Physiological Measurement of the Small Airways

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Key Words

Lung disease · Small airways indices · Physiological measurements

Abstract

Noninvasive physiological measurements are reviewed that have been reported in the literature with the specific aim being to study the small airways in lung disease. This has mostly involved at-the-mouth noninvasive measurement of flow, pressure or inert gas concentration, with the intent of deriving one or more indices that are representative of small airway structure and function. While these measurements have remained relatively low-tech, the effort and sophistication increasingly reside with the interpretation of such indices. When aspiring to derive information at the mouth about structural and mechanical processes occurring several airway generations away in a complex cyclically changing cul-de-sac structure, conceptual or semi-quantitative lung models can be valuable. Two assumptions that are central to small airway structure-function measurement are that of an average airway change at a given peripheral lung generation and of a parallel heterogeneity in airway changes. While these are complementary pieces of information, they can af-

fect certain small airways tests in confounding ways. We critically analyzed the various small airway tests under review, while contending that negative outcomes of these tests are probably a true reflection of the fact that no change occurred in the small airways. Utmost care has been taken to not favor one technique over another, given that most current small airways tests still have room for improvement in terms of rendering their content more specific to the small airways. One way to achieve this could consist of the coupling of signals collected at the mouth to spatial information gathered from imaging in the same patient.

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Previous articles in this series: 1. Usmani OS: Unravelling the small airways: structure-function-treatment relationships in asthma and COPD. *Respiration* 2012;84:1–3. 2. Hamid Q: Pathogenesis of small airways in asthma. *Respiration* 2012;84:4–11. 3. Baraldo S, Turato G, Saetta M: Pathophysiology of the small airways in COPD. *Respiration* 2012;84:89–97.

Introduction

We provide here an overview of the physiological techniques that have been applied in a clinical context to study the contribution of small airways to various disease processes, i.e. those for which reasonable evidence exists that small airways could be implicated at all. Over the past decade, dedicated small airways studies with invasive or imaging techniques have gathered evidence to substantiate the presence of structural abnormalities in the small airways of asthma patients [1–3], smokers [4–6], patients with chronic obstructive pulmonary disease [7–11], lung transplant patients developing bronchiolitis obliterans syndrome [12], acute respiratory distress syndrome patients [13] and cystic fibrosis patients [14]. Based on these solid datasets collected over the past decade and all studies preceding these, it is fair to assume that the small airways are a potential target for disease, and hence for therapy whenever this is possible. At the same time, there is a risk that in these diseases where small airways may potentially be involved, physiological measurement of small airways dysfunction becomes a self-fulfilling prophecy. In a worst case scenario, physiological measurement would unduly identify the lung periphery as a therapeutic target and steer alternative therapies specifically towards the lung periphery. This review aims to present various aspects of noninvasive physiological measurement techniques that are currently being used including potential pitfalls, which should enable critical appraisal of published or indeed future physiological studies of the small airways.

Rather than reiterating the milestone publications that have been reported in a considerable number of existing reviews about the small airways, this chapter has been deliberately restricted to the small airway work achieved and the tools used in the past decade. We review original contributions with data gathered on adult patients, where physiological measurement provides one of the primary outcome measures in order to make clinical statements about the functional status of the small airways. We limited our Medline search to English language publications in the past decade, and after careful examination of all proposed contributions and excluding animal studies, we were surprised to be left with only 155 original contributions with the primary objective of studying the small airways in adult patients with physiological tests. This means that, despite the growing awareness over the past 10 years that the small airways may be important in various disease processes, little more than one attempt per month has been made to try and measure it with the fi-

Table 1. Overview of small airways tests

<i>Flow-volume loop (spirometry)</i>
End- or mid-expiratory flows
FVC
Density dependence of maximal expiratory flow
<i>FOT/impulse oscillometry</i>
Resistance at various frequencies
Reactance at 5 Hz
Resonance frequency
Inspiratory versus expiratory differences in resistance and reactance
<i>SBW or MBW</i>
Phase III slopes
Closing volume
Dependence of tracer gas diffusivity
<i>Other techniques</i>
Monodisperse aerosol bolus
Exhaled aerosols
Crackle sounds
Response to small-particle provoking agent
Pletysmographic versus dilution lung volume difference

