tissue pH during sudden hypoperfusion.[2 36] The latter may also relate to the erroneous bicarbonate assumption discussed above.

Normal values

Normal values for gastric tonometry have been defined, taking *in vivo* determined correction factors and blood-gas analyser bias (see below) into account.[79] The upper limit of normal values for P_{CO_2} was 6.5 kPa and for the tonometer–blood P_{CO_2} gradient, 1.2 kPa, so that tonometric P_{CO_2} is normally a few kPa higher than that in the blood supply. The lower limit of normal for pHi is 7.33 and for the pH gradient, –0.06.[79] This agrees in part with other reports, where the upper limit of normal pH varied between 7.32 and 7.35.[12 19 30 35 49 59 60 65 68 79 83 89 98 99 108 126] Data on normal P_{CO_2} or the P_{CO_2} gradient in the human gut are lacking. Bass and colleagues noted that the control intestinal (jejunal or ileal) mass spectrometer P_{CO_2} was 11.9 kPa in dogs, but arterial values were not given.[9] The normal fibreoptic/tonometric ileum to blood P_{CO_2} gradient may, as in the stomach, amount to 1.3–2.7 kPa in pigs and dogs.[73 82 101 115 119] The normal oesophagus to blood P_{CO_2} gradient is also in that range.[52 82] There is no information on the normal tonometer balloon equilibration characteristics from the oesophagus to the large bowel, where changes in luminal contents and diffusion conditions may have an effect.

Gastric P_{CO_2} as a measure of gastrointestinal mucosal P_{CO_2}

It is generally assumed that rapid diffusion results in luminal P_{CO_2} being identical to mucosal P_{CO_2}. Nevertheless, the increase in tonometric P_{CO_2} may underestimate that of directly measured P_{CO_2}.[39 103] Carbon dioxide diffuses rapidly from mucosa into the lumen with complete equilibration in 60 min, while diffusion in the opposite direction is about four times slower.[38] Even though carbonic anhydrase, present in the gastric mucosa, may contribute to the difference in diffusion rate, inhibition of carbonic anhydrase activity did not decrease the rate of P_{CO_2} build-up in the tonometer

balloon.[76] This suggests that the balloon P_{CO_2} arises from gastric contents as opposed to the gastric mucosa. Indeed, gastric carbon dioxide content may decrease by 6% and P_{CO_2} may decrease by 0.3 kPa during equilibration of 1.5 ml of tonometer balloon saline, in the absence of transmucosal diffusion.[76] Gastric balloon rather than transmucosal carbon dioxide diffusion may be the rate limiting step during gastric P_{CO_2} tonometry.[76]

Gastric secretion of acid

The close approximation of luminal and mucosal P_{CO_2} may be lost in the stomach when carbon dioxide is produced by buffering of gastric acid, contributing to a relatively poor reproducibility of gastric pHi.[134] Indeed, in the normally perfused upper gastrointestinal tract, luminal P_{CO_2} may directly relate to the amount of acid secreted and buffered in the stomach,[105 116] and has even been used as a measure of gastric acid secretion.[105 116] This luminally produced carbon dioxide stems from the buffering of gastric acid by bicarbonate secreted by the gastric mucosa[105] or by bicarbonate entering the stomach through duodenal reflux or from saliva via the oesophagus. The increase in P_{CO_2} resulting from buffering can be prevented by inhibition of acid secretion.[38 105] Hence it has been recommended to perform tonometry after H_2 block of gastric acid secretion.[36 46] In fact, gastric P_{CO_2} in human volunteers is 1.3–2.7 kPa above blood levels and decreases towards arterial levels with less interindividual variation after inhibition of acid secretion by the H_2 blocker ranitidine, so that calculated pHi is higher in the presence of prior H_2 block.[75 112 126] When duodenogastric reflux is simulated by oral administration of bicarbonate in an amount approximating the hourly pancreaticoduodenal production, gastric P_{CO_2} increases to approximately 10.7 kPa above blood levels but only in the absence and not in the presence of prior H_2 block.[75] Removal of gastric acid by suction may not decrease gastric P_{CO_2} towards blood values.[112] This can be explained by the fact that gastric acid, which is produced in the deep pits of the gastric mucosa, is buffered by gastric bicarbonate in the mucus layer covering these pits.[75] Buffering of gastric acid by administration of non-carbon dioxide releasing antacids such as aluminium oxide–magnesium hydroxide also releases large amounts of carbon dioxide *in vitro* and is therefore not useful.[132]

