Continuous glucose and exhaled breath analysis in the Intensive Care Unit

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Chapter 10

Summary and General Discussion

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The objectives of this thesis outlined in the introduction were divided into three parts. First, we aimed to compare and test different (continuous) blood glucose measurement methods (part I). Second, we aimed to predict blood glucose levels by analysis of exhaled breath in intubated and ventilated ICU patients (part II). Finally, we aimed to investigate further development of exhaled breath analysis techniques and data analysis methods (part III). In this chapter, we will summarize the three parts of this thesis and will draw final conclusions, followed by future perspectives.

**SUMMARY**

**Part I**

Chapters 2-4 of this thesis show that many different techniques are currently being investigated and used for the continuous measurement of blood glucose levels in patients in the ICU [1-3]. Most methods of the studied blood glucose measurement systems require the insertion of a catheter in the blood stream or measure subcutaneously and are thus invasive in one way or another. Also, while measurement accuracy is often good, continuous glucose measurement methods tend not to be as accurate as point of care-based methods, which are used in daily practice. The interstitial continuous glucose monitoring (CGM) device tested in chapter 3 performed poorly with only 77% of 929 comparative measurements in zone A of the Clarke error grid [2]. Therefore, it did not meet the set accuracy standards set by consensus implying that 95% of paired values need to be in zones A of the Clarke error grid to qualify a device as point accurate [4]. In addition, many reliability problems concerning the subcutaneous sensors were encountered. With 93.6% of values in zone A of the Clarke error grid in the study using a micro-dialysis-based device in chapter 4, accuracy was moderate to good [3]. However, these results indicate that this device also does not meet the standards. As in the study in chapter 3, there were reliability problems: both glucose sensors and specialized central venous catheters had to be replaced prematurely, or where malfunctioning unexpectedly. Therefore, it cannot be recommended that any of the tested devices is used in clinical practice before these practical problems are overcome.

**Part II**

We set out to review literature available on the correlation between volatile organic compounds (VOCs) in exhaled breath and the plasma concentration of glucose to evaluate the state of the art evidence. In chapter 5, we showed that seven out of nine studies included in our systematic review indeed found a strong correlation between VOCs in exhaled breath and blood glucose levels [5]. Glucose levels were associated with VOCs such as ketone bodies, VOCs produced by gut flora, exogenous compounds and markers of oxidative stress.
While many of these studies used an oral glucose tolerance test or clamp study design, which resulted in a predictable trajectory of blood glucose levels, it does indicate that using exhaled breath for prediction of blood glucose is feasible. Because of the chosen study design in the literature and the non-continuous fashion of the measurements, we had no indication on how breath analysis for glucose prediction would perform in an ICU setting. In addition, there had not been any continuous eNose measurements in critically ill ICU patients. Therefore, we had to investigate how to filter possible noise from the derived signal. In chapter 6 this was investigated by continuously monitoring exhaled breath in 23 ICU patients for a total of 1251 hours [6]. Ventilator variables were also collected prospectively. We aimed to investigate whether changes in humidity in the side-stream, patient-ventilator disconnections and changes in ventilator settings introduced noise into the signal, and to discuss several approaches to reduce this noise. We found that humidity in the side-stream had an effect on eNose sensor values and were able to correct for this. Also, sensor values were associated with end-tidal CO₂, tidal volume and the pressure variables and were corrected accordingly. This study paved the way to investigating the correlation between the eNose signal, and continuous glucose measurements in Chapter 7. The same dataset collected in the previous chapter was combined with CGM values collected in chapter 2 and 3 [7]. A total of 1165 hours of paired measurements in 23 patients were investigated. We hypothesized that continuous exhaled breath analysis using an eNose could be used to predict blood glucose levels in intubated and mechanically ventilated ICU-patients. We tested several regression models to correlate the two signals but we were not able to find a meaningful correlation between the two. This was in contrast to previous studies under controlled conditions that did find a strong correlation between exhaled breath and blood glucose [5]. A possible explanation for why we were unable to find a correlation was large inter-patient variation in ICU patients. Due to their critical illness, ICU-patients may have great variance in VOCs in exhaled breath. Additionally, the sensors in the eNose used in this study were possibly not specific enough in detecting VOCs that are associated with changes in glucose levels.

Part III
Chapter 8 of this manuscript dives into the different methods used throughout the field for the analysis of eNose data [8]. Our objective for this manuscript was to investigate which statistical methods were best for eNose data analysis. To get an insight into the current state of the art on pre-processing, classification and validation, we systemically reviewed the literature and listed all the statistical analyses and validation techniques that were used. A total of 64 studies were included in our analysis. Authors of studies that included an
external validation cohort were contacted and asked to share their original datasets with us to compare the analysis methods we found. Four datasets were used for the comparison. No single combination of dimension reduction and classification methods gave consistently better results between internal and external validation sets in this sample of four datasets. Also, performance of analysis methods was compared between the training cohort, after internal validation, and after external validation to assess the external validity of the performance. As expected, performance of the classification methods decreased after internal validation, and decreased further after external validation. We concluded that it is not meaningful to estimate diagnostic performance without external validation and that several classification methods should be assessed when performing studies on eNose data. Authors should set out to define the statistical techniques they will use before finalizing the data and should report adhering strictly to their analysis plan. In Chapter 9, we studied whether or not it is safe to investigate air coming from the membrane of extracorporeal support devices. Also, we compared signals to those in exhaled breath. We hypothesized that there is a correlation between VOCs in exhaled breath and VOCs collected in extracorporeal support devices for VOCs that are known to be of non-pulmonary origin. After assessment of the safety of connecting a breath-sampling device to four different extracorporeal support membranes, ten critically ill patients were monitored in this study. This was done by using an eNose to continuously monitor breath and air from extracorporeal support devices at the same time. In addition, a daily sample for analysis by gas chromatography and mass spectroscopy (GC-MS) was simultaneously taken at both sites. We found that eNose signals showed a moderate correlation ($R^2$ between 0.25 and 0.44) between the two measurement sites. Using GC-MS, we found that 96 VOCs were present both in breath and air from the extracorporeal support devices. Of these 96, 29 correlated significantly between the two sites, of which 17 were identified. VOCs that did not correlate were found in a higher concentration in breath than in air from the extracorporeal support devices, suggesting pulmonary production of these molecules. The results of this study suggest that in critically ill patients, VOCs that are most likely of non-pulmonary origin could be measured reliably in air coming from the membrane of extracorporeal support devices.

