Bronchial Thermoplasty in Asthma

Wayne Mitzner¹

ABSTRACT
In this review we discuss the potential of a new procedure, termed Bronchial Thermoplasty to prevent serious consequences resulting from excessive airway narrowing. The most important factor in minimizing an asthmatic attack is limiting the degree of smooth muscle shortening. The premise that airway smooth muscle can be either inactivated or obliterated without any long-term alteration of other lung tissues, and that airway function will remain normal, albeit with reduced bronchoconstriction, has now been demonstrated in dogs, a subset of normal subjects, and mild asthmatics. Bronchial Thermoplasty may thus develop into a useful clinical procedure to effectively impair the ability for airway smooth muscle to reach the levels of pathologic narrowing that characterizes an asthma attack. It may also enable more successful treatment of asthma patients who are unresponsive to more conventional therapies. Whether this will remain stable for the lifetime of the patient still remains to be determined, but at the present time, there are no indications that the smooth muscle contractility will return. This successful preliminary experience showing that Bronchial Thermoplasty could be safely performed in patients with asthma has led to an ongoing clinical trial at a number of sites in Europe and North America designed to examine the effectiveness of this procedure in subjects with moderately severe asthma.

KEY WORDS
airway responsiveness, airway smooth muscle, asthma therapy, bronchodilator, FEV1

INTRODUCTION
Asthma is an often debilitating disease characterized by dyspnea, wheezing, coughing, respiratory distress, and sometimes death. Subjects with asthma typically have hyperresponsive and often chronically inflamed airways. Chronic asthma is also characterized by extensive airway remodeling,¹ with a thickening of airway walls, increased mucus glands and goblet cells, increased vascularization, and most importantly, hypertrophy of airway smooth muscle. Although there are many different opinions on the causes and mechanisms involved in asthma, there is universal agreement that airways narrow during an asthmatic attack. It is from this perspective that we will begin this review of a procedure, termed Bronchial Thermoplasty, in asthma.

Once we agree that the problem in asthma is caused by airway narrowing, then it is reasonable to ask what the cause of this airway narrowing might be. There are several possibilities. One is that the fluid that lines the airway becomes thicker. This could occur because of increased mucus secretion, something that is known to occur in many individuals with asthma,² and is often observed pathologically in subjects who have died from a severe attack.³,⁴ Indeed, sometimes in these post-mortem cases, the secretions are sufficient to completely fill parts of the airway tree. In this review, we will not have more to say about this potential cause of airway narrowing, not because it is unimportant, but rather because its extent and manifestation in the general population of asthmatic subjects is not well characterized.

Another possible mechanism of airway narrowing is loss of mechanical support from the surrounding parenchyma. It is now well understood that within the lung airways are tethered by attachments to the parenchyma, and loss of this support leads to airway narrowing. Although this is a serious problem in emphysema, there is little evidence that the airway narrowing in asthma is caused by loss of parenchymal support. Related to this potential loss of structural tethering is the effect of lung volume and elastic recoil on airway size. Airways would be smaller at lower lung volume, but in asthma, lung volumes are generally increased. There has also been some evidence of altered surfactant in asthma,⁵ although it is not clear how an increased surface tension in the alveoli would
act on airway size. The effect would depend on the relative changes in lung volume and elastic recoil pressure, but one recent report did show a slight positive effect of synthetic surfactant in asthmatic subjects.6

The third possible cause of airway narrowing, that of airway smooth muscle contraction, is the one that will be the focus of the remainder of this review. All of the conducting airways down to the level of respiratory bronchioles are lined with smooth muscle. This smooth muscle has a great capacity to shorten. Indeed, all airways in the lung (including large cartilaginous ones) can narrow to complete closure if the airway smooth muscle is stimulated sufficiently.7 Smooth muscle shortening is considered to be the primary cause of the difficulties in breathing during an acute asthma attack. Narrowed airways require increased transpulmonary pressure and energy expenditure during inspiration, and during expiration are much more likely to reach flow limitation at low lung volumes. It is for this reason, that all of the therapeutic research related to asthma has focused on minimizing the ability of the airway smooth muscle to shorten.

