The role of the large airways on smooth muscle contraction in asthma

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The major symptoms of asthma are produced by airway smooth muscle contraction. The role of intrinsic airway structure as a determinant of the magnitude of the contraction is controversial. We evaluated the effect of the smooth muscle contraction in volunteers with moderately severe asthma [forced expiratory volume (FEV) = 64% predicted] by virtually eliminating the smooth muscle tension with repeated doses of a β-agonist, albuterol, until a maximum response in FEV occurred and compared the pulmonary function and the high-resolution computed tomography-airways structure on that day with the pulmonary function and structure measured on a previous day under baseline conditions with a steady state of smooth muscle tension (2).

We considered the difference in pulmonary function and structure between the 2 days the result of the baseline smooth muscle tension (BSMT). We found that the effect of the muscle contraction on pulmonary function was not related to the magnitude of the contraction, but rather the airway structure that was present in the relaxed airways before the contraction occurred.

The major effect of the BSMT was a nearly 50% increase in the residual volume (RV) and a 15% decrease in FEV. The major correlate of the baseline FEV was the magnitude of the percent change in forced vital capacity (FVC; mean decrease 7%; range −30 to 14%) produced by the BSMT.

The magnitude of the increase in RV was significantly correlated with the ratio of the wall thickness to the diameter of the large airways and the diameter of the medium airways when relaxed with albuterol at total lung capacity (TLC). The dimensions of the small airways had no relationship to the increase in RV. We were surprised that the structural determinants of the increase in RV with BSMT had no effect on the change in FVC. This was because these structural determinants were also correlated with an increase functional residual capacity (FRC) and TLC that nullified the effect of the increase in RV on reducing the FVC. The magnitude of the decrease in the FVC and FEV produced by BSMT was correlated with how much the FRC changed relative to RV; i.e., the greater the increase in FRC relative to the increase in RV, the smaller the decrease in FVC. The increase in FRC from the BSMT was highly correlated with the increase in TLC, and we infer that the increase in TLC compensated for the increase in RV and diminished the response of the FVC to the BSMT.

The index we used to quantify how much the FRC increased in relation to the increase in RV [the FRCratio = (FRCBSMT/FRCALB)/(RVBSMT/RVALB)] was significantly correlated with the response to a methacholine challenge; i.e., the lower the FRCratio, the lower the methacholine log10PC20. Furthermore, the lower the FRCratio, the greater the decrease in FVC and FEV from the BSMT. The correlation of the FRCratio with the log10PC20 and the magnitude of the change in FEV and FVC from the BSMT suggested to us that hyperresponsiveness to a contractile agonist might be more determined by a decreased compensatory change in lung volume than by an increase in the response of the airways smooth muscle itself. Indeed, despite the BSMT causing a significant decrease in the luminal diameter of the three sizes of airways studied, not a single change in pulmonary function produced by the BSMT correlated with the magnitude of the decrease in the diameter.

The FRCratio was correlated with the luminal diameter of the large airways at TLC when the smooth muscle tension was suppressed with albuterol. There was no correlation of the FRCratio with either the small or medium airways, with or without albuterol, or with the wall thickness or ratio of the wall thickness to the luminal diameter of the large airways. The smaller the luminal diameter at TLC of the relaxed large airways, the smaller was FEV/FVCALB% predicted and the greater was FRCALB%, TLCALB%, and FVCALB%. The magnitude of each of these three lung volumes that was present when the smooth muscle tension was suppressed was significantly correlated with the response to a methacholine challenge; i.e., the greater the lung volume, the smaller the log10PC20. We infer that the increased albuterol lung volumes were the result of dynamic hyperinflation from the increased expiratory resistance arising from the narrowed lumen of the large airways and the decreased FEV/FVCALB%.

The structure of the relaxed large airways with albuterol played the dominant role in the magnitude of the responsiveness to smooth muscle tension. The ratio of wall thickness to the diameter of the large airways and the diameter of the medium airways were the determinants of the effect of the smooth muscle tension in increasing the RV, presumably through airway closure; but there was no relationship of these determinants to either FEV/FVCALB% or the magnitude of the albuterol lung volumes. Apparently, the wall thickness of the large airways and the diameter of the medium airways had no significant effect on expiratory resistance; thus no contribution to the magnitude of the dynamic hyperinflation.

It was the diameter of the large airways that determined the magnitude of the dynamic hyperinflation through its effect on FEV/FVCALB% and expiratory resistance. We formulated a hypothesis (see Fig.1) that it was the degree of dynamic hyperinflation that was the principal determinant of the mag-
Hypothesis: A high FRC from dynamic hyperinflation before tone attenuates increase in FRC with tone.

If so, then:
For the same increase in RV with tone, the greater the ERV before the tone, the less the increase in FRC with tone and the smaller the FRC ratio.

Fig. 1. FRC, functional residual capacity; RV, residual volume; ERV, expiratory reserve volume.

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magnitude of the FRC ratio, and it was the FRC ratio that quantified how much reduction in FVC and FEV1 occurred from the increase in RV from smooth muscle tension and how responsive the change in pulmonary function would become to a challenge with a contractile agonist. These findings are summarized in Tables 3 and 4 of Ref. 2.

Most consideration of the effect of smooth muscle tone on the RV, presumably through airway closure, has focused on small airways (9). Indeed, a theoretical analysis suggested that an increased wall thickness in small airways is likely the principal cause of airway closure in response to an increase in smooth muscle tension (8). A significant reduction in the increase in RV with methacholine challenge following steroid treatment in mild asthma was considered to be through the effect of the steroids on small airways (5). In the current study, however, there was no evidence that the small airways were playing a significant role in the increase in RV produced by the BSMT. Nevertheless, the results of the current study are compatible with other studies on the role of closure of large airways. Even large, cartilaginous airways can completely close from smooth muscle contraction (1, 10). There is evidence that small airways respond less to cholinergic stimulation than large airways (3, 11). There have been several studies that have shown that the degree of responsiveness to an inhaled spasmogen was a function of the distribution of its deposition within the airways. The more the deposition was in larger than in smaller airways (central over peripheral deposition), the greater the responsiveness to an inhaled spasmogen (4, 6, 7, 12).

In conclusion, dynamic hyperinflation caused by narrowing of large airways is a major determinant of airway hyperresponsiveness in asthma.

REFERENCES