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Small airway function in obese individuals with self-reported asthma

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ABSTRACT Diagnosis of asthma in obese individuals frequently relies on clinical history, as airflow by spirometry may remain normal. This study hypothesised that obese subjects with self-reported asthma and normal spirometry will demonstrate distinct clinical characteristics, metabolic comorbidities and enhanced small airway dysfunction as compared with healthy obese subjects.

Spirometry, plethysmography and oscillometry data pre/post-bronchodilator were obtained in 357 obese subjects in three groups as follows: no asthma group (n=180), self-reported asthma normal spirometry group (n=126), and asthma obstructed spirometry group (n=51). To assess the effects of obesity related to reduced lung volume, oscillometry measurements were repeated during a voluntary inflation to predicted functional residual capacity (FRC).

Dyspnoea was equally prevalent in all groups. In contrast, cough, wheeze and metabolic comorbidities were more frequent in the asthma normal spirometry and asthma obstructed spirometry groups *versus* the no asthma group ($p<0.05$). Despite similar body size, oscillometry measurements demonstrated elevated R_{5-20} (difference between resistance at 5 and 20 Hz) in the no asthma and asthma normal spirometry groups (0.19±0.12; 0.23±0.13 kPa/(L·s^{-1}), $p<0.05$) but to a lesser degree than the asthma obstructed spirometry group (0.34±0.20 kPa/(L·s^{-1}), $p<0.05$). Differences between groups persisted post-bronchodilator ($p<0.05$). Following voluntary inflation to predicted FRC, R_{5-20} in the no asthma and asthma normal spirometry groups fell to similar values, indicating a reversible process (0.11±0.07; 0.12±0.08 kPa/(L·s^{-1}), p=NS). Persistently elevated R_{5-20} was seen in the asthma obstructed spirometry group, suggesting chronic inflammation and/or remodelling (0.17±0.11 kPa/(L·s^{-1}), $p<0.05$).

Thus, small airway abnormalities of greater magnitude than observations in healthy obese people may be an early marker of asthma in obese subjects with self-reported disease despite normal airflow. Increased metabolic comorbidities in these subjects may have provided a milieu that impacted airway function.

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Obese subjects with self-reported asthma have exaggerated small airway dysfunction even when spirometric airflow is normal. Cough and wheeze are associated with metabolic comorbidities providing a milieu with impact on small airway function. https://bit.ly/2VFrA9O

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Introduction

Asthma in obese individuals presents a diagnostic challenge and frequently relies on clinical history as spirometry may not reveal airflow obstruction [1–7]. Airway hyperreactivity is frequently used as a diagnostic criterion of asthma when airflow by spirometry is normal [8]. However, its use in obesity may be limited as airway smooth muscle reactivity is also enhanced as a consequence of obesity-induced reduction of lung volume [9–11]. Therefore, in the presence of normal airflow by spirometry, it may be difficult to distinguish the effects of increased body size from intrinsic airway disease.

In the absence of asthma, obesity impacts respiratory system mechanics by inducing airway narrowing attributed to the mechanical effects of excess body weight (mass loading) compressing the respiratory system [12–14]. The resulting small airway collapsibility/closure manifests as a decrease in functional residual capacity (FRC) and expiratory reserve volume (ERV) [13, 15, 16]. Small airway dysfunction is usually missed by spirometry and the ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) is frequently normal [13, 17]. In contrast, forced oscillation testing (FOT) demonstrates an increase in respiratory system resistance and elastance that may reflect distal airway collapsibility [14, 18, 19].

When asthma coexists with obesity, a reduction in FEV_1/FVC may be evident, indicating presence of airway disease. However, for obese individuals with asthma that present with a normal FEV_1/FVC ratio, increased collapsibility of peripheral airways may be demonstrated by FOT to a magnitude greater than observations in healthy obese people [18, 19]. This finding was demonstrated in individuals with asthma confirmed by either bronchodilator response of FEV_1 or bronchial hyperreactivity, which may not available in all clinical settings [19]. Based on these considerations, the present study evaluates whether FOT abnormalities are demonstrable in a large group of obese subjects that reported a clinical diagnosis of asthma despite normal spirometry and in the absence of physiological confirmation (bronchodilator response and/or methacholine challenge test). We hypothesised that these obese individuals will demonstrate enhanced small airway dysfunction as compared with healthy obese subjects. Furthermore, we evaluate whether there are additional clinical characteristics that differentiate these subjects with asthma from otherwise healthy obese individuals. To characterise the full spectrum of obese asthma, this study includes obese asthmatic individuals with chronic airflow limitation on spirometry.

