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An electronic nose discriminates exhaled breath of patients with untreated pulmonary sarcoidosis from controls

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Summary
Background: Sarcoidosis is a systemic granulomatous disease of unknown cause that affects the lungs in over 90% of cases. Breath analysis by electronic nose technology provides exhaled molecular profiles that have potential in the diagnosis of several respiratory diseases.
Objectives: We hypothesized that exhaled molecular profiling may distinguish well-characterized patients with sarcoidosis from controls. To that end we performed electronic nose measurements in untreated and treated sarcoidosis patients and in healthy controls.
Methods: 31 sarcoidosis patients (11 patients with untreated pulmonary sarcoidosis [age: 48.4 ± 9.0], 20 patients with treated pulmonary sarcoidosis [age: 49.7 ± 7.9]) and 25 healthy controls (age: 39.6 ± 14.1) participated in a cross-sectional study. Exhaled breath was collected twice using a Tedlar bag by a standardized method. Both bags were then sampled by an electronic nose (Cyranose C320), resulting in duplicate data. Statistical analysis on sensor responses was performed off-line by principal components (PC) analyses, discriminant analysis and ROC curves.
Results: Breathprints from patients with untreated pulmonary sarcoidosis were discriminated from healthy controls (CVA: 83.3%; AUC 0.825). Repeated measurements confirmed those results. Patients with untreated and treated sarcoidosis could be less well discriminated (CVA 74.2%), whereas the treated sarcoidosis group was undistinguishable from controls (CVA 66.7%)

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Conclusion: Untreated patients with active sarcoidosis can be discriminated from healthy controls. This suggests that exhaled breath analysis has potential for diagnosis and/or monitoring of sarcoidosis.
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Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology, which commonly affects young and middle-aged adults throughout the world.[1] The estimated life-time risk varies between 1 and 2% in different ethnic groups.[2] Pulmonary involvement occurs in over 90% of cases.[3] Due to its wide variety in clinical presentation and subsequent disease course, the diagnosis of sarcoidosis is challenging and often requires invasive approaches such as bronchoscopy.[1] As a consequence, decisions on whether or not starting treatment often have to be taken on arbitrary grounds. Therefore, It would be desirable to have new diagnostic methods in sarcoidosis that are simple, quick, non-invasive, cost-effective and with high selectivity. In the past years, several serum markers have been associated with the presence of sarcoidosis, including angiotensin-converting enzyme, neopterin and soluble IL-2 receptor, but none of them showed an adequate sensitivity to be useful for screening for the diagnosis of sarcoidosis.[4]

During the past few years, the analysis of exhaled breath has been proposed as a novel diagnostic tool for a variety of lung diseases.[5] It is well known that exhaled breath contains thousands of volatile organic compounds (VOCs) deriving from various metabolic and inflammatory pathways in the body.[6,7] These can be measured by techniques like gas chromatography—mass spectrometry (GC—MS), Time of Flight Mass Spectrometry (TOF-MS) and Ion-Mobility spectrometry (IMS), which are the gold-standard for VOCs analysis. A feasibility study by Westhoff et al. showed characteristic peaks of volatile organic compounds in exhaled air of patients with sarcoidosis by using IMS.[8]

However, these procedures are arduous and expensive, which has limited their clinical applicability.

Electronic noses represent an innovative method of VOCs sampling, because these devices can identify a mixture of VOCs translating it into a breath profile (breathprint).[9] Differently from GC—MS, they allow a relatively inexpensive, on-site and instantaneous distinction of breathprints by pattern recognition, without identification of the individual molecular components.[10] Notably, several proof of concept studies have shown that exhaled breath molecular profiling by electronic noses could be useful in the medical diagnostics,[5] in particular in the diagnosis of several respiratory diseases such as lung cancer[11—13] asthma,[14,15] COPD[15] and pleural malignant mesothelioma.[16]

Based on the above, we hypothesized that the exhaled breath molecular profiling by an electronic nose can correctly discriminate patients with pulmonary sarcoidosis from controls with adequate repeatability.

Methods

Patients

A total number of 56 patients volunteered to participate to this study. All individuals were never-smoking adults (18—75 years). The study population included 3 groups of patients: patients with untreated pulmonary sarcoidosis, patients with treated pulmonary sarcoidosis and a healthy control group. Measurements were performed in May 2011. During January—March 2011 otherwise unselected patients, however fulfilling the inclusion criteria, were approached during regular visits to the outpatient clinic of the Amsterdam University Medical Center. Those who volunteered participated in the study, whilst controls were recruited amongst personal contacts.

The untreated pulmonary sarcoidosis group was composed of 11 patients with a more recently established diagnosis or longer standing stable disease without previous or current medical treatment. The treated pulmonary sarcoidosis group consisted of 20 patients with stage 0—IV pulmonary sarcoidosis currently under inhaled and/or systemic therapy (corticosteroids alone, corticosteroids combined with azathioprine, methotrexate or, hydroxychloroquine). Sarcoidosis was defined as presence of histological evidence of non-caseating granulomas in patients with bilateral hilar adenopathy on the chest roentgenogram, except for those with particular conditions where a diagnosis was based on clinical-radiographic findings alone, such as Löfgren syndrome, Heerfordt syndrome, bilateral hilar gallium-67 uptake and positive PET scan.[1] Patients were radiologically staged using currently accepted consensus criteria.[1] Patients with clinically established conditions affecting the exhaled VOCs spectrum were not eligible for participation, in particular Diabetes Mellitus, respiratory disease other than sarcoidosis, autoimmune disease, renal dysfunction, cardiac failure, prior or current malignancies and respiratory tract infections requiring antibiotics and/or oral steroids in the 4 weeks preceding the study.

The control group was composed by 25 subjects with a negative history of chest symptoms and without of any known disease.

The study was approved by the Amsterdam University Medical Centre Ethics Committee and all patients gave their written informed consent.

Study design

The study had a cross-sectional case-control design. The measurements were performed at one visit. Patients were asked to refrain from eating and drinking at least for 3 h before the study. Exhaled breath was collected in duplicate and sampled by the electronic nose.

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