Volatile Organic Compounds in Uremia

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Abstract

Background: Although “uremic fetor” has long been felt to be diagnostic of renal failure, the compounds exhaled in uremia remain largely unknown so far. The present work investigates whether breath analysis by ion mobility spectrometry can be used for the identification of volatile organic compounds retained in uremia.

Methods: Breath analysis was performed in 28 adults with an eGFR ≥60 ml/min per 1.73 m², 26 adults with chronic renal failure corresponding to an eGFR of 10–59 ml/min per 1.73 m², and 28 adults with end-stage renal disease (ESRD) before and after a hemodialysis session. Breath analysis was performed by ion mobility spectrometry after gas-chromatographic preseparation. Identification of the compounds of interest was performed by thermal desorption gas chromatography/mass spectrometry.

Results: Breath analyses revealed significant differences in the spectra of patients with and without renal failure. Thirteen compounds were chosen for further evaluation. Some compounds including hydroxyacetone, 3-hydroxy-2-butanone and ammonia accumulated with decreasing renal function and were eliminated by dialysis. The concentrations of these compounds allowed a significant differentiation between healthy, chronic renal failure with an eGFR of 10–59 ml/min, and ESRD (p<0.05 each). Other compounds including 4-heptanal, 4-heptanone, and 2-heptanone preferentially or exclusively occurred in patients undergoing hemodialysis.

Conclusion: Impairment of renal function induces a characteristic fingerprint of volatile compounds in the breath. The technique of ion mobility spectrometry can be used for the identification of lipophilic uremic retention molecules.

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Introduction

For centuries physicians have tried to make diagnostic use of specific odors in the air their patients exhale. Hippokrates was one of the first to use the odor of exhaled air for diagnosis [1,2]. More recently it was Linus Pauling who draw our attention to the fact that the exhaled air is a micro-cosmos of volatile organic compounds (VOCs) [3]. The diagnostic use of exhaled VOCs has been rather modest so far. Although among the various odor qualities of exhaled air “uremic fetor” has long been felt to be diagnostic of renal failure, the VOCs exhaled in uremia attracted little interest. In 1977 Simenhoff et al found that ammonia, trimethylamine and dimethylamine most probably underlie the fishy odor in uremia [4]. However, the exhaled VOCs in renal failure have not been further studied so far, which may be explained by lack of an adequate technique for a systematic global analysis. The present work constitutes the first global analysis of uremic breath using a combination of ion mobility spectrometry and gas chromatography.

There is increasing evidence that lipophilic protein-bound toxins are responsible for several biochemical and functional alterations in uremia [5]. Due to the protein binding the removal of these substances by dialysis is less efficient than for water soluble substances. The retention niveau of lipophilic toxins may still be highly increased although water soluble substances have been successfully removed of the body. The kinetics of urea and creatinine therefore do not adequately reflect the removal of these substances. Hence, there is an ongoing search for alternative diagnostic tools to identify and quantify the retention niveau of lipophilic toxins. The alveolar capillary membrane is most permeable for lipophilic substances, since the membranes of endothelial and alveolar cells are predominantly composed of phospholipids. Therefore primarily lipophilic substances are expected to be exhaled. The present work investigates whether breath analysis may be used for the identification of lipophilic uremic retention molecules.

Materials and Methods

Ethics Statement

Written informed consent was obtained from all participants before inclusion in the study. The study was approved by the local
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Identification of analyte molecules by thermal desorption gas chromatography/mass spectrometry (TD-GC/MS)

