Exhaled breath analysis for the diagnosis of pneumonia

van Oort, P.M.P.

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SUMMARY
Chapter 9

EXHALED BREATH ANALYSIS FOR THE DIAGNOSIS OF PNEUMONIA

In chapter 1, the general introduction, we laid out the problem and rationale behind the studies included in this thesis. In short, VA-LRTI represents the most common complication of mechanical ventilation. Current diagnostics are time-consuming, making a prompt and accurate diagnosis challenging. Exhaled breath may contain volatile organic compounds (VOCs) that derive from pathophysiological processes, either from pathogens or from the host in response to infection. The promising new field of exhaled breath metabolomics may provide new perspectives for the diagnosis of VA-LRTI.

The primary aim of this thesis was to study the diagnostic value of exhaled breath analysis for VA-LRTI. Not only did we aim to examine the ability of breathomics to differentiate between pneumonia patients and patients with negative cultures, also the potential to distinguish between different causative pathogens was investigated.

Chapter 2 showed that most of the available studies on exhaled breath analysis for diagnosis of pneumonia (published before March 2017) solely provided proof-of-concept data, came with a substantial risk of bias and often did not test a clearly pre-defined hypothesis. There was a wide variation of results among these studies, due to the lack of standardization of the applied collection and analytical methods, confusing interpretation of the results. It was concluded that combinations of VOCs in breath had good diagnostic accuracy for pneumonia within the specific study populations (internal validity) but lacked reproduction in other cohorts (external validity). At present, no breath test delivered sufficient diagnostic accuracy to enable clinical implementation.

In chapter 3, two different breath sampling techniques were compared using an ex vivo ventilator circuit. Breath sampling via both methods had been used in previous studies. One method was completely non-invasive and the other was referred to as “semi-invasive" due to the use of a suction catheter that requires manual insertion down the endotracheal tube. The injection of a test VOC mix followed by air sampling using both methods was analysed via gas chromatography-mass spectrometry (GC-MS). Subsequently these results were compared to analysed breath from clinically sampled intensive care unit (ICU) patients. Both methods had their strengths and limitations, as discussed in chapter 3. The non-invasive character of exhaled breath analysis is one of great advantage for clinical ICU practice. Current diagnostics for VA-LRTI (endotracheal
aspirate or protected specimen brush samples or bronchoalveolar lavage, BAL) require invasive procedures. As a result, the investigated non-invasive method seemed to be more eligible for widespread clinical implementation and this technique was used in the studies discussed in the following chapters. Especially when further developed in the future, it showed potential to be used for real-time analysis at the bedside.

In chapter 4 we described the study protocol of the prospective multicentre observational clinical BreathDx study, including patients suspected of ventilator-associated pneumonia (VAP) patients. This study was designed in accordance with the problem sketched in the general introduction: antibiotic use may be limited when breathomics can discriminate between patients suspected of VAP who have confirmed positive cultures and those who have negative cultures. Also, a highly specific test enabling identification of the causative pathogen might lead to a more targeted antimicrobial therapy in these patients.

In chapter 5 a number of VOCs were found that discriminated (1) between patients with confirmed pneumonia compared to patients without signs of pneumonia and without colonized airways; and (2) between colonized patients and non-colonized patients, irrespective of a clinical suspicion of pneumonia. Interestingly, abundances of all of these discriminative VOCs were decreased in the breath of the cases versus the controls.

In chapter 6 we investigated the performance of exhaled breath metabolomics for discrimination between specific pathogens in an animal model. Rats received an intratracheal inoculation of either Streptococcus pneumoniae, Pseudomonas aeruginosa or saline (NaCl solution). The exhaled breath samples were analysed with GC-MS as well as with selected ion flow tube–mass spectrometry (SIFT-MS). Using GC-MS, the exhaled breath of rats with respiratory infection could be distinguished from that of uninfected controls with good accuracy with area under the receiver operating characteristic curve (AUROCC) of 0.85. An even better accuracy (AUROCC 0.98) was seen for the discrimination between the two different pathogens. For these comparisons, SIFT-MS resulted in lower AUROCCs of 0.54 and 0.89 respectively. These results indicated that the focus of breathomics might have to be shifted from primarily detecting general presence of infection, to discrimination between specific pathogens.
In chapter 7 we performed a post-hoc study into the predictive value of soluble urokinase plasminogen activator receptor (suPAR) for VAP. Plasma suPAR levels were measured three days before and on the day of VAP diagnosis. SuPAR concentrations were significantly elevated in confirmed VAP patients compared with controls for both measuring days. For the prediction of VAP, suPAR showed an AUROCC of 0.68 on its own. C-reactive protein (CRP) had an AUROCC of 0.68 and procalcitonin (PCT) 0.73. Combining the three resulted in an AUROCC of 0.91. In order to investigate the diagnostic accuracy, the suPAR levels were measured on the day of diagnosis (versus three days before diagnosis for the predictive value). Also here, the AUROCC was much higher when biomarkers were combined. In addition, in conjunction with the clinical pulmonary infection score (CPIS), higher accuracies were reached.

In chapter 8 we described the results of our clinical BreathDx study. 108 patients were recruited on four ICUs. We found an AUROCC of 0.86 (95%-CI: 0.79-0.94) for the discrimination of patients with and without positive cultures for VA-LRTI, with a specificity of 49%, negative predictive value of 96% and positive predictive value of 63% at our pre-defined sensitivity of 98%. The breath test excluded pneumonia in half of the patients with subsequent negative cultures. Exhaled breath analysis also enabled prediction of the presence of the most common causative pathogens in this cohort: Pseudomonas aeruginosa, Staphylococcus aureus and Klebsiella spp.

In chapter 10 the thesis results are interpreted and put into perspective in a general discussion.
REFERENCES


