Gastric mucosal end-tidal PCO$_2$ difference as a continuous indicator of splanchnic perfusion

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Gastric mucosal and arterial blood PCO$_2$ must be known to assess mucosal perfusion by means of gastric tonometry. As end-tidal PCO$_2$ (Pe$^{\text{e}}$CO$_2$) is a function of arterial Pco$_2$, the gradient between Pe$^{\text{e}}$CO$_2$ and gastric mucosal Pco$_2$ may reflect mucosal perfusion. We studied the agreement between two methods to monitor gut perfusion. We measured the difference between gastric mucosal Pco$_2$ (air tonometry) and Pe$^{\text{e}}$CO$_2$ (=DPCO$_2$$_{2gas}$) and the difference between gastric mucosal Pco$_2$ (saline tonometry) and arterial blood Pco$_2$ (=DPCO$_2$$_{2sal}$) in 20 patients with or without lung injury. DPCO$_2$$_{2gas}$ was greater than DPCO$_2$$_{2sal}$ but changes in DPCO$_2$$_{2gas}$ reflected changes in DPCO$_2$$_{2sal}$. The bias between DPCO$_2$$_{2gas}$ and DPCO$_2$$_{2sal}$ was 0.85 kPa and precision 1.25 kPa. The disagreement between DPCO$_2$$_{2gas}$ and DPCO$_2$$_{2sal}$ increased with increasing dead space. We propose that the disagreement between the two methods studied may not be clinically important and that DPCO$_2$$_{2gas}$ may be a method for continuous estimation of splanchnic perfusion.

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Gastrointestinal hypoperfusion may lead to organ dysfunction, increased mortality and increased cost of care of critically ill patients. However, we do not have a practical method for assessment of gut mucosal perfusion. Gastrointestinal saline tonometry is still controversial and not routinely used in critical care, for several reasons. Originally the gastric tonometer was designed to measure gastric mucosal Pco$_2$ which was then used to calculate gastric mucosal pH (pH$_{m}$). Gastric mucosal pH was assumed to reflect splanchnic perfusion and oxygenation. However, the calculation of pH$_{m}$ necessitates both taking arterial blood sample to measure bicarbonate concentration and the use of a cumbersome formula. In addition, experimental and clinical studies have shown that the calculation of pH$_{m}$ using arterial blood bicarbonate concentration may be incorrect, the use of pH$_{i}$ alone ignores the effects of systemic acid–base status on gastric mucosal pH and there is also a potential bias from the measurement of saline Pco$_2$ with different blood gas analysers.

The measurement of gastric mucosal Pco$_2$ has become more popular in experimental and clinical studies and avoids the potential problems of pH$_{m}$. An automated gas tonometer was developed to measure gastric mucosal Pco$_2$, so that repeated analysis of saline samples for Pco$_2$ and the potential errors of analysis are eliminated and the measurements are now easier. Clinical and experimental studies have validated gas tonometry using conventional saline tonometry as a reference. However, the gradient between systemic Pco$_2$ and gastric mucosal Pco$_2$ is the variable of interest that reflects mucosal perfusion. Repeated arterial blood samples are needed to measure blood Pco$_2$ which may not be feasible in clinical practice and may make clinicians unwilling to use gastric tonometry. On the other hand, without continuous or semi-continuous measurements important episodes of splanchnic hypoperfusion may not be noticed.

The partial pressure of carbon dioxide (CO$_2$) of end expiratory gas (end tidal CO$_2$, Pe$^{\text{e}}$CO$_2$) can be used to estimate arterial Pco$_2$. Pe$^{\text{e}}$CO$_2$ is routinely monitored in intubated patients although Pe$^{\text{e}}$CO$_2$ does not necessarily accurately represent arterial CO$_2$ if the proportion of dead space ventilation is increased as in patients with lung hyperinflation.
injury. However, the difference between $P_{\text{E}}'_{\text{CO}_2}$ and gastric mucosal $\text{CO}_2$ (measured by gas tonometry) could reflect gastric mucosal perfusion continuously or semi-continuously without a need for laboratory testing. We hypothesized that this would be the case even in patients with increased physiologic dead space, providing that the dead space remains relatively constant. To our knowledge this possibility has not been tested. We designed our study to investigate if the gradient between gastric mucosal $\text{PCO}_2$ and end-tidal $\text{CO}_2$ can be used to monitor gastric mucosal perfusion.

