Early detection of cardiac ischemia using a conductometric pCO$_2$ sensor: real-time drift correction and parameterization

This article has been downloaded from IOPscience. Please scroll down to see the full text article.

2010 Physiol. Meas. 31 1241

(http://iopscience.iop.org/0967-3334/31/9/013)

View the table of contents for this issue, or go to the journal homepage for more

Download details:
IP Address: 129.240.84.207
The article was downloaded on 18/08/2011 at 09:08

Please note that terms and conditions apply.
Early detection of cardiac ischemia using a conductometric pCO₂ sensor: real-time drift correction and parameterization

Christian Tronstad¹, Soeren E Pischke²,³, Lars Holhjem², Tor Inge Tønnessen³,⁴, Ørjan G Martinsen¹,⁵ and Sverre Grimnes¹,⁵

¹ Department of Clinical and Biomedical Engineering, Oslo University Hospital-Rikshospitalet, Norway
² The Interventional Centre, Oslo University Hospital-Rikshospitalet, Norway
³ Clinic for Acute Medicine, Oslo University Hospital-Rikshospitalet, Norway
⁴ Medical Faculty, University of Oslo, Norway
⁵ Department of Physics, University of Oslo, Norway

Received 2 April 2010, accepted for publication 8 July 2010
Published 11 August 2010
Online at stacks.iop.org/PM/31/1241

Abstract

For detection of cardiac ischemia based on regional pCO₂ measurement, sensor drift becomes a problem when monitoring over several hours. A real-time drift correction algorithm was developed based on utilization of the time-derivative to distinguish between physiological responses and the drift, customized by measurements from a myocardial infarction porcine model (6 pigs, 23 sensors). IscAlert™ conductometric pCO₂ sensors were placed in the myocardial regions supplied by the left anterior descending coronary artery (LAD) and the left circumflex artery (LCX) while the LAD artery was fully occluded for 1, 3, 5 and 15 min leading to ischemia in the LAD-dependent region. The measured pCO₂, the drift-corrected pCO₂ (ΔpCO₂) and its time-derivative (TDpCO₂) were compared with respect to detection ability. Baseline stability in the ΔpCO₂ led to earlier, more accurate detection. The TDpCO₂ featured the earliest sensitivity, but with a lower specificity. Combining ΔpCO₂ and TDpCO₂ enables increased accuracy. Suggestions are given for the utilization of the parameters for an automated early warning and alarming system. In conclusion, early detection of cardiac ischemia is feasible using the conductometric pCO₂ sensor together with parameterization methods.

Keywords: ischemia, pCO₂ sensor, biomedical signal processing, parameterization, drift
1. Introduction

1.1. pCO2 as a clinical parameter

Monitoring of regional pCO2 enables early detection of organ ischemia (Tønnessen and Kvarstein 1996, Tønnessen 1997, Kvarstein et al. 2003, 2004). When the supply of O2 to an organ is reduced below its O2 demand, the cellular metabolism turns anaerobic. This change leads to a generation of protons by lactic acid and consumption of energy-rich phosphate compounds like ATP, which has to be buffered in order to reduce acidity. The buffering reaction of protons by bicarbonate yields CO2 as a byproduct. In the case of arterial occlusion, the transport of excessive CO2 from the affected region is impaired, leading to an increase in pCO2 before anaerobic metabolism occurs. These processes contribute to the shape of the pCO2 curve during an arterial occlusion. Using the generation rate of CO2 together with the pCO2 level may enable discrimination between these processes, utilizing the parameter TDCO2 as introduced by Pischke et al. (2010a, 2010b). Early detection of organ ischemia during hospitalization can ensure that intervention is performed before irreversible damage is caused. Cardiac ischemia (e.g. myocardial infarction) in the course of cardiac surgery and especially coronary artery bypass grafting (CABG) remains a major concern (Paparella et al. 2007, Yau et al. 2008) as it is a major determinant of post-operative mortality, morbidity and recurrence of angina pectoris symptoms (Force et al. 1990, Steuer et al. 2005). To date, reliable detection of perioperative myocardial infarction is insufficient as current clinical monitoring using ECG, blood pressure and observation of enzymatic blood parameters is confounded by the surgery, not specifically, or only taken once a day, respectively (Nass and Fleisher 2002).

1.2. The conductometric pCO2 sensor

A biomedical pCO2 sensor was presented by Mirtaheri et al. (2004a). The sensor works by the principle of conductivity changes within an aqueous solution separated from the tissue by a gas-permeable membrane. The relation between the conductance of the solution volume and the pCO2 at equilibrium is given by

\[
G_{\text{total}} = \Psi \cdot (\sigma_0 + (\Lambda_{\text{H}^+} \cdot \vartheta_{\text{H}^+} + \Lambda_{\text{HCO}_3^-} \cdot \vartheta_{\text{HCO}_3^-}) (K \cdot K_H \cdot \text{pCO}_2^{1/2}),
\]

where \(\Psi\) (m) is a geometrical factor, \(\sigma_0\) (S m\(^{-1}\)) is the conductivity at 0 kPa pCO2, \(\Lambda\) (m\(^2\)(\(\Omega\) mol\(^{-1}\))\(^{-1}\)) is the molar conductivity of ions, \(\vartheta\) (unitless) is the activity of ions in the solution, \(K\) (mol l\(^{-1}\)) is the activity coefficient and \(K_H\) (mol (l kPa\(^{-1}\))\(^{-1}\)) is Henry’s constant.