THERAPEUTIC APPROACHES

Acute relaxation of the airway contractile response can be accomplished with cholinergic blockade, but in recent decades it has been achieved primarily with β-adrenergic stimulation. Either of these stimulations will lead to bronchodilation. Another more common contemporary approach in patients with moderate and severe asthma has involved anti-inflammatory agents, either alone or with short or long-acting β-adrenergic agonists.8 This combined use of anti-inflammatory agents with inhaled bronchodilators is a successful therapy for control of asthma in many patients. Furthermore, in the very recent past, a number of newer inhibitors of inflammatory pathways have been available for those patients who do not respond well to the conventional therapy.9-11 Nevertheless, despite this attempt to control the inflammatory pathways in asthma, serious exacerbations still often occur in patients with even mild asthma,12 and some patients with severe asthma are poorly responsive to all forms of therapy. Indeed mortality from asthma has remained fairly steady for the past 15 years.13

Thus it is clear the there is still much to be learned about this pathology. Despite much experimental evidence linking inflammation to airway smooth muscle shortening, the detailed mechanistic pathways remain elusive. There exists a very poor understanding of why conventional therapy works well in some patients but manifests such poor pharmacological responsiveness in others. While it has been suggested that a poor responsiveness to drug therapy in asthma is genetically determined,14 this hasn’t helped in clarifying the mechanisms, nor helped in providing better therapy. Furthermore, while it is true that increasing knowledge of immunological pathways may lead to therapeutic value in asthma, the fact remains that an asthma attack can often be triggered by non-allergic stimuli, such as infection, exercise, or cold air. Thus we always return to the fact that whether the initial cause results from an allergen, an irritant, infection, psychological stress, or other neural activation, the cascade during an attack always ends with airway muscle contraction.

This lack of success in pharmacologically treating asthmatic airways has led to a recent proposal that takes a very different approach. If the smooth narrowing is the problem, then why not try to physically impair the ability of this smooth muscle to shorten? Ignoring for the moment the potential difficulty in doing this, it seems clear that, in the extreme, if the smooth muscle were completely eliminated, then there could be no acute airway narrowing. Thus, if we could eliminate airway smooth muscle, then perhaps we would a permanent cure for asthma. Of course this potential raises the issue of whether the airway smooth muscle has any normal functions, and this will be discussed in subsequent section.

In this review, we will describe a method that is now undergoing limited clinical trials in the U.S., whereby locally applied thermal energy is used to damage the smooth muscle of conducting airways sufficiently to impair their ability to narrow. The general hypothesis underlying this clinical trial is that even partially impairing the ability of the conducting airways to narrow will not only attenuate the bronchoconstrictor response, but will also be effective in relieving the dyspnea associated with asthmatic attacks. In subsequent sections, we will present experimental evidence in a canine model and preliminary studies in human subjects that was used to justify the current clinical trial.

ROLE OF SMOOTH MUSCLE IN ASTHMA

With the understanding that airway smooth muscle holds the key to dealing with the asthma pathology, we next address several relevant issues.

WHICH AIRWAYS CAUSE THE PROBLEM IN ASTHMA?

One important question in asthma is which generation of airways contributes most to airflow obstruction during an asthma attack. This is a critical issue that bears on the whole approach of Bronchial Theromplasty, since as will be described later, the current technique cannot treat airways smaller than about 3 mm diameter. However, after many years of debate on whether large or small airways are more responsible for airflow obstruction during asthma attacks, there remains little experimental evidence on which to base any conclusive answer. It is well accepted and known from morphometric models of Weibel,15 Hors-
field, and others, that nearly all of the baseline airway resistance lies in the conducting airways >2 mm. With smooth muscle contraction this partitioning can surely change, but this situation has not been extensively modeled. Indeed, for many years it was thought that the cartilagenous structure of large airways was such that it might limit their ability to contract as much as the smaller ones. However, a study using CT imaging of airways showed that even large cartilagenous airways could narrow to complete closure if sufficiently stimulated, thereby dispelling that myth. Such large airway closure was also reported in human subjects. Thus, the locus of airway constriction during an acute asthma attack is still not fully elucidated. Is it a global narrowing of small airways, an acute narrowing of a few large airways, or a generalized narrowing of all airways in the entire bronchial tree? Lacking any convincing experimental evidence to the contrary, one can assume the simplest explanation, which is that it is a generalized narrowing of all airways. Since, as mentioned, most of the airway resistance at baseline lies in the larger airways, an equivalent degree of narrowing throughout the airway tree will have its greatest impact on resistance in these larger airways. Furthermore, a recent theoretical analysis of constriction in the three dimensional airway tree has shown how it is possible for large airway narrowing to directly affect narrowing in small airways. For these reason, it is reasonable to expect that impairment of the ability of the conducting airways to narrow could have a substantial beneficial effect on the ability to breath during an asthma attack.

