Continuous glucose and exhaled breath analysis in the Intensive Care Unit
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ABSTRACT

**Introduction**: Continuous glucose monitoring (CGM) can be beneficiary in critically ill patients. Current CGM devices rely on subcutaneous or blood plasma glucose measurements and consequently there is an increased risk of infections and the possibility of loss of blood with each measurement. A potential method to continuously and non-invasively measure blood glucose levels is using exhaled breath. A correlation between blood glucose levels and volatile organic compounds (VOCs) in the exhaled breath was already reported. VOCs can be analyzed continuously using a so-called electronic nose (eNose). We hypothesize that continuous exhaled breath analysis using an eNose can be used to accurately predict blood glucose levels in intubated, mechanically ventilated ICU-patients.

**Methods**: Mechanically ventilated patients whose blood glucose concentration was monitored with a CGM device were eligible. An eNose with 4 metal oxide sensors was used to continuously measure changes in exhaled breath. After pre-processing the data, several regression models were trained, consisting of: (1) only eNose sensor values. (2) only the 1st and 2nd principal components (PC) of eNose values. (3) eNose sensor values and last known blood glucose value as random effect. (4) 1st and 2nd PC of eNose sensor values and CGM value of one minute ago as fixed effect. (5) CGM value of one minute ago as fixed effect. Model performance was measured using the R² value, the Akaike Information Criterion (AIC) and the Clarke error grid.

**Results**: 23 patients were included in the study and 1165 hours of measurements were collected. Performance was low in model 1, 2 and 3 with a mean R² of 0.07 [95%-CI: 0.00 – 0.28], 0.10 [95%-CI: 0.00 – 0.40] and 0.30 [0.02 – 0.79], respectively. Performance in models 4 and 5 was better with a mean R² of 0.77 [0.02 – 1.00]. Subsequently, eNose data in model 4 had no added value over using CGM only in model 5.

**Conclusion**: In our study, continuous exhaled breath analysis using an eNose cannot be used to accurately predict blood glucose levels in intubated, mechanically ventilated ICU-patients.

**Keywords**: eNose, breath, analysis, glucose, critically ill, continuous

INTRODUCTION

Dysglycemia, and glycemic variability are associated with an increased risk of morbidity and mortality in critically ill patients [1-3]. While there is no consensus whether tight glucose control is beneficiary for patients on the intensive care unit (ICU) [4-6], it has been suggested that continuous glucose monitoring (CGM) will improve glucose control. The CGM devices that have been developed so far rely on subcutaneous or blood plasma glucose measurements and consequently there is an increased risk of infections, the possi-
bility of loss of blood with each measurement and discomfort for the patient. Additionally the accuracy for the prediction of blood glucose greatly varies between devices [7]. A potential method to continuously and non-invasively measure blood glucose levels is using exhaled breath [8]. Since the majority of ICU patient is ventilated, collection of exhaled breath would not be invasive for these patients.

**Exhaled breath analysis**
The scent of acetone in the breath of patients with diabetic keto-acidosis is a famous example of breath analysis and supports the theory that blood glucose levels may be measured via analysis of exhaled volatile organic compounds (VOCs) [9]. Recently, exhaled breath had been investigated as a diagnostic tool in various medical domains [10] using several technologies [11]. Several researchers have found a correlation between blood glucose levels and concentrations of different VOCs in the exhaled breath of healthy volunteers and diabetic patients [8]. However, there are currently no reports on continuous exhaled breath analysis for the monitoring of the plasma glucose concentration.

Many studies use gas chromatography and mass spectroscopy (GC/MS) for breath analysis [12-14]. This technique takes a detailed snapshot of VOCs in breath but is not suitable for use in clinical practice as it is relatively expensive, not available at the bedside and time-consuming. VOCs can also be analyzed continuously and at the bedside, using a so-called electronic nose (eNose) [15]. eNoses rely on a cross-reactive sensor array to detect changes in VOC-profiles. These breath fingerprints can subsequently be used to train an algorithm that aims at predicting the plasma glucose level. We hypothesized that continuous exhaled breath analysis using an eNose could be used to accurately predict blood glucose levels in intubated, mechanically ventilated ICU-patients.