The identification of analytes detected in MCC/IMS spectra is possible only by comparison with a data base of the characteristic mobility and retention time of analytes. Therefore, a further analytical method is required for the identification of unknown signals in the spectra. Random breath samples (2 l) were drawn on adsorption tubes (Tenax®, SKC Inc., USA) for later analysis using thermal desorption gas chromatography/mass spectrometry (TD-GC/MS) immediately after the MCC/IMS analysis of the same sample. TC-GC/MS was performed as published previously using an Agilent Technologies 6890N GC system connected with an Agilent Technologies 5973 mass-selective detector (MSD, Gerstel, Mülheim, Germany) [9]. After evaluation of the GC/MS data and correlation with the unknown signals in the MCC/IMS spectra using an alignment procedure for the retention time of the GC and the MCC (alignment t0), a proposal for the analyte responsible for the MCC/IMS signal was made. The proposal was then validated by reference measurements carried out using a calibration gas generator (HovaCAL, IAS, Frankfurt, Germany). This procedure has been routinely performed at the ISAS for years. Thus, a database was established allowing a rapid identification of molecules underlying the MCC-IMS spectra. Only the unknown signals in the present study, required identification by TD-GC/MS.

Analysis of spectral data

Spectra of the MCC/IMS were presented as t0/K0 with a colour coding of signal intensity (Figure 2). Analytes with the intensity rank order “group A>B>C>D” were selected by using software tools developed at ISAS (IPHEX, BB_IMSanalyse) for further evaluation [10,11]. The algorithms that are used by these software tools to select peaks of interest are described in the literature [12]. Moreover, analytes that preferentially or exclusively occurred in patients undergoing hemodialysis were selected. Thirteen analytes were selected for further investigation by this procedure. TD-GC/MS was used in an attempt to identify these fourteen analytes. Those analytes, that could not be definitely identified, are presented as “1/K0–t0” in the following. The diagnostic performance of the substances in discriminating normal and impaired renal function was performed as described below.

Statistics

Data are presented as mean ± standard deviation. Existence of significant intergroup differences in signal intensities was tested by univariate ANOVA. The individual groups were compared by two-sided two-sample Student’s t-tests. P<0.05 was regarded significant. All statistical analyses were done using PASW Statistics 18.0 (SPSS Inc, Chicago, Illinois, USA).

Results

Breath analysis was successfully performed by IMS in 28 adults with an eGFR ≥60 ml/min per 1.73 m² (group A), 26 adults with chronic renal failure (CKD) corresponding to an eGFR of 10–59 ml/min per 1.73 m² (group B), and 28 adults with end-stage renal disease (ESRD) undergoing renal replacement therapy (before and after hemodialysis corresponding to group C and D). A characterization of the study population is provided in Table 1. Spectra of healthy study participants and patients with ESRD differed markedly as visualized in Figure 2. Using the above mentioned software tools, thirteen analytes with apparent differences between healthy controls and ESRD patients were chosen.
### Table 1. Study population.

| Parameter                      | Control (n = 28) | CRF, stage 2–4 (n = 26) | CRF, stage 5D (n = 28) |
|-------------------------------|-----------------|-------------------------|------------------------|
| Female                        | 12 (42.9%)      | 14 (53.8%)              | 11 (39.3%)             |
| Male                          | 16 (57.1%)      | 12 (46.2%)              | 17 (60.7%)             |
| Age                           | 48.8 ± 14.0     | 68.2 ± 14.6             | 66.9 ± 11.1            |
| BMI (kg/m²)                   | 28.1 ± 7.7      | 26.7 ± 4.9              | 24.1 ± 5.6             |
| Creatinine (mg/dl)            | 0.8 ± 0.2       | 1.9 ± 0.8               | 5.1 ± 2.0              |
| Urea (mg/dl)                  | 26.4 ± 8.1      | 73.0 ± 34.8             | 106.2 ± 51.0           |
| eGFR (ml/min per 1.73 m²)     | 96.4 ± 22.6     | 37.2 ± 14.0             | <10 (dialysis)         |

#### Comorbidities
- **Diabetes mellitus**: 4 (14.3%) in Control, 6 (23.1%) in CRF stage 2–4, 12 (42.9%) in CRF stage 5D.
- **Hypertension**: 13 (46.4%) in Control, 22 (84.6%) in CRF stage 2–4, 26 (92.9%) in CRF stage 5D.
- **Malignoma**: 1 (3.6%) in Control, 0 (0%) in CRF stage 2–4, 1 (3.6%) in CRF stage 5D.
- **Liver cirrhosis**: 1 (3.6%) in Control, 0 (0%) in CRF stage 2–4, 1 (3.6%) in CRF stage 5D.

