Gastric tonometry: where do we stand?

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Gastric tonometry has proved to be a sensitive but not specific predictor of outcome in the critically ill. The data accumulated to date indicate that those patients able to achieve or maintain a normal gastric mucosal pH do better than those who do not. In addition, therapy aimed at improving an abnormal gastric mucosal pH has proved to be less successful. These findings may simply indicate that tonometry identifies those "responders" and "nonresponders," as becomes increasingly apparent in populations of critical care patients receiving interventional therapy. Gastric tonometry has undergone a number of methodologic changes over the last decade, seeing a switch from saline to automated gas tonometry. Along with this switch of methodology has come a deeper scrutiny of the indices used to assess gut perfusion. Most studies (including all the interventional ones) have used gastric mucosal pH. The newer indices of gut luminal P_{CO_2} (P_{gCO_2}) referenced to arterial $_{CO_2}$ ($P_{gCO_2} - P_{aCO_2}$) or end tidal $_{CO_2}$ ($P_{gCO_2} - P_{eCO_2}$), although relatively well validated, remain to be proven as predictors of outcome or guides to interventional therapy. If we take a fresh look at the interventional trials in intensive care patients, there is a very definite trend toward benefit in the protocol groups, although they are generally reported as negative studies. There is much to be accomplished, however, before we accept the gastric tonometer as a routine tool with which to guide therapy based on gastrointestinal perfusion, including a greater understanding of gastrointestinal physiology and, as ever, the call for an adequately powered prospective randomized controlled trial to evaluate the clinical utility of gas tonometry. Curr Opin Crit Care 2001, 7:122–127

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Abbreviation

pHi gastric mucosal pH

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There is general agreement among the critical care community that monitoring of end-organ perfusion is desirable, but there is strikingly little evidence to support this consensus. Many of our traditional markers of resuscitation, such as capillary refill, core peripheral temperature gradient, urine output, central venous pressure, heart rate, and blood pressure, have all proved unreliable clinically, yet we continue to place a heavy reliance on monitors such as the pulse oximeter in clinical medicine because they make such obvious physiologic sense. Gastric tonometry as a monitor of resuscitation also suffers from a lack of conclusive scientific proof. There can be little doubt that the complexities of gastrointestinal physiology that are still to be resolved as highlighted recently by Ackland *et al.* [1•] add still further to this difficulty. So why do we persist with such a monitor? We know from observational studies that there is a high incidence of gastrointestinal hypoperfusion in surgical and intensive care patients, and that variables such as gastric mucosal pH are sensitive but not very specific predictors of outcome. We know that the splanchnic circulation is "sacrificed" early in the course of hypovolemic shock to maintain flow to those more precious organs such as the heart and brain. It seems logical then to pursue the measurement of splanchnic perfusion, as this may give us the earliest clue to hypovolemia as well as many other insults that affect gastrointestinal perfusion and thus the potential to correct it, hopefully in time to prevent harm. We are well aware that preventative medicine is universally more productive than reactive therapy. We have long concentrated on the hard data of mortality in assessing clinical trial outcome, but morbidity has an even greater economic impact and relevance for the majority of patients who survive and may be more amenable to treatment with simple measures such as fluid optimization.

Hollow viscous tonometry has been around since the 1960s, but only in the 1990s did we see the appearance of studies that employed gastric tonometry in predictive and interventional roles. Many of the early studies to involve gastric tonometry were based on saline tonometry, and the most common variable measured was gastric mucosal pH (pHi). The technique demanded a high degree of familiarity to produce accurate and repeatable results and was prone to well documented errors.

Mathematically derived pHi was not immune to criticism either and assumed in its calculation that mucosal bicarbonate was the same as arterial bicarbonate. This is

unlikely to be true [2,3] but may explain why it has been such a good predictor of poor outcome, because it contains a measure of systemic acid-base balance. Gas tonometry then developed and is now an established and well validated technique that has superseded saline tonometry. Along with gas tonometry came the search for better and more reliable surrogates of gastrointestinal hypoperfusion. Arterial P_{CO_2} (Pa_{CO_2}) has been referenced to gastric mucosal P_{CO_2} (Pg_{CO_2}) and proposed as a better marker of gastrointestinal ischemia [4]. We know that a reduced gap ($Pg_{CO_2} - Pa_{CO_2}$) is associated with increased mucosal blood flow [5], and that in healthy volunteers the first sign of hypovolemia was an increase in the gap [6]. There are, however, some animal data to suggest that this gap may not be sensitive or specific for detecting mesenteric ischemia [7]. Along with the switch to gas tonometry came the development of automated gas tonometry, the chosen variable being Pg_{CO_2} referenced to end tidal CO_2 (Pe_{CO_2}). There are few data to indicate what a normal gap is or at what point ischemia occurs, but consensus opinion suggests that a gap of greater than 1.5 to 2 kpa is abnormal, and recent studies suggest a good clinical correlation between saline and gas tonometry results [8•]. Pe_{CO_2} is not without error and will change with increasing dead-space, a fact we already accept in the use of end tidal CO_2 as a respiratory monitor, but this should, in theory, highlight the abnormal signal earlier. It is important to bear this change in technique in mind when interpreting the available literature, because all of the interventional trials to date have used saline tonometry and pHi. We will have to wait for larger prospective randomized controlled trials using gas tonometry and the gap indices described to see whether gas tonometry has the same predictive power as saline and pHi.