**Patients and methods**

The study was approved by the Ethics Committee of the Kuopio University Hospital and a written informed consent was obtained either from the patient (patients recovering from cardiac surgery), or from the relatives (patients with acute lung injury, ALI). We studied 10 patients who were recovering from cardiac surgery (and who did not have lung injury) and 10 patients who had ALI. We defined ALI as $P_{\text{a}}_{\text{CO}_2}/P_{\text{O}_2}$ less than 200 mm Hg (26.7 kPa). We studied patients with ALI because increased dead space ventilation increases the difference between arterial $\text{CO}_2$ and $P_{\text{E}}'_{\text{CO}_2}$, and this may reduce the accuracy of gastric-mucosal end-tidal $\text{PCO}_2$ difference to indicate gastric-mucosal arterial $\text{PCO}_2$ difference (gastric-mucosal end-tidal $\text{PCO}_2$ tends to be higher than gastric-mucosal arterial $\text{PCO}_2$ difference). All patients were intubated, mechanically ventilated (Servo 900C, Siemens AB, Solna, Sweden) and sedated as clinically appropriate during the measurements.

Two gastric tonometers, a gas and a saline tonometer, were inserted in each patient via mouth. The correct positions of the tips of the tonometers were confirmed by x-ray. We used continuous gastric suctioning but H$_2$-blockers were not given to any patient. Gas tonometer (Tonocap®, Datex/Instrumentarium, Helsinki, Finland) was used to measure gastric mucosal partial pressure of carbon dioxide ($P_{\text{r}}_{\text{CO}_2}$) in 15 min intervals during the 8 h study period. In Tonocap® the device fills the tonometer TRIP-catheter (Tonometrics, Datex/Instrumentarium, Finland) with 5 ml gas (air) and a sample of this gas is drawn after an equilibration period. The $\text{PCO}_2$ of this sample is measured by Tonocap® using the same standard infra-red method that is used to measure the partial pressure of end-tidal $\text{CO}_2$ ($P_{\text{E}}'_{\text{CO}_2}$). A time dependent correction factor of 1.12 (for incomplete equilibration time of 15 min) for the mucosal $\text{PCO}_2$ ($P_{\text{r}}_{\text{CO}_2}$) was used. The Tonocap® was calibrated before the measurements according to the manufacturer's recommendation using calibration gas (5±0.03% $\text{CO}_2$ in 95% oxygen, Datex/Instrumentarium, Helsinki, Finland). The mean value of $P_{\text{r}}_{\text{CO}_2}$ was calculated each hour to allow comparison between gas and saline tonometers. End-tidal $\text{CO}_2$ was measured from the expired air immediately distal to the intubation tube using an AS3 monitor (Datex/ Instrumentarium, Helsinki, Finland). The gastric-mucosal end-tidal $\text{PCO}_2$ difference ($\text{DPCO}_{2\text{gas}}$) was calculated by subtracting end-tidal $\text{PCO}_2$ from gastric mucosal $\text{PCO}_2$ (as measured by Tonocap®).

We measured $P_{\text{r}}_{\text{CO}_2}$ using conventional saline tonometry and arterial $\text{PCO}_2$ each hour throughout the study. With the saline tonometry $P_{\text{r}}_{\text{CO}_2}$ was measured using 2.5 ml of sodium chloride in the tonometer balloon. Both the saline and arterial blood samples were analysed within 2 min of withdrawal using a blood–gas analyser (ABL-520, Radiometer, Copenhagen, Denmark). We did not take into account the potential bias related to blood gas analyser. A time dependent correction factor of 1.13 (for incomplete equilibration time of 60 min) for the $P_{\text{r}}_{\text{CO}_2}$ was used with saline tonometry and the measurements were carried out according to the manufacturer’s recommendations. Gastric-mucosal arterial $\text{PCO}_2$ difference ($\text{DPCO}_{2\text{sal}}$) was calculated by subtracting arterial $\text{PCO}_2$ from gastric mucosal $\text{PCO}_2$ (as measured by saline tonometry). We regarded this difference ($\text{DPCO}_{2\text{sal}}$) as the reference to represent true systemic-gastric mucosal $\text{PCO}_2$. In addition to the comparison between $\text{DPCO}_{2\text{sal}}$ and $\text{DPCO}_{2\text{gas}}$, we also compared the differences between gastric mucosal $\text{PCO}_2$ (measured using gas tonometry) and arterial blood $\text{PCO}_2$ or end-tidal $\text{PCO}_2$. This was done to eliminate potential errors in the saline technique, such as those related to blood–gas analyser bias, inappropriate equilibration factors and tonometer catheter dead space effects.

