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ASSESSMENT OF A NEW PROTOTYPE HYDROGEL CO_2 SENSOR; COMPARISON WITH AIR TONOMETRY

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ABSTRACT. Objective. Gastrointestinal ischemia is always accompanied by an increased luminal CO_2. Currently, air tonometry is used to measure luminal CO_2. To improve the response time a new sensor was developed, enabling continuous CO_2 measurement. It consists of a pH-sensitive hydrogel which swells and shrinks in response to luminal CO_2, which is measured by the pressure sensor. We evaluated the potential clinical value of the sensor during an in vitro and in vivo study. **Methods.** The response time to immediate, and stepwise change in pCO_2 was determined between 5 and 15 kPa, as well as temperature sensitivity between 25 and 40 °C at two pCO_2 levels. Three sensors were compared to air tonometry (Tonocap®) in healthy volunteers using a stepwise incremental exercise test, followed by a period of hyperventilation and an artificial CO_2-peak. **Results.** The in vitro response time to CO_2 increase and decrease was mean 5.9 and 6.6 min. The bias, precision and reproducibility were +5%, 3% and 2%, resp. Increase of 1 °C at constant pCO_2 decreased sensor signal by 8%. In vivo tests: The relation with the Tonocap was poor during the exercise test. The response time of the sensor was 3 min during hyperventilation and the CO_2 peak. **Conclusion.** The hydrogel carbon dioxide sensor enabled fast and accurate pCO_2 measurement in a controlled environment but is very temperature dependent. The current prototype hydrogel sensor is still too unstable for clinical use, and should therefore be improved.

KEY WORDS. Gastrointestinal tract, mucosal perfusion, gastrointestinal ischemia, carbon dioxide, measurement techniques, air tonometry, hydrogel-based CO_2 sensor, mesenteric, hydrogel.

INTRODUCTION

Detection of an increased pCO_2 as measure of gastrointestinal (GI) ischemia is based on the association between ischemia and luminal hypercapnia. This CO_2 stems from buffering of protons produced during anaerobic glycolysis and diminished CO_2 clearance by reduced blood flow [1]. The mucosal CO_2 equilibrates with luminal CO_2. The latter can be measured by air tonometry using a balloon-tipped catheter, placed in the stomach. Gastric acid suppression is used to avoid increases in CO_2 from buffering of gastric acid by duodenal bicarbonate [2, 3]. The current standard for luminal pCO_2 measurement is the Tonocap® (Datex-Engstrom, Finland). The Tonocap® consists of a capnograph and balloon tipped catheter, allowing for semi-automated pCO_2 measurement every ten minutes.

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Intraluminal CO_2 diffuses into the balloon and after a 10 min dwell time, the air is aspirated and measured ex-vivo with an infrared sensor. It has been shown that an increased luminal-blood pCO_2 gradient indicates gastrointestinal ischemia [4].

Air tonometry has several limitations. First, the maximal measurement frequency is once every 10 min. Second, air tonometry may influence the environment because CO_2 is removed and O_2 delivered during measurement [5, 6]. Finally, air tonometry is unsuitable for ambulant measurements. This led us to develop a new sensor. The hydrogel-based carbon-dioxide sensor consists of a pH-sensitive hydrogel in a bicarbonate solution mounted on a catheter-tip pressure sensor. It is covered by a gas permeable membrane (Figure 1). The hydrogel will swell or shrink dependent on the CO_2. Because it is tightly mounted on the pressure sensor, this will be reflected by pressure changes [7].

This study was developed to assess the performance of the hydrogel-based sensor and its potential clinical value.

MATERIALS AND METHODS

Air tonometry

The balloon tipped catheter was connected to an air tonometry device (TC-200 Tonocap®, Tonometrics Division, Finland). The Tonocap® automatically fills the tonometer catheter with 5 ml of room air, which is then kept in the catheter balloon for ten minutes. A sample is automatically drawn from the catheter and the concentration of CO_2 is measured externally by an infrared sensor, which takes 30 seconds. The aspirated air is then recycled to the catheter balloon for the next measurement cycle. The Tonocap® was calibrated according to its standard procedure.

