Effect of Bronchial Thermoplasty on Airway Closure

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Abstract

Background: Bronchial Thermoplasty, a procedure that applies thermal energy to the airway wall has been shown to impair the ability of airway to contract in response to methacholine chloride (Mch). The technique has been advocated as an alternative treatment for asthma that may permanently limit airway narrowing. In previous experimental studies in dogs and humans, it was shown that those airways treated with bronchial thermoplasty had significant impairment of Mch responsiveness.

Methods: In the present study, we investigated the ability of canine airways to close completely with very high concentrations of Mch after bronchial thermoplasty. Bronchial thermoplasty was performed on dogs using the Alair System, comprising a low power RF controller and a basket catheter with four electrodes. A local atomization of Mch agonist was delivered directly to the epithelium of the same airway locations with repeated challenges. Airway size was measured with computed tomography, and closure was considered to occur in any airway where the lumen fell below the resolution of the scanner ($<$1 mm).

Results: Our results show that, while treated airways still have the capacity to close at very high doses of Mch, this ability is seriously impaired after treatment, requiring much higher doses.

Conclusions: Bronchial thermoplasty as currently applied seems to simply shift the entire dose response curve toward increasing airway size. Thus, this procedure simply serves to minimize the ability of airways to narrow under any level of stimulation.

Keywords: asthma, airway smooth muscle, COPD, heterogeneity

Introduction

Several studies have shown that the application of thermal energy to the airway wall, termed bronchial thermoplasty, can impair the ability of airways to constrict in response to methacholine chloride (Mch) (Danek et al. 2004; Brown et al. 2005). The technique has been advocated as an innovative treatment for asthma by attenuating airway narrowing (Cox et al. 2006; Cox et al. 2004). In a previous experimental study in dogs, it was shown that those airways treated with bronchial thermoplasty had significantly increased lumenal area at any dose of inhaled Mch compared to untreated airways (Brown et al. 2005).

There have been several recent imaging studies that have emphasized the potential importance of airway closure in asthmatic subjects (Samee et al. 2003; Salerno et al. 2001). There is also some suggestion that the heterogeneous nature of airway closure may occur in large and small airways (Venegas et al. 2005), and may cause substantial worsening of ventilation and pulmonary function. In previous work, it was shown that with sufficient agonist stimulation even large cartilaginous airways could be made to close in vivo (Brown and Mitzner, 1998). Bronchial thermoplasty, which treats these conducting airways, has been suggested as a possible therapy for asthma, and has been shown to decrease Mch sensitivity in dogs (Brown et al. 2005) and asthmatics subjects (Cox et al. 2006). Whether bronchial thermoplasty can attenuate maximal stimulation, i.e. stimulation sufficient to close airways, remains to be determined. While the importance of large airway closure in asthma may still be controversial, knowledge of how bronchial thermoplasty affects this process may help in understanding the potential for this treatment. In the present study, we investigated the ability of canine airways to close after bronchial thermoplasty. Our results show that, while treated airways still have the capacity to close at high doses of Mch, this ability is seriously impaired after treatment.

Methods

The study protocol was approved by The Johns Hopkins Animal Care and Use Committee. Six dogs weighing approximately 20 kg were anesthetized with thiopental (15 mg/kg induction dose followed

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by 10 mg/kg/hr intravenous maintenance dose). After induction of anesthesia, the dogs were paralyzed with 0.5 mg/kg of succinylcholine with occasional supplemental doses as required to ensure no respiratory motion during imaging. Following endotracheal intubation with an 8.0 mm ID endotracheal tube, the dogs were placed supine and their lungs were ventilated with room air with a volume-cycled ventilator (Harvard Apparatus, Millus, MA) at a tidal volume of 15 ml/kg and a rate of 18 breaths/minute. A stable depth of anesthesia was maintained by monitoring heart rate changes and eyelash reflex.

