Lung clearance index: should we really go back to nitrogen washout?

To the Editor:

A recent editorial in the *European Respiratory Journal* [1] recognises that the fundamental scientific data on lung clearance index (LCI) obtained by sulfur hexafluoride (SF_6) multiple-breath washout (MBW) have paved the way for clinical use of LCI. Although the editorial stresses the need for standardisation, it also appears to suggest that SF_6 can be replaced by nitrogen (N_2) as the washout gas.

We (Innovision ApS, Odense, Denmark) are the manufacturer of the AMIS 2000 medical mass spectrometer system that, using user-specific software and hardware, was adapted to perform MBW. The AMIS 2000-based devices are now considered the ''gold standard'' device for SF_6 LCI measurements in cystic fibrosis patients by opinion leaders in the field [2]. This device has been used in the vast majority of studies demonstrating the clinical value of SF_6 LCI in cystic fibrosis patients, with one recent notable exception: the demonstration of the change in LCI caused by Ivacaftor in cystic fibrosis patients with normal forced expiratory volume in 1 s, where a prototype version of our other system, Innocor, adapted for open-circuit SF_6 LCI, was used [3].

The AMIS 2000 adapted MBW system is too complex and too expensive for routine clinical use, and the LCI version and the required SF_6 gas mixture have no regulatory approval (CE mark or US Food and Drug Administration approval). To facilitate the clinical availability of SF_6-based MBW, we have introduced the Innocor system, which, together with the gases used, is approved for clinical use and provides a much less complex and cheaper alternative to the mass spectrometer system.

In the light of the strong emphasis on standardisation in the editorial, we find the suggestion to replace SF_6 with N_2 surprising, as this is a major change both from a technological and a physiological standpoint for the following reasons. 1) As N_2 cannot be measured by clinically available technologies, it is necessary to rely on indirect measurements, *i.e.* assuming that whatever is not recorded as oxygen (O_2) or carbon dioxide (CO_2) must be N_2. At the LCI point, where the N_2 concentration is only ~2%, the ability to accurately identify the N_2 concentration is significantly below that recommended by the expert consensus statement to which the editorial refers [2]. 2) Washout with 100% O_2 is not equivalent to that performed with room air. During N_2 washout using 100% O_2, gas viscosity changes by $\geqslant$10%, which causes a significant dynamic change in the gas analyser delay time during the test and affects flow resistance in the upper airways. O_2 flow across the alveolar membrane in poorly ventilated regions with end-capillary O_2 saturations <98% will also be affected when breathing 100% O_2. As this effect is smaller in well ventilated regions, distribution of ventilation will change. 3) As N_2 is not insoluble in blood and tissue, the washout curve is affected by a simultaneous washout of N_2 from blood and tissue (back diffusion).

Does all of this matter? Mathematically, the use of indirect measurement of N_2 amplifies the relative measurement error in the sum of CO_2 and O_2 concentrations at the LCI point by a factor of 49. Assuming no measurement error in CO_2:

$$\text{Indirect } N_2 \text{ at } 2\% = 100\% - 98\% \pm O_2 \text{ measurement error at } 98\%$$

At a relative error in O_2 measurement of 0.2%:

$$\text{Indirect } N_2 = 2 \pm 0.196\%$$

This means that if there is a relative measurement error in the sum of O_2 and CO_2 concentrations of, say, $\pm$0.2% (as seen with the best O_2 analysers), the relative error in the N_2 concentration at the end of the washout will be $\pm$10%, far in excess of that recently recommended [2].

As recognised by the consensus statement [2], the physiological impact of the use of 100% O_2 is unclear: ''Thresholds at which factors such as age, sleep state and sedation interact with 100% O_2 to affect breathing pattern remain unclear''.

With a reference to a study published in 1953, the consensus statement [2] states that only limited data are available on N_2 back diffusion. However, a much more recent study [4] has shown a very significant N_2 back diffusion from blood and tissue within the time frame of a normal washout test. The data from this study imply that almost 25% of the N_2 in the lungs at the LCI point stems from back diffusion of N_2.

A recent study [5] has compared N_2 LCI with SF_6 LCI obtained with the gold standard method. Significant differences were found, and the authors concluded that independent normative values are required and that interventional studies are needed to clarify the role of N_2 LCI as an outcome measure in clinical trials in cystic fibrosis patients. The limits of agreement between N_2 and SF_6 LCI in cystic fibrosis patients were >7 LCI units, far in excess of the treatment related change reported in the Ivacaftor study of 2.1 units [3].

Finally, both the editorial [1] and the consensus statement [2] reported that the SF_6 mixture required to perform LCI testing is often not universally available and not approved. This is a misunderstanding. The mixture used with the Innocor system is an off-the-shelf, 150-mL gas tank in the European Union, the USA, Canada and in all other European countries where Innocor is used.

If the reference for clinical use of the LCI test is the scientific data obtained with the gold standard mass spectrometer device over many years of research, the suggestion to switch to N_2 LCI is premature and scientifically unfounded. Notwithstanding the well recognised problems of indirect N_2 measurement and the physiological effects of pure O_2, recent research has also highlighted that N_2 back diffusion may be much more important than previously thought.

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From the authors:

We thank J.G. Nielson for his comments about our editorial related to the consensus statement for inert gas washout measurement using multiple- and single-breath tests recently published in the *European Respiratory Journal* [1, 2]. Given that we are unable to identify relevant new information concerning the topic at hand, we prefer not to add any further comments and kindly refer to the previously mentioned, very elaborate, consensus statement [2].

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Consensus statement for inert gas washout measurement http://ow.ly/rm6nI

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