To enable compensation for the temperature dependence on the total conductance, a thermistor was embedded close to the electrodes within the sensor. This sensor was miniaturized into a biocompatible cylindrical design (1 mm diameter) for clinical use (Mirtaheri et al. 2004b) and named the IscAlert\textsuperscript{TM} sensor. Sensors, connection units and calibration equipment used in this study were all produced and kindly provided by Alertis Medical ASA, Norway.

1.3. Sensor drift

Long-term instability is a well-known problem for the conductometric pCO2 sensor (Varlan and Sansen 1997, Mirtaheri et al. 2004a, 2004b) and the potentiometric pCO2 (Zhao and Cai 1997) and pH (Gumbrell et al. 1997, Mindt et al. 1978, Drake and Treasure 1986) sensors. For the potentiometric sensors, a drift is significantly determined by the potential stability of the reference electrode (Guth et al. 2009). For the conductometric sensor, there are several possible causes. As (1) shows, the total conductance is dependent on the sensor cell geometry.
For this sensor, the geometry depends on the tightness of the elastic membrane, which may change over time causing a drift as suggested by Mirtaheri et al (2004b). Another possibility is contamination of the aqueous solution from sensor parts or through ion leakage, which changes the total conductance by increasing the ion concentration or affecting the ion activity in (1). Electrically in series with the cell solution conductor, the electrode polarization impedance (EPI) is an important factor to the total conductance measurement and becomes increasingly dominant as the electrode area is reduced through sensor miniaturization. In vitro characterizations of electrodes of various sizes, materials and surface structures have revealed significant long-term changes in the EPI (Franks et al 2005, Kalvøy et al 2010), which makes this a likely cause of the conductometric drift. Increasing the excitation frequency for the measurement reduces the EPI contribution (Schwan 1992), but this is limited by the parasitic capacitance which becomes dominant at higher frequencies, especially for miniature sensor constructions. Until this problem is thoroughly investigated and the cause and remedy is found, other means of reducing drift such as real-time signal processing may offer an alternative.

For an automated detection and warning system for cardiac ischemia, a threshold pCO2 detection limit cannot be used when a baseline wander is present. The aim of this study was to develop a real-time signal processing method for the earliest accurate detection of cardiac ischemia given the properties of the sensor, based on measurements from a porcine cardiac ischemia model.

2. Materials and methods

2.1. Animals and surgical procedure

The following protocol was approved by the Norwegian Animal Care and Use Committee and animals were handled according to the Revised Guide for the Care and Use of Laboratory Animals (NIH GUIDE, 1996).

Nine conventional landrace pigs (Sus scrofa), mean weight 59.2 kg (range 55–62 kg), male or female, were anesthetized, titrated to no reaction to skin incision during the whole experiment using pentobarbital (2–3 mg kg\(^{-1}\)), isoflurane (1, 5% flow) and morphine (0.5–1 mg kg\(^{-1}\) h\(^{-1}\)). Pigs were mechanically ventilated via a tracheostomy tube (Servo ventilator system 900 C, Siemens, Germany), and arterial pO2 was kept above 11 kPa and arterial pCO2 close to 5.5 kPa.

After sternotomy, the left anterior descending coronary artery (LAD) on the surface of the heart was identified and a flexible occluding string was placed distal to the second diagonal branch. Manual tightening of the occluding string leads to total occlusion of the LAD. This method has been shown to reliably reduce flow to <10% compared to the baseline (Nilsson et al 1995) and leads to loss of regional systolic contraction already after 1 min of occlusion (Espinoza et al 2010).

For gradual occlusion experiments, off-pump CABG from the left internal mammary artery to LAD was performed on three other pigs.

A sensor measuring tissue pO2, pCO2, pH and temperature (Neurotrend®, Codman, MA, USA) was inserted into the myocardium via a split needle in the LAD distribution area distal to the occlusion. Likewise, two or more IscAlertTM sensors were placed at the apex of the heart, in the area supplied by the LAD. After identification of the left circumflex artery (LCX), one sensor was placed in the area supported by blood from this artery. All sensors were consistently inserted approximately 5 mm subendocardially and at a distance of at least 5 mm from the designated coronary artery.
2.2. Experimental protocol

When stable measurements were achieved, the LAD was fully occluded for 1, 3, 5 and 15 min leading to ischemia in the LAD-dependent distribution area. For the gradual occlusions, blood flow in the bypass graft was measured with Doppler ultrasound flow probes (Medistim KirOp AS, Norway) and reduced to 75%, 50%, 25% and 0% in 18 min intervals using inflatable vascular occlusion devices (In-Vivo Metric, USA). Between ischemic events, at least 30 min of reperfusion with fully opened LAD was carried out. The animal was monitored for 2 h after the last occlusion and euthanized thereafter.