It can be questioned whether data in healthy subjects would apply to critically ill patients as H_2 blockers, which would be expected to lower P_{CO_2}, had no effect on gastric P_{CO_2} in the seriously ill.[22] Together with the concept that inhibition of acid secretion may predispose to gastric bacterial colonization and nosocomial infections, this may be the reason that many authors do not use H_2 block before tonometry in critically ill patients.[17 31 34 109–111 121 129] Similarly, administration of sucralfate, which has acid-buffering capacities and increases gastric bicarbonate secretion, and could therefore be expected to increase P_{CO_2} in the presence of acid, had no effect on P_{CO_2} in critically ill patients.[21] This may be explained by a reduction in gastric acid secretion, as shown by a relatively high gastric juice pH that fails to decrease after pentagastrin infusion in many critically ill patients after operation.[6 44 60] During the first 24 h after cardiopulmonary bypass surgery, gastric fluid may be acidic (pH <4.0) in a minority of patients.[6] Simulation of duodenogastric reflux by gastric bicarbonate administration had no effect on gastric P_{CO_2} immediately after surgery, indicating lack of gastric acid secretion but increased gastric P_{CO_2}, on the first postoperative day by 2.7 kPa in six of 10 subjects.[6] The observations suggest postoperative recovery occurs after reduced gastric acid secretion caused by transient hypoperfusion.

Indeed, gastric acid secretion is an active, energy-demanding process.[69] During haemorrhagic hypotension, gastric mucosal blood flow and gastric acid (and bicarbonate) secretion diminish, but less so in pentagastrin- or histamine-stimulated conditions than in animals pretreated with H_2 blockers.[69] This suggests that gastric acid secretion in shock is blood flow dependent and that administration of H_2 blockers (or proton pump inhibitors) may further diminish energy-demanding gastric acid secretion and blood flow and may protect against the development of stress ulcers related to hypoperfusion.[66 69 92] In fact, a low pHi may be associated with failure to acidify the gastric lumen in response to pentagastrin.[60] The combination of a reduced demand and an increased perfusion reserve during inhibition of acid secretion probably results in lowered sensitivity of tonometry as an indicator of early perfusion failure or gastric mucosal hypoperfusion. A patient who develops an increased P_{CO_2} gradient might either have mucosal hypoperfusion or recurrence of gastric acid secretion after amelioration of hypoperfusion. Inhibition of acid secretion reduces the incidence of this dilemma, thereby increasing the validity of gastric tonometry, and simple measurement of gastric juice pH, preferably by continuous monitoring, could solve the problem. An aspirated juice pH above 4.0–5.0, checked with the help of litmus paper, would suggest minimum or no buffering effects,[6 76 85 126] so that changes in gastric P_{CO_2} would probably result from changes in mucosal perfusion only.

However, H_2 blockers such as ranitidine may fail to control gastric juice pH, even in critically ill patients.[97] The efficacy of the first dose after i.v. administration is reduced within 24 h,[95] and after 48 h, the gastric juice pH is again less than 4.0 for 60% of the time.[44] The proton pump inhibitor omeprazole increases gastric juice pH more efficiently and continuously than H_2 antagonists, even 24 h after administration.[95] While abolishing acid and inhibiting bicarbonate secretion, the drug may maintain mucosal perfusion, in contrast with H_2 blockers that decrease both acid secretion and mucosal blood flow.[92] Preserved blood flow after proton pump inhibitors may contribute to preventing stress ulcer bleeding during haemorrhagic hypotension.[66]

Tonometry in fed or fasting state?

