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Smelling heart failure from human skin odor with an electronic nose*

A. Voss, K. Witt, C. Fischer, S. Reulecke, W. Poitz, V. Kechagias, R. Surber, HR. Figulla

Abstract— **The human body odor contains different volatile organic compounds which can be used as biomarkers for various diseases. The early detection of heart failure (HF) through periodical screening provides an early treatment application. Therefore we have developed a completely new non-invasive method to identify HF applying an "electronic nose" (e-nose) which provides a "smelling" of the disease based on the analysis of sweat volatile gases from the skin surface. For this e-nose a special applicator carrying the sensor chip was developed which can be applied directly on the skin surface. 27 patients with decompensated HF (DHF), 25 patients with compensated HF (CHF, mean age 70.72 ± 12.02) and 28 controls (CON) were enrolled in this first pilot study.**

Principal component analysis (PCA) was performed in combination with discriminant function analysis (DA) to discriminate between the patient groups. DHF were separated from CHF with an accuracy of 87% whereas the CON were successfully discriminated from CHF in 85%.

The results of this pilot study suggest that an e-nose could be successfully applied for diagnosing and monitoring of HF patients analyzing the human body odor from skin surface.

I. Introduction

Metabolic changes in the body are sometimes connected with typical odors which can be measured on breath [1, 2], sweat [3] or other excreta from humans [4, 5]. The human body odor contains different volatile organic compounds which can be used as biomarkers for diseases [6]. Experiments with special trained dogs showed that they are able to smell diseases as e.g. cancer, hypoglycemia or hyperglycemia. However, until now we do not know exactly what these dogs really smell (which substance is related to a dedicated disease) [7]. If we would know the diseases specific odor components we could develop artificial noses as electronic odor detection systems.

An electronic nose (e-nose) system is a technical instrument for determination of volatile compounds by using an sensor array [8].

Recent advances in e-nose technologies, based on many different electronic aroma detection principles and mechanisms [5], have made possible the development of a wide variety of new e-nose applications that have proven useful in a range of diverse commercial industries, including food [9, 10], pharmaceutical [11] and automotive industry and in many fields of applied sciences with the purpose of quality control and alarming in case of dangerous gases (e.g. carbon monoxide) [12].

The number of e-nose applications in the medical field has grown rapidly. Some of these applications are the detection of mycobacterium tuberculosis in sputum samples and cultures [13], diagnosis of urinary tract infection [14], bacteria classification [15], identification of schizophrenic patients and diabetes [16], and analysis of the exhaled breath in different diseases such as lung cancer and asthma [17, 18].

In a first study we could demonstrate the ability of an e-nose to detect changes in the human body odor in patients with different degrees of renal dysfunction in comparison with healthy subjects [19]. All healthy subjects (n=11) could completely be discriminated from patients with renal failure (n=62) applying principal component analysis (PCA) and quadratic discriminant analysis. The discrimination between patients with end stage renal failure (n=42) and with chronic renal failure was successful in 92.5 %.

First results for a clinical pilot study have revealed a classification rate of 100% between healthy subjects, patients with liver cirrhosis and primed alcoholic addicted patients [20].

The objective of this study is the application of an e-nose system for diagnosis of heart failure based on the detection of disease dependent sweat volatile gases from the skin surface caused by an impaired metabolic.

II. Methods

A. Electronic nose

The applied e-nose system consists on a metal oxide gas sensor with three different sensitive layers. These tin oxide layers have different sensitivities and selectivities for various gas molecules at different temperatures such as CO-, H_2- and C_2H_5OH sensitivities. The measuring principle is based on electrical conductivity changes caused by interactions between molecules and the sensor layers (oxidizing and reducing reactions caused by volatile gases such as oxygen resp. carbon monoxide) [21, 22]. The controller unit regulates the operating temperature between 200°C up to 400°C per measuring cycle. Each conductivity value (sensor resistance) at each different temperature is stored on the data logger. The principal measurement setup of the applied e-

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A. Voss*, K. Witt, C. Fischer, S. Reulecke and W. Peutz are with the University of Applied Sciences Jena, Department of Medical Engineering and Biotechnology, Carl-Zeiss-Promenade 2, 07745 Jena, Germany (* corresponding author to provide phone: 49-3641-205-625; fax: 49-3641-205-626; e-mail: andreas.voss@fh-jena.de).

V. Kechagias, R. Surber and H.R. Figulla are with the Clinic of Internal Medicine I, Friedrich Schiller University Jena, Erlanger Allee 101, 07743 Jena, Germany (e-mail: Ralf.Surber@med.uni-jena.de).

nose system is shown in fig.1. More detailed information about this e-nose can be found in [19].

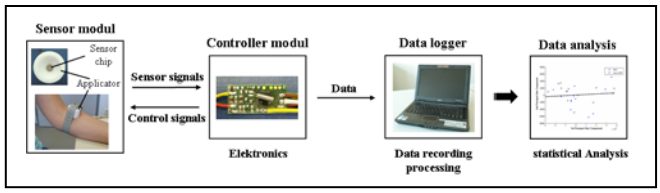

Figure 1. Configuration of the applied electronic nose system

This e-nose system was developed in cooperation with UST Umweltsensortechnik, Jencontrol GmbH, enverdis GmbH and the Department of Internal Medicine I, Friedrich-Schiller-University of Jena.