**GENERAL DISCUSSION**

A wide number of different techniques for glucose measurement are currently studied on the ICU. All of these techniques are invasive to a varying extent and most are not as accurate as point of care methods that are routinely available. In addition, the tested CGM devices have varying accuracy and low reliability due to problems with sensors and other disposables. While there is hope that
CGM can be beneficial for ICU patients, both in quality and safety of blood glucose control, this is still up for discussion. In a systematic review, we found that studies suggest that there is a possible association between VOCs in exhaled breath and blood glucose levels. However, designs of the studies reviewed in chapter 5 all lead to a very predictable trajectory of blood glucose levels. In addition, patients in these studies were fairly similar and apart from having DM type 1 & 2, lacked many co-morbidities. Therefore, it is likely that an actual breath-based glucose measurement device can be developed for this particular group of patients. Trying to get similar results in critically ill ICU patients using a continuous eNose however, was not successful. This means that currently, continuous exhaled breath analysis using an eNose cannot be used to accurately predict blood glucose levels in intubated, mechanically ventilated patients. Large inter-patient variation and a limited specificity of the used sensor array are the most likely cause for this. Nonetheless, we now have a clear picture on the sources of noise that disturb the eNose signal in this group of patients and know how to filter this noise out. A breath based technique for glucose measurement in this group though, is still far from reality.

A wide variety of statistical techniques are used when analyzing eNose datasets. When comparing these techniques, there does not seem to be a single best method for analysis of eNose data. Therefore, several (combinations of) analysis techniques should be tested. The data clearly show that it is not meaningful to interpret study performance without use of an external validation set to check the obtained results. Finally, it seems safe to monitor air coming from the membrane of extracorporeal support devices. We found that there is a moderate overall correlation between exhaled breath and air coming from the membrane of extracorporeal support devices. This correlation was better for VOCs thought to be of non-pulmonary origin. VOCs that did not correlate between the two sites were found in a higher concentration in the exhaled breath, suggestive of an alveolar or interstitial source of production.

The results of the various chapters in this thesis call for investing in further research in several topics. While most clinicians agree that some form of glycemic control is necessary, the optimal range of blood glucose is still unknown [9]. This should therefore be the main focus of studies on glycemic control in the ICU. To further investigate whether glucose can be monitored through exhaled breath several steps could be taken. First, the continuous eNose used in our study should be adapted to contain sensors which are more sensitive to the VOCs we found in our systematic review. Second, a more homogenous group of intubated and ventilated patients with a smaller number of co-morbidities should be investigated to determine the potential of the technique. A possibility would be to use patients who undergo non-critical surgery.
This would minimize inter-patient variation and would possibly yield better results. As for the analysis of air coming from the membrane of extracorporeal support devices, more research is necessary. The first experiments as described in chapter 9 show promise but were performed under sub optimal conditions. Future studies should have a pre-defined group of patients, preferably using one type of extracorporeal support membrane. In addition, more clinical parameters should be registered continuously.

FUTURE PERSPECTIVES

The data analysis methods used in several chapters of this thesis can be considered machine learning techniques. These techniques enable researchers and physicians to increasingly rely on computers to make decisions for them based on previous collected data. While computerized decision support systems (CDDS) previously relied on hard-coded rules programmed by their developers, it is now possible that these systems make their own conclusions based on the data we feed in. This enables the systems to keep improving while they gather new data, and most importantly, learn from their mistakes. While a simple CDDS may only need little knowledge to function, more complex problems can only be solved with a large amount of data. It is therefore important that investments are made in platforms that enable researchers to share their (anonymized) patient data for others to use. Ideally, this is combined with a world-wide network of computers to analyze this immense amount of data. This method of extreme-parallel computing, already successfully used in the search for extra-terrestrial life [10] and gene folding [11], will help to vastly speed up the process of analyzing large datasets. Continuous eNose data combined with the many clinical parameters gathered in intensive care units today is the perfect candidate for such a platform. We must however keep in mind that while these approaches may make the use of highly intelligent CDDS a reality, they will most likely solely act as a tool for physicians for the years to come because personal contact between patients and their doctor is hard to replace.

References

diagnostics in critically ill patients in comparison to continuous glucose monit... - PubMed - NCBI. J Breath Res 2017, 11, 026002.