Gastrointestinal perfusion

The splanchnic circulation contributes to the regulation of volume and blood pressure in humans [9], as well as less well-defined effects on acid-base regulation [10]. There is a natural flux of volume during exercise and feeding, which may represent physiologic models of more extreme insults, as seen in major surgery and intensive care patients. There is continued debate as to whether the gut plays a pivotal role in the development of systemic inflammatory response syndrome and multiple organ dysfunction syndrome, much of which has been reviewed recently and will not be dealt with any further here [1•]. Gastric tonometry as a measure of splanchnic perfusion assumes that as local gut perfusion is compromised, there is a switch to anaerobic metabolism with the consequent production of lactic acid and CO_2. What is less certain, however, is the source of the CO_2, which may arise from the mucosal or serosal layers. The relation is more complex, however, and it may be that low-flow states simply do not "wash out" the CO_2, leading to a local build-up. As ever, the truth is probably somewhere in between. There remain valid concerns about the heterogeneity of the P_{CO_2} measurement, with evidence to suggest that the small bowel may be a much better place to measure gut perfusion [11]. The evidence also points to intraabdominal differences in pH occurring during shock and that directly measured submucosal pH probably gives an earlier signal than tonometry-derived variables [12].

Povoas *et al.* [1•] provide tempting insights by demonstrating that in profound pig hemorrhagic shock models, sublingual capnometry values were interchangeable with gastric tonometry variables. This finding, however, has been difficult to repeat in exercise models of healthy volunteers, which may represent much less severe insults.

Clinical applications

Gastric tonometry has proved to be a very sensitive but poorly specific technique for predicting outcome in the critically ill. Gastrointestinal tonometric variables have proved significant in predicting multiple organ failure or death in many conditions such as mechanical ventilation, trauma, sepsis, emergency vascular surgery, cardiovascular surgery, acute pancreatitis, and orthoptic liver transplantation [13•]. The vast majority of studies that have looked at outcome used pHi and saline tonometry. As has already been mentioned, there are distinct differences between these techniques and variables and those of modern automated gas tonometry, and it may be unscientific at best to apply these results to modern automated gas tonometry. It is our opinion, however, that the results are translatable to modern-day methods and an analysis of the three interventional studies in intensive care patients to date reveals an interesting trend towards significance, even though only one of the studies was reported as positive. This is in stark contrast to those therapies, such as with anti–tumor necrosis factor, in which smaller or at best similar benefit has been shown, but which have led to further large scale prospective randomized controlled trials [14].

Intensive care

The use of pHi as a predictor of outcome is well established, but its use in guiding interventional therapy is less clear. For those people who have an established low pHi, interventional therapy has been disappointing. For those that have a normal pHi, attempts to maintain it have been more promising. Two early observational studies in critically ill patients showed that pHi was a predictor of poor outcome and that there was a significant incidence of gut hypoperfusion [15,16]. These observational studies led the way for the interventional trials that followed. One of the earliest interventional studies was undertaken by Gutierrez *et al.* [17], who

studied 260 patients admitted to intensive care. The authors took a pHi of 7.35 to be normal and found, for patients admitted with a low pHi, that there was little difference in outcome between control and protocol groups, but for those with a normal or high pHi there was significantly greater survival in the protocol group (58% *vs* 42%). The study has been criticized, however, because there was a high mortality rate in the control group and a lack of standardization in their treatment. Ivatury *et al.* [18] undertook a further interventional trial in a group of 57 trauma victims admitted to the intensive care unit. They found pHi–guided therapy to be superior in the first 24 hours, but a persistently low pHi, in common with findings of other studies, was still associated with a worse outcome.

