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Assessing and accessing the small airways; implications for asthma management

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ABSTRACT

Despite the wealth of experience in the management of asthma, the disease remains inadequately controlled in some patients, who face long-term respiratory impairment and disability. The disease has been characterised as an inflammatory condition affecting first the larger airways and eventually the smaller airways, but there is evidence that peripheral airway involvement defines a particular and more severe phenotype of asthma. For this reason, assessing functional and biological parameters reflective of small airways involvement is important prognostically. No assessment method is universally and directly representative of peripheral airway function, but the traditional spirometric tests, including vital capacity, residual volume and forced vital capacity, are somewhat correlated with this function; useful methods for further assessment include the single-breath nitrogen wash-out test, impulse oscillometry, nitrous oxide and exhaled breath concentrate measurements, as well as computed tomography to reflect air trapping and response to treatment. Formulation advancements have made for easier treatment access to the smaller airways, with the new extrafine formulations resulting in better asthma control compared with non-extrafine formulations.

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1. The role of small airways in asthma: old concepts and new challenges

The prevalence of asthma, which affects up to 10% of adults and 35% of children, is increasing worldwide [1,2]. The disease remains inadequately controlled on currently available therapies in a large proportion of patients [3], despite a deeper understanding and growing knowledge of the pathology, and attention and adherence to detailed treatment guidelines [4]. The consequences of this inadequate control of the disease are long-term respiratory impairment and disability [2,5,6].

The role of the peripheral airways in asthma is increasingly being recognized as a relevant target (Fig. 1) for asthma treatment [7,8]. The contribution of small airways to the pathophysiology of asthma, combined with the presence of the relevant receptors in these airways, suggests that this site should not be neglected in the monitoring of asthma or in the development of treatments for the disease [9]. Asthma is a chronic inflammatory disease of the airways including the most peripheral ones. There is abundant evidence that inflammatory and functional abnormalities of the lung periphery occur in all stages of the disease from the mildest [10,11] to the most severe form [12,13]. Interestingly, a correlation between disease severity and the magnitude of small airway impairment has been documented [14]. The question arises as to whether peripheral airways are a site of structural and functional alterations in asthma irrespective of the clinical manifestation or

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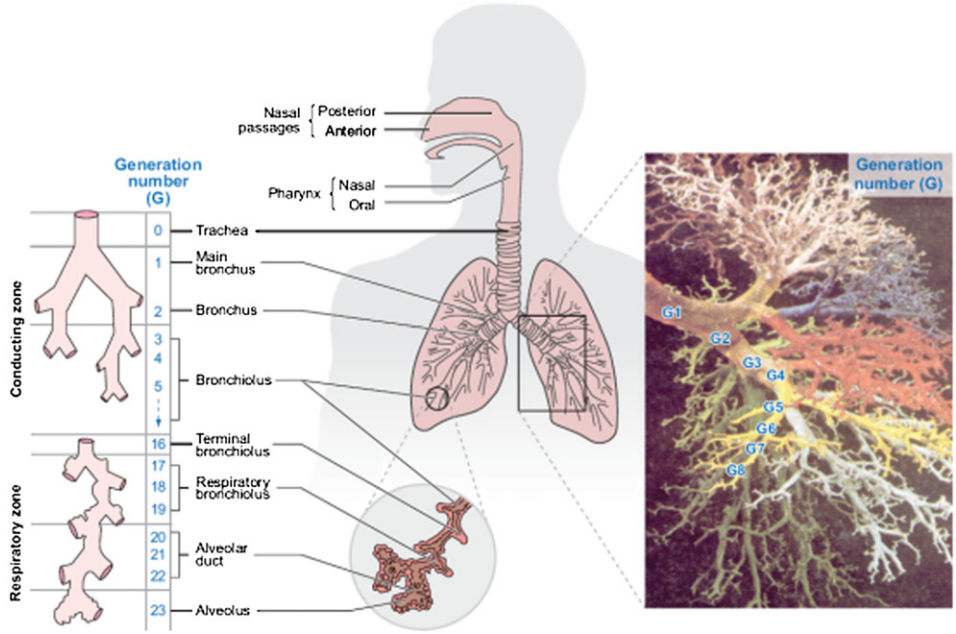