Arterial end-tidal $\text{PCO}_2$ difference was calculated by subtracting end-tidal $\text{PCO}_2$ from arterial blood $\text{PCO}_2$. This gradient was calculated to indirectly estimate dead space ventilation of the lung. The higher the gradient between arterial ($P_{\text{a}}_{\text{CO}_2}$) end-tidal $\text{PCO}_2$ ($P_{\text{E}}'_{\text{CO}_2}$), the higher is the dead space ventilation of the lung. The fraction (%) of dead space ventilation ($\text{Vd/VT}$) was estimated using the following equation: $\text{Vd/VT} = (P_{\text{a}}_{\text{CO}_2} - P_{\text{E}}'_{\text{CO}_2})/P_{\text{a}}_{\text{CO}_2}$.

**Statistical analysis**

Our main interest in the analysis was to study the agreement between $\text{DPCO}_{2\text{gas}}$ and $\text{DPCO}_{2\text{sal}}$. We studied this agreement using the method described by Bland and Altman. In addition to graphical display we also calculated bias (the mean difference between the two measurements) and precision (SD of the bias) for this comparison. Because we repeated measurements, the effect of time, and particularly time by group ($\text{DPCO}_{2\text{gas}}$ or $\text{DPCO}_{2\text{sal}}$) interaction, was analysed using general linear model with repeated measures option (statistical package SPSS for Windows, version 7.5). This analysis was carried out to test whether changes in gastric-mucosal systemic $\text{PCO}_2$ difference during the study were similar for $\text{DPCO}_{2\text{gas}}$ and $\text{DPCO}_{2\text{sal}}$. We used regression analysis to study the correlation between two variables and t-test when appropriate. A P-value of <0.05 was considered statistically significant. Results are given as mean (SD).
Results
The fraction of dead space ventilation was 11 (7)% (mean (SD)) in CABG patients and 25 (12)% in patients with ALI (P<0.001). The mean values and standard deviations of gastric mucosal end tidal PCO2 difference (ΔPCO2gas) and gastric mucosal arterial PCO2 difference (ΔPCO2a) for each hour during the whole study period are shown in Figure 1. When all patients were analysed together there was a significant effect of time (P<0.01) but no time by group interaction (P=0.33) indicating that the changes of gastric mucosal-systemic PCO2 difference were similar for ΔPCO2a and ΔPCO2gas. Also in this analysis the group effect was not significant (P=0.084). ΔPCO2gas tended to be greater that ΔPCO2a in patients with ALI and in patients recovering from cardiac surgery. However, the difference between the two methods was greater in patients with ALI. Figure 2 shows that the agreement between the two methods to reflect gastric mucosal systemic PCO2 is reasonably good, except for higher mean gastric mucosal systemic PCO2 differences. With greater mean gastric mucosal-systemic PCO2 differences, ΔPCO2gas tends to overestimate ΔPCO2a (Fig. 2). The bias and the precision of this comparison are 0.85 and 1.25 kPa, respectively. The comparison between gastric mucosal PCO2 (measured by gas tonometry) and arterial blood PCO2 or end-tidal CO2 is shown in Figure 3. The difference between gastric mucosal PCO2 (gas tonometry) and end-tidal CO2 was higher (P=0.022, ‘group’ effect) than the difference between gastric mucosal PCO2 (gas tonometry) and arterial blood PCO2. In addition, the effect of time was significant (P<0.001) but there was no time by group interaction (P=0.9). In Bland and Altman analysis the bias and the precision of this comparison are 1.08 and 0.85 kPa, respectively (figure not shown).