2.3. Sensors, calibration and pCO₂ prediction

As the conductance of the pCO₂ sensor also has a temperature dependence, calibration was performed according to the following model:

\[ G_{\text{total}} = G_0 + k_{pCO_2} \cdot pCO_2 + k_T \cdot T, \]  

(2)

where \( G_0 \) (S) is the sensor conductance at 0 kPa pCO₂ at 0 °C, \( k_{pCO_2} \) (μS kPa⁻¹) is a linear pCO₂ coefficient and \( k_T \) (μS °C⁻¹) is a linear temperature coefficient. With the sensor drift present, using the quadratic \( G \) versus pCO₂ relationship (1) for calibration and prediction would cause false changes in the pCO₂ versus \( G \) slope as \( G \) is reduced by the drift. A linear calibration ensures an equal slope over the whole range. Previous calibrations have shown that within the physiologically interesting pCO₂ range, the prediction accuracy is not reduced by this approximation. With large offsets often observed between calibration and usage, the linear relationship (2) was thus used in favor of the quadratic relationship (1).

Reference CO₂ solutions were produced by streaming of 5%, 10% and 15% CO₂ in N₂ gas standards (AGA AS) into sealed 100 ml glass bottles with 75 ml phosphate-buffered saline (Sigma-Aldrich Chemie). Five minutes of streaming with the respective CO₂ gases at 190 ml min⁻¹ at room temperature (23 °C) produced CO₂ solutions at approximately 4, 7.5 and 11 kPa. The samples from the solutions were analyzed using an ABL700 blood-gas analyzer (Radiometer®) to obtain the 37 °C pCO₂ reference values. The temperature of the solutions was controlled using a Hart Scientific micro-bath (Fluke®). Sensor conductance was measured in each of the pCO₂ levels at three temperature levels of 30 °C, 34 °C and 38 °C giving a total of nine calibration points. Least-squares regression on these values was used to obtain the \( k_{pCO_2} \) and \( k_T \), which would then be used for pCO₂ estimation by

\[ pCO_2 = \frac{1}{k_{pCO_2}}(G_{\text{total}} - G_0 - k_T \cdot T). \]

(3)

2.4. Data and acquisition

The sensor conductance was acquired using an IscAlert™ connection unit (CU) with 700 Hz ac conductance measurements using a 50 mV rms sine excitation. Acquisition was made using the IscAlert™ 2.0 software. The sampling rate was one sample every 5 s, which was the highest sampling rate available on the CU. The total length of the analyzed time series was from 2533 samples (3 h 31 min 5 s) at the minimum to 4426 samples (6 h 8 min 50 s) at the maximum. All the time series began at 30 min prior to the first occlusion, but due to differences in the length of the reperfusion phases given between occlusions, the total lengths varied.

Data from one pig were excluded due to ventricular fibrillation after 3 min of occlusion leading to death. The data from two other pigs were excluded due to IscAlert™ sensor malfunction with artifacts burying the signal of interest.
2.5. Drift correction and parameter extraction

The method of drift correction was based on utilization of the time derivative of the pCO2 time series to distinguish between cases of sensor drift and true physiological pCO2 changes in an ischemic heart. In the symbolic form, it is expressed as

\[
\hat{p}(t) = \int_t^\infty \dot{p}(t) \cdot g(\dot{p}(t)) \, dt, \quad g(\dot{p}(t)) = \begin{cases} 1, & \dot{p}(t) > D_{\text{max}} \\ 1, & \dot{p}(t) < D_{\text{min}} \\ 0, & \text{else}, \end{cases}
\]

where \( \dot{p}(t) = \frac{dp(t)}{dt} \).

\( D_{\text{min}} \) and \( D_{\text{max}} \) set the boundaries for the range of \( \dot{p}(t) \) to be categorized as drift. The \( \dot{p}(t) \) of the true responses are in general either higher than \( D_{\text{max}} \) during ischemia or lower than \( D_{\text{min}} \) during reperfusion. However, there can be some overlap between the \( \dot{p}(t) \) of the drift and the last period of the return to baseline upon reperfusion due to its trend of exponential decay. This can cause a slight mismatch between the baselines before and after an occlusion and is solved by letting the \( \hat{p}(t) \) return to baseline by exponential decay with a time constant matching the true decay when the \( \hat{p}(t) \) is close to the defined baseline and the \( \dot{p}(t) \) is within the drift range.