Fig. 1. Schematics of the human respiratory system [83]. (Reproduced with permission from Kleinstreuer C, Zang Z, Donohue JF. & Zhang Z. Targeted drug-aerosol delivery in the human respiratory system. Annu Rev Biomed Eng. 2008; 10:195–220. published by Annual Reviews).

does the involvement of the peripheral airways in asthma represent a specific phenotype of the disease that leads to more severe manifestations, poor clinical control and/or poor response to treatment. From a purely speculative perspective, the distinction carries pathophysiological implications: in the first case, the alterations of the peripheral airways do not describe the most important pathogenetic features of asthma but merely represent the consequence of the disease progression. On the other hand, if the pathophysiological changes of the peripheral airways are considered as defining a phenotype of asthma, it is logical to assume that, at least in this group of asthmatics, the peripheral airway involvement is a relevant pathogenetic mechanism. Specifically designed studies are needed to clarify the matter.

From a clinical standpoint, the identification of a specific asthma phenotype characterised by prevalent small airway impairment advocates the need for functional and biological tools that can accurately assess the peripheral area of the lung. Most importantly, assessing and accessing the peripheral airways becomes mandatory when the small airway involvement potentially carries prognostic implications. From this perspective, the identification of: i) asthma phenotypes characterised by enhanced small airway impairment and, ii) the link between poor control/asthma severity and small airway abnormalities, raises the question whether pharmacological approaches able to increase drug deposition within the airways will result in further clinical benefit in these patients.

In the field of asthma, the concept of “future risk” is gaining increasing importance in the management of the disease, as emphasized by recent guidelines [2]. Whether the detection of small-airway abnormalities indicates those patients at major risk of asthma attacks or more severe disease, or predicts those likely to benefit from a specific intervention, is unknown and should be pursued in future studies.

The following sections will discuss the pathology of peripheral airways in asthma, methods of assessment of the peripheral airways function, and formulation advancements for better drug delivery throughout the airways.

2. Peripheral airways pathology: the strength of evidence

Evidence accumulating in recent decades indicates that inflammatory changes of the proximal airways of asthmatics also occur in the distal airways [15]. The assessment of the distal tract of the bronchial tree has always been a difficult task due to its relative inaccessibility. However, with the improvement of bronchoscopic, morphometric and immunohistochemical techniques, a better evaluation of airways less than 2 mm in diameter has been made possible [16]. It is now accepted that inflammation is present throughout the bronchial tree of asthmatics; this inflammatory process is characterized by the presence of activated T lymphocytes and activated eosinophils, increased mucus plugging obstructing the lumen, and smooth muscle hyperplasia [17]. In a study designed to evaluate the inflammatory changes of large and small airways on lung tissue obtained from surgical resections of asthmatic subjects, the number of activated eosinophils was significantly greater in the distal portion of the airways and in the context of the alveolar walls [11,18].

Additional studies performed in asthmatics confirmed that the inflammatory changes to the peripheral airways parallel the severity of the disease. In a study by Carroll et al. [19], the increased expression of mast cell chymase in the outer area of the distal airways was significantly associated with impaired lung function in individuals with severe asthma. In subjects with severe asthma compared with those with mild to moderate asthma, an increased production of alveolar nitric oxide (NO), but not bronchial NO, was also found [20], implying that a more intense degree of inflammation occurs in the periphery of the bronchial tree in the most severe forms of asthma.

In patients with severe or fatal asthma, there is increased thickness of the airway smooth muscle layer in the proximal and distal airways and increased smooth muscle cell size [21]. Recent findings suggest that parenchymal abnormalities may also affect airflow obstruction in asthmatics [13]. Indeed, a loss of alveolar attachments was demonstrated in association with a reduction in lung elastic recoil, leading to airway collapse. In patients with

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severe asthma, the progressive loss of lung function is caused by structural alterations and remodelling of the proximal and distal airways, and destruction of lung parenchyma [22].

Specific abnormalities of the distal airways and lung parenchyma have also been described in nocturnal asthma, which occurs in 30–75% of the asthmatic population [23]. In nocturnal asthma, but not in non-nocturnal asthma, a more pronounced inflammation in the peripheral airways rather than in the large central airways was described, with a significant increase in lymphocytes, macrophages and eosinophils during the night [24]. The percentage of eosinophils and macrophages was also significantly increased in the alveolar tissue and was related to a nocturnal reduction in lung function. The inflammatory response observed in the context of the alveolar tissue could explain the loss of airways-parenchyma coupling detected in individuals with nocturnal asthma [25].