The hydrogel-based CO_2 sensor

The current prototype hydrogel-based CO_2 sensor was connected to a measurement device (Luna, Medical Measurement Systems B.V, the Netherlands). The Luna reads out the hydrogel-based sensor signal and transmits it every second wireless to a laptop. LabVIEW software (National Instruments, USA) was used to convert the hydrogel-based sensor data to pCO_2 on the basis of a calibration curve. All data were automatically logged every second.

In vitro test

Equilibration chamber

A 30 ml Perspex chamber was filled with 5 ml distilled water to obtain high relative humidity. Both the hydrogel-based sensor and the balloon tipped catheter (TRIP® tonometer, Tonometrics Division, Instrumentarium Corp, Finland) were placed in the chamber after

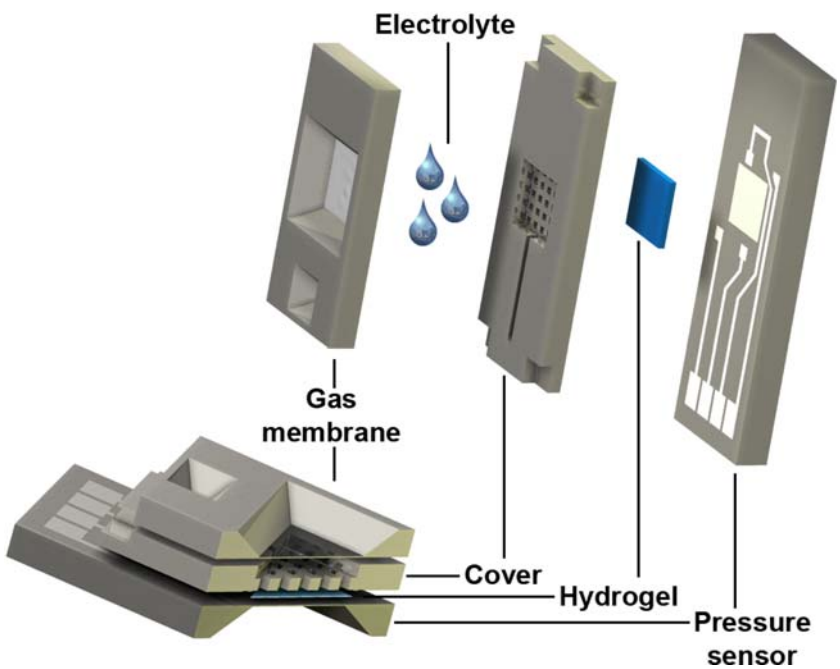

Fig. 1. Exploded view of all parts and assembly drawing of the final hydrogel-based CO_2 sensor.

calibration. The temperature was held at 37.0 °C in a thermostat bath regulated by a temperature controller (MTCA series, Melcor Corporation, USA). A gas mixing setup was used, consisting of two mass flow controllers (El-Flow, Bronkhorst Nederland B.V, The Netherlands) which accurately mix 100% N_2 and premixed gas of 50% CO_2/50% N_2 (Hoek Loos B.V, Amsterdam, the Netherlands). The gas mixture continuously flowed through the equilibration chamber with 50 ml/min. The total error in the mixing process was calculated at <2%. The gas chamber was sealed airtight (Parafilm ''M'', America National Can, USA) with the exception of a ventilation hole, to avoid overpressure in the chamber due to the continuous gas flow. It was estimated that it would take approximately one minute before a new steady state CO_2 concentration is reached in the chamber after setting a different gas mixture (chamber equilibration time).

Experiment 1

A baseline pCO_2 of 5.1 kPa was accomplished. The pCO_2 was increased within 1 minute and maintained at 15.2 kPa for 40 min. Then the pCO_2 was reduced within 1 minute and maintained at 5.1 kPa for 40 min. This cycle was repeated 3 times.