Treatment with the Alair® system

Treatments were performed selectively along the target airway regions in the lung. Bronchial thermoplasty was performed on dogs using the Alair System (Asthmatx, Inc., Mountain View, CA), comprising a low power RF controller and a basket catheter with four electrodes. The RF generator supplied power using temperature feedback control, to maintain the target treatment setting for 10 seconds at each treatment site. The left and right sides of the lungs were used to assign treatment and control regions in this study. The target airways on one side of the lungs in each dog received treatments at a temperature setting of 75 °C. The allocation of treatment and control (untreated) lung side for each dog was selected at random such that 3 dogs were assigned treatment to the left and 3 to the right. The untreated lung served as an internal control in each animal. Observers were blinded to treatment conditions for all HRCT measurements of airway area.

Mch challenges

On a separate day prior to treatment (pretreatment), 20 min after the induction of anesthesia, a local atomization of Mch agonist was delivered directly to the epithelium of the same airway locations with repeated challenges as previously described (Brown and Mitzner, 1998). Briefly, the atomization was accomplished with a specially designed catheter that could be placed with bronchoscopic visualization. A short (2 mm) plastic tube was inserted into a PE 190 catheter. This tube had 6 tiny (0.15 mm) side holes drilled circumferentially 1 mm from the end, and was plugged at its distal end with a short (1 mm) stainless steel rod. This metal plug greatly aided visualization in the CT scanner. In practice, the catheter was filled outside the lung with the desired agonist concentration and advanced 1.5 cm beyond the tip of the bronchoscope. Rapid injections of the 20 μl boluses caused the liquid to be sprayed on the adjacent airway wall. The dogs received cumulative local atomized challenges of methacholine (Sigma Chemical, St Louis MO), in concentrations of 0.03, 0.3, 3 and 30 mg/ml. At the completion of the scans after the 30 mg/ml Mch dose, the dogs received 0.2 mg/kg atropine, a dose previously shown to completely block vagal tone in the dog (Brown and Mitzner, 1996), and the HRCT scans were repeated 10 minutes following atropine administration.

Imaging and analysis of airways

HRCT scans were obtained with a Somatom Volume Zoom scanner (Siemens, Iselin, NJ) using a spiral mode to acquire 60 CT images during an 8 second breath hold (apnea) at 137 kVp, and 165 mA. The images were reconstructed as 1 mm slice thickness and a 512 × 512 matrix using a 125 mm field of view and a high spatial frequency (resolution) algorithm that enhanced edge detection, at a window level of –450 Hounsfield units (HU) and a window width of 1,350 HU. These settings have been shown to provide accurate measurement of lumenal size as small as 0.5 mm in diameter (Herold et al. 1991; Wood et al. 1995). For repeated airway measurements in a given dog within each experimental protocol, adjacent anatomic landmarks, such as airway or vascular branching points, were defined and used to measure the airway size at the same anatomic cross sections. Using these landmarks, it was possible to correlate the location of each airway in the stacked series of CT images with that obtained from the bronschoscopic treatment location. Airways with a maximum to minimum diameter ratio of greater than 1.5 to 1 were not analyzed. The bronchoscopic location of each treated airway was determined by mapping the airway location with the procedure previously described in detail by Danek et al. (Danek et al. 2004).

The HRCT images were analyzed using the airway analysis module of the Volumetric Image and Display Analysis (VIDA) image analysis software package (Dept. of Radiology, Division of Physiologic Imaging, Univ. of Iowa, Iowa City, IA) as previously described and validated (Amirav et al. 1993; Brown and Mitzner, 1996). The HRCT

images were transferred to a UNIX-based Sun workstation. An initial isocontour was drawn within each airway lumen, and the software program then automatically located the perimeter of the airway lumen by sending out rays in a spoke-wheel fashion to a predesignated pixel intensity level (full width half maximal method) that defines the lumenal edge of the airway wall. Intra- and inter-observer accuracy and variability of the software program using this HRCT technique in phantoms, consisting of rigid tubes to measure known areas, has been previously shown by us (Herold et al. 1991) and by others (Amirav et al. 1993) to be highly resistant to operator bias.