A more recent trial by Gomersall *et al.* [19•], still using saline tonometry looked at the effect of intervention based on pHi. The authors randomized 210 critically ill patients to two groups, both of which were resuscitated to set targets. For those in the intervention group whose pHi was less than 7.35, they were given further fluid followed by dobutamine if the pHi did not increase. They reported a failure to show any significant outcome improvement in the intervention group. As a subset analysis, however, they report modified duration of hospital stay as 60 days in the control group and 42 days in the protocol group, a finding that was not statistically significant. If one looks at an analysis of the three interventional trials, however, there is a very marked trend toward benefit in the treatment groups, with an odds ratio that only just bridges 1 (Table 1). It should be noted that there were many significant differences in the three study protocols, however.

Although there are many fewer data to infer benefit in a pediatric population, children with septic shock who have a low pHi that fails to correct do badly [20]. Incidentally it was noted that pHi was a better predictor than acid-base values or lactate [20]. Tonometry was also able to distinguish survivors form nonsurvivors, but again was at odds with standard variables [21], and the authors concluded that low pHi measurements are not predictive of concurrent or subsequent adverse clinical events.

Weaning

The weaning of patients from mechanical ventilation is a continuing problem in intensive care, and tonometry has failed to show any conclusive benefit over existing predictors of weaning success, such as frequency divided by tidal volume (f/V_t) [22], the studies are, however, few in number and present some conflicting data. It was also noted in two studies that many patients with a low pHi failed to wean successfully [23,24].

Vasoactive drugs

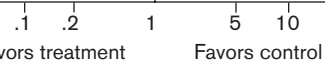
The use of vasoactive compounds is commonplace in many of the patients who may potentially benefit from perfusion monitoring. The role of these various vasoactive compounds on gastrointestinal physiology is far from clear. There is a body of evidence that points toward low-dose dopexamine being protective to the gut [25,26,27•] but maybe not affording the expected clinical benefit, as shown recently in a large multicenter trial [28•]. There are, in contrast, some animal data suggesting that dopexamine in high doses (10 μg/kg/min) has adverse effects in that it increases lactate levels and heart rate [29].

Dopamine, however, compared less favorably to norepinephrine in a population of septic patients [30], with other studies reporting little or no effect on splanchnic perfusion [31]. Winters points out that in animal experiments, dopamine directly acidifies mucosal crypt cells in a mechanism that involves a cAMP–mediated inhibition of sodium–hydrogen exchange. This finding may account for the acidification of intestinal mucosa during low-dose dopamine infusion despite a demonstrable improvement in splanchnic perfusion. Direct mucosal effects of pharmacologic agents must be considered in the evaluation of perfusion parameters based on tonometric data [32]. It is very unlikely that vasoactive compounds influence perfusion in the same way. Indeed, despite increasing oxygen transport, dopamine

Table 1. Hospital mortality

Study (year)	Treatment, *n/N*	Control, *n/N*	OR (95% CI fixed)	Weight, %	OR (95% CI Fixed)
Gomersall *et al.* [19•] (2000)	44/104	48/106		39.00	0.89[0.51,1.53]
Gutierrez *et al.* [17] (1992)	68/135	76/125		55.70	0.65[0.40,1.07]
Ivatury *et al.* [18] (1996)	1/11	5/16		5.30	0.22[0.02,2.22]
Total (95% CI)	113/250	129/147		100.00	0.72[0.50,1.03]

Test for heterogeneity chi square = 1.71 (df = 2; $P = 0.43$)
Test for overall effect (z = 1.78; $P = 0.08$)



and dobutamine appeared to have affected gastric mucosal perfusion in different ways during a prospective crossover trial [5]. Despite no improvement in tonometry variables, dobutamine did increase gastric mucosal perfusion as assessed by Doppler flow cytometry [33]. Septic patients initially volume-resuscitated were given an infusion of dobutamine once hemodynamically stable, which resulted in an improvement in systemic hemodynamics and a concordant improvement in tonometry variables (12 of the 14 patients also received norepinephrine in their initial resuscitation) [34]. It is tempting to speculate that the improvement seen with dopexamine is due to selective splanchnic vasodilatation and the benefit of dobutamine is its ability to increase the cardiac index, but this remains physiologically unproven.

Trauma

In addition to the study by Ivatury described earlier [18], there have been a number of other studies that point toward a useful role for the gastric tonometer in resuscitation. Barquist *et al.* [35] observed that gastric tonometry–guided resuscitation led to a lower incidence of multiple organ dysfunction when compared with controls. The prediction of death and multiple organ failure was found to be maximal at a pHi of less than 7.25, by analysis of receiver operated curves by Miller *et al.* [36], whereas Kirton *et al.* [37] monitored the pHi in 19 consecutive critically ill trauma patients and found that a pHi of less than 7.32 carried a relative risk of 4.5 for death and 5.4 for occurrence of multisystem organ failure. Furthermore, the attainment of pHi greater than 7.32 at 24 hours carried a significantly reduced risk of multisystem organ failure.