3. Assessing the peripheral airways: from the research perspective to clinical practise

Methods of peripheral airways assessment include lung function tests, measurements of biomarkers, and imaging techniques. However, no universally accepted criteria for these tests have been proposed as being directly representative of peripheral airways involvement, and changes in these parameters have not yet been proven to affect the clinical outcomes of patients with asthma [7,8].

3.1. Functional assessment of peripheral airways

Commonly employed spirometric tests, such as forced expiratory volume in 1 s (FEV_1) and the ratio of FEV_1 to forced vital capacity (FEV_1/FVC), generally reflect large airways function and loss of lung elastic recoil [26,27]. Measures of lung volumes, such as vital capacity (VC), residual volume (RV) and forced vital capacity (FVC) are, to some extent, correlated to the functional state of the peripheral airways. VC is reduced in patients with peripheral airways obstruction, and this reduction may occur before that of the FEV_1/VC ratio [26]. RV is increased in patients with air trapping, a phenomenon that is secondary to alterations that mainly occur at the level of peripheral airways [7]. FVC is reduced at any level of airway obstruction, but may be also a reflection of air trapping [7]. In the late nineties, spirometric pattern characterized by a decrease in VC and FEV_1, an increase in RV and RV/total lung capacity (TLC), and normal TLC and FEV_1/FVC was described by Stănescu [28]. Since an increase in RV and RV/TLC represents a marker of hyperinflation and air trapping, this pattern has been proposed as an early detector of peripheral airways disease [29,30]. This alteration has been observed in the early stages of emphysema, elderly people and asymptomatic asthma [29,30]. Although the measurement of RV is an easy-to-perform test, with good reproducibility and low intra-patient variability, it is commonly envisaged as a rough method of estimating the function of small airways, mainly because it only allows a volumetric characterization of premature airway closure and air trapping, and is not able to detect less evident functional changes of distal airways conductance and ventilation patterns.

Other spirometric tests are under investigation for the assessment of peripheral airways function. The mean forced expiratory flow (FEF) between 25% and 75% of FVC (FEF_{25-75}) is one of the most popular indices of peripheral airways obstruction, resembling the concavity of the flow-volume curve [31]. However, its use in clinical practise is limited by physiological variability and measurement inconsistency issues [32]. Its value as a predictor of peripheral obstruction has also been questioned following findings from the Severe Asthma Research Program of the National Heart Lung and Blood Institute, which showed a lack of correlation between FEF_{25-75} and other indices of air trapping [32].

Among the non-invasive techniques that are proposed to evaluate small airways function, the forced oscillation technique (FOT) is gaining increasing importance. FOT uses the non-invasive superimposition of pressure fluctuations on the airway over the subject's tidal breathing. FOT was first described by DuBios in 1956 as a method to characterize respiratory impedance [33]. Similar to FOT, impulse oscillometry (IOS) is easy to perform and requires only passive patient cooperation [34]. IOS delivers a regular square wave of pressure 5 times per second, and has the advantage of generating a larger sample during measurements thereby emitting a continuous spectrum of frequencies that provide a more detailed characterization of respiratory mechanics [35]. IOS has been employed in adults as well as in preschool asthmatic children to identify lung dysfunction [34,36] and in the clinical diagnostic testing of individuals with airway hyperreactivity and airway obstruction. IOS could also be used during bronchoprovocation challenges. The advantage of continuous spectra could be important in conditions of regional non-homogeneities.

A recent paper from Takeda et al. [37] reported that parameters obtained by IOS are strongly correlated with clinical symptoms and asthma control in asthmatics. Peripheral and proximal airway functions, as assessed separately by IOS, independently contribute to health status, dyspnoea and disease control. IOS also appears to be a sensitive screening tool for the early detection of bronchial obstruction [38]. More recently, Oppenheimer et al. proposed that IOS can be used as a non-invasive tool for assessment of distal airway function when spirometry is normal [39], and can be applied to various clinical settings including early diagnosis of COPD and asthma in clinical remission and occupational/environmental irritant exposure.

