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Dual gas techniques for peripheral airway function: diffusing the issues

To the Editor:

In the quest to investigate small airway function in a range of lung diseases, multiple-breath washout tests have been applied for their potential to represent the most peripheral air spaces [1, 2]. The aim of reducing the burden on the patient has recently also revived interest in the single-breath washout. A single-breath washout test has now been proposed which involves an inhalation of 5% SF_6, 26.3% He, 21% O_2 and the balance as N_2 in order to obtain a so-called dual gas tracer (DTG) phase III slope [3]. After having been introduced as a practical and promising lung function tool [3] and as an early detection tool in cystic fibrosis lung disease [4], the DTG phase III slope is now advocated as a specific index of acinar function abnormality in children with mild asthma [5]. An editorial in the *European Respiratory Journal* [6], reflecting upon a DTG reproducibility study in normal subjects and chronic obstructive pulmonary

disease (COPD) patients [7], rightly pointed out that the clinical utility of DTG indices will depend on their actual physiological meaning. We provide here a critical appraisal of the physiological meaning of the DTG phase III slope.

Why use two gases, such as He and SF_6, at all? Because the He diffusion front is located a few generations proximal to the SF_6 diffusion front [8], and the He and SF_6 phase III slopes are thought to represent airway function in the proximal and peripheral part of the acinus, respectively. Ventilation heterogeneities generated in the conductive airways are expected to affect the He and SF_6 phase III slopes to the same extent. Hence, the difference between He phase III slope and SF_6 phase III slope (SF_6–He phase III slope difference) has been used as an indicator of intra-acinar function. Even if lung geometry were to change dramatically so as to push the He and SF_6 diffusion fronts out of, or further into the acinus, similar principles would apply, with SF_6 representing more peripheral structures than He. The SF_6–He phase III slope difference has been used as an indicator of peripheral lung disease: it has been correlated to histomorphometry of airways in the smoker's lungs [9], indicated peripheral changes in asthmatics [10], detected a specific peripheral response to methacholine in lung transplant recipients [11], and suggested peripheral sites of allergic reaction [12]. One pitfall when interpreting dual gas washout tests is that an absence of change in SF_6–He phase III slope difference cannot exclude an intra-acinar effect, for instance when both proximal and peripheral acinar structures affect He and SF_6 phase III slopes to the same extent. By contrast, however, a change in SF_6–He phase III slope difference definitely signals an intra-acinar effect.

The interpretation problem with the DTG phase III slope lays much closer to the way it is determined: derived from the molar mass (MM) signal, the DTG signal is generally referred to as an "aggregate" measure of He and SF_6. Yet it is assumed that the DTG phase III slope somehow also differentiates between He and SF_6 diffusive transport in the lungs, and that ternary diffusion (between He, SF_6 and N_2) can be neglected. Also, as pointed out in the editorial [6], the confounding effect of, for instance, the partial N_2 washout on the DTG curve is not understood. In an attempt to better understand the potential of the DTG curve, we first considered a set of physiologically plausible He, SF_6, O_2, CO_2 and N_2 traces as a function of exhaled volume during a DTG experiment (fig. 1a). Besides considering dilution of the various inhaled gas components (26.3% He, 5% SF_6, 21% O_2 and 47.7 %N_2), we imposed the following physiological constraints (based on published experimental data for normal subjects [8, 13–15]): Fowler dead space for He and SF_6 was considered to differ by 40 mL [13, 14]; He and SF_6 normalised phase III slopes were set to 0.07 and 0.13 L^{-1}, respectively [8, 13, 14]; at mid-expiration, CO_2 and O_2 concentrations were set to 4 and 17%, respectively, and their phase III slopes were considered to be opposite but equal in magnitude [3, 15]. Finally, N_2 concentration traces were obtained by mass balance at each instance during the expiration. Using 146, 44, 32, 28 and 4 $g \cdot mol^{-1}$ for SF_6, CO_2, O_2, N_2 and He, respectively, we then derived the corresponding MM signal and removed an offset based on the MM signal for air breathing, as previously described [3, 7], to obtain MM(He,SF_6) or the so-called DTG curve. From this curve, the DTG peak (0.6 $g \cdot mol^{-1}$) and DTG phase III slope (-0.2 $g \cdot mol^{-1} \cdot L^{-1}$ between 0.6 and 0.9 L expired volume) correspond to that obtained by Husemann *et al.* [7] in their normal group. Basically, this approach consists of considering a set of internally consistent He, SF_6, O_2, CO_2, N_2 traces, and calculating the MM(He,SF_6) curve as its mathematical consequence.