**IS AIRWAY SMOOTH MUSCLE DIFFERENT IN ASTHMATICS?**

The fact that airways of asthmatic subjects narrow more than normal subjects is axiomatic. The cause of this excessive narrowing, however, remains unclear. There are structural, chemical, and physiological reasons why airways in this pathology might narrow excessively. There may be more smooth muscle in the wall, the wall may be thicker causing the narrowing to start from a smaller baseline size [which would amplify the effect of any further muscle shortening], the elasticity of the wall and surrounding parenchyma may be reduced, the smooth muscle may have intrinsic differences in contractility, there may be more receptors on the muscle for agonist stimulation, the intracellular signaling pathways may be upregulated, or extracellular signals for smooth muscle contraction may become elevated. Although much research has been directed toward investigating these different factors, how these all integrate in an intact lung becomes less important if the smooth muscle cannot contract or is eliminated.

**WHAT IS THE FUNCTION OF AIRWAY SMOOTH MUSCLE?**

The human body contains many organs, which no longer provide evolutionary advantage and have no known function, e.g., the appendix, most body hair, wisdom teeth, male nipples, and external ear muscles. It recently has been argued that airway smooth muscle falls into this category—that of an organ with no known physiologic purpose, whose sole contemporary contribution is the potential to cause problems. This argument supports an earlier discussion by Seow and Fredberg, who emphasized that there is no known disease entity or physiological deficit associated with loss of airway smooth muscle. They further suggested that airway smooth muscle was perhaps a vestigial remnant of its common embryologic origin with the GI system. So from where does the widespread feeling, that airway smooth muscle must have some function, arise? Some of this background is summarized below.

Despite that fact that the function of smooth muscle in the airway wall has been speculated on for many years, from a functional perspective, there has never been strong experimental evidence for its functional importance in the lung. Not withstanding this lack of experimental evidence, Macklin, in his classic extensive and influential review article on airway smooth muscle, could not imagine that such a system existed for no physiologic purpose, stating, “Organized as it is, into a very complex system, this muscle would seem of the utmost functional importance—in fact quite indispensable in respiration.”

At least 10 postulated roles for airway smooth muscle have appeared in the literature. These possible roles consist of the following: 1. Peristalsis to assist exhalation; 2. Peristalsis to assist mucus propulsion; 3. Peristaltic contraction in the fetal lung to generate fluid pressure; 4. Promoting lymphatic and venous flow; 5. Ventilation/Perfusion matching; 6. Protecting the peripheral lung; 7. Protecting airway structure; 8. Stabilizing airways; 9. Enhancing the effectiveness of cough; and 10. Optimizing anatomic dead space volume. Details of each of these have been presented elsewhere and will not be repeated here. However, it should be noted that none of these potential functions of airway smooth muscle have been shown to be essential to normal lung physiology. If airway smooth muscle were eliminated, then the airways might enlarge slightly due to loss of basal tone, but there would be no other obvious physiologic consequence. The evidence thus strongly supports the suggestion that airway smooth muscle is indeed like a vestigial organ, analogous to the appendix, which also has no known purpose other than to cause serious medical problems. Such being the case, if there were a way to treat airway smooth like an inflamed appendix, that is, to effectively cut it out, then asthma, like appendicitis, could be cured. Airway inflamm-
Fig. 1  Schematic illustration of the instrument used to perform radiofrequency alteration of airway smooth muscle responsiveness in dogs and humans. The catheter conducts RF energy to the airway by direct contact to heat the airway wall. The bronchoscope is directed to the area, the basket is then expanded, and RF heat treatment is activated for very short duration, typically 10 s. The basket is then withdrawn and the instrument is directed to the next site. (Alair® device developed by Asthmatx, Inc.).