#### Medication
- **Antihypertensives**: 12 (42.9%) in Control, 22 (84.6%) in CRF stage 2–4, 25 (89.3%) in CRF stage 5D.
- **Proton pump inhibitors**: 5 (17.9%) in Control, 15 (57.7%) in CRF stage 2–4, 16 (57.1%) in CRF stage 5D.
- **Statins**: 2 (7.1%) in Control, 9 (34.6%) in CRF stage 2–4, 7 (25.0%) in CRF stage 5D.
- **Antibiotics**: 1 (3.6%) in Control, 2 (7.7%) in CRF stage 2–4, 5 (17.9%) in CRF stage 5D.

#### Cause of renal failure
- **Nephrosclerosis**: 5 (19.2%) in CRF stage 2–4, 1 (3.6%) in CRF stage 5D.
- **Diabetic nephropathy**: 4 (15.4%) in CRF stage 2–4, 8 (28.6%) in CRF stage 5D.
- **History of tubular necrosis**: 2 (7.7%) in CRF stage 2–4, 0 (0%) in CRF stage 5D.
- **Tubulointerstitial nephritis**: 3 (11.5%) in CRF stage 2–4, 4 (14.3%) in CRF stage 5D.
- **Cystic kidney disease**: 1 (3.8%) in CRF stage 2–4, 0 (0%) in CRF stage 5D.
- **Glomerulonephritis**: 1 (3.8%) in CRF stage 2–4, 3 (10.7%) in CRF stage 5D.
- **Urinary tract obstruction**: 2 (7.7%) in CRF stage 2–4, 0 (0%) in CRF stage 5D.
- **Unknown**: 6 (23.1%) in CRF stage 2–4, 12 (42.9%) in CRF stage 5D.

Classification to stages of chronic renal failure according to the National Kidney Foundation. CRF: chronic renal failure BMI: body mass index. eGFR: estimated glomerular filtration rate, calculated by MDRD formula.
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### Table 2. Analytes with signal intensities indicating renal elimination or association to hemodialysis.

| Signal intensity in each group | Peak | Analyte                  | $1/K_0$ | $t_n$ | $\Delta 1/K_0$ | $\Delta t_n$ | P (ANOVA) |
|-------------------------------|------|--------------------------|---------|-------|----------------|--------------|-----------|
| A, B, C, D only               |      |                          |         |       |                |              |           |
| P1                            |      | Hydroxyacetone           | 0.5341  | 9.1   | 0.0041         | 8.3          | 0.001     |
| P2                            |      | 3-Hydroxy-2-butanone     | 0.5670  | 7.1   | 0.0025         | 0.6          | <0.001    |
| P3                            |      | Ammonia                  | 0.4484  | 126.4 | 0.0100         | 75.7         | 0.03      |
| P4                            |      | 0.5985–55.6              | 0.5985  | 55.6  | 0.0023         | 4.5          | 0.03      |
| P5                            |      | 0.5468–17.0              | 0.5468  | 17.0  | 0.0041         | 8.3          | 0.008     |
| C, D only                     |      |                          |         |       |                |              |           |
| P6                            |      | Heptanal                 | 0.6678  | 10.5  | 0.0031         | 2.8          | <0.001    |
| P7                            |      | 4-Heptanone Monomer      | 0.6050  | 9.5   | 0.0030         | 3.2          | <0.001    |
| P8                            |      | 4-Heptanone Dimer        | 0.7820  | 10.4  | 0.0030         | 3.2          | <0.001    |
| P9                            |      | 2-Heptanone              | 0.6210  | 11.2  | 0.0030         | 3.2          | <0.001    |
| P10                           |      | 0.6623–10.7              | 0.6623  | 10.7  | 0.0020         | 2.1          | <0.001    |
| P11                           |      | 0.5659–11.2              | 0.5659  | 11.2  | 0.0036         | 1.9          | <0.001    |
| P12                           |      | 0.6308–11.4              | 0.6308  | 11.4  | 0.0034         | 3.8          | <0.001    |
| P13                           |      | 0.7517–10.6              | 0.7517  | 10.6  | 0.0046         | 2.4          | <0.001    |