Feeding

Marvin *et al.* [38] identified 13 cases of nonocclusive bowel necrosis over a 64-month period. They looked for early markers of gastrointestinal dysfunction and found that three patients had gastric tonometry results and all three had a significant reduction in pHi (< 7.3) after enteral feeding, possibly pointing to a way of identifying an at-risk population.

Surgery

Cardiac surgery

The data from cardiac surgical patients represents the largest and most consistent body of evidence we have on the use of the gastric tonometer. We know that a significant proportion of patients undergoing cardiac surgery display abnormal tonometry variables [39], a finding confirmed in a later study by Bennett-Guerrero *et al.* [40•], who also found the abnormal tonometry variables to be highly predictive of outcome compared with standard haemodynamic variables and base excess, and that intraoperative variables were less predictive than postoperative ones. The value of pHi less than 7.32 as a predictor of poor outcome (death and multiple organ failure) also holds true for pediatric patients after cardiac surgery [41]. Mythen and Webb [42] demonstrated that fluid optimization guided by the esophageal Doppler monitoring significantly improved the outcome in the protocol group who had less evidence of gut mucosal hypoperfusion. Although we concentrate on the fact that compromising the splanchnic circulation is detrimental to the patient's outcome, not all studies support this view. Many patients do not have a complicated postoperative course but still show signs of high splanchnic oxygen extraction and gastric mucosal acidosis [43,44].

Of interest recently is the study by Jakob *et al.* [45], who looked at the changes in systemic, hepatosplanchnic, and femoral blood flow after cardiac surgery. The authors found that the increase in peripheral blood flow led to a mismatch in splanchnic perfusion and metabolism, as shown by the tonometer, a finding that may provide an explanation for this commonly observed phenomenon. Whether tonometry provides a practical or improved way of detecting circulatory failure after cardiac surgery is debatable. In 1999, LeBuffe *et al.* [46•] reported that regional and automated air tonometry may be used to identify those patients at risk of circulatory failure after cardiovascular surgery earlier than with conventional hemodynamic variables. Earlier that year, Bams *et al.* [47•] reported, in contrast, that hemodynamic variables were better predictors of outcome after cardiovascular surgery than regional tonometric variables. There is some supporting evidence to show that tonometry variables change before standard hemodynamic variables in models of hemorrhagic shock in healthy volunteers [6].

General surgery

The only interventional trial in general surgery patients was undertaken by Pargger *et al.* [48]. They looked at 55 patients undergoing elective infrarenal aneurysm repair and randomized them to a control and a protocol group. They found that a low pHi was predictive of poor outcome and that treatment to elevate it did not result in improvement of outcome. Patients undergoing major abdominal surgery benefit from thoracic epidurals [49]. The reason for this is probably better maintained visceral perfusion, so one would expect improved tonometry variables in support. Karpal *et al.* [50] confirmed this hypothesis when they found that the gastrointestinal pH was significantly higher in a group randomized to receiving a thoracic epidural.

Tonometry has also been used in an attempt to grade the severity of acute pancreatitis, but it simply confirmed the presence of moderate gastric mucosal hypoperfusion early in the course of the disease and was unable to distinguish the severity of disease [51].

If we postulate that there is a link between gastric mucosal hypoperfusion and mucosal damage, tonometry should help us identify those patients in whom hypoperfusion exists and allow us to examine the mucosa for damage. This is exactly what Byers *et al.* [27•] reported by directly analyzing histologic specimens from a group of high-risk surgical patients undergoing abdominal surgery. They found that approximately half the patients with a low pHi had evidence of mucosal damage. They also noted that dopexamine in doses of 0.5 or 2 μg/kg/min afforded a significant degree of benefit.

The study of liver transplant patients has given us further insight into the control of the splanchnic circulation. Hypocapnic vasoconstriction has been postulated as a control mechanism for the splanchnic circulation, but Krenn *et al.* [52] looked at the effect of deliberate hyperventilation in 14 patients undergoing liver transplantation and did not observe any statistically significant circulatory effects.

Conclusions

Gastric tonometry, despite the many changes in technique and observed indices, almost certainly represents a real signal of a compromised splanchnic circulation. Our understanding of the physiology of gut perfusion is far from complete and can only lead to further speculation on what we are really measuring. A critical review of the literature suggests that there is a role for gastric tonometry as an observational monitor and an interventional guide, although we will need to be convinced by an adequately powered prospective randomized controlled trial using gas tonometry, in these days of evidence-based medicine. It would seem a dreadful shame to throw the baby out with the bath water by abandoning gastric tonometry on the strength of the available evidence. Indeed, the very fact that hypercarbia persists in sepsis and is not influenced by active hemodynamic manipulation may be exactly why we should continue to measure it.

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