The single-breath nitrogen (sbN_2) washout test is another non-invasive tool to assess small airways dysfunction and ventilation inhomogeneity, and has been used since the 1960s to detect early closure of peripheral airways. It is based on the detection of regional differences in ventilation distribution, represented by the phase III slope of the flow-volume curve following the washout test. Towards the end of expiration, an abrupt increase in N_2 concentration is observed, which corresponds to the beginning of phase IV. This is due to the preferential emptying of the apex, following closure of airways at the base of the lung. The volume at which phase IV begins is termed closing volume, and reflects small airways abnormalities. Despite being an easily performed and sensible technique [40], it suffered from poor reproducibility and predictability in the past [41]. This is no longer a limitation; sbN_2 has been employed in studies specifically addressing the relationship between asthma severity and small airways dysfunction [42].

The multiple breath nitrogen washout (MBW) test measures functional residual capacity (FRC). Patients with high airways resistance take longer to clear the nitrogen, and the test can distinguish between obstructions in the large or small airways. Dutrieue et al. [43] and Verbanck et al. [44] used the MBW test to derive the two variables, Scond (index of conductive ventilation heterogeneity) and Sacin (index of acinar ventilation heterogeneity). In asthmatic subjects, the clinical application of MBW includes evaluation of ventilation heterogeneity after an airway challenge, and analysis of response differences to inhaled steroids when comparing non-extrafine and extrafine particles [45,46].

The influence of ageing on the ventilation heterogeneity needs to be taken into consideration. In this scenario, Verbanck and colleagues recently found that, with respect to the clinical response, age has a small but consistent effect that needs to be factored in when using the MBW indices for the detection of small airways abnormality in disease [47].

The oesophageal balloon technique represents the gold standard for the measurement of changes in pleural pressure, and is one of the most reliable methods to disclose the premature closure of

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small airways [48]. Through the reading of the *quasi* static pressure volume curve, and its departure from the exponential curve, the volume at which closure of the most peripheral airways occurs is recorded. It is a rather uncomfortable procedure, which cannot be proposed, in daily clinical practise. With regard to the assessment of the lung periphery, the oesophageal balloon technique allows measurement of dynamic compliance. As opposed to static compliance, which is measured at points of no flow, dynamic compliance is measured during airflow. While in healthy subjects, dynamic and static compliance are equal, in chronic obstructive diseases, the ratio between the two decreases as the breathing frequency rises. This is due to the effect of uneven time constants on ventilation. The lung compartments with obstructed airways, and therefore long time constants, continue to fill while the rest of the lung has begun to exhale. The asynchronous behaviour of different areas of the lung implies a frequency dependence of compliance determined by their different time constants. As the breathing pattern increases, the dynamic compliance falls. This asynchronous behaviour of lung units has been ascribed primarily to obstruction in the small airways. Indeed, increased resistance of peripheral airways is responsible for uneven time constants and, therefore, for the change in dynamic compliance with breathing frequency [49–51].

3.2. Biological assessment of peripheral airways

Fractional exhaled nitric oxide (FeNO) is a non-invasive measure of airways inflammation. By monitoring the expiratory flow, it is possible to differentiate selectively between NO from the conducting airways and that coming from the respiratory zone (alveolar NO). The detection of alveolar NO is associated with nocturnal asthma, symptomatic asthmatics and asthmatics with more severe disease [8,52]. Moreover, alveolar NO is more sensitive to oral than to inhaled corticosteroids, suggesting that it may represent true abnormalities of peripheral airways, which are better reached by systemic drugs than by conventional inhaled formulations [20]. More recently, a method of monitoring the daily fluctuations in FeNO values with quantification over a period of time has been established, providing information on a subject's asthma severity with regard to asthma control and exacerbation risk [53].

Exhaled breath condensate (EBC) obtained by the cooling of the exhaled breath contains evaporated and condensed components plus some droplets from the airway lining fluid, but EBC markers of oxidative stress such as hydrogen peroxide, isoprostanes, nitrogen oxides, pH, ammonia, prostanoids and leukotrienes are abnormal in bronchial asthma [54]. Remarkably, both FeNO and 8-isoprostane concentrations in EBC were positively correlated with small airways function in asthmatics [55]. However, it is unlikely that one single marker might be representative of small airways involvement in asthma. EBC is a suitable matrix for metabonomic studies, which involve measurements of the dynamic multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification. The method includes reference analytical techniques such as mass spectrometry or nuclear magnetic resonance spectroscopy (NMR) [56]. By applying this approach, NMR-based metabonomic analyses of EBC clearly discriminated between asthmatic and healthy children, with a 95% success rate in their classification [57]. Whether a metabonomic study of EBC could reveal a distinct profile of small airways disease in asthma is currently unknown.

