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The influence of distinct asthma phenotypes on lung function following weight loss in the obese

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Abstract

Background and objective—There appears to be two distinct clinical phenotypes of obese patients with asthma – those with early-onset asthma and high serum IgE (T_H2-high) and those with late-onset asthma and low serum IgE (T_H2-low). The aim of the present study was to determine in the two phenotypes of obese asthma the effect of weight-loss on small airway function.

Methods—T_H2-low (n=8) and T_H2-high (n=5) obese asthmatics underwent methacholine challenge before and 12 months following bariatric surgery. Dose response slopes as measures of sensitivity to airway closure and narrowing were measured as maximum %fall FVC and FEV_1/FVC, respectively, divided by dose. Resting airway mechanics were measured by forced oscillation technique.

Results—Weight-loss reduced sensitivity to airway closure in T_H2-low but not T_H2-high obese asthmatics (pre-post mean change ± 95%CI: 1.8 ± 0.8 doubling doses vs −0.3 ± 1.7 doubling doses, p=0.04). However, there was no effect of weight loss on the sensitivity to airway narrowing in either group (p=0.8, T_H2-low: 0.8 ± 1.0 doubling doses, T_H2-high: −1.1 ± 2.5 doubling doses). In contrast, respiratory resistance (20Hz) improved in T_H2-high but not in T_H2-low obese asthmatics (pre-post change median [IQR]: 1.5 [1.3 – 2.8] $cmH_2O/L/s$ vs 0.6 [−1.8 – 0.8] $cmH_2O/L/s$, p=0.03).

Conclusions—T_H2-low obese asthmatics appear to be characterised by increased small airway responsiveness and abnormalities in resting airway function that may persist following weight loss. However, this was not the case for T_H2-high obese asthmatics, highlighting the complex interplay between IgE status and asthma pathophysiology in obesity.

Keywords

Airway closure; Airway hyperresponsiveness; Asthma; Obesity; Weight loss

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INTRODUCTION

The obesity epidemic has had detrimental consequences for the management and treatment of patients with asthma. Compared to non-obese asthmatics, obese asthmatics have worse asthma control (1, 2) and symptoms that are less responsive to inhaled corticosteroid (3, 4). Recent research indicates that obese asthmatic patients segregate into two distinct clinical phenotypes– those with early-onset asthma and high serum IgE (T_H2-high) and those with late-onset asthma and low serum IgE (T_H2-low) (5, 6). This has led to the speculation that T_H2-high obese asthmatics have pre-existing allergic asthma that is complicated by obesity, whereas T_H2-low obese asthmatics develop asthma symptoms as a consequence of obesity. However, the effect of obesity on asthma pathophysiology in these two phenotypes is not well understood.

We recently reported that weight loss following bariatric surgery improves airway hyperresponsiveness (AHR) in T_H2-low obese asthmatics but not in T_H2-high obese asthmatics (5). The mechanisms underlying this divergent effect of obesity on AHR were unclear. Healthy obese non-asthmatics have elevated responses to bronchial challenge compared to their non-obese counterparts, as measured by respiratory system resistance (7, 8), airway closure (9), frequency dependence of respiratory system resistance (7) and expiratory flow limitation (10). Since all of these measurements reflect decrements in small airway function, it suggests that obesity increases small airway responsiveness. However, it is unknown whether obesity alters small airway function differentially in T_H2-high and T_H2-low obese asthmatics, and whether this explains the divergent effects on AHR.

The aim of the present study was to determine the effect of obesity on small airway function in the two phenotypes of obese asthma. Since AHR is reduced by weight loss only in T_H2-low obese asthmatics we hypothesised that weight loss would reduce small airway responsiveness, measured as airway closure, in T_H2-low obese asthmatics but not in T_H2-high obese asthmatics. To test this hypothesis, baseline airway mechanics, assessed with frequency dependent endpoints, and the components of AHR, related to airway narrowing and airway closure, were measured prior to and 12 months following bariatric surgery.

METHODS

Subjects

The asthmatic subjects in the present study comprise a subset of a population reported in a previous publication that investigated the effects of bariatric surgery on airway inflammation, asthma control and AHR, as measured by the traditional lung function parameter FEV_1 (5). Volunteers were recruited from the Bariatric Clinic of Fletcher Allen Health Care, Vermont. The Institutional Review Board of the University of Vermont provided ethics approval and all subjects provided written informed consent.

Asthmatics had a doctor diagnosis of asthma, were using prescribed asthma medications and exhibited objective evidence of asthma in the form of either AHR or bronchodilator responsiveness (>12% or 200mL increase in FEV_1 and/or forced vital capacity (FVC)). Non-asthmatics had no diagnosis of asthma, no symptoms suggestive of asthma and were

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not on any asthma medications. All subjects were free from any other respiratory disease (excluding sleep apnea) and upper respiratory tract infection in the preceding month, had less than a 20-pack year smoking history and had not smoked within the preceding six months. Subjects were excluded if their baseline FEV_1 was less than 60% of predicted or if the maximum fall in FEV_1 during the methacholine challenge was within repeatability limits of the measurement (ie ±150mL) (11). Subjects who did not undergo surgery for personal reasons (n=4) were included in analyses prior to surgery. Data from subjects in whom FEV_1 fell less than the limits of repeatability during methacholine challenge following bariatric surgery were excluded from analyses investigating the effects of weight loss (n=5).

Study Design

Obese asthmatics and non-asthmatics had baseline lung function measured by spirometry and by the forced oscillation technique before undergoing methacholine challenge. Obese asthmatics underwent a second complete study visit 12 months after bariatric surgery to determine the effects of weight loss. Asthmatics withheld their use of short-acting β_2-agonists for 6h and long-acting β2-agonists for 24h prior to testing.

