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MINIREVIEW

Gastric Tonometry and Intramucosal pH - Theoretical Principles and Clinical Application

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Summary

Gastric or intestinal luminal tonometry is a method for monitoring critically ill patients. It offers an index of the adequacy of aerobic metabolism in a tissue that is particularly sensitive to alterations in its perfusion and oxygenation: the gut mucosa. It is based on the measuring the increase in tissue CO_2 production that accompanies anaerobic metabolism. The method simply consists of a balloon in the stomach, which measures intramucosal pCO_2. From this measurement and from the arterial bicarbonate concentration gastric intramucosal pH (pHi) can be calculated, assuming that bicarbonate concentration in the gastric mucosal tissue is in equilibrium with systemic arterial bicarbonate. Despite possible clinical benefit from the measurement and the therapy of low pHi values in critically ill patients, the theoretical, experimental and pathophysiological implications for the monitoring of intramucosal acidosis in the gut are not yet fully understood. There are still some open methodological questions crucial for further clinical interpretation.

Key words

Shock • Diagnostic techniques and procedures • Anoxia • Intensive care • Tonometry • pHi • Splanchnic perfusion

Introduction

Gastric or intestinal luminal tonometry is a rapidly developing tool for the monitoring of critically ill patients. It has been proposed as a relatively non-invasive (or semi-invasive) index of the adequacy of aerobic metabolism in a tissue that is particularly sensitive to alterations in its perfusion and oxygenation status: the gut mucosa. This review discusses the basic physiological principles of gastric tonometry and its possible clinical implications in intensive care.

Gastric tonometry has been proposed as a simple method for assessing regional perfusion of the gut by inserting a balloon into the stomach to measure intramucosal pCO_2. From this measurement and from the arterial bicarbonate concentration one can calculate gastric intramucosal pH (pHi), assuming that the bicarbonate concentration in the gastric mucosal tissue is in equilibrium with systemic arterial bicarbonate. This may not be valid in shock. Because remote systemic metabolic acidosis and alkalosis change systemic bicarbonate levels, gastric mucosal pCO_2, which is not

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confounded by arterial bicarbonate, may be more appropriate than pHi (Vincent 1998). Gastric mucosal pCO_2 is influenced directly by systemic pCO_2. The use of the gastric – arterial pCO_2 differences has been proposed as the primary tonometric variable, even though this measure is not a simple measure of gastric mucosal hypoxia.