To determine the limits \( D_{\text{min}} \) and \( D_{\text{max}} \), the drifting of the sensors during the experiments was estimated by the difference in the temperature-corrected conductances at \( t_1 \) (30 min before the start of the first occlusion) and \( t_2 \) (35 min after the end of the last occlusion):

\[
D = \frac{1}{t_2 - t_1} (G_{\text{total}}[t_2] - G_{\text{total}}[t_1] - k_T(T[t_2] - T[t_1])).
\]

The median sensor drift was \(-0.11 \mu \text{S h}^{-1}\) with a maximum \(0.0072 \mu \text{S h}^{-1}\) and a minimum \(-0.39 \mu \text{S h}^{-1}\). The variation in the drift among the sensors based on the estimated pCO2 was lower than for the temperature-corrected conductance by comparison of the inter-quartile range divided by the median. Thus, the time derivative of the estimated pCO2 was used in favor of the conductance for the drift-correction algorithm. The median drift in pCO2 was \(-0.38 \text{ kPa h}^{-1}\) with a maximum of \(0.025 \text{ kPa h}^{-1}\) and a minimum of \(-1.37 \text{ kPa h}^{-1}\). This equals a minimum of \(-0.0019 \text{ kPa/5 s}\) between two samples. \( D_{\text{min}} \) was set to \(-0.003 \text{ kPa/5 s}\) and \( D_{\text{max}} \) to \(0 \text{ kPa/5 s}\).

Before differentiation, the pCO2 time series was low-pass filtered to avoid amplification of artifacts in the high-frequency range well above the true responses. The type of the filter was third-order zero-phase Butterworth with a cutoff frequency of 5 mHz.

The following real-time drift correction algorithm was developed and used, presented in the pseudo-code with the input \( x \) and output \( y \):

**Initialization:**

\[ y[0] = \text{baseline} \]

**Continuous update:**

\[
dx[i] = x[i] - x[i - 1] \\
\text{if } dx[i] > \text{dmax and } dx[i - 1] > 0 \text{ and } dx[i - 2] > 0 \\
\text{or } dx[i] < \text{dmin and } dx[i - 1] < 0 \text{ and } dx[i - 2] < 0, \\
\text{then } y[i] = y[i - 1] + dx[i], \\
\text{else } \{ y[i] = y[i - 1]; \text{if } |y[i]| < 1, \text{then } y[i] = y[i] + k (\text{baseline} - y[i]) \}
\]

where \( x[i] \) is the current pCO2 measurement and \( y[i] \) is the current drift-corrected pCO2. The baseline variable can for instance be set to the initial value of \( x \), but was set to zero in
our analysis because we were only interested in extracting the pCO₂ deviation from baseline (ΔpCO₂) for the ischemia detection. The coefficient \( k \) decides the speed of return to baseline when there are offsets below 1 kPa in the absolute value. The conditions on the two previous differentials to be larger than zero for the positive response case or less than zero for the negative response case were added to reduce noise and artifact susceptibility.

The algorithm was applied from 5 min into the time series (25 min prior to the first occlusion) to allow stabilization of the low-pass filter.

In addition to the ΔpCO₂ parameter, its time derivative (TDpCO₂), proportional to the generation rate of CO₂, was also calculated between each of the measurements:

\[
TDpCO₂[i] = \frac{\Delta pCO₂[i] - \Delta pCO₂[i - 1]}{T},
\]

where \( T \) is the sampling period.

For comparison between the ΔpCO₂ and the original pCO₂ measurements without drift correction, the original time series were baseline-adjusted to zero at the 5 min point and low-pass filtered using the same Butterworth filter as for the ΔpCO₂.

All the calculations were done using Matlab® v7.5.

2.6. Statistics

The time series of ΔpCO₂ and TDpCO₂ were split into four intervals, one for each of the occlusions including a range of 15 min prior to the occlusion and 25 min after the reperfusion. The maximum values within these intervals were used to determine the statistical significance between the measurements from the sensors placed in the distribution areas of LAD and LCX. The values could not be regarded as normally distributed based on the Lilliefors test; thus, the Wilcoxon rank-sum test was used for the determination of the \( p \)-values. The same values were used to determine the sensitivity and specificity of the ischemia detection ability during the different occlusions. Using the relation between the specificity and the detection limit, the detection limit for ΔpCO₂ was chosen as the value upon where 100% specificity was reached for all the occlusions (0.45 kPa). The TDpCO₂ detection limit was selected where \( 5/6 = 83\% \) specificity (explained in section 4) was obtained (0.092 kPa min\(^{-1}\)). Sensitivity and specificity was calculated for both parameters as

\[
\text{Sensitivity} = \frac{N_{\text{max}(\text{LAD}) \geq \text{lim}}}{N_{\text{max}(\text{LAD}) \geq \text{lim}} + N_{\text{max}(\text{LAD}) < \text{lim}}},
\]

\[
\text{Specificity} = \frac{N_{\text{max}(\text{LCX}) < \text{lim}}}{N_{\text{max}(\text{LCX}) < \text{lim}} + N_{\text{max}(\text{LCX}) \geq \text{lim}}},
\]

where max(\( y \)) is the maximum ΔpCO₂ or TDpCO₂ in the LAD or LCX region within an occlusion interval, and lim is the selected detection limit for the parameter.

