Noninvasive Measures of Lung Structure and Ventilation Heterogeneity

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14.1 Introduction

A major reason for the difficulty in understanding gas transport and mixing in the lung periphery is related to the impossibility to perform direct measurements of gas concentrations in the alveolar region without interfering with the mechanisms of transport. If the measurements are performed at the mouth, the gases are first inspired and convected to the lung periphery. During a breath cycle, they diffuse in a space with linear dimensions that are of the order of magnitude of the square root of the molecular diffusion coefficient. For air, this corresponds to a few millimeters. During expiration, the recorded concentration at the mouth gives an information about the last lung generations, where O_2 and N_2 have diffused. Part of this information is contained in the slope of the alveolar plateau of the single-breath (N_2) washout (SBW). Georg et al. [1] used gases of different diffusivities such as He and SF_6. Indeed, the different expiratory concentration profile of these gases carries information about the lung structure in a specific lung region. A renewed interest in SBW came also from the work of Cosio et al. [2] demonstrating correlations of SBW-derived indices, such as N_2 phase III slope and closing capacity, with morphological measures of peripheral lung lesion in smokers. A series of epidemiological studies followed, investigating the potential of these tests to predict a decline in forced expired volume in 1 s (FEV_1) in smokers, but with conflicting outcomes [3–6]. However, the interest in the SBW test increased with the results of a 13-year

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follow-up study [7] indicating that the N_2 phase III slope of the vital capacity SBW test was a key index in predicting the smoker developing overt COPD.

In the meanwhile, several groups had continued their investigations into the basic mechanisms of gas transport in, and its heterogeneous distribution over, the lungs. As reports of the actual geometrical configuration of the human lungs emerged [8–10], new models could be developed in an effort to simulate the SBW test. An essential feature of the anatomical basis for the lung models to be developed was that the lung was asymmetrical, in the conductive airway [8] as well as in the acinar airway segment [9, 10]. It was shown, for instance, how the interaction of convective and diffusive gas transport in the asymmetrical acinar air spaces could generate N_2 concentration differences that are reflected in a N_2 gradient in the alveolar phase III of an SBW exhalation [11]; in addition, this N_2 phase III gradient was expected to increase with increasing asymmetry. Although this is just one potential mechanism of ventilation heterogeneity, it illustrates how the delivery and recovery of gas concentrations can provide noninvasive indexes of ventilatory heterogeneity that are representative of lung structure, or its abnormality in the case of lung disease.

A different technique can be used as a tool to investigate pulmonary ventilation. It consists of aerosol inspiration and the analysis of particle concentration during the subsequent expiration. When aerosols are inspired as a bolus, the very low (Brownian) diffusion coefficient of the particles enables to target specific generations of the bronchial tree. For decades, fields of gas and particle transport in the lung proceeded in parallel, with very limited cross-fertilization. Despite being more difficult to generate and measure experimentally than gases, aerosols can be a very elegant tool to sample the structure in the lung periphery. We describe, at the end of this chapter, aerosol applications showing the complementarity of both approaches.

14.2 Gas Washout Tests

The washout technique basically consists of delivering to the lungs a gas mixture that is not originally present in the lungs and then characterizing the exhaled gas mixture as a function of exhaled volume. Figure 14.1 shows the concentration plot of N_2 as a function of exhaled volume after a vital capacity inhalation of 100 % O_2 (SBW test). One can clearly distinguish an initial phase where the inhaled gas is exhaled again without having been mixed with lung resident air (phase I), a transitional phase II, an alveolar phase III, and a final rise in phase IV. Depending on the subject under study, cardiogenic oscillations are superimposed on phases III and IV; yet, in most lung diseases which give rise to steeper phase III slopes, cardiogenic oscillations cannot be distinguished.

On the basis of experimental and modeling studies of gas transport in the human lungs, we can summarize the contributions to the phase III slope as follows:

- *Ventilation heterogeneity between upper and lower lung regions, generated by the weight of the lung on earth:* In normal lungs, the gravity-dependent contribution to the phase III slope has been investigated in studies involving different body positions [12, 13], in experiments aboard parabolic flights [14, 15], or

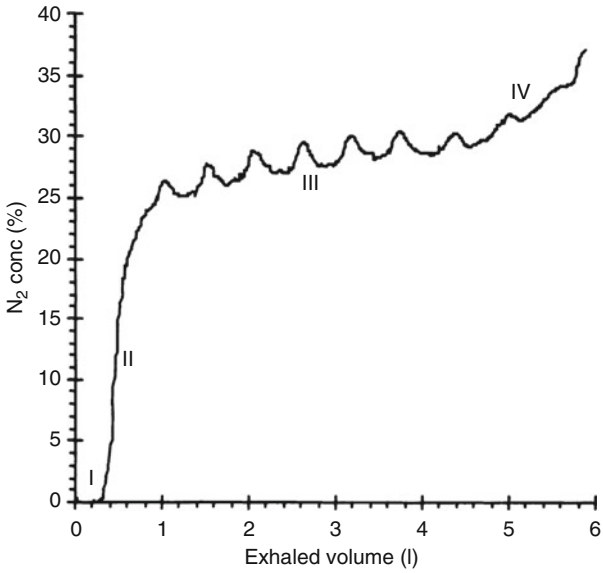

Fig. 14.1 Vital capacity SBW test in a healthy subject; exhaled N_2 concentration versus exhaled volume down to residual volume, showing phases I, II, III, and IV