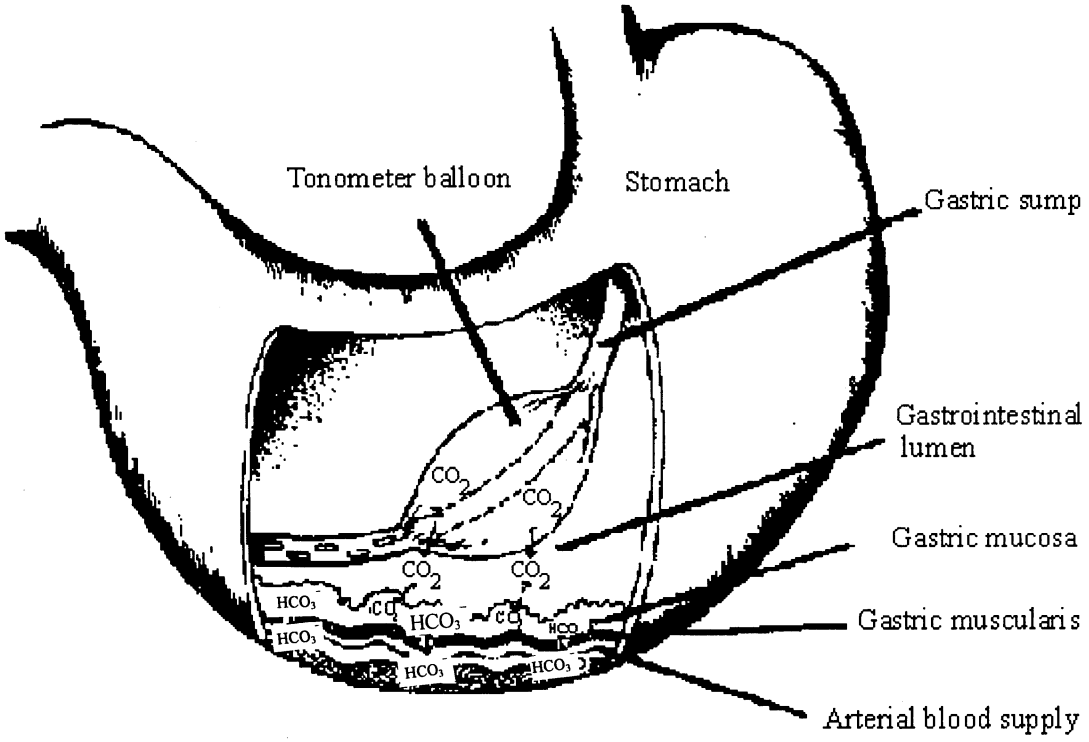

Fig. 1. *Schematic diagram of the gastric tonometry.*

The physiological basis of tonometry is measuring an increase in tissue CO_2 production that accompanies anaerobic metabolism. During aerobic metabolism the cellular production of CO_2 is a function of oxygen consumption determined by the respiratory quotient. Anaerobic metabolism results in the generation of hydrogen ions that are buffered by tissue bicarbonates resulting in excess CO_2 production.

The concept of using tonometry for measuring mucosal partial pressure of carbon dioxide (pCO_2) in a hollow organ is not new. Boda and Muranyi (1959) used a thin rubber balloon attached to a tube introduced into the stomach estimating the arterial pCO_2 in mechanically ventilated patients. They noted that gastric tonometry of pCO_2 approximated the end-tidal pCO_2 allowing them to adjust the mechanical ventilation in children paralyzed by poliomyelitis. Moreover, they already noted that: "..gastric pCO_2 may be misleadingly high in severe shock..". The significance of the finding indicating local dysoxia at the tissue level was not recognized at that time. Tonometry was used for measuring pO_2 and pCO_2 of the gallbladder and the urinary bladder mucosa by injecting saline into the lumen of these organs (Bergfolsky 1964). The pO_2 and pCO_2 of the intraluminal fluid were assumed to be in equilibrium with the mucosal pO_2 and pCO_2 and could thus serve as an indirect measure of mucosal oxygenation. Fluid extracted from the intestine was used to measure gut mucosal oxygenation in humans and dogs (Dawson 1965). In some animals, the intestinal luminal pCO_2 was observed to rise above the arterial pCO_2 and the author speculated that this could be due to the combination of hydrogen ions and bicarbonate. The pO_2 and pCO_2 were measured in saline filled silicone tubes inserted into the dog intestine (Kivisaari and Niinikoski 1973). Intraluminal pCO_2 was measured with a small fluid-filled balloon made of polytetrafluorethylene permeable to O_2 and CO_2 (Grum *et al.* 1984). The major methodological advance was based on development of the concept applying tonometric values to estimate tissue pH – intramucosal pHi (Fiddian-Green *et al.* 1982).

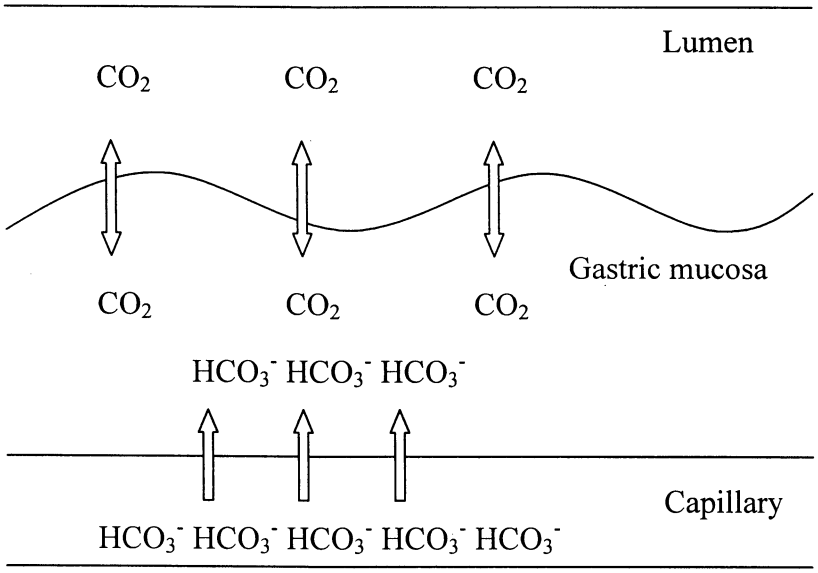

Fig. 2. *Anaerobic metabolism results in the generation of hydrogen ions that are buffered by tissue bicarbonates resulting in excess CO_2 production.*