Data analysis

Airway closure was analyzed by Chi-squared test comparing the treated and untreated airways. Analysis was performed separately for pre- and post-bronchial thermoplasty treatment. Significance was considered if the p-value was <0.05.

Results

A total of 16 treated and 14 untreated airways in the 6 dogs were identified and measured under all conditions (range 4.7–11.5 mm in diameter at baseline).

Prior to treatment, the mean sizes of the subsequently treated and the untreated airways were not different. Treated airways were 7.23 ± 0.42 mm in diameter and untreated airways were 6.85 ± 0.45 mm in diameter ($p = 0.54$). Increasing doses of locally atomized Mch caused increasing constriction and closure of all airways at the highest dose.

Two weeks after bronchial thermoplasty, there were no significant changes in baseline size of the treated ($p = 0.86$) and the untreated ($p = 0.20$) airways at baseline compared to their pretreatment size. Treated airways were 7.27 ± 0.39 and untreated airways were 7.34 ± 0.42 ($p = 0.89$). Furthermore, there were also no differences between the baseline size of treated and the untreated airways after the bronchial thermoplasty treatment ($p = 0.87$).

After treatment, however, there were significant differences in the sensitivity to airway closure between the two groups (Fig. 1). At the 0.3 mg/ml dose, 16 of 16 (100%) treated airways were open, while 12 of 14 (86%) untreated airways remained open ($p = 0.21$). At the 3 mg/ml dose, 12 of 16 (75%) treated airways were open, while only 4 of 14 (29%) to be untreated airways remained open ($p = 0.03$). However, at maximum stimulation at the 30 mg/ml dose, 1 of 16 (6%) treated airways