**METHODS**
Mechanically ventilated patients included in one of two other studies conducted in the ICU of the Academic Medical Center, Amsterdam, the Netherlands were eligible [16,17]. These studies investigated CGM devices and therefore plasma glucose concentration was monitored continuously. Patient age had to be > 18 years and anticipated life expectancy had to be > 96 hours. When patients were not expected to survive for a considerable amount of time, they were excluded. The Institutional Review Board of the Academic Medical Center approved the two aforementioned studies but concluded that the legislation on human participation in research was not applicable on this study because of its non-invasive nature and the need for informed consent was waived. The study was conducted in the 34 bed mixed medical/surgical ICU of the Academic Medical Center in Amsterdam, the Netherlands.
Standard of care for ventilated patients
Intubated and mechanically ventilated patients on the ICU of the Academic Medical Center in Amsterdam were ventilated according to a standardized protocol. This protocol included, but was not limited to: tidal volume between 6 and 8 mg/kg predicted body weight and Positive End Expiratory Pressure (PEEP) ≥ 5 cm H2O. In addition, a pulmonary toilet and nebulization of salbutamol and acetylcysteine were performed every 6 hours. Patients were routinely ventilated with passive humidification with a heat-moist exchanger. Blood gas analysis with the measurement of glucose were performed three times per day at minimum, or more frequently when deemed necessary.

Study design
Exhaled breath measurements initiated when CGM measurements were started in a mechanically ventilated patient. Breath was monitored continuously for the entire duration of CGM measurements and mechanical ventilation. Continuous breath measurements were halted when either CGM measurements or mechanical ventilation was stopped.

Continuous glucose measurements
Glucose was measured using one of two different CGM devices and was stored every minute. Sentrino® (Medtronic MiniMed, Northridge, CA) is a CGM that measures interstitial glucose levels using a subcutaneous sensor. EIRUS® (Maquet Critical Care AB, Solna, Sweden) used a specialized central venous catheter to measure blood glucose using microdialysis. CGM measurements were saved every minute on the measurements device and exported when measurements were done. Both devices were used on the ICU as part of clinical research into their accuracy.

Exhaled breath data collection
Breath was monitored using an eNose that was specifically adapted for continuous clinical use in the ICU (Comon Invent, Delft, the Netherlands). A similar device has been described in earlier studies [18]. The eNose consisted of one sensor array with 4 metal oxide sensors (Figaro, Osaka, Japan), chosen for their stability and safety, a roller pump for a continuous flow of exhaled breath, a plastic body that can easily be cleaned and an offline mode to prevent interference with other medical devices at bedside. Using a T-piece, the eNose was connected to the expiratory tube of the ventilator. Metal oxide and humidity sensor data were stored every minute.
Pre-processing
Data were pre-processed to diminish noise introduced by normal patient care. These sources of noise include time delay of sensors to reach steady state, changes in humidity in the side-stream connector, disconnections and nebulization of medication and changing ventilator settings. We have discussed our approach and considerations in a previous study [19].

Model development
Using the pre-processed data, several linear mixed effects models were trained, these models are used for the analysis of continuous dependent and independent variables with a grouping variable that serves as random intercept. In this way a linear regression coefficient is obtained for all independent variables, while correcting for correlated data within a patient. We developed the following models:

1. A linear mixed model with patient ID as random intercept and the four different sensors as fixed effects. This model only used pre-processed eNose data and is the simplest: Predicted Blood Glucose Level ~ eNose sensors + Patient ID as intercept.
2. A model similar to model (1), but using principal components obtained from the four metal oxide sensors: Predicted Blood Glucose Level ~ First two principle components of eNose sensors + Patient ID as intercept.
3. A model similar to model (2) with the last measured blood glucose value as random intercept. As blood glucose was measured at least three times a day, the last measurement was taken between 0 and 8 hours before the predicted value. By using the last known blood glucose value as random effect, this model essentially recalibrated when a new blood glucose value was available: Predicted Blood Glucose Level ~ First two principle components of eNose sensors + Patient ID and last known blood glucose value as intercept.
4. A model similar to model (2) with the CGM value of one minute ago as fixed effect. This method could possibly be used to predict the trend of the signal using the eNose: Predicted Blood Glucose Level ~ First two principle components of eNose sensors + CGM value of 1 minute ago + Patient ID as intercept.
5. A model without any eNose sensor data, with the CGM value of 1 minute ago as fixed effect. This model can be used to compare the added value of eNose measurements: Predicted Blood Glucose Level ~ CGM value of 1 minute ago + Patient ID as intercept.