Experiment 2

The chamber pCO_2 was set at 5.1 kPa. At $t = 0$, pCO_2 was increased to 15.2 kPa with steps of 1 kPa every minute. The pCO_2 concentration of 15.2 kPa was maintained for 20 min. Then pCO_2 was decreased with steps of 1 kPa per min to 5.1 kPa again. This pCO_2 was again maintained for 20 min.

Experiment 3

The chamber pCO_2 was kept at 5.1 kPa in the first and 10.2 kPa in the second experiment. At each pCO_2 level, the temperature was increased in 3 °C steps from 25 to 40 °C in steps of 3 °C every 15 min.

In vivo study

Subjects

Three healthy, trained male volunteers, taking no medication, were included in this study. Trained status was defined as >4 hours endurance training per week. Exclusion criteria were; any medication, prolonged QT-syndrome, diabetes mellitus, epilepsy, deformity to throat/nose/ear. All subjects were informed about the nature, purpose, and possible risks involved in the study before giving their consent. The study was performed according to the ethical guidelines of our constitution after approval from the Institutional Ethics Committee.

Preparation

An electrocardiogram was performed to exclude the prolonged QT-syndrome. The subjects were fasted for food ten hours, and fluid two hours before the start of the study. They were not allowed to drink or eat during study time. After calibration of the pH measurement catheter (pHersaflex, Medical Measurements Systems, Enschede, the Netherlands), it was placed transnasally approximately 10 cm below the gastro-esophageal junction in two subjects. This was identified by an abrupt pH decrease as the probe enters the stomach. The values were stored in a microcomputer system for pH analysis (UPS 2020 Orion, Medical Measurement Systems, Enschede, the Netherlands). The gastric tonometer was placed at the same distance from the nose as the pH electrode and connected to the air tonometry device. The pCO_2 was measured every ten minutes. The hydrogel-based sensor was placed nasogastrically at the same distance. An intravenous catheter was placed and Esomeprazole infusion was given by a priming dose of 80 mg, followed by 8 mg/hour to inhibit gastric acid secretion to prevent CO_2 production by buffering of gastric acid.

Protocol

The exercise test was started as soon as the gastric pH was >4 for 30 minutes. A 12-lead electrocardiogram was recorded during the exercise protocol. (Schiller, Switzerland) In subject 3, body temperature was measured at $t = 0$ min, $t = 20$ min and $t = 30$ min (Thermoscan, Braun, Kronberg, Germany). Exercise was performed on a bicycle ergo meter (Lode, Groningen, The Netherlands). From $t = 0$ min to $t = 10$ min, the workload was increased every two minutes to reach sub maximal intensity. This was defined as capillary lactate between 3.5–5 mmol/l. Lactate was measured every two minutes from $t = 0$ min to $t = 10$ min (Accusport, Boehringer, Mannheim, Germany). From $t = 10$ min to $t = 20$ min, exercise intensity was maintained at sub maximal level, which was controlled by lactate measurements every three minutes. From $t = 20$ min to $t = 30$ min, the workload was increased with 10% of the sub maximal workload every three minutes until exhaustion. Lactate was measured every three minutes. The subjects recovered from $t = 40$ min to $t = 75$ min.

At $t = 75$ min, subjects were asked to hyperventilate for 5 minutes to rapidly decrease the arterial CO_2. At $t = 110$ min, an artificial CO_2 peak was induced by oral ingestion of 1 g $NaHCO_3$ and administering 200 ml apple juice through the catheter. At $t = 140$ min, the study was finished. Arteriolized capillary blood samples were drawn for determination of capillary pCO_2 at $t = 0$ min, $t = 20$ min, $t = 30$ min and $t = 75$ min (blood-gas analyzer; Radiometer ABL520, Copenhagen, Denmark).