Methods

Subjects

The present study evaluated 357 obese subjects referred to the André Cournand Pulmonary Physiology Laboratory in Bellevue Hospital for pulmonary evaluation prior to weight reduction surgery. Subjects were divided into three groups (table 1): 1) no asthma: 180 obese subjects without a diagnosis of asthma and with normal airflow by spirometry (FEV_1/FVC$\geqslant$0.75); 2) asthma normal spirometry: 126 obese subjects who reported a clinical diagnosis of asthma but with normal airflow by spirometry (FEV_1/FVC$\geqslant$0.75); and 3) asthma obstructed spirometry: 51 obese subjects with both a clinical diagnosis of asthma and airflow obstruction on spirometry (FEV_1/FVC<0.72).

Medical records were reviewed to determine symptoms, comorbid conditions, medical and smoking history, laboratory and radiographic findings. In the asthma normal spirometry group, subjects reported a clinical diagnosis of asthma but no previous documentation of airway hyperreactivity was available for diagnosis confirmation.

Study design

All subjects underwent pulmonary evaluation by spirometry, plethysmography, diffusion capacity and FOT as part of their preoperative evaluation. Testing included spirometry and FOT post-inhalation of bronchodilator. In addition, to assess the effects of reduced lung volume due to mass loading on FOT,

TABLE 1 Spirometry data for each group

	No asthma (n=180)	Asthma normal spirometry (n=126)	Asthma obstructed spirometry (n=51)
FVC % pred	92±15	88±14	84.3±17.0
FEV_1 % pred	90±14	86±13	67.4±14.5
FEV_1/FVC %	82±4	81±4	66±5

Data are presented as mean ±SD. FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; % pred: % predicted.

pre-bronchodilator measurements were repeated during a voluntary inflation to restore end-expiratory lung volume to predicted FRC.

Spirometry and lung volumes

Spirometry data were available in all subjects at baseline and post-bronchodilation. Testing was performed in accordance with the American Thoracic Society/European Respiratory Society standards (Vmax Encore, SensorMedics, Yorba Linda, CA, USA) [20, 21]. The data collected included FEV_1, FVC, FEV_1/FVC, ERV, and inspiratory capacity (IC). Specific criteria were used to ensure maximal effort for the spirometric measurements of vital capacity, IC, and ERV: 1) an exhalation time of $\geqslant$6 s; 2) a plateau of the exhaled volume *versus* the time tracing; and 3) two or more trials with reproducible data. The FRC was determined by plethysmography or nitrogen washout in one individual; technically acceptable data were available in 351 of 357 subjects. The residual volume (RV) and total lung capacity (TLC) were calculated from these measurements [21]. Pulmonary function data were analysed with respect to published normative data [22–24].

Forced oscillation testing

FOT was performed at baseline and post-bronchodilation using the Jaeger impulse oscillation system (Jaeger USA; Yorba Linda, CA, USA). Measurements were obtained at FRC during tidal breathing with patients in the seated position with a nose clip, while firmly supporting the cheeks. At the end of measurement, patients were instructed to perform an inspiratory capacity manoeuvre to confirm that measurements were performed at FRC in comparison to the IC determined by spirometry. Measurements were repeated during a voluntary inflation to restore end-expiratory lung volume to predicted FRC; this technique mitigates the effect of excess body weight on airway compression, as previously described [12].

Respiratory resistance and reactance were calculated by analysing airflow and pressure oscillations between frequencies of 5 to 35 Hz. Parameters obtained included: 1) resistance at an oscillation frequency of 5 Hz (R_5); 2) resistance at an oscillation frequency of 20 Hz (R_{20}); frequency dependence of resistance calculated as the difference between resistance at 5 and 20 Hz (R_{5-20}); and 4) reactance at 5 Hz (X_5) as a measure of respiratory elastance. Only data from trials with constant tidal volume and end-expiratory volume were analysed. The volume time tracings were inspected to ensure that there were no pauses suggestive of glottis closure and that there was no leak around the mouthpiece. A minimum of three trials were performed; the average value was reported for reproducible trials (coefficient of variation for R_5<10%) was required for all parameters at both lung volumes. Valid data were available in 343 of 357 subjects. Data are presented as raw data and are compared to an upper limit of normal selected from previous publications [25–30].