A separate analysis was done for the 15 min occlusion period, where the maximum ΔpCO₂ and TDpCO₂ at 1 min intervals each minute after the onset of the occlusion were extracted and used to calculate the sensitivity versus time. The same detection limits were used for the ΔpCO₂ and the TDpCO₂. The same statistics were also determined for the raw pCO₂ time series for comparison with the detection ability of the ΔpCO₂ using the same detection limit.

The tests were based on a total of 17 sensors from the LAD region and 6 control sensors in the LCX region.

To demonstrate that the presented drift correction method would also work for cases of gradual occlusion, especially with regard to preservation of the true responses, five time
Early detection of cardiac ischemia using a conductometric pCO2 sensor

3. Results

The algorithm corrected the drift for all the sensors while preserving the true physiological responses in the LAD-supplied region (figure 1). For the original data and at close to 3 h, the median baseline wandered to $-1.3$ kPa for the LAD sensors and $-2.3$ kPa for the LCX sensors, while the medians were 0.025 for the LAD and 0.0066 for the LCX when drift correction was applied. At the same time, the inter-quartile ranges of the LAD and LCX sensors were 0.77 and 1.85 kPa, respectively, while for the drift corrected time series they were 0.071 and 0.022 kPa. The true variations in the responses among the sensors during the occlusions were however preserved.

As shown in table 1, the 1 min occlusion led to a hypoxia (baseline was 4.95 kPa) within the LAD-supplied region, while the 3, 5 and 15 min occlusions caused anoxia. The drift-corrected pCO2 ($\Delta$pCO2) had higher maximum values within the occlusion intervals than series from an ongoing study on gradual LAD occlusion were also included. The number of measurements from this protocol was not sufficient for a statistical analysis.

The statistics were also calculated using Matlab® v7.5.
Figure 2. Medians (solid), 25% and 75% quartiles (dotted) for the TDpCO2 in LAD (N = 17) (a) and in LCX (N = 6) (b). The time series in the plots were constructed from the occlusion intervals for synchronicity.

Table 1. Statistics for the original pCO2 (lowpass-filtered and baseline adjusted), the drift-corrected pCO2 ($\Delta$1pCO2) and the time-derivative of the pCO2 (TDpCO2) from the sensors placed in the LAD distribution area.

<table>
<thead>
<tr>
<th>Occlusion duration (min)</th>
<th>Max pCO2 (kPa)</th>
<th>Max $\Delta$pCO2 (kPa)</th>
<th>Max TDpCO2 (kPa min$^{-1}$)</th>
<th>Min pO2 (kPa)</th>
<th>Sensitivity pCO2</th>
<th>Sensitivity $\Delta$pCO2</th>
<th>Sensitivity TDpCO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.10*</td>
<td>0.22**</td>
<td>0.12*</td>
<td>1.60</td>
<td>0.12</td>
<td>0.24</td>
<td>0.65</td>
</tr>
<tr>
<td>3</td>
<td>0.31**</td>
<td>0.69***</td>
<td>0.37***</td>
<td>0.00</td>
<td>0.35</td>
<td>0.82</td>
<td>1.00</td>
</tr>
<tr>
<td>5</td>
<td>0.78**</td>
<td>1.32***</td>
<td>0.45***</td>
<td>0.00</td>
<td>0.76</td>
<td>0.94</td>
<td>1.00</td>
</tr>
<tr>
<td>15</td>
<td>5.25***</td>
<td>5.74***</td>
<td>0.52***</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

The median of the maximum values within the different occlusion intervals among all the LAD sensors is presented along with the median of the minimum pO2 within these intervals, measured by the Neurotrend sensor in the same region. The LAD max values are compared with the LCX max values (data not shown) within the same intervals using the Wilcoxon rank-sum test, *$p < 0.05$, **$p < 0.005$, ***$p < 0.0005$. The sensitivities are calculated with a detection limit of 0.45 kPa (100% specificity) for pCO2 and 0.092 kPa min$^{-1}$ (83% specificity) for the TDpCO2. The statistics are based on 17 LAD sensors and 6 LCX sensors.