Statistical analysis

In vitro test

Data are expressed as mean (standard deviation). The error of pCO_2 measurement, calculated from experiment 1, was defined as the percentage difference between the applied pCO_2 and measured values of the hydrogel-based sensor and Tonocap® after a change in bath pCO_2. The precision is the standard deviation of the error, and standard deviation divided by means was calculated as a measure of reproducibility. The 90% response time of the hydrogel-based sensor was established as follows. First, the 90% value between the baseline (b) and ultimate (u) value was calculated following the formula

$$90\%\ \text{value} = (u - b)\star 0.9 + b \quad (1)$$

Second,the corresponding times to this 90% value (=90%vt) and the baseline value (=Bvt) was derived from the data sheet containing the hydrogel-based sensor response. Finally, the 90% response time was calculated following the formula

$$90\%\,\text{response time} = 90\%\text{vt} - \text{Bvt} - 1\,\text{minute}\ (\text{chamber equilibration time}) \quad (2)$$

The response time of upward and downward pCO2 changes were compared with an unpaired *t*-test. To assess the drift of the hydrogel-based sensor, the three steady state values of the hydrogel-based sensor at each pCO2 were compared using the one-way ANOVA. $p < 0.05$ was considered significant.

In vivo test

The peak pCO2 at sub-maximal and maximal intensity exercise was determined. The pCO_2 response on hyperventilation and following the artificial CO_2 peak was assessed. The hydrogel-based sensors were individually compared to the Tonocap® and the differences between the hydrogel-based sensors were assessed. Luminal-capillary CO_2 gradient was calculated at $t = 0$ min, $t = 20$ min and $t = 30$ min from the Tono-Cap® values. A CO_2 gradient ≤ 0.8 kPa was considered as normal [4].

RESULTS

In vitro test

Experiment 1

Bias, precision and reproducibility of air tonometry and the hydrogel-based sensor are presented in Table 1. As shown in Figure 2, the sensor exhibits an upward drift. The hydrogel-based sensor reading during the second and third period of at 15.2 kPa was 0.4% and 3% higher compared to the first period. At 5.1 kPa, this upward change was 1.9% and 2.8%, respectively. This drift was significant at both values of applied pCO_2 ($p < 0.001$). After changing the chamber pCO_2, the sensor signal started to change after 200 seconds. The response time for an increase in pCO_2 was slightly, but significant faster than for a decrease (353 (14) versus 394 (10) seconds, $p = 0.01$).

Table 1. Bias, precision and reproducibility of steady state bath pCO_2 measurements by the (A) Tonocap® ($n = 12$ at each pCO_2) (B) sensor ($n = 5400$ at each pCO_2)

	Hydrogel Sensor		Tonocap	
Applied pCO_2 (kPa)	5.1	15.2	5.1	15.2
Measured pCO_2 (kPa)(SD)	5.2 (0.2)	16.2 (0.3)	5.3 (0.1)	15.6 (0.1)
Bias (%)	+4.0	+6.4	+4.4	+2.5
Precision (%)	3.0	1.8	0.2	0.1
Reproduciblity (%)	2.4	1.7	0.5	0.4

Experiment 2

The response of the hydrogel-based sensor and air tonometry to a gradual change in pCO_2 is presented in Figure 3. There was no difference in response time