during Spacelab missions [16, 17], and depending also on the washout maneuver used, the gravity contribution to the N_2 phase III slope is seen not to exceed approximately one fifth; in fact, the largest contribution from gravity could be found in the phase III slope of a vital capacity SBW maneuver (as opposed to washout maneuvers covering the near-tidal volume range). Since certain disease patterns may be linked to distinct locations (e.g., in patients with predominant emphysema in upper lung zones), the effect of gravity can actually be exploited to investigate structure-function in these zones. Van Muylem et al. [18] proposed to place single-lung transplant patients in such a body posture that the SBW phase III could actually be linked to structure-function of the dependent and non-dependent lungs.

- *Ventilation heterogeneity between units within the acinus, which results from convective and diffusive gas transport competing in the structural asymmetry of the lung periphery:* Due to this so-called diffusion-convection interdependence [19], the smallest intra-acinar lung unit subtended by any pair of daughter branches shows the lowest N_2 concentration during inhalation; during subsequent exhalation, the differential convection from smaller and larger intra-acinar units and back diffusion of N_2 into the smaller of two units leads to a slope in the exhaled N_2 concentration versus volume trace. Over a wide range of structural asymmetries, interdependence predicts that the larger structural asymmetry leads to the greater N_2 phase III slope. In addition, the complex interaction of hundreds of parallel and serial branch points inside each acinus plays a key role [20, 21]. A model simulation study [22] has shown that not only the mean structural asymmetry at branch points of any given peripheral lung generation is a determinant of the phase III slope but also the heterogeneity in asymmetry among

parallel branch points of that generation. For any given mean asymmetry, the larger parallel heterogeneity in asymmetry also leads to a steeper N_2 phase III slope. In fact, with simulations incorporating a realistic heterogeneity of intra-acinar asymmetry, the potential intra-acinar contribution to the N_2 phase III slope ranges 80–100 % [22] depending on the washout maneuver.

- *Ventilation heterogeneity between lung units, probably much smaller than the upper and lower lung regions, but larger than acini,* i.e.*, at the level of lung units where convective gas transport dominates over diffusive gas transport:* This mechanism implies differences in specific ventilation (unit inspired volume per unit lung volume) and flow asynchrony between lung units upon emptying. This mechanism of ventilation heterogeneity can be generated by a heterogeneity in P-V characteristics of such lung units or a heterogeneity in airway resistance of the subtending airways; yet, in human subjects, no quantitative data on these properties at this scale exist. Also, heterogeneity in airway resistance or P-V characteristics should be such that the best ventilated lung unit is the one to empty preferentially early in expiration, in order to produce a positive contribution to the N_2 phase III slope. There are a huge number of branch points located in the conductive airways where such convection-dependent heterogeneity can occur. Maybe the number of possibilities can be limited by use of so-called integrated models such as the one offered by Tawhai et al. e.g., [23], with a very realistic appearance from a structural viewpoint. However, the way it simulates airway function is currently still burdened by oblique parameter fitting, which makes it almost impossible to determine where some highly unrealistic simulations, acknowledged by the authors, find their origin. Nevertheless, further development of such models, closely guided by the wealth of experimental washout data, should make it possible to quantitatively determine the confines within which this mechanism accounts for the phase III slope in normal man. While the net contribution to the N_2 phase III slope from this mechanism may actually be relatively modest during an SBW obtained from the normal lungs, its effect can be exaggerated in the diseased lung [24, 25] or in the asymptomatic lung after histamine bronchoprovocation [26].
- *Gas exchange:* The fact that the respiratory coefficient is <1 brings about volume shrinkage and hence a progressive concentration of all gases as the exhalation proceeds, leading to an amplification of the phase III slope for the lung resident gas N_2; in human lungs, its effect has been estimated at 10 % for a vital capacity SBW maneuver [27].
- *Airway closure:* When decomposing a vital capacity SBW, involving a continuous O_2 inhalation starting from residual volume, into separate washout experiments whereby 150 mL volumes of O_2 are inhaled at different lung volumes over the vital capacity range, it is possible to study the effect of ventilation heterogeneity at any given lung volume and relate it to the SBW phase III slope [28]. In this way, it has been shown that in the case of a vital capacity SBW test in normal subjects, the heterogeneous distribution of gas inhaled at lung volumes below FRC in fact produces a negative contribution to the N_2 phase III slope. Hence, exaggerated airway closure below FRC has an attenuating effect on phase III slope, while disease states, where airway closure also appears around and above

FRC, could yield a positive contribution to phase III slope. Hence, the actual contribution to N_2 phase III slope from airway closure is not straightforward.