We now apply this same approach to two potential scenarios of lung disease: 1) He and SF_6 phase III slope are increased by a same amount, leaving the SF_6–He phase III slope difference unaltered at 0.06 L^{-1} (fig. 1b); or 2) both He and SF_6 phase III slopes are increased proportionally, resulting in an increased SF_6–He phase III slope difference (fig. 1c). In both hypothetical disease states, the average of the He and SF_6 phase III slope is five-fold that of the normal case (0.5 *versus* 0.1 L^{-1}). Let us now observe the corresponding behaviour of the DTG curve and its phase III slope. Scenario 1, where the He and SF_6 phase III slopes increase to the same extent (by 0.4 L^{-1}), can be representative of either a conductive airway change (*e.g.* bronchoprovocation) or an intra-acinar change coincidently affecting He and SF_6 by the same fixed amount. As expected in this case, the SF_6–He phase III slope difference is unaffected, yet the DTG phase III slope does change (in this particular case, it becomes zero). Scenario 2, where the He and SF_6 phase III slopes show the same relative increase (by a factor of five), both the SF_6–He phase III slope difference and the DTG phase III slope increase in absolute value, probably due to an acinar effect. In fact, the DTG curve obtained with scenario 2 probably represents a typical COPD patient in [7], even if a rigorous approach should include perfusion inequality (affecting O_2 and CO_2 curves). However, in a first approximation, DTG phase III slope in COPD patients with low diffusing capacity [7] probably relates to the acinar defect. It is in other disease states that extreme caution is warranted when propagating DTG phase III slope as an indicator of acinar change. Otherwise, some patients with a modified DTG phase III slope, *e.g.* in a state of bronchoprovocation leading to scenario 1, might get treated for peripheral lung defects that are simply not there.
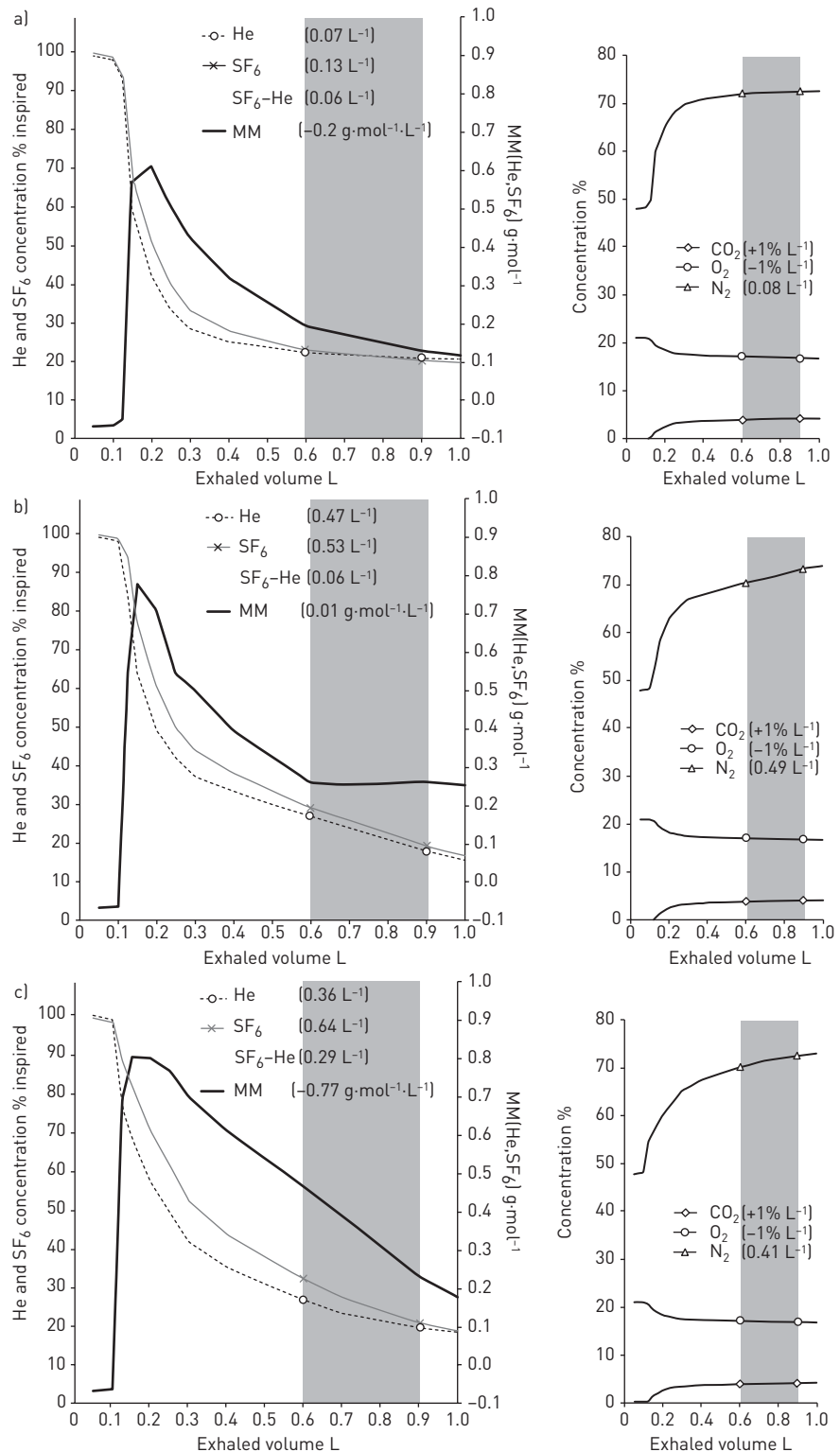