Fig. 2  Effect of Bronchial Thermoplasty treatment in vivo in a canine airway. The airway on the left received treatment, but did not constrict by local administration of Mch through the bronchoscope. By contrast, the untreated airway on the right (arrow) constricts nearly to closure with the same stimulus.

dogs to determine the optimal temperature and treatment times to effect selective ablation of airway smooth muscle without causing long-term damage to other tissues. Initial studies mapped different sites in the airways of the same dogs so that these sites could be revisited for visual and, eventually, histological examination. The major variables at each site were temperature and duration of treatment. In this first study airway caliber was measured with a semiquantitative optical system, but subsequent studies using high resolution CT provided more accurate quantification of airway responsiveness. Figure 2 shows optical images taken through a bronchoscope of locally applied methacholine (Mch) to a treated and untreated airway. The lack of responsiveness in the treated airway is readily apparent.

BRONCHIAL THERMOPLASTY METHODOL- OGY

Bronchial Thermoplasty is performed using the Alair® System from Asthmatx, Inc., Mountain View, CA, USA. This system has been used safely in animals, and non-asthmatic and asthmatic human subjects.

Airways to be treated are approached through a bronchoscope, and an expandable basket with four electrode arms is opened to make contact with the airway wall circumferentially. This is illustrated in Figure 1. Treatment generally causes an acute blanching at the site of treatment, and histology shows epithelial disruption at treated sites. There is no charring of the treated area, and subsequent regrowth occurs in the epithelium, blood vessels, mucosa, and nerves. Airway smooth muscle, however, seems to have almost no capacity for regeneration. The airway smooth muscle at is replaced by loose connective tissue. Studies have been performed in

ANIMAL VALIDATION AND EXPERIMENTAL RESULTS

Danek et al. studied the clinical manifestation and long term effects of Bronchial Thermoplasty on canine airways. Dogs tolerated the treatment well. There were no adverse physiological or clinical observations made during the 3-year study. With direct visualization through a bronchoscope, they recorded the ability of treated and untreated airways to respond to topically applied Mch. They followed a group of dogs for up to 3 years following treatment. A summary of their findings is shown in Figure 3. These results clearly show a substantial and prolonged attenuation of airway constriction to locally applied Mch. Gross histology showed no gross narrowing of airways, generalized fibrosis beyond the boundaries of the smooth muscle, or retained mucus.
in the airways. As shown in Figure 4, the degree of attenuation of the contractile response to Mch was also shown to correlate well to the degree of smooth muscle loss. Similar treatment parameters determined from studies in dogs are now being used for preliminary trials in the conducting airways of the human lung (see next section). After treatment, some degree of airway responsiveness to locally applied Mch still remains in airways in dogs in which smooth muscle appears to be replaced by loose connective tissue. As the treatment effect is localized to the site of treatment, smooth muscle between treatment sites may be less affected, the muscle being sufficiently contractile to cause some airway narrowing upon challenge. These results further support the conjecture that with the current treatment paradigm, the muscle at treatment sites is not fully ablated. While it might be desirable to cause greater impairment of smooth muscle.
Thermoplasty.

response curve in airways treated with Bronchial Thermoplasty could contribute to a slight dilation of the airways even without a reduction in baseline airway smooth muscle tone. However, such changes are not consistent with the results of Danek et al. that showed no significant histologic changes to the airways other than to the smooth muscle after a similar Bronchial Thermoplasty in dogs. A more likely cause of the slight dilation of the airways prior to Mch relates to the loss of baseline tone. There is normally a variable amount of baseline tone, which is dependent on variable amounts of smooth muscle activation. This fact may explain why there was also a slightly larger airway size at baseline in the untreated airways at the selected time points. However, if the muscle is reduced or impaired by Bronchial Thermoplasty, then not only would the ability to respond to Mch be impaired, but the normal baseline tone would also be expected to decrease.