The problem with these different mechanisms generating a N_2 phase III slope is that their relative contribution – positive or negative – may be hard to determine and is expected to vary, depending on the disease state of the lungs. Let us first reconsider the reason why tests of ventilation heterogeneity were thought of as a promising diagnostic tool:

- *For early detection of lung alterations:* It was expected that heterogeneity in structural change could reveal abnormality before a global change (e.g., overall airway narrowing) sets in to such an extent that spirometry becomes abnormal. An experimental demonstration of this potential was the observation that heart-lung transplant patients showed an abnormal SBW phase III slope with a median of 1 year before FEV_1 became abnormal to reflect a rejection episode [29].
- *For monitoring the lung periphery:* Experimental and theoretical work conducted over the years indicated that the phase III slope is in fact predominantly affected by peripheral air spaces, where resistance to flow is small and hence referred to as the "silent lung zone."

If it were possible to separate ventilation heterogeneity originating in the peripheral air spaces from that in the more proximal airways, this could bring about a sensitive diagnostic tool that is also more specific to structural alterations in a lung zone where spirometry performs poorly. In the mid-1980s, experimental work by Crawford et al. [30–33] emerged which displayed the potential of delivering such a tool, based on earlier modeling work [34]. Instead of having a subject perform one inhalation and exhalation (single-breath washout, SBW), the subject is asked to perform subsequent inhalations and exhalations (multiple-breath washout, MBW) such that by the nature of the mechanisms involved, their respective contributions to phase III slope will be accentuated as the MBW proceeds. Figure 14.2 shows how N_2 concentration continuously decreases during an MBW test, but also that each breath can be considered as an SBW curve where the N_2 phase III slope progressively increases relative to its mean expired N_2 concentration (insets of Fig. 14.2).

When the N_2 phase III slope of each expiration is normalized by its mean expired or end-expired N_2 concentration, the resulting normalized phase III slope (S) steadily increases as a function of breath number, even in a normal subject (Fig.14.3). For the sake of illustration, the exaggerated S increase in the same subject after histamine provocation is also shown, and for methodological reasons, S is represented as a function of lung turnover (TO, i.e., cumulative expired volume divided by FRC) instead of breath number [30].

While diffusion-convection interaction can indeed account for most of the S value of the first breath of an experimental MBW test [21], it is intrinsic to this mechanism that S only slightly increases as the MBW proceeds, and that after the first few breaths, a horizontal S asymptote is reached. An alternative mechanism to explain the increasing S as a function of breath number (or TO) beyond the first few breaths is the one where two units are ventilated to a different extent creating a concentration difference between them, which serves as the initial condition to the next inhalation. In any subsequent inhalation, concentration differences will become

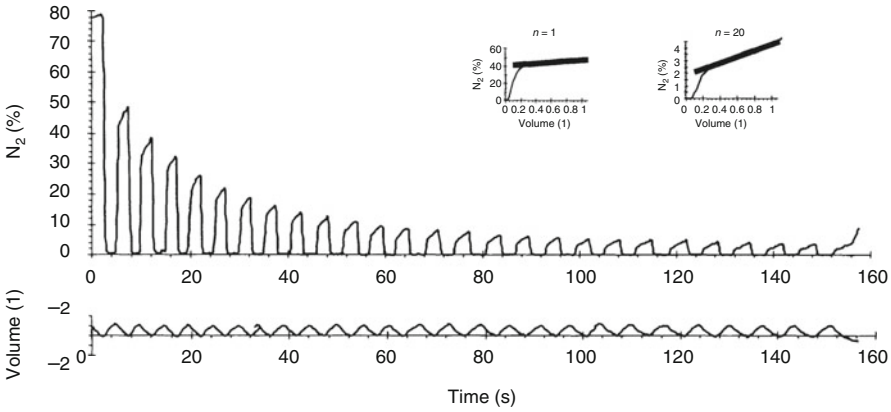

Fig. 14.2 MBW test obtained in a normal subject after histamine provocation to illustrate the rate of rise of the N_2 phase III slope with respect to the mean expired N_2 concentration as a function of breath number (*n*)

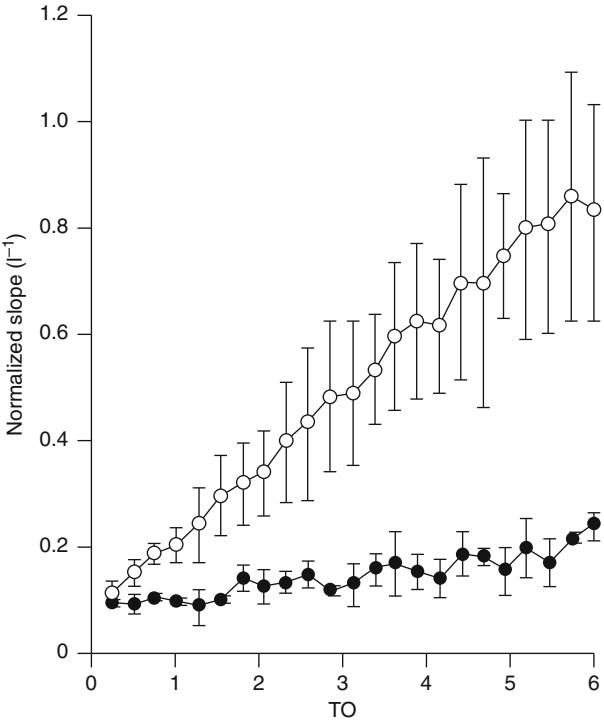

Fig. 14.3 Normalized slopes (*S*; mean ± SD) versus lung turnover (*TO*) obtained on a normal subject before (*closed circles*) and after (*open circles*) histamine

relatively greater, i.e., the concentration difference divided by the average concentration will progressively increase. This mechanism predicts an increasing S as a function of TO, however with an extrapolation to $S=0$ for $TO=0$ [34].