Statistical analysis

Data were summarised as mean±SD. Differences between the three groups were analysed using ANOVA with *post hoc* pair-wise testing performed utilising Tukey's honestly significant difference test. Statistical significance was set as a p-value <0.05. Data were analysed using SPSS version 25.

This study was approved by the Institutional Review Board of New York University School of Medicine and Bellevue Hospital.

Results

Table 2 outlines the clinical characteristics of the three groups. The no asthma group was younger compared to both asthma normal spirometry and asthma obstructed spirometry groups (39±12, 44±11, 45±13 years, respectively; p<0.05). All groups had a majority of female subjects and demonstrated similar body size and fat distribution. Comorbidities associated with metabolic syndrome were noted in each group, but with highest proportion in the asthma normal spirometry and asthma obstructed spirometry groups. White blood cell and eosinophil counts were normal and similar in all three groups, suggesting absence of allergic asthma. The majority of subjects in each group experienced at least one of several lower respiratory symptoms. Nevertheless, differences between groups were apparent when specific symptoms were analysed. The predominant symptom in the no asthma group was dyspnoea with low prevalence of cough and wheeze. While dyspnoea was also highly prevalent in both the asthma normal spirometry and asthma obstructed spirometry groups, there was a significantly greater proportion of subjects with cough and wheeze (p<0.05 *versus* the no asthma group).

Lung volume data are illustrated in figure 1. In accord with the expected physiological phenotype of obesity, the no asthma group exhibited reductions of FRC, ERV and RV with no evidence of air trapping (*i.e.* normal RV/TLC) compatible with lung compression from mass loading. The asthma normal spirometry group demonstrated a similar pattern with no significant difference compared with the no asthma group. In contrast, the asthma obstructed spirometry group demonstrated higher values for FRC

TABLE 2 Clinical characteristics of the study subjects

	No asthma (n=180)	Asthma normal spirometry (n=126)	Asthma obstructed spirometry (n=51)
Age years	39±12[#,¶]	44±11	45±13
Female %	88[#]	87[+]	67
Anthropometric data			
Height m	1.62±0.09	1.60±0.08[+]	1.65±0.1
Weight kg	117±23	119±23	123±24
BMI kg·m^{-2}	44±7	46±8	45±7
Waist to hip ratio			
Male	1.03±0.1	1.04±0.07	1.00±0.06
Female	0.94±0.09	0.94±0.11	0.93±0.1
Respiratory symptoms %			
Any symptom	57	70	61
Chest pressure/pain	23	23	18
Dyspnoea	46	60	54
Cough	19[#,¶]	41	40
Wheeze	8[#,¶]	45	32
Associated diseases %			
Hyperlipidaemia	14	25	28
Hypertension	34[#,¶]	52[+]	46
Sleep apnoea	16[#,¶]	33	32
Diabetes	21	32	29
Blood counts			
WBC 10^{3}·µL^{-1}	7.78±2.04	8.13±2.15	7.75±1.96
Eosinophils %	2.28±1.99	2.52±1.99	2.58±2.07
Eosinophils 10^{3}·µL^{-1}	0.17±0.13	0.20±0.18	0.20±0.20

Data are presented as mean±SD, unless otherwise stated. BMI: body mass index; WBC: white blood cell count. [#]: p<0.05 no asthma *versus* asthma obstructed spirometry; [¶]: p<0.05 no asthma *versus* asthma normal spirometry; [+]: p<0.05 asthma normal spirometry *versus* asthma obstructed spirometry.

and RV that were often in the normal range coupled with higher values of RV/TLC, suggesting relative hyperinflation and air trapping (p<0.05 for comparison with both no asthma and asthma normal spirometry). Taken together, this pattern of lung volumes in the asthma obstructive spirometry group denotes "pseudo-normalisation" of resting lung volume due to airflow limitation on the background of mass loading. Diffusion capacity data were available in 345 subjects; mean values were normal and similar

