The role of the small airways in (ex-)smokers with or without asthma

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Chapter 7.
General discussion and future perspectives
This thesis aimed to add to the knowledge about asthma and airway hyperresponsiveness (AHR) in (ex-)smokers, focusing on treatment and small airways involvement. Smokers and ex-smokers with asthma were, for a long time, systematically excluded from clinical research on treating asthma, leading to a knowledge gap regarding the treatment of this specific group. Furthermore, this thesis aimed to evaluate an adjustment of the spirometric small airways parameters; the forced expiratory flows (FEFs). Throughout the years, the adjustment of the FEFs by the forced vital capacity (FVC) has been suggested several times but was disregarded due to a lack of normal reference equations and knowledge of clinical applicability. We, therefore, performed a study presenting such normal reference equations, followed by an evaluation of their clinical applicability.

First, this thesis assessed how to better treat asthmatic smokers and ex-smokers. We were interested because both smokers and ex-smokers with asthma do not respond as well as never-smoker asthmatics when treated with inhaled corticosteroids (ICS)—the cornerstone treatment of asthma. Additional research was required on improving the treatment of these patients. Cigarette smoke causes small airways disease (SAD). Hence, treatment of the small airways seemed important. Therefore, we hypothesized that extrafine particles ICS treatment which reaches the small airways better would be a better treatment option than larger-sized, non-extrafine, ICS in asthmatic smokers and ex-smokers (chapter 2). However, we found that both ICS formulations improved pulmonary function to the same extent. The larger-sized ICS even induced larger improvements in measures of the large airways (FEV$_1$ and R$_{20}$), and all airways (R$_5$). This might be interpreted as confirmation that treatment with larger-sized ICS is a good choice for asthmatic (ex-)smokers. On the other hand, that would disregard the findings of others [1, 2], who found that extrafine ICS treatment evoked a larger improvement than larger sized ICS treatment in small airways function. These studies, however, investigated extrafine ICS in combination with an extrafine long-acting $\beta_2$-antagonist (LABA). This LABA could have increased the susceptibility to the ICS by bronchodilation and the stabilization of the mast cells, as suggested in a study that found that adding
a LABA increases pulmonary function to a greater extent than doubling the ICS dose in current smokers [3].

We were also interested in (the assessment of) dyspnea in asthmatic (ex-)smokers. To study dyspnea and evoke it experimentally, provocation tests can be employed. As dyspnea is associated with both large and small airways dysfunction, we performed provocations with larger and smaller size particles (nebulized adenosine 5′-monophosphate (AMP) and dry powder adenosine, respectively) aiming to selectively target the large and small airways (chapter 3). We hypothesized that with an equal drop in FEV\textsubscript{1}, dry power adenosine compared to AMP would evoke more severe dyspnea which would associate with deteriorations in the small airways parameters. However, both AMP and adenosine evoked equal increases in dyspnea sensation and this dyspnea sensation was associated weakly with both large and small airways parameters. A possible explanation is the assumption that either the large or the small airways were provoked by the different agents is incorrect. Especially particles aiming for the small airways have to pass the large airways where some will deposit and trigger a reaction in the more central airways. Furthermore, the dry powder adenosine particles (2.6-2.9 μm) may still have been too large to reach the small airways properly. Therefore, the triggers may have overlapped more than expected with corresponding overlapping results. Another reason for the equal dyspnea sensation may be the lack of differentiation in types of dyspnea. After all, patients describe their dyspnea with a large number of terms (e.g. unable to get enough air, air hunger, breathlessness, increased work-of-breathing, chest tightness, tachypnea) and we only investigated the intensity of the dyspnea. For the interpretation of this study, it should be noted that the evaluation was performed only in asthmatic (ex-)smokers, who are known to have an impaired dyspnea sensation [4]. Lastly, the hypothesis that dyspnea sensation can originate from either large or small airways may be incorrect. Potentially, dyspnea originates from interactions in the entire lung.

As airway hyperresponsiveness (AHR) is a distinctive characteristic of asthma, the absence of AHR is commonly used to select respiratory healthy controls for pulmonary research. However, even though the response to one provocative agent, like the direct provocative agent methacholine (MCh), may
be negative, another, like the indirect agent AMP, can evoke a positive response. In a cohort of 108 healthy subjects, with pulmonary function within normal ranges, eight of such subjects were found (chapter 4). Upon investigation, this was associated with current smoking, a larger number of cigarettes per day, lower small airways function, and a lower quality of life. Apparently, the cigarette smoke somehow evoked a susceptibility to the indirect agent in these subjects. As these subjects also reported more symptoms that are associated with pulmonary disease (as indicated by a higher CCQ score) and had worse small airways function compared to the subjects without AHR to AMP, it could be speculated that these subjects are at risk for developing a pulmonary disease. Currently, however, this is still speculation and requires follow-up and further research in sufficient numbers of patients.