B. *Patients*

In this study 27 patients with decompensated heart failure (DHF, mean age 74.30 ± 11.18), 25 patients with compensated heart failure (CHF, mean age 70.72 ± 12.02) and 28 patients without heart failure (CON, mean age 58.93 ± 13.49) as a control group were enrolled. The patients were admitted at the Clinic of Internal Medicine I, Friedrich Schiller University Jena. The patients were classified in accordance to the New York Heart Association (*NYHA*) classification [23]. In addition patients in both groups were similar treated (such as beta-blockers, diuretics, ACE-inhibitors).

Before each measurement did start the skin surface was prepared to avoid any contaminating gas components from applying personal hygiene products and in addition the sensor was regenerated. The sensor head was placed in the crook of the arm. For every patient 10 measurements were performed over 35 minutes in the same air-conditioned room to avoid environmental influences. Additionally, blood samples of each patient were collected from every patient for routine clinical laboratory test and to correlate the odor components with clinical parameters.

C. *Data Analysis*

Before starting the statistical analyses some preprocessing was applied. First the sensor signals were interpolated in relation to the temperature and second a drift compensation of the averaged sensor curves was performed.

The three sensor signals were analyzed by using principal component analysis (PCA). This method reduces the multidimensional data space to its main components that are linear combinations of the sensor values and contain the maximum variance. For this the information from each complete sensor signal were reduced to the first and second components (POC – principal odor component) and are displayed in a score plot. The first component has the largest variance and the second component is orthogonal to the first one with the next largest variance [19, 24].

To estimate the relation between clinical parameters (e.g. bicarbonate, pH-value, and bilirubin) and the first two components the Pearson correlation coefficients were calculated.

Finally, the discriminant function analysis (DFA) (linear and quadratic) as a statistical analysis technique was used [25] to differentiate the groups using pairwise analyses..

III. Results

The results from the PCA were summarized for the first and second principal odor components. DHF and CHF were discriminated with a classification accuracy of 87% (fig. 2). It is obvious that already the linear DFA generated an acceptable classification result. To separate between DHF and CON the PCA in combination with DFA was successful in 76% of all cases.

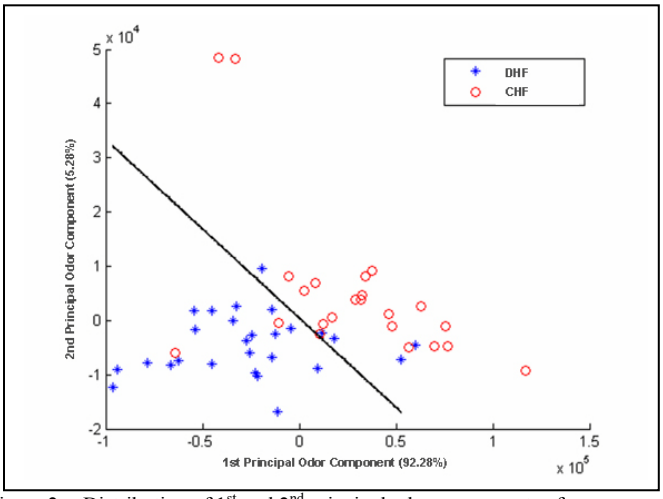

Figure 2. Distribution of 1st and 2nd principal odor components of decompansated heart failure (stars) and compensated heart failure (circle); the groups are separated by linear DFA.

Furthermore, CON and CHF could be separated by applying quadratic DFA leading to an accuracy of 85% (fig. 3).

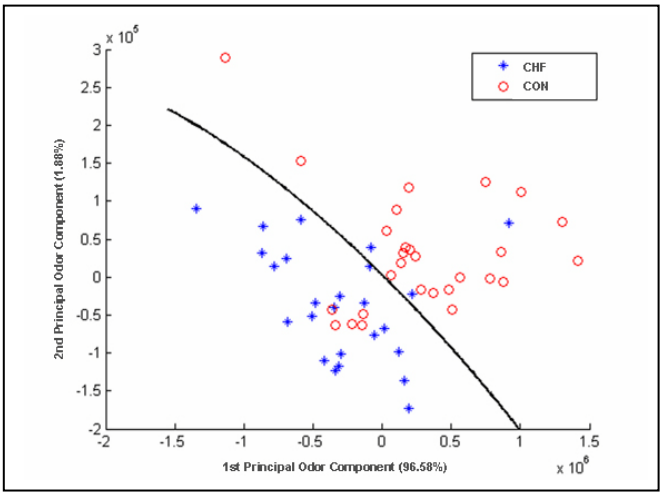

Figure 3. Distribution of 1st and 2nd principal odor components of compensated heart failure (stars) and controls (circle) ; the groups are separated by quadratic DFA.