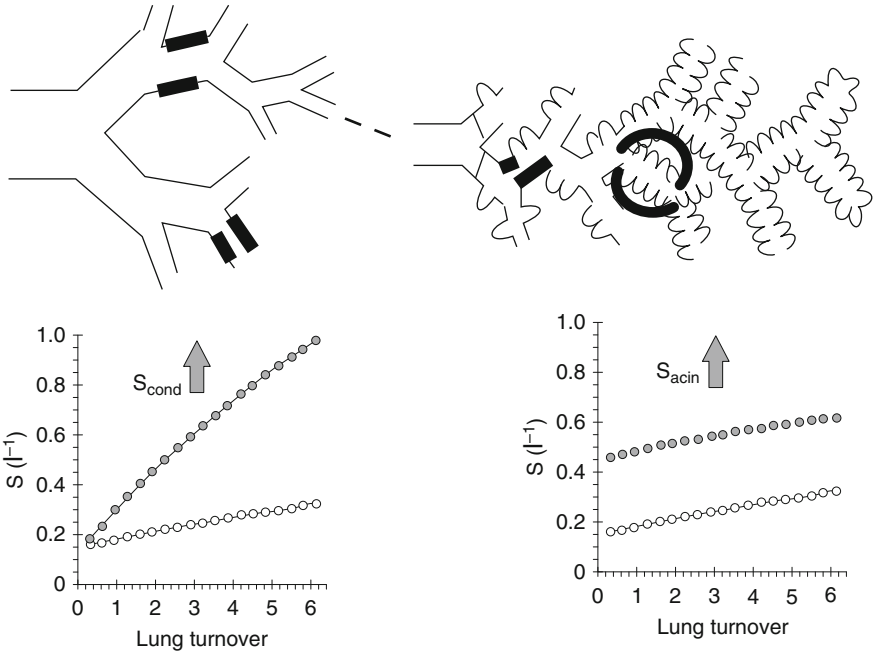

Fig. 14.4 Schematic representation of conductive and acinar structural alteration and its predicted effect on normalized phase III slopes (*S*) versus lung turnover (TO) and derived indices S_{cond} and S_{acin}

On basis of the above explanations, and without displaying the details here (these can be found in [35]), two indices of ventilation heterogeneity can be derived from the S versus TO curves as follows. The diffusion-convection interdependence mechanism (operational in the acinar lung zone) mainly affects the height of the S versus TO curve, but hardly contributes to the rate of S increase versus TO. Hence, the index of acinar ventilation heterogeneity (S_{acin}) is computed as the S value of the first breath minus a small contribution from the rate of S rise in the remainder of the MBW test ($S_{acin} = S(n=1) - TO(n=1)$. S_{cond}, where S_{cond} is given below). Convective ventilatory heterogeneity (operational in the conductive lung zone) mainly affects the increase of the S versus TO curve, but hardly contributes to the initial S value. Hence, the index of conductive ventilation heterogeneity (S_{cond}) corresponds to the regression slope of the S versus TO curve beyond the first few breaths ($TO > 1.5$). Figure 14.4 schematically displays S versus TO curves and the behavior of derived S_{acin} and S_{cond} in two schematic cases of acinar or conductive airway structural alterations. Whenever a patient displays an increased S_{cond}, this is thought to reflect an increased heterogeneity in airway lumen or in elastic properties of relatively large lung units subtended from the conductive airways. Whenever a patient displays an increased S_{acin}, this may be interpreted as result of a change in intra-acinar asymmetry either by cross-sectional heterogeneity or by changes in subtended volumes.

Two advantages of the MBW test are (1) that it involves near-tidal breathing above FRC which not only corresponds to lung volumes during natural breathing but also avoids the effect of airway closure at residual volume, and (2) that the S versus TO curves derived from the MBW are only poorly affected by the blurring effect of gravity [36]. Hence, the MBW indices can be almost entirely attributed to intrinsic structural and elastic properties of the lung, which renders this test particularly useful in the clinical context of the lung function laboratory. We summarize here the use of the normalized slope analysis of the MBW test in clinical applications, with Fig. 14.5 displaying average S_{acin} and S_{cond} values obtained from the same laboratory in either of the study groups described below. These results are then placed against other washout data from the literature.

