Exhaled volatile organic compounds for better asthma control: could it be a future noninvasive adherence test?

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VOCs are surrogate markers for salbutamol and OCS use, which are part of the definition of poor asthma control. This suggests that VOCs are promising biomarkers that could possibly be used to detect poor adherence to inhaled therapy. http://bit.ly/2SgE44R

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In the study presented in this issue of the *European Respiratory Journal*, Brinkman *et al.* [1] investigated the link between traces of asthma medication in urine of severe asthmatic patients and exhaled volatile organic compounds (VOCs). One potential application of this study in clinical practice would be an easy, indirect measurement of compliance using detection of exhaled breath biomarkers resulting from metabolism and excretion of medications by the lungs.

Severe asthma represents 5 to 10% of the asthmatic population and is associated with a high rate of exacerbations and high healthcare costs [2]. The diagnosis of severe asthma is of utmost importance but often challenging. Very expensive therapies are now available to reduce exacerbations and to improve quality of life of severe asthmatics. Distinguishing patients with difficult-to-control asthma who respond to inhaled corticosteroids (ICS) from refractory asthma is an important clinical challenge. The diagnosis of severe asthma requires first the exclusion of poor adherence to treatment [2]. The monitoring of adherence and compliance is, however, complex in chronic diseases such as asthma. The access to pharmacist's data, which is not available in all countries all over the world, gives an idea on patients' compliance but does not mean that patients are taking their treatments [3]. By relating exhaled metabolites to urinary metabolites, which is the gold-standard for drug monitoring, the study of Brinkman *et al.* [1] highlights the potential of breath tests in the context of treatment monitoring. The appeal of the use of VOCs to determine adherence to treatment is that it would be a noninvasive technique, providing quick results and being comfortable for patients.

Moreover, the identification of surrogate markers for salbutamol and oral corticosteroids (OCS) is an indirect measure of uncontrolled asthma. Severe asthma may indeed require frequent or chronic use of OCS. Furthermore, OCS intake and use of rescue medications are part of the definition of uncontrolled asthma [2]. Evaluation of asthma control is, however, easier than that of compliance, as pulmonologists have access to easy-to-use questionnaires, such as the asthma control test [4] or asthma control questionnaire [5].

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Here, Brinkman *et al.* [1] are presenting a study on the link between exhaled VOCs and urinary detection of salbutamol and OCS. The authors recruited 78 severe asthmatics from the U-BIOPRED cohort. In this study, two well-established and complementary chromatographic methodologies, *i.e.* gas chromatography coupled to time-of-flight mass spectrometry (GC-MS) and liquid chromatography coupled to high-resolution mass spectrometry were used. This strengthened the analysis by highlighting the link between exhaled VOCs and well-known metabolism kinetics of drugs. Moreover, the robustness of the study is demonstrated by the true validation of the results performed using independent cohorts of patients. The external validation is essential for confirming the validity of exhaled breath biomarkers for drug intake monitoring. In addition, the multicentre character of this study reinforces the link between breath and urine metabolites. It is reassuring that consistency in the obtained results was observed while collecting the exhaled breath and urine samples at eight different sites and analysing the samples in two different institutes.

As it is often the case in studies involving the search of chemical markers, the chemical validation of the reported markers could ideally be further improved. Currently, based on the formal definitions of metabolite annotation and identification of the Metabolomics Standards Initiative [6], the chemical annotation of the compounds of interest in the present study reaches a level of confidence of 3. In GC-MS, retention times together with mass spectral library forward match are specific to chemical classes of organic compounds. As an example, branched hydrocarbons, although having various retention times, are characterised by similar mass spectra, which makes their accurate identification challenging. Therefore, the use of such information specific solely to chemical classes of compounds, enables to reach a level of confidence of 3. Ideally, a level of confidence of 1 would be required to propose accurate identification for the selected chemical markers. Although the lack of such a confirmation of the chemical identification (level 1) does not impact the biological interpretation of the study, aiming for the collection of more orthogonal identification data points would reinforce the findings of such a high-end study. As an example, when possible, mass spectral library forward and reverse match factors (including probability scores) should be considered together with the injection of neat standards and the calculation of alkane-based retention indices. Such an accurate chemical identification of potential biomarkers would further facilitate the transposition of these compounds from one study to another, bringing even higher level of confidence for the usage of breath analysis in the medical field.

Brinkman *et al.* [1] found that some exhaled VOCs correlate with the presence of OCS and salbutamol urine metabolites. The usefulness of VOCs in the management of severe asthma would be even stronger if the usage of VOCs could allow to identify adherence to ICS and long-acting β_2-agonists (LABA), which is the main issue for respiratory physicians managing difficult-to-treat asthmatics. As previously said, the definition of severe asthma requires the exclusion of poor adherence to ICS/LABA. We have previously shown that monitoring a set of VOCs permitted to detect the presence of sputum eosinophilic and neutrophilic inflammation [7, 8]. As inhaled corticosteroids act in part by decreasing local eosinophilic inflammation, this suggests that VOCs are promising biomarkers that would possibly be used to detect poor adherence to ICS. Fractional exhaled nitric oxide (F_{eNO}), another exhaled biomarker, has also been suggested as a good surrogate marker for sputum eosinophil counts [9] and adherence to ICS [10]. Certain considerations should, however, be applied when interpreting F_{eNO} values as they are influenced by various factors [11]. This might be due to the fact that F_{eNO} is more linked to the epithelial function than to type-2 inflammation *per se*. The biological complexity of asthma and the influence of inhaled therapy is likely to be more comprehensively captured by composite molecular fingerprints than the sole measure of F_{eNO} level. VOCs could therefore be more informative than F_{eNO} to clinicians.

Taken together, the study of Brinkman *et al.* [1] is a first encouraging step to the development of future quick and noninvasive adherence test for inhaled therapies. VOCs are indeed easy to measure in clinical practice and may reflect compliance by the detection of exhaled breath biomarkers resulting from metabolism of drugs excreted by the lungs. The univocal chemical identification of such biomarkers requires the collection of further orthogonal analytical data.

Conflict of interest: None declared.

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