Physiological and metabolic principles of tonometry

The concept of the intramucosal pH

The pH of the gut mucosa could be calculated using tonometry (Fiddian-Green *et al.* 1982). This hypothesis was based on three assumptions:

1. CO_2 diffuses freely in tissues,
2. pCO_2 in the luminal fluid is in the equilibrium with the mucosal pCO_2,
3. arterial bicarbonate concentration equals that of intestinal mucosal bicarbonate.

Mucosal pCO_2 and $[H^+]$ or mucosal pH (pHi) are related by the Henderson-Hasselbalch equation, where

$$pHi = 6.1 + \log \frac{[HCO_3^-]}{\alpha \text{ mucosal } pCO_2}$$

pHi is calculated intramucosal pH, 6.1 is pKa of carbonic acid, $[HCO_3^-]$ of the mucosa is assumed to be equal to arterial $[HCO_3^-]$, α is a constant which represents the solubility of CO_2 in plasma (= 0.03).

The assumptions underlying the calculation of pHi (equality of mucosal and arterial bicarbonate levels) are valid except for conditions when partial or total intestinal ischemia is present. The tonometer will underestimate the intestinal pHi in underperfused tissue. During low-flow states of the tissues mucosal bicarbonate falls more rapidly than arterial bicarbonate (Antonsson *et al.* 1990). Similar problem arises when interpreting a low mucosal pH during clinical conditions accompanied by low arterial pH. Here the situation reflects generalized acidosis more than local tissue hypoxia. Given these potential difficulties with the interpretation of pHi, the consideration of the difference between tonometric and arterial pCO_2 called pCO_2 gap (or pHi – pH arterial gap) is gaining in popularity. In order to distinguish between effects of systemic acid base status and regional hypoperfusion on the calculated pHi, Fiddian-Green recommended a "standard" pHi, which should be used rather than "actual calculated" pHi. The standard pHi is calculated as:

$$\text{Standard pHi} = 7.40 - \log \frac{\text{tonometer } pCO_2}{paCO_2}$$

Normal value pHi = 7.37±0.04 (mean, SD) (Guttierez and Brown 1996)

Tonometric pCO_2 and metabolism

Two basic mechanisms may elevate regional (mucosal) pCO_2. While normal tissue pCO_2 approximates arterial pCO_2 ($paCO_2$), increased tissue pCO_2 values may reflect a low flow state with the accumulation of CO_2 and normal aerobic metabolism. Alternatively, increased tissue pCO_2 may be the result of anaerobic metabolism and net hydrogen ion production with subsequent buffering by tissue bicarbonate:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$$

The source of hydrogen ions produced during anaerobic metabolism is often attributed to glycolysis and the conversion of pyruvate to lactic acid. For each mole of oxygen consumed by the mitochondria to generate ATP from glucose, one mole of carbon dioxide and three moles of ATP are generated for a phosphate–to–oxygen ratio (P:O) of 3. Glucose has greater P:O ratio than either fats or proteins and therefore it is preferred cellular substrate during hypoxia, the condition being associated with a burst of glucose consumption. This phenomenon is called the "reverse Pasteur effect" or the "Crabtree effect". Although fixed production of H^+ during hypoxic or dysoxic states is commonly assumed to be the result of lactate generation during anaerobic glycolysis, this mechanism does not seem to be a principal source of tissue acidosis (Russell 1997). During hydrolysis of ATP produced by anaerobic glycolysis, hydrogen ions are produced in the cell:

$$2\ ATP \rightarrow 2\ ADP + P_i + 2H^+ + energy$$

The sum of glycolysis and ATP hydrolysis is:

$$D\ glucose \rightarrow 2\ lactate + 2H^+ + energy \rightarrow \rightarrow 2\ lactic\ acid + energy$$