14.2.1 Bronchoprovocation

For an average FEV_1 decrease of 26 % after a 2 mg cumulative dose of histamine, S_{cond} was shown to increase by 390 % with no significant change in S_{acin}, indicating that during provocation large ventilation heterogeneities occur and that the airways affected by the provocation process are situated proximal to the entrance of the acinar lung zone [26]. A methacholine provocation study showed a significant but small S_{acin} increase and a large S_{cond} increase [37]. The observed S_{cond} increase likely represents the inequality in response of parallel airways, superimposed on global airway narrowing. This could reflect density differences in muscarine receptors and/or cholinergic innervation between airways located at a given lung depth (i.e., airways of more or less the same lung generation) in addition to the reported proximal versus peripheral density differences along the bronchial tree [38]. Since the conductive airways (as reflected in S_{cond}) constitute the main source of ventilation heterogeneity during bronchoprovocation, and because this component is only poorly reflected in the SBW phase III slope, this could explain the moderate SBW phase III slope increases observed by others after provocation e.g., [39]. Although it is intrinsically impossible to determine the contribution from acinar and conductive air spaces by only studying the decline in mean expired concentration of an MBW test, several such reports in the case of bronchoprovocation [40, 41] did speculate on an important contribution from convection-dependent ventilation heterogeneity. A comparative study of two aspecific bronchoprovocation aerosols revealed an apparent paradox of a greater ventilation heterogeneity (largest S_{cond} increase) for the bronchoprovoking agent (methacholine) which induces the least deterioration of spirometry, at least in terms of FEV_1 [42]. It was suggested that the differential action of histamine and methacholine is confined to the conductive airways, where histamine likely causes greatest overall airway narrowing and methacholine induces largest parallel heterogeneity in airway narrowing, probably at the level of the large and small conductive airways, respectively. The observed ventilation heterogeneities predict a risk for dissociation between ventilation-perfusion mismatch and spirometry, particularly after methacholine challenge, as has been observed

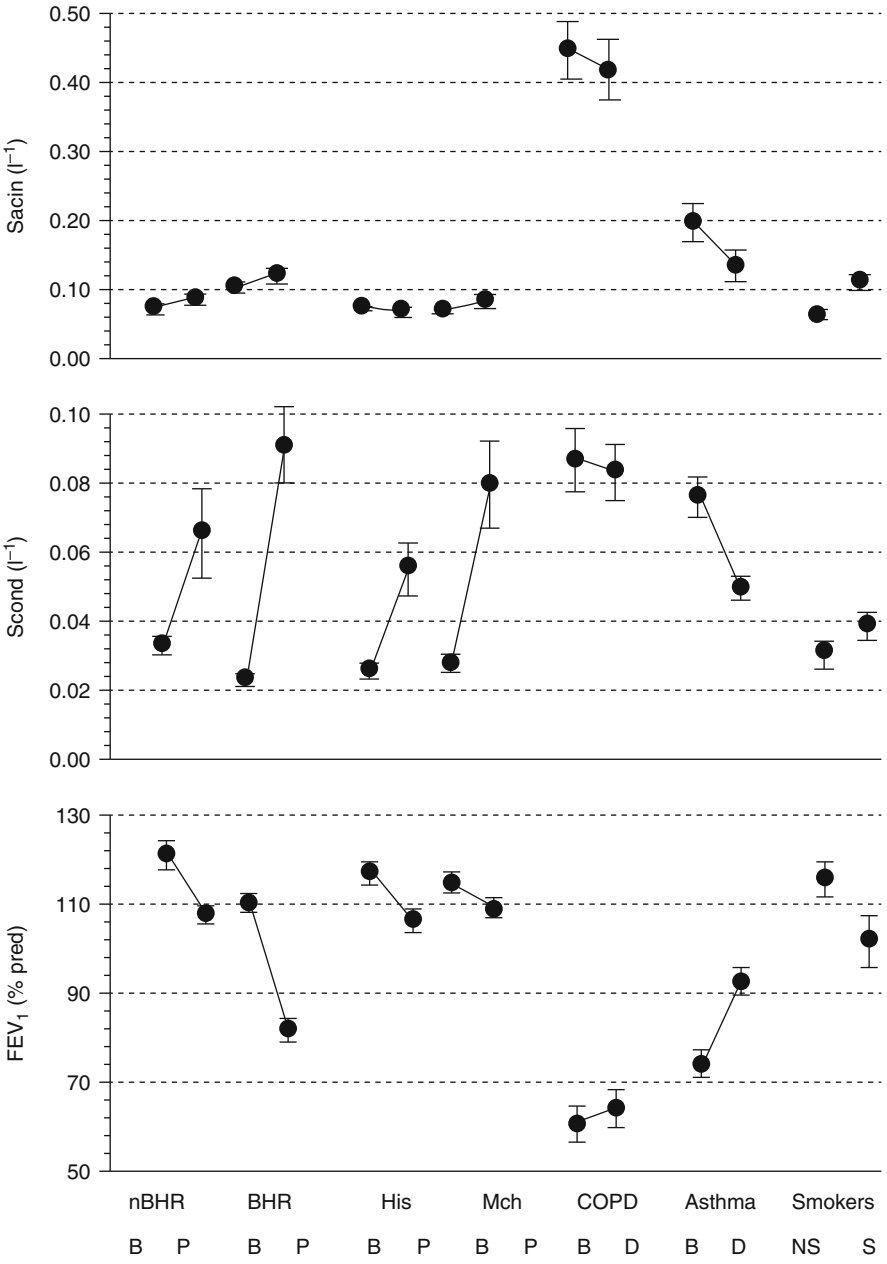

Fig. 14.5 Average values (±SE) of S_{acin} and S_{cond} and corresponding FEV_1 in normal subjects with bronchial hyperresponsiveness (*BHR*) or not (*nBHR*), in nBHR subjects provoked with histamine (*His*) or methacholine (*MCh*), in COPD and asthmatic patients, and in smokers (*S*) or never-smokers (*NS*); *B* baseline, *P* provocation, *D* dilatation

experimentally by others [43]. On the basis of SBW phase III slopes with different diffusivity gases, it has been suggested that adenosine 5'-monophosphate has an even more peripheral effect than methacholine [44].