Finally, we re-assessed the value of specific parameters of small airways, and especially the adjustment of the spirometry-derived forced expiratory flows (FEFs) by forced vital capacity (FVC), which has been mentioned repeatedly in the literature since the 1970ies. Spirometry is the most frequently used pulmonary function test, mainly due to its availability and ease to perform it. As a result, FEFs are the most available small airways parameters. However, due to the large variability of the FEFs, their usefulness is questioned and they are often neglected. Consequently, the importance of the small airways is often overlooked, especially when only spirometry is available. The adjustment of the FEFs is proposed to make them less variable, albeit marginally. To increase clinical usability, we established reference equations for the Dutch Caucasian population, using pulmonary-healthy never-smokers from the Lifelines biobank (chapter 5). These equations, however, are far from perfect. The variance of the adjusted FEFs that these equations explain is low to moderate, which indicates that the models used to predict the normal FEF₅₀/FVC range for a certain subject may be too simplistic. Maybe the use of more sophisticated statistical methods (compared to the structure of our reference equations and the original reference equations for spirometry by Quanjer [5]), and as done by the global lung initiative (GLI) for other spirometry parameters, will yield better results [6, 7].
Subsequently, we evaluated the clinical applicability of the adjusted FEFs (chapter 6). The correlation of the adjusted FEFs with the unadjusted FEFs was high which suggested that the adjustment might offer little additional information. Additionally, in further analyses, it became clear that the unadjusted FEFs had a higher correlation with clinical characteristics and parameters of asthma severity, specifically of small airways. Therefore, we concluded that the adjustment of the FEFs failed to clearly improve the clinical applicability. A possible explanation may be that the FEF adjustment is indeed too simple. The FEFs are now divided by the FVC. The FVC represents the lung’s capacity and is an accepted surrogate for individual airway size. The FVC is measured over the entire expiration. The FEFs—the flows at a point in the expiration—are calculated when the expiration is completed. This assumes a linear association between the decrease in flow and capacity. In asthmatic subjects, the lung’s compliance and elastic recoil often change in a non-linear manner during the expiration. Another explanation may be that at the end of the expiration, small airways may collapse and the FVC may be an underestimation of the lung’s capacity. Mathematically a smaller denominator with unchanged numerator results in a larger outcome. Hence, an underestimation of the denominator (FVC) results in an overestimation of the outcome (adjusted FEF). This may wrongly indicate an adjusted FEF within the normal ranges in case of small airways disease. Thus, the individual variability in the degree of FVC underestimation may contribute to the lack of improvement in the clinical applicability of the FEFs adjusted for FVC.
Future perspectives

As consensus on how to best treat (ex-)smokers with asthma remains absent, more research is required. Our finding that extrafine particle ICS treatment improves small airways function to the same extent as larger-sized particle ICS treatment in (ex-)smokers with asthma is in contrast with several other studies. However, the studies that found extrafine treatment to be beneficial commonly added an (extrafine) LABA to the treatment. Combining this information, it might be worthwhile to better assess the actual amount of deposition of different-sized particles of both ICS and LABA in the larger airways, and vice versa, of larger particles in the smaller airways, accepting that the distribution of “extrafine” and “non-extrafine” particles has a bandwidth, and similarly “large” and “small” airways is a concept without very exact boundaries. Depending on the outcome, perhaps other mixtures of smaller and larger particles might be beneficial. So far, size in relation to deposition location has been largely modeled by set-ups such as the cascade impactor and less by actual in vivo data [8, 9].

To treat asthmatic (ex-)smokers, one of the main symptoms of asthma, dyspnea, should be understood. We, therefore, studied dyspnea sensation, by triggering the large airways with AMP and the small airways with dry powder adenosine. This showed that both provocations evoked similar levels of dyspnea. As pulmonary function parameters were only weakly associated with the dyspnea sensation, further research, to understand dyspnea sensation should take into account other factors like anxiety, exercise capacity, educational level, and the patient’s disease-related knowledge. Furthermore, it would be interesting to assess dyspnea differentiated by the terminology patients use to describe their dyspnea (e.g. unable to get enough air, air hunger, breathlessness, increased work-of-breathing, chest tightness, tachypnea) instead of using the joint term and evaluating only the intensity of the dyspnea. This study should evaluate whether the dyspnea category can be associated with large or small airways dysfunction.