Eating a meal might serve as a stress test for mucosal vasodilator reserve as the meal stimulates gastric acid secretion, and small bowel secretions, and active resorption of nutrients. The increased energy expenditure of the gut causes an increase in blood flow to both the stomach and small gut mucosa.[84] Indeed, luminal P_{CO_2} may increase to 53.5 kPa in the normal stomach and duodenum after gastric feeding, as a result of buffering of the increased acid by the increased bicarbonate output.[116] As the increased postprandial P_{CO_2} is caused by acid buffering, it might be expected that acid suppression could circumvent this increase. However, although H_2 antagonists can effectively block basal or fasting acid secretion, suppression of meal-stimulated gastric acid secretion may be incomplete, even in critically ill patients.[97] Even in the presence of H_2 blockers, gastric feeding of critically ill patients may increase gastric P_{CO_2} relative to blood values, presumably as a consequence of the production of carbon dioxide.[75 90] This may also occur in some individuals where acid secretion has been inhibited completely by a combination of ranitidine and the muscarinic receptor antagonist pirenzepine.[77 97] The cause of this increase proved to be the buffering of amino acid-containing food by gastroduodenal bicarbonate.[77 90] P_{CO_2} may also decrease shortly after gastric feeding because of dilution. Hence the volume of food given and the gastric emptying rate determine this dilutional effect.[77] Finally, when the reserve in cardiac output is limited, a meal may increase blood flow in the proximal gastrointestinal tract while diminishing blood flow and pHi in the distal gastrointestinal tract.[84] Hence normal tonometry variables after a meal do not exclude gastrointestinal hypoperfusion. Taken together, it is recommended to perform gastric tonometry in the fasting state as this may increase specificity, even though it may decrease the sensitivity of the method.[36 46 47 77 90] Alternatively, duodenal feeding may affect gastric tonometry less than gastric feeding.

Confounding factors

In the colon, carbon dioxide production by bacteria may lead to a lower normal pHi than in the stomach.[12 37] Indeed, normal colonic P_{CO_2} may amount to 40.0 kPa, depending on the diet.[20] In horses, who have a large bacterial flora and eat almost exclusively carbohydrates, the normal colonic P_{CO_2} was $>$26.7 kPa.[123] These observations should prompt collection of data for normal values of colonic P_{CO_2} or the effects of bowel preparation, laxatives or antibiotics, as sigmoid tonometry has been reported to be of value in aortic surgery patients.

Entry of environmental air into the stomach may transiently lower gastric P_{CO_2}.[20] Hence a negative gradient may indicate a measurement artefact. This occurs particularly in non-intubated, spontaneously breathing patients.

Sources of error during manual fluid tonometry

Manual fluid (usually saline) P_{CO_2} tonometry is laborious and involves seven steps, each carrying a risk of error so that reproducibility may be relatively poor (Table 2).[28 134] The steps are: (1) infusion of exactly 2.5 ml in the catheter, (2) waiting a fixed dwell time to allow for (partial) equilibration with surrounding luminal P_{CO_2} (in most studies 30 min), (3) withdrawing and discarding the first 1.0 ml representing catheter deadspace, (4) aspiration of the final 1.5 ml into a syringe, capping it and storage on ice, (5) sending the capped syringe to the laboratory for analysis in the blood-gas analyser without delay and (6) calculation of steady-state P_{CO_2} using a correction factor for each dwell time that is less than that needed for full equilibration (Fig. 1). With the help of P_{CO_2}, arterial blood bicarbonate content and the Henderson–Hasselbalch equation, a regional, mucosal pH (pHi) can be calculated. It is likely that the sources of error involved in manual fluid tonometry have limited its widescale clinical application.[28 46]

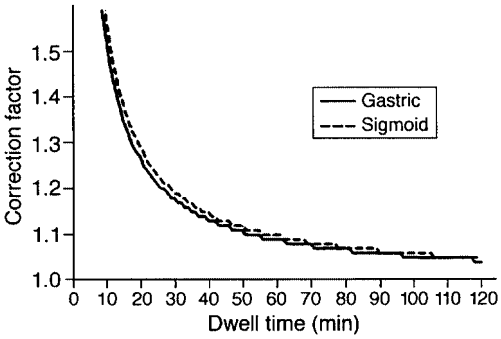

Fig 1 Manual saline tonometry: the correction factor is obtained for use in calculating steady-state P_{CO_2} from measured P_{CO_2} when a dwell time is used which is less than that needed for full equilibration. Gastric- and sigmoid-type tonometers are shown.