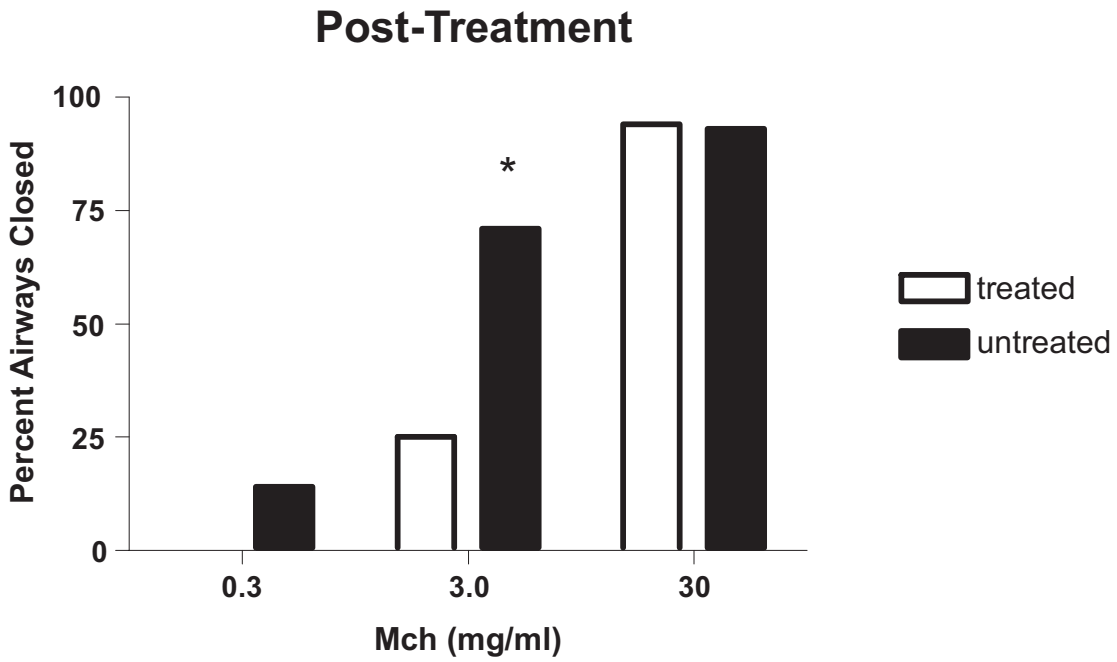

Figure 1. Fraction of airways closed in two randomly selected populations of control and treated airways at three doses of Mch. At the 0.3 mg/ml dose, 16 of 16 (100%) treated airways were open, while 12 of 14 (86%) untreated airways remained open ($p = 0.21$). At the 3 mg/ml dose, 12 of 16 (75%) treated airways were open, while only 4 of 14 (29%) to be untreated airways remained open (*$p = 0.03$). However, at maximum stimulation at the 30 mg/ml dose, 1 of 16 (6%) treated airways were open, while 1 of 14 (7%) to be untreated airways remained open ($p = 0.79$).

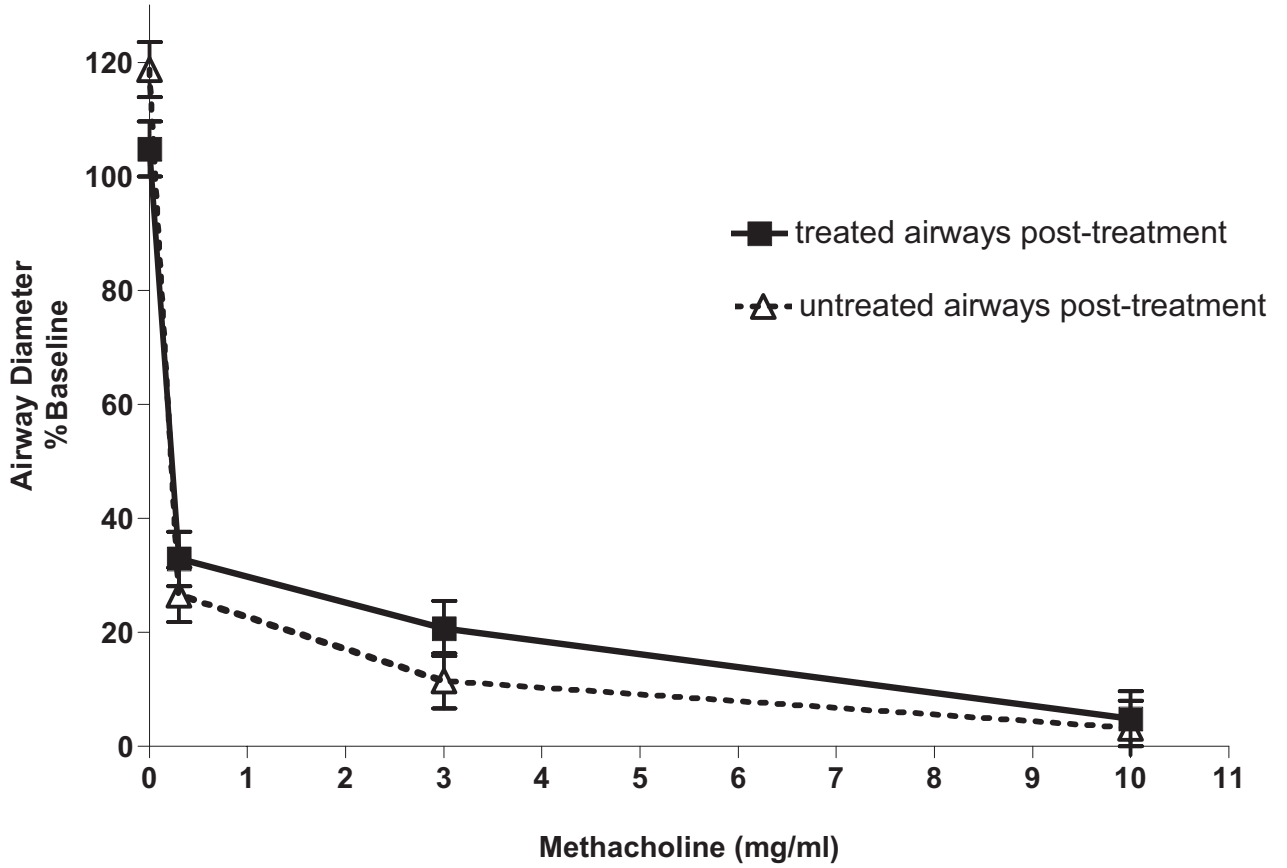

Figure 2. Mean (± SEM) Mch Dose-response curves in treated and untreated airways, two weeks following the time of thermoplasty treatment. Airway size is plotted as a percent of the pretreatment baseline size.