14.2.2 COPD Patients

In a group of COPD patients with various degrees of airway obstruction (FEV_1/FVC = 52 ± 11(SD) %) and transfer factor (TL_{CO} = 77 ± 25(SD) %), the relationship of S_{cond} and S_{acin} to standard lung function indices was evaluated by means of a principal component factor analysis [24], which linked correlated indices to independent factors accounting for 81 % of the total variance within the COPD group. S_{acin} was linked to the so-called acinar lung zone factor, comprising also diffusing capacity measurements. S_{cond} was linked to the so-called conductive lung zone factor, comprising also specific airway conductance and forced expiratory flows. The fact that S_{cond} and S_{acin} were linked to independent factors is a statistical confirmation of the hypothesis that S_{cond} and S_{acin} can reflect independent lung alterations, corresponding to different functional lung units. FEV_1/FVC was the only variable linked to both the conductive and the acinar lung zone factor, indicating a combined conductive and acinar contribution to airway obstruction in these COPD patients.

14.2.3 Asthmatics

Baseline S_{acin} values were found to be abnormal in asthmatics, despite normal diffusing capacity in this group [25]; these S_{acin} values were intermediate between those obtained in normal subjects and in COPD patients. Baseline S_{cond} was also abnormal in the asthmatics but similar to that obtained in the COPD patients. After salbutamol inhalations, significant changes in S_{cond} and S_{acin} were only observed in the asthmatics. These results indicate significant – but partially reversible – acinar airway impairment in asthmatics, as compared to the more severe baseline acinar airway impairment in COPD patients, none of which was reversible after salbutamol inhalation. The involvement of the peripheral airways in asthmatic patients in the baseline condition and after inhaled β_2-mimetic drugs has been a subject of considerable interest in the past, where the terminology "peripheral airways" actually covers a large range of airway generations depending on the measurement method used [45–47]. Ventilation distribution has also been previously investigated in asthmatics in terms of N_2 phase III slope of the SBW [47–51] or in terms of decaying concentration curves of the MBW [52], with a general observation of a diminished overall lung ventilation heterogeneity after inhalation of β_2-mimetic drugs. A modified single-breath washout maneuver employed by Cooper et al. [50] in asthmatic children started the O_2 inhalation from FRC rather than from residual volume, a maneuver which was indeed expected to better detect lung structural alterations [53]. Cooper et al. [50] found that the asthmatic patients with the steepest baseline N_2 phase III slopes were also the ones showing the largest decreases

following isoproterenol inhalation, and that post-isoproterenol N_2 phase III slopes were still elevated with respect to normal values. Using the same SBW maneuver, Gustaffson et al. [51] studied the respective behavior of He and SF_6 phase III slopes to detect an intra-acinar contribution to ventilation distribution in asthma patients. Ventilation heterogeneity in the conductive airways (S_{cond}) has been identified as an independent contributor to airway hyperresponsiveness in asthma [54], and recent reports have also linked S_{cond} and S_{acin} to asthma control [55, 56].

14.2.4 Smokers

An early study in smokers with normal lung function found that S_{acin} was significantly larger than in never-smokers, while S_{cond} remained unaffected [57]. While being less abnormal than previously reported in COPD patients, S_{acin} did detect significant acinar airway alterations in these asymptomatic individuals. Previous reports of the decline in mean expired concentration of an MBW in smokers with relatively normal lung function had revealed an impaired ventilation distribution [58, 59], without however being able to indicate the location of structural alterations. An MBW study in larger cohorts of smokers with a range of smoking history (10–50 pack years) has since indicated structure-function alterations in the lung periphery around the acinar entrance affecting both S_{cond} and S_{acin}; in smokers with emphysema, S_{acin} was further enhanced [60]. In a subsequent smoking cessation study in smokers without airway obstruction [61], a transient S_{acin} decrease and a sustained S_{cond} decrease could be observed over the course of 1 year of smoking cessation. Previous ventilation distribution studies in smokers that made use of phase III slope analysis were essentially derived from the vital capacity SBW maneuver [1–5] where increased phase III slopes were often unduly referred to as an indication of peripheral alterations only.

Taken together, we can state that indices S_{acin} and S_{cond} can be used for the abovementioned purposes: early detection of lung alterations and monitoring the lung periphery. For early detection purposes, it is important to realize that these indices also slightly vary with age in normal man, and reference values have now been produced [62]. For monitoring, potentially moving into advanced disease stages, care has to be taken that the basic assumptions for separating conductive and acinar effects are still met [35].

