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Title: Explorative breath analysis study for the detection and classification of PAH

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**Body:** Background: The diagnosis of PAH requires invasive right-heart catheterization, which is unsuitable for widespread screening, particularly in at risk patients. Aims: To explore the possibility of detecting and classifying PAH by a non-invasive approach, via exhaled breath samples. Methods: Samples of alveolar breath from 22 PAH patients and 23 healthy volunteers were analyzed by gas chromatography-mass spectrometry (GC-MS), to identify volatile organic compounds (VOCs). Then, the discriminative power of a tailor-made array of cross-reactive gold nanoparticle sensors, which perform VOC detection in breath samples, was tested. Part of the samples (65-75%) were used as a training set and the other part (25-35%) was used for blind analysis. Results: GC-MS analysis revealed differences in VOCs' concentrations between PAH patients subgroups and controls. The sensor array discriminated between breath samples of PAH patients and controls (accuracy 92%). Moreover, it was capable to classify idiopathic (n=15) and heritable (n=7) PAH cases (accuracy 87%), indicating a relationship between breath fingerprint and a genetic mutation. Further classification was made according to NYHA functional class, I-II vs. III (accuracy 91%), suggesting a potential for discriminating disease severity. Finally, the sensor array was able to distinguish acute vasodilator responders (n=5) from non-responders (accuracy 95%), indicating that management strategy might be directly spotted through breath analysis. Conclusions: Our results constitute explorative evidence that the breath fingerprint can form a basis of non-invasive approach for detection and classification of PAH, and, probably, as a screening tool for at-risk subjects.