Forced Oscillation Technique (FOT)

Resting respiratory system mechanics were measured at oscillation frequencies of 5–35Hz during tidal breathing (Impulse Oscillometry System, Jaeger, Wurzburg, Germany). Measurements were made over 20 seconds and values are reported as the average of three acceptable trials. Respiratory system resistance (Rrs) and reactance (Xrs) were calculated at 5Hz, designated as Rrs5Hz and Xrs5Hz, respectively. We also calculated Rrs at 20 Hz (Rrs20Hz) and the difference between Rrs at 5 Hz and at 20 Hz (Rrs5–20Hz), the latter providing a measure of the frequency dependence of resistance.

Methacholine Challenge

Methacholine challenges were performed according to ATS guidelines using the five-breath dosimeter method (12). Challenges consisted of inhaling five vital capacity breaths of doubling concentrations of methacholine from 0.031mg/mL to 16.0mg/mL. FEV_1 and FVC were measured after each concentration step, with FVC maneuvers continued for a minimum of 6s and until a clean plateau in the expiratory volume trace. Baseline spirometry was expressed as percent predicted (13).

Analysis of Methacholine Challenge Data

FEV_1 is a global non-specific measure of lung function (14), with reductions in FEV_1 during bronchial challenge reflecting changes in both airway narrowing and airway closure. FEV_1 is reduced by *airway narrowing* because a narrowed airway loses some of its capacity to transmit flow. However, FEV_1 is also determined by the number of parallel airways contributing to flow and is thus reduced by atelectasis or sufficiently severe narrowing of subtending airways, both of which constitute functional *airway closure*. By contrast, FVC is determined by the volume of expirable air in communication with the airway opening which is reduced by functional airway closure but not by airway narrowing. Air narrowing, *per se*, is thus reflected in the ratio FEV_1/FVC (9, 15). We therefore measured the overall airway

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response to methacholine as the % fall in FEV_1, and its components related to airway narrowing (% fall in FEV_1/FVC) and airway closure (% fall in FVC). In addition, we used the ratio % fall in FVC/% fall in FEV_1 as an index of the proportion of the change in FEV_1 attributable to airway closure, termed the *closing index* (9).

Airway hyperresponsiveness was assessed by the dose response slope for FEV_1 ($DRSFEV_1$), calculated as the percent change in FEV_1 at the end of challenge divided by the dose in μmoles (16, 17). A subject was defined as having AHR if $DRSFEV_1 > 4.4$ $\%\Delta FEV_1$/μmole, equivalent to a provocative concentration causing a 20% fall in FEV_1 of less than 16.0mg/mL. Sensitivity to airway narrowing and airway closure were similarly calculated for FEV_1/FVC and FVC, designated as DRS(FEV_1/FVC) and DRSFVC, respectively.

Serum IgE

Serum IgE levels were measured using a near-infrared particle immunoassay and a Beckman Image 800 Immunochemistry Analyzer (Beckman Coulter, Fullerton, California). Serum IgE was only measured in asthmatics and the upper limit of normal was defined as 100 IU/mL based on previous population data (18). IgE was measured at baseline in all obese asthmatics and repeated following surgery only in obese asthmatics with elevated baseline levels.

Data analysis

Obese asthmatics were grouped into those with normal serum IgE levels (T_H2-low) and those with elevated serum IgE levels (T_H2-high). Comparisons between T_H2-low, T_H2-high and obese non-asthmatics at baseline were done using one-way ANOVA with Tukey post-hoc comparisons or Kruskal-Wallis tests with Dunn post-hoc comparison. Comparisons of obese asthmatic data before and 12 months following bariatric surgery were performed using mixed model repeat measures analysis of variance with terms for T_H2 group, effect of surgery, and a test of interaction using an interaction term of T_H2 group × surgery. Summary data are presented as mean ± 95% confidence intervals (95% CI) unless otherwise stated. The data were analysed using JMP® Pro 10 (SAS Institute Inc., Cary, NC, USA). DRS data were log transformed and presented as geometric mean ± 95% CI with changes in DRS presented as doubling doses. P values < 0.05 were regarded as statistically significant.

RESULTS

Lung function and the response to methacholine challenge prior to bariatric surgery

Data from eight obese non-asthmatics, ten obese asthmatics with elevated IgE levels (T_H2-high) and 12 obese asthmatics with normal IgE levels (T_H2-low) were analysed. There was no difference in age or BMI between the groups (Table 1). Similarly, there was no difference in resting lung function, measured by either spirometry or FOT. Compared to obese non-asthmatics, airway responsiveness as measured by $DRSFEV_1$ was increased in both T_H2-high obese asthmatics and T_H2-low asthmatics ($p<0.05$ for both) although there was no difference between the two asthmatic groups ($p = 0.74$). Despite a reduced overall response to methacholine in the obese non-asthmatics ($p< 0.05$ for both) the closing index did not differ between the three groups (ANOVA, $p= 0.26$) (Figure 1).

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Lung function and the response to methacholine challenge 12 months following bariatric surgery