Using HRCT imaging we also measured effect of Bronchial Thermoplasty on the distensibility of treated airways. Figure 6 summarizes the effect 5 weeks following treatment. The figure shows airway pressure-area relations in two groups of airways prior to treatment and then at 5 weeks following treatment in one group. Airway areas were measured at increasing levels of end expiratory pressure curves, and Figure 6 shows the results with no smooth muscle tone. The curves show that even in relaxed airways, the size is increased at all levels of inflation. This increase at baseline (no tone), however, is relatively small, being between 10 and 15% at the higher levels of pressure. Such slight baseline increases in airway size would likely be difficult to detect clinically using gross pulmonary function measures, such as FEV₁.
And as will be shown in the next section, this prediction is what was observed in the preliminary human trial. In this same canine study, we also measured the distensibility with a moderate level of airway contraction with Mch. In this situation, the cross sectional area of treated airways was more than doubled that of untreated airways at all but the highest pressure, a result consistent with the dose-response curves shown in Figure 5.

**PRELIMINARY HUMAN DATA**

The first studies using Bronchial Thermoplasty were carried out in nonasthmatic subjects who were scheduled to undergo pulmonary resection for suspected neoplasm. Those subjects scheduled to have a bronchoscopy for preoperative evaluation 1–3 weeks prior to surgery lung resection for suspected or proven lung cancer were enrolled. This provided the opportunity to carry out the procedure in airways that would be available for histological examination soon thereafter. Thus, while this first study did provide any assessment of lung function, it did provide an ideal opportunity to evaluate whether the acute pathologic response of human airways was similar to that observed in canine airways. Specifically, this study design enabled determination of the safety of the Bronchial Thermoplasty in humans over the short term, examination of the histologic effects of the procedure in the human airway, and comparison of the extent of airway smooth muscle loss to that observed in the canine model. As bronchoscopy was repeated at the time of surgery, there was also opportunity to inspect the bronchial lining at the sites of treatment to evaluate possible *in vivo* consequences.

The nine subjects treated in this study had no adverse events related to the procedure, and there were no interruptions or delays to the planned management of their primary clinical problem. Treated sites exhibited slight redness and edema of the mucosa within 2 weeks of treatment, and appeared normal at later time points. There was some narrowing in four individual airways in two subjects examined at 5 days and 13 days after treatment, with excess mucus in two of these airways. There was no bronchoscopic evidence of scarring in any of the airways examined. Histologic examination showed a reduction in airway smooth muscle, and the extent of the treatment effect was confined to the airway wall and the immediate peribronchial region, as was expected from observations in the canine model. This study thus showed that application of Bronchial Thermoplasty to the human airway was well tolerated, leading to a significant reduction of smooth muscle mass in the airways.

A longer term evaluation was more recently reported in 16 asthmatic subjects. These 16 adult subjects with mild or moderate asthma were followed for 12 months without any evidence of chronic or progressive airway injury. The procedure treated all accessible airways greater than 3 mm in the lower and upper lobes. This was accomplished in 3 bronchoscopy sessions, each at least 3 weeks apart. All subjects tolerated the procedure well and were discharged at the end of a 6-hour observation period for each treatment session. In the days after treatment there was an increase in the frequency of airway symptoms, such as cough, mucous production, hoarseness and dyspnea. Examination of daily records of peak flows showed modest reduction suggesting that the symptoms were primarily those of bronchial irritation rather than airflow obstruction.

**Fig. 6** Airway size (mean±sem) at baseline and at increasing airway pressure after atropine in the subsequently treated (circles) and untreated (squares) airways. Results are shown for pretreatment and 5 weeks post-treatment. There were no significant differences in the airway size either at baseline or after any of the airway pressures between the two groups at pretreatment. At 5 weeks post-treatment there were highly significant differences (*p* < 0.0001) in the size of treated airways during Mch infusion compared to untreated airways.
The symptoms experienced by the subjects in this trial after Bronchial Thermoplasty were similar to those experienced by other subjects with asthma undergoing bronchoscopy and related procedures. Subjects were followed for 2 years following treatment. Results showed the following significant changes in FEV₁, symptom free days, and airway responsiveness to Mch challenge.