Seven of the analytes could be identified by gas chromatography/mass spectrometry (TD-GC/MS). The remaining analytes are described by data of retention time ($t_n$) and ion mobility ($1/K_0$). Group A: healthy controls; group B: chronic renal failure corresponding to an eGFR of 10–59 ml/min per 1.73 m²; group C: end-stage renal disease (ESRD) prior to hemodialysis; group D: ESRD after hemodialysis. Signal intensities were checked for intergroup differences by univariate ANOVA, p < 0.05 was regarded significant.
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for further analysis (Table 2). Seven of them were successfully identified by TD-GC/MS. These analytes fall into two categories:

1) The concentrations of five analytes increased with decreasing renal function and were reduced by hemodialysis (signal intensity group rank order “A, B, C, D”). Three of these peaks could be identified by TD-GC/MS (P1: hydroxyacetone, P2: 3-hydroxy-2-butanone, P3: ammonia) and two are unknown yet (P4: 0.5985–55.6, and P5: 0.5468–17.0). These analytes are displayed in Figure 2 (P1–5) and Figure 3.

2) There were eight analytes that preferentially or exclusively occurred in patients undergoing hemodialysis (group C and D only). Four of these analytes could be identified (P6: heptanal, P7: 4-heptanone monomer, P8: 4-heptanonedimer, P9: 2-heptanone) and four remain elusive (P10: 0.6623–10.7, P11: 0.5659–11.2, P12: 0.6308–11.4, P13: 0.7517–10.6). These analytes are visualized in Figure 2 (P6–13) and Figure 4.

For the five analytes with the group rank order A, B, C, D, t-tests were used to compare the means of the signal intensities corresponding to the individual stages of renal disease and to compare the intensity before and after hemodialysis (Figure 3). All five analytes showed significant differences in signal intensity before and after dialysis. Hydroxyacetone revealed significant differences between all the individual stages of renal failure (p < 0.05 each). In an attempt to optimize the diagnostic accuracy of the compounds in differentiating healthy subjects from those with impaired renal function, the sum of the five analytes with the rank order A, B, C, D was calculated. As presented in Figure 3D, the sum was 0.12 ± 0.065 a.u. (group A), 0.21 ± 0.11 a.u. (group B), 0.36 ± 0.29 a.u. (group C), and 0.19 ± 0.19 a.u. (group D). ANOVA analysis indicated a highly significant difference between the signal intensities of the different groups (p < 0.001). T-test analysis showed that the signal intensity sum of “healthy” adults (eGFR ≥ 60 ml/min per 1.73 m²) was significantly different from patients with an eGFR of 10–59 ml/min per 1.73 m² (p = 0.001), and from ESRD patients prior to dialysis (p < 0.001) as presented in Figure 3D. Moreover, patients with an eGFR of 10–59 ml/min per 1.73 m² were significantly different from ESRD patients prior to dialysis (p = 0.01). The signal intensity was significantly reduced by hemodialysis (groups C and D, p = 0.02).

ROC curves were built to assess the diagnostic performance of the sum of the signal intensities in distinguishing different stages of renal failure. As shown in Figure 5A, this value achieved an area under the curve (AUC) of 0.76 in differentiating healthy subjects from patients with impaired renal function corresponding to an eGFR of 10–59 ml/min per 1.73 m² (Figure 5A) and an AUC of 0.83 to differentiate healthy and ESRD (Figure 5B). ROC curve for the differentiation of “healthy” (eGFR ≥ 60 ml/min per 1.73 m²) and “ill” (eGFR < 60 ml/min per 1.73 m²) provided an AUC of 0.80 (Figure 5C). The latter ROC curve revealed an optimal threshold of 0.15 a.u. to distinguish “healthy and ill”. This threshold provided a sensitivity of 72.2%, a specificity of 82.1%, a

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**Figure 1. Scheme of an ion mobility spectrometer (MCC/IMS).** The multi-capillary column (MCC) provides a preseparation of the molecules in the gas phase. In the ionization chamber, proton transfer from the reactant ions to the analyte molecules takes place, thus forming protonated analyte ions. The drift time of the ions in the electric field depends on size and shape of the analytes. The retention time in the MCC and mobility in the IMS characterize the identity of the analyte. The intensity of the signal is a measure of the analyte’s concentration.