Our research suggested that healthy subjects with AHR to AMP, but without AHR to MCh, may be at risk of developing a pulmonary disease. It would therefore be interesting to re-investigate the NORM-cohort to check their
current pulmonary health status. To evaluate if a positive response to AMP provocation in MCh negative subjects is indeed predictive of future pulmonary disease development. When the entire cohort would be re-investigated, it would be possible to evaluate if more subjects with a positive AMP provocation developed the pulmonary disease—as indicated by, for example, an obstructive pulmonary function, positive MCh test, or doctor’s diagnosis—compared to those with a negative AMP response. However, the sample would still be relatively small, as the NORM was a small cohort (108 subjects). To increase the power, data from more healthy subjects who did both provocation tests should be obtained. For example, MCh and AMP provocation tests could be added to the next LifeLines follow-up. In the future follow-ups of LifeLines—which include questionnaires assessing pulmonary complaints (dyspnea or troubled breathing, shortness of breath attacks, wheezing, chronic cough, or phlegm), assessment of a doctor’s diagnosis, and reported medication—it would become clear if the development of pulmonary disease is associated with a positive response to AMP in those with no response to MCh. In clinical practice, this information could be used as an additional motivator to quit smoking, to identify candidates eligible for a closer follow-up, or maybe even to start treatment in an early disease phase.

As the FVC adjustment of the FEFs was suggested repeatedly in the literature, but the absence of reference equations might have impeded clinical use, we generated these equations. They are based on a large cohort but led to equations with a low explanatory value. With an increased fit, the model would be more accurate. The current models assume a linear relationship between age, height, and pulmonary function. However, this is simplistic. With more sophisticated models, it would be possible to consider a non-linear relationship. For example, by adding a spline to the model, like the GLI consortium did to improve the reference equations for the unadjusted spirometric parameters. When the spline is added, the reference equations gain a term for piecewise definition of the normal reference curve per age and height group. These groups are defined per small units, like one year or 10 centimeters, instead of just distinguishing between childhood and adulthood. Another factor that may increase the model's fit could be
including other predictive parameters. For example, a factor to describe the deviation of the subject's FVC from the normal range, possibly the FVC’s percentage of predicted, the number of residual standard deviations below the predicted value (Z-score), or when loss of information is accepted, a dichotomous factor indicating that the FVC was below the lower limit of normal. This would be beneficial because the equation could take into account whether the correction was performed with a normal FVC in line with the age and height, or with an FVC that was too small. In other words, the reference equation would take into account whether the obtained adjusted FEF was overestimated due to an underestimation of the FVC.

Our study investigating the clinical applicability of the adjusted FEFs shows that the adjustment did not increase the clinical applicability of the FEFs. Again, the adjustment may have been too simple for the complexity of the relationship between the FEFs and the FVC. When the FVC is performed submaximally, the FEFs are affected too. To adjust for FVC dependency the correction could be made with a proportion of the FVC corresponding with the flow. That means a correction of the flow at 50% of the FVC (FEF_{50}) with the volume exhaled at 50% of the forced expiration instead of the entire FVC. In this case, the correction would be performed with the portion of the volume actually exhaled at the measured flow. Furthermore, to understand the clinical applicability of the adjustment of the FEFs by the FVC, the decrease in flows and volumes in asthma should be better understood. If the deterioration of the pulmonary function is differentially represented by the FEFs and FVC, the adjustment as was performed may have falsely corrected for disease activity. For the clinical interpretation of the adjusted FEFs, this may be crucial. Potentially, the amount of FEF and FVC decrease should help guide the interpretation of the adjusted FEF. Thus, even though, the clinical applicability of adjusting the FEFs as small airways parameters seem not worthwhile, we should perhaps not fully disregard it yet.

In conclusion, in this thesis, we discussed findings regarding the treatment of (ex-)smoker asthmatics and the role of the small airways in their dyspnea sensation. Additionally, we evaluated airway hyperresponsiveness in subjects without asthma. This thesis ended with the generation of normal reference equations for FVC-adjusted FEFs and an assessment of the clinical
applicability of the FVC-adjusted FEFs. To sum up the findings, the treatment of asthma in (ex-)smoker asthmatics with extrafine particle treatment turned out to be as effective as a larger-sized treatment. The dyspnea sensation in (ex-)smoker asthmatics was associated more with small compared to large airways dysfunction. AHR to AMP occurs in a subset of subjects without asthma and is associated with current smoking and a higher cigarette consumption per day. Finally, normal reference equations for the adjusted FEFs were presented, however, clear clinical applicability in asthma seemed absent.
References