Although bariatric surgery resulted in substantial weight loss, two of five T_H2-high obese asthmatics and seven of eight T_H2-low obese asthmatics still had a BMI in the overweight or obese range (> 30kg/m^2). There was a trend towards greater reductions in BMI in the T_H2-high obese asthmatics (interaction p=0.07). IgE levels remained elevated in all T_H2-high asthmatics following weight loss, although there was a trend towards a small reduction in absolute levels (median [range] 283 IU/mL [170–593] vs 251 IU/mL [152 – 490], p=0.06). Weight loss improved baseline lung function measured by FEV_1 and FVC (p<0.001 and =0.001, respectively) which was similar in the T_H2-high and T_H2–low groups (interaction p=0.86 and 0.70, respectively). In contrast, there was no improvement in FEV_1/FVC or PEF (p=0.35 and 0.28, respectively). On the other hand, weight loss following bariatric surgery affected respiratory system mechanics differently between the groups. Although the improvement in Xrs5Hz was similar in both groups (interaction p=0.44), Rrs20Hz was unaltered by bariatric surgery in the T_H2-low group, whereas Rrs20Hz improved in the T_H2-high group (interaction p=0.03, Figure 2). Similarly, there was a trend towards a greater improvement in Rrs5Hz following weight loss in the T_H2-high asthmatics (interaction p=0.11). In contrast, weight loss did not alter Rrs5–20 in either group (interaction p=0.73). There was an improvement in the closing index following weight loss (p=0.03) that was not different between the groups (interaction p=0.47, Figure 3). However, the sensitivity to airway closure (logDRSFVC) improved in the T_H2-low group but not in the T_H2-high group (interaction p=0.04), despite no change in the sensitivity to airway narrowing (logDRSFEV_1/FVC) in either group (p=0.79, Figure 4). Therefore the improvement in AHR, as measured by FEV_1, following bariatric surgery is due to a reduction in airway closure during methacholine challenge.

DISCUSSION

Recent evidence of two distinct clinical phenotypes of obese asthma highlights the complexity of the relationship between asthma and obesity (5, 6). In the present study, weight loss in obese asthmatics with early-onset disease and elevated IgE levels (T_H2-high) led to an improvement in resting airway mechanics but no effect on the sensitivity to airway closure or AHR. In direct contrast, weight loss in obese asthmatics with late-onset disease and normal serum IgE levels (T_H2-low) led to an improvement in airway closure during methacholine challenge and AHR, while resting respiratory resistance was unaltered. These findings suggest a clear differential effect of obesity on the two phenotypes of obese asthma; weight loss does not alter small airway responsiveness in T_H2-high obese asthmatics whereas weight loss is associated with a reduction in small airway responsiveness in T_H2-low obese asthmatics and may lead to abnormalities in resting airway mechanics that persist following weight loss.

The response to bronchial challenge in obese non-asthmatics is known to be characterised by exaggerated reductions in small airway function as compared to non-obese subjects (7–10). In the present study we found that the contribution of airway closure to the overall response, as measured by the closing index, was similar between obese subjects with and without

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asthma. Furthermore, weight loss led to a similar improvement in the closing index in T_H2-high and T_H2-low obese asthmatics. Taken together, these findings suggest that obesity itself increases the contribution of airway closure to the overall response, independent of asthma or atopic status. This is consistent with a lack of difference in closing index between healthy weight non-asthmatics and asthmatics (9). However, the closing index does not correlate with airway responsiveness (9, 15) so to determine the contribution of airway closure and airway narrowing to AHR we calculated dose-response slopes for FVC and FEV_1/FVC, respectively. Weight loss reduced the sensitivity to airway closure in T_H2-low obese asthmatics but not T_H2-high obese asthmatics. On the other hand, the sensitivity to airway narrowing was unaltered by weight loss in either group. Therefore, these findings suggest that obesity increases small airway responsiveness in T_H2-low obese asthmatics, but not in T_H2-high obese asthmatics.

The present finding that weight loss improves AHR through a reduction in the sensitivity of airway closure is consistent with the role of increased airway closure in AHR (9). Obesity reduces end-expiratory lung volume, thereby reducing the tethering forces of the parenchyma on the small airways potentially predisposing them to closure. This effect of reduced lung volume on AHR has been demonstrated in normal healthy subjects breathing at reduced lung volumes (19, 20). However, although airway responsiveness is associated with FRC in men, this association was not found in women (21), suggesting that non-mechanical factors may underlie the present findings in our predominantly female cohort. Obesity is associated with resistance to leptin (22), a hormone that plays an important role in surfactant synthesis (23). If leptin resistance causes reduced surfactant levels in obese subjects then one would also expect an increased predisposition to airway closure. In keeping with this hypothesis, we recently reported an association between visceral fat leptin expression and AHR (24) in the same cohort of obese asthmatic patients as used in the present study. Similarly, enhanced pro-inflammatory activity of alveolar macrophages in obese asthmatics (25) may predispose to airway closure through effects on surfactant function (26), although this is not a consistent finding (24).

Interestingly, weight loss in T_H2-high obese asthmatics did not alter the sensitivity to airway closure and therefore did not improve AHR. This was despite improvements in resistance consistent with the increase in resting lung volume expected to occur with weight loss. Additionally, Xrs5Hz, which reflects the stiffness of the respiratory system, improved similarly in both the T_H2-high and T_H2-low groups. This was likely due to reductions in the stiffness of the chest wall following weight loss and recruitment of airways that had previously been closed due to compression by excess adipose tissue. Nonetheless, the improvements in both reactance and resistance in T_H2-high obese asthmatics are consistent with an increase in end-expiratory lung volume following weight loss. Surprisingly, this did not alter small airway responsiveness. Absolute end expiratory lung volume in obese asthmatics is determined by the combined effects of reduced lung volume due to obesity and hyperinflation due to asthma pathophysiology (27). Therefore, one could speculate that lung volume in T_H2-high obese asthmatics may be relatively reduced, but remain at an absolute lung volume that does not predispose to airway closure. On the other hand, airway inflammation appears reduced in the obese (5, 28) while weight loss in obese asthmatics appears to increase production of pro-inflammatory cytokines from stimulated T-

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lymphocytes (5). It is therefore possible that weight loss in T_H2-high obese asthmatics leads to restoration of active airway inflammation which counteracts the beneficial effects of increased lung volume on airway closure.