3.3. Imaging assessment of peripheral airways

Computed tomography (CT) has emerged as a useful tool to assess peripheral airways disease noninvasively in patients with asthma. The cardinal CT sign of peripheral airways disease in asthma is the presence of pulmonary decreased attenuation areas, which are more conspicuous and extensive on expiratory CT scans [58–60]. They reflect air trapping, which may be either secondary to transient small airway obstruction or spasm or caused by fixed peripheral remodelling [61–63]. There are two systems for quantifying air trapping on CT: the visual score and the densitometric analysis. The major disadvantage of a subjective approach is the variation between observers, and the densitometric analysis, despite its limitations, has been the technique of choice in recent scientific investigations and pharmaceutical trials. Specifically, either mean lung density or −850 HU cut-off CT density has been used to quantify air trapping in asthmatic subjects [63,64].

Quantification of air trapping in expiratory studies may provide additional information regarding response to therapy targeted for small airways disease that is not readily captured by physiologic measures [62,65]. This technique was used to compare the relative efficacy of two different inhaled medications on small airway hyper-reactivity; small-size inhaled particles prompted a significant improvement in air trapping compared with traditional-size particles [62,65]. These studies demonstrate the potential use of quantitative imaging in asthmatic patients as a surrogate end point for small airways remodelling in response to therapies.

Air trapping quantification has also been used to define asthmatic phenotypes. A recent study by Busacker and colleagues showed that quantitative CT can identify a group of individuals with a high risk of severe disease [64]. Individuals in the group with air trapping above the median level were significantly more likely to have a history of asthma-related hospitalizations, intensive care unit visits and/or mechanical ventilation [64].

CT imaging of pulmonary ventilation patterns in patients with asthma has evolved over the last decade with the introduction of more sophisticated techniques. Although the direct assessment of peripheral remodelling by CT measurements is still limited, due to the difficulty in accurately measuring the distal small airways (typically <2 mm diameter), computer-assisted 3-dimensional analysis of the airway tree structure is currently advancing the evaluation of the small airways disease (Fig. 2a and b). By using this technique in asthmatic patients, it has been shown that the strongest correlation with airflow obstruction was found through airway wall measurements of the more distal airways [66]. Although current evidence indicates that small airways obstruction could be routinely assessed using CT scanning, this technique does have some limitations, including lack of standardization of the technical parameters of the CT scanner, lack of consensus on the best index for small-airways disease assessment, and exposure of subjects to ionizing radiation. Indeed, the regular assessment of small airway disease via CT imaging is still not part of routine clinical practise for young asthmatic patients.

In conclusion, clinical trials have demonstrated that several methodologies are currently available to assess specifically the peripheral airways, and to investigate the presence of structural and functional changes in this bronchial area. These methodologies differ, however, in terms of accuracy, reliability, accessibility and cost, and their validation in real-life studies is lacking. From a clinical approach, individualized choices should be made based on the specific need and resources available. We propose an algorithm that takes into account the criteria described above: when assessing peripheral airways in daily practise, parameters of the flow-volume spirometric curve, such as the FEF_{25-75}, are easily accessible to general practitioners. If peripheral airway involvement is suspected, referral to a pulmonologist is recommended for a complete lung function evaluation, including the sbN_2 washout test; IOS may also be useful as an alternative lung function test. Measurement of alveolar NO, which should always be accessible,