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**Table 3. Experimental parameters of the multi-capillary column ion mobility spectrometer (MCC/IMS) as used in the present study.**

| Parameter       | Settings                                      |
|-----------------|-----------------------------------------------|
| Ionization source| β-radiation (63Ni, 550 MBq)                    |
| Drift length    | 12 cm                                         |
| Drift field     | 330 V/cm                                      |
| Grid opening time| 300 μs                                        |
| Drift gas       | 100 ml/min synthetic air                     |
| Carrier gas     | 150 mL/min synthetic air                     |
| Preseparation   | MCC OV-5, 20 cm, operated isothermal at 40 °C |

*Multichrom, Novosibirsk, Russia.

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Figure 2. Representative multi-capillary column/ion mobility spectra (MCC/IMS) of breath samples. Breath sample of (A) a healthy adult, (B) an end-stage renal disease proband before and (C) after hemodialysis treatment. Areas of interest are marked and labeled by numbers. Substances corresponding to these numbers are given in Table 2. Signal intensity is coded by colours (yellow: very high; red high, blue: moderate, white: no signal).

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positive predictive value of 88.6%, and a negative predictive value of 60.5% in predicting an impairment of renal function.

Further signals with visually recognizable intergroup differences occurred in the breath of the study population. In the present proof of principle study, however, we limited the analysis to the above mentioned peaks for two reasons: First, we focused on those analytes with low intragroup variabilities. Second, some signals overlapped with others, thus precluding an accurate identification and quantification with the predefined settings of the IMS. A typical example of such analytes was dimethylamine and di-/trimethylamine, which were detected in the shoulder of the significantly more intense ammonia signal. Due to this overlap

Figure 3. Signal intensities of exemplary analytes that accumulate with decreasing renal function and are eliminated by dialysis. Figures A–C present signal intensities of exemplary analytes P1–P3 and Figure D the sum of the signal intensities of the five analytes that accumulate with decreasing function and are eliminated by dialysis (P1–P5) in 28 healthy controls, 26 patients with chronic renal failure (CRF) stage 2–4 according to K/DOQI-criteria, 28 patients with end-stage renal disease (ESRD, CRF stage 5D) prior to and 22 after hemodialysis. Signal intensities were tested for statistical significance by two-tailed t-tests; *p<0.05, **p<0.01, ***p<0.001.
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Figure 4. Signal intensities of exemplary analytes that accumulate during hemodialysis. Signal intensities of analytes P9 and P11 in 28 healthy controls, 26 patients with chronic renal failure (CRF) stage 2–4 according to K/DOQI-criteria, 28 patients with end-stage renal disease (ESRD, CRF stage 5D) prior to and 22 after hemodialysis. Signal intensities were tested for statistical significance by two-tailed t-tests; *p<0.05, **p<0.01, ***p<0.001.
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exact quantification was difficult and we refrained from including these compounds in the quantitative analysis.

**Discussion**

The present work shows that breath analysis by ion mobility spectrometry is able to identify VOCs that are retained in uremia. Breath analysis revealed significant differences in the spectra of patients with and without renal failure. This “uremic fingerprint” encompasses several compounds that accumulate in renal failure and are eliminated by hemodialysis. Due to the lipophilic nature of the alveolo-capillary membrane the retention molecules in the exhaled air are predominantly lipophilic. The current approach may be of clinical interest since it may reflect the retention level of lipophilic uremic retention molecules. As stated above, there is increasing evidence that lipophilic protein-bound toxins are responsible for several biochemical and functional alterations in uremia and are inadequately reflected by the kinetics of urea and creatinine [5].