were open, while 1 of 14 (7%) to be untreated airways remained open ($p = 0.79$). Figure 2 shows the dose response curves from control and treated airways on which the data in figure 1 are based. This figure shows that, although the treated airways are larger at any given dose of Mch, if they are challenged sufficiently, they can be made to close.

Discussion

The results in this study clearly show that bronchial thermoplasty impairs the ability of airways to fully close. Although all treated airways could eventually close with sufficient agonist stimulation, the dose required to accomplish this was much greater in the bronchial thermoplasty treated airways than in untreated airways. This observation supports the notion that with the current treatment parameters, insufficient destruction of smooth muscle occurs to eliminate the possibility of airway closure. Why might this limitation have occurred? The most likely explanation stems from the fact that bronchial thermoplasty is not currently designed to eliminate all of the airway smooth muscle from the airway wall; indeed the responsiveness of individual airways was correlated with the degree of smooth muscle destruction (Danek et al. 2004). If significantly more smooth muscle were eliminated a further reduction in the ability of airways to close in response to methacholine might be observed.

This study extends the observation previously observed in a similar canine model (Brown et al. 2005). In this previous work, we measured airway areas in control airways and airways treated with bronchial thermoplasty, with increasing doses of inhaled aerosolized Mch. These results showed that at any dose of inhaled Mch, the treated airways were always larger. However, with an aerosol to the whole lung there is a limit to how high a dose can be delivered. Airway closure in dog airways is rarely observed even at the highest doses used in aerosol administration. For this reason, we used an approach that specifically delivered the Mch to a very localized segment of an individual airway, typically with an axial spread of less than 10 mm (Brown and Mitzner, 1998). This method allowed

sufficiently high locally applied doses to cause airways smooth muscle contraction to close an airway without causing systemic or even regional effects (Brown and Mitzner, 1998). It is important to note that the amount of Mch delivered by this local challenge to a single airway is much greater than that which can be achieved by a more conventional inhaled aerosol challenge. We have previously estimated the total amount of Mch delivered to the whole lung during an aerosol challenge at the highest possible concentration to be on the order of 10 mg [20 µl at 500 mg/ml] (Brown and Mitzner, 1998). With the local challenge used here we delivered 0.3 to 1.5 mg of Mch, respectively, over the surface of an airway only ≈1 cm in length. This very focal stimulation was not done to mimic what happens during a conventional whole lung aerosol challenge, but rather to deliberately study the ability of airways to close. What directs specific airways in asthmatics to close is not known, but it clearly involves a very strong localized smooth muscle contraction, similar to what was studied here.

Another difference between our local challenge and a whole lung aerosol challenge is that when the whole lung is challenged with aerosol, all airway smooth muscle is contracted, and this results not only in airways narrowing, but also in parenchymal stiffening (Mitzner et al. 1992) and increased tissue resistance (Ludwig et al. 1989). Such a stiffened parenchyma and increased shear modulus should cause an increased elastic load on the airways that could reduce the degree of narrowing. Without the increased stiffening concomitant with the aerosol challenge, the parenchyma does not provide a sufficient load to prevent closure *in vivo*. One issue raised with the RF treatment in its present form is the extent of the airway injury. Preliminary theoretical modeling of the RF energy distribution in biological tissues with air-tissue interfaces suggest that the parenchymal-air interface that surrounds the airway wall can act as an insulator, causing the thermal energy field to spread preferentially within the airway wall, while sparing the parenchyma from any significant tissue damage. Our results are consistent with this model, since excessive if the bronchial thermoplasty treatment had damaged the parenchyma, we should have observed increased airway contraction and closure. In contrast, we observed just the opposite, i.e. a decreased airway closure with bronchial thermoplasty treatment.