nality of inferring a clinical statement about the functional status of the small airways. When subdividing physiological measurements of the small airways into 4 categories according to technical requirements (table 1), 52% of the original studies use solely flow-volume measurement during forced expiratory maneuvers (spirometry), 21% use pressure-flow measurement [forced oscillation technique (FOT) or impulse oscillometry], 22% are based on exhaled gas concentration volume measurement after inhalation of a test gas mixture [mostly single- or multiple-breath washout (SBW or MBW)] and approximately 5% apply various other techniques. The 74 studies using more than just spirometry for clinical statements about the small airways have all been included in the reference list. Not included in this review are studies where an inflammatory marker such as alveolar nitric oxide (NO) concentration (derived from exhaled NO) is sometimes referred to as a small airway test; alveolar NO and its relation to NO production in the bronchial (small) airways are the subject of a compilation provided elsewhere [15]. While being primarily a reflection of biochemical processes occurring in the small airways, this and other exhaled biomarker results are potentially influenced by airway mechanical factors that can be characterized by the physiological tests of small airway structure-function presented here.

Fig. 1. Schematic overview of the most widely used tests to identify small airway dysfunction. Clockwise: spirometric forced expiratory curve, resistance and reactance during tidal breathing, MBW and SBW.

Spirometry

Spirometry is still the most widely used primary end point when studying the small airways in disease, probably because it is a relatively easy and quick test to perform with very basic lung function equipment requirements. Particularly in interdisciplinary studies, where the lung periphery is considered as a potential site of collateral damage of a disease pertaining to a different organ, end-expiratory flows are examined in search of small airway dysfunction. This is not surprising, given that the text book definition of small airways disease is

based on spirometric end-expiratory flows. While end-expiratory flows are undoubtedly influenced by flow obstruction in the small airways, it has been shown that FEV₁ and/or FEV₁/FVC can also be linked to structural changes in the small airways, such as volume fraction of elastic fibers [16], airway dimensions (lumen and wall area) [17] or total airway wall thickness [18], or number of leukocytes in the small airways [19]. It has also been suggested that a decreased FEV₁ in the face of normal FEV₁/FVC actually reflects small airway obstruction [20].

This begs the question of what precisely is meant by physiological measurement of the small airways. The minimum requirement is that a small airway test is potentially sensitive to small airways structure and/or functional changes. This is true for end-expiratory flows, but also true to some extent for FEV₁ and FEV₁/FVC in particular disease situations. Conversely, when large airways flow obstruction or overall restriction are also present, isolating the small airways effect in FEV₁, but also in end-expiratory flows, becomes more difficult. For instance, in the case of an FVC change, end-expiratory flow determined at a fixed percentage of FVC is no longer deemed valid and isovolume end-expiratory flows measured at the same absolute volume are used instead [21, 22]. Alternatively, FVC is also used as an indicator of small airways function, more specifically of airway closure and trapped air beyond them [23–26]. Another way to identify the small airway content from forced expiration is by examining the density dependence of forced expiratory flows, comparing air and heliox [27–29]. There is probably no easy way of extracting small airway information from spirometry in a disease state which involves more than a pure small airway change. An elegant example of a model-based approach is the one by Morlion and Polak [30], where the particular shapes of flow volume loops in lung transplant patients are reproduced by simulating the effects of lung denervation and airway obstruction associated with the development of bronchiolitis obliterans syndrome in the lung periphery.

Forced Oscillation Technique

Possibly because of the interpretation problems with spirometry, but also in an effort to attribute flow limitation in the small airways to their resistive or compliance properties or a combination of both, the FOT has been proposed. The basic idea is that oscillating pressures and flows lead to a measure of impedance, with a real component (flow and pressure in phase) and an imaginary component (flow and pressure out of phase) respectively referred to as resistance and reactance. The FOT is usually performed at distinct frequencies (typically between 5 and 25 Hz), or alternatively the impulse oscillometry method is used which aims to measure all frequencies at once. Both techniques have been applied for the study of small airways, mostly to characterize or phenotype asthma and COPD patients [31–36], assess the small airways effect of inhaled therapy [37–39], follow up lung trans-