In this proof of concept study, we found several volatile compounds that accumulated in renal failure and are eliminated by hemodialysis. Five of these analytes were prompted to an identification procedure by TD-GC/MS. We identified ammonia, 3-hydroxy-2-butanone and hydroxyacetone (Table 3). It has previously been demonstrated that the elimination of ammonia by hemodialysis can be monitored by measurement of ammonia in the breath [13,14]. The authors showed that breath ammonia correlated with blood urea nitrogen and creatinine levels during hemodialysis and concluded that breath ammonia measurements could be used as a real-time surrogate measure of the retention status of patients with ESRD [13,14]. In the present study an increasing impairment of renal function went along with an increase in breath ammonia concentration. In accordance with the above mentioned study, dialysis reduced the concentration of ammonia (Figure 3C). Ammonia is a compound of predominantly endogenous origin. 3-hydroxy-2-butanone (acetoin) is an organic compound generated primarily by bacteria and plants. Acetoin is used for the production of artificial flavors and is a natural ingredient of yoghurt, and several fruits and vegetables. Thus, 3-hydroxy-2-butanone in the breath may be of exogenous origin. In pathological situations, however, it may be generated endogenously as well: There are increased breath concentrations of 3-hydroxy-2-butanone in patients with and without renal failure. This “uremic fingerprint” strongly indicates renal elimination. The compound is completely removed by hemodialysis. Hence, there are no refilling effects from third compartments that impede the accuracy of current approaches to assess the efficacy of dialysis. Fourth, the technique has proven to be able to detect compounds derived from the hemodialysis extracorporeal circuit. Therefore, it may be a helpful adjunct in the assessment of treatment linked toxicity.

The present study is limited by the fact that we identified only a subgroup of volatile compounds in uremic breath so far. The selection of the thirteen analytes that were forwarded to the attempt of TD-GC/MS identification was based on three aspects: 1) association to renal function or hemodialysis, 2) low intragroup variability, and 3) differentiability to other peaks. Comparison of the spectra of healthy subjects and patients with ESRD revealed many other analytes that accumulated in renal failure. The majority of these analytes were excluded from analysis for the third reason. In this proof of principle study we made use of a standard setting of the MCC/IMS and a limited number of subjects. An optimization of the settings – e.g. preseparation temperature, field strength, drift gas and carrier gas flow, preseparation and drift length – and a larger population of patients with renal failure will allow a more distinct separation of analytes that are now displayed very close to one another. Harinaran et al. recently demonstrated the potential of optimizing experimental parameters with regard to peak resolution [20]. Moreover, TD-GC/MS was not able to identify two analytes, potentially due to the low number of patients and low concentrations in the breath. The identification of the unknown analytes will be a major objective of larger studies in the future.

What are the next steps to transfer this promising method to clinical practice? Larger studies yielding at an optimization of MCC/IMS and GC/MS settings for volatile uremic compounds
are required. An optimization of the settings will allow the detection and identification of more substances that are currently displayed too close to one another for separation. Moreover, the studies should include clinical signs, symptoms, and endpoints in order to define either a potential pathophysiological meaning or the reflection of clinical parameters of the detected substances. Finally, sequential breath analyses should be performed during hemodialysis and should be correlated to current standard procedures for the calculation of dialysis efficacy.

The present study shows that breath analysis by a combination of gas chromatography and ion mobility spectrometry can be used for the identification of volatile organic compounds retained in uremia. The combination of these techniques was of crucial relevance, since it provides a sensitive and rapid (10 min) measurement without a need of sample pretreatment. It may be speculated that the lack of an adequate technical solution like this is the reason why uremic breath has not been analyzed in a systematic manner so far. The present first global analysis of uremic breath shows that renal impairment induces a characteristic fingerprint of volatile compounds in the breath. Future studies have to elucidate whether the findings on this new class of uremic toxins can be transferred into clinical practice.

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**Author Contributions**

Conceived and designed the experiments: WV WZ THW. Performed the experiments: NP LS RS JJ. Analyzed the data: NP WV LS WS THW. Contributed reagents/materials/analysis tools: WV. Wrote the paper: NP WV THW.

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