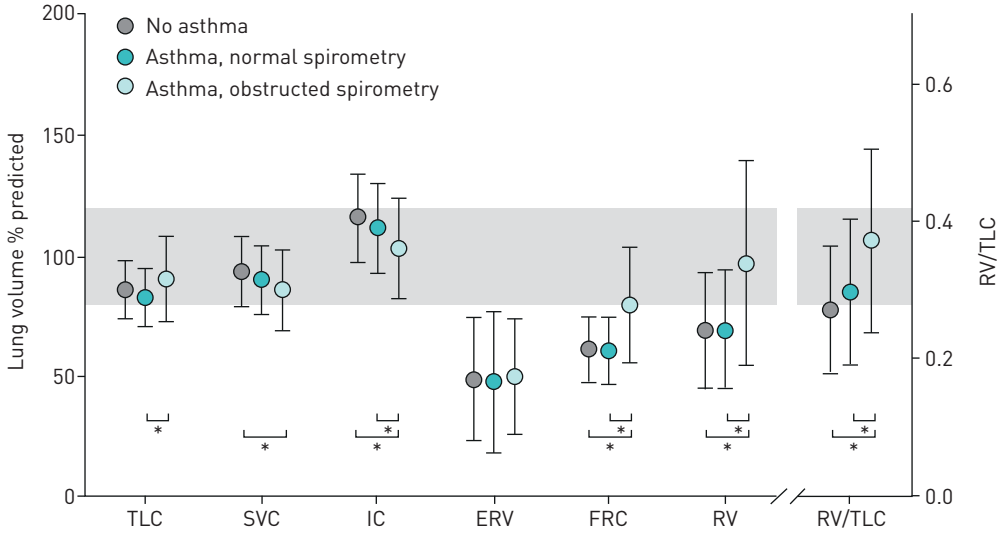

FIGURE 1 Lung volumes are depicted for each of the subject groups. Data are presented as mean±SD. TLC: total lung capacity; SVC: slow vital capacity; IC: inspiratory capacity; ERV: expiratory reserve volume; FRC: functional residual capacity; RV: residual volume. *: p<0.05.

in all three groups (94±19, 92±16, and 91±21% predicted for the no asthma, asthma normal spirometry and asthma obstructed spirometry groups, respectively; p=NS).

Data for airway resistance (R_{aw}) and specific conductance by plethysmography (sG_{aw}) in each subject group are shown in the top panels of figure 2. Despite clinical diagnosis of asthma, median R_{aw} and sG_{aw} were normal and similar in the no asthma and asthma normal spirometry groups (R_{aw} 0.23±0.09 *versus* 0.26±0.11 kPa/(L·s^{-1}), p=NS; SG_{aw} 2.02±0.63 *versus* 1.87±0.74 kPa^{-1}·s^{-1}, p=NS). In contrast, R_{aw} and sG_{aw} were abnormal in the asthma obstructed spirometry group in accord with the presence of chronic airflow limitation on spirometry (R_{aw} 0.40±0.19 kPa·L^{-1}·s^{-1}, sG_{aw} 1.05±0.53 kPa^{-1}·s^{-1}, p<0.05 for both parameters compared with the other groups).

FOT assessment of respiratory resistance (R_{rs}) and specific conductance (sG_{rs}) in each group is shown in the bottom panels of figure 2. While plethysmographic resistance was normal in the no asthma and asthma normal spirometry groups, FOT demonstrated elevated median R_{20} to a similar degree in all