As expected, the difference between ΔPCO2gas and ΔPCO2a increased with increasing arterial end-tidal PCO2 difference (Fig. 4). Figure 5 shows a reasonable correlation between the maximum change from baseline in ΔPCO2a and the corresponding change in ΔPCO2gas. The correlation in gastric mucosal PCO2, when it was measured both by saline and by gas tonometry, is shown in Figure 6 and the Bland-Altman plot for the same comparison in Figure 7. The bias in this Bland-Altman analysis was -0.26 kPa and the precision 0.81 kPa. Finally, the correlation showing the mean gastric mucosal PCO2 (measured by air and saline tonometry) for each patient during the whole study period is shown in Figure 8.

Discussion
We found that the difference between gastric mucosal PCO2 (measured by gas tonometry) and end-tidal PCO2 (ΔPCO2gas) reflects the difference between gastric mucosal PCO2 (measured by saline tonometry) and arterial PCO2 (ΔPCO2a). We also found that ΔPCO2gas systematically overestimated ΔPCO2a and that ΔPCO2gas has some obvious limitations. However, the agreement between the two methods is acceptable and allows ΔPCO2gas to be used in clinical practice as a semi-continuous indicator of the adequacy of splanchnic perfusion.

The advantage of ΔPCO2gas is that it reflects the adequacy of gastric mucosal perfusion continuously. A monitor is a warning device that reveals progressive change, e.g. perfusion abnormalities, promptly, and continuous monitoring is the best option in clinical practice. The gastric mucosal systemic PCO2 (arterial blood) gradient best reflects mucosal perfusion. Also, gut perfusion decreases early in shock, often when splanchnic haemodynamics are stable. Saline tonometry, and gas tonometry, both need repeated samples for arterial blood or saline PCO2. It is not feasible in
clinical practice to draw and analyse arterial blood and gastric tonometer saline samples at frequent, e.g., 10–15 min intervals, if patients are clinically stable. However, because splanchnic perfusion deteriorates early in shock, this clinically stable phase of critical illness would be ideal to monitor gastrointestinal perfusion. The measurement of gastric mucosal-end-tidal CO$_2$ is a convenient method to continuously monitor gastric mucosal perfusion without a need to repeatedly analyse saline or arterial blood samples. Because no laboratory work is needed, several potential errors and problems related with sample handling and analysis are avoided. We used a separate monitor to analyse end-tidal CO$_2$ but a newer version of Tonocap® automatically analyses and displays both gastric mucosal and end-tidal P$_{CO_2}$. Tonocap® (both mucosal P$_{CO_2}$ and end-tidal P$_{CO_2}$) has to be calibrated once every 2 months with a gas of known P$_{CO_2}$. There is no need for recalibration after ventilatory adjustments and also temperature has no effect on the measurements. The potential problem of water evaporation in the tubing of capnometer is avoided because Tonocap® includes a water separation system which is based on a hydrophilic membrane.

We are not aware of any studies that have evaluated the gastric-mucosal end-tidal P$_{CO_2}$ difference to assess splanchnic perfusion. There are several studies that examined the agreement between gastric mucosal P$_{CO_2}$ measured by saline and gas tonometry. In our study the correlation between gastric mucosal P$_{CO_2}$ measured by saline and gas tonometry was not as good as has been reported elsewhere. We do not have a clear explanation for this discrepancy. Also, we do not know why gas tonometry systematically gave higher values than saline tonometry (Figs 6 and 8). We did not use H$_2$-blockers in our patients but this should not affect the agreement between the two methods. It is not clear if H$_2$-blockers are needed in critically ill patients to improve the performance of gastric tonometry. In patients with cardiogenic shock, a systematic disagreement between saline and gas tonometry was found. Under-correction of saline samples may be responsible although correction was done according to manufacturer’s recommendations. We regarded saline technique as a gold standard but this may not necessarily be true. In vivo, gas tonometry gave a closer agreement with the P$_{CO_2}$ of the test solution. Also, the bias between gas and saline tonometry was reduced by replacing saline by buffered electrolyte solutions. We used saline with our conventional tonometry and this may have contributed to the differences in our study. The degree of clinically important disagreement between different...
methods to estimate mucosal perfusion is more important than the disagreement per se.