plant patients [40] or assess small airway changes in cardiac patients [41, 42]. When resistance is measured at various frequencies, the frequency dependence of resistance is proposed to be particularly sensitive to the small airways. This premise has been adopted to study the small airways in response to: different inhalation therapies in asthma and COPD [43–46], deep inspiration [47], *Mycoplasma pneumoniae* infection in asthma [48], mucus clearance techniques in bronchiectasis [49], specific challenges in asthma [50] or environmental exposure [51, 52]. Frequency dependence of resistance was also used for correlating small airway function to disease control [53] or to the noninvasive measurement of peripheral lung inflammation in terms of alveolar nitric oxide concentration [54, 55]. Overall, the observed increases in resistance and frequency dependence of resistance observed experimentally in adult patients are small, and the actual contribution from the small airways remains unclear. A more convincing signal in response to lung disease comes from the reactance, requiring a slightly more elaborate analysis by separately considering reactance during inspiratory and expiratory phases [56]. Reactance at 5 Hz during the expiratory phase (using the inspiratory reactance as a baseline) appears to be particularly sensitive to expiratory flow limitation involving small airway closure or near closure, and this has been used in an effort to distinguish small airways function in asthma and COPD patients [57, 58]. Another advantage of the FOT is that resistance and reactance measurements – or at least their small airway content – can also be examined at different lung inflations [59]. While the potential of the FOT continues to be explored, the interpretation of resistance and reactance and their relationship to the small airways is less than straightforward, depending also on whether actual airway or parenchymal characteristics are being considered. Hence, we refer to model-based reviews on the topic pertaining to disease in the adult human lung [60–62].

Spirometry and FOT measurement of flow and pressure, in their most common interpretation, rely on a conceptual model with several serial compartments representing upper, central and small airways and distal lung units (and sometimes serial subcompartments of these). In other words, the clinical interpretation emanating from the spirometric or forced-oscillation studies of small airways function in disease are mostly related to all small airways as a whole or to ‘an average’ small airway. While invasive or imaging procedures suggest that disease-induced lung changes may occur heterogeneously [63], it is difficult to assess just how het-

erogeneous the small airway changes really are because of the relatively low number of samples or images that can be analyzed. However, it is plausible that any disease affecting the small airways will not necessarily do so in a uniform way, either affecting any two parallel lung units in a different way or primarily affecting apical or basal lung zones. It was shown conceptually [64] how a probability function representing heterogeneous narrowing of parallel airways not only results in a wide probability spread of the resulting resistance of the conducting airway tree as whole, but also in an increased mean resistance. In the clinic, the effect of heterogeneity of the parallel airway changes on FOT-derived resistance has also been investigated, and at least part of the frequency dependence of resistance appears to be affected by it [65, 66]. Hence, the difference between resistance obtained at, for instance, 25 and 5 Hz, which is an FOT parameter frequently reported to be a reflection of the small airways, may well be the result of uniform small airways changes, of parallel heterogeneity in airways of undetermined size or both. Lung models incorporating varying degrees of realism have been developed either in combination with experimental FOT measurements [65, 67, 68], or to simulate distinct patterns of small airways changes compatible with a disease state [66] and assess the impact from the upper airways [67, 69]. In an effort to narrow down the number of possibilities compatible with a given FOT pattern, a particularly promising approach has been to combine it with imaging. In what is proposed as an integrated functional imaging approach [70–72], a realistic model is constructed corresponding to the discernable boundaries of a lung for which ventilation is imaged by PET or MRI. Constriction patterns of varying heterogeneity on airways of varying size are then imposed on the model until a pattern is found that is compatible with the ventilation patches observed in the images and the FOT data obtained at the mouth in the same patient. Because of the limited availability of such infrastructure, integrated functional imaging studies will probably be most useful to validate and identify those FOT parameters that are most likely to maximize small airways information in the adult patient, such that these can then be used in the clinic with a greater degree of confidence about what they are measuring.

This raises another aspect of physiological measurement of the small airways. In the strictest noninvasive sense, i.e. that no wedged bronchoscopes are being used to measure lung mechanics more peripherally [60] or esophageal balloons being used to compute HRCT aided

small airway compliance *in vivo* [73], a physiological measurement implies that we can only measure a cumulative effect at the mouth, from which the small airways content has to be isolated. Despite this potential disadvantage, it also presents the obvious advantage that potentially all small airways of the lung can be represented. First, this comprises the airways of a size that is still visible at the resolution scale of the imaging modality, but it includes all airways and not only those in the imaged lung slices. Second, the airway sizes below the resolution of the imaging modality can still be represented in a physiological test. Given that the lower limit for measuring airway size with HRCT typically is of the order of 1- to 2-mm-diameter airways, the small airways beyond that resolution scale are located in the zone where ventilation distribution by diffusive gas transport is gradually taking over from ventilation distribution by convective gas transport [74]. In this transition lies the potential to measure the small airways via ventilation distribution tests such as SBW and MBW tests.