It is also intriguing that weight loss did not cause an improvement in Rrs20Hz in T_H2-low asthmatics since our findings are consistent with an increase in resting lung volumes that would be expected to increase airway calibre. One possible explanation is that the increased predisposition to airway closure in the T_H2-low group may have resulted in permanent small airways disease. This may have occurred due to cyclic opening and closing of small airways, which has been shown to cause airway remodeling that is sustained even upon restoration of normal lung volume (29, 30). Indeed, increased airway remodelling has been reported in obese mice following chronic allergen challenge (31). An effect of obesity on airway calibre independent of lung volume is consistent with the recent finding that resistance remains elevated in two thirds of obese patients during lung inflation to predicted FRC (32). On the other hand, the extent of weight loss in the T_H2-low obese asthmatics was somewhat less than the T_H2-high group, so it is also possible that the T_H2-low group did not lose enough weight to cause a significant decrease in resistance. In fact, FRC does not differ between subjects with a BMI of 35–40 and those with BMI > 40kg/m^2 (33).

The present study does have limitations. Firstly, the small sample size may have reduced our ability to detect differences in the effect of weight loss on Rrs5Hz between the asthmatic groups (interaction term p=0.11); however, significance would only further support the notion of persistent airway abnormalities in T_H2-low obese asthmatics. On the other hand, it is unlikely that a larger sample size would reveal a reduction in the sensitivity to airway closure following weight loss in T_H2-high obese asthmatics since the data trended towards an increase in DRSFVC. Secondly, our body plethysmograph was unable to accommodate the morbidly obese patients so we inferred improvements in lung volume following weight loss from changes in FOT parameters. However, direct measurement of FRC with helium dilution would have been helpful in quantifying these improvements. Additionally, our population is almost exclusively female, reflecting the demographics presenting at our bariatric clinic. Since the mechanisms underlying the effect of obesity on airway responsiveness appear distinct between males and females (21), our findings may not translate to males. Lastly, our measure of obesity by BMI does not differentiate between general and abdominal adiposity. However, BMI and waist circumference appear to indicate similar risks for AHR in women (33), suggesting that differences in fat distribution between T_H2-high and T_H2-low obese asthmatics may not explain the distinct effects of weight loss on airway responsiveness.

In summary, the present findings support the conclusion that there are two distinct clinical phenotypes of obese asthma with distinct pathophysiology, contributed to by disparate effects of obesity and atopic status on small airway function. Obesity appears sufficient to increase small airway responsiveness in obese asthmatics with normal IgE, which may promote permanent abnormalities in resting airway function. In contrast, obesity does not alter small airway responsiveness in obese asthmatics with high serum IgE. These findings of distinct effects of obesity on small airway function highlight the complex interplay between IgE status and asthma pathophysiology in the obese.

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Abbreviations

AHR	airway hyperresponsiveness
DRS	dose response slope
FEV_1	forced expiratory volume in one second
FOT	forced oscillation technique
FRC	functional residual capacity
FVC	forced vital capacity
PEF	peak expiratory flow
Rrs	respiratory system resistance
Xrs	respiratory system reactance

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Summary at a Glance

In obese asthmatic patients with low IgE, weight loss improves airway hyperresponsiveness related to airway closure, but does not improve resting airway resistance. In obese asthmatics with high IgE, weight-loss improves resting lung mechanics but does not improve airway hyperresponsiveness.

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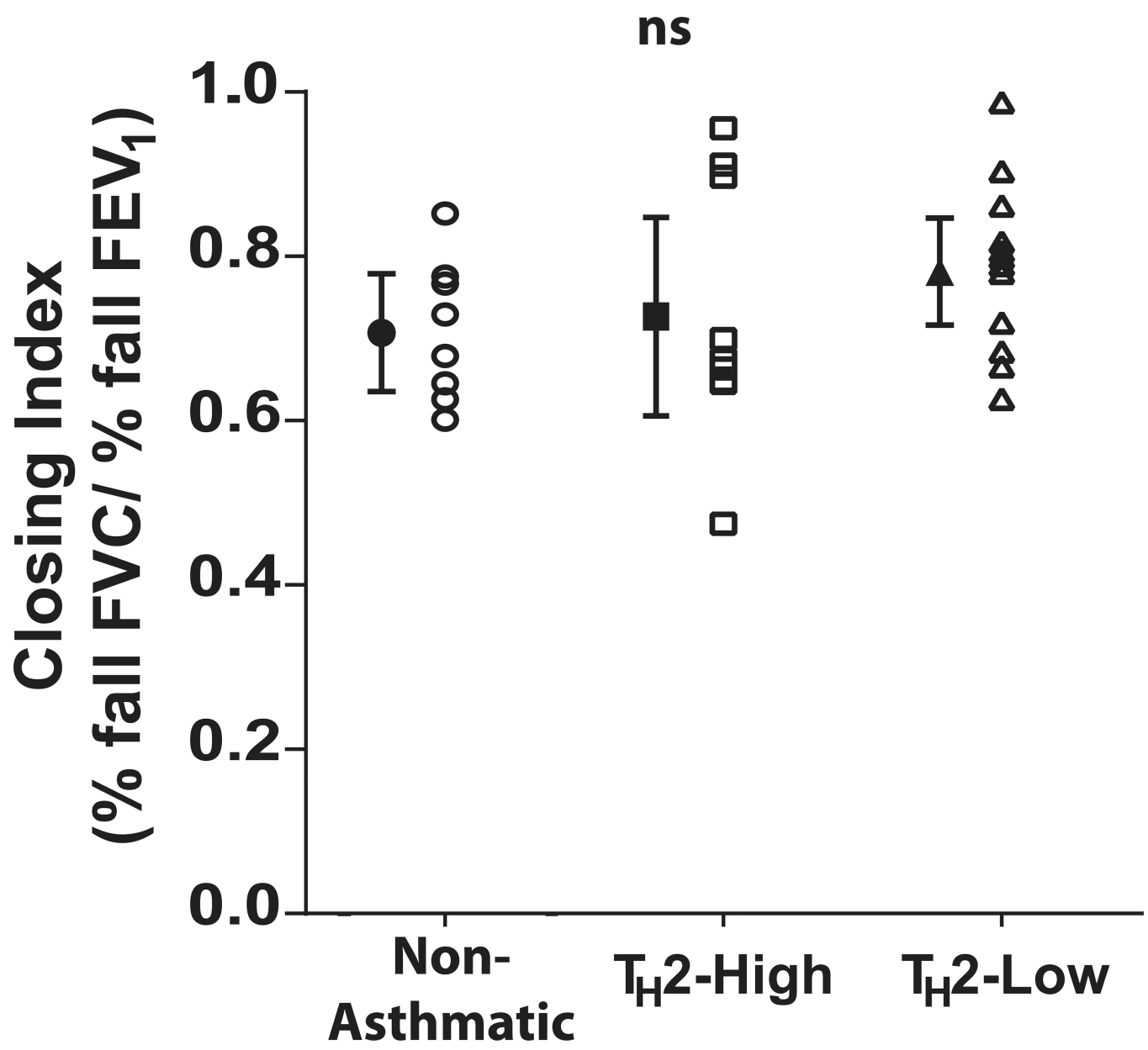