Catheter deadspace

With each tonometer measurement, the balloon fluid is aspirated and measured in a blood-gas analyser. However, as the volume of the tonometer tube itself is approximately 1.0 ml, the last 1 ml from the balloon resides in this deadspace. With a new measurement, this 1.0 ml deadspace volume is then pushed into the balloon and mixed with freshly infused fluid. Thus the P_{CO_2} in the balloon at the start of the dwell time is variable and depends partly on the last measured P_{CO_2}. We found that with dwell times of 10 and 20 min, this phenomenon may cause errors in measured P_{CO_2} of 10% and 6%, respectively, at a deadspace P_{CO_2} of 4.0 kPa. At longer dwell times this error becomes negligible.[124] The deadspace error can be avoided either by a calculation based on the last measured P_{CO_2} and the dwell time or by flushing the tonometer four times with fresh saline to remove all remaining, carbon dioxide-containing saline in the catheter deadspace, thus ensuring a P_{CO_2} of 0 kPa in the tonometer balloon before each subsequent measurement.[124] Errors associated with an unrecognized deadspace effect may have influenced the manufacturer's correction factors for short dwell times.

Table 2 Sources of error associated with manual fluid tonometry

Problem	Result	Solution
Blood-gas analyser bias	Error, dependent on fluid and analyser	Evaluate and correct
Measurement error	*In vitro* 3%, *in vivo* 6–8%	–
Poor anaerobic technique	Decrease in P_{CO_2} of 8%	Careful anaerobic technique
Improper storage of syringe	Decrease in P_{CO_2} after 60 min of at least 8%	No delay before analysis
Imprecise dwell time	Error	Instructions and training, or using dwell times >60 min
Deadspace contamination	Error of 6–10% at 10 or 20 min dwell times	Rinse tonometer four times before fluid installation
Incorrect correction factors	Error	Use correct correction factors

Table 3 Blood-gas analyser bias for P_{CO_2} measurements in saline. Bias=Percentage difference from true P_{CO_2} at a P_{CO_2} of approximately 5.3 kPa

Manufacturer	First author and source	Bias
Radiometer		
ABL2	Knichwitz, *Anaesthesia* 1995	–10
ABL3	Temmesfeld, *Intensive Care Medicine* 1997	–12
ABL130	Knichwitz, *Anaesthesia* 1995	–12
ABL300	Riddington, *Critical Care Medicine* 1994	–18
ABL330	Temmesfeld, *Intensive Care Medicine* 1997	–7
ABL505	Knichwitz, *Anaesthesia* 1995	–6
ABL520	Takala, *Critical Care Medicine* 1994	–6
ABL620	Venkatesh, *Anaesthesia and Intensive Care* 1998	–20
Ciba-Corning		
Ciba238	Takala, *Critical Care Medicine* 1994	–5
Ciba278	Kolkman, *Intensive Care Medicine* 1997	–15
Ciba288	Knichwitz, *Anaesthesia* 1995	–29
Ciba840	Kolkman, *Intensive Care Medicine* 1997	–11
Instrumentation Laboratories		
IL1302	Takala, *Critical Care Medicine* 1994	–8
Novastat		
Nova4	Takala, *Critical Care Medicine* 1994	–26
Nova5	Temmesfeld, *Intensive Care Medicine* 1997	–46
Nova7	Riddington, *Critical Care Medicine* 1994	–49
Nova9	Knichwitz, *Anaesthesia* 1995	–57
Eschweiler	Knichwitz, *Anaesthesia* 1995	–51