the uncorrected pCO2 measurement, leading to a higher detection ability when using a pCO2 threshold. The TDpCO2 already reached a high value relative to the 15 min maximum after 3 min occlusion (table 1, figure 2) when anoxia occurred, leading to an earlier detection ability than the other parameters. Although all parameters yielded 100% sensitivity during the 15 min occlusion, figure 3 shows that this was first obtained at the 15th minute for the pCO2, the 8th minute for the $\Delta$pCO2 and the 4th minute for the TDpCO2, although with 83% specificity. The earliness of the detection ability was expectedly dependent on the detection limit, at the cost of the specificity as the limit is lowered toward zero. This relationship is shown in figure 4 with the time until 100% sensitivity was reached and the specificity is plotted against the detection limit. As presented in figure 5, combining the $\Delta$pCO2 and the TDpCO2 can yield a 100% sensitivity with a 96% specificity for the 3, 5 and 15 min occlusions grouped together.
Early detection of cardiac ischemia using a conductometric pCO2 sensor

Figure 3. Sensitivities at each minute interval after the start of the 15 min occlusion for ΔpCO2 (•) and the original pCO2 (■) measurements with a detection limit of 0.45 kPa (100% specificity) and TDpCO2 (▲) with a detection limit of 0.092 kPa min⁻¹ (83% specificity).

Figure 4. Time to 100% sensitivity after the start of occlusion (⦁) and specificity (◦) versus detection limit for ΔpCO2 (a) and TDpCO2 (b) for the 15 min occlusion.

An example from one sensor during 15 min occlusion with a proposed utilization of the parameters for warning and alarm function is presented in figure 6. Figure 7 demonstrates that the method was also able to remove the drift without removing the true responses for cases of 25%, 50% and 75% LAD flow reduction.

4. Discussion

The drift correction causes stable values when there are slow negative changes in the measured pCO2. The pCO2 has been shown to return to the same baseline after successive occlusions in the same animal experiment, measured with the Neurotrend sensor (Pischke et al 2010a). Thus, we believe that the slow negative changes in the conductometrically measured pCO2 are
Figure 5. $\Delta pCO_2$ versus TD$pCO_2$ plotted on logarithmic scales for the maximum values within the intervals of 3 min ($\circ$), 5 min ($\Box$) and 15 min ($\Delta$) occlusion for the LAD-placed sensors and 1 min ($\bullet$), 3 min ($\bullet$), 5 min ($\blacksquare$) and 15 min ($\triangle$) for the LCX-placed sensors. 1 min LAD is not included as this occlusion did not yield anoxia. The dashed lines show the ability to separate the sensor responses from the ischemic area from those in the non-ischemic area using a combination of the $\Delta pCO_2$ and TD$pCO_2$ as detection limits. In this case, the total sensitivity is 100% with a specificity of 96%.

Figure 5 shows the distribution of $\Delta pCO_2$ and TD$pCO_2$ values for different occlusion periods. The data points are plotted on logarithmic scales to visualize the relationship between $\Delta pCO_2$ and TD$pCO_2$.

As shown in table 1, all the occlusion periods led to changes in p$CO_2$ measured by the sensors placed in the LAD region, which were significantly different ($p < 0.05$) from those placed in the control region LCX. Even though the 1 min occlusion did not lead to a real ischemia with p$O_2$ reaching zero, the small but significant p$CO_2$ increase may have been caused by the reduced flow inhibiting the CO$2$ transport. The drift correction results in a better sensitivity for all the occlusions except for the 15 min event, where both sensitivities are 100%. However, the sensitivity versus time plot in figure 3 shows that within this interval, the event is detected earlier for the drift-corrected p$CO_2$ parameter.

The comparison between the original and the drift-corrected p$CO_2$ as presented in figure 1 shows the ability of the algorithm to extract only the physiologically interesting part of the time series. The evident drift in the negative direction in (a) and (b) eventually causes the offset to become large compared to the detection limit. To detect an ischemic event based on a p$CO_2$ level $L$, the measured p$CO_2$ would first have to increase above this offset and then reach $L$, resulting in an increased detection time as shown in figure 3 for the 15 min occlusion. A short occlusion at this time would perhaps not be detected at all. The offset increases linearly with time, as does the variance due to the differences in the drifting slopes.

The TD$pCO_2$ parameter is much less sensitive to drift. In addition, it brings additional information about the physiological processes by representing the CO$2$ generation rate (Pischke et al 2010a, 2010b), which is not clearly seen by the shape of the p$CO_2$ curves. The transition between stasis and onset of metabolic ischemia could be distinguished by the TD$pCO_2$ parameter as the maximum CO$2$ production will occur only during anaerobic metabolism when an excess of protons has to be buffered. TD$pCO_2$ will stay at its maximum until the substrate supply starts to wane. As the plot in figure 2(a) shows, the maximum TD$pCO_2$
Early detection of cardiac ischemia using a conductometric pCO₂ sensor

Figure 6. ΔpCO₂ (solid) and TDpCO₂ (dotted) before, during and after the 15 min occlusion (● = start, ◦ = end) for one of the sensors in the LAD region. The boxes in the lower end of the plot display different periods which are determined using the detection limits for the two parameters. Case 1 (white area) represents stable conditions when both parameters are below their limits. Case 2 (gray area) is a warning of a beginning ischemia when the TDpCO₂ is above its detection limit but ΔpCO₂ is still low. Case 3 (black area) shows the case of full ischemia when both parameters are above their detection limits. Case 4 (hatched gray area) indicates when the ΔpCO₂ is high but stable, with the TDpCO₂ between its detection limit and the negative drift limit. Case 5 (hatched white area) shows when the ΔpCO₂ is high, but returns toward the baseline with the TDpCO₂ below the negative drift limit.