Figure 1. Comparison of the proportion of the fall in FEV_1 during methacholine challenge that is due to airway closure prior to bariatric surgery

The Closing Index, calculated as the % fall in FVC/ % fall in FEV_1 at the highest dose of the methacholine challenge, was compared between obese non-asthmatic, obese asthmatics with elevated serum IgE (T_H2-high) and obese asthmatics with normal serum IgE (T_H2-low). A larger closing index represents a greater proportion of overall bronchoconstriction attributed to airway closure. The mean± SEM closing index in normal weight non-asthmatics is 0.54 ± 0.03 (9). ns = non-significant ANOVA.

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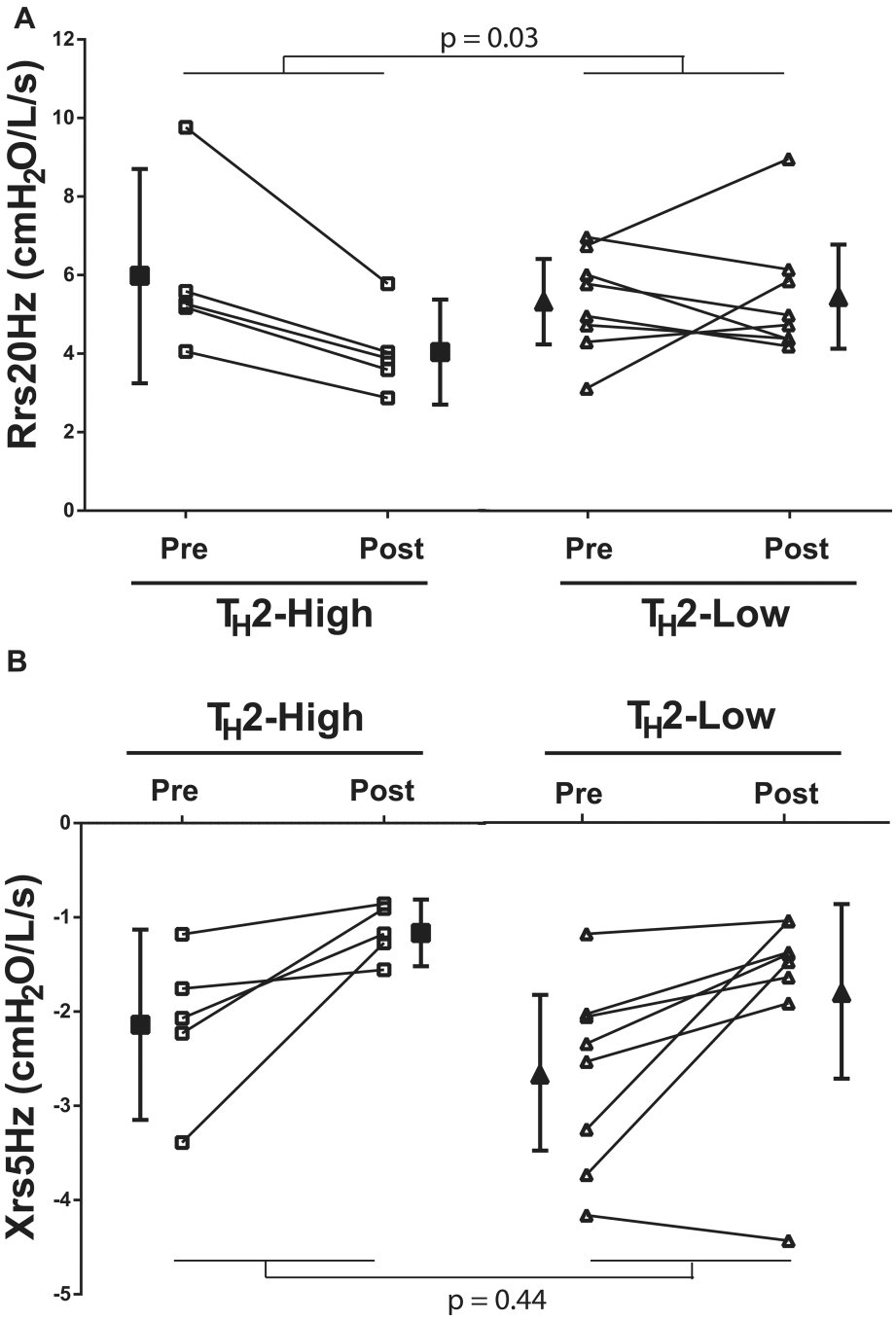

Figure 2. Comparison of resting respiratory system resistance (Rrs20Hz, A) and reactance (Xrs5Hz, B) in obese asthmatic subjects before (pre) and 12 months following bariatric surgery (post)

Obese asthmatic subjects were grouped into those with elevated IgE (T_H2-high) and those with normal IgE (T_H2-low).