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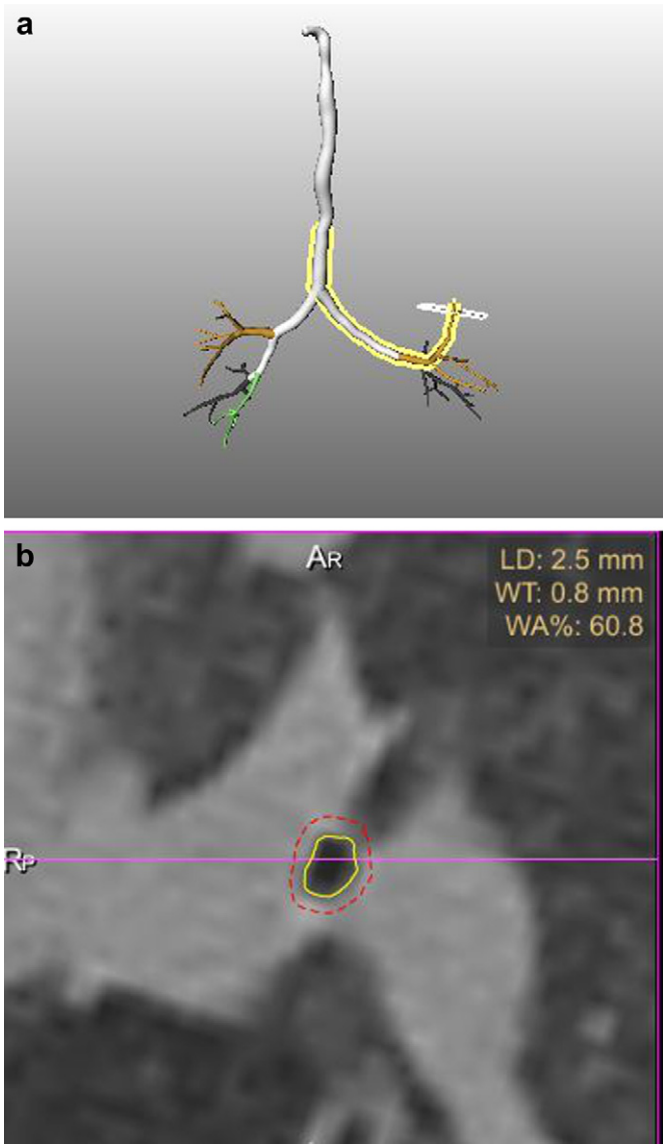

Fig. 2. Quantitative analysis of airway lumen and wall area in a young patient with severe asthma. (a) Multidetector CT permits reconstruction of airway tree using proprietary software (MEVIS Airway Examiner) which automatically provides bronchial measurements for selected pathways. (b) Orthogonal image through the airway provides measurement of airway dimensions. The airways are moderately thick-walled. (Courtesy of Michael Schmidt, Fraunhofer MEVIS, Bremen, Germany).

facilitates the definition of future risk and the optimal choice of treatment, and predicts potential benefits. Imaging assessment is advocated in patients with severe or difficult-to-control asthma.

4. Accessing the peripheral airways: current evidence and future approaches

Despite the evidence supporting the contribution of peripheral airways to asthma pathophysiology and clinical manifestations, very few studies have been designed to address specifically the importance of treating the distal part of the lung. Following the outlawing of chlorofluorocarbons (CFC) for environmental reasons, the development of the new hydrofluoroalkane (HFA) inhaler propellant also enabled the development of extrafine particle size inhaled drug formulations, which means treatment can reach the peripheral airways. The use of an HFA propellant is necessary, but it is not the only prerequisite for extrafine particle formulations. Indeed, most HFA pressured metered dose inhalers (pMDIs) on the market have similar characteristics to the corresponding CFC pMDIs [67]. To date, there are some single-agent extrafine formulations on the market (beclometasone, ciclesonide, formoterol), and only one combination product available (beclometasone/formoterol) [68]. Extrafine solution pMDIs can deliver compounds with a mass median aerodynamic diameter that is smaller than that delivered by other available devices [69]. Thus, these devices are able to deliver particles to both large and small airways, resulting in a significant increase in peripheral airways drug deposition with respect to the delivered dose [70].

Initial studies evaluating the efficacy of extrafine formulations in asthmatic patients were performed with inhaled corticosteroids (ICS) alone. These studies revealed that ICS extrafine formulations were superior to non-extrafine formulations in modulating functional and inflammatory parameters, reflecting small airway abnormalities [45,62,71]. The relative superiority of extrafine formulations was also observed for clinical outcomes that are not directly linked to small airways. Indeed, it was calculated that 2.6-fold non-extrafine beclometasone (BDP) is required to achieve the same improvement in FEV_1 as extra-fine HFA–BDP [72]. Moreover, in an open-label, 12-month randomised controlled trial, Juniper et al. showed that in asthmatic patients previously treated with non-extrafine CFC–BDP and switching to equipotent doses of extra-fine HFA–BDP (half of the dose of non-extra-fine CFC–BDP), there was a significant improvement in asthma quality of life compared with those patients who continued to receive non-extrafine CFC–BDP [73].