Figure 7. Median (solid), 25% and 75% quartiles (dotted) for the gradual occlusion time series from five sensors placed in the LAD-supplied region. Low-pass filtered and baseline-corrected original time series (a) and drift-corrected time series (b). From the left, flow reduction responses to 25%, 50% and 75% of the baseline LAD flow for 18 min.

within the 3, 5 and 15 min occlusion intervals are much higher than for the 1 min occlusion, where the pO₂ has not yet reached zero.

There is a trade-off between how early the ischemia can be detected and the specificity of the detection, depending on where the detection limit is set. As shown in figure 4(a),

a reduction in nearly 2 min can be gained by lowering the ΔpCO₂ detection limit from 0.45 kPa to a level which yields 66% specificity. For the TDpCO₂ in figure 4(b), a reduction in only about half a minute is gained by changing the detection limit similarly. We believe that a lowering of the detection limit below what gives 100% specificity is not worth the trade-off, as a high accuracy is desired in the clinical setting (Nass and Fleisher 2002). For the most accurate detection of ischemia, a combination of the ΔpCO₂ and the TDpCO₂ may be used as shown in figure 5 where the upper-right corner represents the cases where both the detection conditions for ΔpCO₂ and TDpCO₂ are met. This will avoid TDpCO₂ type 1 errors from transient artifacts and would avoid ΔpCO₂ type 1 errors if a positive drift or baseline offset should occur. However, in the clinical application it may be more important to avoid type 2 errors than type 1. A suggestion for the utilization of both the parameters is given in figure 6.

During an occlusion, the changes are first detectable with the TDpCO₂ reaching a certain threshold (case 2). This case indicates that excessive CO₂ is being produced but the level is still close to the baseline, which could be implemented by a sort of warning. This warning would then turn to an alarm when the ΔpCO₂ crosses its detection limit (case 3). At some point the ΔCO₂ may be high while the TDpCO₂ is close to zero (case 4). However, this has only been observed transiently in our measurements when the TDpCO₂ changes signs. A high ΔpCO₂ with a negative TDpCO₂ below D_min (case 5) indicates that the blood flow has returned, transporting the excessive CO₂ away from the tissue. This case eventually leads to a stable baseline where both parameters are close to zero (case 1). An additional case could be introduced by the condition of a stable, but high TDpCO₂ as an indicator of full ischemia.

It could be argued that the TDpCO₂ during the beginning of the occlusion may reflect the response characteristic of the sensor instead of the changes in tissue pCO₂. However, Mirtaheri et al 2004a reported the typical positive response time of the sensor to lie between 5 and 10 s while the TDpCO₂ increases for minutes during this phase (figure 6).

The source of the high-frequency artifacts was presumably the mechanical pressure oscillations in the beating heart acting on the sensor membrane causing geometrical changes to the volume of the sensor measurement cell, leading to oscillations in the conductance of the same frequency as the heart rate. With measurements sampled every 5 s, which was the highest available sampling rate using the IscAlert™ connection unit, this artifact was greatly undersampled. This caused alias effects with a low-frequency content close to the true responses to appear on several occasions throughout the time series. Thus, the cutoff frequency had to be set as low as 5 mHz to remove as much alias as possible while keeping the true responses. A 5 mHz low-pass filter with a normal phase response would cause an undesired lag of 65 s. If the sample rate was at or above the Nyquist limit of the artifact, the phase lag would be no more than 2 s. Thus, a zero-phase filter was selected to more accurately determine the properties of the sensor regardless of the limits of the measurement electronics. With an excitation frequency of 700 Hz, oversampling the heart rate while keeping a good signal-to-noise ratio should not be an instrumentation problem. An anti-alias filter in the electronics could be an even simpler solution. Not all the alias could be removed from the time series by the low-pass filter without distorting the physiological signal. The remaining artifacts, although few, small in magnitude and transient, affected the TDpCO₂ parameter, especially in one control sensor. The detection limit of 5/6 = 83% specificity was thus selected to reduce type 2 errors. Because this could be avoided with the appropriate instrumentation, we believe that the TDpCO₂ detection limit truly represents 100% specificity when considering the sensor properties regardless of the acquisition. With respect to detection of ischemia, the TDpCO₂ parameter itself is probably best suited for an early warning with a lesser confidence than the ΔpCO₂ or the combination of the two.
A similar method for real-time drift correction is the use of derivative-based operators in an IIR filter to remove low-frequency artifacts (Rangayyan 2002). This filter has the following time-domain form:

\[ y[n] = \frac{1}{T} (x[n] - x[n - 1]) + \alpha \cdot y[n - 1]. \] (8)