Washout Tests

SBW and MBW tests have been around since the mid-20th century and were promoted as promising diagnostic tools for the early detection of any structural abnormality including the large airways, as well as for their potential sensitivity to small airways alterations. The latter is particularly promising when different diffusivity gases are used to compute the SBW- and MBW-derived indices, such as the slope of the alveolar plateau or phase III slope [74]. Since the helium (He) diffusion front is more proximally located than the SF₆ diffusion front, a disease process or therapeutic intervention which affects He phase III slope more than SF₆ phase III slope, signals a proximal acinar effect, i.e. in the respiratory bronchioles. Conversely, if both the He and SF₆ phase III slopes increase and the phase III slope difference does not change, this can either imply a purely conductive airway effect (affecting He and SF₆ to the same extent) or concomitant effects in both the proximal and peripheral parts of the acinus. Hence, with a SBW test the only definite conclusion about a peripheral lung effect can be reached when a difference in the He and SF₆ phase III slopes arises. The SBW test with He and SF₆ has been used to assess a potential effect of different provoking agents [75] or of cold air challenge [76] on the small airways of asthma patients.

Probably because of the demanding technical requirements for measuring different diffusivity gases and the more widespread availability of nitrogen (N_2) SBW and MBW testing in adult pulmonary function equipment, the N_2 SBW is still being used and, indeed, its phase III slope propagated as a small airways index. The SBW N_2 phase III slope has been used to study the small airways in patients with poor asthma control [77], to study gender-dependency [78], the effect of pentosidine [79] and different inhaled steroid formulations [28] in asthma. It has also been applied to the characterization of small airway disease in smokers [80], in overt COPD [81] and in α_1 -antitrypsin-deficient emphysema [82]. A link between the small airway function (SBW N_2 phase III slope) and lung inflammation has been sought in asthma [83, 84] and in COPD [85]. Finally, the SBW N_2 phase III slope was investigated for its diagnostic and predictive capability of bronchiolitis obliterans syndrome in lung transplant patients [86].

The text book explanation of the N_2 phase III slope is that it is positive (non-zero) whenever any 2 lung units are ventilated to a different degree, and a flow asynchrony arises between these 2 units such that the best ventilated unit empties preferentially early in exhalation. For instance, the weight of the lung is known to produce a positive N_2 phase-III slope due to the greater specific ventilation of the dependent versus the nondependent lung zones and the preferential emptying of the basal lung zones at the beginning of expiration. Hence, depending on whether lung diseases preferentially affect the basal or apical lung zones, the N_2 phase III slope may be affected differently, and one study has elegantly shown how gravity can even be exploited to reveal peripheral lung disease in a part of the lung that is brought into a preferential position along the line of gravity [87]. The vital capacity SBW maneuver is also regularly used to simply determine the closing volume (or closing capacity) as a measure of small airways closure, which can also have a preferential topographical distribution. Closing volume or closing capacity has mostly been used to study the effect of inhaled or systemic asthma therapy [28, 37, 88–91], but also to characterize asthma and COPD patients [33, 77, 79] and to look for links with peripheral inflammation [83, 85], or as a measure of peripheral airway abnormality in patients with chronic heart failure [92].

Depending on the SBW maneuver, its N_2 phase III slope can also result from ventilation heterogeneities that develop between lung units much smaller than topographical lung regions, and thus subtending from small airways. While model simulations have shown that, in

the normal adult lung, a major part of the SBW phase III slope can be generated between units subtending from intra-acinar airways [93], a disease state may well bring about structural changes in conductive airways, generating ventilation heterogeneities between units larger than acini, also leading to an increased SBW phase III slope. Hence, besides the above-discussed gravity contribution (which is estimated at 22% in a normal man [94]), the N_2 phase III slope of the SBW test may be sensitive to all airways, including the small airways, but by no means specific for it. An absence of change in N_2 phase III slope in a given lung disease may be a reasonably good indicator that the small airways are not affected. Conversely, a change in N_2 phase III slope in a given lung disease could very well occur without any involvement of the small airways. Finally, it has been suggested that the phase III slope derived from a tidal CO_2 expiration trace could also reflect the small airways [95], but obviously perfusion heterogeneity effects cannot be excluded in this case.