14.3 Aerosol Bolus Tests

Although gas bolus studies can give interesting information on lung volume dependence of ventilation distribution [28], they cannot be associated to specific locations in the bronchial tree. However, this becomes possible with aerosols, as illustrated in Fig. 14.6, because of the very low particle diffusivity. If we consider the symmetrical Weibel model of the lung, a particle bolus followed by a volumetric lung depth (VLD) inhalation of air corresponding to the volume of the first 2 generations would

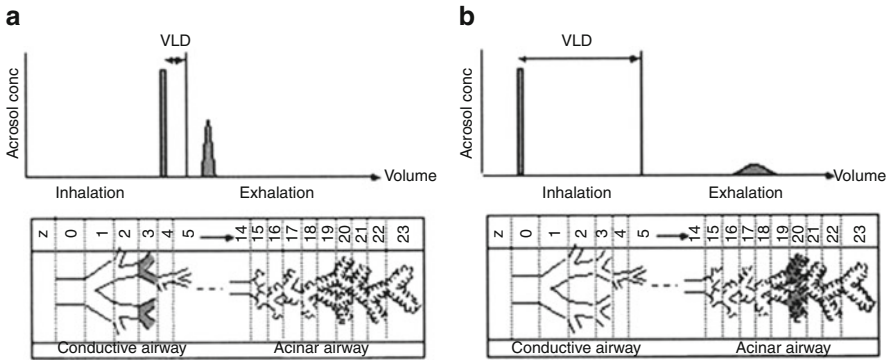

Fig. 14.6 Principle of the aerosol bolus dispersion test. An aerosol bolus is released at different instances during an inhalation, so as to deliver it to the proximal lung, corresponding to a low volumetric lung depth (*VLD*) (panel **a**) or to the peripheral lung and corresponding to a high volumetric lung depth (*VLD*) (panel **b**). Upon exhalation, the bolus is recovered and its dispersion (e.g., its standard deviation) is measured

bring the particles to generation 3 as represented in Fig. 14.6a. Alternatively, an aerosol bolus test with a VLD corresponding to the volume of the first 19 generations would deliver the particles to generation 20 (Fig. 14.6b). For a typical aerosol bolus test, a subject is instructed to inhale a given volume (e.g., 1,000 ml), and a valve system delivers a bolus (e.g., 75 ml) of aerosol at the desired instance of the aerosol-free inhalation. Upon exhalation, the non-deposited portion of the aerosol is recovered in the form of an aerosol bolus which is dispersed over at least twice the inhaled bolus volume.

Depending on the lung level at which the aerosol is inhaled, the aerosol bolus is seen to deposit more and to become more dispersed as it has traveled deeper into the lungs, even in normal subjects [63]. Moreover, it was postulated that in the case of lung structural alterations, particularly if these are heterogeneously distributed over the lungs, aerosol bolus dispersion would be increased. This hypothesis was confirmed experimentally in several lung diseases [64, 65]: in patients with cystic fibrosis [66], emphysema [67], and asthma [68] or in heart-lung transplant patients suffering a rejection period [69]. However, increased aerosol bolus dispersion was also observed in the case of asymptomatic smokers [70–72], suggesting its potential as a marker of lung alterations in the early stages of lung disease. Again, the key issue is how structural heterogeneity can affect aerosol bolus dispersion. Indeed, if a 75 ml aerosol bolus distributes over a complex structure, but recombines in a perfectly reversible fashion, the original aerosol bolus will be restored in its initial 75 ml volume. Heterogeneity in structural alterations that are perceived differently by the aerosol bolus during inspiration than during expiration is expected to introduce an irreversible component of aerosol bolus dispersion.

On the basis of the role of heterogeneity, some studies have indeed measured indices of gas ventilation distribution (SBW, MBW) alongside indices of aerosol distribution (aerosol bolus dispersion). Anderson et al. [71] found an increased N_2

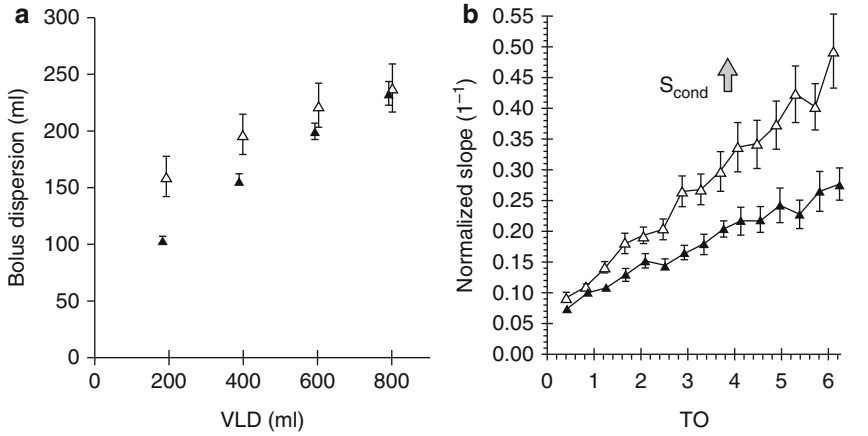

Fig. 14.7 Saline bolus tests (panel **a**) and multiple-breath washout tests (panel **b**) obtained on the same 10 subjects before and after histamine provocation (*closed and open symbols*, respectively). (Panel **a**) Aerosol bolus test: bolus dispersion (±SE) as a function of volumetric lung depth (*VLD*), indicating a structural alteration in the proximal lung. (Panel **b**) MBW test: normalized phase III slope (±SE) as a function of lung turnover, indicating a structural alteration in the conductive airways (S_{cond} increased; see also Fig. 14.4) after histamine

phase III slope of the vital capacity SBW in a smoker group which showed an increased dispersion of the most peripherally inhaled aerosol boluses. Also, in an effort to relate aerosol- and gas-related measures of convective ventilation heterogeneity, Brown et al. [73] found an association between bolus dispersion and ^{133}Xe washout-derived indices in cystic fibrosis patients. An essential issue which is sometimes overlooked in studies comparing gas and aerosol tests of ventilation distribution on the same subjects is the volume range spanned by the various testing procedures. For instance, a vital capacity single-breath washout – including airway closure – and an aerosol bolus test involving lung volumes well above residual volume are bound to only contain partly overlapping information, which may render comparisons disappointing.