Blood-gas analyser bias and dwell time-dependent correction factors

It has become apparent that blood-gas analysers, calibrated for blood or calibration fluid, may underestimate P_{CO_2} measured in saline (or air) by 5–50%.[72 79 81 113 128] The magnitude of the error depends on the fluid and blood-gas analyser used, and potentially on the absolute P_{CO_2}.[72 81 113 128] The mean error among analysers (at P_{CO_2} 40 torr) is 12%, ranging from 5% to 29% (Table 3). Consequently, other fluids have been evaluated and used, including succinylated gelatin,[8 81 113] albumin,[72] Hartmann's solution,[113] phosphate–bicarbonate[81] and phosphate or citrate buffer.[3 72 81 127 128] Buffered solutions, including succinylated gelatin,[113] may have the advantage over non-buffered solutions that the conversion of carbon dioxide to bicarbonate in the buffer decreases the propensity for accidental losses to the environment, either via incompletely aerobic techniques or during processing in the blood-gas analyser. Their use may thus result in less bias and greater precision and reproducibility than for P_{CO_2} measurement in non-buffered solutions.[72 81 128] Indeed, the error in P_{CO_2} measurements in saline and phosphate was approximately 7% after careless syringe handling or after 1 h storage of capped syringes.[81] Measurement bias and handling errors could be reduced to approximately 3% with the use of succinylated gelatin and phosphate–bicarbonate buffer.[81] However, buffered solutions increase the time needed for P_{CO_2} to equilibrate by a factor of 2–5.[81 128] Non-bicarbonate-based buffered solutions could share some of the advantages without these disadvantages. Indeed, saline and phosphate had similar P_{CO_2} build-up kinetics and similar propensity for accidental errors, while the bias for phosphate was smaller.[72 81 128] Nevertheless, saline and phosphate may be equally suitable as a tonometer fluid provided strict anaerobic techniques are used and the blood-gas analyser bias is known and taken into account.[72 81]

It is hard to assess the manufacturer's correction factors[37] as *in vitro* studies from which they have been derived have not been published and the role of the deadspace effect and blood-gas analyser bias has not been taken into account. Blood-gas analyser bias has evoked debates in the literature[74 112] on the issue of whether a correction for the bias should be superimposed on the correction for incomplete equilibration provided in the manufacturer's correction factors.[37] Compared with the manufacturer's correction factors, the correction factors for short dwell times were considerably larger because we avoided the deadspace effect by repeated flushing of the tonometer.[79] However, the difference at long dwell times cannot be explained by these effects and must be attributed to blood-gas analyser bias

incorporated in the manufacturer's correction factors.[74 79] Indeed, the manufacturer's correction factors for dwell times beyond 90 min are large. But we have shown that after a 120 min dwell time, the tonometer P_{CO_2} is 96% of the surrounding value (Fig. 1) with a corresponding correction factor of 1.03 compared with 1.17 advised by the manufacturer.[79] That this 1.17 does not relate to incomplete diffusion can be appreciated from a study by Fiddian-Green and colleagues documenting the same P_{CO_2} after dwell times of 60 and 360 min.[37] In fact, correction for both incomplete equilibration using the factors supplied by the manufacturer and blood-gas analyser bias may result in overestimations of P_{CO_2} while incomplete correction may result in underestimations.[58 63 79]

In vitro corrections factors have been assumed to apply to the *in vivo* situation.[27] However, in comparing P_{CO_2} equilibration kinetics of tonometers placed in a saline bath and in the stomach of healthy volunteers, the rate of P_{CO_2} equilibration in the latter proved 31% slower.[79] This may relate to gastric juice, gastric folds and mucus covering the tonometer balloon *in vivo*. Finally, the rate of P_{CO_2} build-up depends on the size and diameter of the catheter, because of the sink effect of the deadspace.[124] Hence equilibration may be a few percent slower when using a long, sigmoid-type catheter instead of the shorter gastric type. This is relevant at 10-min dwell times only.[124] When the sources of error are taken into account, manual measurements are not only reproducible but accurate.[79] The response of the fluid technique, however, remains relatively slow.

Temperature corrections

As with blood P_{CO_2} and acid–base balance, it is unclear if tonometer fluid P_{CO_2} and pHi should be corrected for body temperature if it is not 37°C, for example during hypothermia or fever, as the correction on the blood-gas machine may yield unpredictable results.[8 29 63] Nevertheless, it seems prudent to calculate the P_{CO_2} blood–tonometer fluid gradient from measurements made at the same temperature.

