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Innovative exhaled breath analysis with old breathing manoeuvres—is there a problem or an advantage?

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Abstract
As the field of exhaled breath research is expanding, the question that arises is can the old usual method of spirometry be used in all cases? The answer is yes for some analysis methods and definitely not for others: it all depends on the result you are looking for. Exhaled breath condensate collection can be accomplished with silent tidal breathing, but not in the analysis of the amount of exhaled particles, as they become very low during tidal breathing. There are gases that are exhalation flow dependent, e.g. nitric oxide, acetone and ethanol, that require a special breathing manoeuvre with flow control. Physiological changes of the lung, i.e. inhalation to total lung capacity or forced exhalation such as during spirometry, will affect the result of exhaled biomarkers. The standardisation of exhaled breath requires further development, and there are many aspects to consider.

The field of exhaled breath research has grown immensely. However, the acceptance of different biomarkers in clinical medicine is very slow. This could be because researchers have not been able to perform the appropriate studies to convince practitioners, or because the technical solutions are impractical in the patient care setting, or due to the impact of economic constraints in health care systems. The research community has presented conflicting results regarding low or high level concentrations of biomarkers, which can possibly depend on the different methods used in the exhalation manoeuvres. As for exhaled breath condensate (EBC) collection, it can be achieved with silent tidal breathing, but in the case of the amount of exhaled particles, these become very low during tidal breathing. There are gases that are flow dependent, e.g. nitric oxide (NO) [1, 2], acetone [3], ethanol [4], isoprene [5, 6] and pentane [5]. Measurement of these gases demands special breathing manoeuvres.

Physiological changes induced by bronchodilation
It is known that bronchodilation is induced in healthy individuals after the distension of the lung. This phenomenon is altered with asthma where bronchoconstriction can occur. In chronic obstructive pulmonary disease (COPD), this bronchodilatory effect is also profoundly impaired with a wide degree of variation in its severity. In addition, the exhaled NO (FENO) due to pharmacologically induced bronchodilation in asthmatic subjects has shown different behaviours [7]. FENO may decrease, increase or present no change depending on the location in the airway tree where the relaxation of the smooth muscle is achieved. The same research group presented similar findings for COPD at the European Respiratory Society’s congress in London in 2016. This can possibly be used to identify the site of the airway obstruction. Hence, different degrees of airway inflammation may cause different responses in different parts of the airway tree. This needs to be considered when the biomarker of interest is from the airways. One must also consider whether the bronchodilator substance per se alters the biomarker response through reactions from the airway lining [8, 9].

Physiological changes induced by distension of the lung
A vital capacity (VC) manoeuvre is frequently used to recruit the lung when there is alveolar collapse, or to prevent such collapse during mechanical ventilation [10]. When the measurement of exhaled particles uses...
a manoeuvre that involves the active emptying of the lung, together with an inhalation to total lung capacity, the production of particles increases enormously compared to tidal breathing [11]. It has been shown that with the use of this extension manoeuvre of the lung, a surfactant is exhaled [12]. It is also likely that other substances, e.g. volatile organic compounds (VOC) and particles, are released. Ventilation pattern has been shown to influence quantification of VOC, hence breathing pattern should be accounted for [13, 14]. The posture of the body also changes VOC in exhaled gas and needs to be considered when interpreting data [15]. With focus on NO, it has been shown in rabbits that the application of positive end-expiratory pressure during mechanical ventilation causes an increase of FEnO due to the stretching of lung parenchyma [16]. Nitric oxide is also released in healthy subjects and is said to be responsible for bronchodilation. When healthy subjects inhaled to total lung capacity and then slowly exhaled with a preset flow, it took nearly 10 s longer to reach a stable NO level than if only deep inhalation was performed [17]. In addition, lung stretch alters airway mechanics in overweight and obese asthmatics with increased resistance, through an increase in lung volume [18].

Since NO analysis is used both in research and in clinical practice we do not know which subject or patient will respond with bronchodilation or NO release with a VC manoeuvre. Therefore, minimal lung volume changes and stretching of lung parenchyma should be the goal for any manoeuvre to measure FEnO.

The use of spirometry for exhaled biomarkers

A standardised method is used to perform spirometry and gives information regarding respiratory function. Exhaled biomarkers are mostly used to detect inflammation. In the field of respiratory diseases, it is most likely that patients will be examined with both a sampling of biomarkers and spirometry. For patients with severe lung disease these two examinations are tiresome and should therefore be done separately in order to save the patient’s energy. VOCs have been examined after spirometry and revealed substance-specific changes [19], giving a 21% increase in isoprene. Regarding NO measurements and spirometry, NO measurements should be performed before spirometry due to transient reduced NO levels [20]. This is almost certainly the result of the NO release seen after a VC manoeuvre in healthy subjects [17]. The resting time between the exhalation manoeuvres during NO measurement for a deep inhalation is at least 30 s, but after a VC, such as during spirometry, this recovery time must be longer [21, 22]. In non-asthmatic subjects there is a drop in exhaled NO after two VC manoeuvres (normally performed for spirometry), a drop that can be as much as 25% [23]. In asthmatic subjects this fall was even greater, at just under 40% [21].

In the future NO parameters, e.g. the airway wall concentration of NO (CawNO), the diffusing capacity of NO from the airway wall to the gas stream (DawNO), and alveolar or acinar NO (CvNO), will also be used to detect specific changes in the tissue associated with different diseases, e.g. chronic obstructive pulmonary disease, scleroderma and obstructive sleep apnoea [24]. Hence, there are examinations for lung function and for the detection of physiological tissue changes, and these different examinations do not necessarily need to be performed with the same technique as for spirometry. So far, there is a weak or no correlation between FEnO at the flow of 50 ml s⁻¹ and lung function in most of the studies.

Thus the patient is subjected to many exhalation procedures. A deep breath compared to a VC is less strenuous and it is easier for the patient to control their breath with less volume in the lung. A maximum inhalation with the following exhalation rate of 20 ml s⁻¹, as used for the estimation of NO parameters, will create dizziness for elderly patients since vascular pressure in the lung is affected. The rising interest in CawNO will result in up to 6–10 multiple exhalations, making the VC manoeuvre unsuitable. Hence with respect to patient comfort it is best to refrain from VC for the NO analysis.

New technology

Another reason to avoid the VC manoeuvre in NO analysis is the new devices with electrochemical cells that do not present the NO signal visually, and automatic aspiration into the cell occurs after approximately 10 s. This will theoretically give a false high NO value when the measurement is done with a VC and the sampling starts before the NO level has reached a plateau [17].

A built in function in one of these NO analysers with chemiluminescence assesses the necessary volume the subject needs to exhale, which is 40% of VC. Hence, the industry has adapted to the deep breath.

Recently de Vries et al have presented a new device to integrate eNose technology with spirometry [25]. This might facilitate the acceptance for easy breath analysis in clinical practice. However, this device captures the spectrum of volatile organic compounds in exhaled gas without the identification of individual compounds, some which might be flow dependent.

In conclusion, is there a problem with old standardized breathing manoeuvres for the new exhaled biomarkers? The answer is clearly yes for some biomarkers. However, a large lung volume change with a lung parenchyma stretch can be used as an intervention in the investigation of lung behaviour in
health and disease. As for today, this conclusion is not necessarily restricted to nitric oxide only, but also for isoprene and possibly other markers to come. For researchers and clinicians that are interested in exhaled biomarkers there is ‘An official European Respiratory Society Statement on technical standard assessment of exhaled biomarkers in lung disease’ published this year [26].

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