The Pearson correlation coefficients between biochemical parameters and the first two principal components were calculated and the results are demonstrated in table 1. The highest and significant correlations between the routine clinical laboratory parameters and the patients group are presented

In the DHF - CHF group only the 1st POC correlates significantly with standard bicarbonate (r = -0.567), base excess (r = -0.562) and other clinical parameters. In the DHF–CON group only the 2nd POC correlates significantly with most routine clinical laboratory parameters as the DHF-CHF group: standard bicarbonate (r = -0.466), base excess (r = -0.455) and others with the exception of bilirubin (r=-0.274). However, potassium and chlorine were not significant correlated. In the group CHF-CON the 1st POC correlates only with BNP (-0.463) and the 2nd POC only with urea (-0.284).

TABLE I. CORRELATION COEFFICIENTS (P<0.05) BETWEEN 1ST AND 2ND PRINCIPAL ODOR COMPONENT AND EACH CLINICAL LABORATORY PARAMETER

	DHF and CHF		**DHF and CON**		**CHF and CON**	
	1st POC	***2nd POC***	***1st POC***	***2nd POC***	***1st POC***	***2nd POC***
standard bicarbonate (mmol/l)	-0.567			-0.466		
act. bicarbonate (mmol/l)	-0.404			-0.309		
base excess (mmol/l)	-0.562			-0.455		
pH-value	-0.483			-0.356		
potassium (mmol/l)	0.404					
chlorine (mmol/l)	0.401					
urea (mmol/l)						-0.284
bilirubin (µmol/l)				-0.274		
BNP (pg/ml)					-0.463	

No entry means not significantly correlated

IV. DISCUSSION

In this study the ability of an e-nose to characterize the human body odor of patients with heart failure was demonstrated. Two groups of patients with different stages of heart failure (compensated vs. decompensated) could be discriminated with an accuracy of 87% combining the first two principal components and separating the groups with DFA (fig. 4). This approach could be useful in monitoring patients in an ICU. Further on, CON and CHF could be discriminated with a correct classification of 85%. This approach could be useful for a first diagnosis of heart failure at the general practitioner.

Discriminating between CON and DHF led to a classification accuracy of only 76%. However, this approach is of less practical use.

Furthermore, the correlation between routine clinical laboratory parameters and principal odor components provides some information about the origin of the biomarkers and supports a possible future improvement of the sensors. A high correlation coefficient of r=-0.463 was revealed between the parameter BNP and the 1st POC of the groups CHF and CON. This parameter BNP is a specific indicator for heart failure [26]. In this study BNP was the most important parameter differentiating between decompensated heart failure and compensated heart failure as well as between decompensated heart failure and controls. Interestingly, this demonstrates the ability of BNP characterizing the severe stage but not the mild and moderate stages of HF that could be detected via the e-nose system.

Limitations of this pilot study are especially that we did not (yet) consider the influence of ambient air, temperature of the skin surface, personal hygiene, nutrition and comorbidities.

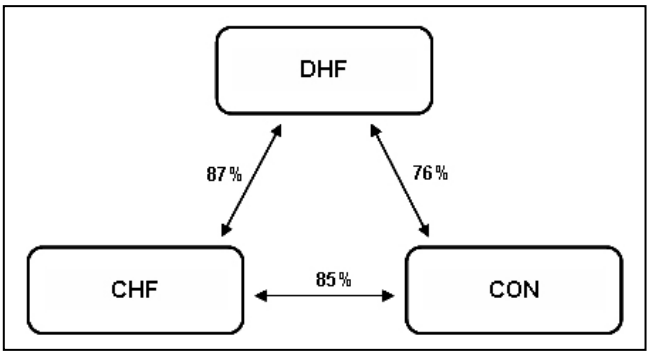

Figure 4. Classification accuracy between each two groups on the basis of 1st and 2nd principal odour components and discriminant function analysis

Further on, there are additional influences on the sensor sensitivity and specificity as e.g. material aging, contamination, changes of the environment and so on [27] that has to be considered in detail.

Finally, a relatively small number of patients was enrolled in this study.

The sensors of our e-nose system indicate changes of conductivity caused by the oxidizing or reducing influence of odor components on the sensor surface but they are not able to characterize the specific odor components. For this characterization one has to use a appropriate analysis technique as e.g. gas chromatography in combination with mass spectrometry (GC/MS) as a reference method [28]. In this study the method of solid phase micro extraction (SPME) was performed to collect the samples and to analyze them with a GC/MS. However, this analysis has not yet been finalized, and therefore, not presented here.

In other studies data analyses were performed applying neuronal networks (NN) or support vector machines (SVM) [29-31]. These methods will be prospectively considered and compared with PCA in future studies.

Another interesting approach would be the application of this e-nose system analyzing exhaled breath to further improve the classification accuracy.

V. Conclusion

This study shows the feasibility and the performance of an e-nose system to differentiate between patients without and with heart failure and in detail between patients with decompensated and compensated heart failure analyzing human body odor from the skin. Applying principal component analysis in combination with discriminant function analysis provided classification accuracies up to 87%.

These findings give compelling evidence for validity that an e-nose detects metabolic changes on the skin surface caused by internal diseases and allows differentiating between physiologic and pathophysiologic mechanisms.

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