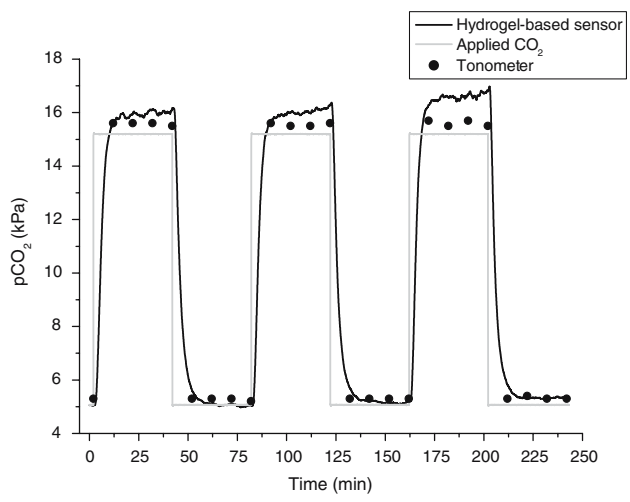

Fig. 2. Response of air tonometry and sensor to prolonged measurement of pCO_2 and a quick change in pCO_2. pCO_2 was changed in three cycles from 5.1 to 15.2 kPa, maintained at 15.2 kPa for 40 minutes, changed to 5.1 kPa again and maintained at 5.1 kPa for 40 min.

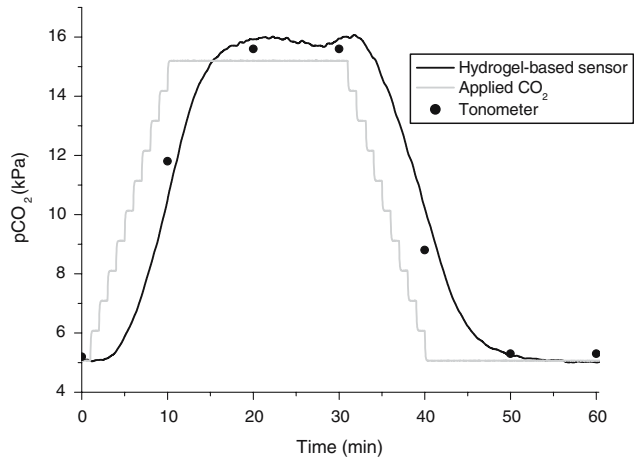

Fig. 3. Response of air tonometry and hydrogel-based CO_2 sensor to stepwise change of pCO_2. pCO_2 was increased with 1 kPa/min to 15.2 kPa. After 20 min pCO_2 was decreased with 1 kPa/min to 5.1 kPa.

between the hydrogel-based sensor and air tonometry. It accurately showed the trend in changes of pCO_2, with a delay of approximately 210 seconds.

Experiment 3

The effect of temperature on the hydrogel-based sensor response is shown in Figure 4. At 25 °C, the real pCO_2 (i.e. 5.1 or 10.2 kPa) is overestimated over 300% by the hydrogel-based sensor in both experiments when comparing it to the hydrogel-based sensor values at calibration temperature (37 °C). On average, a 1 °C increase in temperature caused a decrease of 8% in hydrogel sensor signal at 5.1 kPa, and 7% at 10.2 kPa.

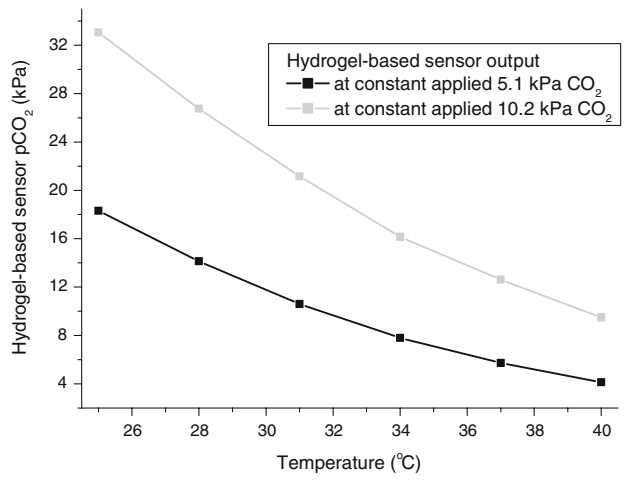

Fig. 4. Effect of temperature change on the signal of the sensor at a constant pCO_2 of 5.1 kPa and 10.2 kPa. Temperature was increased with steps of 3 °C from 25 °C to 40 °C.