FIGURE 1 Expired concentration traces of gases involved (He, SF_6, CO_2, O_2 and N_2) when considering a 1 L inspiration of the dual gas mixture in an air-filled 3 L lung volume, and the corresponding so-called dual tracer gas (DTG) curve based on molar mass (MM(He,SF_6)); see the text for computational details. Also indicated are the phase III slopes computed between 0.6 and 0.9 L of expired volume (grey area) for all gases; for ease of assessing compatibility with phase III slope values in the literature, He and SF_6 phase III slopes are divided by the inspired minus the mean expired He or SF_6 concentration; N_2 phase III slope is divided by the mean expired minus the inspired N_2 concentration; MM(He,SF_6), O_2 and CO_2 phase III slopes are not normalised. Three cases are considered: a) a normal lung; b) a diseased lung showing increased He and SF_6 phase III slopes with SF_6–He phase III slope difference unaffected; or c) with SF_6–He phase III slope difference increased.

The intrinsic problem with using an aggregate MM(He,SF$_6$) signal to derive a DTG phase III slope as an index of acinar ventilation heterogeneity, also points to a possible solution. The O$_2$ and CO$_2$ traces, which are measured independently, can be inspected for variations in respiratory quotient. They can also be converted into their combined molar mass, to then extract a N$_2$ concentration curve. Then, the ensemble of DTG curves can be inspected in order to determine whether a particular patient phenotype is compatible with a scenario of type 1 or 2, or another alternative. We conclude that the noninvasive DTG test does hold promise for clinical use, but inevitably the patient's ease of performing the test is inversely related to the physician's effort to extract physiological meaning from it.

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Peripheral ventilation heterogeneity can be extracted from the dual gas test by considering all its gas components http://ow.ly/I62C8

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