A washout modality that aims to be more specific for the small airways is the MBW analysis of the normalized phase III slope, which distinguishes between convection-dependent and diffusion-convection-dependent ventilation heterogeneities, thought to occur mainly in the conductive and acinar airways, respectively. Essentially, the phase III slope is computed in each exhalation and divided by the mean expired concentration. In this way, a gradual increase of the normalized phase III slope as the MBW test progresses reflects the fact that, with respect to the average concentration still inside the lung as a whole, concentration differences between different lung units are increased due to ventilation heterogeneity. One responsible mechanism for this is a convective gas transport mechanism, whereby convective gas transport into one unit is favored over that into the neighbouring unit due to enhanced constriction of one airway or enhanced stiffness of its subtended unit. The other mechanism generating a slope is the diffusion-convection interaction in the presence of structural asymmetry, which is the case with the acinus. With this mechanism, the normalized phase III slope remains more or less constant throughout the MBW test. Due to these two mechanisms and the fact that the latter generates a quasi-constant normalized phase III slope (due to diffusion-convection in the acinus) and the former a steadily increasing normalized phase III slope, the normalized phase III slope as a function of lung turnover can be reduced to two characteristic indices of ventilation heterogeneity: S_{acin} (which basically corresponds to the normalized phase III slope of the first

breath) and S_{cond} (which corresponds to the rate of rise of the normalized phase III slope); see [74] for details and theory.

S_{acin} and S_{cond} are usually referred to as indices of acinar and conductive ventilation heterogeneity or their mechanistic counterparts, diffusion-convection and convection dependent heterogeneity. These indices have been measured in asthma [96–101], in smokers with or without COPD [102–104], in cystic fibrosis [105] and in the follow-up of small airways function after lung transplant [106] and allogeneic hematopoietic stem-cell transplantation [107]. Whenever S_{acin} , or diffusion-convection-dependent ventilation heterogeneity, is elevated in disease, there is no way to distinguish between proximal and peripheral intra-acinar effects; this would be possible if S_{acin} were determined from MBW tests including He and SF₆ as a test gas mixture. Nevertheless, in terms of the small airway content, S_{acin} is probably the most specific of the indices of ventilation heterogeneity. When it is unchanged, acinar structure is likely to be normal; when a change does occur, this may be safely interpreted as a result of a structural change in the acinus, irrespective of the structural changes occurring more proximally. Whenever S_{cond} or convection-dependent ventilation heterogeneity is elevated in disease, there is no way to distinguish between proximal and peripheral conductive airway effects. Hence, there is a priori no reason to assume that S_{cond} should represent a change occurring specifically in the small conductive airways. In this case, the combination with spirometry can be used to infer from a disease with no change in FEV₁ and a change in S_{cond} that the small (conductive) airways must be the major determinant of change [101, 108]. A similar reasoning can be made for other indices of ventilation heterogeneity that are potentially sensitive to the small airways, but are not a unique reflection of it. A case in point is the lung clearance index [105, 109], which can potentially pick up changes down to the most peripheral airways, but which can only be accurately interpreted as a reflection of small airways changes by combining it with an index of large airway function.

Aerosol Probes

In the second half of the past century, a number of studies showed the potential of using aerosols rather than gases to probe the peripheral airways. The idea is that aerosols can be confined to a small volume (bolus) and inhaled to a given lung depth by having the bolus fol-

lowed by a given volume of aerosol-free air. When recovering the aerosol boluses inhaled to various lung depths, they are then examined for bolus width, area under the curve (deposition) and bolus skewness, in order to infer the structural changes that the aerosol must have experienced while being transported into and out of the most peripheral lung spaces. Despite its elegant concept, the lack of availability of a cheap user-friendly aerosol delivery and recovery device is probably the reason for the limited number of aerosol-based small airway studies in the past decade [110]. Alternatively, aerosol characteristics have been modulated to preferentially reach the small airways, such that small-particle adenosine monophosphate provocation becomes a diagnostic tool to assess inflammation-related changes in the small airways that can, in turn, be treated with small-particle inhaled corticosteroid aerosols [111]. Finally, endogenous aerosols measured at the mouth during the exhalation phase of various breathing maneuvers are thought to originate from the terminal bronchioles due to bronchiolar re-opening following airway closure [112, 113]. Another means to study airway closure and distinguish between inspiratory and expiratory airway opening and closure is by the analysis of crackle sounds in terms of their frequency, amplitude and polarity [114].