The p-values shown are for the T_H2-status × surgery interaction factor

p = 0.05 (A) and 0.01 (B) for effect of surgery

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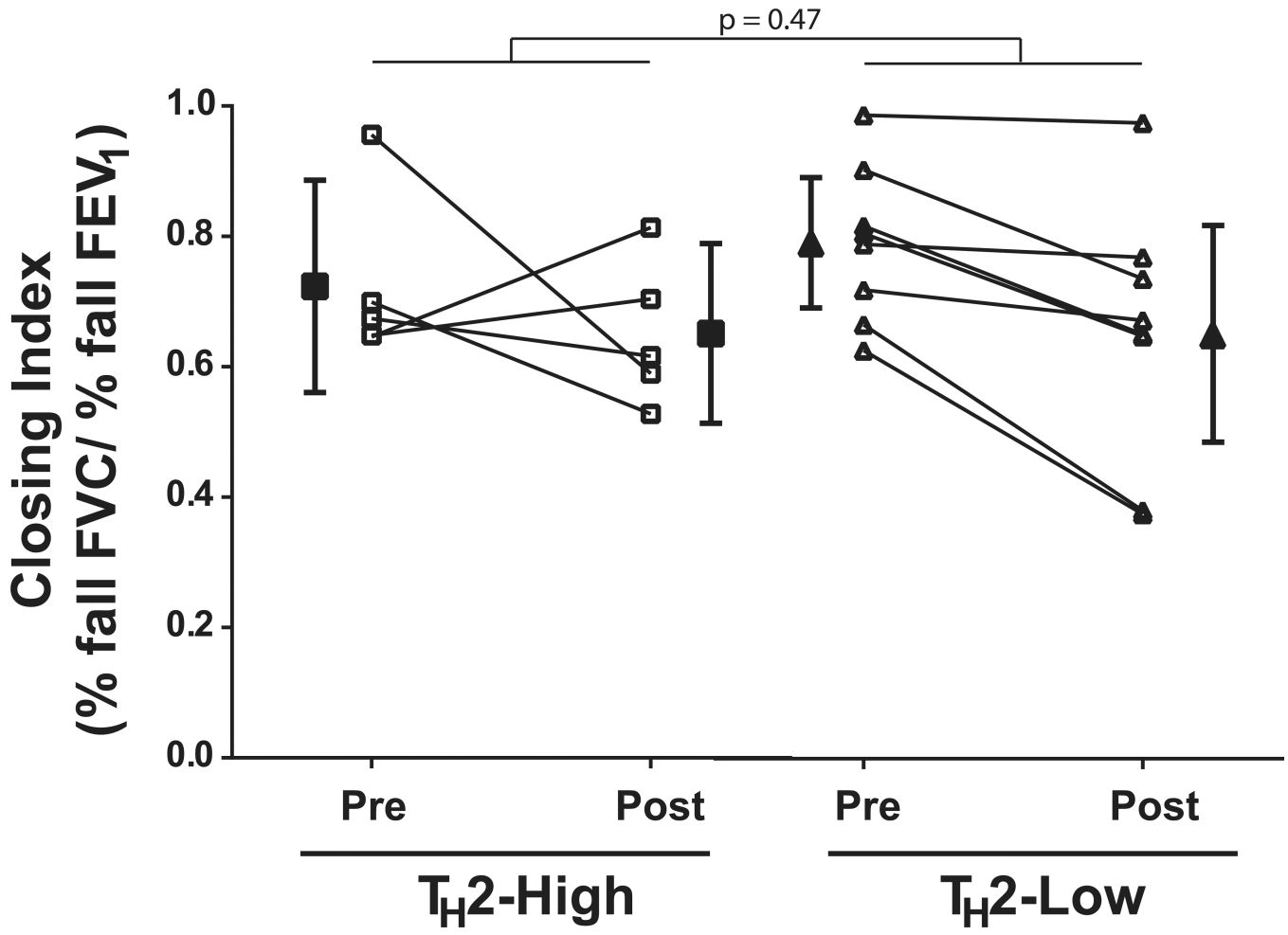

Figure 3. Comparison of the proportion of the fall in FEV_1 during methacholine challenge that is due to airway closure prior to and 12 months following bariatric surgery in obese asthmatic subjects

Obese asthmatic subjects were grouped into those with elevated IgE (T_H2-high) and those with normal IgE (T_H2-low). The Closing Index, calculated as the % fall in FVC/% fall in FEV_1 at the highest dose of the methacholine challenge, was compared prior to and 12 month following bariatric surgery in obese asthmatic subjects. A larger closing index represents a greater proportion of overall bronchoconstriction attributed to airway closure. The p-value shown is for the T_H2-status × surgery interaction factor
p = 0.03 for effect of surgery