Model performance
Performance of the developed models was measured using the coefficient of
determination $R^2$ and the Akaike Information Criterion (AIC). The $R^2$ ranges between 0 (model explains no variance) and 1 (model explains all variance). The AIC penalizes the likelihood of the model based on model complexity. Therefore, the higher the number of variables and thus complexity, the higher the penalty. In this way, model complexity and likelihood are balanced and the model with the lowest AIC will tend to resist overfitting. The AIC value is useful for comparing models but by itself is not informative. Additionally, a Clarke Error Grid, often used in studies evaluating glucose measurement devices, was used to measure point accuracy [20]. There are 5 zones in this grid and >95% of the samples should be in zone A, with a maximum of 5% in zone B to classify the method as accurate [21].

RESULTS

eNose data and CGM data were collected in 23 patients between October of 2012 and July of 2015. A total of 1165 hours of paired CGM eNose measurements were collected with a median duration of 51 (Interquartile range [41 – 65]) hours per patient. Included patients had a median APACHE II–score of 22, a median SAPS II–score of 52 and a median length of stay on the ICU of 12 days. Twenty-one patients were medical admissions, while 2 were planned surgery admissions. Patient characteristics are described in Table 1.

Performance of the eNose as stand-alone test

In Models 1 and 2, in which only use eNose data as predictors, model performance (table 2) had a mean $R^2$ of 0.07 [95%-CI: 0.00 – 0.28] and 0.10 [95%-CI: 0.00 – 0.40] and an AIC of 317503 and 317529, respectively. 73.2% of values in zone A of the Clarke error grid in both models. Model predictions were plotted in Figure 1 for 1 patient. Model coefficients can be found in Table 3.

Performance of the eNose in conjunction with previous glucose measurements

Performance of model 3, in which the last known blood glucose value was added as random effect, had a mean $R^2$ of 0.30 [0.02 – 0.79] and an AIC of 288561. 78.9% of values were in zone A of the Clarke error grid.

Model 4, with the CGM value from one minute before as fixed effect, had a mean $R^2$ of 0.77 [0.02 – 1.00] and an AIC of 277301. 85.7% of values in zone A of the Clarke error grid. Similar to model 4, but without any eNose data, model 5 performed similar with a mean $R^2$ of 0.77 [0.02 – 1.00] and an AIC of 277320 and 85.7% of values in zone A of the Clarke error grid. While the addition of eNose variables in model 4 improved the model significantly ($p = 1.386e-08$) compared to model 5, the quantity of model performance improvement was negligible.

DISCUSSION

Performance of model 1 through 3 is low and as seen in model 5, good perfor-
mance of model 4 is completely due to inclusion of the last known blood glucose level. Therefore, our findings suggest that continuous exhaled breath analysis using an eNose cannot be used to accurately predict blood glucose levels in intubated, mechanically ventilated ICU-patients.

In contrast to our findings, several other studies were able to find a correlation between exhaled breath and blood glucose levels [8,22-27]. In a systematic review by our group, we found that 7 studies reported a correlation with a mean linear regression coefficient of 0.82 [range: 0.08–0.98] between one or more VOCs in exhaled breath, and blood glucose levels [8]. In these studies, an oral glucose tolerance test or clamp study design was often used, which resulted in a predictable trajectory of blood glucose levels. Results were positive in healthy and type 1 diabetes mellitus subjects, but no correlation could be found in type 2 diabetes mellitus patients [28,29]. Studies under less controlled circumstances, such as the present study, have not been reported on yet. In addition, none of these studies used an eNose for exhaled breath measurements. A study that used similar sensors as our eNose was able to distinguish healthy subjects from diabetic patients [30]. However, subject-specific prediction models were used to compensate for inter-subject variance, which makes the results not generalizable to clinical practice.

There are several possible explanations for the low performance of this eNose for continuous measurement of glucose levels in critically ill patients. Large inter-patient variation in critically ill ICU patients makes it harder to use a single predictive model. Metabolites linked to glucose levels, including acetone, ethanol, methanol and propane vary in quantity between healthy individuals with similar glucose levels [8]. In critically ill patients, differences in gut microbiome, also due to varying antimicrobial therapy, further differentiate levels of exhaled VOCs linked to glucose levels [31]. In addition, markers of oxidative stress that are found to be related to high blood glucose levels will be non-specific, as they will also increase with conditions common in the ICU population such as sepsis and acute respiratory distress syndrome [32].