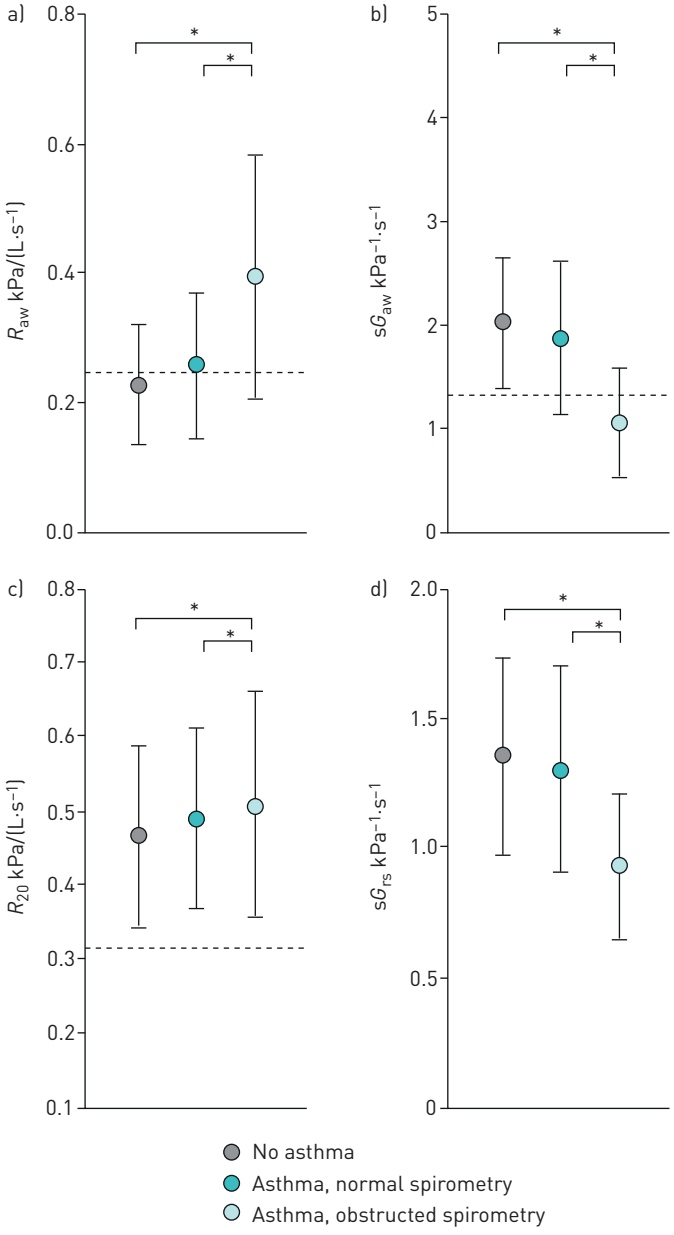

FIGURE 2 a) Airway resistance (R_{aw}) and b) specific conductance (sG_{aw}), measured by plethysmography for each of the subject groups. c) R_{aw} and d) sG_{aw}, measured by forced oscillation for each of the subject groups. Data are presented as mean±SD. Dashed lines indicate the limits of normal. *: p<0.05.

groups (0.47±0.12; 0.50±0.12; 0.52±0.16 kPa/(L·s^{-1}), respectively; p=NS). When R_{20} was related to FRC and re-expressed as sG_{rs}, the asthma normal spirometry group remained indistinguishable from the no asthma group despite clinical diagnosis of asthma (1.35±0.38; 1.30±0.40 kPa^{-1}·s^{-1}, p=NS). In contrast, lower values were noted in the asthma obstructed spirometry group, which were attributable to the relatively preserved FRC (pseudo-normalisation) in these subjects (0.93±0.28 kPa^{-1}·s^{-1}, p<0.05).

Figure 3 shows measurements of respiratory elastance assessed as X_5 in all three groups. At baseline (left panel), all groups demonstrated abnormal X_5. There was a progressive abnormality that was most pronounced in the asthma obstructed spirometry group (−0.27±0.15; −0.34±0.17; −0.43±0.24 kPa/(L·s^{-1}); p<0.05). The middle panel shows data obtained post-bronchodilation and demonstrates persistence of the progressive abnormality in X_5 (−0.22±0.10; −0.26±0.12; −0.31±0.21 kPa/(L·s^{-1}), p<0.05) To evaluate the effects of mass loading on X_5, measurements pre-bronchodilation were repeated during a manoeuvre aimed to restore end-expiratory lung volume to predicted FRC values (right panel). Testing at the restored FRC demonstrated persistently abnormal X_5 that was similar in all groups and may reflect increased chest wall tension during the inflation manoeuvre.