In vivo test

Exercise

The main results of the exercise protocol are presented in Figure 5A–C. All subjects exercised until exhaustion, maximum lactate levels were 10, 10 and 12 mmol/l respectively. As represented in Figure 5A, all subjects had gastrointestinal ischemia at the moment of exercise at maximal intensity, represented by an increased luminal-capillary CO_2 gradient (values: 1.9, 3.5 and 2.3 kPa) as measured by air tonometry. Luminal pCO_2, measured by air tonometry, also increased from $t = 20$ to $t = 30$ (Figure 5B). Figure 5C shows that only the hydrogel-based sensor in subject 2 correctly detected this rise in luminal pCO_2, from $t = 20$ to $t = 30$, during which GI-ischemia developed.

Hyperventilation

Average capillary pCO_2 fell with 42% (from 5.4 kPa to 3.1 kPa). The mean tonometry value fell with 11%, the maximum average decrease of the hydrogel-based sensors in response to hyperventilation was 13%. The results of the response of the hydrogel-based sensors to the hyperventilation test are presented in Figure 6. The hydrogel-based sensor signals of subject 1 and 3 started to fall at $t = 78$, three minutes after starting with hyperventilation. The hydrogel-based sensor signal of subject 2 started to fall at t = 81, six minutes after starting with hyperventilation.

Artificial CO_2 peak

The measurements results of the CO_2 peak are presented in Figure 7. The tonometry value in the three volunteers all increased by 200%. The hydrogel-based sensor signal started to increase within 2 minutes after the CO_2 peak was induced. The increase from its baseline value differed from 1500% in subject 1, 5500% in subject 2 to 280% in subject 3.

DISCUSSION

The prototype hydrogel-based CO_2 sensor was developed to overcome the drawbacks of air tonometry. In the current study it was shown that this prototype met some of the requirements: it enabled continuous measurement of CO_2 and fast detection of both sudden and gradual changes in pCO_2. However, the current state of stability of its measurement signal, in terms of hysteresis and temperature sensitivity, will have to be improved before clinical application is possible.