Two studies [57, 74] have compared the specific patterns of aerosol bolus dispersion and gas washout (MBW) derived indices in two study groups with specific proximal or peripheral structural alterations. In one study, a group of 10 normal subjects underwent a histamine bronchoprovocation test, inducing a conductive airway alteration, as evidenced by an increased S_{cond} after histamine with respect to baseline. In the other study, 12 smokers were studied who differed from 12 never-smokers in terms of acinar airway alterations only as evidenced by an increased S_{acin} in the smokers versus the never-smokers. In the first group, an increased S_{cond} was paralleled by an increased aerosol bolus dispersion of the most shallowly inhaled aerosol boluses (Fig. 14.7). In the latter group, an increased S_{acin} was paralleled by an increased aerosol bolus dispersion of the most peripherally inhaled aerosol boluses (Fig. 14.8). Note that the lungs with the more peripheral structural alteration (Fig. 14.8) will only affect the dispersion of the most deeply inhaled boluses

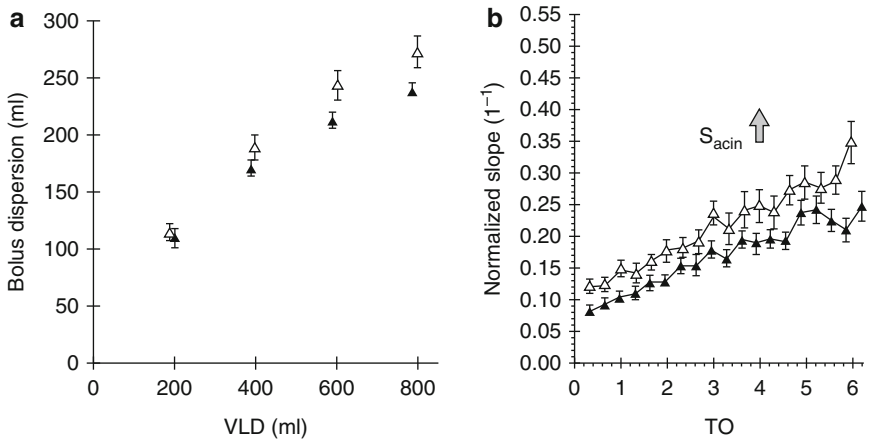

Fig. 14.8 Saline bolus tests (panel **a**) and multiple-breath washout tests (panel **b**) obtained on 12 never-smokers (*closed symbols*) and 12 smokers (*open symbols*). (Panel **a**) Aerosol bolus test: bolus dispersion (±SE) as a function of volumetric lung depth (*VLD*), indicating a structural alteration in the peripheral lung. (Panel **b**) MBW test: normalized phase III slope (±SE) as a function of lung turnover, indicating a structural alteration in the acinar airways (S_{acin} increased; see also Fig. 14.4) after histamine

(largest VLD). By contrast, the lungs with the more proximal structural alteration will affect primarily the most shallow boluses but will also affect the more peripherally inhaled boluses to some extent, since all boluses have to pass the most proximal structures [75] on their way to the lung periphery. Hence, in this case, the effect is most marked for lowest VLD and fades away toward the higher VLD.

Finally, a particularity of the tests shown in Figs. 14.7 and 14.8 was that the aerosol used for these bolus tests was isotonic saline and not the latex particles or oil droplets usually employed for these types of aerosol bolus studies. It was shown indeed that if only bolus dispersion – and not bolus deposition – is to be measured, saline aerosol boluses disperse to the same extent as a 1 μ latex aerosol bolus. Indeed, any potential size change that an isotonic aerosol bolus may undergo in the lungs appears to play a minor role in the dispersion of the bolus, and in fact, lung structure seems to be the major determinant of bolus dispersion. The possibility of using saline instead of latex or oil droplets to detect lung structural alterations may be more appealing for the clinical application of this technique. However, if, in addition to bolus dispersion, there is a need to quantify bolus deposition, for instance, to determine an effective airspace diameter [76], monodisperse aerosols are compulsory.

Conclusion

Depending on the patient population under study, one may consider using either gas- or aerosol-derived noninvasive probes of lung structural alterations. The choice of one technique over the other will essentially be made on basis of technical or practical issues. One practical consideration concerns inhaled volume,

which should be around 1 L for a proper phase III slope analysis of the MBW test. This may be difficult to achieve in some patients, and in that case, a protocol with aerosol bolus tests that is limited to shallow inhaled boluses – involving lesser lung inflations – may still be meaningful, depending on the lung disease under study.

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