Figure 4 shows measurements of frequency dependence of resistance assessed as $R_{5–20}$ in all three groups. At baseline (left panel), the groups demonstrated progressive abnormality in $R_{5–20}$ with the most abnormal values evident in the asthma obstructed spirometry group (0.19±0.12; 0.23±0.13; 0.34±0.20 kPa/(L·s^{-1}), p<0.05). The middle panel shows data obtained post-bronchodilation. All groups showed improvement in frequency dependence of resistance following bronchodilator inhalation; however, the pattern of progressive abnormality is still demonstrable and residual abnormalities were seen in all groups (0.13±0.09; 0.17±0.10; 0.23±0.21 kPa/(L·s^{-1}), p<0.05). When pre-bronchodilator FOT was repeated during inflation to predicted FRC (right panel), the no asthma and asthma normal spirometry groups demonstrated reduction in $R_{5–20}$ to values that were similar, indicating a reversible process (0.11±0.07 *versus* 0.12±0.08 kPa/(L·s^{-1}), p=NS). In contrast, persistent increase of $R_{5–20}$ was seen in the asthma obstructed spirometry group, suggesting a residual abnormality (0.17±0.11 kPa/(L·s^{-1}), p<0.05).

Discussion

The present study evaluated whether obese individuals with a self-reported clinical diagnosis of asthma despite normal spirometry have demonstrable differences in small airway function when compared with healthy obese individuals. These subjects present a clinical dilemma and objective demonstration of a small airway process would be relevant for therapeutic management. The data demonstrated that these

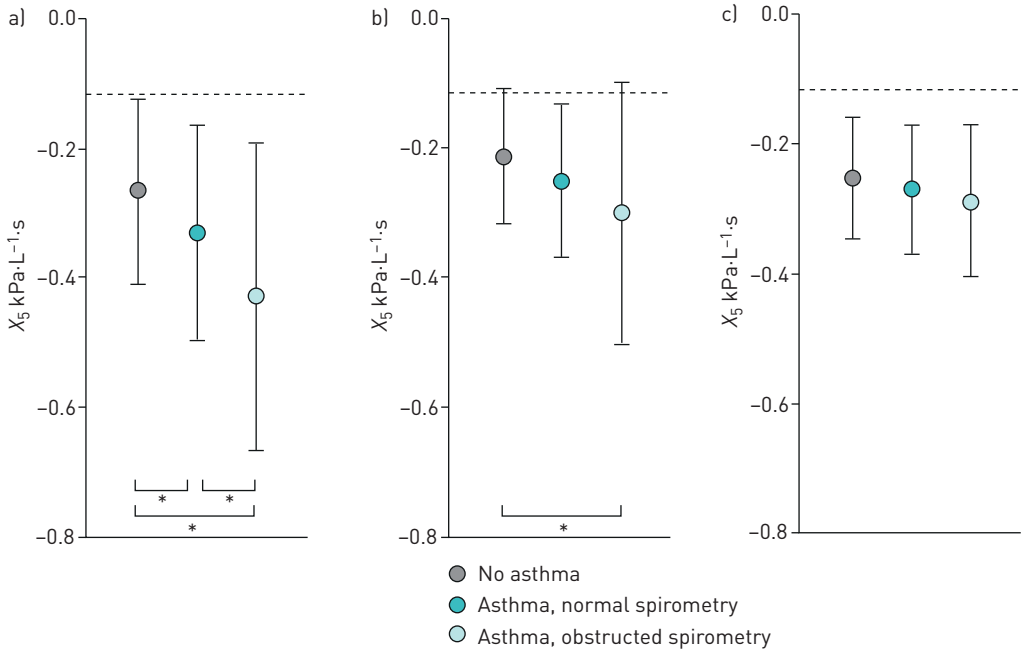

FIGURE 3 Reactance at 5 Hz (X_5) for each of the subject groups measured at a) baseline, b) post-bronchodilator and c) during voluntary inflation targeted to restore end-expiratory lung volume to predicted functional residual capacity. Data are presented as mean±SD. Dashed lines indicate the upper limits of normal. *: p<0.05.