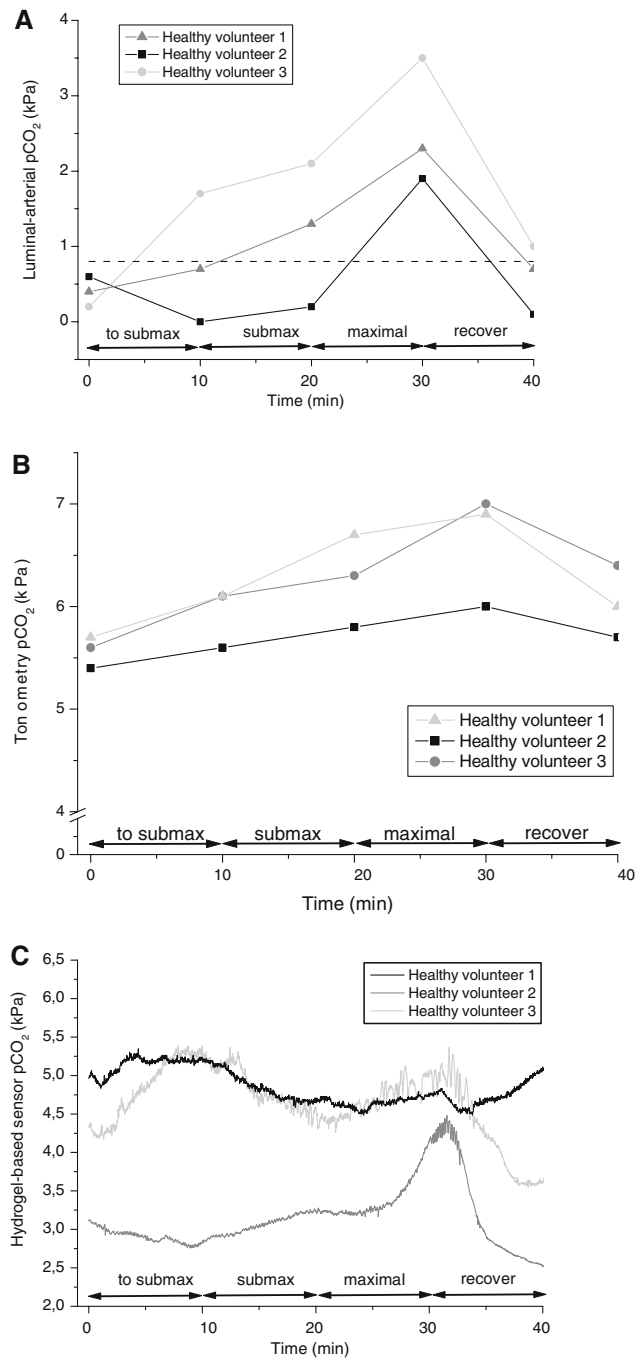

Fig. 5. (A) Response of luminal-arterial pCO_2 gradient to the exercise protocol in 3 healthy volunteers (B) Response of gastric pCO_2 as measured by air tonometry to the exercise protocol in 3 healthy volunteers (C) Response of gastric pCO_2 as measured by the hydrogel-based sensor to the exercise protocol in 3 healthy volunteers.

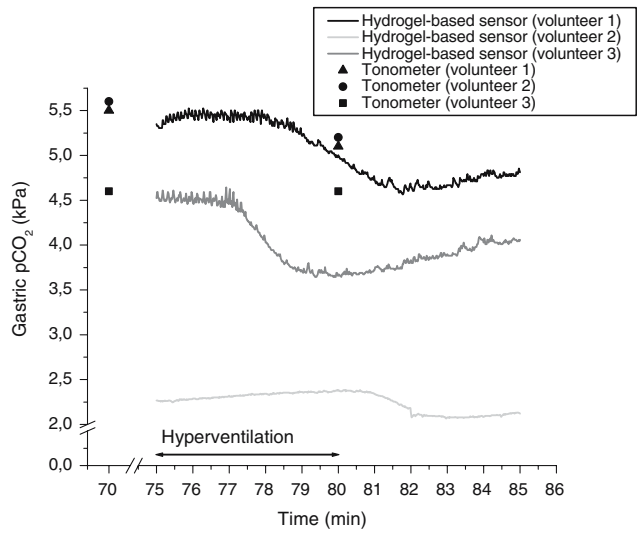

Fig. 6. Response to hyperventilation of the air tonometry values and hydrogel based sensors in 3 healthy volunteers.

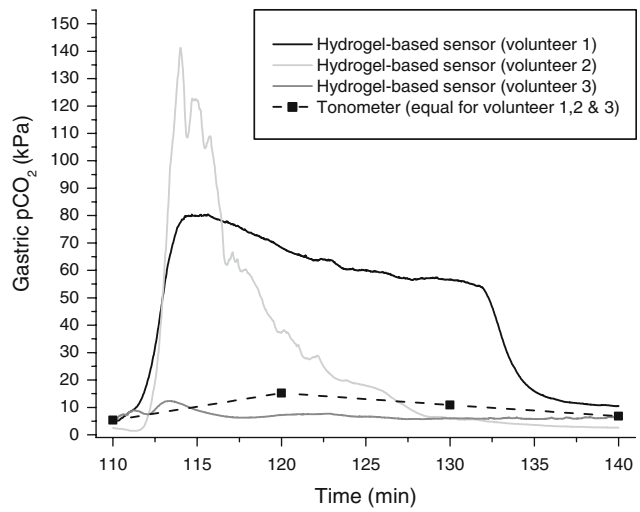

Fig. 7. Response of air tonometry and hydrogel based CO_2 sensor to an artificial CO_2 peak given at t = 110 in 3 healthy subjects.