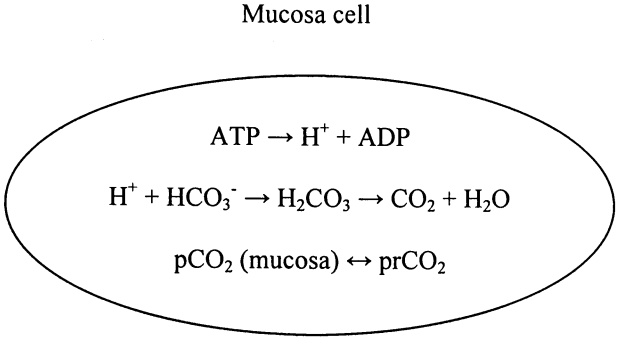

Fig. 3. *Net H^+ production is most likely related to hydrolysis of ATP in an excess of its regeneration following tissue hypoxia. Mucosal pCO_2 is closely related to regional $prCO_2$ in its proximity.*

Thus no significant production of hydrogen ions occurs during glycolysis and lactate generation. Moreover, the dissociation of lactic acid into lactate occurs only when tissue pH falls below 6.0 (Fiddian-Green 1995). A net H^+ production is most likely related to hydrolysis of ATP in an excess of its regeneration following tissue hypoxia. During normoxia the intracellular concentrations of adenosine diphosphate (ADP), phosphate (P_i) and H^+ are very low, since these metabolites are reused in the mitochondria to constitute ATP in the process of oxidative phosphorylation. During tissue hypoxia ATP cannot be regenerated and net H^+ production occurs (Guttierez and Brown 1996). Tissue hypercapnia measured by tonometry is influenced by complex network of CO_2 physiological processes and there are multiple pathophysiological conditions leading to changes in CO_2 production in the mucosa.

The interpretation problems related to tonometry

Intramucosal pHi consist of two components:

1. regional pCO_2, which is organ specific, and
2. arterial bicarbonate, which is a component related to whole body.

Tissue pCO_2 can increase in the absence of tissue dysoxia or hypoxia and increased mucosal pCO_2 may reflect impaired CO_2 clearance instead of the buffering anaerobically produced hydrogen ions. This assumption was supported by the work of Weil *et al.* (1986) who noted increases in venous pCO_2 and decreases in venous pH in patients undergoing resuscitation from cardiac arrest. This may be true under conditions where oxygen stores are consumed and CO_2 is produced but not removed due to the total arrest of organ blood flow. This is relatively rare situation in critical care patients except for those in cardiac arrest. It was studied experimentally, whether the decrease of pHi reflects metabolic acidosis or simply stagnation of CO_2 produced by oxidative phosphorylation as organ blood flow decreases. A relatively small increase in the arteriovenous CO_2 and pH gradients was found during respiratory acidosis, while much larger increases in these gradients developed during oxygen supply dependency and was consistent with metabolic acidosis and hydrogen ion production (Schlichtig and Bowles 1992). Similar results were also found by Zhang and Vincent (1993). Mucosal regional pCO_2 ($prCO_2$) also varies with arterial $paCO_2$ and severe respiratory acid-base disturbances cause similar disturbances in mucosa without dysoxia. It has recently been shown that pHi is influenced by alveolar ventilation, but the difference between mucosal and arterial pCO_2 was independent of respiratory changes (Bernardin *et al.* 1999). Changes in the tissue pCO_2 produced by mucosal CO_2 accumulation are always less important than those produced by buffering H^+ resulting from tissue hypoxia. Systemic acid-base status must always be evaluated before a final interpretation of the tonometry data.

Clinical application

Despite the complexity and ongoing discussion concerning the origin of increased mucosal pCO_2, intramucosal acidosis is associated with a poor prognosis of patients in intensive care (Mythen and Webb 1994, Bjorck and Hedberg 1994, Friedman *et al.* 1995, Roumen *et al.* 1994). Regional tonometry provides information on the level of regional pCO_2 relating to the adequacy of perfusion and metabolism. Gastric tonometry is currently the most widely used application of regional tonometry, although sigmoid colon tonometry is also available.

Why to monitor the gastric mucosa?

1. The gastric mucosa is an early victim of blood flow redistribution, leading to regional hypercapnia.
2. The gastric mucosa is very sensitive to perfusion changes and the gut may have higher critical oxygen delivery thresholds than other organs.
3. Gut mucosal hypoperfusion has been shown to be associated with increased permeability, which together with inadequate mucosal perfusion and deranged tissue metabolism appear to play a critical role in the development of sepsis and its sequelae (multiple organ dysfunction syndrome).