Clearly if the treatment completely eliminated the muscle, there could be no shortening and hence no closure. The treatment depends on both the temperature and the time, and the 10 second duration at 75 °C was chosen to mimic what has been used in previous canine studies and clinical trials. The maximal treatment settings used were initially chosen to limit damage to other airway tissues. Although there is likely acute damage to other airway structures from bronchial thermoplasty, epithelium, blood vessels, and nerves all have a good capacity for regeneration, a fact supported by histological observations of the airways. Airway smooth muscle, however, appears to lack any regenerative capacity at least for several years (Danek et al. 2004). We also should note that although we made our measurements just 2 weeks following the thermoplasty, the effects seem well established by this time. In this same study by Danek et al. 2004, the effect of thermoplasty at several treatment temperatures on impaired responsiveness to Mch was shown to similar at 2 weeks as it was at 2 years after treatment.

Most would agree that excessive airway smooth muscle contraction is the major functional problem in asthma. In fact it has been argued that the airway smooth muscle has no known function, and only serves to cause problems when it is pathologically stimulated to contract excessively (Mitzner, 2004). Furthermore, it has been shown that even normal airways in the lung (including large cartilaginous ones) can narrow to complete closure if the airway smooth muscle is stimulated sufficiently (Brown and Mitzner, 1998). Such large airway closure was also reported in human subjects (Pellegrino et al. 2001). Recently, Brown et al. have shown that when the size of large conducting airways were narrowed in moderate to severe asthmatic subjects, there was an increase in airway closure as demonstrated by an increased RV and a greater fall in FVC to airway tone (Brown et al. 2006). This heterogeneous airway closure may occur in large and small airways (Venegas et al. 2005), and may cause substantial worsening of ventilation and pulmonary function. While the importance of conducting airway closure in asthma remains controversial, it is clear that changes in large airway caliber can effect airway closure throughout the airway tree (Venegas et al. 2005; Brown et al. 2006). Thus to the extent that bronchial thermoplasty can minimize this ability of the conducting airways to narrow or close, it will not only lead to alleviation of symptoms in individuals

with mild asthma, but also may provide even greater benefit in individuals moderate to severe asthma. While bronchial thermoplasty has not been yet used in a trial involving such severe asthmatics, it has been used in a group of mild asthmatics. In this preliminary clinical trial (Cox et al. 2006), the bronchial thermoplasty treatment protocol used was quite similar to that used in the present canine study. Thus it is quite likely that similar impairment of the ability to close would be observed in human subjects after bronchial thermoplasty. The subjects treated with bronchial thermoplasty in these early preliminary clinical trials to date have reported no problems that could be identified with impaired airway smooth muscle. There were only positive outcomes.

In summary, we have shown that, since bronchial thermoplasty as currently applied does not eliminate all of the ASM in the airway, it also does not eliminate the ability of airways to close at very high doses of locally applied Mch. Given a sufficiently high local dose of methacholine, both treated and untreated airways could be made to close, although treated airways required higher doses than previously used to produce significant narrowing in normal canine airways (Brown et al. 2005). The impact of this ability in subjects with asthma remains to be determined.

Competing interests

Dr. Wizeman and Dr. Danek were both employed by Asthmatx, Inc. during the time of this study. Dr. Danek is no longer employed by Asthmatx, but Dr. Wizeman still works there. Asthmatx manufactures the prototype device that was used to apply RF energy to the airway wall. This is a private company and there are no stock options. There are also no patents associated with the device used in this work. Asthmatx is not paying page charges for this manuscript.

Dr. Brown and Dr. Mitzner are employed by the Johns Hopkins University and have no competing interests.

Authors contributions

WM, RB, CD and BW were all involved with the experimental design, planning, analysis of the data, and preparation of the manuscript. RB and WM were involved with quantitative analysis of the CT images.

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