In addition to inter-patient variation, the sensors in the eNose used in our study were possibly not specific enough. While the non-specific sensors in the eNose might be able to pick up differences in breath composition between healthy subjects and patients with a single medical condition such as asthma or lung cancer [18], it may not be possible to use the device in critically ill patients with multiple illnesses [33,34]. Each specific medical condition supposedly has a unique breathprint. With comorbidity, these breathprints may be overlaid within the breath of a single person, which makes it difficult, if not impossible, to infer the state of the disease of interest. This is a major challenge for the clinical application of any electronic nose type breath test, which has to be addressed more thoroughly in the future.
This study has several limitations. First, in order to get a reference standard with a high number of subsequent measurements, we opted to only include patients monitored by CGM. As our hospital only has access to CGM devices used in a study setting, and study patients were limited, we had little control over patient selection. Therefore, patients in our study were admitted for a wide variety of conditions, which may have increased inter-subject variation and therefore decreased the performance of the model. Second, we used an eNose that did not contain sensors that were specifically selected for sensitivity to VOCs of interest in glucose monitoring. Therefore, it is likely that the reported accuracy is an underestimation of the potential of a perfectly adapted eNose. However, performance is so low at the moment, that even with considerable improvements, the eNose would not be likely to accurately predict blood glucose levels in critically ill ICU patients. There were also several strengths to this study. It was the first study to continuously measure exhaled breath in critically ill patients using an electronic nose. In addition, a wide variety of data analysis methods were used for eNose model development, and several metrics were used to evaluate model performance. Finally, this is the first study to evaluate breath analysis for glucose monitoring in a clinical setting, and not in a clamp or glucose infusion study with predictable glucose dynamics. The results of this study have several implications. Further exhaled breath analysis research in critically ill patients should include concurrent measurements with GC–MS to better understand differences in breath profiles between patients. While the results of these measurements can in turn be used to develop an eNose with more specific sensors suitable for continuous glucose measurements in mechanically ventilated critically ill patients, it is unlikely that cross-reactive sensors used in eNoses are sensitive enough for continuous measurement of blood glucose in exhaled breath.

CONCLUSION

In our study, continuous exhaled breath analysis using an eNose cannot be used to accurately predict blood glucose levels in intubated, mechanically ventilated ICU-patients.

References


FIGURES

Figure 1.
Example of the 5 different models in 1 patient. Predictions of the 5 different models. CGM device measurements are indicated by the black dashed line.

TABLES

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, median [IQR]</td>
<td>67 [62 – 75]</td>
</tr>
<tr>
<td>Male gender, number (%)</td>
<td>9 (39%)</td>
</tr>
<tr>
<td>Admission type, number (%)</td>
<td></td>
</tr>
<tr>
<td>– Medical</td>
<td>21 (91%)</td>
</tr>
<tr>
<td>– Planned Surgery</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>APACHE II, median [IQR]</td>
<td>22 [19 – 28]</td>
</tr>
<tr>
<td>SAPS II, median [IQR]</td>
<td>52 [42 – 65]</td>
</tr>
<tr>
<td>ICU LOS, days, median [IQR]</td>
<td>12 [9 – 15]</td>
</tr>
<tr>
<td>ICU mortality, number (%)</td>
<td>10 (43%)</td>
</tr>
<tr>
<td>Measurement duration, median [IQR]</td>
<td>51 [41 – 65]</td>
</tr>
</tbody>
</table>

Table 1.
Patient characteristics| IQR, Interquartile range; BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; SAPS II, Sepsis-related Organ Failure Assessment score II; ICU, Intensive Care Unit; LOS, Length of stay.
<table>
<thead>
<tr>
<th>Model</th>
<th>$R^2$ (mean [Range])</th>
<th>AIC</th>
<th>CEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Pre-processed eNose values.</td>
<td>0.07 [0.00 – 0.28]</td>
<td>317503</td>
<td>73.2%</td>
</tr>
<tr>
<td>2: 1st and 2nd PC of eNose values.</td>
<td>0.10 [0.00 – 0.40]</td>
<td>317529</td>
<td>73.2%</td>
</tr>
<tr>
<td>3: Pre-processed eNose values and last known blood glucose value as random effect.</td>
<td>0.30 [0.02 – 0.79]</td>
<td>288561</td>
<td>78.9%</td>
</tr>
<tr>
<td>4: 1st and 2nd PC of eNose values and CGM value of one minute ago as fixed effect.</td>
<td>0.77 [0.02 – 1.00]</td>
<td>277301</td>
<td>85.7%</td>
</tr>
<tr>
<td>5: CGM value of one minute ago as fixed effect.</td>
<td>0.77 [0.02 – 1.00]</td>
<td>277320</td>
<td>85.7%</td>
</tr>
</tbody>
</table>

Table 2.  
AIC, Akaike Information Criterium, CEG, Clarke error grid, PC, Principal Component, CGM, Continuous glucose measurement.