Air and others types of tonometry

From animal and human (post-cardiac surgery) studies,[117] it has been suggested that P_{CO_2} determination in gastric air or juice would represent mucosal P_{CO_2} and could replace the balloon tonometry technique. The balloon technique facilitates and standardizes gastric sampling, and air as opposed to saline tonometry allows more rapid diffusion and thus a shorter response time.[128]

The recently introduced semi-continuous automated air tonometry involves a pump which automatically inflates (and deflates) via an airtight circuit, 6–8 ml of air into the tonometer balloon every 5–60 min (standard 10 min). This measures P_{CO_2} in the aspirated air using a modified infrared capnograph and may eliminate some of the sources of measurement error of manual fluid tonometry, thereby increasing the clinical applicability of the technique.[8 27 58 63 80 126 128] The device is available commercially (Tonocap, Datex, Finland). The response time of the Tonocap, defined as the time needed to reach a 95% change in P_{CO_2} at dwell times of 5–10 min, was 10–18 min. Bias was +1% to –3% and precision about 1%.[27 58 80 128] The relatively long response time, particularly at a high P_{CO_2} and in comparison with the dwell time, may relate to a deadspace effect. P_{CO_2} measurements by the air tonometry technique may underestimate (high) saline tonometric P_{CO_2}, even if they are highly correlated.[27 58 63 79 117] This may relate to 'overcorrection' of the latter. Air tonometry may also overestimate saline tonometry, possibly as a consequence of the use of wrong correction factors for the saline technique.[8 27] The techniques may have some methodological problems and sources of error in common. This may relate, in part, to the probable need for fasting and inhibition of gastric acid secretion and the value of pHi *vs* the tonometer–blood P_{CO_2} gradient. The accuracy of P_{CO_2} measured by air tonometry is not influenced by temperature corrections.[8]

Capnometric recirculating gas tonometry involves a tonometer with two lumina, connected to a circulation pump and an infrared sensor, yielding P_{CO_2} measurements which correlate highly with those obtained by the manual saline technique.[50–52] Compared with the latter, recirculating gas tonometry has a more rapid response time (5 min), allows online measurements and is more sensitive during haemorrhage and endotoxaemia.[50–52] A new method involves a fibreoptic P_{CO_2} sensor which also allows monitoring of pH and P_{O_2}.[73] The sensor proved faster and more accurate than saline tonometry, both *in vitro* and *in vivo*. The potential for using this probe nasogastrically needs further study. Other techniques that may become available for direct mucosal P_{CO_2} measurements include the ion-sensitive field effect transistor sensor.[100 103 118 125] Finally, the tonometry can also be used to measure gastrointestinal luminal nitric oxide concentrations.[1]

Clinical applications

Diagnostic aid in symptomatic coeliac and mesenteric vascular disease

Some patients with otherwise unexplained abdominal signs of dyspepsia and pain (abdominal angina) may have chronic gastrointestinal vascular disease, but it is hard to establish a relation between signs and symptoms on the one hand and objective indicators of gastrointestinal hypoperfusion, such as abnormal angiographic findings, on the other.[80] The management of these patients and the effect of reconstructive vascular surgery may be hard to predict. A diagnostic test for gastrointestinal hypoperfusion that also predicts the success of surgery is therefore needed.[80 84] It has been suggested that gastric tonometry during a test meal may be used.[16 39] However, feeding may confound tonometry in the stomach and may thereby yield negative results, even in patients with otherwise proven splanchnic hypoper-

fusion.[43 75] Alternatively, during exercise, perfusion of the splanchnic organs is at risk because of the 'steal' effect of the increased blood flow to skeletal muscle. Hence vascular disease in the splanchnic region and diminished vasodilator reserve could increase the risk of hypoperfusion during exercise. Indeed, many patients with presumed gastrointestinal vascular disease may have abdominal complaints on exercise. We therefore assessed the value of exercise gastric tonometry in managing patients with suspected gastrointestinal hypoperfusion.[78] When the patients were divided on the basis of normal angiograms and those with stenotic lesions in the coeliac or superior mesenteric artery, the P_{CO_2} gradient during exercise did not increase in the former but increased to about 2.7 kPa in the latter group, with only a minority of patients exhibiting a supranormal gradient at rest. Furthermore, the exercise tonometric findings correlated with a symptom score, the extent of angiographic abnormalities and the presence of discrete mucosal lesions on gastroscopy, consistent with mucosal hypoperfusion and damage. In some patients re-examined after reconstructive surgery, the exercise tonometry test had normalized.[78] Gastric tonometry could help to diagnose acute mesenteric vascular disease resulting in bowel hypoperfusion and necrosis, provided that the stomach is also partly involved and some tissue metabolism remains.[10 73 117]