The clinical practice of gastric tonometry

Two regional tonometry methods are currently available: saline tonometry and air tonometry. In saline tonometry the balloon is filled with normal saline. After an equilibration period of 30 min or more, pCO_2 in a saline sample from the balloon is determined. The saline method is also referred to as the „manual method" and has been performed since the introduction of catheters in 1991. Gastric tonometry can now also be performed by filling the balloon with air (automatic air tonometry). The tonometer automatically samples the air from the balloon every 10 min and automatically analyses it by an infrared sensor providing continual regional tonometry.

Methodological problems related to the clinical use of tonometry

The determinations of gastric pHi or gastric mucosal $prCO_2$ depend on reliable and reproducible measurement of pCO_2. The choice of tonometer's solution is also important: pCO_2 measured in saline may be underestimated. Based on *in vivo* data, the use of phosphate buffered solution can improve the accuracy and reliability of gastric pHi measurement (Knichwitz *et al.* 1996). The long time constant for CO_2 equilibration (90 min) using the phosphate buffered solution may limit its use in the clinical practice. An additional source of error is the secretion of hydrogen ions by parietal cells of the mucous membrane. Back-diffusion of H^+ at low gastric luminal pH may amplify the interaction of secreted H^+ with HCO_3^- in the mucous layer and increase tonometer pCO_2. H_2-blockers are recommended to reduce the effect of this phenomenon and to improve the accuracy of pHi measurement (Kolkman *et al.* 1994). Reflux of bicarbonate-rich duodenal fluid can also increase $prCO_2$ (Fiddian-Green *et al.* 1982). Enteral feeding which stimulates H^+ secretions may also affect the generation of intraluminal CO_2. Enteral feeding should be discontinued at least 60 min before measuring gastric pHi (Marik and Lorenzana 1996). Currently, the arterio-regional pCO_2 difference appears to be the most reliable index of gastric mucosal perfusion and oxygenation, whereas the pHi and pH gaps are less precise (Brinkman *et al.* 1998).

Tissue hypercapnia measured by tonometry is influenced by a complex network of CO_2 physiology and there are multiple physiological and pathophysiological conditions altering gastric $prCO_2$.

Increase $prCO_2$
- reduced regional blood flow
- reduced regional oxygen supply
- increased regional oxygen consumption
- enteral feeding
- low gastric juice pH
- disturbance of cellular energy metabolism

Decrease $prCO_2$
- increased regional blood flow
- increased regional oxygen supply
- reduced regional oxygen consumption

Application of tonometry in clinical medicine

Tonometry provides the clinician with information on the adequacy of splanchnic circulation and oxygenation. Mucosal pCO_2 increase or pHi decrease are associated with the development of intestinal mucosal ischemia. Most of the studies discussed its potential as an early detector of splanchnic hypoperfusion and an indicator of prognosis. The development of intestinal mucosal ischemia is associated either with mucosal pCO_2 increase or pHi decrease.

1. Perioperative monitoring

Tonometry was used to assess mucosal ischemia intraoperatively and postoperatively (Schiedler *et al.* 1987). The impact of mucosal hypoperfusion on

postoperative complications and cost of treatment in patients undergoing elective major surgery was assessed and association between intraoperative gut mucosal hypoperfusion, low pHi and increase of postoperative complications was shown. Patients with pHi below 7.32 at the end of surgery had a longer stay in the ICU, greater incidence of major complications, greater mortality and higher cost (Mythen and Webb 1994). Low gastric intramucosal pHi was reported to be a predictor of major complications after aortic surgery (Bjorck and Hedberg 1994). Intramucosal pHi has also been shown as a predictor of postoperative complications in patients undergoing cardiac surgery (Fiddian-Green and Baker 1987). Gastric mucosal tonometry detects hypovolemia during cardiopulmonary bypass and can be probably used as an indicator of a sufficient cardiac output (Uhlig *et al.* 1998). Despite observation of decreased gastric pHi in patients undergoing surgery, no correlation between gastric pHi and the levels of endotoxin or TNF-α in blood was found (Andersen *et al.* 1993). Splanchnic and peripheral perfusion during perioperative and postoperative period was assessed in patients undergoing cardiopulmonary bypass. Gastric pHi decreased significantly during the postoperative rewarming despite the fact that the data indicated normal central hemodynamics (Niinikoski and Kuttila 1993). Recently, continuous intramucosal pCO_2 measurement has been shown to allow early detection of intestinal malperfusion in randomized controlled intervention trial (Knichwitz *et al.* 1998).