The normal gastric mucosal systemic $PCO_2$ difference is not known and more importantly we do not know how large a difference is clinically important in critically ill patients. In our previous study with healthy volunteers, the gastric mucosal arterial $PCO_2$ gap varied between 1.4 and 3 kPa depending on whether nasogastric suction or H2-blockers were used.29 A more recent study in healthy volunteers suggested a normal threshold value of $<$1.1 kPa for a gastric mucosal arterial $PCO_2$ difference.29 Gastric mucosal $PCO_2$ depends on several factors such as aerobic and anaerobic production of CO$_2$ and also on perfusion of the gastric mucosa,17 and it is not clear to what extent increased gastric mucosal $PCO_2$ indicates tissue hypoxia or decreased mucosal perfusion. A recent experimental study suggested that gastric mucosal $PCO_2$ has to increase to $>$13 kPa to indicate tissue hypoxia.20 In our study the bias and the precision of the agreement between $DPCO_{2\text{gas}}$ and $DPCO_{2\text{sal}}$ were 0.85 and 1.25 kPa, respectively. Therefore, we propose, that the small disagreement between these methods may not be clinically important.

One obvious problem with the use of the gastric mucosal end-tidal $PCO_2$ difference is that in patients with impaired gas exchange, end-tidal CO$_2$ does not represent arterial (and hence systemic) $PCO_2$.20 In patients who do not have ALI this is not a large problem but in patients who have lung injury, end-tidal CO$_2$ may underestimate systemic $PCO_2$. We found that in patients who have ALI, $DPCO_{2\text{gas}}$ overestimated $DPCO_{2\text{sal}}$ more than in patients who do not have ALI. Figure 3 also shows that the disagreement between $DPCO_{2\text{gas}}$ and $DPCO_{2\text{sal}}$ increases as the arterial end-tidal $PCO_2$ difference increases (indicating increased dead space space ventilation). However, for at least two reasons the potential overestimation of the gastric mucosal systemic $PCO_2$ difference is not a major clinical problem. First, it is physiologically obvious and easily recognizable. A significant difference between arterial blood $PCO_2$ and end-tidal CO$_2$, can be easily measured and used to interpret $DPCO_{2\text{gas}}$. 

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**Fig 4** Correlation between arterial end-tidal $PCO_2$ difference (=$\text{arterial}-P_{\text{e}}(PCO_2)$) and $DPCO_{2\text{gas}}$-$DPCO_{2\text{sal}}$ difference. $DPCO_{2\text{gas}}$=gastric mucosal $PCO_2$; end-tidal $PCO_2$ when gastric mucosal $PCO_2$ is measured using gas tonometry. $DPCO_{2\text{sal}}$=gastric mucosal $PCO_2$-arterial $PCO_2$ when gastric mucosal $PCO_2$ is measured using saline tonometry.

**Fig 5** The maximum change from baseline in $DPCO_{2\text{sal}}$ and the corresponding change in $DPCO_{2\text{gas}}$. $DPCO_{2\text{gas}}$=gastric mucosal $PCO_2$-end-tidal $PCO_2$ when gastric mucosal $PCO_2$ is measured using gas tonometry. $DPCO_{2\text{sal}}$=gastric mucosal $PCO_2$-arterial $PCO_2$ when gastric mucosal $PCO_2$ is measured using saline tonometry.

**Fig 6** Correlation between paired gastric mucosal $PCO_2$ measurements when $PCO_2$ was measured simultaneously using both saline and gas tonometry.

**Fig 7** The agreement between simultaneous gastric mucosal $PCO_2$ measurements when both air (Tonocap$^6$) and saline tonometry were used. Mean $PCO_2$(Tonocap$^6$) $PCO_2$+saline tonometry $PCO_2$X2. Analysis was done using the method by Bland and Altman.20 Solid line indicates bias of this comparison and dotted lines indicate ±2 SD of the bias.
Secondly, an overestimate of the gastric mucosal systemic \( P_{CO_2} \) difference using DPCO2gas means that truly increased \( P_{CO_2} \) differences will not be left undetected. We found that changes in DPCO2gas reflected changes in DPCO2sal during our study period, but the time period for our study was relatively short and probably was during steady state \( CO_2 \) production, lung function and dead space ventilation. Therefore, we cannot address the potential impact of changes in these variables during the progression of critical illness.

The difference between gastric mucosal end tidal \( P_{CO_2} \) is a potentially useful method for continuous monitoring of splanchnic perfusion. It is easy to use and it does not require much additional work from staff, and the limits of the method are easy to assess and they do not jeopardize patient care. Studies of clinical outcome, based on interventions using this information are needed.

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