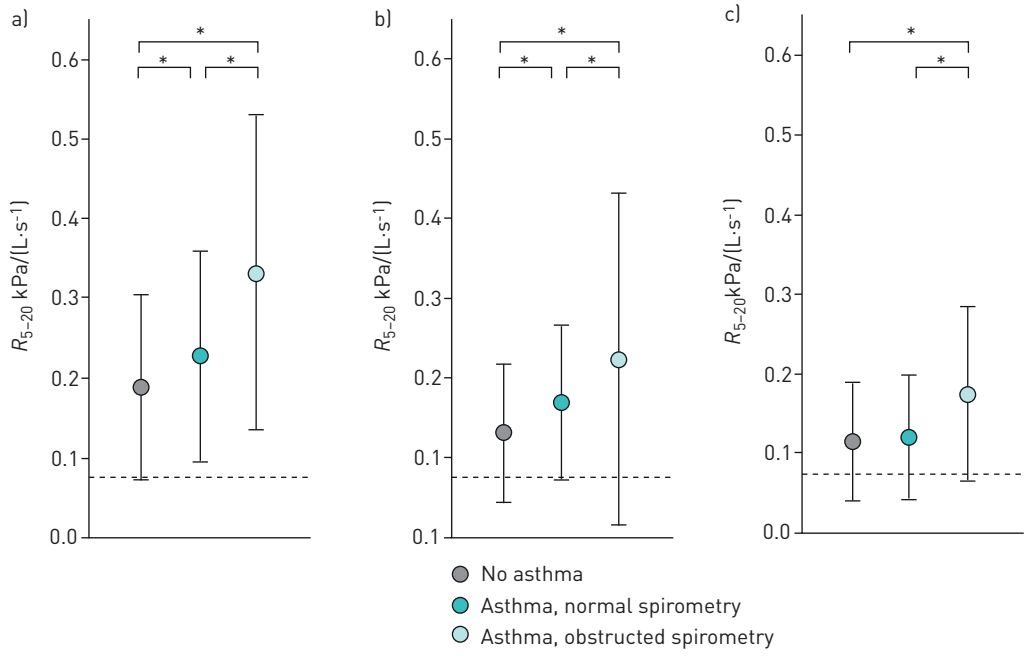

FIGURE 4 Frequency dependence of resistance calculated as the difference between resistance at 5 and 20 Hz (R_{5-20}) for each of the subject groups measured at a) baseline, b) post-bronchodilator and c) during voluntary inflation targeted to restore end-expiratory lung volume to predicted functional residual capacity. Data are presented as mean±SD. Dashed lines indicate the upper limits of normal. *: p<0.05.

obese individuals with asthma have: 1) abnormal small airway function as demonstrated by FOT measurements to a magnitude that is greater than observations in healthy obese subjects that persists after bronchodilator therapy; 2) absence of fixed-airway dysfunction, as repeat FOT during voluntary inflation to predicted FRC returned the peripheral airway function to values that were indistinguishable from healthy obese subjects; and 3) increased prevalence of comorbidities that contribute to diagnosis of metabolic syndrome. Thus, although airflow remained within normal limits by spirometry in these subjects, cough and wheeze were associated with metabolic comorbidities, similarly to obese individuals with established asthma by spirometry, providing a milieu with impact on small airway function.

Physiologic phenotypes

Asthma may present with normal airflow when assessed by spirometry despite presence of respiratory symptoms. In nonobese individuals with asthma, an abnormality in small airway function may be identified by presence of frequency dependence of resistance and abnormal elastance on FOT [18, 31–33]. Frequency dependence of resistance provides a measure of nonuniformity of airflow distribution, which may reflect regional functional abnormalities in the small airways [25, 34, 35]. Extrapolation of these FOT abnormalities to obese subjects is confounded by the effects of mass loading-induced lung and airway compression, which also produces frequency dependence of resistance and abnormal elastance [12, 13, 17, 18, 36–39]. Nevertheless, Desai *et al.* [38] demonstrated increased peripheral airway bronchomotor tone in healthy obese subjects that may contribute to asthma pathogenesis. Furthermore, Al-Alwan *et al.* [19] demonstrated enhanced FOT abnormalities in obese subjects with physiologically confirmed asthma, as compared with healthy obese subjects, which were attributed to peripheral airway collapsibility.

The present study extends the above observations by evaluating a large group of obese subjects with self-reported clinical diagnosis of asthma, including assessment of the role of mass loading by repeat FOT during a voluntary inflation to predicted FRC [12]. In these subjects, the reported diagnosis of asthma is supported by demonstration of small airway dysfunction (abnormal R_{5-20} and X_5) of greater magnitude than values in healthy obese subjects, coupled with responsiveness to inhaled bronchodilation. Although a persistent abnormality was noted post-bronchodilation, airway wall remodelling was not likely as small airway function returned to healthy obese values when assessed during voluntary inflation. Nevertheless, the demonstration that exaggerated FOT abnormalities occur in the setting of normal airflow on spirometry reinforces that small airway dysfunction may be an early marker of asthma in obese subjects.