We have previously demonstrated the development of gastric ischemia within ten minutes of strenuous exercise [8]. However, the precise CO_2 dynamics during these tests are unknown. The current standard, air tonometry, is unable to monitor the trend of pCO_2 because of its ten minutes measurement interval. The ability of the new hydrogel-based sensor to measure pCO_2 continuously is major advantage over routine air tonometry. From the in vitro part of the study can be concluded that the hydrogel-based sensor is suitable for trend monitoring allowing detection of CO_2 changes within 3 minutes. The response time of the hydrogel-based sensor is considerably faster than currently published response times of air tonometry and other (semi)continuous CO_2 measurement devices [5, 9, 10]. A further improvement of the response-time could

be achieved by decreasing the thickness of the hydrogel [7]. The very fast response of air tonometry in this study is probably related to the small volume of the equilibration chamber. In larger volumes, air tonometry proved to be slower, with response times of 18 minutes [11]. The bias, precision and reproducibility of air tonometry in this study are comparable to previous studies [11, 12].

The bias, precision and reproducibility of the hydrogel-based sensor were promising for clinical use. In fact, the hydrogel-based sensor had a comparable accuracy as air tonometry. However, during the in vitro test, it already had an upward drift and during the in vivo tests, it proved to be insufficiently stable for clinical use. An example of instability (i.e. hysteresis) can be seen during the exercise test in subject 3 (Figure 5C): the hydrogel-based sensor in subject 3 reached a stable signal from $t = 35$ min to $t = 40$ min. However, this differed about 1 kPa from its baseline value at $t = 0$ min whereas air tonometry showed a similar pCO_2 at $t = 0$ min and $t = 40$ min.

At first glance, these stability problems are quite disturbing. Interestingly, the calibration curves done after completion of the study, was identical to the one performed before the study. In addition, an earlier prototype of this hydrogel-based sensor, which was not yet mounted on a catheter, proved perfectly stable [7]. These observations indicate that the hydrogel-based sensor itself is stable, and the instability is due to imperfect, manual, assembly into the catheter. Manual assembly causes imperfections in the gluing/fixation of the hydrogel-based sensor parts, and, partly irreversibly, movement of the various parts. This is a well-established cause of varying characteristics, drift and hysteresis in most prototype sensors. For example, in the early phase of development of a pressure transducer for biomedical application by Ko et. al, similar problems were encountered [13]. These authors have shown that the major cause of baseline drift in the device was not related to the sensor design or processing but rather the assembly and structure of the device. As expected, that problem was solved with automated machinated manufacturing techniques, and these in time and such devices are currently used worldwide in large quantities. Therefore, comparable construction and manufacturing techniques will likely eliminate or drastically decrease the drift problem in our hydrogel-based sensor.

During the in vitro tests, the hydrogel-based sensor had a large and irreversible temperature sensitivity. During the in vivo tests, a 1 degree increase in body temperature was measured during the incremental exercise test. This probably decreased the hydrogel-based sensor signal by 8% and may therefore be one of the reasons that GI ischemia was insufficiently detected during maximum intensity exercise. Temperature sensitivity was expected as an intrinsic property of the hydrogel. However, in an earlier prototype, not mounted on the catheter, this effect was both reversible and predictable [7]. Again, incomplete fixation of the hydrogel-based sensor to the catheter is the most probable cause of the irreversible temperature sensitivity. Automated machinated assembly should make temperature sensitivity more predictable. Temperature correction will always be needed, however. This is a disadvantage compared to air tonometry which is not sensitive to temperature [14, 15].

In conclusion, the prototype hydrogel-based CO_2 sensor allows for continuous measurement of pCO_2 in a clinically significant range. It enables fast and continuous luminal CO_2 measurement, picking up changes within 3 minutes. The current stability problems and irreversible temperature sensitivity are mainly related to the hand-made assembly. To meet clinical demands more likely, a next version of the hydrogel sensor will have to be made by automated assembly.

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