Estimating prognosis from pHi or the P_{CO_2} gradient and pHi in critically ill patients

The conditions wherein (gastric) tonometric variables proved prognostically significant for the development of multiple organ failure and subsequent death are: orthotopic liver transplantation[135]; acute pancreatitis[17]; cardiopulmonary bypass and other types of major, emergency vascular surgery[29 30 41 54 94 98 114]; sepsis; trauma[25 26 49 61 65 68 83]; and mechanical ventilation.[31 59 93 96] Furthermore, an increased P_{CO_2} gradient and a low pHi were predictive of failure to wean mechanically ventilated patients, independently of arterial blood and ventilatory variables, presumably because of splanchnic diversion of blood flow to exercising respiratory muscles with an increased workload.[18 31 96]

The fact that tonometric P_{CO_2} depends partly on arterial P_{CO_2}, and that the bicarbonate content is shared between arterial pH and calculated pHi, may explain the correlation observed between arterial pH and pHi, and the approximate similar predictive value of both indices.[19 23 41 45] Although splanchnic hypoperfusion and lactate production may influence the systemic indicators, tonometric variables may nevertheless correlate only poorly with systemic factors.[40 48] As hyperlactataemia-associated metabolic acidosis is prognostically unfavourable in critically ill patients, it can be questioned if tonometry is of additive predictive value.[4 19 48 59 62 65 83] A low (subnormal) pHi or increased P_{CO_2} gradient may be superior or have additive value in the prediction of morbidity, that is multiple organ failure and mortality, to global haemodynamic and metabolic variables, including lactate concentration and acid–base variables in the systemic blood of critically ill patients.[25 26 32 40 42 56 59 61 68 83 93 94 96 98] A subnormal gastric pHi may predict circulating markers of an inflammatory response and a poor outcome with postoperative complications and multiple organ failure after major cardiac, vascular and abdominal surgery.[30 62 98] After cardiopulmonary bypass surgery, however, neither pHi nor the P_{CO_2} gradient in the stomach may constitute an early predictor of increased permeability, endotoxaemia and death in the ICU, whereas global haemodynamics and systemic lactate concentration may predict a worsening disease course.[5 14 54 114]

Even though P_{CO_2} or pH gradients may be more specific indicators of gastric hypoperfusion than pHi, it may be questioned if the former are equally useful prognostic variables as pHi, which incorporates a systemic variable.[25 26 40 42 45 59 61 68 93] In recent studies in critically ill patients, pHi, but not pH or P_{CO_2} gradients, proved prognostic indicators,[45 59] suggesting an additive value of systemic acid–base disorders in predicting outcome. In addition, a low pHi may predict occurrence of stress ulcer bleeding and ischaemic colitis when measured in the stomach and sigmoid colon of critically ill patients.[12 37 71 122 130] Hence, pHi may be superior to the P_{CO_2} gradient in predicting stress ulcer (bleeding) in the stomach, as the development of stress ulcers may not only relate to local factors but also to systemic acidosis.[69] In fact, lowering of the blood bicarbonate content is a risk factor and systemic alkalinization protects against stress ulcer development during haemorrhagic shock and mucosal hypoperfusion in animals.[69] Taken together, it emerges that the components of pHi, P_{CO_2} as a measure of alveolar ventilation and gastric hypoperfusion, and bicarbonate concentration, as a measure of general circulatory status, are of varying importance in different patients and disease stages.