2. *Monitoring in major trauma*

The possible relationship between low pHi values and the development of major medical complications was assessed in 15 patients following severe trauma (Roumen *et al.* 1994). Low pHi (<7.32) was observed in 8 patients and in 3 of them major complications developed. Impact was shown of gastric pHi guided resuscitation in critically ill trauma patients with persistently low pHi on possible decrease of multiple organ dysfunction syndrome (Barquist *et al.* 1998). Strong correlation between the degree of hemorrhage and the change in gastric intramucosal pCO_2 in trauma patients was observed (Guzman and Kruse 1998).

3. *Prediction of mortality*

Clinical studies support the relationship between the low gastric pHi and higher patient mortality. Gastric mucosal pHi was reported as an important index of mortality in patients with low pHi during the first 12 h after admission. They had higher mortality than those with normal pHi (Doglio *et al.* 1991). Similar results were confirmed later (Maynard *et al.* 1993). Gastric pHi is a better predictor of mortality in the ICU than standard measurement of oxygen transport and consumption (Marik 1993). The combination of tonometric values with other monitored variables in the ICU may improve prognostic acuity. In patients with sepsis, combination of lactate and gastric pHi predicted outcome. Higher pHi and pCO_2 gap values were observed in patients with high lactate levels (Friedman *et al.* 1995).

4. *Gastric ulceration and splanchnic ischemia*

Gastric tonometry has also been used to predict the bleeding from the stress ulceration. Low gastric intramucosal pHi (<7.02) was found in those who were bleeding massively (Fiddian-Green *et al.* 1983). These results were confirmed in patients with chronic renal failure maintained on dialysis (Diebel *et al.* 1993).

5. *Mechanical ventilation*

Value of pHi as a predictor of weaning success in mechanically ventilated patients has been shown (Mohsenifar *et al.* 1993). The decrease in pHi was observed in patients who could not be weaned in comparison with those who had no change in pHi and were weaned successfully. These observations were confirmed in a pilot study (Chittock *et al.* 1995).

6. *Liver transplantation and assessing graft viability*

Decrease in pHi may predict graft dysfunction and complications after orthotopic liver transplantation (Downing *et al.* 1993, Frenette *et al.* 1994).

7. *Gastric tonometry values as therapeutic guide*

Intramucosal pH as a guide of the therapy of the critically ill patients was studied in different populations of patients. Special intervention protocol (fluids, dobutamine) was employed in all ICU patients with low pHi at the time of admission. The survival was similar between protocol and control groups in patients admitted with low pHi. For those who were admitted with normal pHi, survival was greater in the protocol group. It is concluded that pHi-guided therapy may improve outcome in patients with normal pHi at admission (Gutierrez 1992). Therapeutic goal of pHi above 7.3 was used; significantly lower mortality rate in pHi-guided group was found (Ivatury *et al.* 1995).

Conclusion

Tonometry is a simple procedure assessing the intramucosal pH and pCO_2. The technique is based on the assumption that pCO_2 in the gastrointestinal lumen is equal to the pCO_2 in the superficial layers of the gut mucosa and that HCO_3^- concentration in the mucosal cells is reflected by the HCO_3^- content in the blood. It is now possible to measure mucosal pCO_2 using air instead of saline in the tonometer balloon. A new automated device pumps the air into the tonometer balloon and pCO_2 is measured by the infrared analysis. Monitoring pHi and regional pCO_2 seems to be of benefit in patients who are at risk of development of splanchnic hypoperfusion and shock. Using H_2-blocking agents enhances the accuracy of pHi measurement.

The future

Despite methodological problems, tonometry is an exciting tool to monitor tissue oxygenation. The technique would rely on measurement of the mucosal pCO_2, not pH (Vincent, 1998). Future research should refine the medical decision-making process in terms of selecting patients who may benefit from this technique and to demonstrate cost-effectiveness of gut tonometer guided therapy. Another future direction would be the technical development of tonometer turning it into a simple, cheaper and user-friendly device.

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