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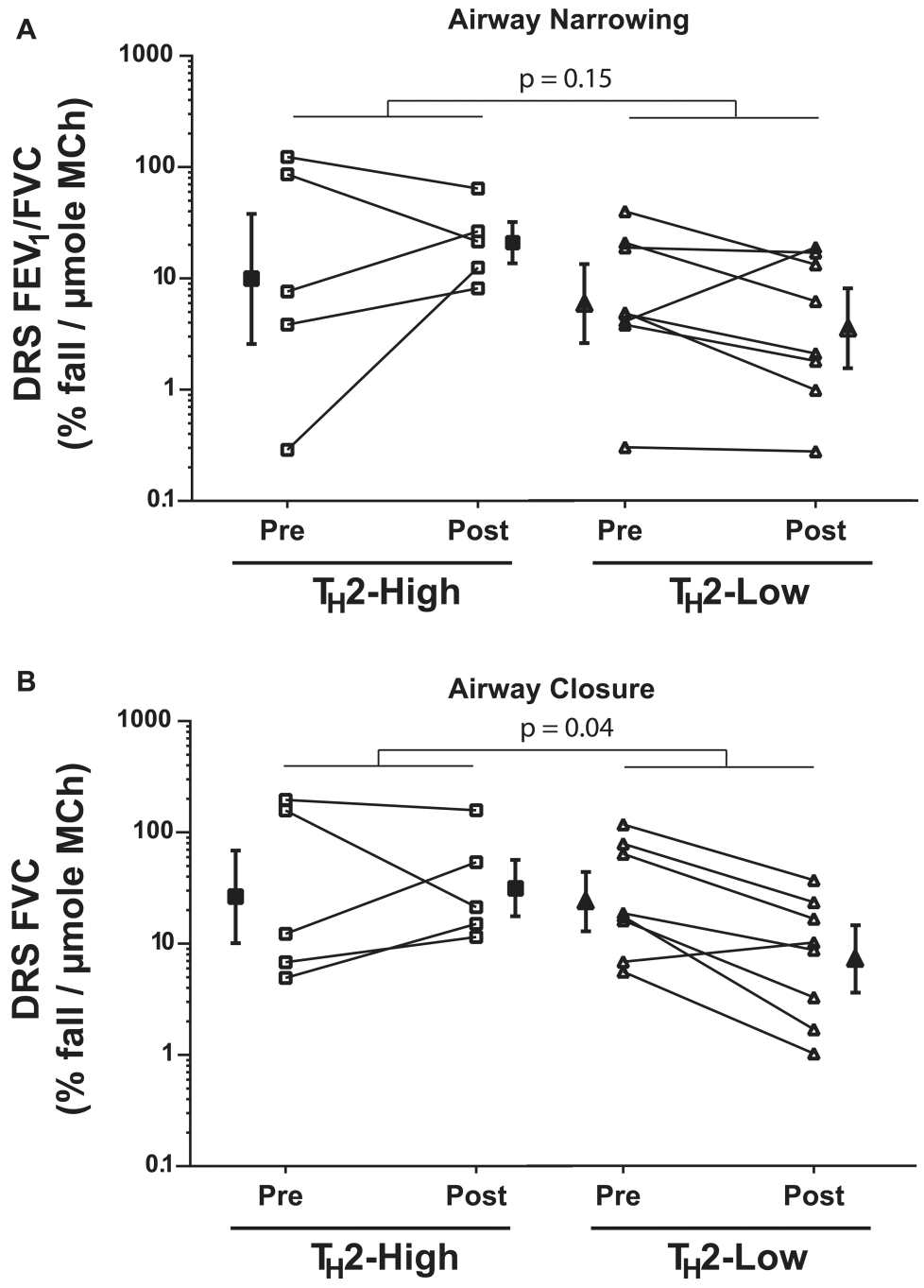

Figure 4. Comparison of the sensitivity to airway narrowing (a) and airway closure (b) in obese asthmatic subjects before (pre) and 12 months following bariatric surgery (post)

Obese asthmatic subjects were grouped into those with elevated IgE (T_H2-high) and those with normal IgE (T_H2-high). Sensitivity to methacholine was measured as the dose response slope (DRS), calculated as the two point slope from the fall in lung function at the end of challenge divided by the dose of methacholine (MCh) in µmoles. The sensitivity to airway narrowing and airway closure was determined by calculating a DRS using % fall in FEV_1/FVC (DRS(FEV_1/FVC)) and % fall in FVC (DRSFVC). DRS is log-normally distributed and is thus plotted on a log-scale

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The p-values shown are for the T_H2-status × surgery interaction factor .p = 0.79 (A) and 0.11 (B) for effect of surgery

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Table 1

Baseline lung function data comparing obese non-asthmatics, obese asthmatics with elevated serum IgE (T_H2-high) and obese asthmatics with normal serum IgE (T_H2-low)

	Obese Non-Asthmatic	Obese Asthma		p-value
		T_H2-high	T_H2-low	
IgE (IU/mL)*	-	282 [175 – 546]	20 [1 – 49]	-
N (female)	8 (8)	10 (9)	12 (11)	-
Age (years)	41.1 ± 7.4	42.1 ± 8.7	44.6 ± 10.7	0.72
BMI (kg/m^2)*	48.6 [42.7 – 57.6]	47.8 [43.3 – 58.7]	46.7 [42.3 – 50.5]	0.85
FEV_1 (% pred)	87.8 ± 9.7	83.2 ± 8.6	80.6 ± 6.9	0.40
FVC (% pred)	91.1 ± 10.4	87.7 ± 8.3	83.1 ± 7.7	0.34
FEV_1/FVC	77.5 ± 5.1	77.5 ± 5.6	78.8 ± 2.2	0.83
PEF (% pred)*	86.1 [76.5 – 90.4]	89.4 [78.3 – 108.2]	91.7 [80.7 – 97.1]	0.45
Rrs 5Hz ($cmH_2O/L/s$) $	7.0 ± 3.2	7.3 ± 2.2	7.3 ± 1.1	0.97
Rrs 20Hz ($cmH_2O/L/s$)$	5.1 ± 1.1	5.3 ± 1.6	5.1 ± 0.7	0.95
Rrs 5Hz–20Hz ($cmH_2O/L/s$)$	2.0 ± 1.9	2.0 ± 1.2	2.1 ± 0.7	0.97
Xrs 5Hz ($cmH_2O/L/s$)*$	−2.2 [−3.3 – −1.7]	−2.2 [−4.9 – −1.8]	−2.7 [−4.0 –−2.0]	0.83
Max fall in FEV_1	15.9 ± 2.9	22.2 ± 3.6A	25.1 ± 3.8A	0.002
DRS (% fall FEV_1/μmol MCh)#	3.8 [3.0 – 4.7]	18.0 [7.4 – 43.4]A	24.5 [13.9 – 43.3]A	0.005
AHR (n)^	2	8	12	
Closing Index	0.71 ± 0.07	0.71 ± 0.12	0.79 ± 0.07	0.26

All data are presented as mean ± 95% CI unless otherwise stated.