As asthma severity increases, chronic airflow limitation may become evident on spirometry. Accordingly, to evaluate the full spectrum of obese asthma, the present study included an obese asthma obstructed

spirometry group. In these subjects, a distinct physiological phenotype was demonstrable. There was preservation of FRC and RV to near normal as compared with the universally low values seen in healthy obese individuals [40]. The near normal values for FRC and RV likely reflect pseudo-normalisation due to air trapping as these subjects also demonstrated the most abnormal resistance on FOT; consequently, specific conductance was most abnormal in this group of subjects. Furthermore, in these obese subjects with obstructed spirometry, residual small airway dysfunction was noted on FOT after bronchodilation with a magnitude that was more severe than the obese asthma normal spirometry group. The small airway dysfunction was also not fully reversible during voluntary inflation targeted to restore resting lung volume to predicted FRC, suggesting presence of chronic airway wall inflammation and/or remodelling

Respiratory symptoms

All groups demonstrated a high prevalence of lower respiratory symptoms, but the distribution of specific symptoms may provide insight into their underlying aetiology. In the no asthma group, there was a high prevalence of dyspnoea which is nonspecific and could be attributed to the mechanical effects of obesity on lung volume and airway function [18]. In this group there was minimal cough and/or wheeze. In the asthma normal spirometry and asthma obstructed spirometry groups, there was a high prevalence of cough and wheeze in addition to dyspnoea that likely reflects the enhanced abnormality in small airway function in these subjects. These findings are in accordance with observed relationships between severity and frequency of wheeze and small airway dysfunction in a group of subjects with inhalational lung injury, even in the presence of normal spirometry [41]. A link to systemic inflammation in these groups is suggested in the present study by the increased prevalence of comorbidities associated with diagnosis of metabolic syndrome and obstructive sleep apnoea.

Study considerations

There are several aspects of the study design that require consideration. First, the present study evaluated a group of obese subjects where a diagnosis of asthma was self-reported without prior documented physiological confirmation. This selection criteria parallels prior studies of asthma phenotypes and obesity–asthma overlap. [42–44]. In the present study, the obese subjects that self-reported asthma without physiological confirmation (*e.g.* bronchodilator response on spirometry and/or presence of bronchial hyperreactivity) demonstrated enhanced small airway dysfunction beyond observations in the obese no asthma group. Small airway dysfunction was reversible in response to bronchodilation, confirming the presence of an intrinsic airway abnormality. Second, there was a higher prevalence of males in the asthma obstructed spirometry group as compared with either of the other groups. However, the primary analysis of this paper is focused on physiological evaluation of the asthma normal spirometry group, where the distribution of males and females was similar to the healthy no asthma group. Lastly, while statistical difference in FOT values were demonstrated between groups, the study was not designed to identify a cut-off point to definitively distinguish obese subjects with asthma and normal airflow from otherwise healthy obese individuals.

Clinical implications

The results of this study demonstrate a mechanical and metabolic rationale for the small airway abnormalities observed in a group of obese subjects with a self-reported diagnosis of asthma despite normal airflow on spirometry. Increased respiratory symptoms in these individuals presumably led to a physician diagnosis of asthma as spirometry remained within normal limits. The association between symptoms and self-reported asthma can become circular if the presence of the symptoms lead to the diagnosis in the first place. However, small airway function was more abnormal in these individuals than would be expected in healthy obesity, likely producing the observed increased prevalence of cough and wheeze. The presence of increased metabolic comorbidities in these obese asthma subjects provides a milieu of systemic inflammation that may impact airway function. Identification of this phenotype distinguishes this group of subjects from healthy obese individuals and may impact therapeutic choices. Weight loss could reduce symptoms by reducing mass loading on the respiratory system, airway reactivity, metabolic comorbidities and circulatory congestion. In addition, continued escalation of corticosteroid dose requires consideration of the balance between a beneficial effect on airway inflammation *versus* detrimental effects on body weight, fluid retention and metabolic syndrome. The optimal therapeutic approach in these obese patients with asthma requires consideration of the multiple pathways leading to airway dysfunction and respiratory symptoms.

Conflict of interest: None declared.

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