More recent studies were conducted using a fixed combination of extrafine beclometasone/formoterol (BDP/F). Huchon et al. showed that extrafine BDP/F delivered by an HFA pMDI (400/24 mcg) was superior in improving asthma control over 24 weeks of treatment to the combination of the same drugs formulated as larger non-extrafine agents, at equipotent doses (1000 mcg BDP + 24 < mcg F) [74]. Moreover, in two large studies (>200 patients in each study), Papi and co-workers [75,76] reported that the extrafine combination of BDP/F was comparable in terms of lung function improvement (as measured by morning peak expiratory flow changes) to the non-extrafine combinations of an ICS with a long-acting β2 agonist (LABA), budesonide/formoterol (BUD/F) and fluticasone/salmeterol (FP/S), at equipotent doses.

Achieving and maintaining asthma control is a major goal of asthma care. A real life observational study was conducted by Müller et al. to compare the asthma control efficacy of a BDP/F pMDI extrafine formulation vs BUD/F and FP/S combinations (non-extrafine formulations, both delivered as dry powder inhalers [DPIs]). In this real life setting, the proportion of patients achieving asthma control was significantly higher in the BDP/F extrafine group than in the non-extrafine BUD/F or FP/S group, and this was achieved with a significantly lower ICS mean daily dose [77]. This was confirmed in a recently published large observational study, showing that the extrafine BDP/F combination resulted in better asthma control and quality of life compared to non-extrafine formulations [78]. However, it remains to be established whether the addictive effect of extrafine formulations compared to no extrafine formulations on asthma control is related to the small airways targeting or whether may represent a consequence of a better distribution of the delivered drugs throughout the bronchial tree.

When functional parameters more related to peripheral airways abnormalities were considered, 12 weeks of extrafine BDP/F combination treatment was significantly superior to an equipotent dose of the non-extrafine FP/S combination in improving air trapping (without increased risk of systemic effects), which was measured by a reduction in FVC [75]. In addition, 12 weeks of

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extrafine BDP/F combination treatment tended to be significantly superior to equipotent doses of non-extrafine FP/S in improving closing capacity measured by the sbN_2 washout test [79]. These latter results provide direct evidence of the superiority of the extrafine ICS/LABA combinations compared to the non-extrafine combinations in improving small-airways function, possibly linked to the higher proportion of small particle delivered by extrafine formulations able to reach the more peripheral airway tract [80]. However, non-extrafine formulations are also able to significantly modify functional parameters reflecting small airways dysfunctions [81]. This finding is in line with the fact that also non-extrafine formulations can deliver a proportion of small particle able to reach the periphery of the lung. Thus, despite the evidence that extrafine formulations are more potent as compared to non extrafine formulations in targeting peripheral airways (peripheral deposition of the BDP/F extrafine combination is 2.55 fold higher compared to the FP/S non-extrafine combination) [80,82], the relative contribution of the modulation of peripheral airway abnormalities on clinical outcomes is still unclear. Head to head (extrafine vs non-extrafine) randomized controlled studies are needed to evaluate whether changes in small-airway abnormalities correlate with improvement in clinical outcomes. Similarly, and even more importantly, clinical trials are needed to evaluate whether extrafine formulations would represent a specific therapeutic option for specific groups of patients characterised by enhanced small airway dysfunctions.

5. Conclusions

Evidence of substantial and severe inflammation in the peripheral airways of patients with asthma has highlighted the importance of the assessment and treatment of this airway compartment. Moreover, several studies document better correlations between inflammatory, functional and imaging parameters reflecting small airway and both asthma control scores and quality of life. Recent data, coming from real-life studies show that extrafine formulations result in better asthma control compared to non-extrafine formulations. Whether this achievement is the result of the broader distribution of the delivered compounds through the airways or whether it is due to specific targeting of small airway dysfunction is still largely unknown, and appropriately designed studies are warranted. Relative inaccessibility of the peripheral airways and inadequacy of routine diagnostic methods to explore the more peripheral airway compartments has limited both the clinical research on small airways and the clinical assessment of small airways in daily clinical practise. However, in particular when managing cases of difficult-to-treat/uncontrolled asthma, we propose that physicians perform lung function assessments to classify the severity of asthma, and assess peripheral airway function and inflammation to detect the involvement of this site, in order to evaluate the possibility of individualized therapeutic decisions. It is no longer acceptable to define the peripheral airways as the “silent zone” and to forget their crucial function in respiratory system. The “silent zone” speaks loudly, but only if we listen carefully.

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