Airway closure regularly appears in the discussion of the parameters deriving from spirometry (mainly FVC), FOTs (mainly reactance) or ventilation distribution tests (mainly closing volume). Alternatively, airway closure is measured by the difference between pletysmographic and dilution functional residual capacity [115] or by inspired capacity measured by pletysmography or with a spirometer [24, 27, 102]. While airway closure is most likely a small airway feature which is often enhanced in disease, it is probably the most difficult small airway characteristic to quantify, because it is almost impossible to infer from physiological tests whether near-closure or full closure has occurred during the inspiratory and/or expiratory phase. While flow and volume measurements mostly reflect airway closure during the inspiratory or expiratory breathing phase, gas concentration measurements are usually the combined effect of closure early in inspiration when concentration differences between open and closed lung zones are built up, and closure towards the end of expiration. For a more exhaustive discussion on the physiological measurement of (small) airway closure, we refer to review articles on the subject [116, 117].

Concluding Remarks

When trying to examine the small airways by simply monitoring flow and gas concentration signals at the mouth, the number of options is relatively limited. Given the differing degrees of sensitivity and specificity of the above-discussed physiological tests to various aspects of the small airways (patency, heterogeneity) it may be wise to combine tests. This can be done by carefully selecting parameters from different tests alongside each other, while in keeping with the time constraints imposed by any given clinical circumstance. Ideally, physiological tests would be combined with imaging modalities of lung structure or function in the same patient, and possibly aided by computer simulations, which should lead to a better estimation of the most likely patterns of airway abnormality in the small airways or elsewhere. A critical issue for model simulations to be successful is to have a realistic idea of the kind of airway alterations, with respect to what is known of a normal human lung, in various lung diseases. For instance, when it is shown that the number of terminal bronchioles in COPD patients is reduced to almost 10% of that encountered in a normal lung [7], the interpretation of any physiological test in these patients critically depends on the way the remaining lung airways and tissue are connected with the mouth, where the signals for physiological tests are obtained [118]. In the case of a ventilation distribution test, which is interpreted on the basis of the diffusion front, severe lung diseases such as COPD or cystic fibrosis may well alter the diffusion front itself. Under these circumstances, model simulations can help interpret ventilation distribution tests, provided that realistic morphological features and at least some quantification of altered air space connectivity can be incorporated. The same considerations apply to an appropriate interpretation of the other noninvasive physiological tests.

Finally, the literature review over the past 10 years shows us that 'early detection' and 'small airway detection' are often used interchangeably. It may well be true that early changes, defined as those changes that are picked up earlier than can be detected by standard lung function tests, are likely to originate in the small airways. However, these physiological tests are also particularly sensitive to the heterogeneity of airway changes, and in diseases where heterogeneity is increased in the small airways, such tests are expected to outperform standard lung function. However, it needs to be borne in mind that structural heterogeneity is not zero in normal subjects and that, for instance, ventilation heterogeneity increases

with age. Hence, in a longitudinal study design or in clinical settings involving older patients, age should also be a factor when measuring the small airways. There is a growing body of evidence that small airway indices derived from spirometry, FOTs and ventilation distribution tests in normal subjects deteriorate with increasing age, in accord with the expected physiological effects [119]. Hence, physiological test results reflecting the small airways should be carefully inspected for disease versus normal ageing effects.

In conclusion, physiological measurement of the small airways can be successful in a clinical context; with a relatively limited effort on the part of the patients, most of the work involved lies with the investigator to accurately interpret the test at hand. Small airway indices with a sensitivity to small airways alteration beyond reasonable doubt are most convincing when they provide a negative result. In this case, it can be safely concluded that the small airways are not implicated in the clinical situation under study. Conversely, any changes in physiological small airway indices need to be interpreted with caution, considering the clinical implications they may entail, most notably that small airways – if abnormal – should be treated with alternative therapeutic options such as finer aerosol medication. Ideally, a positive signal in the index of the small airways should be cross-checked, either by using alternative small airway tests with an independent technique and/or aided by model simulations to make sure that airways other than the small airways are not the cause of observed changes. With lung imaging capabilities steadily evolving, an attractive research tool would consist of a physiological test complemented by an imaging modality and a lung model matching the sophistication of the imaging technique. Even if such an integrated functional imaging approach brings about only 1 study per year over the next decade in a reasonable number of representative patients, this would be an invaluable contribution that could really enable us to better delimit the true potential of physiological small airway tests.

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