*Median [IQR],

#geometric mean ± 95 % CI

$Data are from 5 non-asthmatic subjects

^number of subjects with AHR as defined by $PC_{20}FEV_1$ < 16mg/mL

Ap-value < 0.05 vs obese non-asthmatic

FEV_1 = forced expiratory volume in one second, FVC = forced expiratory volume, PEF = peak expiratory flow, Rrs = respiratory system resistance, Xrs = respiratory system reactance, DRS = dose response slope, MCh = methacholine, AHR = airway hyperresponsiveness, defined as >4.4% fall FEV_1/μmol MCh, N= number.

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Table 2

Comparison of changes in baseline lung function for obese asthmatic subjects prior to bariatric surgery and 12 months following bariatric surgery stratified by IgE levels prior to surgery

	T_H2-high (n = 5)			T_H2-low (n = 8)				
	Pre-surgery	**Post-surgery**	**Pre-post change**	**Pre-surgery**	**Post-surgery**	**Pre-post change**	**Weight loss p-value**	**interaction p-value**
BMI (kg/m^2)	50.9 ± 13.7	32.4 ± 13.1	18.4 ± 6.3	50.7 ± 9.3	38.7 ± 6.3	11.9 ± 5.0	< 0.0001	0.07
FEV_1 (% pred)	86.2 ± 10.1	97.0 ± 8.1	−10.8 ± 7.6	80.1 ± 9.0	91.2 ± 6.7	−11.8 ± 4.6	< 0.0001	0.86
FVC (% pred)	89.2 ± 4.4	99.8 ± 9.2	−10.6 ± 12.7	82.1 ± 9.9	91.0 ± 10.2	−8.9 ± 4.9	0.001	0.70
FEV_1/FVC	79.2 ± 9.8	79.6 ± 9.6	−0.4 ± 5.5	79.0 ± 2.8	80.6 ± 3.1	−1.5 ± 2.2	0.35	0.58
PEF (% pred)	91.2 [79.3 – 105.0]	85.4 [79.5 – 104.3]	−3.4 [−15.0 – 20.1]	94.7 [86.7 – 99.2]	103.1 [90.3 – 114.6]	−10.2 [−22.2 – 0.1]	0.28	0.17
Rrs 5Hz ($cmH_2O/L/s$)	7.0 ± 3.5	4.4 ± 1.7	2.6 ± 1.8	7.2 ± 1.4	7.0 ± 1.9	0.3 ± 2.3	0.05	0.11
Rrs 20Hz ($cmH_2O/L/s$)*	5.3 [4.6 – 7.7]	3.9 [3.2 – 4.9]	1.5 [1.3 – 2.8]	5.4 [4.4 – 6.6]	4.9 [4.4 – 6.1]	0.6 [−1.8 – 0.8]	0.05	0.03
Rrs 5Hz–20Hz ($cmH_20/L/s$)*	0.84 [0.3 – 1.9]	0.21 [0.06 – 0.9]	0.85 [0.16 – 1.05]	1.9 [1.1 – 3.0]	1.1 [0.7 – 2.5]	0.05 [−0.8 – 2.0]	0.14	0.73
Xrs 5Hz ($cmH_2O/L/s$)*	−2.1 [−4.2 – −1.5]	−1.2 [−1.6 – −0.9]	−0.9 [−3.0 –−0.3]	−2.4 [−3.6 – −2.0]	−1.4 [−1.8 – −1.1]	−0.6 [−1.9 –−0.2]	0.01	0.44
Max % fall in FEV_1	22.7 [21.3 – 27.4]	22.7 [21.3 – 41.6]	−0.3 [−19.4 – 5.3]	23.0 [21.7 – 29.2]	21.5 [14.1 – 27.4]	4.4 [−1.3 – 10.5]	0.79	0.16
Closing Index	0.72 ± 0.16	0.65 ± 0.14	0.07 ± 0.26	0.79 ± 0.1	0.65 ± 0.17	0.14 ± 0.09	0.03	0.47
DRSFEV_1 (% fall /µmol MCh)$	36.8 [7.3 – 186.4]	49.2 [21.7 – 111.4]	−0.4 ± 1.8^	31.1 [14.9 – 65.0]	11.7 [5.2 – 26.2]	1.4 ± 0.9	0.29	0.07
DRS(FEV_1/FVC) (% fall /µmol MCh)$	9.9 [1.1 – 86.6]	20.8 [10.5 – 41.4]	−1.1 ± 2.5^	6.0 [2.1 – 17.0]	1.7 [1.2 – 10.2]	0.8 ± 1.0^	0.79	0.15
logDRS FVC (% fall/µmol MCh)$	26.4 [5.6 – 123.7]	31.6 [12.4 – 31.6]	−0.3 ± 1.7^	24.3 [11.1 – 53.2]	7.4 [3.0 – 17.6]	1.8 ± 0.8^	0.11	0.04

Data were analysed only from those subjects in whom methacholine challenge caused a > 5% fall in FEV_1 at both study visits.

All data are presented as mean ±95% CI unless otherwise stated.

P-values shown are from mixed model repeat measures analysis of variance. Interaction designates the T_H2-group × surgery interaction factor.

*Median [IQR],

$geometric mean ± 95 % CI,

^doubling doses

#n = 5 for high IgE and 7 for low IgE

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FEV_1 = forced expiratory volume in one second, FVC = forced expiratory volume, PEF = peak expiratory flow, Rrs = respiratory system resistance, Xrs = respiratory system reactance, DRS = dose response slope, MCh = methacholine. The Closing Index, calculated as the % fall in FVC/ % fall in FEV_1 at the highest dose of the methacholine challenge, with larger numbers represen