Although the filter has a sharp cutoff toward dc, it is not as sharp as the binary gain obtained using the case dependence in the presented filter algorithm. The pCO2 curve contains important information when its derivative is very close to the limit of the drift. Thus, applying the filter (8) to our measurements would result in distortion of the signal shape during an ischemia, losing information about the course of the episode. This filter also has a nonlinear phase response and a tendency to introduce negative undershoot (Rangayyan 2002). We also need to be able to distinguish between the negative and positive drift because the sensor drift is in the negative direction and preservation of all the positive changes is needed. A conventional high-pass filter would always return the curves toward the baseline, but the presented algorithm allows this to occur only when below a limit of e.g. 1 kPa. A special case which may result in a type 2 error would occur if the pCO2 curve was to flatten out completely below the 1 kPa limit with its time derivative within the defined drift range. However, we believe that this is unlikely to occur for a true ischemic event, as complete flattening has never been observed in any of our occlusions, not even above 1 kPa, and the TDpCO2 will always be significantly higher than zero during anoxia. The negative drift would anyway drive this curve toward the baseline if it was not corrected. As shown in figure 7, the algorithm preserves the pCO2 responses also for lesser degrees of blood flow reduction such as 75%, 50% or 25% of baseline flow.

For cases where the measurements contain single-point spike or step artifacts, including new limits in the algorithm for the highest allowed difference between the neighbor points will eliminate these. \( g(\dot{p}(t)) \) in (4) is then redefined to include the lowest allowed positive neighbor difference, \( A_+ \), and the lowest allowed negative neighbor difference \( A_- \) to be regarded as a spike:

\[
g(\dot{p}(t)) = \begin{cases} 
1, & \dot{p}(t) \in \{D_{\text{max}}, A_+\} \\
1, & \dot{p}(t) \in \{D_{\text{min}}, A_-\} \\
0, & \text{else}.
\end{cases}
\] (9)

However, when periodic high-frequency noise is superimposed as in the case of the measurements presented in this paper, a smoothing low-pass filter is necessary in order to preserve the more low-frequent true physiological measurement.

In summary, the following points should be met when applying this method for real-time automatic ischemia detection using the conductometric pCO2 sensor:

- Common for invasive biosensors, there will be an initial stabilization phase after insertion. Applying the drift correction algorithm too early may include such transients in the \( \Delta pCO_2 \), resulting in type 1 errors.
- The slope of the drift has to be separable from the slopes of the true responses. Although there is some overlap between the drift range of \( \dot{p}(t) \) and the \( \dot{p}(t) \) at the tail of the reperfusion phase for the sensor used in this study, this is the least critical part of the event. If the drift however would occur in the positive direction, with a large interindividual variation in slope, the early detection accuracy would be reduced.
- Artifacts in the high-frequency range should be reduced as much as possible in order to avoid TDpCO2 type 1 errors, either by analog or digital filtering, but with a minimum of the phase lag.
In addition, rapid and large temperature fluctuations in the tissue may result in type 1 errors. The closed heart model used in this study ensured stable temperatures and consequently no temperature-induced artifacts in the measurements were observed.

In conclusion, the results show that a good accuracy for early real-time detection of cardiac ischemia is possible despite the inherent sensor drift when using the presented parameterization method.

Acknowledgment

Tronstad C and Pischke S E were financially supported by the Research Council of Norway.

References

Drake H F and Treasure T 1986 Continuous clinical monitoring with ion-selective electrodes: a feasible or desirable objective Intensive Care Med. 12 104–7
Guth U, Vonau W and Zosel J 2009 Recent developments in electrochemical sensor application and technology—a review Meas. Sci. Technol. 20 042002
Kvarstein G, Mirtaheri P and Tønnessen T I 2004 Detection of ischemia by PCO2 before ATP declines in skeletal muscle Crit. Care Med. 32 675–2
Pischke S E, Tronstad C, Holljem L and Tønnessen T I 2010a Real-time measurement of myocardial CO2 tension and CO2 generation rate reliably detects intermittent myocardial ischemia in a porcine model Circulation submitted
Early detection of cardiac ischemia using a conductometric pCO$_2$ sensor

Steuer J, Granath F, de Faire U, Ekbom A and Stahle E 2005 Increased risk of heart failure as a consequence of perioperative myocardial injury after coronary artery bypass grafting Heart 91 754–8

Tønnessen T I 1997 Biological basis for PCO$_2$ as a detector for ischemia (review) Acta Anaesthesiol. Scand. 41 659–69


Varlan A R and Sansen W 1997 Micromachined conductimetric p(CO$_2$) sensor Sensors Actuators B 55 309–15


Zhao P and Cai W J 1997 An improved potentiometric pCO$_2$ microelectrode Anal. Chem. 69 5052–8