Children

In a study in paediatric patients with sepsis, lactate content, but not pHi or P_{CO_2} gradients, predicted outcome, suggesting the superiority of systemic over regional abnormalities.[32] In contrast, in many other studies in critically ill (septic) children, pHi and P_{CO_2} (or pH) gradients were better predictors than systemic haemodynamic and metabolic variables, including blood pH, bicarbonate and lactate concentrations, for haemodynamic complications, multiple organ failure and survival.[23 24 31 32 56 83]

Sigmoid colon

Even though the appropriate methodology of sigmoid tonometry has still to be established, studies have suggested that the technique may be helpful in predicting tissue hypoxia and injury leading to ischaemic colitis, the main cause of morbidity and mortality after major abdominal vascular surgery.[12 37 71 122 130] Colonic hypoperfusion detected by tonometry may be associated with endotoxaemia and cytokine release that might contribute to mortality.[122]

Gastric tonometry may also be of predictive value after (emergency) major vascular surgery.[12 88 94]

Effect of interventions

As a low gastric pHi or increased P_{CO_2} gradient may be prognostically important, studies have examined the effect of various interventions on these tonometric variables, but the beneficial effect on morbidity and mortality of 'pHi guided' treatment is still controversial.[7 49 104 108] A variety of treatment procedures consisting of fluid and drug therapy, such as dopamine, dopexamine, epinephrine and norepinephrine, aimed at restoration of splanchnic blood flow, have been evaluated after cardiopulmonary bypass surgery,[11 42 99 110 111 129] trauma and sepsis.[15 48 49 68 86 87 101 102 107 121 127] Colloid fluids may be superior to crystalloids but different types may differ in their ability to increase global oxygen delivery and uptake, and to ameliorate a low gastric pHi in septic and postoperative patients.[15 91] Some catecholamine treatments in haemodynamically compromised patients may benefit the splanchnic circulation and others may not, as judged by a decrease in gastric P_{CO_2}, an increase in pHi, or both, in a variety of conditions.[7 11 42 48 86 87 91 102 107 110 121 127 129] For example, norepinephrine and dobutamine decreased the (elevated) gastric P_{CO_2} gradient and increased (subnormal) pHi. Dopamine, dopexamine or epinephrine treatment had no effect or tended to further decrease pHi in the treatment of sepsis and shock, even if systemic haemodynamics were unchanged or improved.[48 86 87 91 102 127] Dopexamine or dobutamine treatment may not prevent a decrease in pHi during and after cardiopulmonary bypass surgery, even if they increase systemic and hepatosplanchnic blood flow and oxygen delivery.[11 42 110 129] In other critically ill patients, dopexamine appeared to improve splanchnic blood flow and a subnormal pHi, independent of systemic haemodynamics, suggesting selective splanchnic vasodilatation, while dopamine had no such effect.[121]

Vasodilator therapy by infusion or inhalation of prostacyclin may improve hepatosplanchnic blood flow and decrease the tonometric gastric P_{CO_2} gradient during septic shock.[34] Administration of nitroprusside or angiotensin converting enzyme (ACE) inhibitors did not change the gastric P_{CO_2} gradient or pHi after cardiac surgery and this argues against a role for angiotensin in splanchnic vasoconstriction, although in this study the baseline P_{CO_2} gradient was not markedly increased.[109 111] ACE inhibition may ameliorate an increased P_{CO_2} gradient and a low pHi in trauma, however, even if systemic haemodynamic variables do not change.[67] Pulsatile blood flow may better preserve gastric mucosal perfusion adequacy than non-pulsatile flow during cardiopulmonary bypass.[41] Inducing muscle paralysis in mechanically ventilated patients may increase a reduced pHi, suggesting redistribution of blood flow from respiratory to splanchnic organs.[89] Treatment of sepsis and trauma patients with antioxidants may prevent a decrease in oxygen extraction abilities and gastric pHi, particularly during transient hyperoxia.[7] During large intestinal surgery, gastric P_{CO_2} increased relative to blood values, independent of global haemodynamics; adjunctive clonidine administration did not attenuate this increase.[133] Abdominal decompression in trauma-related intra-abdominal hypertension may normalize a low pHi, particularly in patients who survive.[62]

Conclusion

Gastrointestinal tonometry of the luminal to blood P_{CO_2} gradient can be used to assess the adequacy of mucosal perfusion provided that, if applied to the empty stomach, acid buffering and carbon dioxide generation are avoided. Appropriate use may improve the accuracy of manual fluid tonometry until the semi-continuous automated air tonometry technique, which may eliminate some sources of error inherent to the manual technique, becomes widely available. This may broaden the clinical applicability of gastrointestinal luminal tonometry as a monitoring tool in a variety of conditions.

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