**FEV₁:** Bronchial Thermoplasty had no significant effect on % predicted FEV₁ at 2 years following treatment. The time course of FEV₁ changes is shown in Figure 7. Curiously there were significant increases in FEV₁ observed at 12 weeks ($p = 0.043$) and 1 year ($p = 0.030$). Post-bronchodilator FEV₁ showed no significant change from baseline throughout the time period. As mentioned earlier, this slight and inconsistent behavior of FEV₁ after treatment is what might be expected based on the slight increases in airway area observed in dogs after treatment. The inconsistency may also reflect varying degrees of baseline airway tone.

**Symptom-Free Days.** There was a highly significant ($P = 0.015$) increase in the mean percentage of symptom-free days from 50% pretreatment to 73% 12 weeks after treatment. During this 12-week follow-up period, almost 3/4 of the subjects experienced an increase in percentage of symptom-free days. This observation likely reflects the fact that the ability for airways to narrow has been greatly impaired. This speculation is supported by the results measuring the response to Mch challenge.

**Airway responsiveness to Mch.** After Bronchial Thermoplasty, the geometric mean PC₂₀ increased from 0.92 mg/ml to 4.75 at 12 weeks, 5.45 at 1 year and 3.40 at 2 years. Individual data contributing to these means are shown in Figure 8. It is important to that these means may underestimate the actual effect. This is because several subjects did not experience a 20% drop in FEV₁ even with the highest con-
centration of Mch allowed by the protocol. This dose was 16 mg/ml, and so these subjects were attributed a value of 16. Had it been possible to measure, their actual PC20’s would have been greater, and this would have increased the means. But even with this conservative limitation, the improvements observed throughout the study period represented approximately 2.4 doublings at 12 weeks, 3.0 doublings at 12 months and 2.3 doublings at 1 year.

This preliminary study thus confirms what was observed in the canine model. There was a clinically significant decrease in airway responsiveness following Bronchial Thermoplasty that persisted for at least 2 years after treatment. And since hyperresponsive airways are perhaps the most important functional component of asthma, it likely that this finding was a direct cause of the increase in symptom free days.37

Finally, we note that, although this preliminary clinical study was designed primarily to evaluate the feasibility and safety of Bronchial Thermoplasty, the results revealed several functional and practical clinical improvements. It is worth emphasizing again the potential lack of relevance of FEV1, despite its common use as a clinical endpoint in pharmacologic studies. This lack of change in FEV1 may superficially suggest that there is minimal beneficial effect of Bronchial Thermoplasty. FEV1 is a complex variable that depends on both airway resistance and lung elastance, and is preceded by a very large lung inflation. The effect of this inflation itself has been shown to have variable effects on airways of normal and asthmatic subjects,38-40 with normal subjects showing airway dilation following deep inspiration and asthmatic subjects often showing no change or even a further constriction. The effect of a deep inspiration on airways treated with Bronchial Thermoplasty in humans is unknown at this time. However, if the treatment does in fact make asthmatic airways more like those in normal subjects, then the effect of the preceding deep inspiration would be to result in a decreased airway resistance and higher FEV1. This is pure speculation at this time, but the preliminary data from human subjects is consistent with this conjecture.

SUMMARY

In summary, we have discussed the potential of Bronchial Thermoplasty to prevent serious consequences resulting from excessive airway narrowing. The most important factor in minimizing an asthmatic attack is limiting the degree of smooth muscle shortening. The premise that airway smooth muscle can be either inactivated or obliterated without any long-term alteration of other lung tissues, and that airway function will remain normal, albeit with reduced bronchoconstriction, has now been demonstrated in dogs and a subset of normal subjects and mild asthmatics. Bronchial Thermoplasty may thus develop into a useful clinical procedure to effectively impair the ability for airway smooth muscle to reach the levels of pathologic narrowing that characterizes an asthma attack. It may also enable more successful treatment of asthma patients who are unresponsive to more conventional therapies. Whether this will remain stable for the lifetime of the patient still remains to be determined, but at the present time, there are no indications that the smooth muscle contractility will return. This successful preliminary experience showing that Bronchial Thermoplasty could be safely performed in patients with asthma has led to an ongoing clinical trial at a number of sites in Europe and North America designed to examine the effectiveness of this procedure in subjects with moderately severe asthma.

REFERENCES

14. Israel E, Drazen JM, Liggett SB et al. The effect of polymorphisms of the beta (2)-adrenergic receptor on the re-


